ČESKÁ KARDIOLOGICKÁ SPOLEČNOST
THE CZECH SOCIETY OF CARDIOLOGY

ČESKÁ SPOLEČNOST KARDIOVASKULÁRNÍ CHIRURGIE
CZECH SOCIETY FOR CARDIOVASCULAR SURGERY

Ročník | Volume 63 • Suplementum 1 • Červen/June 2021

ISSN 0010-8650 (print), ISSN 1803-7712 (online)

Cor et Vasa

SUPLEMENTUM 1
Special issue: The year in cardiovascular medicine 2020

– Arrhythmias

– Imaging

– Valvular heart disease

– Heart failure and cardiomyopathies

– Epidemiology and prevention

– Acute coronary syndromes and intensive cardiac care

– Interventional cardiology

– Digital health and innovation

Cor et Vasa

S PŘÍLOHOU Kardio

Časopis České kardiologické společnosti a České společnosti kardiovaskulární chirurgie *Cor et Vasa* vychází šestkrát ročně a pokrývá všechny aspekty kardiologie, angiologie, kardiovaskulární chirurgie, kardiovaskulárního zobrazování, pediatrické kardiologie, hypertenze, kardiovaskulární prevence a některé z aspektů intervenční radiologie.

Obsahuje úvodníky, původní sdělení, přehledové články i krátká sdělení z klinické a experimentální kardiologie. Počínaje rokem 2012 jsou v *Cor et Vasa* publikovány také souhrny (5 000 slov) z doporučených postupů Evropské kardiologické společnosti, připravené předními českými odborníky.

Příloha *Cor et Vasa* Kardio přináší recenze knih, abstrakta z vybraných kongresů, zprávy z kongresů a konferencí, voleb a diskusí, polemiky, komentáře, informace z České kardiologické společnosti, České společnosti kardiovaskulární chirurgie a Evropské kardiologické společnosti i aktuální mezinárodní zprávy a témata.

Příspěvky jsou publikovány v češtině, slovenštině anebo v angličtině.

Časopis vychází ve dvou verzích se stejným obsahem: online a tištěné verzi. *Cor et Vasa* je dostupná v plném rozsahu také na webu ČKS.

Cor et Vasa je citována v databázích EMBASE, Scopus, Bibliographia medica Čechoslovaca, ESC Search Engine a Emerging Sources Citation Index společnosti Thomson and Reuters.

Příspěvky do časopisů zpracované podle pokynů autorům zasílejte prosím prostřednictvím systému ACTAVIA – vstup do něj je na adrese: http://actavia.e-coretvasa.cz/. Příspěvky do Kardia můžete zasílat také na adresu vedoucího redaktora nebo odpovědné redaktorky.

Adresa pro korespondenci s vedoucím redaktorem časopisu *Cor et Vasa*
Prof. MUDr. Michael Aschermann, DrSc., FESC, FACC (vedoucí redaktor)
II. interní klinika kardiologie a angiologie,
1. lékařská fakulta Univerzity Karlovy a Všeobecná fakultní nemocnice,
U Nemocnice 2, 128 08 Praha 2, Česká republika
E-mail: Aschermann@seznam.cz

Vychází 6× ročně (+ suplementum)
Povoleno Ministerstvem kultury ČR E 18519.
ISSN 0010-8650 (print), ISSN 1803-7712 (online)

Vydavatel
Česká kardiologická společnost, z. s.
Netroufalky 6b, 625 00 Brno

Předseda
Prof. MUDr. Aleš Linhart, DrSc., FESC, FCMA

Odpovědná redaktorka
Mgr. Klára Procházková
Tel.: +420 607 932 545
E-mail: ProchazkovaKlara@email.cz

Inzerce
Bc. Denisa Ebelová
Tel.: +420 725 777 880
E-mail: ebelova@kardio-cz.cz

Distribuce, předplatné
Časopis je dostupný zdarma online všem členům ČKS a ČSKVCH na webových stránkách společností (přihlášení cestou osobního účtu). Distribuce vydaných čísel bude zajištěna cestou mailingu všem členům společnosti.

Pro členy ČKS je roční předplatné tištěného časopisu 600 Kč, pro nečleny ČKS 1 000 Kč, v případě zájmu kontaktujte prosím paní Bc. Denisu Ebelovou: ebelova@kardio-cz.cz

Vydavatel neručí za kvalitu a účinnost jakéhokoli výrobku nebo služby nabízených v reklamě nebo jiném materiálu komerční povahy.

Pre-press
Studio Franklin Praha
E-mail: franklin@franklin.cz

Tisk
Tiskárna Knopp s.r.o.
Nové Město nad Metují

Cor et Vasa

WITH SUPPLEMENT

Kardio

Cor et Vasa, the journal of the Czech Society of Cardiology and Czech Society for Cardiovascular Surgery, publishes 6 times a year and covers all aspects cardiology, angiology, cardiovascular surgery, cardiovascular imaging, pediatric cardiology, hypertension, cardiovascular prevention and some aspects of interventional radiology.

It features editorial, original articles, review articles, as well as short communications from clinical and experimental cardiology. Beginning 2012, *Cor et Vasa* has also been publishing summaries (5 000 words) of the European Society of Cardiology guidelines, developed by leading Czech experts in the field.

Its supplement, *Cor et Vasa* Kardio offers book reviews, abstracts from elected congresses and conferences, elections and discussions, polemics, commentaries, information from the Czech Society of Cardiology, Czech Society of Cardiovascular Surgery and European Society of Cardiology as well as topical international news items.

Contributions appear in the Czech, Slovak or English language.

The journal publishes in two version with identical contents: online and printed versions. Fulltext *Cor et Vasa* is also available at the Czech Society of Cardiology website.

Cor et Vasa is indexed in the EMBASE, Scopus, Bibliographia medica Čechoslovaca, ESC Search Engine databases and Emerging Sources Citation Index, the indexing database of Thomson Reuters.

Please submit your contributions formatted as per Instructions to Authors through the ACTAVIA editorial system to be entered at http://actavia.e-coretvasa.cz/. Contributions to Kardio can also be submitted to Editor-in-Chief or Managing Editor.

The Publisher cannot be hold responsible for data or opinions presented by authors in their individual contributions or the factual and linguistic aspects of advertising material.

Address for correspondence with the Editor-in-Chief of *Cor et Vasa*
Prof. MUDr. Michael Aschermann, DrSc., FESC, FACC (Editor-in-Chief)
2nd Department of Internal Medicine – Cardiology and Angiology
School of Medicine I, Charles University and General University Hospital
U Nemocnice 2, 128 08 Prague 2, Czech Republic
E-mail: Aschermann@seznam.cz

Published 6 times a year (+ supplement)
Permission E 18519 granted by the Ministry of Culture of the Czech Republic.
ISSN 0010-8650 (print), ISSN 1803-7712 (online)

Publisher
Česká kardiologická společnost, z. s.
Netroufalky 6b, 625 00 Brno

President
Prof. MUDr. Aleš Linhart, DrSc., FESC, FCMA

Managing Editor
Mgr. Klára Procházková
Tel.: +420 607 932 545
E-mail: ProchazkovaKlara@email.cz

Advertising information
Bc. Denisa Ebelová
Tel.: +420 725 777 880
E-mail: ebelova@kardio-cz.cz

Distribution, subscription
The journal is available online free of charge to all members of the Czech Society of Cardiology and Czech Society for Cardiovascular Surgery on the societies' websites (log-in through your personal account).

Published issues will be distributed to all society members through regular mail.

The annual subscription rate of the printed journal for the Czech Society of Cardiology members is 600 CZK, for non-members 1,000 CZK; for further information, please contact Mrs Bc. Denisa Ebelová at ebelova@kardio-cz.cz.

Pre-press
Studio Franklin Praha
E-mail: franklin@franklin.cz

Print
Tiskárna Knopp s.r.o.
Nové Město nad Metují

Cor et Vasa

Cor et Vasa

Časopis České kardiologické společnosti & České společnosti kardiovaskulární chirurgie
Citován v databázích Scopus, EMBASE, ESC Search Engine a Emerging Sources Citation Index společnosti Thomson and Reuters
The Journal of the Czech Society of Cardiology & the Czech Society for Cardiovascular Surgery
Abstracted / Indexed in: Scopus, EMBASE, ESC Search Engine and Emerging Sources Citation Index by Thomson and Reuters

Obsah | Contents

Svazek | Volume 63 SUPLEMENTUM 1

Úvodník | Editorial

Přehledové články | Review articles

The year in cardiovascular medicine 2020

Michael Aschermann

II. interní klinika kardiologie a angiologie, Kardiovaskulární centrum, 1. lékařská fakulta Univerzity Karlovy a Všeobecná fakultní nemocnice v Praze, Praha

Vážení čtenáři,

Evropská kardiologická společnost (ESC) sdružuje celkem 56 národních kardiologických společností, které vydávají celkem 42 národních kardiologických časopisů – patří mezi ně i *Cor et Vasa*. V letošním roce nabídla ESC pro všechny národní časopisy možnost publikovat celkem osm článků z *European Heart Journal,* které jsou nazvány: *The year in cardiovascular medicine 2020.* Tyto články shrnují to nejdůležitější a nejzajímavější, co se v roce 2020 událo v osmi tematických oblastech kardiologie: v arytmologii,[1] v oblasti zobrazovacích metod,[2] u chlopenních vad,[3] v problematice srdečního selhání a kardiomyopatií,[4] v epidemiologii a prevenci,[5] u akutních koronárních syndromů a v intenzivní péči,[6] v intervenční kardiologii[7] a v inovacích a „digitálním zdraví".[8] Výbor ČKS jednoznačně podpořil možnost vydání těchto článků v suplementu *Cor et Vasa*, v redakci časopisu se pak podařilo tuto publikaci připravit tak, abychom splnili požadavky ESC na tuto publikaci. Některá obrazová dokumentace je z administrativních důvodů dostupná pouze v originálních publikacích, proto u odkazů na dané obrázky najdete odkazy na jejich zdroje. Věřím, že přehledové články uvedených tematických oblastí od špičkových autorů budou přínosem pro vzdělání nás všech.

Literatura

1. Crijns HJGM, Prinzen F, Lambiase PD, Sanders P, Brugada J. The year in cardiovascular medicine 2020: arrhythmias. Eur Heart J 2021;42:499–507.
2. Zamorano JL, Pinto FJ, Solano-López J, Bucciarelli-Ducci C. The year in cardiovascular medicine 2020: imaging. Eur Heart J 2021;42:740–749.
3. Bermejo J, Postigo A, Baumgartner H. The year in cardiovascular medicine 2020: valvular heart disease. Eur Heart J 2021;42:647–656.
4. Bueno H, Moura B, Lancellotti P, Bauersachs J. The year in cardiovascular medicine 2020: heart failure and cardiomyopathies. Eur Heart J 2021;42:657–670.
5. Estruch R, Ruilope LM, Cosentino F. The year in cardiovascular medicine 2020: epidemiology and prevention. Eur Heart J 2021;42:813–821.
6. Ibanez B, Roque D, Price S. The year in cardiovascular medicine 2020: acute coronary syndromes and intensive cardiac care. Eur Heart J 2021;42:884–895.
7. Alfonso F, Gonzalo N, Rivero F, Escaned J. The year in cardiovascular medicine 2020: interventional cardiology. Eur Heart J 2021;42:985–1003.
8. Antoniades C, Asselbergs FW, Vardas P. The year in cardiovascular medicine 2020: digital health and innovation, Eur Heart J 2021;42:732–739.

Adresa: Prof. MUDr. Michael Aschermann, DrSc., FESC, FACC, II. interní klinika kardiologie a angiologie, Kardiovaskulární centrum, 1. lékařská fakulta Univerzity Karlovy a Všeobecná fakultní nemocnice v Praze, U Nemocnice 2, 128 00 Praha 2, e-mail: aschermann@seznam.cz

DOI: 10.33678/cor.2021.075

Tento článek prosím citujte takto: Aschermann M. The year in cardiovascular medicine 2020. Cor Vasa 2021;63(Supl. 1):5.

ESC European Society of Cardiology

Special article

The year in cardiovascular medicine 2020: arrhythmias

Harry J.G.M. Crijns[1*], Frits Prinzen[2], Pier D. Lambiase[3], Prashanthan Sanders[4], and Josep Brugada[5]

[1] Department of Cardiology and Cardiovascular Research Centre Maastricht (CARIM), Maastricht University Medical Centre, Maastricht, The Netherlands; [2] Department of Physiology and Cardiovascular Research Centre Maastricht (CARIM), University of Maastricht, Maastricht, The Netherlands; [3] University College London & Barts Heart Centre, London, UK; [4] Centre for Heart Rhythm Disorders, University of Adelaide and Royal Adelaide Hospital, Adelaide, Australia; and [5] Cardiovascular Institute, Hospital Clinic, Pediatric Arrhythmia Unit, Hospital Sant Joan de Déu, University of Barcelona, Barcelona, Spain

Received 2 November 2020; revised 8 December 2020; accepted 19 December 2020; online publish-ahead-of-print 3 January 2021

Reproduced from: Crijns HJGM, Prinzen F, Lambiase PD, Sanders P, Brugada J. The year in cardiovascular medicine 2020: arrhythmias. Eur Heart J. 2021 Feb 1;42(5):499–507. https://doi.org/10.1093/eurheartj/ehaa1091, by permission of Oxford University Press on behalf of the European Society of Cardiology

* Corresponding author. Tel: +31 433875093, Fax: +31 433875104, Email: hjgm.crijns@mumc.nl

Abstract

Summary of the progress in arrhythmias in 2020. RACE4 and ALL-IN indicated that integrated nurse-led care improves outcomes in AF patients.[3,4] The same was reported for early rhythm control therapy[15] and cryoablation as initial AF treatment.[25,26] Subcutaneous ICD was non-inferior to classical transvenous ICD therapy in PRAETORIAN.[54] One mechanistic study showed that autoantibodies against misexpressed actin, keratin, and connexin-43 proteins create a blood-borne biomarker profile enhancing diagnosis of Brugada syndrome.[50] Another mechanistic study indicated that transseptal LV pacing yields similar improvement in contractility as His bundle pacing whilst being more easy to execute.[44] In PRE--DETERMINE a simple-to-use ECG risk score improved risk prediction in patients with ischemic heart disease possibly enhancing appropriate ICD therapy in high risk patients.[58] (*Graphical Abstract – see in original.*)

Keywords Guidelines • Randomized trial • Integrated care • Life style • Atrial fibrillation • Ventricular arrhythmias • Implantable defibrillator • His/left bundle pacing • Cardiogenetics •

Introduction

The Year in Cardiovascular Medicine: Arrhythmias 2020 reviews the most relevant studies in the field of arrhythmias and pacing. The past year has shown a significant progress: landmark clinical trials in atrial fibrillation (AF) and implantable defibrillator (ICD) therapy, new guidelines, integrated care, life style and arrhythmias, His bundle pacing, risk prediction in sudden cardiac death, and advances in cardiogenetics.

New guidelines

The guidelines on supraventricular tachycardia (SVT) and AF brought many new insights and recommendations.[1,2] The former dealt with SVT ablation as an early strategy and invasive risk assessment in ventricular preexcitation. Its focus also was on what-to-avoid in management of SVT.[2] The new guidelines on AF promote the slogan 'CC to ABC', indicating that electrical Confirmation of AF is mandatory together with in-depth Characterisation of AF (*Figure 1*).[1] For management the AF guidelines advise to follow the Atrial fibrillation Better Care (ABC) pathway, which represents care to (i) avoid stroke, (ii) better symptom control, and (iii) take care of co--morbidities and cardiovascular risk factors. Despite the lack of data to show clinical effectiveness, AF screening is advocated saying that once AF is detected outcome worsens. It is also recommended to measure the quality of care over time and when needed improve care in an iterating cycle of improvement. The guidelines also highlight the importance of longitudinal rather than one-time cross-sectional assessment of stroke and bleeding risks since patients may outgrow their low risk status quite rapidly over time. Catheter ablation is advocated to ameliorate AF symptoms and to manage AF-associated heart failure and may be applied after one antiarrhythmic drug failure including failure on beta-blockade.

Randomized trials on integrated care in atrial fibrillation

Interesting randomized trials on integrated AF management included the ALL-IN trial, a cluster randomized trial in elderly AF patients in primary care, which showed that integrated care delivered by practice nurses supervised by general practitioners reduced all-cause mortality by 45% compared to usual-care.[3] This is impressive and highlights the power of 'simple' interventions if deployed systematically. The integrated care pathway included quarterly AF check-ups by the practice nurse, case management of antithrombotic treatment, and easy-access consultation of a cardiologist. This represents patient-centered shared responsibilities between primary care, anticoagulation clinics, cardiologists, and patients. Similarly, RACE 4 reported that nurse-led, information and communication technology (ICT)-supported, and physician-supervised integrated care reduces morbidity and mortality in experienced centres but not in less-experienced centres and emphasized the importance of training in an integrated environment.[4] Key elements of integrated care in these trials were the multidisciplinary team approach, education, and empowerment of patients and where possible application of decision support technology.

Recent mHealth solutions include TeleCheck-AF[5,6] and a mobile AF application incorporating the ABC pathway (*Figure 1*).[7] The mAFA II trial reported a significant reduction in all-cause death and adverse cardiovascular events compared to routine management in high-risk AF.[7] Notably, single elements of integrated care such as application of a clinical decision support system,[8] an educational[9] or a motivational[10] intervention to improve anticoagulation or introduction of shared decision-making[11] improve the level of care but not prognosis.

In integrated care, patient-driven life-style changes targeting obesity, alcohol, and blood pressure control is important before performing rhythm control with catheter ablation. In a large cohort of 402 406 individuals from the UK Biobank, regular physical activity was related with a lower incidence of AF (especially in women) and ventricular arrhythmias but not of bradyarrhythmias.[12] Also, a randomized trial provided proof-of-concept data to support alcohol cessation as secondary prophylaxis against AF in regular drinkers.[13] Per nature of the trial, it focused on one element of life style whilst a more comprehensive multi-level modification of AF risk factors may be needed to abrogate risks of AF in daily life.[14]

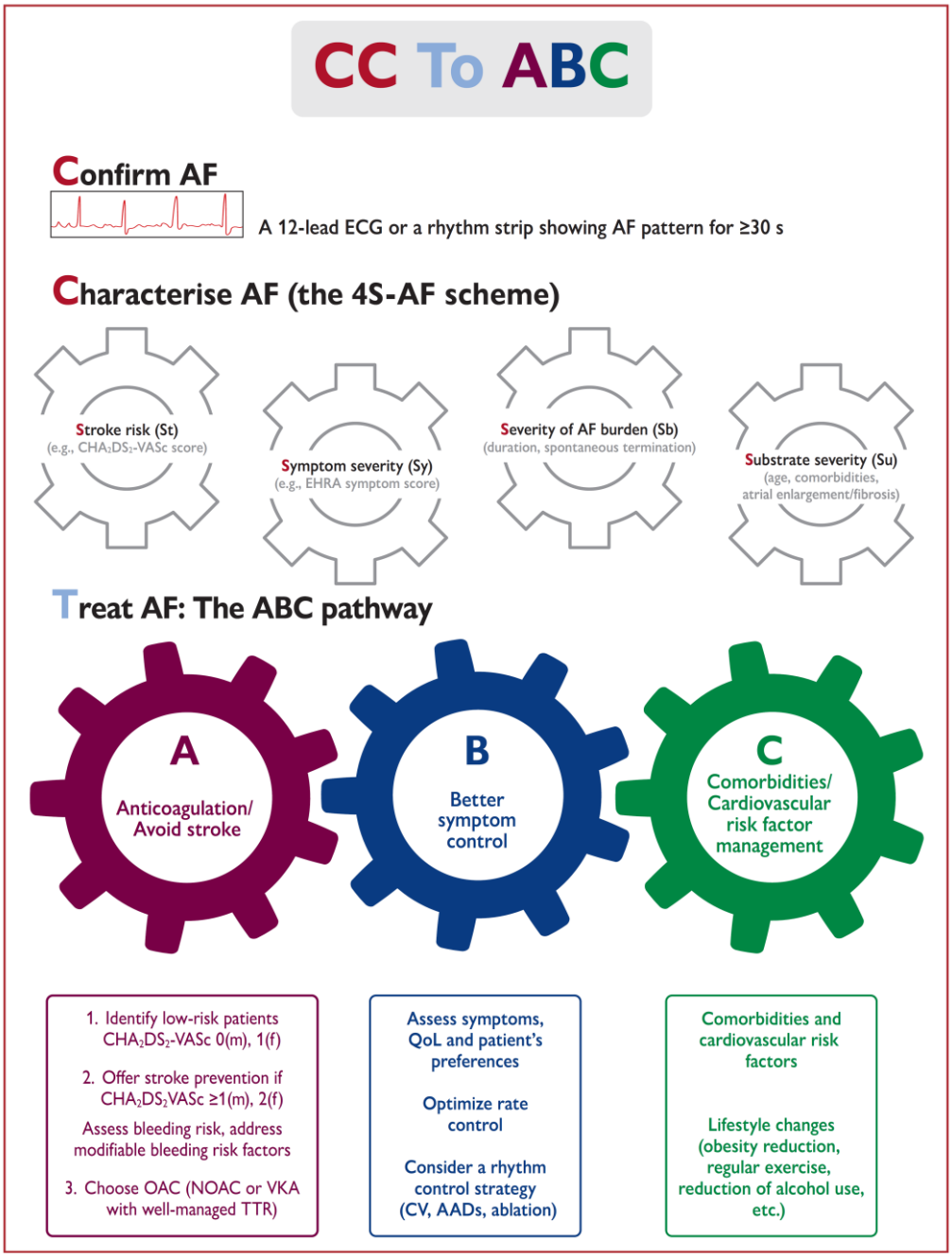


Figure 1 The CC to Atrial fibrillation Better Care paradigm in the latest European Society of Cardiology (ESC) guidelines provides a comprehensive and holistic approach towards diagnosis and management of atrial fibrillation. CC stands for Confirmation (first C) and Characterisation (second C) of atrial fibrillation according to the structured 4S-AF scheme including assessment of stroke risk, symptom severity, severity of atrial fibrillation burden, and substrate severity. From Hindricks *et al.*[1], by permission of OUP on behalf of ESC.

Randomized trials on rhythm control in atrial fibrillation

The EAST-AFNET 4 trial compared a rhythm with a rate control strategy in patients with early AF lasting <1 year. It showed that rhythm control therapy, i.e. antiarrhythmic drugs and ablation, in early AF reduced cardiovascular outcomes without increasing time spent in-hospital, and without safety concerns.[15]

The results are at odds with older trials, which may relate to earlier intervention, safer use of antiarrhythmic drugs, and safe application of catheter ablation. In accordance with the AF Guidelines,[1,16–18] rhythm control was applied on top of cardiovascular prevention. Like previous trials,[19–21] EAST-AFNET4 was a *strategy evaluation* and not a simple comparison of two treatment modalities meant to either maintain sinus rhythm or keeping adequate rate control like the CA-

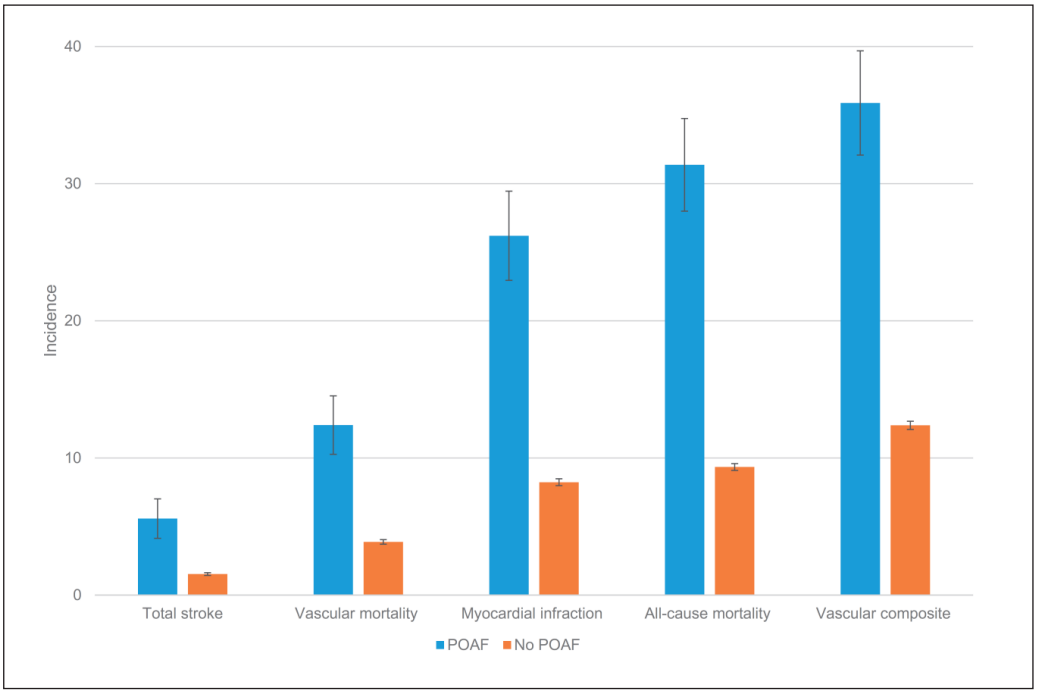


Figure 2 Adverse events per 100 patient-years follow-up in patients with cardiovascular disease after non-cardiac surgery indicate that postoperative atrial fibrillation is associated with a significantly elevated incidence of cardiovascular adverse events. From Conen *et al.*[39], by permission of OUP on behalf of ESC.

BANA trial.[22] EAST-AFNET4 included recently detected AF, which seems crucial since most events occur in the first year after AF detection.[23,24] Early intervention is supported by two recent trials showing that cryoballoon ablation as initial therapy is superior to drug treatment.[25,26] Therefore, initial AF care should be supervised by cardiologists rather than non-cardiologists since 1-year mortality and morbidity are lower if newly diagnosed AF is managed under cardiology care compared to non-cardiology care.[27,28]

Early rhythm control in recent-onset AF in the emergency room was tested in another randomized study comparing procainamide and rescue electrical cardioversion if needed with immediate electrical cardioversion.[29] Both strategies were clinically highly effective, but the authors suggested that immediate cardioversion be preferred since less burdensome for patients and the hospital.

Catheter ablation may be particularly useful in heart failure with AF,[21,30] to improve quality of life[31,32] as well as to save costs.[33] One interesting observational study suggested that catheter ablation compared to drug treatment is associated with a lower incidence of vascular dementia.[34] To support or circumvent catheter ablation, recent reports advocated add-on renal denervation[35] or low level tragus stimulation.[36] In CASA-AF,[37,38] single procedure thoracoscopic surgical left atrial posterior wall isolation was not superior to extensive point-by-point posterior wall isolation plus right and left isthmus ablation and came with higher costs and less gain in QALYs. However, the surgical lesion set was quite limited and surgical learning curve effects may have affected outcome.

Postoperative atrial fibrillation

The risk of stroke and other adverse outcomes after postoperative AF (POAF) was reported from the combined datasets of the randomized POISE trials on the effects of metoprolol vs. placebo, aspirin vs. placebo, and clonidine vs. placebo.[39] Patients with cardiovascular disease were undergoing non-cardiac surgery. POAF within 30 days after surgery was seen in 404 of 18 117 patients and was associated with 1-year stroke incidence of 5.6% compared to 1.5% in no-POAF patients. Also, risk of death (31.3% vs. 9.3%) and myocardial infarction (26.2 vs. 8.2) were increased (*Figure 2*). Risk reduction strategies still need to be investigated. This knowledge gap was unfortunately not filled by a recent randomized trial testing the sedative dexmedetomidine against placebo to reduce new-onset POAF as well as delirium in 798 patients undergoing cardiac surgery.[40] The incidence of new POAF (~32%) and delirium (~15%) did not differ between study groups.

Resynchronization therapy, including His bundle, septal, and left bundle pacing

The year 2020 saw an exponential increase in interest for His bundle (HBP) and left bundle branch area pacing (LBBAP) in cardiac resynchronization therapy (CRT). The number of implants in the USA of the most commonly used lead (Medtronic 3830), showed an increase from 2000 in 2016 to 10 000 in 2018. The number of HBP related publications increased from 5 in 2014 to 75 in 2018.[41]

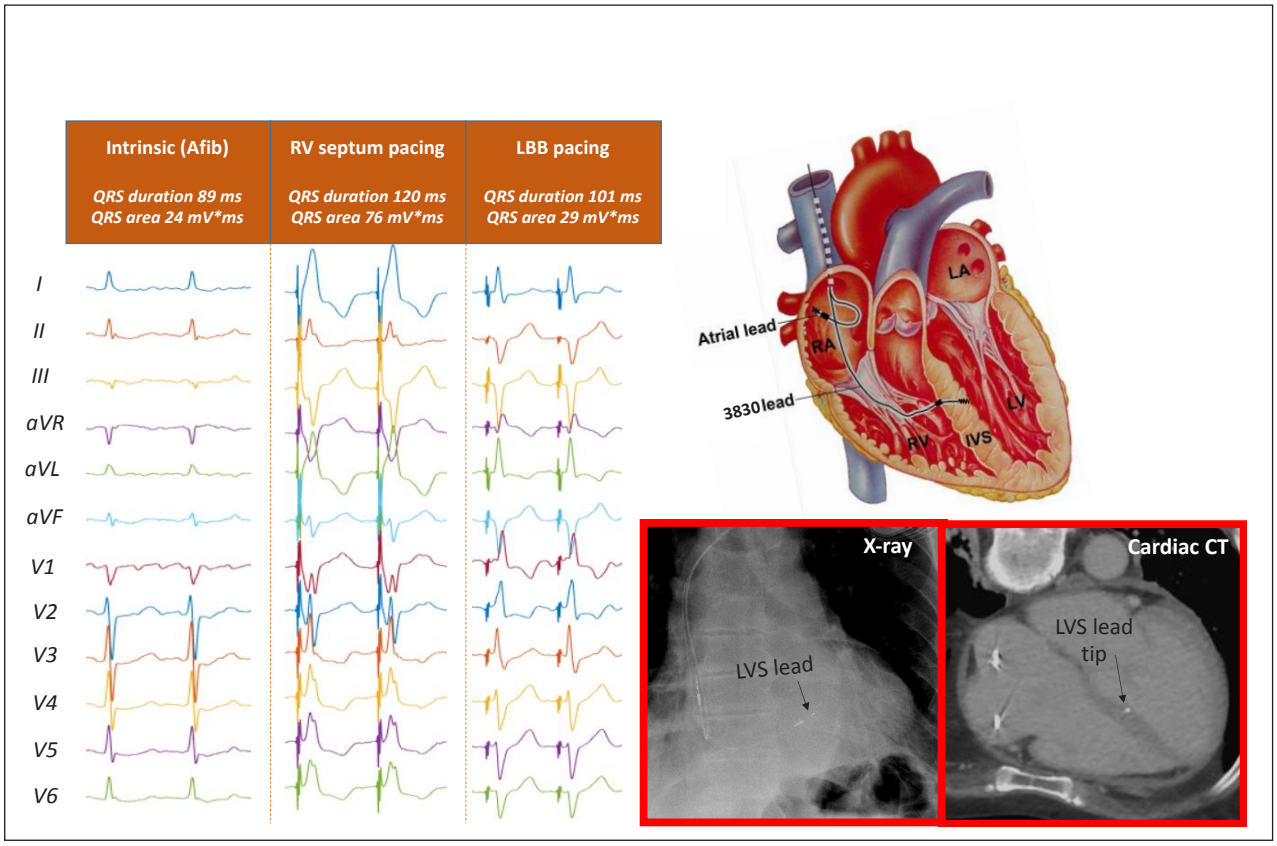


Figure 3 Schematic representation (upper right) and X-ray and computed tomography images (lower right) of positioning the pacing lead at the left side of the septum. Left panels show the electrocardiogram (ECG) during intrinsic rhythm of a patient with atrial fibrillation that received a pacemaker. Middle row of ECGs shows signals when pacing the lead at its initial position at the right of the septum and right row shows signals during pacing at final position. Note almost normalization of signals, QRS duration, and QRS area during LBB pacing.

Worldwide sales of the 3830 lead increased nine-fold between 2014 and 2018. The Twitter '#dontdisthehis' attracted almost 1200 users within 2.5 years.[42] The increased interest in HBP is likely due to the availability of better guiding catheters and the evidence that HBP is also suitable for CRT. In 2020, a few studies indicated that HBP may be equal or superior to conventional biventricular pacing (BVP) with regard to acute hemodynamic improvement, reverse remodeling and clinical outcome.[43–45]

In 2020, LBBAP was only 3 years old but attracted already considerable interest. For LBBAP, the 3830 lead is introduced transvenously and subsequently screwed through the interventricular septum until the tip of the lead is (almost) at the left ventricular (LV) endocardium (*Figure 3*). Compared to HBP, LBBAP lead implantation is easier and pacing thresholds are lower.[46] Some investigators aim at capturing the left bundle branch itself,[45] but others are less critical and accept any 'LV septal' lead position.[44] In 2020, a number of small single and multicenter studies appeared. Hou *et al*.[46] performed a study in 56 patients with bradyarrhythmias and LVEF >55%. These authors found that permanent LBBAP is safe and feasible. A better maintenance of synchrony of contraction, determined using SPECT MPI phase analysis, was observed when the left bundle branch was captured. Three studies comprising a total of 116 patients with LBBAP, 49 with HBP, and 75 with BVP consistently showed a larger reduction in QRS-complex (QRS) duration in combination with a larger increase in LV ejection fraction.[45,47,48]

Salden *et al*.[44] compared the acute hemodynamic and electrophysiological effects of 'LV septum pacing' with that of BVP and HBP. The three pacing modes were comparable with regards to increase in LVdP/dtmax, whilst HBP and LV septum pacing tended to provide better electrical resynchronization. An important finding was also that similar effects were observed when pacing the LV septum at the basal, equatorial and apical part of the septum. To show feasibility, safety (including lead extraction) and clinical effectiveness of these new pacing modalities, randomized studies are required comparing LBBP with HBP and BVP. A prospective randomized study is currently performed in China.[49]

Inherited cardiac conditions, risk assessment, implantable defibrillators, and sudden death

A novel approach to the diagnosis of Brugada syndrome (BrS) described the utilization of autoantibody screening for α-cardiac actin, α-skeletal actin, keratin, and conne-

xin-43. In total, 18/18 BrS subjects demonstrated this autoantibody profile vs. 0/8 normal controls and 0/20 cardiomyopathy cases, which included arrhythmogenic right ventricular cardiomyopathy (ARVC), hypertrophic cardiomyopathy (HCM), and dilated cardiomyopathy (DCM) patients.[50] In a subgroup of BrS patients, each of these proteins and the sodium channel protein type 5 alpha subunit (NaV1.5) aggregated in the sarcoplasm of myocardial cells. The mechanism as to why antibodies to these proteins identified BrS cases is unclear but could relate to sarcolemmal membrane damage either due to a myocarditic process in the disease course or abnormal cell adhesion resulting in an immune response. The novelty of this study is the utilisation of a serological test to identify BrS subjects, which can be challenging given the transient nature of the electrocardiogram (ECG) pattern. This paper is complemented by a study investigating polygenic risk (PRS) of ECG markers to predict a positive ajmaline response.[51] PRS for BrS, baseline QRS duration, presence of Type II or III BrS ECG at baseline and family history of BrS were independently associated with the occurrence of a Type I BrS ECG, with good predictive accuracy (optimism-corrected *C*-statistic 0.74). This provides the first data to enable the combination of genetic and clinical screening to predict ajmaline responses and has implications for risk stratification.

A combined clinical and electrophysiological mapping study showed that SCN5A mutation carriers exhibit more pronounced epicardial electrical abnormalities and a more aggressive clinical presentation than non-carriers.[52]

Recent data support the use of drug therapy to manage patients with catecholaminergic polymorphic VT (CPVT). In a provocative paper by Van der Werf *et al.*,[53] no survival benefit from ICDs was shown in young CPVT patients surviving cardiac arrest. There are a number of caveats to this study, but the main learning point was that such patients can be treated without an ICD.

PRAETORIAN compare d transvenous and subcutaneous ICDs in 849 patients >18 years with a class I or IIa indication for ICD therapy for primary or secondary prevention, followed for 49.1 months.[54] S-ICD demonstrated non-inferiority of the composite primary endpoint of device-related complications and inappropriate shocks. This provides the first multicentre trial evidence that the S-ICD is as effective and safe as transvenous ICD in preventing SCD for patients not requiring brady-pacing, anti-tachycardia VT pacing, or CRT, but challenges remain including longevity of leads and ICD, and inappropriate shocks. Concerning the latter, the UNTOUCHED study of primary prevention ICD therapy supports the PRAETORIAN data by showing an inappropriate shock-free rate of 95.9%, suggesting that the new SMART PASS filter technology and appropriate high rate S-ICD programming may minimize inappropriate shocks in S-ICD recipients.[55]

Two primary prevention ICD registries applying propensity scoring showed beneficial effects but differed concerning efficacy of ICD in women and elderly.[56,57]

To predict sudden arrhythmic death (SAD) in coronary artery disease, the PRE-DETERMINE investigators integrated an ECG risk score with conventional cardiovascular parameters. A high-risk ECG score incorporating contiguous Q waves, LV hypertrophy, QRS duration, and JTc prolongation was more strongly associated with SAD than non-SAD (adjusted hazard ratios 2.87 vs. 1.38) and the proportion of deaths due to SAD was greater in the high vs. low risk groups (24.9% vs. 16.5%).[58] The addition of ECG markers to a clinical risk factor model including LVEF improved discrimination and reclassification, including correct reclassification of 28% of patients in the validation cohort. The strength of this approach is the utilization of simple bedside biomarkers to determine management, but it needs clinical validation in a randomized trial.

To conclude, The Year in Cardiovascular Medicine 2020—Arrhythmias shows significant progress in the field, much of it incremental, some of it attention gathering, and some of it clearly needing further work.

Conflict of interest: none declared.

References

1. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL ; Group ESCSD. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021;**42**:373–498.
2. Brugada J, Katritsis DG, Arbelo E, Arribas F, Bax JJ, Blomström-Lundqvist C, Calkins H, Corrado D, Deftereos SG, Diller G-P, Gomez-Doblas JJ, Gorenek B, Grace A, Ho SY, Kaski J-C, Kuck K-H, Lambiase PD, Sacher F, Sarquella-Brugada G, Suwalski P, Zaza A, De Potter T, Sticherling C, Aboyans V, Basso C, Bocchiardo M, Budts W, Delgado V, Dobrev D, Fitzsimons D, Gevaert S, Heidbuchel H, Hindricks G, Hlivak P, Kanagaratnam P, Katus H, Kautzner J, Kriebel T, Lancellotti P, Landmesser U, Leclercq C, Lewis B, Lopatin Y, Merkely B, Paul T, Pavlović N, Petersen S, Petronio AS, Potpara T, Roffi M, Scherr D, Shlyakhto E, Simpson IA, Zeppenfeld K, Arbelo E, Arribas F, Bax JJ, Blomström-Lundqvist C, Calkins H, Deftereos SG, Diller G-P, Gomez-Doblas JJ, Gorenek B, Grace A, Ho SY, Kaski J-C, Kuck K-H, Lambiase PD, Sacher F, Sarquella-Brugada G, Suwalski P, Zaza A, Windecker S, Aboyans V, Baigent C, Collet J-P, Dean V, Delgado V, Fitzsimons D, Gale CP, Grobbee D, Halvorsen S, Hindricks G, Iung B, Jüni P, Katus HA, Landmesser U, Leclercq C, Lettino M, Lewis BS, Merkely B, Mueller C, Petersen SE, Petronio AS, Richter DJ, Roffi M, Shlyakhto E, Simpson IA, Sousa-Uva M, Touyz RM, Amara W, Grigoryan S, Podczeck-Schweighofer A, Chasnoits A, Vandekerckhove Y, Sokolovich S, Traykov V, Skoric B, Papasavvas E, Kautzner J, Riahi S, Kampus P, Parikka H, Piot O, Etsadashvili K, Stellbrink C, Manolis AS, Csanádi Z, Gudmundsson K, Erwin J, Barsheshet A, De Ponti R, Abdrakhmanov A, Jashari H, Lunegova O, Jubele K, Refaat MM, Puodziukynas A, Groben L, Grosu A, Pavlovic N, Ibtissam F, Trines SA, Poposka L, Haugaa KH, Kowalski O, Cavaco D, Dobreanu D, Mikhaylov EN, Zavatta M, Nebojša M, Hlivak P, Ferreira-Gonzalez I, Juhlin T, Reichlin T, Haouala H, Akgun T, Gupta D ; ESC Scientific Document Group. 2019 ESC Guidelines for the management of patients with supraventricular tachycardia: The Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC): Developed in collaboration with the Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2020;**41**:655–720.
3. Van den Dries CJ, van Doorn S, Rutten FH, Oudega R, van de Leur SJCM, Elvan A, Oude Grave L, Bilo HJG, Moons KGM, Hoes AW, Geersing G-J. Integrated management of atrial fibrillation in primary care: results of the ALL-IN cluster randomized trial. *Eur Heart J* 2020;**41**:2836–2844.

4. Wijtvliet E, Tieleman RG, van Gelder IC, Pluymaekers N, Rienstra M, Folkeringa RJ, Bronzwaer P, Elvan A, Elders J, Tukkie R, Luermans J, Van Asselt A, Van Kuijk SMJ, Tijssen JG, Crijns H. Nurse-led vs. usual-care for atrial fibrillation. *Eur Heart J* 2020;**41**:634–641.
5. Pluymaekers N, Hermans ANL, van der Velden RMJ, Gawałko M, den Uijl DW, Buskes S, Vernooy K, Crijns H, Hendriks JM, Linz D. Implementation of an on-demand app-based heart rate and rhythm monitoring infrastructure for the management of atrial fibrillation through teleconsultation: TeleCheck-AF. *Europace* 2020;doi: 10.1093/europace/euaa201.
6. Linz D, Pluymaekers N, Hendriks JM. TeleCheck-AF for COVID-19. *Eur Heart J* 2020;**41**:1954–1955.
7. Guo Y, Lane DA, Wang L, Zhang H, Wang H, Zhang W, Wen J, Xing Y, Wu F, Xia Y, Liu T, Wu F, Liang Z, Liu F, Zhao Y, Li R, Li X, Zhang L, Guo J, Burnside G, Chen Y, Lip GYH, Guo Y, Lip GYH, Lane DA, Chen Y, Wang L, Eckstein J, Thomas GN, Tong L, Mei F, Xuejun L, Xiaoming L, Zhaoliang S, Xiangming S, Wei Z, Yunli X, Jing W, Fan W, Sitong Y, Xiaoqing J, Bo Y, Xiaojuan B, Yuting J, Yangxia L, Yingying S, Zhongju T, Li Y, Tianzhu L, Chunfeng N, Lili Z, Shuyan L, Zulu W, Bing X, Liming L, Yuanzhe J, Yunlong X, Xiaohong C, Fang W, Lina Z, Yihong S, Shujie J, Jing L, Nan L, Shijun L, Huixia L, Rong L, Fan L, Qingfeng G, Tianyun G, Yuan W, Xin L, Yan R, Xiaoping C, Ronghua C, Yun S, Yulan Z, Haili S, Yujie Z, Quanchun W, Weidong S, Lin W, Chan E, Guangliang S, Chen Y, Wei Z, Dandi C, Xiang H, Anding X, Xiaohan F, Ziqiang Y, Xiang G, Fulin G. Mobile health technology to improve care for patients with atrial fibrillation. *J Am Coll Cardiol* 2020;**75**:1523–1534.
8. Cox JL, Parkash R, Foster GA, Xie F, MacKillop JH, Ciaccia A, Choudhri SH, Hamilton LM, Nemis-White JM, Thabane L *;* Investigators I-A. Integrated Management Program Advancing Community Treatment of Atrial Fibrillation (IMPACT-AF): a cluster randomized trial of a computerized clinical decision support tool. *Am Heart J* 2020;**224**:35–46.
9. Vinereanu D, Lopes RD, Bahit MC, Xavier D, Jiang J, Al-Khalidi HR, He W, Xian Y, Ciobanu AO, Kamath DY, Fox KA, Rao MP, Pokorney SD, Berwanger O, Tajer C, de Barros e Silva PGM, Roettig ML, Huo Y, Granger CB, Carbajales J, Gómez JNC, Principato MB, Von Wulffen MA, Acunzo JGRS, Bonato RR, Ciampi N, Marani AB, Panigadi CG, Pastura SG, Onetto LM, Moya CR, Budassi N, Valle M, Camerini D, Monjes E, Zabala F, Ricart JP, Medesani L, Campos ENO, Ferroni F, Torres MF, Fassi DO, Bosio FJD, Baztarrica GEP, Infantas TZ, Perlo D, García CF, Durán RG, Durán LG, Pettinari CA, Vico ML, Lanchiotti PV, Gómez MS, Poy CA, Grazziani FS, Laspina MJ, Poy ML, Bahit MC, Tajer C, García M, Lopes RD, de Barros e Silva PGM, Berwanger O, Egydio F, Restelli E, Kawakami A, Soares TC, Valois MV, Duarte TB, Barbosa LM, de Paola AAV, Pimenta TL, Jeronimo GDM, da Costa BSF, Coutinho EL, Guerrero AZA, Maia LN, Nakazone MA, Lemos MAT, Costa OMC, Demore AP, Brito RP, Melo CDB, Góes NC, Lorenço O, Gonçalves LOM, Nishiama K, de Lima TAM, Backes LM, de Lima Deucher KLA, Rodrigues MP, Baldissera DM, Reolão JBC, dos Santos TA, Freisleben FMB, da Silveira Kaross NL, Montovani JT, Cantarelli M, Lucion A, do Amarante L, Foscarini P, de Mello Perez C, França FR, Fialho L, Rey HCV, God EMG, Figueiredo EL, Werner GF, de Faria Garcia JC, Azevedo B, Barbosa LCV, Pardi E, Oliveira MD, Martinelli T, Cavalini RG, de Moraes MSM, Filho AML, Palmegiani E, Megid TBC, Queirantes CSP, Cruz TSA, He P, Zhou X, Zhou N, Zhao M, Yu J, Cheng Y, Wang L, Liu L, Liu S, Li L, Li A, Yuan X, Xia G, Wang Z, Li C, Chen W, Tang Q, Tang Q, Xu W, Zhu X, Hou B, Ma W, Wang C, Jin Q, Wang J, Xie X, Joseph J, Davidson D, Thomas JK, Kunjumon TV, Stephen T, Fatania K, Rathi G, Garala K, Doshi D, Varghese K, Ma S, Sheeba L, Kumar S, Rao MB, Rao KD, Vuriya AK, Kumari MP, Khandelwal B, Dhakal M, Srivastava N, Khatri D, Moktan S, Gupta R, Roy S, Kumawat K, Sharma M, Sharma KK, Jathappa N, Lokesh BH, Kariyappa S, Leela AC, Someshwara KC, Desai S, Desai D, Patel K, Patel S, Bhartiya M, Mahanta BN, Dutta DJ, Rajkonwer G, Gupta SK, Mishra AK, Singh A, Kesarwani N, Kumar S, Chioncel O, Balan A, Carstea N, Chitoiu GT, Cornaciu S, Cinteza M, Rimbas RC, Dimulescu D, Ionescu L, Fruntelata A, Dumitru N, Gaita D, Pleava R, Iliesiu A, Uscoiu G, Lighezan D, Buzas R, Sinescu CJ, Avram A-M, Baldea S, Galrinho RD, Magda SL, Matei L; Investigators I-A. A multifaceted intervention to improve treatment with oral anticoagulants in atrial fibrillation (IMPACT-AF): an international, cluster-randomised trial. *Lancet* 2017;**390**:1737–1746.
10. Tzikas A, Samaras A, Kartas A, Vasdeki D, Fotos G, Dividis G, Paschou E, Forozidou E, Tsoukra P, Kotsi E, Goulas I, Karvounis H, Giannakoulas G. Motivational Interviewing to Support Oral AntiCoagulation adherence in patients with non-valvular Atrial Fibrillation (MISOAC-AF): a randomised clinical trial. *Eur Heart J Cardiovasc Pharmacother* 2020;doi: 10.1093/ehjcvp/pvaa039.
11. Kunneman M, Branda ME, Hargraves IG, Sivly AL, Lee AT, Gorr H, Burnett B, Suzuki T, Jackson EA, Hess E, Linzer M, Brand-McCarthy SR, Brito JP, Noseworthy PA, Montori VM; for the Shared Decision Making for Atrial Fibrillation (SDM4Afib) Trial Investigators. Assessment of shared decision-making for stroke prevention in patients with atrial fibrillation: a randomized clinical trial. *JAMA Intern Med* 2020;**180**:1215.
12. Elliott AD, Linz D, Mishima R, Kadhim K, Gallagher C, Middeldorp ME, Verdicchio CV, Hendriks JML, Lau DH, La Gerche A, Sanders P. Association between physical activity and risk of incident arrhythmias in 402 406 individuals: evidence from the UK Biobank cohort. *Eur Heart J* 2020;**41**:1479–1486.
13. Voskoboinik A, Kalman JM, De Silva A, Nicholls T, Costello B, Nanayakkara S, Prabhu S, Stub D, Azzopardi S, Vizi D, Wong G, Nalliah C, Sugumar H, Wong M, Kotschet E, Kaye D, Taylor AJ, Kistler PM. Alcohol abstinence in drinkers with atrial fibrillation. *N Engl J Med* 2020;**382**:20–28.
14. Linz D, Crijns H. Alcohol abstinence in drinkers with atrial fibrillation. *N Engl J Med* 2020;**382**:1768.
15. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, Fetsch T, van Gelder IC, Haase D, Haegeli LM, Hamann F, Heidbüchel H, Hindricks G, Kautzner J, Kuck KH, Mont L, Ng GA, Rekosz J, Schoen N, Schotten U, Suling A, Taggeselle J, Themistoclakis S, Vettorazzi E, Vardas P, Wegscheider K, Willems S, Crijns H, Breithardt G. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* 2020;**383**:1305–1316.
16. Camm AJ, Kirchhof P, Lip GYH, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey J-Y, Ponikowski P, Rutten FH, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas PE, Widimsky P, Vardas PE, Agladze V, Aliot E, Balabanski T, Blomstrom-Lundqvist C, Capucci A, Crijns H, Dahlof B, Folliguet T, Glikson M, Goethals M, Gulba DC, Ho SY, Klautz RJM, Kose S, McMurray J, Perrone Filardi P, Raatikainen P, Salvador MJ, Schalij MJ, Shpektor A, Sousa J, Stepinska J, Uuetoa H, Zamorano JL, Zupan I; Developed with the special contribution of the European Heart Rhythm Association (EHRA). Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;**31**:2369–2429.
17. Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Ž, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Vardas P, Al-Attar N, Alfieri O, Angelini A, Blömstrom-Lundqvist C, Colonna P, De Sutter J, Ernst S, Goette A, Gorenek B, Hatala R, Heidbüchel H, Heldal M, Kristensen SD, Kolh P, Le Heuzey J-Y, Mavrakis H, Mont L, Filardi PP, Ponikowski P, Prendergast B, Rutten FH, Schotten U, Van Gelder IC, Verheugt FWA; Authors/Task Force Members. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation, developed with the special contribution of the European Heart Rhythm Association. *Europace* 2012;**14**:1385–1413.
18. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener H-C, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte

B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GYH, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–2962.

19. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD; Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;**347**:1825–1833.
20. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJ, Tijssen JG, Crijns HJ. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002;**347**:1834–1840.
21. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H, Vogt J, Bänsch D. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* 2018;**378**:417–427.
22. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, Noseworthy PA, Rosenberg YD, Jeffries N, Mitchell LB, Flaker GC, Pokushalov E, Romanov A, Bunch TJ, Noelker G, Ardashev A, Revishvili A, Wilber DJ, Cappato R, Kuck KH, Hindricks G, Davies DW, Kowey PR, Naccarelli GV, Reiffel JA, Piccini JP, Silverstein AP, Al-Khalidi HR, Lee KL, Investigators C; for the CABANA Investigators. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA* 2019;**321**:1261–1274.
23. Nieuwlaat R, Prins MH, Le Heuzey JY, Vardas PE, Aliot E, Santini M, Cobbe SM, Widdershoven JW, Baur LH, Levy S, Crijns HJ. Prognosis, disease progression, and treatment of atrial fibrillation patients during 1 year: follow-up of the Euro Heart Survey on atrial fibrillation. *Eur Heart J* 2008;**29**:1181–1189.
24. Healey JS, Oldgren J, Ezekowitz M, Zhu J, Pais P, Wang J, Commerford P, Jansky P, Avezum A, Sigamani A, Damasceno A, Reilly P, Grinvalds A, Nakamya J, Aje A, Almahmeed W, Moriarty A, Wallentin L, Yusuf S, Connolly SJ, Registry R-L; Cohort Study I. Occurrence of death and stroke in patients in 47 countries 1 year after presenting with atrial fibrillation: a cohort study. *Lancet* 2016;**388**:1161–1169.
25. Wazni OM, Dandamudi G, Sood N, Hoyt R, Tyler J, Durrani S, Niebauer M, Makati K, Halperin B, Gauri A, Morales G, Shao M, Cerkvenik J, Kaplon RE, Nissen SE; Investigators SAFT. Cryoballoon ablation as initial therapy for atrial fibrillation. *N Engl J Med* 2020;doi: 10.1056/NEJMoa2029554.
26. Andrade JG, Wells GA, Deyell MW, Bennett M, Essebag V, Champagne J, Roux JF, Yung D, Skanes A, Khaykin Y, Morillo C, Jolly U, Novak P, Lockwood E, Amit G, Angaran P, Sapp J, Wardell S, Lauck S, Macle L, Verma A; Investigators E-A. Cryoablation or drug therapy for initial treatment of atrial fibrillation. *N Engl J Med* 2020.
27. Hawkins NM, Scheuermeyer FX, Youngson E, Sandhu RK, Ezekowitz JA, Kaul P, McAlister FA. Impact of cardiology follow-up care on treatment and outcomes of patients with new atrial fibrillation discharged from the emergency department. *Europace* 2020;**22**:695–703.
28. Crijns H, Wijtvliet EPJ, Pluymaekers N, Van Gelder IC. Newly discovered atrial fibrillation: who(se) care(s)?. *Europace* 2020;**22**:677–678.
29. Stiell IG, Sivilotti MLA, Taljaard M, Birnie D, Vadeboncoeur A, Hohl CM, McRae AD, Rowe BH, Brison RJ, Thiruganasambandamoorthy V, Macle L, Borgundvaag B, Morris J, Mercier E, Clement CM, Brinkhurst J, Sheehan C, Brown E, Nemnom M-J, Wells GA, Perry JJ. Electrical versus pharmacological cardioversion for emergency department patients with acute atrial fibrillation (RAFF2): a partial factorial randomised trial. *Lancet* 2020;**395**:339–349.
30. Chen S, Purerfellner H, Meyer C, Acou WJ, Schratter A, Ling Z, Liu S, Yin Y, Martinek M, Kiuchi MG, Schmidt B, Chun KRJ. Rhythm control for patients with atrial fibrillation complicated with heart failure in the contemporary era of catheter ablation: a stratified pooled analysis of randomized data. *Eur Heart J* 2020;**41**:2863–2873.
31. Blomström-Lundqvist C, Gizurarson S, Schwieler J, Jensen SM, Bergfeldt L, Kennebäck G, Rubulis A, Malmborg H, Raatikainen P, Lönnerholm S, Höglund N, Mörtsell D. Effect of catheter ablation vs antiarrhythmic medication on quality of life in patients with atrial fibrillation: the CAPTAF randomized clinical trial. *JAMA* 2019;**321**:1059–1068.
32. Mark DB, Anstrom KJ, Sheng S, Piccini JP, Baloch KN, Monahan KH, Daniels MR, Bahnson TD, Poole JE, Rosenberg Y, Lee KL, Packer DL; for the CABANA Investigators. Effect of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA* 2019;**321**:1275–1285.
33. Martinek M, Purerfellner H, Blessberger H, Pruckner G. Impact of catheter ablation therapy for atrial fibrillation on healthcare expenditures in a middle European cohort. *Europace* 2020;**22**:576–583.
34. Kim D, Yang PS, Sung JH, Jang E, Yu HT, Kim TH, Uhm JS, Kim JY, Pak HN, Lee MH, Lip GYH, Joung B. Less dementia after catheter ablation for atrial fibrillation: a nationwide cohort study. *Eur Heart J* 2020;doi:10.1093/eurheartj/ehaa726.
35. Steinberg JS, Shabanov V, Ponomarev D, Losik D, Ivanickiy E, Kropotkin E, Polyakov K, Ptaszynski P, Keweloh B, Yao CJ, Pokushalov EA, Romanov AB. Effect of renal denervation and catheter ablation vs catheter ablation alone on atrial fibrillation recurrence among patients with paroxysmal atrial fibrillation and hypertension: the ERADICATE-AF randomized clinical trial. *JAMA* 2020;**323**:248–255.
36. Stavrakis S, Stoner JA, Humphrey MB, Morris L, Filiberti A, Reynolds JC, Elkholey K, Javed I, Twidale N, Riha P, Varahan S, Scherlag BJ, Jackman WM, Dasari TW, Po SS. TREAT AF (Transcutaneous Electrical Vagus Nerve Stimulation to Suppress Atrial Fibrillation): a randomized clinical trial. *JACC Clin Electrophysiol* 2020;**6**:282–291.
37. Haldar SK, Jones DG, Bahrami T, De Souza A, Panikker S, Butcher C, Khan H, Yahdav R, Jarman J, Mantziari L, Nyktari E, Mohiaddin R, Hussain W, Markides V, Wong T. Catheter ablation vs electrophysiologically guided thoracoscopic surgical ablation in long-standing persistent atrial fibrillation: the CASA-AF Study. *Heart Rhythm* 2017;**14**:1596–1603.
38. Haldar S, Khan HR, Boyalla V, Kralj-Hans I, Jones S, Lord J, Onyimadu O, Satishkumar A, Bahrami T, De Souza A, Clague JR, Francis DP, Hussain W, Jarman JW, Jones DG, Chen Z, Mediratta N, Hyde J, Lewis M, Mohiaddin R, Salukhe TV, Murphy C, Kelly J, Khattar RS, Toff WD, Markides V, McCready J, Gupta D, Wong T; Investigators C-A. Catheter ablation vs. thoracoscopic surgical ablation in long-standing persistent atrial fibrillation: CASA-AF randomized controlled trial. *Eur Heart J* 2020;doi:10.1093/eurheartj/ehaa658.
39. Conen D, Alonso-Coello P, Douketis J, Chan MTV, Kurz A, Sigamani A, Parlow JL, Wang CY, Villar JC, Srinathan SK, Tiboni M, Malaga G, Guyatt G, Sivakumaran S, Rodriguez Funes MV, Cruz P, Yang H, Dresser GK, Alvarez-Garcia J, Schricker T, Jones PM, Drummond LW, Balasubramanian K, Yusuf S, Devereaux PJ. Risk of stroke and other adverse outcomes in patients with perioperative atrial fibrillation 1 year after non-cardiac surgery. *Eur Heart J* 2020;**41**:645–651.
40. Turan A, Duncan A, Leung S, Karimi N, Fang J, Mao G, Hargrave J, Gillinov M, Trombetta C, Ayad S, Hassan M, Feider A, Howard-Quijano K, Ruetzler K, Sessler DI, Bergese S, De Oliveira G, Honar H, Niazi A, Elliott K, Hamadnalla H, Chodavarapu P, Bajracharya G, Fitzgerald P, Cuko E, Akhtar Z, Lokhande C, Khan MZ, Khoshknabi D, Riter Q, Hutcherson M, Yagar S, Glosse L, Saha P, Raza S. Dexmedetomidine for reduction of atrial fibrillation and delirium after cardiac surgery (DECADE): a randomised placebo-controlled trial. *Lancet* 2020;**396**:177–185.
41. Barakat AF, Inashvili A, Alkukhun L, Shalaby AA, Wang NC, Bhonsale A, Wann D, Gardner M, Khan M, Bidani S, Skowronski J, Jain S, Voigt A, Bazaz R, Estes NAM, 3rd, Saba S,

Kancharla K. Use trends and adverse reports of SelectSecure 3830 lead implantations in the United States: implications for His Bundle Pacing. *Circ Arrhythm Electrophysiol* 2020;**13**:e008577.
42. Beer D, Dandamudi G, Mandrola JM, Friedman PA, Vijayaraman P. His-bundle pacing: impact of social media. *Europace* 2019;**21**:1445–1450.
43. Moriña-Vázquez P, Moraleda-Salas MT, Manovel-Sánchez AJ, Fernández-Gómez JM, Arce-Léon Á, Venegas-Gamero J, Barba-Pichardo R. Early improvement of left ventricular ejection fraction by cardiac resynchronization through His bundle pacing in patients with heart failure. *Europace* 2020;**22**:125–132.
44. Salden F, Luermans J, Westra SW, Weijs B, Engels EB, Heckman LIB, Lamerichs LJM, Janssen MHG, Clerx KJH, Cornelussen R, Ghosh S, Prinzen FW, Vernooy K. Short-term hemodynamic and electrophysiological effects of cardiac resynchronization by left ventricular septal pacing. *J Am Coll Cardiol* 2020;**75**:347–359.
45. Wu S, Su L, Vijayaraman P, Zheng R, Cai M, Xu L, Shi R, Huang Z, Whinnett ZI, Huang W. Left bundle branch pacing for cardiac resynchronization therapy: nonrandomized on-treatment comparison with His bundle pacing and biventricular pacing. *Can J Cardiol* 2020;doi: 10.1016/j.cjca.2020.04.037.
46. Hou X, Qian Z, Wang Y, Qiu Y, Chen X, Jiang H, Jiang Z, Wu H, Zhao Z, Zhou W, Zou J. Feasibility and cardiac synchrony of permanent left bundle branch pacing through the interventricular septum. *Europace* 2019;**21**:1694–1702.
47. Huang W, Wu S, Vijayaraman P, Su L, Chen X, Cai B, Zou J, Lan R, Fu G, Mao G, Ellenbogen KA, Whinnett ZI, Tung R. Cardiac resynchronization therapy in patients with nonischemic cardiomyopathy using left bundle branch pacing. *JACC Clin Electrophysiol* 2020;**6**:849–858.
48. Guo J, Li L, Xiao G, Ye T, Huang X, Meng F, Li Q, Chen S, Cai B. Remarkable response to cardiac resynchronization therapy via left bundle branch pacing in patients with true left bundle branch block. *Clin Cardiol* 2020;**43**:1460–1468.
49. Cheng L, Zhang J, Wang Z, Zhou M, Liang Z, Zhao L, Chen J, Wu Y. Efficacy and safety of left bundle branch area pacing versus biventricular pacing in heart failure patients with left bundle branch block: study protocol for a randomised controlled trial. *BMJ Open* 2020;10:e036972.
50. Chatterjee D, Pieroni M, Fatah M, Charpentier F, Cunningham KS, Spears DA, Chatterjee D, Suna G, Bos JM, Ackerman MJ, Schulze-Bahr E, Dittmann S, Notarstefano PG, Bolognese L, Duru F, Saguner AM, Hamilton RM. An autoantibody profile detects Brugada syndrome and identifies abnormally expressed myocardial proteins. *Eur Heart J* 2020;**41**:2878–2890.
51. Tadros R, Tan HL, El Mathari S, Kors JA, Postema PG, Lahrouchi N, Beekman L, Radivojkov-Blagojevic M, Amin AS, Meitinger T, Tanck MW, Wilde AA, Bezzina CR; ESCAPE-NET Investigators. Predicting cardiac electrical response to sodium-channel blockade and Brugada syndrome using polygenic risk scores. *Eur Heart J* 2019;**40**:3097–3107.
52. Ciconte G, Monasky MM, Santinelli V, Micaglio E, Vicedomini G, Anastasia L, Negro G, Borrelli V, Giannelli L, Santini F, de Innocentiis C, Rondine R, Locati ET, Bernardini A, Mazza Bc Mecarocci V, Calovic Z, Ghiroldi A, D'Imperio S, Benedetti S, Di Resta C, Rivolta I, Casari G, Petretto E, Pappone C. Brugada syndrome genetics is associated with phenotype severity. *Eur Heart J* 2020;doi:10.1093/eurheartj/ehaa942.
53. Van der Werf C, Lieve KV, Bos JM, Lane CM, Denjoy I, Roses-Noguer F, Aiba T, Wada Y, Ingles J, Leren IS, Rudic B, Schwartz PJ, Maltret A, Sacher F, Skinner JR, Krahn AD, Roston TM, Tfelt-Hansen J, Swan H, Robyns T, Ohno S, Roberts JD, van den Berg MP, Kammeraad JA, Probst V, Kannankeril PJ, Blom NA, Behr ER, Borggrefe M, Haugaa KH, Semsarian C, Horie M, Shimizu W, Till JA, Leenhardt A, Ackerman MJ, Wilde AA. Implantable cardioverter-defibrillators in previously undiagnosed patients with catecholaminergic polymorphic ventricular tachycardia resuscitated from sudden cardiac arrest. *Eur Heart J* 2019;**40**:2953–2961.
54. Knops RE, Olde Nordkamp LRA, Delnoy PHM, Boersma LVA, Kuschyk J, El-Chami MF, Bonnemeier H, Behr ER, Brouwer TF, Kääb S, Mittal S, Quast ABE, Smeding L, van der Stuijt W, de Weger A, de Wilde KC, Bijsterveld NR, Richter S, Brouwer MA, de Groot JR, Kooiman KM, Lambiase PD, Neuzil P, Vernooy K, Alings M, Betts TR, Bracke F, Burke MC, de Jong J, Wright DJ, Tijssen JGP, Wilde AAM. Subcutaneous or transvenous defibrillator therapy. *N Engl J Med* 2020;**383**:526–536.
55. Gold MR, Lambiase PD, El-Chami MF, Knops RE, Aasbo JD, Bongiorni MG, Russo AM, Deharo JC, Burke MC, Dinerman J, Barr CS, Shaik N, Carter N, Stoltz T, Stein KM, Brisben AJ, Boersma LV; Investigators U. Primary results from the Understanding Outcomes with the S-ICD in Primary Prevention Patients with Low Ejection Fraction (UNTOUCHED) trial. *Circulation* 2020;**143**:7–17.
56. Schrage B, Uijl A, Benson L, Westermann D, Stahlberg M, Stolfo D, Dahlstrom U, Linde C, Braunschweig F, Savarese G. Association between use of primary-prevention implantable cardioverter-defibrillators and mortality in patients with heart failure: a prospective propensity score-matched analysis from the Swedish Heart Failure Registry. *Circulation* 2019;**140**:1530–1539.
57. Zabel M, Willems R, Lubinski A, Bauer A, Brugada J, Conen D, Flevari P, Hasenfuß G, Svetlosak M, Huikuri HV, Malik M, Pavlović N, Schmidt G, Sritharan R, Schlögl S, Szavits-Nossan J, Traykov V, Tuinenburg AE, Willich SN, Harden M, Friede T, Svendsen JH, Sticherling C, Merkely B, Merkely B, Perge P, Sallo Z, Szeplaki G, Szegedi N, Nagy KV, Zabel M, Lüthje L, Schlögl S, Sritharan R, Haarmann H, Bergau L, Seegers J, Hasenfuß G, Munoz-Exposito P, Tichelbäcker T, Kirova A, Hasenfuß G, Friede T, Zabel M, Schlögl S, Friede T, Harden M, Malik M, Hnatkova K, Vos MA, Willich SN, Reinhold T, Willems R, Vandenberk B, Klinika M, Szavits-Nossan J, Rotkvić L, Flevari P, Katsimardos A, Katsaras D, Hatala R, Svetlosak M, Lubinski A, Kuczejko T, Hansen J, Sticherling C, Conen D, Pavlović N, Manola Š, Vinter O, Benko I, Tuinenburg A, Sprenkeler D, Smoczynska A, Vos MA, Bauer A, Meyer-Zürn C, Eick C, Svendsen JH, Brugada J, Arbelo E, Kaliska G, Martinek J, Schmidt G, Dommasch M, Steger A, Kääb S, Bauer A, Sinner MF, Rizas KD, Hamm W, Traykov V, Cygankiewicz I, Ptaszyński P, Kaczmarek K, Poddebska I, Iovev S, Novotný T, Kozak M, Huikuri H, Kenttä T, Pelli A, Kasprzak JD, Qavoq D, Brusich S, Avdovic E, Klasan M, Galuszka J, Taborsky M, Velchev V, Dissmann R, Shalganov T, Guzik P, Krauze T, Bimmel D, Lieberz C, Ludwigsburg K, Stefanow S, Rüb N, Wolpert C, Seegers J, Meier LS, Behrens S, Jurisic Z, Braunschweig F, Blaschke F, Pieske B, Bakotic Z, Anic A, Weiden K, Schwinger RHG, Platonov P, Grönefeld G, Klingenheben T, Merkely B, Perge P, Sallo Z, Szeplaki G, Szegedi N, Nagy KV, Zabel M, Lüthje L, Schlögl S, Sritharan R, Haarmann H, Bergau L, Seegers J, Hasenfuß G, Munoz-Exposito P, Tichelbäcker T, Kirova A, Hasenfuß G, Friede T, Zabel M, Schlögl S, Friede T, Harden M, Malik M, Hnatkova K, Vos MA, Willich SN, Reinhold T, Willems R, Vandenberk B, Klinika M, Szavits-Nossan J, Rotkvić L, Flevari P, Katsimardos A, Katsaras D, Hatala R, Svetlosak M, Lubinski A, Kuczejko T, Hansen J, Sticherling C, Conen D, Pavlović N, Manola Š, Vinter O, Benko I, Tuinenburg A, Sprenkeler D, Smoczynska A, Vos MA, Bauer A, Meyer-Zürn C, Eick C, Svendsen JH, Brugada J, Arbelo E, Kaliska G, Martinek J, Schmidt G, Dommasch M, Steger A, Kääb S, Bauer A, Sinner MF, Rizas KD, Hamm W, Traykov V, Cygankiewicz I, Ptaszyński P, Kaczmarek K, Poddebska I, Iovev S, Novotný T, Kozak M, Huikuri H, Kenttä T, Pelli A, Kasprzak JD, Qavoq D, Brusich S, Avdovic E, Klasan M, Galuszka J, Taborsky M, Velchev V, Dissmann R, Shalganov T, Guzik P, Krauze T, Bimmel D, Lieberz C, Ludwigsburg K, Stefanow S, Rüb N, Wolpert C, Seegers J, Meier LS, Behrens S, Jurisic Z, Braunschweig F, Blaschke F, Pieske B, Bakotic Z, Anic A, Weiden K, Schwinger RHG, Platonov P, Grönefeld G, Klingenheben T; EU-CERT-ICD Study Investigator. Clinical effectiveness of primary prevention implantable cardioverter-defibrillators: results of the EU-CERT-ICD controlled multicentre cohort study. *Eur Heart J* 2020;**41**:3437–3447.
58. Chatterjee NA, Tikkanen JT, Panicker GK, Narula D, Lee DC, Kentta T, Junttila JM, Cook NR, Kadish A, Goldberger JJ, Huikuri HV, Albert CM; for the PREDETERMINE Investigators. Simple electrocardiographic measures improve sudden arrhythmic death prediction in coronary disease. *Eur Heart J* 2020;**41**:1988–1999.

ESC European Society of Cardiology

Special article

The year in cardiovascular medicine 2020: imaging

José Luis Zamorano[1*], Fausto J. Pinto[2], Jorge Solano-López[1], and Chiara Bucciarelli-Ducci[3]

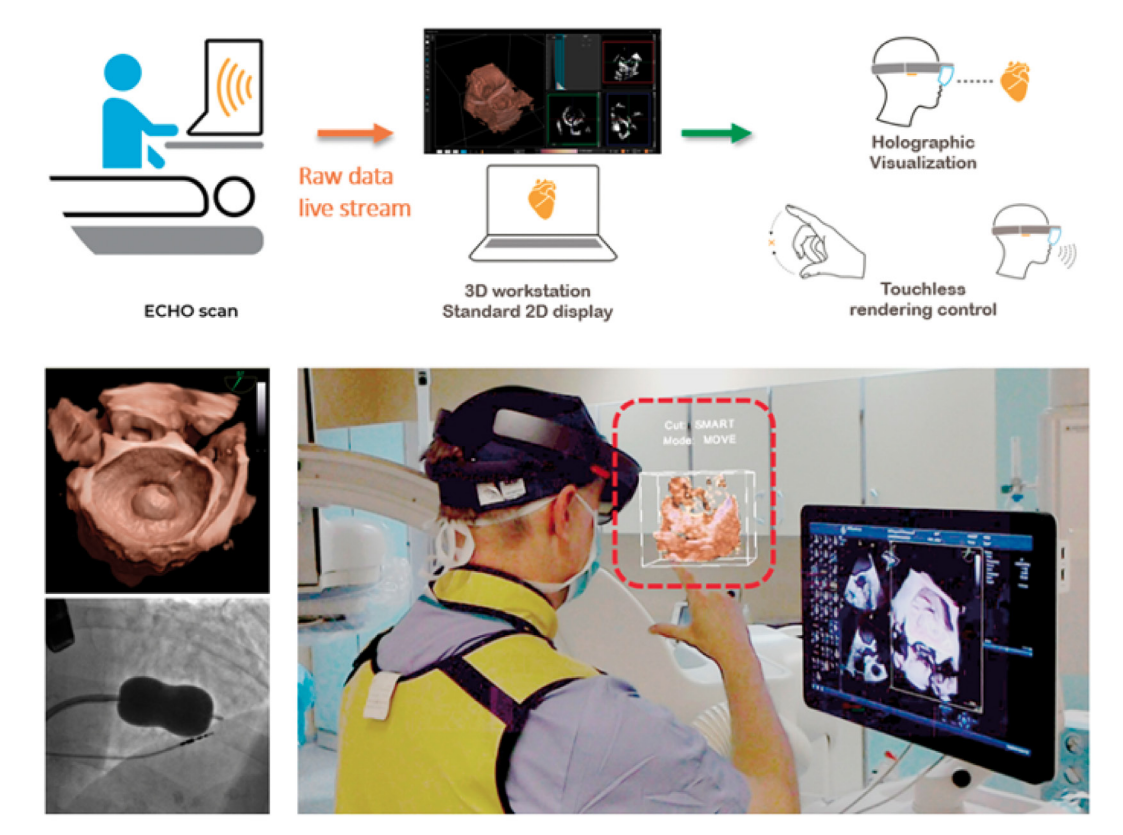
[1] Department of Cardiology, University Hospital Ramon y Cajal, Carretera de Colmenar Km 9.100, 28034 Madrid; Spain; [2] Department of Cardiology, Centro Hospitalar Universitário Lisboa Norte (CHULN), CCUL, Universidade de Lisboa, Av. Prof. Egas Moniz MB 1649-028 Lisboa, Portugal; and [3] Department of Cardiology, Bristol Heart Institute, University Hospitals Bristol and Weston NHS Trust and University of Bristol, UK

Received 9 October 2020; revised 13 November 2020; editorial decision 3 December 2020; accepted 7 December 2020

Reproduced from: Zamorano JL, Pinto FJ, Solano-López J, Bucciarelli-Ducci C. The year in cardiovascular medicine 2020: imaging. Eur Heart J. 2021 Feb 14;42(7):740–749, https://doi.org/10.1093/eurheartj/ehaa1035, by permission of Oxford University Press on behalf of the European Society of Cardiology

* Corresponding author. Tel: +34 913368515; Email: zamorano@secardiologia.es

Graphical Abstract



Raw 3D data were streamed from standard echocardiograph using custom connection to 3D DICOM viewer workstation (CarnaLife Holo, MedApp, Krakow, Poland) for real-time, dynamic 3D rendering and wirelessly transferred into HoloLens mixed reality display (Microsoft, Redmond, USA) to overlay non-obstructive 3D data hologram upon reality view. Data were visible as a semitransparent holographic cube positioned in a convenient sector of visual field of echocardiographist and shared by interventional cardiologist. From Kasprzak *et al.*[7], by permission of OUP on behalf of the ESC.

Keywords Echocardiography • CT scan • Cardiac magnetic resonance • Nuclear cardiology

Introduction

The past year has been a unique one owing to the outbreak of COVID-19, which has affected the population worldwide, with the ensuing economic and social consequences. The field of cardiology has not escaped this reality bringing with it changes in our everyday clinical praxis. The contribution of different imaging techniques to the cardiac involvement of COVID-19 with diagnostic and prognostic implications has been published very expeditiously. It is still pending to ascertain the long-term outcome of the different degrees of cardiac injury.

The recent publication of the ISCHEMIA trial[1] has resulted in a heated debate on the role of ischaemia testing in patients with stable coronary artery disease (CAD), with some colleagues advocating that ISCHEMIA has sanctioned the limited role of myocardial ischaemia in patients with stable CAD. However, this is not the conclusion of the trial, nor its primary hypothesis nor the study design and extrapolation beyond these boundaries could be incorrect. Ischaemia imaging will continue to play a major role in the diagnosis and management of stable CAD as both physicians and patients still need to clarify the cause of symptoms, coronary anatomy does not infer ischaemia or explains symptoms, and chest pain can also be of non-coronary origin. Most importantly, there is no randomized trial demonstrating that an imaging approach of coronary anatomy is superior to functional testing. In fact, PROMISE[2] is the only trial that compared the two strategies and it did not demonstrate any difference in outcome between the two approaches.

Furthermore, advances in the knowledge and application of artificial intelligence (AI) are consolidating the need for greater attention and interest regarding a tool that in a few years will become part of our daily clinical practice. Finally, we highlight the introduction of new rec-

ommendations in the use of imaging techniques in the new practice guidelines.

We then summarize the most outstanding studies from the last year relating to the most relevant imaging techniques in current cardiology.

Echocardiography

Echocardiography continues to be one of the most used methods to better understand cardiac pathophysiology and different pathological and even normal aspects of cardiac function and also plays a central role in daily patient management. Several papers have been published in 2020, and here, we highlight just a small proportion of the large amount of literature that has been produced during this year, a very unusual one, considering the COVID-19 pandemic that affected all of us.

One area of great current interest is transthyretin amyloidosis cardiomyopathy (ATTR-CM), an increasingly recognized cause of heart failure (HF) and with the new treatment strategies underway, some already with important clinical results; its recognition is becoming a must in clinical scenarios. Echocardiography has always played a role in the diagnosis of amyloidosis and that role is further strengthened with the exponential increase in relevance of amyloidosis. Chacko *et al*.[3] in an international network characterized the structural and functional echocardiographic phenotype across the spectrum of wild-type (wtATTR-CM) and hereditary (hATTR-CM) transthyretin cardiomyopathy and the echocardiographic features predicting prognosis. They studied 1240 patients with ATTR-CM, comprising 766 with wtATTR-CM and 474 with hATTR-CM, of whom 314 had the V122I variant and 127 the T60A variant. At diagnosis, patients with V122I-hATTR-CM had the most severe degree of systolic and diastolic dysfunction across all echocardiographic parameters and patients with T60A-hATTR-CM the least; patients with wtATTR-CM had intermediate features. Stroke volume index, right atrial area index, longitudinal strain, and *E*/*e*′ were independently associated with mortality ($P<0.05$ for all). Severe aortic stenosis (AS) was also independently associated with prognosis, conferring a significantly shorter survival (median survival 22 vs. 53 months, $P=0.001$). In this study, the three distinct genotypes presented with varying degrees of severity. Echocardiography indicated a complex pathophysiology in which both systolic and diastolic functions were independently associated with mortality. The presence of severe AS was also independently associated with significantly reduced patient survival.

The need for normal values is very important to set the references to determine the pathological boundaries. In this regard, the NORRE study provided useful reference ranges of 2D echocardiographic measurements of left ventricular (LV) layer-specific strain from a large group of healthy volunteers of both genders over a wide range of ages.[4]

The importance of developing parameters that may help the clinician to better understand the severity of certain disease conditions, as well as risk stratify the patients, is of utmost clinical relevance. That is the case of patients with bicuspid aortic valve (BAV). Kong *et al*.,[5] realized a study to evaluate the proportion and prognostic value of impaired LV global longitudinal strain (GLS) in patients with BAV and preserved LV ejection fraction (EF). It evaluated the proportion and prognostic value of impaired LV GLS in patients with BAV and preserved LVEF. Five hundred and thirteen patients with BAV and preserved LVEF (>50%) were divided into five groups according to the type of BAV dysfunction: (i) normal function BAV, (ii) mild AS or aortic regurgitation (AR), (iii) ≥ moderate isolated AS, (iv) ≥ moderate isolated AR, and (v) ≥ moderate mixed AS and AR. LV systolic dysfunction based on 2D speckle-tracking echocardiography was defined as a cut-off value of left ventricular global longitudinal strain [LVGLS (–13.6%)]. The primary outcome was aortic valve intervention or all-cause mortality. The proportion of patients with LVGLS ≤–13.6% was the highest in the normal BAV group (97%) and the lowest in the group with moderate and severe mixed AS and AR (79%). During a median follow-up of 10 years, 210 (41%) patients underwent aortic valve replacement and 17 (3%) died. Patients with preserved LV systolic function (LVGLS ≤-13.6%) had significantly better event-free survival compared to those with impaired LV systolic function (LVGLS >-13.6%). LVGLS was independently associated with increased risk of events (mainly aortic valve replacement): hazard ratio (HR) 1.09; $P<0.001$. Therefore, impaired LVGLS in BAV with preserved LVEF is not infrequent and was independently associated with increased risk of events.

GLS is a strong predictor of adverse cardiovascular outcome in men. However, studies have indicated that GLS may not predict cardiovascular outcomes as effectively in women. Lundorff *et al*.[6] identified echocardiographic predictors of cardiovascular morbidity and mortality in 1245 women from the general population free of HF and atrial fibrillation, who had an echocardiographic examination performed including tissue Doppler imaging. In this subset, 747 women had images eligible for strain analysis. Endpoint was a composite of acute myocardial infarction (MI), HF, and cardiovascular death. During follow-up (median 12.5 years), 162 women (13.0%) reached the composite outcome. These women had higher LV mass index (LVMI), more LV hypertrophy, lower *E*/*A*, higher *E*/*e*′, larger LV dimensions, and longer deceleration time. LVMI and *e*′ remained as significant predictors of the composite outcome. GLS was not an independent predictor of outcome after multivariable adjustment. The authors concluded the degree of LV hypertrophy assessed as LVMI and diastolic dysfunction evaluated by *e*′ were associated with adverse cardiovascular outcome in women from the general population.

Some new technological developments in echocardiography have also been described in some short papers, such as the development of a method of real-time streaming of 3D-transesophageal echocardiography data into head-mounted mixed-reality holographic display allowing for touchless control and data sharing within the cath-lab. The method was tested for the first time in human during percutaneous mitral balloon commissurotomy.[7] In another paper, it was presented a novel fusion pipeline that first aligns 3D echocardiography and magnetic resonance imaging (MRI) in time (mid-diastole)

and space using a landmark-based registration algorithm and second fuses both images enabling combined image segmentation for 3D printing. This pipeline was demonstrated in young girl with VSD and straddling mitral valve after an arterial switch operation.[8]

Another outstanding study exploring the use of artificial intelligence in cardiac imaging is that of Ghorbani *et al*.[9] in which a model (Echonet) of deep learning is developed. After training with 2.6 million echocardiograms the model is capable of measuring with good accuracy different cardiac structures and function such as LV end systolic and diastolic volumes (R2 = 0.74 and R2 = 0.70), EF (R2 = 0.50), left atrial enlargement, and LV hypertrophy. Moreover, like other AI models, Echonet is capable to identify phenotypes of age (R2 = 0.46), sex (AUC = 0.88), weight (R2 = 0.56), and height (R2 = 0.33) difficult to assess by human evaluation. Considering that echocardiography is the most widely used imaging test in cardiology, it is anodyne and quite accessible; having the support of AI could reduce the need for human resources in the interpretation of the images allowing the study to be offered to a broader population. Furthermore, it could generate predictive models of cardiovascular events by identifying parameters that are difficult to evaluate by humans.

Finally, in the latest published guidelines, we have appreciated the inclusion of echocardiography with class I recommendation, reflecting the relevance of this technique in routine cardiology practice.[10–13]

Cardiovascular magnetic resonance

Over the last year, cardiovascular magnetic resonance (CMR) has confirmed an established role in the diagnosis, management, and prognosis of patients with chest pain, ischaemic heart disease, and non-ischaemic cardiomyopathies, further improved by AI and machine learning (ML).

The MR-INFORM trial is an unblinded, multicentre, clinical-effectiveness trial in patients with typical angina whose management was randomly assigned to a CMR stress perfusion-based strategy or an fractional flow reserve (FFR)-based strategy.[14] The primary outcome of death, non-fatal MI, or target-vessel revascularization within 1 year occurred in 15 of 421 patients (3.6%) in the cardiovascular MRI group and 16 of 430 patients (3.7%) in the FFR group [risk difference, -0.2 percentage points; 95% confidence interval (CI) -2.7 to 2.4], demonstrating the non-inferiority of stress CMR to FFR with respect to major adverse cardiac events. Stress CMR was also associated with lower incidence of coronary revascularisation than FFR.

The Stress CMR Perfusion Imaging in the United States (SPINS) study demonstrated excellent diagnostic and prognostic value of stress CMR in single-centre study.[15] Patients with no ischaemia or late gadolinium enhancement (LGE) by CMR ($n = 1583$, 67%) experienced low annualized rates of primary outcome of cardiovascular death or non-fatal MI (<1%) and coronary revascularization (1–3%). In contrast, patients with ischaemia and LGE experienced a more than four-fold higher annual primary outcome rate and a >10-fold higher rate of coronary revascularization during the first year after CMR. The implication is that patients without ischaemia or LGE on CMR have a low incidence of cardiac events, little need for coronary revascularization, and low spending on subsequent ischaemia testing. The cost-effectiveness study of SPINS demonstrated that, stress CMR can be a cost-effective gatekeeping tool prior to invasive coronary angiography (ICA) in patients at risk for obstructive CAD.[16] In particular, the incremental cost-effectiveness ratio for the CMR-based strategy compared with the no-imaging strategy was $52 000/quality-adjusted life years (QALY), whereas the incremental cost-effectiveness ratio for the immediate ICA strategy was $12 million/QALY compared with CMR.

Recent developments on quantitative CMR stress perfusion with automated measurements using AI[17] have been validated clinically.[18] The advances in computation power permit inline automated annotation and the use sophisticated myocardial perfusion models (e.g. the blood-tissue exchange model) to be solved with low variability in real time during scanning vs. hours of complex analysis with potentially variable results (*Figure 1 – see in original*).

Knott *et al*. assessed the prognostic significance of this new technology in 1 049 patients with known or suspected coronary artery disease reduced myocardial blood flow (MBF) and myocardial perfusion reserve (MPR) quantified automatically inline were strong independent predictors of adverse cardiovascular outcome. For each 1 mL g^{-1} min^{-1} decrease in stress MBF, the adjusted HRs for death and major cardiovascular event (MACE) were 1.93 (95% CI 1.08–3.48; $P = 0.028$) and 2.14 (95% CI 1.58–2.90; $P < 0.0001$), respectively, even after adjusting for age and comorbidities.[19]

AI and ML are providing new opportunities and pushing the envelope in cardiovascular imaging on faster better image analysis. Bhuva *et al*.[20] conducted a multicentre, human and ML CMR study to test generalizability and precision in imaging biomarker analysis. The precision in calculating LVEF in 110 patients with a range a disease, multiple institutions, and different scanner manufacturers and field strengths were similar among expert, trained junior, and automated [coefficient of variation 6.1 (5.2–7.1%), $P = 0.2581$; 8.3 (5.6–10.3%), $P = 0.3653$; 8.8 (6.1–11.1%), $P = 0.8620$]. However, the automated analysis was 186 times faster than humans (0.07 vs. 13 min), concluding that automated ML analysis is faster with similar precision to the most precise (expert) human assessment.

The increasing use of AI in CMR post-processing and image analysis is improving measurements' precision, accuracy and reliability which become less dependent on operator's experience. This can have the direct consequence of empowering less-experienced centres to perform CMR, thus increasing CMR availability. Moreover, the improved diagnostics is also coupled with rapid image analysis which translated in improved physician time of efficiency, an attracting feature for busy clinical schedules.

Up to 30–40% of patients undergoing cardiac resynchronization therapy (CRT) show no improvement, and there is a necessity to improve the selection of patients. In a prospective multicentre study of 200 CRT recipients, Aalen *et al*. demonstrated that the combination of septal

and lateral wall function measured by myocardial work with pressure-strain analysis on echocardiography and myocardial scar assessed by CMR LGE can offer a precise and relative simple approach to improve selection of CRT candidates, particularly in patients with ischaemic cardiomyopathy and/or intermediate QRS complex (QRS) duration. CRT response was predicted by the work difference between septum and lateral wall with an area under the curve (AUC) of 0.77 (95% CI 0.70–0.84). The combination of septal viability by CMR combined with myocardial work difference assessment significantly increased predicted CRT response reaching an AUC of 0.88 (95% CI 0.81–0.95).[21]

The role of CMR in the diagnosis of cardiac amyloidosis (CA) is becoming increasingly established. One of the most impactful technical developments this year is the demonstration that a novel approach called diffusion tensor CMR (DT-CMR) can characterize the myocardial microstructural effects of amyloid infiltration in patients. Khalique *et al*. showed that this contrast-free and radiation-free technique can identify the location and extent of the expanded disorganized myocardium. Moreover, novel imaging biomarkers of diffusivity and fractional anisotropy can effectively discriminate CA ($n=20$) from hypertrophic cardiomyopathy (HCM) ($n=11$). The preliminary results of this innovative in vivo technique suggest novel pathophysiological mechanisms and improved diagnostics, proving a promising new dimension in the assessment heart muscle disorders.[22]

The Hypertrophic Cardiomyopathy Registry (HCMR Registry) recruited 2755 patients with HCM from 44 sites in 6 countries, and includes CMR, genetic, and biomarkers data in order to improve risk prediction. The baseline data identified two distinct subgroups of patients: a group with sarcomere positive mutation and more fibrosis by CMR and a group sarcomere mutation negative with less fibrosis.[23] The group that was sarcomere mutation positive and more fibrosis had less resting obstruction, whereas the other group had more likely isolated basal septal hypertrophy with obstruction. The degree of obstruction appears an important feature that differs between the two groups.

In a single-centre study, Raman *et al*.[24] investigated the mechanisms of fibrosis progression in patients with HCM. LGE increment was significantly higher in those with impaired MPR < 1.40 and energetics (phosphocreatine/adenosine triphosphate) <1.44 on baseline CMR ($P \leq 0.01$ for both). Substantial LGE progression was associated with LV thinning, LV dilatation, and reduced systolic function and conferred a five-fold increased risk of subsequent clinical events (HR 5.04, 95% CI 1.85–13.79; $P=0.002$).

Since the beginning of the COVID-19 pandemic, there are an increasing number of publications on the role of CMR in detecting myocardial damage in infected individuals. Whilst CMR has a clear clinical role in identifying cardiac damage in patients with a range of cardiovascular disease, the results of the CMR studies in COVID-19 patients to date (at the time of writing this manuscript) are still preliminary. Confirmatory results are warranted from large-scale multicentre studies with robust methodology before change in clinical management can be advocated. Most notably, an observational single-centre study in Germany[25] describes the CMR findings in 100 asymptomatic patients recently recovered from the COVID-19 infection (>2 weeks from original diagnosis and resolution of the respiratory symptoms and negative results on a swab test at the end of the isolation period) of whom $n=67$ recovered at home ($n=18$ asymptomatic, $n=49$ minor-to-moderate symptoms) and only $n=33$ with severe symptoms requiring hospitalization. The cohort was compared to 50 healthy and risk factor-matched controls. They showed that 78 patients (78%) had abnormal CMR findings, including raised myocardial native T1 ($n=73$), raised myocardial native T2 ($n=60$), presence of myocardial LGE ($n=32$), or presence of pericardial enhancement ($n=22$). At the time of the CMR, high-sensitivity troponin T (hsTnT) was detectable (>3 pg/mL) in 71 patients recently recovered from COVID-19 (71%) and significantly elevated (>13.9 pg/mL) in 5 patients (5%). Compared with healthy controls and risk factor-matched controls, patients recently recovered from COVID-19 had lower LVEF, higher left ventricle volumes, and raised native T1 and T2. Whilst the results of widespread cardiac changes detected by CMR in asymptomatic patients previously infected by the SARS-CoV-2 virus are intriguing, the clinical significance of these findings is unclear and still needs to be determined. Unfortunately, the results of this study have been overemphasized, and in part sensationalized, by the media with the inevitable results of creating concerns among members of the public, confusion among physicians, and a degree of scepticism among imaging experts internationally. Multicentre large-scale prospective CMR studies to detect and measure acute and chronic cardiac damage of the COVID-19 infection are currently underway, COVID-Heart and COVID-PHOSP among others.

The recommendations for the use of CMR in the diagnosis and management of patients with cardiovascular disease are increasing. In the latest release of ESC guidelines in 2020, the Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-segment Elevation[12] includes for the first time CMR as a class I recommendation, level of evidence B in all patients with MI and unobstructed coronary arteries without an obvious cause.

Computed tomography

Over the past year, studies concerning computed tomography (CT) in the cardiovascular scenario have strengthened its ability as a predictor of cardiovascular events, and as a therapeutic guide in primary prevention.

Recently, ROBINSCA trial assessed the effectiveness of cardiovascular disease (CVD) screening in asymptomatic participants using the SCORE model ($n=12\,185$) or coronary artery calcium (CAC) scoring ($n=12\,950$). Both arms were stratified into low, intermediate, or high 10-year risk for developing fatal and non-fatal cardiovascular disease. SCORE screening arm identified 45.1% at low risk (SCORE <10%), 26.5% at intermediate risk (10–20%), and 28.4% at high risk (≥20%). According to the CAC screening, 76.0% were at low risk (Agatston <100), 15.1% at high risk (100–399), and 8.9% at very high risk (≥400). CAC scoring significantly reduced the proportion of individu-

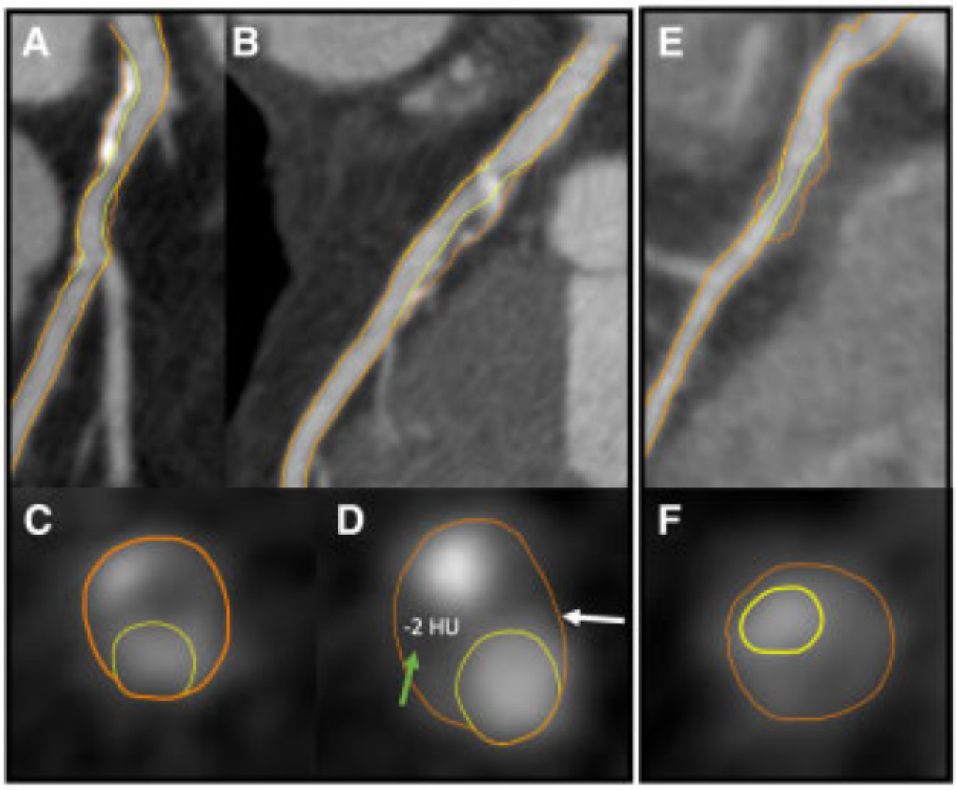


Figure 2 Coronary computed tomography angiograms demonstrating high-risk plaque (HRP) in culprit lesion precursors. A 61-year-old male ex-smoker exhibited a high-risk plaque extending from the (*A*) left main to the (*B*) proximal left anterior descending artery with (*C*) 41% diameter stenosis severity, (*D*) positive remodelling (white arrow), and low-attenuation plaque (green arrow). There is also diffuse calcification. One month later, the patient presented with a non-ST-elevation myocardial infarction. A 55-year-old male with hypertension and hyperlipidaemia exhibited a high-risk plaque with (*E*) only 35% DS severity, but (*F*) positive remodelling, low-attenuation plaque, and napkin-ring sign. The patient presented with a non-ST-elevation myocardial infarction 2 months later. From Ferraro *et al*.[33], by permission of OUP on behalf of the ESC.

als needing preventive treatment compared to SCORE (relative reduction women: 37.2%; men: 28.8%).[26]

From the multicentre CAC Consortium study, 66 636 asymptomatic patients with a CT were assessed, utilizing multivariate regression models for the risk of all-cause mortality and cause-specific mortality based on their CAC score. After adjustments, individuals with CAC ≥1000 had a 5.04-, 6.79-, 1.55-, and 2.89-fold risk of CVD, CAD, cancer, and all-cause mortality, respectively, compared to those with CAC score of 0. The CAC ≥1000 group had a 1.71-, 1.84-, 1.36-, and 1.51-fold increased risk of CVD, CAD, cancer, and all-cause mortality in comparison to those with CAC scores of 400–999. These lead to consider more aggressive preventive treatment for patients with CAC score ≥1000.[27]

The MESA Study investigators assessed the value of CAC for guiding aspirin allocation in primary prevention. All participants ($n=6470$) underwent a baseline CAC score. CVD risk was estimated using the pooled cohort equation (PCE), defining three strata: <5%, 5–20%, and >20%. Based on PCE the number needed to treat at 5 years (NNT5) was greater than or similar to the number needed to harm (NNH5) among the three estimated cardiovascular risk strata. Conversely, CAC ≥100 and CAC ≥400 identified subgroups in which NNT5 was lower than NNH5. This was true both overall (for CAC ≥100, NNT5 = 140 vs. NNH5 = 518) and within all cardiovascular risk strata. Also, CAC = 0 identified subgroups in which the NNT5 was much higher than the NNH5.[28]

Olesen *et al*. stratified 48 731 patients by diabetes status and CAD severity (no, non-obstructive, or obstructive) assessed by coronary CT angiography (CCTA). With the median follow-up of 3.6 years, they found that diabetic patients had higher death rates than non-diabetic patients, irrespective of CAD severity. Still, those diabetic patients without CAD have a low risk of MI similar to non-diabetic patients.[29]

Finck *et al*. conducted a study with 1615 patients with suspected CAD who underwent a CCTA with morphological analysis of the atheromatous plaque. After an average of 10.5 years, there were 36 cardiac deaths and 15 non-fatal MI. Among characteristics of the plaque; the spotty or gross calcification pattern and the napkin ring sign (NRS) (low-attenuating central portion with ring-like higher attenuation) were predictive for events. Yet, only spotted calcified plaques and NRS convey further prognostic value above clinical features and the severity of coronary stenosis. In a stepwise approach, the prediction of endpoint beyond clinical risk could be improved by including the severity of CAD (x^2 of 27.5, $P<0.001$) and

further discrimination for spotty calcified plaques (x^2 of 3.89, $P=0.049$).[30]

Another study assessed whether non-calcified low-attenuation plaque burden on CCTA might have a better predictor of MI than CAC or coronary stenosis severity. They followed up 1769 patients with suspected angina for median 4.7 years finding that low-attenuation plaque burden was the strongest predictor of MI ($P=0.014$), irrespective of cardiovascular risk score, CAC score, or coronary artery stenosis. Patients with low-attenuation plaque burden >4% were almost five times more likely to have subsequent MI ($P<0.001$).[31]

From the PARADIGM Study, 2252 patients who underwent clinically indicated serial CCTA at an interscan interval of ≥2 years with non-obstructive plaques (<50%) at baseline were studied. The aim was to prove whether the plaque atheroma volume (PAV), the percentage of diameter stenosis (%DS) or high-risk plaques (HRPs) were more likely to progress to obstructive lesions (>50%). On multivariate analysis, only the baseline total PAV and %DS independently predicted the development of obstructive lesions ($P<0.05$), whereas the presence of HRP did not ($P>0.05$).[32]

The investigators of the ICONIC study performed a nested case–control study of patients who underwent a CCTA prior developing an acute coronary syndrome. Culprit lesions were confirmed by invasive coronary angiography and coregistered to baseline CCTA images. They found that HRPs on baseline CCTA were less prevalent in non-obstructive plaques (19.7%) than in obstructive plaques (46.8%). Even though non-obstructive plaque comprised 81.3% of HRP lesions overall. Among patients with identifiable culprit lesion precursors, the adjusted HR was 1.85 (95% CI 1.26–2.72) for HRP, with no interaction between %DS and HRP. Compared to non-obstructive HRP lesions, obstructive lesions without HRP exhibited a non-significant HR of 1.41 (95% CI 0.61–3.25) (*Figure 2*).[33]

Recently, the ADVANCE Registry presented its 1-year results of 4288 patients with suspected CAD in whom a 30% coronary stenosis was identified by CCTA. They evaluated the relationship of fractional flow reserve derived from CCTA (FFR_{CT}) with clinical outcomes. There were 55 events; 78% of them occurred in patients with an $FFR_{CT} \leq 0.80$ ($P=0.06$). Time to first event (cardiovascular death or MI) occurred more in patients with an $FFR_{CT} \leq 0.80$ compared with $FFR_{CT} > 0.80$ patients (25 [0.80%] vs. 3 [0.20%]; relative risk (RR): 4.22; 95% CI: 1.28–13.95; $P=0.01$). Concerning the downstream care, the majority of patients in whom medical therapy was the recommended treatment strategy following FFR_{CT} continued on only medical therapy at 1 year (92.9%), and when the site recommendation was for revascularization, the majority (68.9%) were revascularized.[34]

An innovative study introduces a new parameter of dynamic CT perfusion (CTP) called stress MBF rate (SFR). This is defined as the ratio of hyperaemic (ATP infusion) MBF in an artery with stenosis to the hyperaemic MBF in a non-diseased artery. Eighty-two patients were derived to invasive angiography for suspected CAD. Stress dynamic CTP and CCTA was performed before invasive angiography. Out of 101 vessels with 30–90% stenosis on invasive angiography, FFR resulted hemodynamically significant (<0.80) in 47.5% of them. SFR was lower for invasive FFR < 0.80 lesions (0.66 vs. 0.90; $P<0.01$). Compared with ≥50% stenosis by computed tomography angiography (CTA), the specificity for detecting ischaemia by SFR increased from 43% to 91%, whilst the sensitivity decreased from 95% to 62%. The combination of stenosis ≥50% by CTA and SFR resulted in an AUC of 0.91, which was significantly higher than MBF alone.[35]

Nuclear imaging

Nowadays, the potential survival benefit of ischaemia-guided early coronary revascularization in patients with stable coronary artery disease (CAD) is still in debate.

Patel *et al*. performed a single-centre cohort study including 16 029 patients with suspected or known CAD (mean age 68.6 ± 11.9 years) who underwent a Rubidium-82 (Rb82) rest-stress positron emission tomography (PET) myocardial perfusion imaging (MPI), excluding those with LVEF < 40%. After a median follow-up of 3.7 years, 1277 patients underwent early revascularization (87% PCI, 13% CABG), and 2493 (15.6%) died. After a propensity score adjustment for potential confounders, a Cox model found an interaction between %ischaemia and early revascularization ($P<0.001$ for both all-cause and cardiac death). They also report medical therapy survival equipoise at 5% ischaemia. This ischaemia threshold for survival benefit is lower than previously reported with single photon emission CT (SPECT) MPI.[36]

In a phase-III prospective multicentric clinical study, the novel PET MPI tracer Fluorine-18 flurpiridaz is evaluated for its diagnostic efficacy detecting significant CAD (>50% stenosis in quantitative ICA) vs. SPECT. 755 patients (mean age 62.3 ± 9.5 years) were included. The PET MPI with the novel tracer demonstrated to have superior sensitivity than SPECT [71.9%, 95% CI 67.0–76.3%; $P<0.001$ vs. 53.7% (95% CI: 48.5–58.8%)]. It was also superior to SPECT for defect size ($P<0.001$), image quality ($P<0.001$), diagnostic certainty ($P<0.001$), and radiation exposure (6.1 ± 0.4 vs. 13.4 ± 3.2 mSv; $P<0.001$). This is a new diagnostic tool with better diagnostic performance comparing to SPECT, in particular for women, obese, and patients undergoing pharmacological stress testing.[37,38]

Kwiecinski *et al*. presented a *post hoc* analysis of 293 patients with previous CAD who underwent 18-F-NaF PET. Of those, 203 (69%) showed increased coronary activity [represented by quantitative coronary microcalcification activity (CME)]. After a median follow-up of 42 months, 20 patients (7%) experienced fatal or non-fatal MI. All of them presented previously increased coronary 18F-NaF activity. On an ROC analysis, MI prediction was better for 18F-NaF CME score than coronary calcium scoring and different clinical risk scores. This represents a powerful and safe tool for the detection of coronary atherosclerotic inflammation.[39]

Another proof of improvements of imaging's ability to predict events is the international multicentre study by Miller *et al*. in which they sought to determine the interactions between SPECT-MPI ischaemia, high-risk non-perfusion SPECT-MPI findings and MACE. In total, 16 578 patients with known or suspected CAD were analysed.

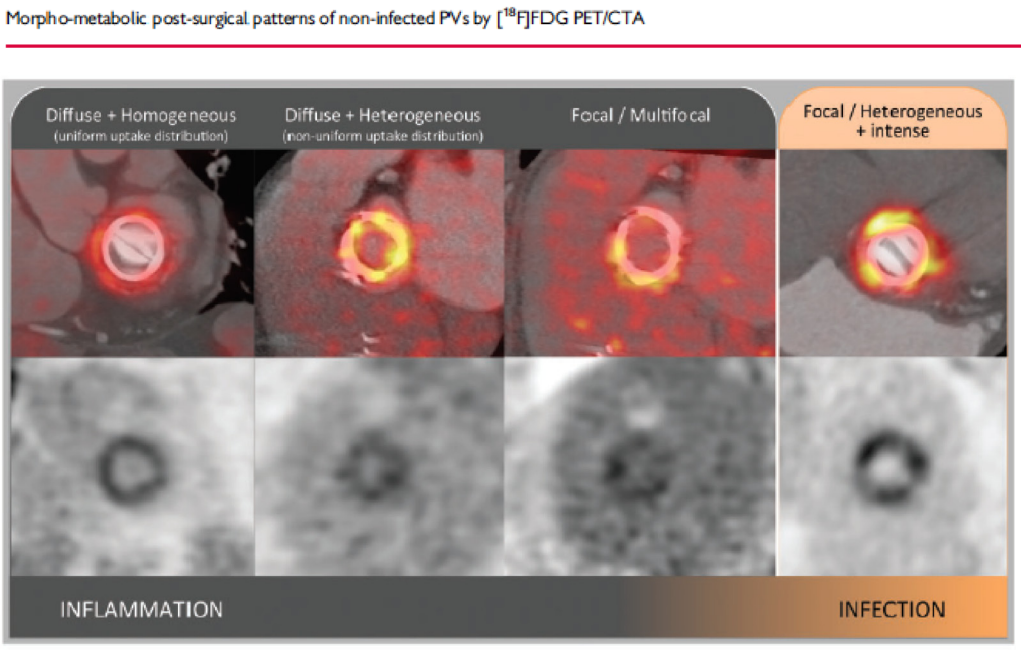


Figure 3 18F-fluorodeoxyglucose uptake distribution patterns (visual assessment). 18F-fluorodeoxyglucose uptake in non-infected prostheses (left panel), compared with an example of prosthetic valve endocarditis (right panel). Positron emission tomography/CTA fusion images of the valve plane (upper row), and their corresponding attenuation-corrected positron emission tomography images (lower row). From left to right, the characteristic inflammation patterns in order of descending frequency: diffuse homogeneous (93%), diffuse heterogeneous (7%), and focal/multifocal (2%). The diffuse homogeneous pattern is characteristic of inflammation and clearly differentiable from infection, whereas more focal. 18F-fluorodeoxyglucose uptake may overlap with infective endocarditis. No anatomic lesions were detected in any patient. From Roque *et al*.[44], by permission of OUP on behalf of the ESC.

Transient ischaemic dilation (TID) and post-stress wall motion abnormalities (WMA) were non-perfusion markers of ischaemia. After a median follow-up of 4.7 years, 1842 individuals presented one event. In a univariate analysis, the authors found that patients with mild ischaemia (<10%) and TID were more likely to present MACE compared with patients without TID (adjusted HR 1.42, $P=0.023$). There were similar findings in patients with post-stress WMA. However, multivariable analysis of patients with mild ischaemia, TID (adjusted HR 1.50, $P=0.037$), but not WMA, was independently associated with increased MACE.[40]

Heart to mediastinum (H/M) ratio measured by cardiac 123I-metaiodobenzylguanidine (123I-mIBG) scintigraphy has demonstrated prognostic significance in the setting of chronic HF. The OPAR Registry investigators describe a single-centre observational cohort study with 349 patients admitted for acute decompensated HF. 123I-MIBG imaging and echocardiography were performed before discharge. Of those 127 presented reduced EF, 78 mid-range EF, and 144 preserved EF. After a median follow-up period of 2.1 (±1.4) years, 128 patients presented cardiac events (HF hospitalization or cardiac death). A multivariable Cox analysis demonstrates that late H/M (after 200 min of tracer) was significantly associated with cardiac events in overall cohort ($P=0.0038$), as in each EF subgroup ($P=0.0235$ in reduced, $P=0.0119$ in mid-range and $P=0.0311$ in preserved). The authors conclude that H/M ratio reflects cardiac sympathetic nerve dysfunction, which is associated with cardiac events in acute HF patients, irrespective of EF.[41]

One-third of chronic HF patients who assign to CRT therapy based on guidelines classical eligibility criteria does not present benefits. Verschure *et al*. presented their results in 78 stable HF individuals with guideline-based criteria for CRT who underwent a cardiac 123I-mIBG imaging before device implantation. Late H/M ratio was an independent predictor of LVEF improvement to >35% ($P=0.0014$) and early H/M for LVEF improvement of at least 10% from basal.[42]

CA implies ominous prognosis for patients. Early diagnosis with sufficient accuracy and safety remain still challenging. Rosengren *et al*. published the largest study of CA patients (both AL and ATTR) examined with Pittsburgh compound (11C-PIB) PET. In this study, the diagnostic accuracy of 11C-PIB PET is remarkable with high sensitivity (94%) and specificity (93% to 100%) for distinguishing CA patients from both non-amyloid hypertrophic and healthy controls. 11C-PIB uptake was significantly higher in AL-CA patients than in ATTR-CA patients ($P<0.001$). In the study from Lee *et al*., they also demonstrate correlation between 11C-PIB uptake and myocardial histology in CA. In addition, after a median follow-up of 423 days, the degree of myocardial 11C-PIB uptake was a significant predictor of clinical outcome (death, heart transplantation, and acute decompensated HF) on multivariate Cox regression analysis (adjusted HR: 1.185; 95% CI 1.054–1.332; $P=0.005$).[43]

Roque *et al*. used serial 18F-fluorodeoxyglucose (FDG PET/CT) after 1, 6, and 12 months in 37 post-aortic or mitral valve replacement patients. They obtained the standardized uptake values (SUVs) and a new proposed value

denominate valve uptake index [(SUVmax – SUVmean)/SUVmax]. Of the 111 PET/CT performed, FDG uptake was visually detectable in 79.3% of patients, presenting a diffuse, homogeneous distribution pattern in 93%. No patient presented endocarditis during follow-up (*Figure 3*). Surprisingly, no significant differences were encountered in FDG distribution or uptake values between 1, 6, or 12 months, questioning the 3-month post-surgical period for the assessment of prosthetic infection.[44]

Tam *et al*. presented a study of FDG PET/CT in suspected LV assist devices (LVAD) associating their single-centre retrospective cases between September 2015 and February 2018 with a systematic review of PubMed from database inception through March 2018 involving in total 119 scans. Pooled sensitivity was 92% (95% CI: 82%–97%) and specificity was 83% (95% CI: 24%–99%) for FDG PET/CT in diagnosing LVAD infections. The ROC curve analysis demonstrated an AUC of 0.94 (95% CI 0.91–0.95).[45]

Another infectious scenario in which nuclear imaging techniques play an important diagnostic role is cardiac device-related infected endocarditis (CDRIE). Holcman *et al*. assessed the diagnostic accuracy of the hybrid technique of SPECT CT with technetium99mhexamethylpropyleneamine oxime-labelled leucocytes (99mTc-HMPAO-SPECT/CT). In a single-centre prospective study, 103 patients with suspected CDRIE who underwent 99mTc-HMPAO-SPECT/CT were included. They found that adding this nuclear technique improves the sensitivity of the modified Duke criteria alone (87% vs. 48%, $P<0.001$), whereas a negative scan excludes CDRIE with high probability. This yielded a reduction in possible CDRIE diagnoses.[46]

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Conflict of interest: none declared.

References

1. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, Chaitman BR, Senior R, López-Sendón J, Alexander KP, Lopes RD, Shaw LJ, Berger JS, Newman JD, Sidhu MS, Goodman SG, Ruzyllo W, Gosselin G, Maggioni AP, White HD, Bhargava B, Min JK, Mancini GBJ, Berman DS, Picard MH, Kwong RY, Ali ZA, Mark DB, Spertus JA, Krishnan MN, Elghamaz A, Moorthy N, Hueb WA, Demkow M, Mavromatis K, Bockeria O, Peteiro J, Miller TD, Szwed H, Doerr R, Keltai M, Selvanayagam JB, Steg PG, Held C, Kohsaka S, Mavromichalis S, Kirby R, Jeffries NO, Harrell FE, Rockhold FW, Broderick S, Ferguson TB, Williams DO, Harrington RA, Stone GW, Rosenberg Y; ISCHEMIA Research Group. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med* 2020;**382**:1395–1407.
2. Budoff MJ, Mayrhofer T, Ferencik M, Bittner D, Lee KL, Lu MT, Coles A, Jang J, Krishnam M, Douglas PS, Hoffmann U ; PROMISE Investigators. Prognostic value of coronary artery calcium in the PROMISE study (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). *Circulation* 2017;**136**:1993–2005.
3. Chacko L, Martone R, Bandera F, Lane T, Martinez-Naharro A, Boldrini M, Rezk T, Whelan C, Quarta C, Rowczenio D, Gilbertson JA, Wongwarawipat T, Lachmann H, Wechalekar A, Sachchithanantham S, Mahmood S, Marcucci R, Knight D, Hutt D, Moon J, Petrie A, Cappelli F, Guazzi M, Hawkins PN, Gillmore JD, Fontana M. Echocardiographic phenotype and prognosis in transthyretin cardiac amyloidosis. *Eur Heart J* 2020;**41**:1439–1447.
4. Tsugu T, Postolache A, Dulgheru R, Sugimoto T, Tridetti J, Nguyen Trung ML, Piette C, Moonen M, Manganaro R, Ilardi F, Chitroceanu AM, Sperlongano S, Go YY, Kacharava G, Athanassopoulos GD, Barone D, Baroni M, Cardim N, Hagendorff A, Hristova K, Lopez T, de la Morena G, Popescu BA, Penicka M, Ozyigit T, Rodrigo Carbonero JD, van de Veire N, Von Bardeleben RS, Vinereanu D, Zamorano JL, Rosca M, Calin A, Magne J, Cosyns B, Galli E, Donal E, Santoro C, Galderisi M, Badano LP, Lang RM, Lancellotti P. Echocardiographic reference ranges for normal left ventricular layer-specific strain: results from the EACVI NORRE study. *Eur Heart J Cardiovasc Imaging* 2020;**21**:896–905.
5. Kong WKF, Vollema EM, Prevedello F, Perry R, Ng ACT, Poh KK, Almeida AG, González A, Shen M, Yeo TC, Shanks M, Popescu BA, Galian Gay L, Fijałkowski M, Liang M, Chen RW, Ajmone Marsan N, Selvanayagam J, Pinto F, Zamorano JL, Pibarot P, Evangelista A, Delgado V, Bax JJ. Prognostic implications of left ventricular global longitudinal strain in patients with bicuspid aortic valve disease and preserved left ventricular ejection fraction. *Eur Heart J Cardiovasc Imaging* 2020;**21**:759–767.
6. Lundorff I, Modin D, Mogelvang R, Godsk Jørgensen P, Schnohr P, Gislason G, Biering-Sørensen T. Echocardiographic predictors of cardiovascular morbidity and mortality in women from the general population. *Eur Heart J Cardiovasc Imaging* 2020;doi:10.1093/ehjci/jeaa167.
7. Kasprzak JD, Pawlowski J, Peruga JZ, Kaminski J, Lipiec P. First-in-man experience with real-time holographic mixed reality display of three-dimensional echocardiography during structural intervention: balloon mitral commissurotomy. *Eur Heart J* 2019;**41**:801.
8. Gomez A, Gomez G, Simpson J, Valverde I. 3D hybrid printed models in complex congenital heart disease: 3D echocardiography and cardiovascular magnetic resonance imaging fusion. *Eur Heart J* 2020;**41**:ehaa654–4214.
9. Ghorbani A, Ouyang D, Abid A, He B, Chen JH, Harrington RA, Liang DH, Ashley EA, Zou JY. Deep learning interpretation of echocardiograms. *NPJ Digit Med* 2020;**3**:10.
10. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2020.10.1093/eurheartj/ehaa612.
11. Baumgartner H, De Backer J, Babu-Narayan SV, Budts W, Chessa M, Diller GP, Lung B, Kluin J, Lang IM, Meijboom F, Moons P, Mulder BJM, Oechslin E, Roos-Hesselink JW, Schwerzmann M, Sondergaard L, Zeppenfeld K; ESC Scientific Document Group. 2020 ESC Guidelines for the management of adult congenital heart disease. *Eur Heart J* 2020. 10.1093/eurheartj/ehaa554.
12. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2020. 10.1093/eurheartj/ehaa575.
13. Pelliccia A, Sharma S, Gati S, Bäck M, Börjesson M, Caselli S, Collet JP, Corrado D, Drezner JA, Halle M, Hansen D, Heidbuchel H, Myers J, Niebauer J, Papadakis M, Piepoli MF, Prescott E, Roos-Hesselink JW, Graham Stuart A, Taylor RS, Thompson PD, Tiberi M, Vanhees L, Wilhelm M; ESC Scientific Document Group. 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J* 2020.10.1093/eurheartj/ehaa605.

14. Nagel E, Greenwood JP, McCann GP, Bettencourt N, Shah AM, Hussain ST, Perera D, Plein S, Bucciarelli-Ducci C, Paul M, Westwood MA, Marber M, Richter WS, Puntmann VO, Schwenke C, Schulz-Menger J, Das R, Wong J, Hausenloy DJ, Steen H, Berry C; MR-INFORM Investigators. Magnetic resonance perfusion or fraction flow reserve in coronary disease. *N Engl J Med* 2019;**380**:2418–2428.
15. Kwong RY, Ge Y, Steel K, Bingham S, Abdullah S, Fujikura K, Wang W, Pandya A, Chen YY, Mikolich JR, Boland S, Arai AE, Bandettini WP, Shanbhag SM, Patel AR, Narang A, Farzaneh-Far A, Romer B, Heitner JF, Ho JY, Singh J, Shenoy C, Hughes A, Leung SW, Marji M, Gonzalez JA, Mehta S, Shah DJ, Debs D, Raman SV, Guha A, Ferrari VA, Schulz-Menger J, Hachamovitch R, Stuber M, Simonetti OP. Cardiac magnetic resonance stress perfusion imaging for evaluation of patients with chest pain. *J Am Coll Cardiol* 2019;**74**:1741–1755.
16. Ge Y, Pandya A, Steel K, Bingham S, Jerosch-Herold M, Chen YY, Mikolich JR, Arai AE, Bandettini WP, Patel AR, Farzaneh-Far A, Heitner JF, Shenoy C, Leung SW, Gonzalez JA, Shah DJ, Raman SV, Ferrari VA, Schulz-Menger J, Hachamovitch R, Stuber M, Simonetti OP, Kwong RY. Cost effectiveness analysis of stress cardiovascular magnetic resonance Imaging for stable chest pain syndromes. *JACC Cardiovasc Imaging* 2020;**13**:1505–1517.
17. Kellman P, Hansen MS, Nielles-Vallespin S, Nickander J, Themudo R, Ugander M, Xue H. Myocardial perfusion cardiovascular magnetic resonance: optimized dual sequence and reconstruction for quantification. *J Cardiovasc Magn Reson* 2017;**19**:43.
18. Kotecha T, Martinez-Naharro A, Boldrini M, Knight D, Hawkins P, Kalra S, Patel D, Coghlan G, Moon J, Plein S, Lockie T, Rakhit R, Patel N, Xue H, Kellman P, Fontana M. Automated pixel-wise quantitative myocardial perfusion mapping by CMR to detect obstructive coronary artery disease and coronary microvascular dysfunction: validation against invasive coronary physiology. *JACC Cardiovasc Imaging* 2019;**12**:1958–1969.
19. Knott KD, Seraphim A, Augusto JB, Xue H, Chacko L, Aung N, Petersen SE, Cooper JA, Manisty C, Bhuva AN, Kotecha T, Bourantas CV, Davies RH, Brown LAE, Plein S, Fontana M, Kellman P, Moon JC. The prognostic significance of quantitative myocardial perfusion: an artificial intelligence-based approach using perfusion mapping. *Circulation* 2020;**141**:1282–1291.
20. Bhuva AN, Bai W, Lau C, Davies RH, Ye Y, Bulluck H, McAlindon E, Culotta V, Swoboda PP, Captur G, Treibel TA, Augusto JB, Knott KD, Seraphim A, Cole GD, Petersen SE, Edwards NC, Greenwood JP, Bucciarelli-Ducci C, Hughes AD, Rueckert D, Moon JC, Manisty CH. A multicentre, scan-rescan, human and machine learning CMR Study to test generalizability and precision in Imaging biomaker analisis. *Circ Cardiovasc Imaging* 2019;**12**:e009214.
21. Aalen JM, Donal E, Larsen CK, Duchenne J, Lederlin M, Cvijic M, Hubert A, Voros G, Leclercq C, Bogaert J, Hopp E, Fjeld JG, Penicka M, Linde C, Aalen OO, Kongsgård E, Galli E, Voigt JU, Smiseth OA. Imaging predictors of response to cardiac resynchronization therapy: left ventricular work asymmetry by echocardiography and septal viability by cardiac magnetic resonance. *Eur Heart J* 2020;**41**:3813–3823.
22. Khalique Z, Ferreira PF, Scott AD, Nielles-Vallespin S, Martinez-Naharro A, Fontana M, Hawkins P, Firmin DN, Pennell DJ. Diffusion tensor cardiovascular magnetic resonance in cardiac amyloidosis. *Circ Cardiovasc Imaging* 2020;**13**:e009901.
23. Neubauer S, Kolm P, Ho CY, Kwong RY, Desai MY, Dolman SF, Appelbaum E, Desvigne-Nickens P, DiMarco JP, Friedrich MG, Geller N, Harper AR, Jarolim P, Jerosch-Herold M, Kim D-Y, Maron MS, Schulz-Menger J, Piechnik SK, Thomson K, Zhang C, Watkins H, Weintraub WS, Kramer CM, Mahmod M, Jacoby D, White J, Chiribiri A, Helms A, Choudhury L, Michels M, Bradlow W, Salerno M, Heitner S, Prasad S, Mohiddin S, Swoboda P, Mahrholdt H, Bucciarelli-Ducci C, Weinsaft J, Kim H, McCann G, van Rossum A, Williamson E, Flett A, Dawson D, Mongeon FP, Olivotto I, Crean A, Owens A, Anderson L, Biagini E, Newby D, Berry C, Kim B, Larose E, Abraham T, Sherrid M, Nagueh S, Rimoldi O, Elstein E, Autore C, Kramer CM; HCMR Investigators. Distinct subgroups in hypertrophic cardiomyopathy from the NHLBI HCM Registry. J Am Coll Cardiol 2019;74:2333–2345.
24. Raman B, Ariga R, Spartera M, Sivalokanathan S, Chan K, Dass S, Petersen SE, Daniels MJ, Francis J, Smillie R, Lewandowski AJ, Ohuma EO, Rodgers C, Kramer CM, Mahmod M, Watkins H, Neubauer S. Progression of myocardial fibrosis in hypertrophic cardiomyopathy: mechanisms and clinical implications. *Eur Heart J Cardiovasc Imaging* 2019;20:157–167.
25. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, Shchendrygina A, Escher F, Vasa-Nicotera M, Zeiher AM, Vehreschild M, Nagel E. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;**5**:e203557.
26. van der Aalst CM, Denissen SJAM, Vonder M, Gratama JWC, Adriaansen HJ, Kuijpers D, Vliegenthart R, van Lennep JER, van der Harst P, Braam RL, van Dijkman PRM, van Bruggen R, Oudkerk M, de Koning HJ. Screening for cardiovascular disease risk using traditional risk factor assessment or coronary artery calcium scoring: the ROBINSCA trial. *Eur Heart J Cardiovasc Imaging* 2020;**21**(11):1216–1224.
27. Peng AW, Mirbolouk M, Orimoloye OA, Osei AD, Dardari Z, Dzaye O, Budoff MJ, Shaw L, Miedema MD, Rumberger J, Berman DS, Rozanski A, Al-Mallah MH, Nasir K, Blaha MJ. Long-term all-cause and cause-specific mortality in asymptomatic patients with CAC ≥1,000. *JACC Cardiovasc Imaging* 2020;**13**:83–93.
28. Cainzos-Achirica M, Miedema MD, McEvoy JW, Al Rifai M, Greenland P, Dardari Z, Budoff M, Blumenthal RS, Yeboah J, Duprez DA, Mortensen MB, Dzaye O, Hong J, Nasir K, Blaha MJ. Coronary artery calcium for personalized allocation of aspirin in primary prevention of cardiovascular disease in 2019: the MESA Study (Multi-Ethnic Study of Atherosclerosis). *Circulation* 2020;**141**:1541–1553.
29. Olesen KKW, Riis AH, Nielsen LH, Steffensen FH, Nørgaard BL, Jensen JM, Poulsen PL, Thim T, Bøtker HE, Sørensen HT, Maeng M. Risk stratification by assessment of coronary artery disease using coronary computed tomography angiography in diabetes and non-diabetes patients: a study from the Western Denmark Cardiac Computed Tomography Registry. *Eur Heart J Cardiovasc Imaging* 2019;**20**:1271–1278.
30. Finck T, Stojanovic A, Will A, Hendrich E, Martinoff S, Hausleiter J, Hadamitzky M. Long-term prognostic value of morphological plaque features on coronary computed tomography angiography. *Eur Heart J Cardiovasc Imaging* 2020;**21**(3):237–248.
31. Williams MC, Kwiecinski J, Doris M, McElhinney P, D'Souza MS, Cadet S, Adamson PD, Moss AJ, Alam S, Hunter A, Shah ASV, Mills NL, Pawade T, Wang C, Weir McCall J, Bonnici-Mallia M, Murrills C, Roditi G, Beek E. V, Shaw LJ, Nicol ED, Berman DS, Slomka PJ, Newby DE, Dweck MR, Dey D. Low-attenuation noncalcified plaque on coronary computed tomography angiography predicts myocardial infarction: results from the multicenter SCOT-HEART Trial (Scottish Computed Tomography of the HEART). *Circulation* 2020;**141**:1452–1462.
32. Lee S-E, Sung JM, Andreini D, Budoff MJ, Cademartiri F, Chinnaiyan K, Choi JH, Chun EJ, Conte E, Gottlieb I, Hadamitzky M, Kim YJ, Kumar A, Lee BK, Leipsic JA, Maffei E, Marques H, Pontone G, Raff G, Shin S, Stone PH, Samady H, Virmani R, Narula J, Berman DS, Shaw LJ, Bax JJ, Lin FY, Min JK, Chang H-J. Differential association between the progression of coronary artery calcium score and coronary plaque volume progression according to statins: the Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging (PARADIGM) study. *Eur Heart J Cardiovasc Imaging* 2019;**20**:1307–1314.
33. Ferraro RA, Rosendael AV, Lu Y, Andreini D, Al-Mallah MH, Cademartiri F, Chinnaiyan K, Chow BJW, Conte E, Cury RC, Feuchtner G, Araújo Gonçalves PD, Hadamitzky M, Kim Y-J, Leipsic J, Maffei E, Marques H, Plank F, Pontone G, Raff GL, Villines TC, Lee S-E, Al'Aref SJ, Baskaran L, Cho I, Danad I, Gransar H, Budoff MJ, Samady H, Stone PH. Non-obstructive high-risk plaques increase the risk of future culprit lesions comparable to obstructive plaques without high-risk features: the ICONIC study. *Eur Heart J Cardiovasc Imaging* 2020;**21**(9):973–980.
34. Patel MR, Nørgaard BL, Fairbairn TA, Nieman K, Akasaka T, Berman DS, Raff GL, Hurwitz Koweek LM, Pontone G, Kawasaki

T, Sand NPR, Jensen JM, Amano T, Poon M, Øvrehus KA, Sonck J, Rabbat MG, Mullen S, De Bruyne B, Rogers C, Matsuo H, Bax JJ, Leipsic J. 1-Year impact on medical practice and clinical outcomes of FFRCT. *JACC Cardiovasc Imaging* 2020;**13**:97–105.
35. Yang J, Dou G, He B, Jin Q, Chen Z, Jing J, Di Carli MF, Chen Y, Blankstein R. Stress myocardial blood flow ratio by dynamic CT perfusion identifies hemodynamically significant CAD. *JACC Cardiovasc Imaging* 2020;**13**:966–976.
36. Patel KK, Spertus JA, Chan PS, Sperry BW, Thompson RC, Al Badarin F, Kennedy KF, Case JA, Courter S, Saeed IM, McGhie AI, Bateman TM. Extent of myocardial ischemia on positron emission tomography and survival benefit with early revascularization. *J Am Coll Cardiol* 2019;**74**:1645–1654.
37. Maddahi J, Lazewatsky J, Udelson JE, Berman DS, Beanlands RSB, Heller GV, Bateman TM, Knuuti J, Orlandi C. Phase-III clinical trial of fluorine-18 flurpiridaz positron emission tomography for evaluation of coronary artery disease. *J Am Coll Cardiol* 2020;**76**:391–401.
38. Joshi NV, Vesey AT, Williams MC, Shah ASV, Calvert PA, Craighead FHM, Yeoh SE, Wallace W, Salter D, Fletcher AM, van Beek EJR, Flapan AD, Uren NG, Behan MWH, Cruden NLM, Mills NL, Fox KAA, Rudd JHF, Dweck MR, Newby DE. 18F-fluoride positron emission tomography for identification of ruptured and high-risk coronary atherosclerotic plaques: a prospective clinical trial. *Lancet* 2014;**383**:705–713.
39. Kwiecinski J, Tzolos E, Adamson PD, Cadet S, Moss AJ, Joshi N, Williams MC, van Beek EJR, Dey D, Berman DS, Newby DE, Slomka PJ, Dweck MR. Coronary 18F-sodium fluoride uptake predicts outcomes in patients with coronary artery disease. *J Am Coll Cardiol* 2020;**75**:3061–3074.
40. Miller RJH, Hu L-H, Gransar H, Betancur J, Eisenberg E, Otaki Y, Sharir T, Fish MB, Ruddy TD, Dorbala S, Carli MD, Einstein AJ, Kaufmann PA, Sinusas AJ, Miller EJ, Bateman T, Germano G, Tamarappoo BK, Dey D, Berman DS, Slomka PJ. Transient ischaemic dilation and post-stress wall motion abnormality increase risk in patients with less than moderate ischaemia: analysis of the REFINE SPECT registry. *Eur Heart J Cardiovasc Imaging* 2020;**21**:567–575.
41. Seo M, Yamada T, Tamaki S, Watanabe T, Morita T, Furukawa Y, Kawasaki M, Kikuchi A, Kawai T, Abe M, Nakamura J, Yamamoto K, Kayama K, Kawahira M, Tanabe K, Kimura T, Ueda K, Sakamoto D, Sakata Y, Fukunami M. Prognostic significance of cardiac I-123-metaiodobenzylguanidine imaging in patients with reduced, mid-range, and preserved left ventricular ejection fraction admitted for acute decompensated heart failure: a prospective study in Osaka Prefectural Acute Heart Failure Registry (OPAR). *Eur Heart J Cardiovasc Imaging* 2020;doi:10.1093/ehjci/jeaa025.
42. Verschure DO, Poel E, De Vincentis G, Frantellizzi V, Nakajima K, Gheysens O, Groot JD, Verberne HJ. The relation between cardiac 123I-mIBG scintigraphy and functional response 1 year after CRT implantation. *Eur Heart J Cardiovasc Imaging* 2020;doi: 10.1093/ehjci/jeaa045.
43. Rosengren S, Skibsted Clemmensen T, Tolbod L, Granstam S-O, Eiskjær H, Wikström G, Vedin O, Kero T, Lubberink M, Harms HJ, Flachskampf FA, Baron T, Carlson K, Mikkelsen F, Antoni G, Frost Andersen N, Hvitfeldt Poulsen S, Sörensen J. Diagnostic accuracy of [11C]PIB positron emission tomography for detection of cardiac amyloidosis. *JACC Cardiovasc Imaging* 2020;**13**:1337–1347.
44. Roque A, Pizzi MN, Fernández-Hidalgo N, Permanyer E, Cuellar-Calabria H, Romero-Farina G, Ríos R, Almirante B, Castell-Conesa J, Escobar M, Ferreira-González I, Tornos P, Aguadé-Bruix S. Morpho-metabolic post-surgical patterns of non-infected prosthetic heart valves by [18F]FDG PET/CTA: "normality" is a possible diagnosis. *Eur Heart J Cardiovasc Imaging* 2020;**21**:24–33.
45. Tam MC, Patel VN, Weinberg RL, Hulten EA, Aaronson KD, Pagani FD, Corbett JR, Murthy VL. Diagnostic accuracy of FDG PET/CT in suspected LVAD infections. *JACC Cardiovasc Imaging* 2020;**13**:1191–1202.
46. Holcman K, Małecka B, Rubiś P, Ząbek A, Szot W, Boczar K, Leśniak-Sobelga A, Hlawaty M, Wiśniowska-Śmiałek S, Stępień A, Podolec P, Kostkiewicz M. The role of 99mTc-HMPAO-labelled white blood cell scintigraphy in the diagnosis of cardiac device-related infective endocarditis. *Eur Heart J Cardiovasc Imaging* 2020;**21**:1022–1030.

ESC European Society of Cardiology

Special article

The year in cardiovascular medicine 2020: valvular heart disease

Javier Bermejo[1*], Andrea Postigo[1], and Helmut Baumgartner[2]

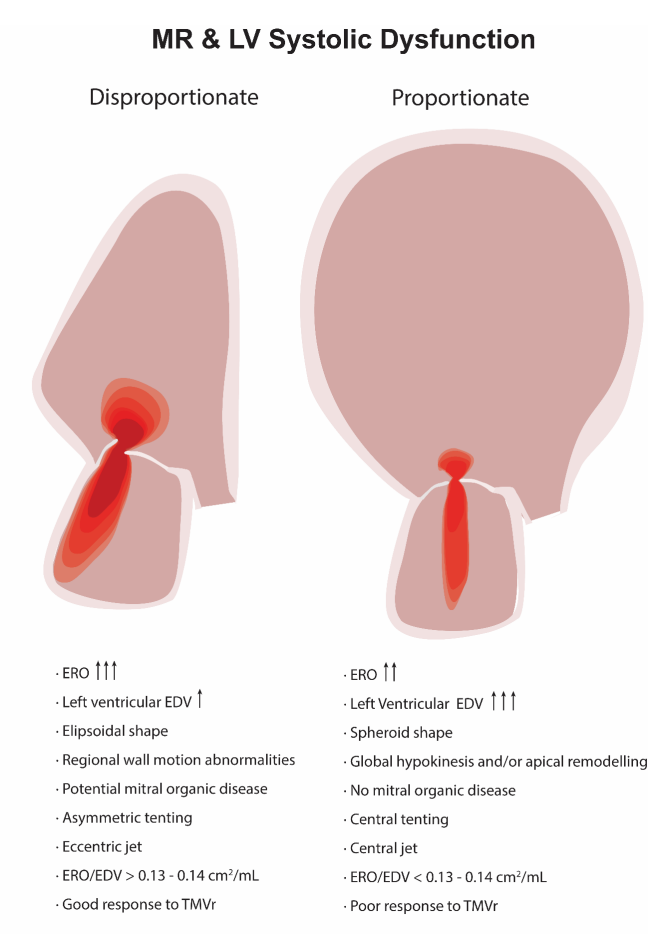
[1] Department of Cardiology, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, Facultad de Medicina, Universidad Complutense de Madrid and CIBERCV, Dr Esquerdo 46, Madrid 28007, Spain; and [2] Department of Cardiology III—Adult Congenital and Valvular Heart Disease, University Hospital Muenster, Albert-Schweitzer-Campus 1, 48149 Münster, Germany

Received 30 September 2020; revised 11 November 2020; editorial decision 10 December 2020; accepted 16 December 2020; online publish-ahead-of-print 3 January 2021

Reproduced from: Bermejo J, Postigo A, Baumgartner H. The year in cardiovascular medicine 2020: valvular heart disease. Eur Heart J. 2021 Feb 11;42(6):647–656. https://doi.org/10.1093/eurheartj/ehaa1060, by permission of Oxford University Press on behalf of the European Society of Cardiology.

* Corresponding author. Tel: +34 91 5868279, Fax: +34 91 5866727, Email: javier.bermejo@salud.madrid.org

Graphical Abstract



Proposed framework for classifying coexisting mitral regurgitation and severe LV systolic dysfunction. This framework is based on ancillary analyses of randomized clinical trials and prospective validation is pending. ERO: effective regurgitant orifice. EDV: end-diastolic volume. TMVr: transcatheter mitral valve repair.

Keyword Valvular heart disease

Introduction

Valvular heart disease (VHD) is one of the most rapidly changing disciplines in cardiovascular medicine. During the past year, important basic research has provided new insight into disease mechanisms and identified new potential targets for pharmacological treatment. Despite the unequivocal impact of COVID-19 on global research and management of VHD,[1] the results of landmark clinical trials with percutaneous devices have become available. Aspects of adjuvant medical therapies after device implantation have also been clarified. Technical improvements in next-generation valvular medical devices are taking place in parallel, showing promising preliminary clinical results. As the risk related to interventional procedures and their consequences is becoming lower, new opportunities for an earlier treatment arise. The most important achievements during 2020 are summarized herein.

Epidemiological issues and risk stratification of valvular heart disease

Rheumatic heart disease is still a major cause of VHD worldwide. In this regard, a trend towards a decrease in its incidence in the Americas has been reported. Between 1990 and 2017, the burden of mortality due to rheumatic heart disease has decreased from 88.4 to 38.8 years of life lost per 100 000 population in these regions. Importantly, this positive trend has taken place in parallel to the reduction in income-related inequalities.[2] In western countries, degenerative-calcific disease is the leading aetiology of VHD. Population-based epidemiological data from the multi-ethnic study of atherosclerosis (MESA) have shown a direct association between mitral annular calcification (MAC) and the risk of peripheral artery disease and stroke.[3,4] Severe MAC progresses towards the valve leaflets, leading to progressive mitral stenosis (MS). MAC-re-

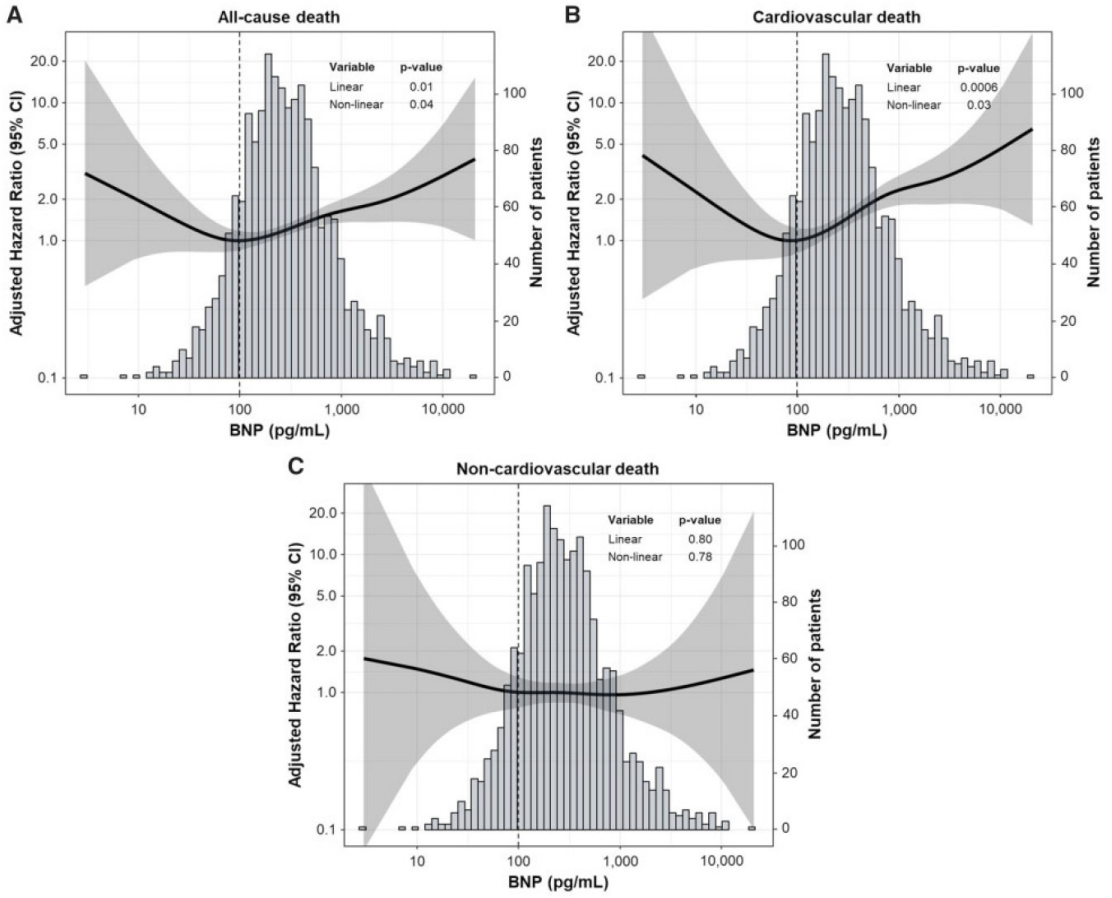


Figure 1 Nonlinear relationship between plasma BNP levels and 2-year clinical outcomes of patients in the PARTNER II trial and registry. Multivariable Cox proportional hazards regression using a spline function to model log-transformed baseline B-type natriuretic peptide as a continuous metric for *(A)* all-cause death; *(B)* cardiovascular death; and *(C)* non-cardiovascular death, at 2 years. BNP, B-type natriuretic peptide (from Chen *et al.*[8], by permission of OUP on behalf of the ESC).

lated MS has recently been recognized as a major hemodynamic problem and its natural history is progressively being better understood. A large retrospective series of 200 patients demonstrates that patients with MAC-related MS are frequently symptomatic, present with a high burden of comorbidities and have impaired survival.[5]

Regarding aortic stenosis (AS), registry data from the nationwide Australian echocardiographic database show that patients with moderate disease (i.e. a pressure gradient of >20 mmHg) are at an increased risk of cardiovascular and all-cause mortality.[6] This finding could be a consequence of limited sensitivity of current severity criteria, and prospective data are required before it can be incorporated in recommendations for patient management. In this regard, levels of brain natriuretic peptides (BNPs) provide physicians with incremental prognostic information in all sources of VHD but particularly AS.[7] However, the relationship between BNP levels and risks in AS seems more complex than previously understood. In an ancillary analysis of the Placement of AoRTic TraNscathetER Valve Trial II (PARTNER II), the relationship between baseline BNP levels and 2-year all-cause and cardiovascular mortalities followed a J-shaped pattern (*Figure 1*).[8] Importantly, the hazard ratio for cardiovascular mortality was 2.3–4.4 for patients with a BNP value of <50 pg/mL compared to those with reference levels (50–100 pg/mL). The biological basis of this association is uncertain, but abnormally low levels of BNP could express an inability of the myocardium to compensate for the pressure overload by means of hypertrophy.

The burden of tricuspid regurgitation (TR) in the community remains poorly studied. Population data from the Olmsted County (Minnesota, USA) demonstrated an overall prevalence of moderate or severe TR of 0.55%. Although most cases of TR are secondary to left-heart disease, isolated TR is present in 8.1% of subjects and independently related to mortality.[9] The bases of the relationship between secondary TR and left-heart diseases have been investigated. Interestingly, atrial fibrillation induces annular remodelling even in the absence of left-heart disease.[10] In patients with heart failure and reduced EF (HFrEF), secondary TR is a very frequent finding. Although TR in HFrEF is associated with a more severe presentation, with atrial fibrillation and pulmonary hypertension, it is an independent predictor of clinical outcomes.[11] In patients with degenerative mitral regurgitation (MR), moderate or severe functional TR also predicts mortality, independently from baseline confounders.[12]

The bacteriological profile of endocarditis is continuously evolving due to population aging, increasing cardiac instrumentation, and device implantation. A contemporary European series shows that 40% of cases of endocarditis are now caused by infections of intracardiac devices and prostheses.[13] Despite improvements in antimicrobial therapies and technical advances in imaging and microbiological diagnosis, in-hospital mortality is still 17%.[13] Enterococcal endocarditis is health care-related in ~50% of cases, characteristically in elderly patients with concomitant degenerative valve disease and comorbidities such as chronic HF and lung disease.[14] Enterococcus spp. are the most common microorganisms involved in endocarditis in TAVI (transcatheter aortic valve implantation) prostheses and are related to a considerable mortality and risk of stroke.[15] However, data from the PARTNER trial suggest that the incidence and predictors of endocarditis are similar in percutaneously and surgically implanted aortic valve prostheses.[16,17]

Molecular and cellular mechanisms of valvular heart disease

In mitral valve prolapse syndrome, leaflet morphological changes take place in parallel to increased mechanical stress acting on the valve and the subvalvular apparatus. However, whether anatomical remodelling is the cause or consequence of abnormal valve biomechanics remains unclear. In an elegant ex vivo biomechanical experiment, normal leaflet tissue was subjected to increased mechanical stresses ex vivo. As a resultant, superimposed tissue proliferated on the atrial side of the mitral leaflets, demonstrating that biomechanical-biological transduction plays a major role in mitral valve prolapse syndrome.[18]

Although statins have failed to slow the disease progression of established AS, the relationship between AS and plasma lipids remains controversial. Mendelian randomization is a particularly well-suited methodology to test causality in this type of associations. Genetic data from 188 577 patients from the UK Biobank database were analysed for 157 genetic variants known to be associated with plasma lipid levels.[19] Remarkably, the odds ratio per 0.98 mmol/L of LDL-cholesterol was 1.52 (95% CI (confidence interval) 1.22–1.90) for developing AS, whereas no association was observed between plasma levels and aortic or MR. This study strongly demonstrates a causal association between lifetime exposure to high cholesterol levels and the risk of symptomatic AS. Identifying novel metabolic pathways involved in AS is a matter of continuing research, and two important studies have been reported this year. In a murine model of AS, inhibition of microRNA significantly attenuated aortic valve calcification and its consequences (flow acceleration, LV (left ventricle) hypertrophy).[20] Zinc transporter molecules have been proven as regulators of valvular interstitial cell calcification in vitro.[21] This finding, combined with the identification of a significant reduction in serum levels of zinc in patients with calcific AS, suggests a role of zinc metabolism in early valve degeneration.[21] Acquired somatic mutations in haematopoietic precursors are increasingly being reported in several chronic conditions. Patients with AS show an age-related prevalence of acquired somatic mutations in haematopoietic lineages related with pro-inflammatory leucocyte subsets, up to a prevalence of nearly 53% in >90-year-old TAVI candidates.[22] Remarkably, identifying these somatic mutations predicted poor survival despite successful valve implantation. These four mechanistic studies open the door to potential pharmacological interventions at the primordial and advanced phases of calcific AS.[18]

Imaging

Ultrasound remains the cornerstone technique for guiding AS patient management, whereas the role of computed tomography (CT) and cardiac magnetic resonance (CMR) is rapidly increasing.[24] Grading the severity of AS relies on peak-jet velocity, the mean pressure gradient and aortic valve area.[25] Unfortunately, cut-off values of these three parameters should be reconciled, as inconsistencies are frequent, particularly in patients with low-flow condition.[26] In this regard, mean transvalvular flow rate,[27] or sex-specific thresholds of stroke-volume index (40 mL/m^2 for men and 32 mL/m^2 for women)[28] may be most valuable for risk assessment. Beyond these conventional indices of severity, additional metrics are still being proposed. The first-phase ejection fraction (the proportion of stroke volume ejected before peak-jet velocity) may be of value in unselected AS patients but has also shown to be related to vascular hemodynamics.[29] The sensitivity of CMR to detect and quantify myocardial fibrosis can be exploited to stratify the impact of AS on the LV, using late gadolinium-enhancement, direct T1 mapping, or estimation of the extracellular volume.[30–32] The relationship between fibrosis and outcomes has been confirmed in 100 patients undergoing myocardial biopsies after TAVI, demonstrating a direct relationship between histological findings and mortality.[33] As bone scintigraphy is progressively being performed in patients with AS, the diagnosis of concomitant amyloidosis is increasing. Although this association is found in roughly 13% of patients referred for TAVI, observational data suggest similar benefit from intervention in AS patients with and without amyloidosis.[34]

Timing of intervention

The multicentric Korean RECOVERY randomized clinical trial compared early surgery vs. conservative care in 145 asymptomatic patients with very severe AS (AVA ≤0.75 cm^2 with velocity ≥4.5 m/s or mean transaortic gradient ≥50 mmHg).[35] With an operative mortality of zero, the study demonstrated a 91% reduction in cardiovascular death at a median follow-up of 6.2 years (hazard ratio, 0.33; 95% CI: 0.12–0.90). These results must, however, be viewed with caution. The difference in mortality was primarily driven by the difference in sudden cardiac deaths (11% vs. 0%). This rate is much higher than in other reports, and 6 of the 8 deaths occurred in patients who had become symptomatic but did for unclear reasons nevertheless not undergo valve replacement. Thus, the results of ongoing trials such as the EARLY-TAVI trial and others

must be awaited before changing treatment strategies in asymptomatic patients with severe AS.

Transcatheter interventional treatment

Aortic valve stenosis

A global registry of 867 658 interventions for AS performed in the USA between 2003 and 2016 shows that the number of patients undergoing valve replacement is linearly increasing in all ranges of age with TAVI accounting in 2016 for >40% of the procedures.[36] Unfortunately, results of the EAPCI-Atlas Project demonstrate that in Europe the national access to TAVI is very heterogeneous and closely related to national economic resources (*Figure 2*).[23] Nevertheless, the trend towards preference of percutaneous over surgical strategies will continue to increase as long-term results of TAVI are becoming available. In a meta-analysis of four randomized controlled trials (RCTs) comparing TAVI and surgical valve replacement in 2887 low-risk patients (mean age 75.4 years, mean STS score 2.3%), TAVI was associated with a significantly lower all-cause and cardiovascular mortality, lower rates of new-onset atrial fibrillation, life-threatening bleeding and acute kidney injury but higher rates of moderate/severe paravalvular regurgitation and pacemaker implantation.[37] No difference was found for major vascular complication, endocarditis, aortic valve re-intervention, and symptom improvement. When considering to expand a preference for TAVI to surgical low-risk and younger patients one needs, however, to take into account that (i) these RCTs included selected patients in particular excluding patients with bicuspid valves and with anatomic features increasing the risk for either procedure, (ii) data on long-term durability are still limited, (iii) higher rates of left bundle branch block, pacemaker implantation and more than mild aortic regurgitation (AR) have an increasing impact when treating patients with longer life expectancy, and (iv) options for future repeat re-interventions may be limited. Although recently reported 8-year data show a very low incidence of structural deterioration (moderate 3.0%, severe 1.6%) and late failure (2.5%) of percutaneously implanted prostheses,[38] currently available durability and re-intervention data must be viewed with caution considering the very high mortality in the studies with now available long-term data and the higher threshold for re-intervention in this population. Five-year data of patients from the intermediate-risk PARTNER 2 trial show no difference in the incidence of death or disabling stroke between the percutaneous and the surgical groups and comparable valve performance but confirm once more excess mortality in patients with more than mild paravalvular AR.[39] A meta-analysis demonstrates the association of new-onset persistent left bundle branch block and of pacemaker implantation after TAVI with a significantly worse outcome regarding heart failure and survival.[40] In patients with bicuspid aortic valves (typically not included in RCT), observational registries using new generation TAVI devices show a slightly lower rate of procedural success, more frequent residual regurgitation (2.7% vs. 2.1%, $P<0.001$), but outcomes comparable to patients with tricuspid valves.[41] Short- and long-term

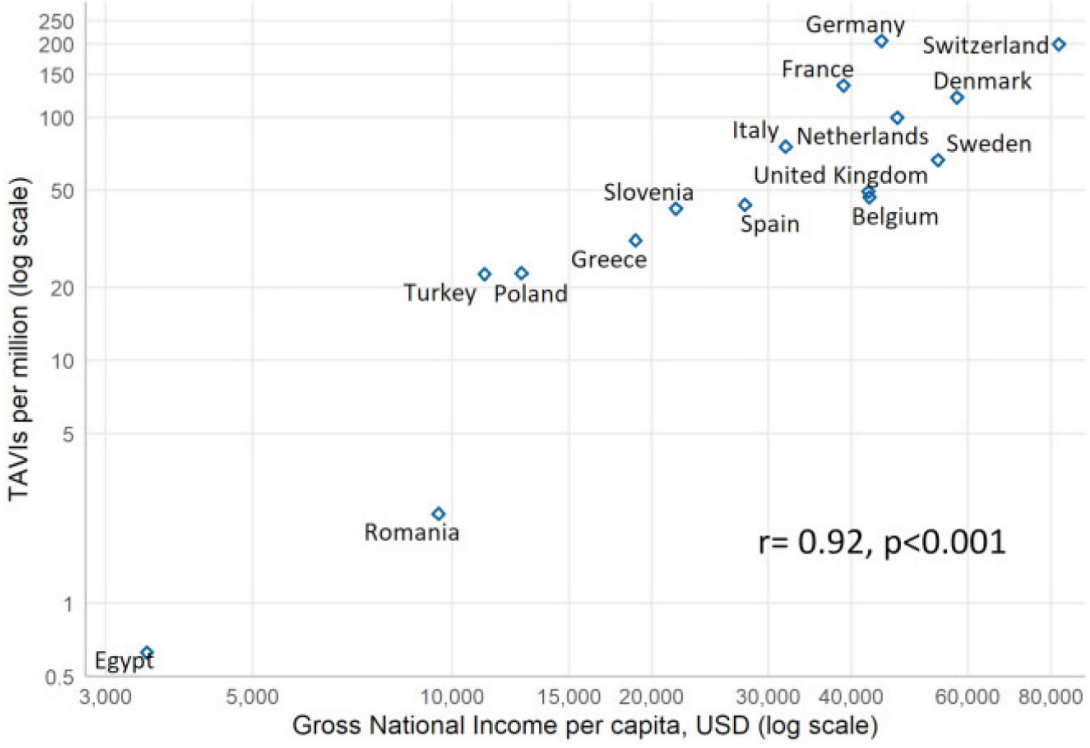


Figure 2 Relationship between gross national income and the usage of TAVI in selected countries. Data show the usage of TAVI per million inhabitants by gross national income per capita (2016 or least available year; from Barbato *et al.*[23], by permission of OUP on behalf of the ESC).

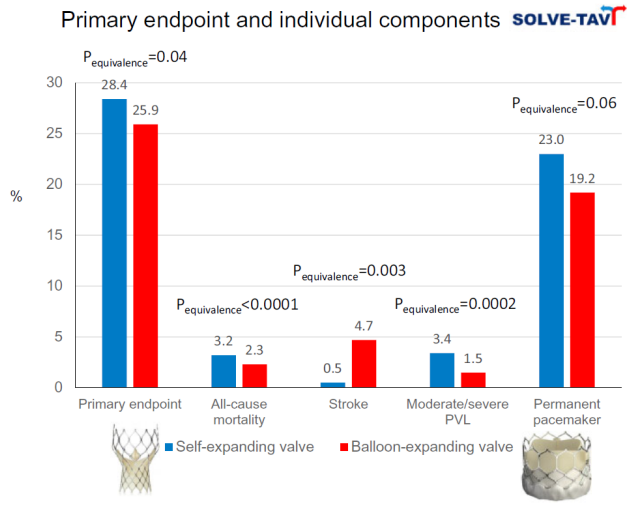


Figure 3 Results of the SOLVE-TAVI trial comparing 30-day outcomes of second-generation self-expanding and balloon-expanding percutaneous valves. PVL, paravalvular leakage (from Thiele *et al.*[43], by permission of OUP on behalf of the ESC).

outcomes are related to the degree of raphe and leaflet calcification.[42] Regarding device selection, the compari-Son of secOnd-generation seLf-expandable vs. balloon-expandable Valves and gEneral vs. local anaesthesia (SOLVE-TAVI) trial was an open-label randomized equivalence clinical trial comparing new generation models of self-expandable and balloon-expandable transcatheter valves. For the composite of all-cause mortality, stroke, permanent pacemaker implantation, and paravalvular leakage (PVL) at 30 days, the two prostheses were reported to be equivalent. The lower over-all mortality and lower PVL rate of the balloon-expandable valve were counterbalanced by a higher stroke rate and pacemaker rates were similar for both valves in this trial (*Figure 3*).[43] The stroke rate of 4.7% and pacemaker rate of 19% for the balloon-expandable valve are, however, unusually high and in contrast to the large volume of data available from RCTs and registries of this valve. Two propensity-matched analyses of large registries looking not only at 30-day but on average 1–2-year outcomes reported indeed lower pacemaker and moderate/severe PVL rates, as well as lower mortality and rehospitalization for heart failure for the balloon-expandable valve.[44,45] Compared to these two prostheses, the Portico device delivered larger valve areas and lower mean gradients, but it was associated with higher rates of vascular complications and mortality at 30 days.[46]

Mitral regurgitation

In the field of transcatheter mitral valve repair (TMVr) for secondary MR, new data are being helpful for reconciling the discordant results of the COAPT and the MITRA-FR clinical trials.[47] Ancillary analyses of these two clinical trials have suggested the utility of the proportionate vs. disproportionate classification of MR in patients with severe LV systolic function. Patients with *disproportionate* MR would show larger effective regurgitant orifice areas, more eccentric regurgitant jets, less dilated ventricles, more frequently abnormal regional wall motion and may benefit most of TMVr. Patients with *proportionate* MR would have less severe regurgitation, more central jets, and severely and diffusedly impaired ventricles and are less prone to improve after TMVr (*Graphical abstract*).[48] The best criterion for discriminating disproportionate and proportionate MR would be a regurgitant orifice/end-diastolic volume ratio of > or <0.13–0.14 mm^2/mL, respectively. However, this framework must be further validated,[49] as it is based on pooled secondary analyses and has not been confirmed when the MITRA-FR data were analysed in this respect.[50] Although the 5-year follow-up is pending, intermediate-term data of the COAPT trial show that acute results predict improved outcomes at 2 years.[51] On the other hand, the 2-year results of MITRA-FR confirmed no difference in all-cause mortality and unplanned hospitalization for heart failure.[52] A planned individual participant data meta-analysis from both trials and the ongoing RESHAPE II trial will hopefully help to better identify those patients most likely to respond to secondary MR intervention.

Tricuspid regurgitation

The field of percutaneous tricuspid valve repair is evolving rapidly, as outcome data are being reported and novel transcatheter devices are becoming available. Data of the TriValve Registry including 472 patients with mostly secondary TR treated with different transcatheter techniques in 22 centres and control cohorts of 2 large retrospective registries enrolling medically managed patients were used for a propensity-score matched analysis (268 pairs) that showed improved survival and a reduced rate of rehospitalizations in the intervention group.[53] However, we have learned from secondary MR that RCTs will be required to determine the effect of secondary TR treatment on outcome. A specific device for edge-to-edge repair of the tricuspid valve has undergone successful clinical testing with excellent implant success and favourable imaging and functional outcomes at 6 months.[54] Also, short-term data of the percutaneous annuloplasty approach are promising.[55] As expected, pulmonary hypertension (defined by an invasive systolic pulmonary pressure >50 mmHg) is an important predictor of poor outcomes in patients undergoing percutaneous tricuspid valve repair with the MitraClip system.[56] In this population, echocardiography shows important limitations to estimate pulmonary pressure. Remarkably, it is the group with a false negative ultrasound diagnosis of pulmonary hypertension that shows the poorest outcomes.[56] Consequently, further studies are needed to clarify the baseline characteristics that may be useful to predict treatment futility.

Prosthetic valve dysfunction

Transcatheter valve-in-valve implantation is a feasible and safe option for patients in whom re-operation would be at high risk. In a propensity-score matched analysis using the US National Readmission Database providing 2181 pairs of high-risk patients with degenerated bioprosthetic aortic valves, patients undergoing transcatheter procedures had significantly lower 30-day morbidity and mortality as well as less bleeding complications

than those undergoing surgery.[57] Long-term outcomes of valve-in-valve procedures were analysed in the VIVID registry.[58] Long-term survival after the procedure was directly related to the size of the original failed valve, ranging from 40.5% to 33.2% at 8 years for internal diameters larger and smaller than 20 mm, respectively. Predictors for the need of re-intervention were pre-existing severe patient-prosthesis mismatch, valve malposition during the procedure, and use of the Edwards balloon-expandable valve.[58] When the native valve is a previous percutaneous prosthesis, results of the Redo-TAVR Registry show that the valve-in-valve procedure is a safe and effective option, with the 1-year survival rates of 84% and 88% depending on whether the re-TAVI procedure is before or after the first year since the original implant.[59] Thus, currently available data demonstrate that valve-in-valve procedures can be performed safely with high success rate. However, good long-term results can only be achieved with reasonable hemodynamics, which may frequently not be achieved when the original valve is small. When performing valve-in-valve procedures in small failed bioprostheses all efforts must therefore be made to achieve good hemodynamics (choice of valve type and size, implantation techniques including valve fracture); when achievement of reasonable hemodynamics is unlikely, the potentially resulting negative impact on outcome must be carefully weighed against the risk of surgery before deciding about the treatment modality.[60]

Medical therapies pre- and post-correction

Subclinical leaflet thrombosis (SLT) has been recognized as an important late complication of transcatheter aortic bioprostheses, but its clinical implications remain unclear. SLT is typically diagnosed using CT as characteristic signs of hypo-attenuated leaflet thickening and reduced leaflet motion. Prospective CT sub-studies of the Evolut Low-Risk and the PARTNER 3 trials show that the one-year incidence of leaflet thickening and reduced leaflet motion is roughly 25–30% each, similarly frequent in self-expanding and balloon-expandable prostheses, and has a small impact on valve hemodynamics.[61,62] In addition, both studies demonstrated dynamic incidences of SLT including spontaneous resolution and late development in serial CT scans at 30 days and 1 year. Importantly, at 1 year, the incidence of SLT among TAVI and surgical prostheses was similar.

For preventing thrombosis, current guidelines recommend dual antiplatelet therapy for 3–6 months after TAVI followed by life-long single antiplatelet therapy, with no supporting evidence. The cohort A of the POPular (Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic-Valve Implantation) trial compared aspirin alone with aspirin plus clopidogrel in patients undergoing TAVI without indication of oral anticoagulation. A total of 665 patients were 1:1 randomized to receive either aspirin or aspirin plus clopidogrel (for 3 months), and after 1 year of follow-up, the composite endpoint of bleeding or thromboembolic events were significantly less frequent with aspirin than with aspirin plus clopidogrel.[63] The Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy after Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes (GALILEO) clinical trial explored whether rivaroxaban 10 mg daily (combined with low-dose aspirin for the first 3 months) would be a suitable alternative to double antiplatelet therapy.[64] The trial was prematurely interrupted because, after a median of 17 months, rivaroxaban was associated with a higher incidence of death (HR: 1.69, 95% CI: 1.13–2.53), of bleeding, and of the composite primary endpoint of death or thromboembolic complications than the antiplatelet-based group.[64] However, in the subset of 231 patients studied by CT, rivaroxaban showed a lower incidence of reduced leaflet motion at 90 days. This observation emphasizes the need for better understanding the clinical implications of subclinical leaflet thrombosis findings.

A different group of patients are those with a formal indication for oral anticoagulation after the TAVI procedure. The cohort B of the POPular TAVI Trial randomized patients taking anticoagulants before the pro-

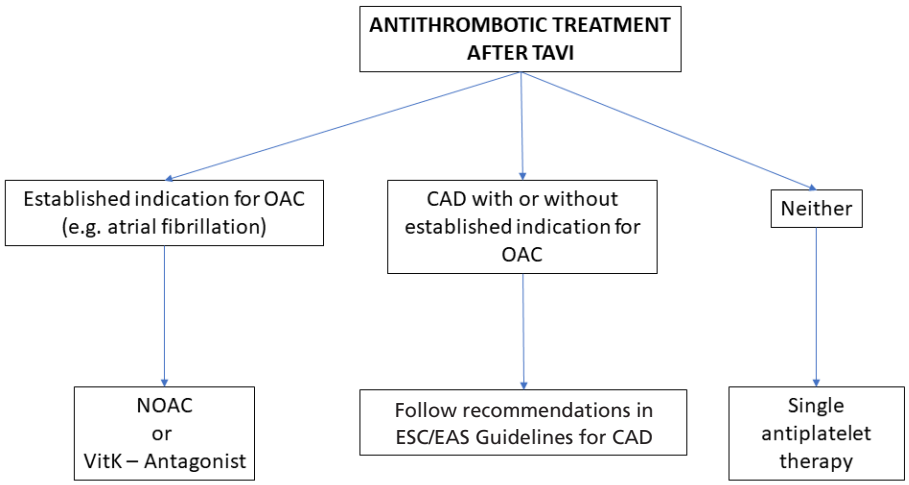


Figure 4 Algorithm for antithrombotic treatment after TAVI based on the POPULAR A and B and the GALILEO clinical trials. CAD, coronary artery disease; NOAC, non-vitamin K antagonist oral anticoagulant; VitK, vitamin K.

cedure to receive or not receive additional clopidogrel for 3 months. Patients on oral anticoagulation alone presented with a lower incidence of serious bleeding both at 1 month and 1 year (risk ratio 0.63), with a significant reduction in the composite endpoint of cardiovascular death, non-procedure-related bleeding, stroke, or myocardial infarction at 12 months (risk ratio, 0.69; 95% CI for superiority, 0.51–0.92).[65] Whether direct anticoagulants are a suitable alternative to vitamin-K antagonists in TAVI subjects is being explored in ongoing large-scale clinical trials, but registry data suggest a similar bleeding risk but higher ischaemic event rates with these drugs.[66] Thus, either single antiplatelet treatment with aspirin or oral anticoagulants alone (for patients with a formal indication for anticoagulation) is the most suitable antithrombotic strategy for most patients after TAVI (*Figure 4*).

Beyond antithrombotic treatment, no co-adjuvant medical treatment is currently indicated in patients after TAVI and patients receive conventional medications for treating concomitant risk factors and/or heart failure whenever present. A recent sub-analysis of the PARTNER trial shows that in high- or intermediate-risk patients, TAVI pre-intervention with ACEIs is associated with better survival.[67] In hypertensive patients, blood pressure needs to be monitored keeping in mind that target values carriers of prosthetic aortic valves are higher than in the general population.[68]

Regarding other medical therapies for patients with valvular heart disease, the Pharmacological Reduction of Functional, Ischaemic Mitral Regurgitation (PRIME) study has demonstrated that sacubitril/valsartan is more effective than valsartan in reducing the severity of functional MR at 12 months.[69]

Conclusions

In this difficult year, positive trends in epidemiological data of rheumatic heart disease anticipate a potential reduction of the burden of VHD. Basic and clinical research is providing new understanding of the basis of calcific-degenerative VHD, opening the door to future new pharmacological interventions in early phases. The role of percutaneous aortic valve interventions is expanding worldwide as long-term results and data for low-risk patients become available. Unfortunately, large worldwide registries show important income inequalities in the access to catheter procedures. Despite COVID-19 pandemic has radically changed health priorities worldwide, the global aims of the Agenda 2030 for Sustainable Development must be encouraged, keeping in mind that VHD is a major cause of mortality and disability in moderate and low-income countries.

Conflict of interest: Dr Baumagartner has received speaker fees and congress travel support from Actelion and Edwards Lifesciences. Dr Bermejo and Dr Postigo have no potential conflicts of interest to disclose.

References

1. The European Society of Cardiology. ESC guidance for the diagnosis and management of CV disease during the COVID-19 pandemic. https://www.escardio.org/Education/COVID-19-and-Cardiology/ESCCOVID-19-Guidance. 2020 (2 November 2020).
2. Ordunez P, Martinez R, Soliz P, Giraldo G, Mujica OJ, Nordet P. Rheumatic heart disease burden, trends, and inequalities in the Americas, 1990-2017: a population-based study. *Lancet Glob Health* 2019;**7**:e1388–e1397.
3. Garg PK, Buzkova P, Meyghani Z, Budoff MJ, Lima J, Criqui M, Cushman M, Allison M. Valvular calcification and risk of peripheral artery disease: the Multi-Ethnic Study of Atherosclerosis (MESA). *Eur Heart J Cardiovasc Imaging* 2020;**21**:1152–1159.
4. Fashanu OE, Bizanti A, Al-Abdouh A, Zhao D, Budoff MJ, Thomas IC, Longstreth WT, Michos ED. Progression of valvular calcification and risk of incident stroke: the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis* 2020;**307**:32–38.
5. Kato N, Padang R, Scott CG, Guerrero M, Pislaru SV, Pellikka PA. The natural history of severe calcific mitral stenosis. *J Am Coll Cardiol* 2020;**75**:3048–3057.
6. Strange G, Stewart S, Celermajer D, Prior D, Scalia GM, Marwick T, Ilton M, Joseph M, Codde J, Playford D. Poor long-term survival in patients with moderate aortic stenosis. *J Am Coll Cardiol* 2019;**74**:1851–1863.
7. Zhang B, Xu H, Zhang H, Liu Q, Ye Y, Hao J, Zhao Q, Qi X, Liu S, Zhang E, Xu Y, Gao R, Pibarot P, Clavel M-A, Wu Y. Prognostic value of N-Terminal Pro-B-Type natriuretic peptide in elderly patients with valvular heart disease. *J Am Coll Cardiol* 2020;**75**:1659–1672.
8. Chen S, Redfors B, O'Neill BP, Clavel M-A, Pibarot P, Elmariah S, Nazif T, Crowley A, Ben-Yehuda O, Finn MT, Alu MC, Vahl TP, Kodali S, Leon MB, Lindman BR. Low and elevated B-type natriuretic peptide levels are associated with increased mortality in patients with preserved ejection fraction undergoing transcatheter aortic valve replacement: an analysis of the PARTNER II trial and registry. *Eur Heart J* 2020;**41**:958–969.
9. Topilsky Y, Maltais S, Medina Inojosa J, Oguz D, Michelena H, Maalouf J, Mahoney DW, Enriquez-Sarano M. Burden of tricuspid regurgitation in patients diagnosed in the community setting. *JACC Cardiovasc Imaging* 2019;**12**:433–442.
10. Ortiz-Leon XA, Posada-Martinez EL, Trejo-Paredes MC, Ivey-Miranda JB, Pereira J, Crandall I, DaSilva P, Bouman E, Brooks A, Gerardi C, Ugonabo I, Chen W, Houle H, Akar JG, Lin BA, McNamara RL, Lombo-Lievano B, Arias-Godinez JA, Sugeng L. Understanding tricuspid valve remodelling in atrial fibrillation using three-dimensional echocardiography. *Eur Heart J Cardiovasc Imaging* 2020;**21**:747–755.
11. Benfari G, Antoine C, Miller WL, Thapa P, Topilsky Y, Rossi A, Michelena HI, Pislaru S, Enriquez-Sarano M. Excess mortality associated with functional tricuspid regurgitation complicating heart failure with reduced ejection fraction. *Circulation* 2019;**140**:196–206.
12. Essayagh B, Antoine C, Benfari G, Maalouf J, Michelena HI, Crestanello JA, Thapa P, Avierinos J-F, Enriquez-Sarano M. Functional tricuspid regurgitation of degenerative mitral valve disease: a crucial determinant of survival. *Eur Heart J* 2020;**41**:1918–1929.
13. Habib G, Erba PA, Iung B, Donal E, Cosyns B, Laroche C, Popescu BA, Prendergast B, Tornos P, Sadeghpour A, Oliver L, Vaskelyte J-J, Sow R, Axler O, Maggioni AP, Lancellotti P, Gale CP, Beleslin B, Budaj A, Chioncel O, Dagres N, Danchin N, Emberson J, Erlinge D, Glikson M, Gray A, Kayikcioglu M, Maggioni AP, Nagy VK, Nedoshivin A, Petronio A-S, Roos-Hesselink J, Wallentin L, Zeymer U, Habib G, Lancellotti P, Cosyns B, Donal E, Erba P, Iung B, Maggioni AP, Popescu BA, Prendergast B, Tornos P, Andarala M, Berle C, Brunel-Lebecq A, Fiorucci E, Laroche C, Missiamenou V, Taylor C, Ali Tatar-Chentir NN, Al-Mallah M, Astrom Aneq M, Athanassopoulos G, Badano LP, Benyoussef S, Calderon Aranda E, Cardim NM, Chan K-L, Cosyns B, Cruz I, Edvardsen T, Goliasch G, Habib G, Hagendorff A, Hristova K, Iung B, Kamp O, Kang D-H, Kong W, Matskeplishvili S, Meshaal M, Mirocevic M, Neskovic AN, Pazdernik M, Plonska-Gosciniak E, Popescu BA, Prendergast B, Raissouni M, Ronderos R, Sade LE, Sadeghpour A, Sambola A, Sengupta S, Separovic-Hanzevacki J, Takeuchi M, Tucay E, Tude Rodrigues AC, Varga A, Vaskelyte J, Yamagata K, Yiangou K,

Zaky H, Granada I, Mahia M, Ressi S, Nacinovich F, Iribarren A, Fernandez Oses P, Avegliano G, Filipini E, Obregon R, Bangher M, Dho J, Cartasegna L, Plastino ML, Novas V, Shigel C, Reyes G, De Santos M, Gastaldello N, Granillo Fernandez M, Potito M, Streitenberger G, Velazco P, Casabé JH, Cortes C, Guevara E, Salmo F, Seijo M, Weidinger F, Heger M, Brooks R, Stöllberger C, Ho C-Y, Perschy L, Puskas L, Binder C, Rosenhek R, Schneider M, Winter M-P, Hoffer E, Melissopoulou M, Lecoq E, Legrand D, Jacquet S, Massoz M, Pierard L, Marchetta S, Dulgheru R, Emal CD´, Oury C, Droogmans S, Kerkhove D, Plein D, Soens L, Weytjens C, Motoc A, Roosens B, Lemoine I, Rodrigus I, Paelinck B, Amsel B, Unger P, Konopnicki D, Beauloye C, Pasquet A, Vanoverschelde JL, Pierard S, Vancraeynest D, Sinnaeve F, Andrade JL, Staszko K, Dos Santos Monteiro R, Miglioranza MH, Shuha DL, Alcantara M, Cravo V, Fazzio L, Felix A, Iso M, Musa C, Siciliano AP, Villaca Filho F, Rodrigues A, Vilela F, Braga J, Silva R, Rodrigues D, Silva L, Morhy S, Fischer C, Silva R, Vieira M, Afonso T, Abreu J, Falcao SN. <snam,. EURO-ENDO Investigators Clinical presentation, aetiology and outcome of infective endocarditis. Results of the ESC-EORP EURO-ENDO (European infective endocarditis) registry: a prospective cohort study. *Eur Heart J* 2019;**40**:3222–3232.

14. Pericàs JM, Llopis J, Muñoz P, Gálvez-Acebal J, Kestler M, Valerio M, Hernández-Meneses M, Goenaga MÁ, Cobo-Belaustegui M, Montejo M, Ojeda-Burgos G, Sousa-Regueiro MD, de Alarcón A, Ramos-Martínez A, Miró JM, Sánchez FF, Noureddine M, Rosas G, de la Torre Lima J, Blanco R, Boado MV, Campaña Lázaro M, Crespo A, Goikoetxea J, Iruretagoyena JR, Irurzun Zuazabal J, López-Soria L, Montejo M, Nieto J, Rodrigo D, Rodríguez R, Vitoria Y, Voces R, García López MV, Georgieva RI, Ojeda G, Rodríguez Bailón I, Ruiz Morales J, María Cuende A, Echeverría T, Fuerte A, Gaminde E, Goenaga MÁ, Idígoras P, Antonio Iribarren J, Izaguirre Yarza A, Kortajarena Urkola X, Reviejo C, Carrasco R, Climent V, Llamas P, Merino E, Plazas J, Reus S, Álvarez N, Bravo-Ferrer JM, Castelo L, Cuenca J, Llinares P, Miguez Rey E, Rodríguez Mayo M, Sánchez E, Sousa Regueiro D, Javier Martínez F, Alonso M. D M, Castro B, García Rosado D, Durán M. D C, Miguel Gómez MA, Lacalzada J, Nassar I, Plata Ciezar A, Reguera Iglesias JM, Asensi Álvarez V, Costas C, de la Hera J, Fernández Suárez J, Iglesias Fraile L, León Arguero V, López Menéndez J, Mencia Bajo P, Morales C, Moreno Torrico A, Palomo C, Paya Martínez B, Rodríguez Esteban Á, Rodríguez García R, Telenti Asensio M, Almela M, Ambrosioni J, Azqueta M, Brunet M, Bodro M, Cartañá R, Falces C, Fita G, Fuster D, García de la Mària C, García-Pares D, Hernández-Meneses M, Llopis Pérez J, Marco F, Miró JM, Moreno A, Nicolás D, Ninot S, Quintana E, Paré C, Pereda D, Pericás JM, Pomar JL, Ramírez J, Rovira I, Sandoval E, Sitges M, Soy D, Téllez A, Tolosana JM, Vidal B, Vila J, Adán I, Bermejo J, Bouza E, Celemín D, Cuerpo Caballero G, Delgado Montero A, García Mansilla A, García Leoni ME, González Ramallo V, Kestler Hernández M, Hualde AM, Marín M, Martínez-Sellés M, Muñoz P, Rincón C, Rodríguez-Abella H, Rodríguez-Créixems M, Pinilla B, Pinto Á, Valerio M, Vázquez P, Verde Moreno E, Antorrena I, Loeches B, Martín Quirós A, Moreno M, Ramírez U, Rial Bastón V, Romero M, Saldaña A, Agüero Balbín J, Armiñanzas Castillo C, Arnaiz A, Arnaiz de las Revillas F, Cobo Belaustegui M, Fariñas MC, Fariñas-Álvarez C, Gómez Izquierdo R, García I, González Rico C, Gutiérrez-Cuadra M, Gutiérrez Díez J, Pajarón M, Parra JA, Teira R, Zarauza J, Calderón Parra J, Cobo M, Domínguez F, Fortaleza A, García Pavía P, González J, Fernández Cruz A, Múñez E, Ramos A, Sánchez Romero I, Centella T, Hermida JM, Moya JL, Martín-Dávila P, Navas E, Oliva E, del Río A, Rodríguez-Roda Stuart J, Ruiz S, Hidalgo Tenorio C, Almendro Delia M, Araji O, Barquero JM, Calvo Jambrina R, de Cueto M, Gálvez Acebal J, Méndez I, Morales I, López-Cortés LE, de Alarcón A, García E, Haro JL, Lepe JA, López F, Luque R, Alonso LJ, Azcárate P, Azcona Gutiérrez JM, Blanco JR, Cabrera Villegas A, García-Álvarez L, Oteo JA, Sanz M, de Benito N, Gurguí M, Pacho C, Pericas R, Pons G, Álvarez M, Fernández AL, Martínez A, Prieto A, Regueiro B, Tijeira E, Vega M, Canut Blasco A, Cordo Mollar J, Gainzarain Arana JC, García Uriarte O, Martín López A, Ortiz de Zárate Z, Urturi Matos JA, Gloria G-D, Antonio S-P, Arribas Leal JM, García Vázquez E, Hernández Torres A, Blázquez A, de la Morena Valenzuela G, Alonso Á, Aramburu J, Calvo FE, Moreno Rodríguez A, Tarabini-Castellani P, Heredero Gálvez E, Maicas Bellido C, Largo Pau J, Sepúlveda MA, Toledano Sierra P, Iqbal-Mirza SZ, Cascales Alcolea E, Keituqwa Yañez I, Martínez JN, Ballesta AP, Moreno Escobar E, Peña Monje A, Sánchez Cabrera V, Vinuesa García D, Arrizabalaga Asenjo M, Cifuentes Luna C, Núñez Morcillo J, Pérez Seco MC, Villoslada Gelabert A, Aured Guallar C, Fernández Abad N, García Mangas P, Matamala Adell M, Palacián Ruiz MP, Porres JC, Alcaraz Vidal B, Cobos Trigueros N, Del Amor Espín MJ, Giner Caro JA, Jiménez Sánchez R, Jimeno Almazán A, Ortín Freire A, Viqueira González M, Pericás Ramis P, Ribas Blanco MÁ, Ruiz de Gopegui Bordes E, Vidal Bonet L, Bellón Munera MC, Escribano Garaizabal E, Tercero Martínez A, Segura Luque JC, Badía C, Boix Palop L, Xercavins M, Ibars S, Nebreda EG, Horcajada Herrera I, Menduiña Gallego I, Marrero Santiago H, de Miguel Martínez I, Pisos Álamo E, Díaz Pedroche C, Chaves F, de Cossío S, López Medrano F, López MJ, Solera J, Solís J, Ardanuy C, Cuervo Requena G, Grillo S, Ruiz Majoral A. A contemporary picture of enterococcal endocarditis. *J Am Coll Cardiol* 2020;**75**:482–494.
15. Stortecky S, Heg D, Tueller D, Pilgrim T, Muller O, Noble S, Jeger R, Toggweiler S, Ferrari E, Taramasso M, Maisano F, Hoeller R, Wenaweser P, Nietlispach F, Widmer A, Huber C, Roffi M, Carrel T, Windecker S, Conen A. Infective endocarditis after transcatheter aortic valve replacement. *J Am Coll Cardiol* 2020;**75**:3020–3030.
16. Summers MR, Leon MB, Smith CR, Kodali SK, Thourani VH, Herrmann HC, Makkar RR, Pibarot P, Webb JG, Leipsic J, Alu MC, Crowley A, Hahn RT, Kapadia SR, Tuzcu EM, Svensson L, Cremer PC, Jaber WA. Prosthetic valve endocarditis after TAVR and SAVR: insights from the PARTNER Trials. *Circulation* 2019;**140**:1984–1994.
17. Bjursten H, Rasmussen M, Nozohoor S, Götberg M, Olaison L, Rück A, Ragnarsson S. Infective endocarditis after transcatheter aortic valve implantation: a nationwide study. *Eur Heart J* 2019;**40**:3263–3269.
18. Kruithof BPT, Paardekooper L, Hiemstra YL, Goumans MJ, Palmen M, Delgado V, et al. Stress-induced remodelling of the mitral valve: a model for leaflet thickening and superimposed tissue formation in mitral valve disease. *Cardiovasc Res* 2020;**116**:931–943.
19. Nazarzadeh M, Pinho-Gomes AC, Bidel Z, Dehghan A, Canoy D, Hassaine A, et al. Plasma lipids and risk of aortic valve stenosis: a Mendelian randomization study. *Eur Heart J* 2020;doi:10.1093/eurheartj/ehaa1070.
20. Toshima T, Watanabe T, Narumi T, Otaki Y, Shishido T, Aono T, Goto J, Watanabe K, Sugai T, Takahashi T, Yokoyama M, Kinoshita D, Tamura H, Kato S, Nishiyama S, Arimoto T, Takahashi H, Miyamoto T, Sadahiro M, Watanabe M. Therapeutic inhibition of microRNA-34a ameliorates aortic valve calcification via modulation of Notch1-Runx2 signalling. *Cardiovasc Res* 2020;**116**:983–994.
21. Chen Z, Gordillo-Martinez F, Jiang L, He P, Hong W, Wei X, et al. Zinc ameliorates human aortic valve calcification through GPR39 mediated ERK1/2 signaling pathway. *Cardiovasc Res* 2020.doi:10.1093/cvr/cvaa1090.
22. Mas-Peiro S, Hoffmann J, Fichtlscherer S, Dorsheimer L, Rieger MA, Dimmeler S, Vasa-Nicotera M, Zeiher AM. Clonal haematopoiesis in patients with degenerative aortic valve stenosis undergoing transcatheter aortic valve implantation. *Eur Heart J* 2020;**41**:933–939.
23. Barbato E, Noc M, Baumbach A, Dudek D, Bunc M, Skalidis E, Banning A, Legutko J, Witt N, Pan M, Tilsted H-H, Nef H, Tarantini G, Kazakiewicz D, Huculeci R, Cook S, Magdy A, Desmet W, Cayla G, Vinereanu D, Voskuil M, Goktekin O, Vardas P, Timmis A, Haude M. Mapping interventional cardiology in Europe: the European Association of Percutaneous Cardiovascular Interventions (EAPCI) Atlas Project. *Eur Heart J* 2020;**41**:2579–2588.
24. Michalski B, Dweck MR, Marsan NA, Cameli M, D'Andrea A, Carvalho RF, Holte E, Podlesnikar T, Manka R, Haugaa KH. The evaluation of aortic stenosis, how the new guidelines are implemented across Europe: a survey by EACVI. *Eur Heart J Cardiovasc Imaging* 2020;**21**:357–362.

25. Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, Lancellotti P, LeFevre M, Miller F, Otto CM. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging* 2017;**18**:254–275.
26. Kebed K, Sun D, Addetia K, Mor-Avi V, Markuzon N, Lang RM. Progression of aortic stenosis and echocardiographic criteria for its severity. *Eur Heart J Cardiovasc Imaging* 2020;**21**:737–743.
27. Namasivayam M, He W, Churchill TW, Capoulade R, Liu S, Lee H, Danik JS, Picard MH, Pibarot P, Levine RA, Hung J. Transvalvular flow rate determines prognostic value of aortic valve area in aortic stenosis. *J Am Coll Cardiol* 2020;**75**:1758–1769.
28. Guzzetti E, Poulin A, Annabi M-S, Zhang B, Kalavrouziotis D, Couture C, Dagenais F, Pibarot P, Clavel M-A. Transvalvular flow, sex, and survival after valve replacement surgery in patients with severe aortic stenosis. *J Am Coll Cardiol* 2020;**75**:1897–1909.
29. Einarsen E, Hjertaas JJ, Gu H, Matre K, Chowienczyk PJ, Gerdts E, et al. Impact of arterio-ventricular interaction on first-phase ejection fraction in aortic stenosis. *Eur Heart J Cardiovasc Imaging* 2020.doi:10.1093/ehjci/jeaa1154.
30. Papanastasiou CA, Kokkinidis DG, Kampaktsis PN, Bikakis I, Cunha DK, Oikonomou EK, Greenwood JP, Garcia MJ, Karamitsos TD. The prognostic role of late gadolinium enhancement in aortic stenosis: a systematic review and meta-analysis. *JACC Cardiovasc Imaging* 2020;**13**:385–392.
31. Hwang I-C, Kim H-K, Park J-B, Park E-A, Lee W, Lee S-P, Kim Y-J, Sohn D-W, Oh JK. Aortic valve replacement-induced changes in native T1 are related to prognosis in severe aortic stenosis: T1 mapping cardiac magnetic resonance imaging study. *Eur Heart J Cardiovasc Imaging* 2020;**21**:653–663.
32. Everett RJ, Treibel TA, Fukui M, Lee H, Rigolli M, Singh A, Bijsterveld P, Tastet L, Musa TA, Dobson L, Chin C, Captur G, Om SY, Wiesemann S, Ferreira VM, Piechnik SK, Schulz-Menger J, Schelbert EB, Clavel M-A, Newby DE, Myerson SG, Pibarot P, Lee S, Cavalcante JL, Lee S-P, McCann GP, Greenwood JP, Moon JC, Dweck MR. Extracellular myocardial volume in patients with aortic stenosis. *J Am Coll Cardiol* 2020;**75**:304–316.
33. Puls M, Beuthner BE, Topci R, Vogelgesang A, Bleckmann A, Sitte M, Lange T, Backhaus SJ, Schuster A, Seidler T, Kutschka I, Toischer K, Zeisberg EM, Jacobshagen C, Hasenfuß G. Impact of myocardial fibrosis on left ventricular remodelling, recovery, and outcome after transcatheter aortic valve implantation in different haemodynamic subtypes of severe aortic stenosis. *Eur Heart J* 2020;**41**:1903–1914.
34. Scully PR, Patel KP, Treibel TA, Thornton GD, Hughes RK, Chadalavada S, Katsoulis M, Hartman N, Fontana M, Pugliese F, Sabharwal N, Newton JD, Kelion A, Ozkor M, Kennon S, Mullen M, Lloyd G, Menezes LJ, Hawkins PN, Moon JC. Prevalence and outcome of dual aortic stenosis and cardiac amyloid pathology in patients referred for transcatheter aortic valve implantation. *Eur Heart J* 2020;**41**:2759–2767.
35. Kang D-H, Park S-J, Lee S-A, Lee S, Kim D-H, Kim H-K, Yun S-C, Hong G-R, Song J-M, Chung C-H, Song J-K, Lee J-W, Park S-W. Early surgery or conservative care for asymptomatic aortic stenosis. *N Engl J Med* 2020;**382**:111–119.
36. Alkhouli M, Alqahtani F, Ziada KM, Aljohani S, Holmes DR, Mathew V. Contemporary trends in the management of aortic stenosis in the USA. *Eur Heart J* 2020;**41**:921–928.
37. Kolte D, Vlahakes GJ, Palacios IF, Sakhuja R, Passeri JJ, Inglessis I, Elmariah S. Transcatheter versus surgical aortic valve replacement in low-risk patients. *J Am Coll Cardiol* 2019;**74**:1532–1540.
38. Testa L, Latib A, Brambilla N, De Marco F, Fiorina C, Adamo M, Giannini C, Angelillis M, Barbanti M, Sgroi C, Poli A, Ferrara E, Bruschi G, Russo CF, Matteo M, De Felice F, Musto C, Curello S, Colombo A, Tamburino C, Petronio AS, Bedogni F. Long-term clinical outcome and performance of transcatheter aortic valve replacement with a self-expandable bioprosthesis. *Eur Heart J* 2020;**41**:1876–1886.
39. Makkar RR, Thourani VH, Mack MJ, Kodali SK, Kapadia S, Webb JG, Yoon S-H, Trento A, Svensson LG, Herrmann HC, Szeto WY, Miller DC, Satler L, Cohen DJ, Dewey TM, Babaliaros V, Williams MR, Kereiakes DJ, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Brown DL, Fearon WF, Russo MJ, Pibarot P, Hahn RT, Jaber WA, Rogers E, Xu K, Wheeler J, Alu MC, Smith CR, Leon MB. Five-year outcomes of transcatheter or surgical aortic-valve replacement. *N Engl J Med* 2020;**382**:799–809.
40. Faroux L, Chen S, Muntané-Carol G, Regueiro A, Philippon F, Sondergaard L, Jørgensen TH, Lopez-Aguilera J, Kodali S, Leon M, Nazif T, Rodés-Cabau J. Clinical impact of conduction disturbances in transcatheter aortic valve replacement recipients: a systematic review and meta-analysis. *Eur Heart J* 2020;**41**:2771–2781.
41. Halim SA, Edwards FH, Dai D, Li Z, Mack MJ, Holmes DR, Tuzcu EM, Thourani VH, Harrison JK, Brennan JM. Outcomes of transcatheter aortic valve replacement in patients with bicuspid aortic valve disease: a report from the Society of Thoracic Surgeons/American College of Cardiology transcatheter valve therapy registry. *Circulation* 2020;**141**:1071–1079.
42. Yoon S-H, Kim W-K, Dhoble A, Milhorini Pio S, Babaliaros V, Jilaihawi H, Pilgrim T, De Backer O, Bleiziffer S, Vincent F, Shmidt T, Butter C, Kamioka N, Eschenbach L, Renker M, Asami M, Lazkani M, Fujita B, Birs A, Barbanti M, Pershad A, Landes U, Oldemeyer B, Kitamura M, Oakley L, Ochiai T, Chakravarty T, Nakamura M, Ruile P, Deuschl F, Berman D, Modine T, Ensminger S, Kornowski R, Lange R, McCabe JM, Williams MR, Whisenant B, Delgado V, Windecker S, Van Belle E, Sondergaard L, Chevalier B, Mack M, Bax JJ, Leon MB, Makkar RR. Bicuspid aortic valve morphology and outcomes after transcatheter aortic valve replacement. *J Am Coll Cardiol* 2020;**76**:1018–1030.
43. Thiele H, Kurz T, Feistritzer H-J, Stachel G, Hartung P, Eitel I, Marquetand C, Nef H, Doerr O, Lauten A, Landmesser U, Abdel-Wahab M, Sandri M, Holzhey D, Borger M, Ince H, Öner A, Meyer-Saraei R, Wienbergen H, Fach A, Frey N, König IR, Vonthein R, Rückert Y, Funkat A-K, de Waha-Thiele S, Desch S. Comparison of newer generation self-expandable vs. balloon-expandable valves in transcatheter aortic valve implantation: the randomized SOLVE-TAVI trial. *Eur Heart J* 2020;**41**:1890–1899.
44. Deharo P, Bisson A, Herbert J, Lacour T, Saint Etienne C, Grammatico-Guillon L, Porto A, Collart F, Bourguignon T, Cuisset T, Fauchier L. Impact of Sapien 3 balloon-expandable versus Evolut R self-expandable transcatheter aortic valve implantation in patients with aortic stenosis: data from a nationwide analysis. *Circulation* 2020;**141**:260–268.
45. Van Belle E, Vincent F, Labreuche J, Auffret V, Debry N, Lefèvre T, Eltchaninoff H, Manigold T, Gilard M, Verhoye J-P, Himbert D, Koning R, Collet J-P, Leprince P, Teiger E, Duhamel A, Cosenza A, Schurtz G, Porouchani S, Lattuca B, Robin E, Coisne A, Modine T, Richardson M, Joly P, Rioufol G, Ghostine S, Bar O, Amabile N, Champagnac D, Ohlmann P, Meneveau N, Lhermusier T, Leroux L, Leclercq F, Gandet T, Pinaud F, Cuisset T, Motreff P, Souteyrand G, Iung B, Folliguet T, Commeau P, Cayla G, Bayet G, Darremont O, Spaulding C, Le Breton H, Delhaye C. Balloon-expandable versus self-expanding transcatheter aortic valve replacement: a propensity-matched comparison from the FRANCE-TAVI Registry. *Circulation* 2020;**141**:243–259.
46. Makkar RR, Cheng W, Waksman R, Satler LF, Chakravarty T, Groh M, Abernethy W, Russo MJ, Heimansohn D, Hermiller J, Worthley S, Chehab B, Cunningham M, Matthews R, Ramana RK, Yong G, Ruiz CE, Chen C, Asch FM, Nakamura M, Jilaihawi H, Sharma R, Yoon S-H, Pichard AD, Kapadia S, Reardon MJ, Bhatt DL, Fontana GP. Self-expanding intra-annular versus commercially available transcatheter heart valves in high and extreme risk patients with severe aortic stenosis (PORTICO IDE): a randomised, controlled, non-inferiority trial. *Lancet* 2020;**396**:669–683.
47. Gaasch WH, Aurigemma GP, Meyer TE. An appraisal of the association of clinical outcomes with the severity of regurgitant volume relative to end-diastolic volume in patients with secondary mitral regurgitation. *JAMA Cardiol* 2020;**5**:476–481.

48. Packer M, Grayburn PA. New evidence supporting a novel conceptual framework for distinguishing proportionate and disproportionate functional mitral regurgitation. *JAMA Cardiol* 2020;**5**:469–475.
49. Bartko PE, Hulsmann M, Hung J, Pavo N, Levine RA, Pibarot P, et al. Secondary valve regurgitation in patients with heart failure with preserved ejection fraction, heart failure with mid-range ejection fraction, and heart failure with reduced ejection fraction. *Eur Heart J* 2020;**41**:2799–2810.
50. Messika-Zeitoun D, Iung B, Armoiry X, Trochu JN, Donal E, Habib G, et al. Impact of mitral regurgitation severity and left ventricular remodeling on outcome after MitraClip implantation: results from the MITRA-FR trial. *JACC Cardiovasc Imaging* 2020. doi:10.1016/j.jcmg.2020.1007.1021.
51. Arnold SV, Stone GW, Mack MJ, Chhatriwalla AK, Austin BA, Zhang Z, Ben-Yehuda O, Kar S, Lim DS, Lindenfeld JAnn, Abraham WT, Cohen DJ. Health status changes and outcomes in patients with heart failure and mitral regurgitation: COAPT trial. *J Am Coll Cardiol* 2020;**75**:2099–2106.
52. Iung B, Armoiry X, Vahanian A, Boutitie F, Mewton N, Trochu J-N, Lefèvre T, Messika-Zeitoun D, Guerin P, Cormier B, Brochet E, Thibault H, Himbert D, Thivolet S, Leurent G, Bonnet G, Donal E, Piriou N, Piot C, Habib G, Rouleau F, Carrié D, Nejjari M, Ohlmann P, Saint Etienne C, Leroux L, Gilard M, Samson G, Rioufol G, Maucort-Boulch D, Obadia JF, Obadia J-F, Barthelet M, Grinberg D, Rioufol G, Thibault H, Thivolet S, Furber A, Benard T, Debrux J-L, Pinaud F, Rouleau F, Chocron S, Chopard R, Meneveau N, Schiele F, Gilard M, Boschat J, Castellant P, Jobic Y, Le Ven F, Romain D, Beygui F, Sabatier R, Saloux E, Motreff P, Clerfond G, Azarnoush K, Lusson JR, Vorilhon C, Teiger E, Antoine C, Champagne S, Couetil J-P, Damy T, Dubois-Rande J-L, Ernande L, Guendouz S, Lim P, Monin J-L, Nguyen A, Riant E, Ternacle J, Zerbib C, Bertrand B, Bouvaist H, Saunier C, Vaislic C, Khelifa RC, Favereau X, Hilpert L, Maribas P, Azmoun A, Angel J-Y, Baruteau A, Brenot P, Deleuze P, Garcon P, Raoux F, Slama M, Van Belle E, Prat A, Coisne A, Duvapentiah A, Juthier F, Modine T, Polge A-S, Richardson M, Rousse N, Spillemaeker H, Sudre A, Vincent F, Vincentelli A, Jeu A, Ketelers R, Bonnet J-L, Bonnet G, Habib G, Michel N, Pankert M, Salaun E, Collart F, Houël R, Bille J, Commeau P, Joly P, Michel N, Philip E, Collet F, Arméro S, Bayet G, Giacomoni M-P, Maximovitch A, Lefèvre T, Cormier B, Romano M, Leclercq F, Albat B, Cade S, Cransac F, Macia J-C, Piot C, Francois F, Pons M, Raczka F, Sportouch C, Juillière Y, Folliguet T, Huttin O, Popovic B, Selton-Suty C, Venner C, Guérin P, Baron O, Letocart V, Letourneau T, Piriou N, Trochu J-N, Belliard O, Allouch P, Bensouda C, Janower S, Makowski S, Pasquier D, Pillière R, Rosencher J, Moceri P, Vahanian A, Brochet E, Himbert D, Iung B, Nataf P, Spaulding C, Achouh P, Berrebi A, Jouan J, Karam N, Mirabel M, Puscas T, Riant E, Suen PW, Caussin C, Berrebi A, Diakov C, Philippe F, Veugeois A, Collet JP, Choussat R, Isnard R, Montalescot G, Leroux L, Coste P, Dijos M, Labrousse L, Lafitte S, Picard F, Raud-Raynier P, Degrand B, Bedossa M, Corbineau H, Donal E, Leurent G, Eltchaninoff H, Bauer F, Tron C, Nejjari M, Attias D, Gerbay A, Pierrard R, Fuzellier J-F, Drogoul L, Elebeze J-P, Lopez S, Mariottini C, Meyer P, Mihoubi A, Tapia M, Teboul J, Ohlmann P, Goette-Dimarco P, Kretz J-G, Mommerot A, Morel O, Petit-Eisenmann H, Samet A, Trinh A, Carrié D, Gautier M, Badie YL, Lhermusier T, Marcheix B, Tchétché D, Abouliatim I, Bonfils L, Dumonteil N, Farah B, Fondard O, Pathak A, Etienne CS, Bernard A, Dion F, Loardi C, Quilliet L, Seemann A, Antoine C, Arnoult MA, Meurisse Y, Wautot F, Champagnac D, Dementhon J, Doisy V, Frieh J-P, Garrier O, Jamal F, Lamartine S, Leroux P-Y, Lienhart Y, Staat P, Zouaghi O; on behalf of the MITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation: outcomes at 2 years. *Eur J Heart Fail* 2019;**21**:1619–1627.
53. Taramasso M, Benfari G, van der Bijl P, Alessandrini H, Attinger-Toller A, Biasco L, Lurz P, Braun D, Brochet E, Connelly KA, de Bruijn S, Denti P, Deuschl F, Estevez-Loureiro R, Fam N, Frerker C, Gavazzoni M, Hausleiter J, Ho E, Juliard J-M, Kaple R, Besler C, Kodali S, Kreidel F, Kuck K-H, Latib A, Lauten A, Monivas V, Mehr M, Muntané-Carol G, Nazif T, Nickening G, Pedrazzini G, Philippon F, Pozzoli A, Praz F, Puri R, Rodés-Cabau J, Schäfer U, Schofer J, Sievert H, Tang GHL, Thiele H, Topilsky Y, Rommel K-P, Delgado V, Vahanian A, Von Bardeleben RS, Webb JG, Weber M, Windecker S, Winkel M, Zuber M, Leon MB, Hahn RT, Bax JJ, Enriquez-Sarano M, Maisano F. Transcatheter versus medical treatment of patients with symptomatic severe tricuspid regurgitation. *J Am Coll Cardiol* 2019;**74**:2998–3008.
54. Nickenig G, Weber M, Lurz P, von Bardeleben RS, Sitges M, Sorajja P, Hausleiter J, Denti P, Trochu J-N, Näbauer M, Dahou A, Hahn RT. Transcatheter edge-to-edge repair for reduction of tricuspid regurgitation: 6-month outcomes of the TRILUMINATE single-arm study. *Lancet* 2019;**394**:2002–2011.
55. Nickenig G, Weber M, Schueler R, Hausleiter J, Näbauer M, von Bardeleben RS, Sotiriou E, Schäfer U, Deuschl F, Kuck K-H, Kreidel F, Juliard J-M, Brochet E, Latib A, Agricola E, Baldus S, Friedrichs K, Vandrangi P, Verta P, Hahn RT, Maisano F. 6-Month outcomes of tricuspid valve reconstruction for patients with severe tricuspid regurgitation. *J Am Coll Cardiol* 2019;**73**:1905–1915.
56. Lurz P, Orban M, Besler C, Braun D, Schlotter F, Noack T, Desch S, Karam N, Kresoja K-P, Hagl C, Borger M, Nabauer M, Massberg S, Thiele H, Hausleiter J, Rommel K-P. Clinical characteristics, diagnosis, and risk stratification of pulmonary hypertension in severe tricuspid regurgitation and implications for transcatheter tricuspid valve repair. *Eur Heart J* 2020;**41**:2785–2795.
57. Hirji SA, Percy ED, Zogg CK, Malarczyk A, Harloff MT, Yazdchi F, Kaneko T. Comparison of in-hospital outcomes and readmissions for valve-in-valve transcatheter aortic valve replacement vs. reoperative surgical aortic valve replacement: a contemporary assessment of real-world outcomes. *Eur Heart J* 2020;**41**:2747–2755.
58. Bleiziffer S, Simonato M, Webb JG, Rodés-Cabau J, Pibarot P, Kornowski R, Windecker S, Erlebach M, Duncan A, Seiffert M, Unbehaun A, Frerker C, Conzelmann L, Wijeysundera H, Kim W-K, Montorfano M, Latib A, Tchetche D, Allali A, Abdel-Wahab M, Orvin K, Stortecky S, Nissen H, Holzamer A, Urena M, Testa L, Agrifoglio M, Whisenant B, Sathananthan J, Napodano M, Landi A, Fiorina C, Zittermann A, Veulemans V, Sinning J-M, Saia F, Brecker S, Presbitero P, De Backer O, Søndergaard L, Bruschi G, Franco LN, Petronio AS, Barbanti M, Cerillo A, Spargias K, Schofer J, Cohen M, Muñoz-Garcia A, Finkelstein A, Adam M, Serra V, Teles RC, Champagnac D, Iadanza A, Chodor P, Eggebrecht H, Welsh R, Caixeta A, Salizzoni S, Dager A, Auffret V, Cheema A, Ubben T, Ancona M, Rudolph T, Gummert J, Tseng E, Noble S, Bunc M, Roberts D, Kass M, Gupta A, Leon MB, Dvir D. Long-term outcomes after transcatheter aortic valve implantation in failed bioprosthetic valves. *Eur Heart J* 2020;**41**:2731–2742.
59. Landes U, Webb JG, De Backer O, Sondergaard L, Abdel-Wahab M, Crusius L, Kim W-K, Hamm C, Buzzatti N, Montorfano M, Ludwig S, Schofer N, Voigtlaender L, Guerrero M, El Sabbagh A, Rodés-Cabau J, Guimaraes L, Kornowski R, Codner P, Okuno T, Pilgrim T, Fiorina C, Colombo A, Mangieri A, Eltchaninoff H, Nombela-Franco L, Van Wiechen MPH, Van Mieghem NM, Tchétché D, Schoels WH, Kullmer M, Tamburino C, Sinning J-M, Al-Kassou B, Perlman GY, Danenberg H, Ielasi A, Fraccaro C, Tarantini G, De Marco F, Witberg G, Redwood SR, Lisko JC, Babaliaros VC, Laine M, Nerla R, Castriota F, Finkelstein A, Loewenstein I, Eitan A, Jaffe R, Ruile P, Neumann FJ, Piazza N, Alosaimi H, Sievert H, Sievert K, Russo M, Andreas M, Bunc M, Latib A, Govdfrey R, Hildick-Smith D, Sathananthan J, Hensey M, Alkhodair A, Blanke P, Leipsic J, Wood DA, Nazif TM, Kodali S, Leon MB, Barbanti M. Repeat transcatheter aortic valve replacement for transcatheter prosthesis dysfunction. *J Am Coll Cardiol* 2020;**75**:1882–1893.
60. Baumgartner H. Transcatheter valve-in-valve implantation in failed aortic bioprosthetic valves: a word of caution in times of euphoria. *Eur Heart J* 2020;**41**:2743–2746.
61. Blanke P, Leipsic JA, Popma JJ, Yakubov SJ, Deeb GM, Gada H, Mumtaz M, Ramlawi B, Kleiman NS, Sorajja P, Askew J, Meduri CU, Kauten J, Melnitchouk S, Inglessis I, Huang J, Boulware M, Reardon MJ. Bioprosthetic aortic valve leaflet thickening in the EVOLUT low risk sub-study. *J Am Coll Cardiol* 2020;**75**:2430–2442.
62. Makkar RR, Blanke P, Leipsic J, Thourani V, Chakravarty T, Brown D, Trento A, Guyton R, Babaliaros V, Williams M,

Jilaihawi H, Kodali S, George I, Lu M, McCabe JM, Friedman J, Smalling R, Wong SC, Yazdani S, Bhatt DL, Bax J, Kapadia S, Herrmann HC, Mack M, Leon MB. Subclinical leaflet thrombosis in transcatheter and surgical bioprosthetic valves: PARTNER 3 cardiac computed tomography substudy. *J Am Coll Cardiol* 2020;**75**:3003–3015.

63. Brouwer J, Nijenhuis VJ, Delewi R, Hermanides RS, Holvoet W, Dubois CLF, Frambach P, De Bruyne B, van Houwelingen GK, Van Der Heyden JAS, Toušek P, van der Kley F, Buysschaert I, Schotborgh CE, Ferdinande B, van der Harst P, Roosen J, Peper J, Thielen FWF, Veenstra L, Chan Pin Yin DRPP, Swaans MJ, Rensing BJWM, van't Hof AWJ, Timmers L, Kelder JC, Stella PR, Baan J, ten Berg JM. Aspirin with or without clopidogrel after transcatheter aortic-valve implantation. *N Engl J Med* 2020;**383**:1447–1457.
64. Dangas GD, Tijssen JGP, Wöhrle J, Søndergaard L, Gilard M, Möllmann H, Makkar RR, Herrmann HC, Giustino G, Baldus S, De Backer O, Guimarães AHC, Gullestad L, Kini A, von Lewinski D, Mack M, Moreno R, Schäfer U, Seeger J, Tchétché D, Thomitzek K, Valgimigli M, Vranckx P, Welsh RC, Wildgoose P, Volkl AA, Zazula A, van Amsterdam RGM, Mehran R, Windecker S. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. *N Engl J Med* 2020;**382**:120–129.
65. Nijenhuis VJ, Brouwer J, Delewi R, Hermanides RS, Holvoet W, Dubois CLF, Frambach P, De Bruyne B, van Houwelingen GK, Van Der Heyden JAS, Toušek P, van der Kley F, Buysschaert I, Schotborgh CE, Ferdinande B, van der Harst P, Roosen J, Peper J, Thielen FWF, Veenstra L, Chan Pin Yin DRPP, Swaans MJ, Rensing BJWM, van't Hof AWJ, Timmers L, Kelder JC, Stella PR, Baan J, ten Berg JM. Anticoagulation with or without clopidogrel after transcatheter aortic-valve implantation. *N Engl J Med* 2020;**382**:1696–1707.
66. Jochheim D, Barbanti M, Capretti G, Stefanini GG, Hapfelmeier A, Zadrozny M, Baquet M, Fischer J, Theiss H, Todaro D, Chieffo A, Presbitero P, Colombo A, Massberg S, Tamburino C, Mehilli J. Oral anticoagulant type and outcomes after transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2019;**12**:1566–1576.
67. Chen S, Redfors B, Nazif T, Kirtane A, Crowley A, Ben-Yehuda O, Kapadia S, Finn MT, Goel S, Lindman BR, Alu MC, Chau KH, Thourani VH, Vahl TP, Douglas PS, Kodali SK, Leon MB. Impact of renin-angiotensin system inhibitors on clinical outcomes in patients with severe aortic stenosis undergoing transcatheter aortic valve replacement: an analysis of from the PARTNER 2 trial and registries. *Eur Heart J* 2020;**41**:943–954.
68. Lindman BR, Goel K, Bermejo J, Beckman J, O'Leary J, Barker CM, et al. Lower blood pressure after transcatheter or surgical aortic valve replacement is associated with increased mortality. *J Am Heart Assoc* 2019;**8**:e014020.
69. Kang D-H, Park S-J, Shin S-H, Hong G-R, Lee S, Kim M-S, Yun S-C, Song J-M, Park S-W, Kim J-J. Angiotensin receptor neprilysin inhibitor for functional mitral regurgitation. *Circulation* 2019;**139**:1354–1365.

ESC European Society of Cardiology

Special article

The year in cardiovascular medicine 2020: heart failure and cardiomyopathies

Héctor Bueno[1,2,3,4,*], Brenda Moura[5,6], Patrizio Lancellotti[7,8], and Johann Bauersachs[9]

[1] Multidisciplinary Translational Cardiovascular Research Group. Centro Nacional de Investigaciones Cardiovasculares (CNIC), Melchor Fernández Almagro, 3, Madrid 28029, Spain; [2] Cardiology Department, Hospital Universitario 12 de Octubre and Instituto de Investigación Sanitaria Hospital, 12 de Octubre (imas12), Madrid, Spain; [3] Centro de Investigación Biomédica en Red Enfermedades Cardiovaculares (CIBERCV), Madrid, Spain; [4] Facultad de Medicina, Universidad Complutense de Madrid, Plaza de Ramón y Cajal, s/n, 28040 Madrid, Spain; [5] Cardiology Department, Military Hospital, Av. da Boavista S/N, 4050-115 Porto, Portugal; [6] CINTESIS—Center for Health Technology and Services Research, R. Dr. Plácido da Costa, 4200-450 Porto, Portugal; [7] Department of Cardiology, CHU SartTilman, University of Liège Hospital, GIGA Cardiovascular Sciences, Avenue de L'Hôpital 1, 4000 Liège, Belgium; [8] Cardiology Departments, Gruppo Villa Maria Care and Research, Maria Cecilia Hospital, Cotignola Bari, Italy and Via Corriera, 1, 48033 Cotignola RA, Italy and Anthea Hospital, Via Camillo Rosalba, 35/37, 70124 Bari BA, Italy; and [9] Department of Cardiology and Angiology, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany

Received 1 October 2020; revised 26 November 2020; editorial decision 10 December 2020; accepted 22 December 2020; online publish-ahead-of-print 3 January 2021

Reproduced from: Bueno H, Moura B, Lancellotti P, Bauersachs J. The year in cardiovascular medicine 2020: heart failure and cardiomyopathies. Eur Heart J. 2021 Feb 11;42(6):657-670., https://doi.org/10.1093/eurheartj/ehaa1061, by permission of Oxford University Press on behalf of the European Society of Cardiology

* Corresponding author. Tel: (+34) 914 531 200 - Ext 4110; Email: hector.bueno@cnic.es

Abstract

During year 2020, we learned new options to better stratify patients with heart failure and preserved left ventricular ejection fraction (HFpEF) (*A*), the clinical benefit of three new drugs to improve prognosis of patient with heart failure and reduced left ventricular ejection fraction (HFrEF): empagliflozin, vericiguat and omecamtiv mecarbil (*B*), the potential benefit of a broader utilization of recommended drugs for HFrEF in patients with left ventricular ejection fraction higher than 40% (*C*), and the potential added clinical benefit of a comprehensive use of recommended drugs for HFrEF (*D*) in a year marked by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic (central cartoon). Reprinted or adapted from: (A) Selvaraj *et al*.,[23] (B) Packer *et al*.,[115] Armstrong *et al*.,[126] and Teerlink *et al*.,[132] (C) Böhm *et al*.,[100] (D) Vaduganathan *et al*.[139] (*Graphical Abstract – see in original.*)

Keywords Heart failure • Epidemiology • Clinical practice • Imaging • Biomarkers • Pharmacotherapy • Randomized control trials • SGLT-2 inhibitor • Angiotensin receptor–neprilysin inhibitors • Activators of soluble guanylate cyclase • Cardiac myosin activators and inhibitors • Telemedicine

Introduction

Heart failure (HF) prevalence remains high worldwide with significant sex-related and regional differences in its presentation, management, and outcomes. In 2020, advances in biomarkers and imaging techniques were reported for the diagnosis and prognosis of diastolic dysfunction, HF with preserved ejection fraction or monitoring cardiotoxicity; a new definition of HF with recovered left ventricular ejection fraction (LVEF) was released. Benefits of renin–angiotensin–aldosterone system inhibitors and β-blockers may extend to patients with an LVEF up to 55%. Sacubitril–valsartan improved LV remodelling, biomarker levels, and rates of sudden cardiac death. Two studies investigating the sodium-glucose cotransporter 2 inhibitors empagliflozin and sotagliflozin in patients with HF were reported: the EMPEROR-Reduced trial in patients with HF with reduced EF with or without type 2 diabetes (T2DM) demonstrated a significant reduction in cardiovascular (CV) death and HF hospitalisations (HFH). In patients with T2DM and HF across the whole EF spectrum after a recent HFH, the SOLOIST trial showed a reduction in the primary endpoint of CV deaths, total HFH, and urgent visits for HF. In addition, in patients with kidney disease with or without diabetes mellitus (DAPA-CKD), dapagliflozin prevented the deterioration of renal function. Two novel drugs, the activator of soluble guanylate cyclase vericiguat and the myosin activator omecamtiv mecarbil, in the large outcome trials VICTORIA and GALACTIC-HF predominantly reduced HFH in high-risk patients with worsening HF. In the AFFIRM-AHF trial, intravenous ferric carboxymaltose reduced HFH in patients with iron deficiency after an HF decompensation.

Year 2020 will be remembered as the year of coronavirus disease of 2019 (COVID-19). The pandemia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a massive impact on global health and economy. When this article is published, >80 million people will have been infected and >1.75 million will have died of the disease. Many others will have died or worsen of their diseases, many with cardiovascular (CV) disease, as an indirect effect of the fear to seek assistance or the collapse of healthcare systems. Yet, advances in science and medical care continued developing during the year. This article reviews important advances in the field of heart failure (HF) presented in 2020.

Epidemiology

More than 64 million people are living with HF in the world, with an estimated prevalence of 1–2% among adults in developed countries, most often with several comorbidities (*Figure 1 – see in Groenewegen et al.*[1]).[1] The incidence of HF may be stabilizing globally, with decreases in higher-income countries,[2] but increases in lower-income countries, and a shift towards HF with preserved ejection fraction (HFpEF), and increasing due to population ageing and the increase in obesity.[1] Age, traditional risk factors for HF, a sedentary lifestyle, and social deprivation are associated with incident HF.[3] Actually, lifestyle and social determinants of health are attracting more attention in the epidemiology and care of patients with HF.[4] In patients with new-onset HF, the most common first events are cardiac events (36%), recurrent HF (28%), and death (29%).[5]

Non-traditional risk factors, such as pacemaker implantation may play a role in the development of HF: within the first 2 years after implantation in patients without known HF, the incidence of fatal and non-fatal HF is 10.6%, six times higher than for age- and gender-matched individuals without HF and pacemaker.[6]

Mortality rates of HF seem to be declining less rapidly than previously in the general population.[1] Among patients with cardiac resynchronization therapy (CRT), a gradual decrease in sudden cardiac death risk has been observed since the early 2000s[7] with implications for the role of implantable defibrillators and the design of comprehensive HF care models.

Significant regional differences in the management of acute HF have been identified, including timing and types of treatments used,[8] and rates and time trends of readmission.[2,9,10] However, the importance of distinguishing worsening/chronic HF from new-onset HF in patients with first

hospitalization has been highlighted, as patients with worsening/chronic HF have a significantly greater comorbidity burden and higher adjusted risks of mortality and HF readmission.[10,11]

Clinical aspects

Diagnostics and risk stratification

Imaging

Imaging is pivotal in the diagnosis and risk stratification of patients with HF. The European Society of Cardiology (ESC) Heart Failure Association (HFA) has recently highlighted in a position statement the central role of full echocardiographic examination in patients admitted for acute heart failure (AHF).[12] Once the patient is stabilized, the added value of routine cardiac magnetic resonance (CMR) over echocardiography alone to help diagnose the causes of HF not related to ischaemic heart disease has been questioned.[13] Selective rather than routine CMR for identifying specific HF aetiologies is more cost effective. Noteworthy, CMR could serve to better define HFpEF phenotypes and to select patient specific therapies, such as MRA may be for HFpEF patients with myocardial fibrosis.[14–17] The diagnosis of HFpEF remains challenging especially in patients with coexisting conditions that account for dyspnoea. Diastolic dysfunction, left atrial enlargement, elevated left atrial pressure, and pulmonary hypertension are common in these patients.[18,19] The 2016 diastolic dysfunction grading algorithm proposed by the European Association of Cardiovascular Imaging has shown improved prognostic value compared to the 2009 one.[20] However, the high number of patients with doubtful classification renders clinical decision making challenging.[21] The analysis of LA mechanics, LA strain, and left ventricular (LV) global longitudinal strain[22] allows to better classify the degree of diastolic dysfunction and improves individual risk stratification. Two algorithms (H_2FPEF and ESC HFA-PEFF) may facilitate HFpEF diagnosis. These two scores have equivalent predictive power of incident HF hospitalization or death among patients without a clinical diagnosis of HF.[23] Although LV ejection fraction (LVEF) is key for HF classification, it remains a crude estimate of LV function. Intriguingly, 17% of patients with initially preserved LV systolic function show a decrease in LVEF below 40% at 6 months follow-up, which is associated with more cardiac events.[24] Parameters of LV mechanics (LV strain, multilayer strain and myocardial work) provide incremental prognostic information over LVEF.[22,25] The benefit of treatment [i.e. sacubitril/valsartan (SV)] on LV remodelling is also better captured by LV strain.[26] Myocardial mechanics is linked to coronary microvascular dysfunction in patients with hypertensive HF.[27,28] In AHF, cardiac sympathetic nerve dysfunction, as evaluated by ^{123}I-metaiodobenzylguanidine imaging, is associated with poor outcome irrespective of LVEF.[29]

Biomarkers

Biomarkers are key for diagnosis and prognostic evaluation in patients with HF. Circulating biomarkers related to extracellular matrix regulation were abnormal in patients with HFpEF, displayed prognostic value, and were influenced favourably by SV in PARAGON-HF.[30] In HF with reduced LVEF (HFrEF), absolute NT-proBNP, hs-TnT, and sST2 levels predict outcomes independent of age, sex, and LVEF category.[31] Differential circulating levels of biomarkers associated with ageing in patients with HF have been reported, with increasing levels of proteins associated with extracellular matrix organization, inflammatory processes, and tumour cell regulation and lower expression of tumour proliferation functions.[32]

In AHF, a specific challenge is to identify infection as a trigger of AHF. Procalcitonin (PCT) has emerged as an alternative for C-reactive protein in diagnosing bacterial infection. In a recent randomized, multicentre, open study, a strategy of PCT-guided initiation of antibiotic therapy was more effective than standard care in improving clinical outcomes.[33] Omics phenotyping is likely the next frontier to unravel disease mechanisms and heterogeneity.[34] As a recent example, incorporating a panel of three metabolite-based biomarkers into a risk score improved the prognostic utility of NT-proBNP by predicting long-term CV death.[35]

Heart failure during the COVID-19 pandemic

The role of the angiotensin-converting enzyme (ACE) receptor 2 in the infection of human cells by SARS-CoV-2 and in the pathophysiology of COVID-19,[36] and the poor prognosis of cardiac patients with COVID-19[37] raised the concern of a potential deleterious effect of the treatment with ACE inhibitors and angiotensin receptor blockers (ARB). These drugs may either decrease acute lung damage, prevent angiotensin-II-mediated pulmonary inflammation or increase the SARS-CoV-2 pulmonary damage by the up-regulation of ACE2 receptors.[38,39] Observational studies refuted the hypothesis of a deleterious effect of ACEI/ARB.[40–43] The BRACE CORONA trial found no worse outcomes in patients with COVID-19 allocated to continuation or interruption of their chronic ACEI/ARB treatment (presented at the ESC Congress, data not published). The incidence of AHF or decompensation of chronic HF among patients with COVID-19 is high and with poor prognosis.[44] Indirect effects of the pandemic included the reduction in HF hospitalizations during local outbreaks[45–47] with increases in their hospital mortality,[45,47] and major challenges for the management and follow-up of HF patients, and the conduct of clinical trials. Recommendations to overcome these challenges have been released.[48–50]

Sex and heart failure

Women account for half of patients with HF with a lower incidence rate until the age of 75 years, a higher proportion of HFpEF, probably related to the higher prevalence of obesity and diabetes mellitus.[1] Women with HF present a greater symptom burden and poorer quality of life as compared with men.[51] Significant sex-related differences have been described in Europe in the management of acute and chronic HF[8,52] including a lower use of guideline-directed medical therapies—which seem to be mostly explained by older age and comorbidity rather than by sex itself—with lower crude rates of death and HF hospi-

talization in women. The lack of sex-related differences in the clinical effect of HF therapies[53,54] does not justify these differences, although the possibility has been suggested that women with HF might benefit from treatment to a higher level of LVEF than previously considered.[54] A different perspective of the gender gap in HF is the lower proportion of female authors in HF practice guidelines and trials, ranging between 11% and 24% only, with modest increases over time in European and US guidelines references but not in HF trials. Importantly, HF trials with a woman first or senior author are associated with a higher proportion of enrolled female participants.[55]

Comorbidities

Comorbidities are important because they impact the clinical presentation, management, and outcomes of HF patients. The burden of comorbidities is higher in older patients, women and those with HFpEF,[56–58] which are often ignored.[59] Particularly relevant conditions in HF patients include atrial fibrillation,[60] which has complex interrelations with HF needing more research.[61,62] One example is the lack of increase in mortality risk associated with elevated heart rate in patients with HFrEF and atrial fibrillation, as compared to sinus rhythm.[60,63] Renal disease is one other, with renal function often changing during the course of the disease or as a response to HF therapies. Clinical responses, including worsening renal function and pseudo-worsening renal function, and their pathophysiological correlates, i.e. tubular function (diuretic response) beyond estimated glomerular filtration rate (eGFR), need to be understood to be properly managed, adapting therapies to the changing situation.[64,65]

Specific situations

Acute heart failure

In patients with acute HFrEF, istaroxime, an inhibitor of the sarcolemmal Na^+/K^+ pump activating the SERCA2a pump, improved cardiac function without major adverse effects in a small mechanistic trial.[66] Cimlanod, a nitroxyl donor infused over 48 h, was reasonably well tolerated at a lower dose whereas higher doses caused unacceptable hypotension. There was improvement of NT-proBNP but not on dyspnoea (presented at HFA Discoveries, data not published). A number of position papers have summarized the role of imaging[12] or the management of AHF in specific situations, such as acute coronary syndromes[67] or atrial fibrillation.[68]

Cardiogenic shock

While its incidence seems to be decreasing, cardiogenic shock still conveys a high mortality risk.[69] A new clinical classification,[70] and two position papers[71,72] on cardiogenic shock have been published this year. The SWEdish evaluation of left Ventricular Assist Device (SweVAD) will examine the impact of mechanical circulatory support vs. guideline-directed medical therapy on survival in a population of AHF patients ineligible for heart transplant.[73]

Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) is the first cause of HF in women during/after pregnancy.[74–76] The ESC EORP registry on PPCM enrolled >700 women with this condition from 49 countries. It showed that PPCM affects women from any region or ethnicity. Within 6 months after diagnosis, the average rates of maternal mortality, readmission, and neonatal mortality were, respectively, 6%, 10%, and 5%, with marked regional variations. Recovery of LVEF occurred in 46% of women.[77] The management of these patients is reviewed in a recent paper.[78]

HF with recovered left ventricular ejection fraction

This year, a working definition of HF with recovered left ventricular ejection fraction (HFrecEF) has been proposed. This includes: (i) documentation of a decreased LVEF < 40% at baseline; (ii) ≥10% absolute improvement in LVEF; and (iii) a second measurement of LVEF >40%.[79] Reverse LV remodelling is associated with improved myocyte and LV chamber contractility and better clinical outcomes. However, a significant proportion of patients with HFrecEF develop recurrences of LV dysfunction and HF. Despite improvements in structural and functional abnormalities, many of the multilevel molecular changes occurring during LV remodelling remain dysregulated in reverse remodelled hearts. Therefore, guideline-directed medical and device therapy for patients with HFrecEF should be continued indefinitely with close clinical follow-up.[79]

HF in cancer patients

The role of CV imaging in cancer patients receiving cardiotoxic therapies has been highlighted in a position statement by the HFA[12] and in the European Society for Medical Oncology guidelines.[80] The role of focus echocardiography[81] and CMR[82] has also been recently discussed. In daily practice, caution should, however, be given if using late gadolinium enhancement or qualitative T2-weighted STIR imaging-only approach for the exclusion of checkpoint inhibitor-associated myocarditis.[83] Imaging is cornerstone for monitoring cardiotoxicity and identifying subtle impairment of myocardial function occurring prior crossing the traditionally defined threshold of LV systolic dysfunction (LVEF < 50%).[84,85]

Right ventricular dysfunction (RVD)

RV and right atrium dysfunction contribute to HFpEF pathophysiology. Also, RV dysfunction (lower RV systolic velocity and RV fractional area change) and impairment in RV-pulmonary artery coupling are more frequently found in HFpEF patients developing acute lung congestion with exercise.[86] Activation of the endothelin and adrenomedullin neurohormonal pathways is associated with pulmonary haemodynamic derangements, reduced RV functional reserve, reduced cardiac output, and more severe impairment of peak VO_2 in HFpEF patients.[87] The most common causes of RVD are left-sided heart diseases (46%), pulmonary thromboembolic disease (18%), chronic lung disease/hypoxia (17%), and pulmonary arterial hypertension

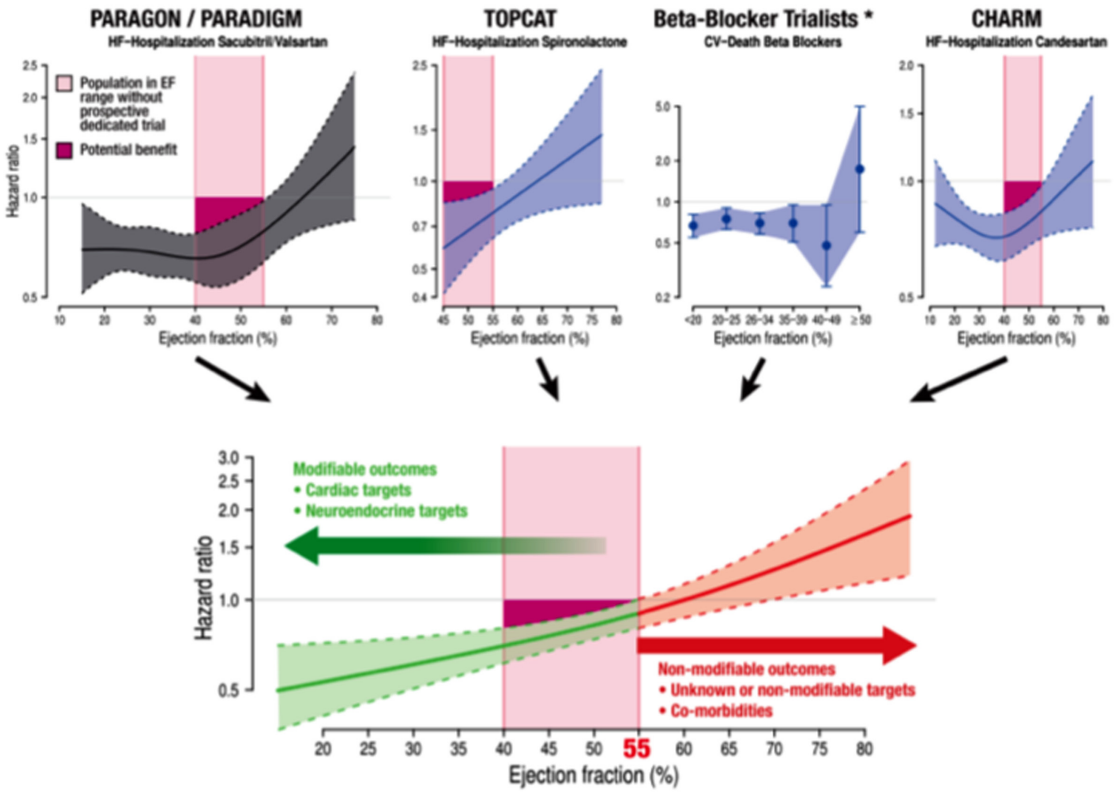


Figure 2 Results from different trials testing a number of drugs commonly used to treat heart failure, pointing to an extended benefit up to a left ventricular ejection fraction of 55%. For patients with left ventricular ejection fraction >55%, a population group usually presenting several comorbidities, there is still no evidence of a drug improving prognosis. Reprinted from Böhm *et al.*[100], by permission of OUP on behalf of the ESC.

(11%). Average 1-year mortality in patients with RVD is high (>40%), highest among chronic lung disease patients.[88] The presence of RVD at CRT implantation predicts worsening LV remodelling and survival.[89]

Pharmacotherapies

Angiotensin receptor–neprilysin inhibitors (paragon, paradigm, parallax)

Angiotensin receptor–neprilysin inhibitor (ARNI) showed, in a sub-analysis of PARADIGM-HF, a reduction in sudden cardiac death risk regardless of the use of implantable cardiac defibrillators.[90] Reduction in ventricular volumes and increase in LVEF have been observed with standard echocardiography in patients after 6 months on SV, but improvement in global longitudinal strain is apparent after 3 months.[26] In a small cohort of patients with end stage renal disease, SV showed efficacy and safety.[91] The LIFE Trial, comparing SV to valsartan in NYHA Class IV HFrEF patients, although prematurely interrupted because of the COVID-19 pandemia, will still provide information about ARNI as a treatment option for advanced HF patients.[92]

The PARALLAX trial tested the efficacy of SV vs. optimal individualised background therapy in HFpEF patients and found a reduction in NT-proBNP from baseline to 12 weeks but no effect on six-minute walk distance from baseline to 24 weeks (presented at ESC 2020—data not published). In the PARAGON Trial in patients with HFpEF, SV did not result in a lower rate of total hospitalizations for HF and death. Of the 12 pre-specified subgroup analyses, sex and LVEF appeared to modify the effect of SV vs. valsartan on the primary composite outcome. Although no benefit was apparent in men, there was a significant reduction in HF hospitalizations in women.[93] Also, patients seemed to derive more benefit from SV when started early after hospitalization.[94] Baseline and mean achieved systolic blood pressure of 120–129 mm Hg identified the lowest risk HFpEF patients, but the blood pressure-lowering effects of SV did not account for its effects on outcomes, regardless of sex.[95] Compared with valsartan, SV reduced the risk of renal events and slowed the decline in estimated glomerular filtration rate.[96] Reduction in serum uric acid was also associated with improved outcomes.[97] A meta-analysis assessing the efficacy of different renin–angiotensin–aldosterone system (RAAS) antagonists in clinical trials performed in HFpEF patients (PEP-CHF, CHARM-preserved, I-PRESERVE, TOPCAT, PARAGON-HF) showed no statistical difference in all-cause and CV mortality among RAAS antagonists and placebo, but a significantly decreased risk in HF hospitalizations in patients allocated to receive ARNI compared with controls (OR, 0.73, 95% CI, 0.61–0.87) and ARB (OR 0.80, 95% CI, 0.71–0.91).[98]

A patient-level data analysis from the PARADIGM-HF and PARAGON-HF trials (SV vs. enalapril in HFrEF and SV vs. valsartan in HFpEF, respectively), and the CHARM-

Alternative and CHARM-Preserved trials (candesartan vs. placebo) showed that, compared with RAAS inhibitors, SV improved outcomes across the range of LVEF, with a risk reduction (RR) of 0.54 [95% confidence interval (CI) 0.45–0.65] for the recurrent primary endpoint compared with putative placebo ($P<0.001$). Treatment benefits were robust in patients with LVEF<60%, but not in those with LVEF>60%.[99] These results are in line with prior *post hoc* analyses from the TOPCAT study and β-blocker trials suggesting that the cut-off of LVEF for a beneficial treatment effects is ~55%. These analyses show that in the sparsely studied population of patients with an LVEF of 40–55%, several HF treatments might provide benefit (*Figure 2*).[100]

Sodium-glucose cotransporter 2 inhibitors (EMPEROR-Reduced, DAPA-HF, SOLOIST, VERTIS, SUGAR-DM-HF, EMPA-TROPISM [ATRU-4])

In patients with type 2 diabetes, the sodium-glucose cotransporter 2 (SGLT-2) inhibitors empagliflozin and dapagliflozin reduce the risk of HF hospitalization regardless of baseline CV risk or history of HF.[101,102] In The VERTIS trial, ertugliflozin did neither significantly reduce CV events, nor the combined endpoint of CV death/HF hospitalization[103] but reduced HF hospitalizations.[104]

In patients with HFrEF, DAPA-HF has demonstrated a significant reduction in CV mortality and HF events.[105,106] This robust effect was analysed in more detail in several seminal papers published in 2020. The benefit of dapagliflozin was independent of the diabetes status, occurring across all levels of HbA1c,[107] as well as of baseline renal function or blood pressure, patient age, or background HF therapy.[108–111] Dapagliflozin improved symptoms, physical function, and quality of life[112] and was shown to be a cost-effective treatment for HFrEF in the UK, German, and Spanish healthcare systems.[113] Dapagliflozin also reduces the rate of decline in renal function in HFrEF patients.[111] as well as in patients with chronic kidney disease, as shown in the DAPA-CKD trial, where treatment with dapagliflozin reduced the risk of worsening renal function, end-stage kidney disease, or death. This protective effect was observed in patients with or without diabetes.[111,114]

Empagliflozin also showed marked beneficial effects in HFrEF patients independently from diabetes status (*Figure 3 – see in Packer et al.[115], Armstrong et al.[126] and Teerlink et al.[132]*), with a significant reduction in the primary composite endpoint of CV death and HF events (hazard ratio (HR), 0.75; 95% CI, 0.65–0.86; $P<0.001$), the secondary endpoints of total HF hospitalizations (HR, 0.70; 95% CI, 0.58–0.85; $P<0.001$), the annual rate of decline in the estimated glomerular filtration rate (–0.55 vs. –2.28 mL/min/1.73 m^2 of body-surface area per year, $P<0.001$), the risk of serious renal outcomes,[115] and the risk and total number of inpatient and outpatient worsening HF events, which starts early after the initiation of treatment and remains during the duration of treatment.[116] These beneficial effects were also observed to a similar extent in patients pre-treated with ARNI[117] and were independent of baseline diabetes status and across the continuum of HbA1c,[118] and in patients with and without CKD and regardless of the severity of kidney impairment at baseline.[119]

In the SUGAR-DM-HF study, empagliflozin reduced LV volumes measured by CV magnetic resonance in patients with HFrEF and type 2 diabetes or prediabetes.[120] The mechanistic trial EMPA-TROPISM (ATRU-4) showed the beneficial effect of empagliflozin in improving LV volumes, LV mass, LV systolic function, functional capacity, and quality of life in non-diabetic patients with HFrEF[121] (ref). Taken the evidence together, SGLT-2 inhibitors reduce all-cause and CV mortality and improve renal outcomes in patients with HFrEF, supporting the role of dapagliflozin and empagliflozin as a new standard of care for patients with HFrEF.[119,122]

Sotagliflozin, another SGLT-2 inhibitor that displays also gastrointestinal SGLT-1 inhibition and thus reduces intestinal glucose absorption, was investigated in patients with type 2 diabetes after a recent hospitalization for worsening heart failure (SOLOIST-WHF). Patients were included independent of their ejection fraction, and 78% of patients had an ejection fraction <50%. The primary endpoint of CV death, total hospitalizations, and urgent visits for HF was significantly reduced in patients treated with sotagliflozin (HR, 0.67; 95% CI, 0.52–0.85; $P<0.001$). The results were consistent among subgroups and especially also in patients with an EF>50%.[123] Sotagliflozin was also investigated in patients with type 2 diabetes, chronic kidney disease, and elevated CV risk (SCORED);[124] primary endpoint (changed during the study to a composite of CV death, total HF hospitalizations and urgent visits for HF) was significantly reduced in patients treated with sotagliflozin (HR, 0.67; 95% CI, 0.52–0.85; $P<0.001$). It has to be mentioned that both sotagliflozin trials had to be stopped earlier than planned because of loss of funding from the sponsor.

Activators of soluble guanylate cyclase (VICTORIA, VITALITY, CAPACITY)

The activator of soluble guanylate cyclase (sGC) vericiguat was investigated in the VICTORIA study in 5050 patients with recently decompensated chronic HF and LVEF<45%.[125,126] Vericiguat significantly reduced the primary outcome of CV death or first HF hospitalisation (HR, 0.90; 95% CI, 0.82–0.98; $P=0.02$) (*Figure 3 – see in Packer et al.[115], Armstrong et al.[126] and Teerlink et al.[132]*). While vericiguat significantly reduced HF hospitalisations (HR, 0.90; 95% CI, 0.81–1.00), CV deaths were not significantly diminished. Adverse events were largely similar among the vericiguat and placebo groups. An analysis comparing HRs and absolute RR in three large recent HFrEF trials demonstrated that while the HR suggests a smaller treatment effect in VICTORIA than in the DAPA-HF and PARADIGM-HF trials, a comparison of 12-month event rates for the primary outcome pointed to a comparable benefit across the three trials.[127,128] Given the significant interaction of vericiguat effects according to baseline NT-proBNP levels, a *post hoc* analysis showed an association of vericiguat benefit on the primary outcome in patients with NT-proBNP levels up to 8000 pg/mL, with greatest benefit in patients with NT-proBNP <4000 pg/mL (HR, 0.77, 95% CI, 0.68–0.88).[129]

Vericiguat was evaluated In HFpEF patients in the VITALITY trial,[128] showing no benefit in quality of life and exercise tolerance.[130] Similarly, in the CAPACITY trial, the

sGC stimulator praliciguat was well-tolerated but did neither affect the primary efficacy endpoint of pVO_2 nor other predefined outcome parameters.[131]

Cardiac myosin activators and inhibitors

Omecamtiv mecarbil (GALACTIC-HF, EXPLORER-HCM)

Omecamtiv mecarbil, a cardiac myosin activator that enhances cardiomyocyte contraction, given twice daily on the basis of plasma levels of the drug, significantly reduced the primary endpoint of HF hospitalisation and CV death in patients with HFrEF and a recent HF event (HR, 0.92; 95% CI, 0.86–0.99; P=0.03) (*Figure 3 – see in Packer et al.[115], Armstrong et al.[126] and Teerlink et al.[132]*) but had no impact on any of the secondary outcomes (CV death, change in symptom score, first HF hospitalization, and death from any cause).[132]

A similar compound, *danicamtiv*, increased stroke volume, improved global longitudinal and circumferential strain, decreased LA minimal volume index, and increased LA function index when compared to placebo in a small phase 2a trial in 40 patients with stable HFrEF.[133]

On the other hand, *mavacamten*, a myosin inhibitor, significantly improved the combined primary endpoint of increase in peak oxygen consumption (pVO_2) and reduction in NYHA class in a phase 3 trial in patients with obstructive hypertrophic cardiomyopathy. Also, outflow tract obstruction and health status were improved.[134]

Other therapies

Ferric carboxymaltose (AFFIRM-AHF)

In iron-deficient patients hospitalized for acute HF (AFFIRM-AHF),[135] intravenous ferric carboxymaltose compared to placebo was associated with a trend to reduced total HF hospitalizations and CV death (rate ratio 0.79, 95% CI 0.62–1.01, *P*=0.059). In a pre-specified sensitivity analysis considering the impact of the COVID-19 pandemic, a statistically significant difference in favour of ferric carboxymaltose was reported for the primary endpoint was reported, but not in CV death risk.[136]

MicroRNA-132 inhibition

In a first clinical trial limited by a small number of HF patients, the antisense oligonucleotide drug directed against miR-132, CDR132L,[137] was well tolerated and showed first hints for a cardiac functional improvement.[138]

Comprehensive disease-modifying pharmacological therapies

Using data from the EMPHASIS-HF, PARADIGM-HF, and DAPA-HF trials lifetime gains in survival have been estimated with comprehensive therapy (SV, β-blocker, MRA, and SGLT-2 inhibitor) vs. RAAS and β-blockers in patients with chronic HFrEF.[11,139] The HR for the composite endpoint of CV death or hospitalisation for HF was 0.38 (95% CI 0.30–0.47). Favourable results were also calculated for CV death alone, hospitalization for HF alone, and all-cause mortality. Comprehensive therapy could prolong overall survival 6.3 years in average in a 55-year-old patient. These results support the combination use of SV, β-blockers, mineralocorticoid receptor antagonists, and SGLT-2 inhibitors as a new therapeutic standard.

Device/interventional therapies

Secondary (or functional) mitral regurgitation (COAPT)

Secondary (or functional) mitral regurgitation (SMR) occurs frequently in HFrEF and is associated with progressive symptoms and worse prognosis. If SMR is treated by edge-to-edge repair, patients with optimal result at discharge and 12-month follow-up displayed best outcomes.[140]

Cardiac resynchronization therapy (STOP-CRT)

Cardiac resynchronization therapy (STOP-CRT) is an integral part of treatment in patients with HFrEF, especially with left bundle branch block and wide QRS. In a selected cohort of patients with LVEF >50% during CRT and neurohormonal blockade, the STOP-CRT study investigated the feasibility and safety of neurohormonal blocker withdrawal. The incidence of adverse LV remodelling or clinical outcomes was low after discontinuation of betablockade/RAAS inhibition. However, comorbidities prompted the continuation of neurohormonal blockers in many patients.[141]

In patients with HFrEF who are ineligible for CRT, *baroreflex activation therapy* (BAT) may be useful in addition to optimal drug therapy. In the BeAT-HF study, BAT was safe and significantly improved symptoms, quality of life, exercise capacity, and NT-proBNP.[142] On the basis of these data, BAT was approved in the USA, while ongoing follow-up in the BeAT-HF study will assess effects on hard outcomes.

Specific management issues

Telemedicine and remote monitoring

The role of telemedicine and remote monitoring in the management of HF patients is still controversial. An observational study in three European countries showed that pulmonary artery pressure-guided HF management is feasible and safe and associated with better haemodynamic outcomes and clinical outcomes.[143] Also, preliminary results testing non-invasive remote physiological monitoring from a wearable sensor showed promising results in the early detection of impending HF rehospitalisation.[144] However, different modes of remote monitoring failed to show a benefit in improving treatment, quality of life,[145] or clinical outcomes.[146] Moreover, remote monitoring with a cardiac implanted electronic device increased clinical activity for patients with HF and AF, with no associated reduction in mortality, and conversely, greater risk of CV hospitalisation amongst patients with persistent/permanent AF.[147] In the COVID-19 era, remote monitoring is a useful tool for managing HF patients.[148]

Self-care and palliative care

Self-care is essential in the management of chronic HF. Practical advice for key activities and priorities for

self-care is given in an HFA manuscript.[149] At the end of the HF pathway, palliative care should be introduced early, focusing on symptom management,[150] regardless of prognosis, but actually only a minority in Europe receive it.[151] Providing palliative care substantially reduces hospitalizations, with no clear adverse effect on survival.[152]

Funding

There was no specific funding for the development of this manuscript. J. Bauersachs is supported by the Deutsche Forschungsgemeinschaft, KFO 311, "Advanced cardiac and pulmonary failure: mechanical unloading and repair".

Disclosures: Dr. Bueno reports grants from Instituto de Salud Carlos III, grants from Sociedad Española de Cardiología, grants from Astra-Zeneca, grants and personal fees from Bayer, grants and personal fees from BMS, grants and personal fees from Novartis.

Dr. Moura reports personal fees from Astra Zeneca, personal fees from Vifor, personal fees from Servier, personal fees from Novartis, personal fees from Merck Serono, personal fees from Elly -Lilly, personal fees from Boerhringer-Ingelheim.

Dr. Bauersachs reports personal fees from Abbott, grants and personal fees from Abiomed, personal fees from Astra Zeneca, personal fees from Bayer, personal fees from BMS, personal fees from Boehringer Ingelheim, grants and personal fees from CvRX, personal fees from Daiichi Sankyo, personal fees from Medtronic, personal fees from MSD, personal fees from Novartis, personal fees from Pfizer, personal fees from Servier, grants and personal fees from Vifor, grants from Zoll, personal fees from Cardior. In addition, Dr. Bauersachs is Board Member of Cardior and has a patent PCT/EP2007/008772 with royalties paid, and a patent PCT/EP2009/051986 with royalties paid both on microRNA (miRNA) and downstream targets for diagnostic and therapeutic.

Dr Lancellotti has no relevant disclosures.

References

1. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. *Eur J Heart Fail* 2020;**22**:1342–1356.
2. Sulo G, Igland J, Øverland S, Egeland GM, Roth GA, Vollset SE, Tell GS. Heart failure in Norway, 2000-2014: analysing incident, total and readmission rates using data from the Cardiovascular Disease in Norway (CVDNOR) Project. *Eur J Heart Fail* 2020;**22**:241–248.
3. Uijl A, Koudstaal S, Direk K, Denaxas S, Groenwold RHH, Banerjee A, Hoes AW, Hemingway H, Asselbergs FW. Risk factors for incident heart failure in age- and sex-specific strata: a population-based cohort using linked electronic health records. *Eur J Heart Fail* 2019;**21**:1197–1206.
4. White-Williams C, Rossi LP, Bittner VA, Driscoll A, Durant RW, Granger BB, Graven LJ, Kitko L, Newlin K, Shirey M; on behalf of the American Heart Association Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Epidemiology and Prevention. Addressing social determinants of health in the care of patients with heart failure: a scientific statement from the American Heart Association. *Circulation* 2020;**141**:e841–e863.
5. Velagaleti RS, Larson MG, Enserro D, Song RJ, Vasan RS. Clinical course after a first episode of heart failure: insights from the Framingham Heart Study. *Eur J Heart Fail* 2020;**22**:1768–1776.
6. Tayal B, Fruelund P, Sogaard P, Riahi S, Polcwiartek C, Atwater BD, Gislason G, Risum N, Torp-Pedersen C, Kober L, Kragholm KH. Incidence of heart failure after pacemaker implantation: a nationwide Danish Registry-based follow-up study. *Eur Heart J* 2019;**40**:3641–3648.
7. Barra S, Providência R, Narayanan K, Boveda S, Duehmke R, Garcia R, Leyva F, Roger V, Jouven X, Agarwal S, Levy WC, Marijon E. Time trends in sudden cardiac death risk in heart failure patients with cardiac resynchronization therapy: a systematic review. *Eur Heart J* 2020;**41**:1976–1986.
8. Motiejūnaitė J, Akiyama E, Cohen-Solal A, Maggioni AP, Mueller C, Choi D-J, Kavoliūnienė A, Čelutkienė J, Parenica J, Lassus J, Kajimoto K, Sato N, Miró Ò, Peacock WF, Matsue Y, Voors AA, Lam CSP, Ezekowitz JA, Ahmed A, Fonarow GC, Gayat E, Regitz-Zagrosek V, Mebazaa A. The association of long-term outcome and biological sex in patients with acute heart failure from different geographic regions. *Eur Heart J* 2020;**41**:1357–1364.
9. Parizo JT, Kohsaka S, Sandhu AT, Patel J, Heidenreich PA. Trends in readmission and mortality rates following heart failure hospitalization in the Veterans Affairs Health Care System from 2007 to 2017. *JAMA Cardiol* 2020;**5**:1042–1047.
10. Butt JH, Fosbøl EL, Gerds TA, Andersson C, McMurray JJV, Petrie MC, Gustafsson F, Madelaire C, Kristensen SL, Gislason GH, Torp-Pedersen C, Køber L, Schou M. Readmission and death in patients admitted with new-onset versus worsening of chronic heart failure: insights from a nationwide cohort. *Eur J Heart Fail* 2020;**22**:1777–1785.
11. Jhund PS. The recurring problem of heart failure hospitalisations. *Eur J Heart Fail* 2020;**22**:249–250.
12. Čelutkienė J, Lainscak M, Anderson L, Gayat E, Grapsa J, Harjola V-P, Manka R, Nihoyannopoulos P, Filardi PP, Vrettou R, Anker SD, Filippatos G, Mebazaa A, Metra M, Piepoli M, Ruschitzka F, Zamorano JL, Rosano G, Seferovic P. Imaging in patients with suspected acute heart failure: timeline approach position statement on behalf of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:181–195.
13. Paterson DI, Wells G, Erthal F, Mielniczuk L, O'Meara E, White J, Connelly KA, Knuuti J, Radja M, Laine M, Chow BJW, Kandolin R, Chen L, Dick A, Dennie C, Garrard L, Ezekowitz J, Beanlands R, Chan K-L, Brown P, Kartikainen J, Hedman M, Larose E, Pibarot P, Tardif J-C, Leipsic J, Kiess M, Howarth A, Hanninen H, Duchesne L, Freeman M, Leong-Poi H, Wright G, Ukkonen H. OUTSMART HF: a randomized controlled trial of routine versus selective cardiac magnetic resonance for patients with nonischemic heart failure (IMAGE-HF 1B). *Circulation* 2020;**141**:818–827.
14. Quarta G, Gori M, Iorio A, D'Elia E, Moon JC, Iacovoni A, Burocchi S, Schelbert EB, Brambilla P, Sironi S, Caravita S, Parati G, Gavazzi A, Maisel AS, Butler J, Lam CSP, Senni M. Cardiac magnetic resonance in heart failure with preserved ejection fraction: myocyte, interstitium, microvascular, and metabolic abnormalities. *Eur J Heart Fail* 2020;**22**:1065–1075.
15. Pezel T, Viallon M, Croisille P, Sebbag L, Bochaton T, Garot J, et al. Imaging interstitial fibrosis, left ventricular remodeling, and function in stage A and B heart failure. *JACC Cardiovasc Imaging* 2020. 10.1016/j.jcmg.2020.05.036 (accessed 24 December 2020).
16. Emrich T, Hahn F, Fleischmann D, Halfmann MC, Düber C, Varga-Szemes A, Escher F, Pefani E, Münzel T, Schultheiss H-P, Kreitner K-F, Wenzel P. T1 and T2 mapping to detect chronic inflammation in cardiac magnetic resonance imaging in heart failure with reduced ejection fraction. *ESC Heart Fail* 2020;**7**:2544–2552.
17. Chamsi-Pasha MA, Zhan Y, Debs D, Shah DJ. CMR in the evaluation of diastolic dysfunction and phenotyping of HFpEF: current role and future perspectives. *JACC Cardiovasc Imaging* 2020;**13**:283–296.
18. Putko BN, Savu A, Kaul P, Ezekowitz J, Dyck JR, Anderson TJ, et al. Left atrial remodelling, mid-regional pro-atrial natriuretic

peptide, and prognosis across a range of ejection fractions in heart failure. *Eur Heart J Cardiovasc Imaging* 2020. 10.1093/ehjci/jeaa041(accessed 24 December 2020).
19. Guazzi M, Ghio S, Adir Y. Pulmonary hypertension in HFpEF and HFrEF: JACC review topic of the week. *J Am Coll Cardiol* 2020;**76**:1102–1111.
20. Lin T-T, Wang Y-C, Juang J-MJ, Hwang J-J, Wu C-K. Application of the newest European Association of Cardiovascular Imaging Recommendation regarding the long-term prognostic relevance of left ventricular diastolic function in heart failure with preserved ejection fraction. *Eur Radiol* 2020;**30**:630–639.
21. Romano G, Magro S, Agnese V, Mina C, Di Gesaro G, Falletta C, Pasta S, Raffa G, Baravoglia CMH, Novo G, Gandolfo C, Clemenza F, Bellavia D. Echocardiography to estimate high filling pressure in patients with heart failure and reduced ejection fraction. *ESC Heart Fail* 2020;**7**:2268–2277.
22. Tanacli R, Hashemi D, Neye M, Motzkus LA, Blum M, Tahirovic E, Dordevic A, Kraft R, Zamani SM, Pieske B, Düngen H-D, Kelle S. Multilayer myocardial strain improves the diagnosis of heart failure with preserved ejection fraction. *ESC Heart Fail* 2020;**7**:3240–3245.
23. Selvaraj S, Myhre PL, Vaduganathan M, Claggett BL, Matsushita K, Kitzman DW, Borlaug BA, Shah AM, Solomon SD. Application of diagnostic algorithms for heart failure with preserved ejection fraction to the community. *JACC Heart Fail* 2020;**8**:640–653.
24. Yoshihisa A, Sato Y, Kanno Y, Takiguchi M, Yokokawa T, Abe S, Misaka T, Sato T, Oikawa M, Kobayashi A, Yamaki T, Kunii H, Takeishi Y. Prognostic impacts of changes in left ventricular ejection fraction in heart failure patients with preserved left ventricular ejection fraction. *Open Heart* 2020;**7**:e001112.
25. Wang C-L, Chan Y-H, Wu VC-C, Lee H-F, Hsiao F-C, Chu P-H. Incremental prognostic value of global myocardial work over ejection fraction and global longitudinal strain in patients with heart failure and reduced ejection fraction. *Eur Heart J Cardiovasc Imaging* 2020. doi: 10.1093/ehjci/jeaa162.
26. Mazzetti S, Scifo C, Abete R, Margonato D, Chioffi M, Rossi J, Pisani M, Passafaro G, Grillo M, Poggio D, Mortara A. Short-term echocardiographic evaluation by global longitudinal strain in patients with heart failure treated with sacubitril/valsartan. *ESC Heart Fail* 2020;**7**:964–972.
27. Zhou W, Brown JM, Bajaj NS, Chandra A, Divakaran S, Weber B, Bibbo CF, Hainer J, Taqueti VR, Dorbala S, Blankstein R, Adler D, O'Gara P, Di Carli MF. Hypertensive coronary microvascular dysfunction: a subclinical marker of end organ damage and heart failure. *Eur Heart J* 2020;**41**:2366–2375.
28. Escaned J, Lerman LO. Coronary microcirculation and hypertensive heart failure. *Eur Heart J* 2020;**41**:2376–2378.
29. Seo M, Yamada T, Tamaki S, Watanabe T, Morita T, Furukawa Y, et al. Prognostic significance of cardiac I-123-metaiodobenzylguanidine imaging in patients with reduced, mid-range, and preserved left ventricular ejection fraction admitted for acute decompensated heart failure: a prospective study in Osaka Prefectural Acute. *Eur Heart J Cardiovasc Imaging* 2020. https://doi:10.1093/ehjci/jeaa025 (accessed 24 December 2020).
30. Cunningham JW, Claggett BL, O'Meara E, Prescott MF, Pfeffer MA, Shah SJ, Redfield MM, Zannad F, Chiang L-M, Rizkala AR, Shi VC, Lefkowitz MP, Rouleau J, McMurray JJV, Solomon SD, Zile MR. Effect of sacubitril/valsartan on biomarkers of extracellular matrix regulation in patients with HFpEF. *J Am Coll Cardiol* 2020;**76**:503–514.
31. Aimo A, Januzzi JL, Vergaro G, Richards AM, Lam CSP, Latini R, Anand IS, Cohn JN, Ueland T, Gullestad L, Aukrust P, Brunner-La Rocca H-P, Bayes-Genis A, Lupón J, Boer RA, Takeishi Y, Egstrup M, Gustafsson I, Gaggin HK, Eggers KM, Huber K, Gamble GD, Ling LH, Leong KTG, Yeo PSD, Ong HY, Jaufeerally F, Ng TP, Troughton R, Doughty RN, Passino C, Emdin M. Circulating levels and prognostic value of soluble ST2 in heart failure are less influenced by age than N-terminal pro-B-type natriuretic peptide and high-sensitivity troponin T. *Eur J Heart Fail* 2020;**22**:2078–2088.
32. Ferreira JP, Ouwerkerk W, Santema BT, van Veldhuisen DJ, Lang CC, Ng LL, et al. Differences in biomarkers and molecular pathways according to age for patients with HFrEF. *Cardiovasc Res* 2020. hhtps://doi.org/10.1093/cvr/cvaa279.
33. Möckel M, Boer RA, Slagman AC, Haehling S, Schou M, Vollert JO, Wiemer JC, Ebmeyer S, Martín-Sánchez FJ, Maisel AS, Giannitsis E. Improve management of acute heart failure with ProcAlCiTonin in EUrope: results of the randomized clinical trial IMPACT EU Biomarkers in Cardiology (BIC) 18. *Eur J Heart Fail* 2020;**22**:267–275.
34. Bayes-Genis A, Liu PP, Lanfear DE, de Boer RA, González A, Thum T, Emdin M, Januzzi JL. Omics phenotyping in heart failure: the next frontier. *Eur Heart J* 2020;**41**:3477–3484.
35. McGranaghan P, Düngen H-D, Saxena A, Rubens M, Salami J, Radenkovic J, Bach D, Apostolovic S, Loncar G, Zdravkovic M, Tahirovic E, Veskovic J, Störk S, Veledar E, Pieske B, Edelmann F, Trippel TD. Incremental prognostic value of a novel metabolite-based biomarker score in congestive heart failure patients. *ESC Heart Fail* 2020;**7**:3029–3039.
36. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu N-H, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;**181**:271–280.e8.
37. Inciardi RM, Adamo M, Lupi L, Cani DS, Di Pasquale M, Tomasoni D, Italia L, Zaccone G, Tedino C, Fabbricatore D, Curnis A, Faggiano P, Gorga E, Lombardi CM, Milesi G, Vizzardi E, Volpini M, Nodari S, Specchia C, Maroldi R, Bezzi M, Metra M. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. *Eur Heart J* 2020;**41**:1821–1829.
38. Sama IE, Ravera A, Santema BT, van Goor H, ter Maaten JM, Cleland JGF, Rienstra M, Friedrich AW, Samani NJ, Ng LL, Dickstein K, Lang CC, Filippatos G, Anker SD, Ponikowski P, Metra M, van Veldhuisen DJ, Voors AA. Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin-angiotensin-aldosterone inhibitors. *Eur Heart J* 2020;**41**:1810–1817.
39. Tomasoni D, Italia L, Adamo M, Inciardi RM, Lombardi CM, Solomon SD, Metra M. COVID-19 and heart failure: from infection to inflammation and angiotensin II stimulation. Searching for evidence from a new disease. *Eur J Heart Fail* 2020;**22**:957–966.
40. de Abajo FJ, Rodríguez-Martín S, Lerma V, Mejía-Abril G, Aguilar M, García-Luque A, Laredo L, Laosa O, Centeno-Soto GA, Ángeles Gálvez M, Puerro M, González-Rojano E, Pedraza L, de Pablo I, Abad-Santos F, Rodríguez-Mañas L, Gil M, Tobías A, Rodríguez-Miguel A, Rodríguez-Puyol D, Barreira-Hernandez D, Zubiaur P, Santos-Molina E, Pintos-Sánchez E, Navares-Gómez M, Aparicio RM, García-Rosado V, Gutiérrez-Ortega C, Pérez C, Ascaso A, Elvira C. Use of renin-angiotensin-aldosterone system inhibitors and risk of COVID-19 requiring admission to hospital: a case-population study. *Lancet* 2020;**395**:1705–1714.
41. Bean DM, Kraljevic Z, Searle T, Bendayan R, Kevin O, Pickles A, Folarin A, Roguski L, Noor K, Shek A, Zakeri R, Shah AM, Teo JTH, Dobson RJB. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are not associated with severe COVID-19 infection in a multi-site UK acute hospital trust. Eur J Heart Fail 2020;22:967–974.
42. Reynolds HR, Adhikari S, Pulgarin C, Troxel AB, Iturrate E, Johnson SB, Hausvater A, Newman JD, Berger JS, Bangalore S, Katz SD, Fishman GI, Kunichoff D, Chen Y, Ogedegbe G, Hochman JS. Renin-angiotensin-aldosterone system inhibitors and risk of Covid-19. *N Engl J Med* 2020;**382**:2441–2448.
43. Mancia G, Rea F, Ludergnani M, Apolone G, Corrao G. Renin-angiotensin-aldosterone system blockers and the risk of Covid-19. *N Engl J Med* 2020;**382**:2431–2440.
44. Rey JR, Caro-Codón J, Rosillo SO, Iniesta ÁM, Castrejón-Castrejón S, Marco-Clement I, et al. Heart failure in Covid-19 patients: prevalence, incidence and prognostic implications. *Eur J Heart Fail* 2020. 10.1002/ejhf.1990.
45. Bromage DI, Cannatà A, Rind IA, Gregorio C, Piper S, Shah AM, McDonagh TA. The impact of COVID-19 on heart failure hospitalization and management: report from a Heart Failure

Unit in London during the peak of the pandemic. *Eur J Heart Fail* 2020;**22**:978–984.
46. Andersson C, Gerds T, Fosbøl E, Phelps M, Andersen J, Lamberts M, et al. Incidence of new-onset and worsening heart failure before and after the COVID-19 epidemic lockdown in Denmark: a nationwide cohort study. *Circ Heart Fail* 2020;**13**:e007274.
47. Cannata A, Bromage DI, Rind IA, Gregorio C, Bannister C, Albarjas M, et al. Temporal trends in decompensated heart failure and outcomes during COVID-19: a multisite report from heart failure referral centres in London. *Eur J Heart Fail* 2020. 10.1002/ejhf.1986 (accessed 24 December 2020).
48. Zhang Y, Coats AJS, Zheng Z, Adamo M, Ambrosio G, Anker SD, Butler J, Xu D, Mao J, Khan MS, Bai L, Mebazaa A, Ponikowski P, Tang Q, Ruschitzka F, Seferovic P, Tschöpe C, Zhang S, Gao C, Zhou S, Senni M, Zhang J, Metra M. Management of heart failure patients with COVID-19: a joint position paper of the Chinese Heart Failure Association & National Heart Failure Committee and the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:941–956.
49. D'Amario D, Restivo A, Canonico F, Rodolico D, Mattia G, Francesco B, Vergallo R, Trani C, Aspromonte N, Crea F. Experience of remote cardiac care during the COVID-19 pandemic: the V-LAPTM device in advanced heart failure. *Eur J Heart Fail* 2020;**22**:1050–1052.
50. Anker SD, Butler J, Khan MS, Abraham WT, Bauersachs J, Bocchi E, Bozkurt B, Braunwald E, Chopra VK, Cleland JG, Ezekowitz J, Filippatos G, Friede T, Hernandez AF, Lam CSP, Lindenfeld JAnn, McMurray JJV, Mehra M, Metra M, Packer M, Pieske B, Pocock SJ, Ponikowski P, Rosano GMC, Teerlink JR, Tsutsui H, Van Veldhuisen DJ, Verma S, Voors AA, Wittes J, Zannad F, Zhang J, Seferovic P, Coats AJS. Conducting clinical trials in heart failure during (and after) the COVID-19 pandemic: an Expert Consensus Position Paper from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J* 2020;**41**:2109–2117.
51. Truby LK, O'Connor C, Fiuzat M, Stebbins A, Coles A, Patel CB, Granger B, Pagidipati N, Agarwal R, Rymer J, Lowenstern A, Douglas PS, Tulsky J, Rogers JG, Mentz RJ. Sex differences in quality of life and clinical outcomes in patients with advanced heart failure: insights from the PAL-HF trial. *Circ Heart Fail* 2020;**13**:e006134.
52. Lainščak M, Milinković I, Polovina M, Crespo-Leiro MG, Lund LH, Anker SD, Laroche C, Ferrari R, Coats AJS, McDonagh T, Filippatos G, Maggioni AP, Piepoli MF, Rosano GMC, Ruschitzka F, Simić D, Ašanin M, Eicher J-C, Yilmaz MB, Seferović PM; on behalf of the European Society of Cardiology Heart Failure Long-Term Registry Investigators Group. Sex- and age-related differences in the management and outcomes of chronic heart failure: an analysis of patients from the ESC HFA EORP Heart Failure Long-Term Registry. *Eur J Heart Fail* 2020;**22**:92–102.
53. Rossello X, Ferreira JP, Pocock SJ, McMurray JJV, Solomon SD, Lam CSP, Girerd N, Pitt B, Rossignol P, Zannad F. Sex differences in mineralocorticoid receptor antagonist trials: a pooled analysis of three large clinical trials. *Eur J Heart Fail* 2020;**22**:834–844.
54. Dewan P, Jackson A, Lam CSP, Pfeffer MA, Zannad F, Pitt B, Solomon SD, McMurray JJV. Interactions between left ventricular ejection fraction, sex and effect of neurohumoral modulators in heart failure. *Eur J Heart Fail* 2020;**22**:898–901.
55. Reza N, Tahhan AS, Mahmud N, DeFilippis EM, Alrohaibani A, Vaduganathan M, et al. Representation of women authors in international heart failure guidelines and contemporary clinical trials. *Circ Heart Fail* 2020;**13**:e006605.
56. Pandey A, Vaduganathan M, Arora S, Qamar A, Mentz RJ, Shah SJ, Chang PP, Russell SD, Rosamond WD, Caughey MC. Temporal trends in prevalence and prognostic implications of comorbidities among patients with acute decompensated heart failure: the ARIC study community surveillance. *Circulation* 2020;**142**:230–243.
57. Khan MS, Samman Tahhan A, Vaduganathan M, Greene SJ, Alrohaibani A, Anker SD, Vardeny O, Fonarow GC, Butler J. Trends in prevalence of comorbidities in heart failure clinical trials. *Eur J Heart Fail* 2020;**22**:1032–1042.
58. Bhatt AS, Ambrosy AP, Dunning A, DeVore AD, Butler J, Reed S, Voors A, Starling R, Armstrong PW, Ezekowitz JA, Metra M, Hernandez AF, O'Connor CM, Mentz RJ. The burden of non-cardiac comorbidities and association with clinical outcomes in an acute heart failure trial—insights from ASCEND-HF. *Eur J Heart Fail* 2020;**22**:1022–1031.
59. Aimo A, Barison A, Castiglione V, Emdin M. The unbearable underreporting of comorbidities in heart failure clinical trials. *Eur J Heart Fail* 2020;**22**:1043–1044.
60. Docherty KF, Shen L, Castagno D, Petrie MC, Abraham WT, Böhm M, Desai AS, Dickstein K, Køber LV, Packer M, Rouleau JL, Solomon SD, Swedberg K, Vazir A, Zile MR, Jhund PS, McMurray JJV. Relationship between heart rate and outcomes in patients in sinus rhythm or atrial fibrillation with heart failure and reduced ejection fraction. *Eur J Heart Fail* 2020;**22**:528–538.
61. Al-Khatib SM, Benjamin EJ, Albert CM, Alonso A, Chauhan C, Chen P-S, Curtis AB, Desvigne-Nickens P, Ho JE, Lam CSP, Link MS, Patton KK, Redfield MM, Rienstra M, Rosenberg Y, Schnabel R, Spertus JA, Stevenson LW, Hills MT, Voors AA, Cooper LS, Go AS. Advancing research on the complex interrelations between atrial fibrillation and heart failure: a report from a US National Heart, Lung, and Blood Institute Virtual Workshop. *Circulation* 2020;**141**:1915–1926.
62. Packer M. Do most patients with obesity or type 2 diabetes, and atrial fibrillation, also have undiagnosed heart failure? A critical conceptual framework for understanding mechanisms and improving diagnosis and treatment. *Eur J Heart Fail* 2020;**22**:214–227.
63. Bauersachs J, Veltmann C. Heart rate control in heart failure with reduced ejection fraction: the bright and the dark side of the moon. *Eur J Heart Fail* 2020;**22**:539–542.
64. Mullens W, Damman K, Testani JM, Martens P, Mueller C, Lassus J, Tang WHW, Skouri H, Verbrugge FH, Orso F, Hill L, Ural D, Lainscak M, Rossignol P, Metra M, Mebazaa A, Seferovic P, Ruschitzka F, Coats A. Evaluation of kidney function throughout the heart failure trajectory—a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:584–603.
65. Cox ZL, Hung R, Lenihan DJ, Testani JM. Diuretic strategies for loop diuretic resistance in acute heart failure: the 3T trial. *JACC Heart Fail* 2020;**8**:157–168.
66. Carubelli V, Zhang Y, Metra M, Lombardi C, Felker GM, Filippatos G, O'Connor CM, Teerlink JR, Simmons P, Segal R, Malfatto G, La Rovere MT, Li D, Han X, Yuan Z, Yao Y, Li B, Lau LF, Bianchi G, Zhang J; the Istaroxime ADHF Trial Group. Treatment with 24 hour istaroxime infusion in patients hospitalised for acute heart failure: a randomised, placebo-controlled trial. *Eur J Heart Fail* 2020;**22**:1684–1693.
67. Harjola V-P, Parissis J, Bauersachs J, Brunner-La Rocca H-P, Bueno H, Čelutkienė J, Chioncel O, Coats AJS, Collins SP, Boer RA, Filippatos G, Gayat E, Hill L, Laine M, Lassus J, Lommi J, Masip J, Mebazaa A, Metra M, Miró Ò, Mortara A, Mueller C, Mullens W, Peacock WF, Pentikäinen M, Piepoli MF, Polyzogopoulou E, Rudiger A, Ruschitzka F, Seferovic P, Sionis A, Teerlink JR, Thum T, Varpula M, Weinstein JM, Yilmaz MB. Acute coronary syndromes and acute heart failure: a diagnostic dilemma and high-risk combination. A statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:1298–1314.
68. Gorenek B, Halvorsen S, Kudaiberdieva G, Bueno H, Van Gelder IC, Lettino M, et al. Atrial fibrillation in acute heart failure: a position statement from the Acute Cardiovascular Care Association and European Heart Rhythm Association of the European Society of Cardiology. *Eur Heart J Acute Cardiovasc Care* 2020;**9**:348–357.
69. Aissaoui N, Puymirat E, Delmas C, Ortuno S, Durand E, Bataille V, Drouet E, Bonello L, Bonnefoy-Cudraz E, Lesmeles G, Guerot E, Schiele F, Simon T, Danchin N. Trends in cardiogenic shock complicating acute myocardial infarction. *Eur J Heart Fail* 2020;**22**:664–672.
70. Hanson ID, Tagami T, Mando R, Kara Balla A, Dixon SR, Timmis S, Almany S, Naidu SS, Baran D, Lemor A, Gorgis S, O'Neill W, Basir MB; National Cardiogenic Shock Investigators. SCAI shock classification in acute myocardial infarction: insights from the

National Cardiogenic Shock Initiative. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv* 2020;**96**:1137–1142.
71. Zeymer U, Bueno H, Granger CB, Hochman J, Huber K, Lettino M, Price S, Schiele F, Tubaro M, Vranckx P, Zahger D, Thiele H. Acute Cardiovascular Care Association position statement for the diagnosis and treatment of patients with acute myocardial infarction complicated by cardiogenic shock: a document of the Acute Cardiovascular Care Association of the European Society of Car. *Eur Heart J Acute Cardiovasc Care* 2020;**9**:183–197.
72. Chioncel O, Parissis J, Mebazaa A, Thiele H, Desch S, Bauersachs J, Harjola V-P, Antohi E-L, Arrigo M, Gal TB, Celutkiene J, Collins SP, DeBacker D, Iliescu VA, Jankowska E, Jaarsma T, Keramida K, Lainscak M, Lund LH, Lyon AR, Masip J, Metra M, Miro O, Mortara A, Mueller C, Mullens W, Nikolaou M, Piepoli M, Price S, Rosano G, Vieillard-Baron A, Weinstein JM, Anker SD, Filippatos G, Ruschitzka F, Coats AJS, Seferovic P. Epidemiology, pathophysiology and contemporary management of cardiogenic shock—a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:1315–1341.
73. Karason K, Lund LH, Dalén M, Björklund E, Grinnemo K, Braun O, Nilsson J, Wal H, Holm J, Hübbert L, Lindmark K, Szabo B, Holmberg E, Dellgren G; the SweVAD Investigators. Randomized trial of a left ventricular assist device as destination therapy versus guideline-directed medical therapy in patients with advanced heart failure. Rationale and design of the SWEdish evaluation of left Ventricular Assist Device (SweVAD) trial. *Eur J Heart Fail* 2020;**22**:739–750.
74. Phan D, Duan L, Ng A, Shen AY-J, Lee M-S. Characteristics and outcomes of pregnant women with cardiomyopathy stratified by etiologies: a population-based study. *Int J Cardiol* 2020;**305**:87–91.
75. Bauersachs J, König T, Meer P, Petrie MC, Hilfiker-Kleiner D, Mbakwem A, Hamdan R, Jackson AM, Forsyth P, Boer RA, Mueller C, Lyon AR, Lund LH, Piepoli MF, Heymans S, Chioncel O, Anker SD, Ponikowski P, Seferovic PM, Johnson MR, Mebazaa A, Sliwa K. Pathophysiology, diagnosis and management of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Study Group on peripartum cardiomyopathy. *Eur J Heart Fail* 2019;**21**:827–843.
76. Sliwa K, Bauersachs J, Coats AJS. The European Society of Cardiology Heart Failure Association Study Group on Peripartum Cardiomyopathy—what has been achieved in 10 years. *Eur J Heart Fail* 2020;**22**:1060–1064.
77. Sliwa K, Petrie MC, van der Meer P, Mebazaa A, Hilfiker-Kleiner D, Jackson AM, Maggioni AP, Laroche C, Regitz-Zagrosek V, Schaufelberger M, Tavazzi L, Roos-Hesselink JW, Seferovic P, van Spaendonck-Zwarts K, Mbakwem A, Böhm M, Mouquet F, Pieske B, Johnson MR, Hamdan R, Ponikowski P, Van Veldhuisen DJ, McMurray JJV, Bauersachs J. Clinical presentation, management, and 6-month outcomes in women with peripartum cardiomyopathy: an ESC EORP registry. *Eur Heart J* 2020;**41**:3787–3797.
78. Davis MB, Arany Z, McNamara DM, Goland S, Elkayam U. Peripartum cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol* 2020;**75**:207–221.
79. Wilcox JE, Fang JC, Margulies KB, Mann DL. Heart Failure With recovered left ventricular ejection fraction: JACC Scientific Expert Panel. *J Am Coll Cardiol* 2020;**76**:719–734.
80. Curigliano G, Lenihan D, Fradley M, Ganatra S, Barac A, Blaes A, Herrmann J, Porter C, Lyon AR, Lancellotti P, Patel A, DeCara J, Mitchell J, Harrison E, Moslehi J, Witteles R, Calabro MG, Orecchia R, de Azambuja E, Zamorano JL, Krone R, Iakobishvili Z, Carver J, Armenian S, Ky B, Cardinale D, Cipolla CM, Dent S, Jordan K. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. *Ann Oncol Off J Eur Soc Med Oncol* 2020;**31**:171–190.
81. Keramida K, Farmakis D, López Fernández T, Lancellotti P. Focused echocardiography in cardio-oncology. *Echocardiography* 2020;**37**:1149–1158.
82. Harries I, Liang K, Williams M, Berlot B, Biglino G, Lancellotti P, Plana JC, Bucciarelli-Ducci C. Magnetic resonance imaging to detect cardiovascular effects of cancer therapy. *JACC CardioOncology* 2020;**2**:270–292.
83. Zhang L, Awadalla M, Mahmood SS, Nohria A, Hassan MZO, Thuny F, Zlotoff DA, Murphy SP, Stone JR, Golden DLA, Alvi RM, Rokicki A, Jones-O'Connor M, Cohen JV, Heinzerling LM, Mulligan C, Armanious M, Barac A, Forrestal BJ, Sullivan RJ, Kwong RY, Yang EH, Damrongwatanasuk R, Chen CL, Gupta D, Kirchberger MC, Moslehi JJ, Coelho-Filho OR, Ganatra S, Rizvi MA, Sahni G, Tocchetti CG, Mercurio V, Mahmoudi M, Lawrence DP, Reynolds KL, Weinsaft JW, Baksi AJ, Ederhy S, Groarke JD, Lyon AR, Fradley MG, Thavendiranathan P, Neilan TG. Cardiovascular magnetic resonance in immune checkpoint inhibitor-associated myocarditis. *Eur Heart J* 2020;**41**:1733–1743.
84. Border WL, Sachdeva R, Stratton KL, Armenian SH, Bhat A, Cox DE, Leger KJ, Leisenring WM, Meacham LR, Sadak KT, Sivanandam S, Nathan PC, Chow EJ. Longitudinal changes in echocardiographic parameters of cardiac function in pediatric cancer survivors. *JACC CardioOncology* 2020;**2**:26–37.
85. López-Sendón J, Álvarez-Ortega C, Zamora Auñon P, Buño Soto A, Lyon AR, Farmakis D, Cardinale D, Canales Albendea M, Feliu Batlle J, Rodríguez Rodríguez I, Rodríguez Fraga O, Albaladejo A, Mediavilla G, González-Juanatey JR, Martínez Monzonis A, Gómez Prieto P, González-Costello J, Serrano Antolín JM, Cadenas Chamorro R, López Fernández T. Classification, prevalence, and outcomes of anticancer therapy-induced cardiotoxicity: the CARDIOTOX registry. *Eur Heart J* 2020;**41**:1720–1729.
86. Reddy YNV, Obokata M, Wiley B, Koepp KE, Jorgenson CC, Egbe A, Melenovsky V, Carter RE, Borlaug BA. The haemodynamic basis of lung congestion during exercise in heart failure with preserved ejection fraction. *Eur Heart J* 2019;**40**:3721–3730.
87. Obokata M, Kane GC, Reddy YNV, Melenovsky V, Olson TP, Jarolim P, Borlaug BA. The neurohormonal basis of pulmonary hypertension in heart failure with preserved ejection fraction. *Eur Heart J* 2019;**40**:3707–3717.
88. Padang R, Chandrashekar N, Indrabhinduwat M, Scott CG, Luis SA, Chandrasekaran K, Michelena HI, Nkomo VT, Pislaru SV, Pellikka PA, Kane GC. Aetiology and outcomes of severe right ventricular dysfunction. *Eur Heart J* 2020;**41**:1273–1282.
89. Patel D, Trulock K, Kumar A, Kiehl E, Toro S, Moennich LA, Gorodeski E, Hussein A, Cantillon D, Tarakji KG, Niebauer M, Wazni O, Varma N, Wilkoff B, Rickard JW. Baseline right ventricular dysfunction predicts worse outcomes in patients undergoing cardiac resynchronization therapy implantation. *J Card Fail* 2020;**26**:227–232.
90. Rohde LE, Chatterjee NA, Vaduganathan M, Claggett B, Packer M, Desai AS, Zile M, Rouleau J, Swedberg K, Lefkowitz M, Shi V, McMurray JJV, Solomon SD. Sacubitril/valsartan and sudden cardiac death according to implantable cardioverter-defibrillator use and heart failure cause: a PARADIGM-HF analysis. *JACC Heart Fail* 2020;**8**:844–855.
91. Lee S, Oh J, Kim H, Ha J, Chun K-h, Lee CJ, Park S, Lee S-H, Kang S-M. Sacubitril/valsartan in patients with heart failure with reduced ejection fraction with end-stage of renal disease. *ESC Heart Fail* 2020;**7**:1125–1129.
92. Mann DL, Greene SJ, Givertz MM, Vader JM, Starling RC, Ambrosy AP, Shah P, McNulty SE, Mahr C, Gupta D, Redfield MM, Lala A, Lewis GD, Mohammed SF, Gilotra NA, DeVore AD, Gorodeski EZ, Desvigne-Nickens P, Hernandez AF, Braunwald E. Sacubitril/valsartan in advanced heart failure with reduced ejection fraction: rationale and design of the lIFE trial. *JACC Heart Fail* 2020;**8**:789–999.
93. McMurray JJV, Jackson AM, Lam CSP, Redfield MM, Anand IS, Ge J, Lefkowitz MP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Rizkala AR, Sabarwal SV, Shah AM, Shah SJ, Shi VC, van Veldhuisen DJ, Zannad F, Zile MR, Cikes M, Goncalvesova E, Katova T, Kosztin A, Lelonek M, Sweitzer N, Vardeny O, Claggett B, Jhund PS, Solomon SD. Effects of sacubitril-valsartan versus valsartan in women compared with men with heart failure and preserved ejection fraction: insights from PARAGON-HF. *Circulation* 2020;**141**:338–351.
94. Vaduganathan M, Claggett BL, Desai AS, Anker SD, Perrone SV, Janssens S, Milicic D, Arango JL, Packer M, Shi VC,

Lefkowitz MP, McMurray JJV, Solomon SD. Prior heart failure hospitalization, clinical outcomes, and response to sacubitril/valsartan compared with valsartan in HFpEF. *J Am Coll Cardiol* 2020;**75**:245–254.
95. Selvaraj S, Claggett BL, Böhm M, Anker SD, Vaduganathan M, Zannad F, Pieske B, Lam CSP, Anand IS, Shi VC, Lefkowitz MP, McMurray JJV, Solomon SD. Systolic blood pressure in heart failure with preserved ejection fraction treated with sacubitril/valsartan. *J Am Coll Cardiol* 2020;**75**:1644–1656.
96. Mc Causland FR, Lefkowitz MP, Claggett B, Anavekar NS, Senni M, Gori M, Jhund PS, McGrath MM, Packer M, Shi V, Van Veldhuisen DJ, Zannad F, Comin-Colet J, Pfeffer MA, McMurray JJV, Solomon SD. Angiotensin-neprilysin inhibition and renal outcomes in heart failure with preserved ejection fraction. *Circulation* 2020;**142**:1236–1245.
97. Selvaraj S, Claggett BL, Pfeffer MA, Desai AS, Mc Causland FR, McGrath MM, Anand IS, Veldhuisen DJ, Kober L, Janssens S, Cleland JGF, Pieske B, Rouleau JL, Zile MR, Shi VC, Lefkowitz MP, McMurray JJV, Solomon SD. Serum uric acid, influence of sacubitril/valsartan, and cardiovascular outcomes in heart failure with preserved ejection fraction: PARAGON-HF. *Eur J Heart Fail* 2020;**22**:2093–2101.
98. Kuno T, Ueyama H, Fujisaki T, Briasouli A, Takagi H, Briasoulis A. Meta-analysis evaluating the effects of renin-angiotensin-aldosterone system blockade on outcomes of heart failure with preserved ejection fraction. *Am J Cardiol* 2020;**125**:1187–1193.
99. Vaduganathan M, Jhund PS, Claggett BL, Packer M, Widimský J, Seferovic P, Rizkala A, Lefkowitz M, Shi V, McMurray JJV, Solomon SD. A putative placebo analysis of the effects of sacubitril/valsartan in heart failure across the full range of ejection fraction. *Eur Heart J* 2020;**41**:2356–2362.
100. Böhm M, Bewarder Y, Kindermann I. Ejection fraction in heart failure revisited—where does the evidence start? *Eur Heart J* 2020;**41**:2363–2365.
101. Seferović PM, Fragasso G, Petrie M, Mullens W, Ferrari R, Thum T, Bauersachs J, Anker SD, Ray R, Çavuşoğlu Y, Polovina M, Metra M, Ambrosio G, Prasad K, Seferović J, Jhund PS, Dattilo G, Čelutkiene J, Piepoli M, Moura B, Chioncel O, Ben Gal T, Heymans S, Boer RA, Jaarsma T, Hill L, Lopatin Y, Lyon AR, Ponikowski P, Lainščak M, Jankowska E, Mueller C, Cosentino F, Lund L, Filippatos GS, Ruschitzka F, Coats AJS, Rosano GMC. Sodium-glucose co-transporter 2 inhibitors in heart failure: beyond glycaemic control. The position paper of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:1495–1503.
102. Seferović PM, Coats AJS, Ponikowski P, Filippatos G, Huelsmann M, Jhund PS, Polovina MM, Komajda M, Seferović J, Sari I, Cosentino F, Ambrosio G, Metra M, Piepoli M, Chioncel O, Lund LH, Thum T, De Boer RA, Mullens W, Lopatin Y, Volterrani M, Hill L, Bauersachs J, Lyon A, Petrie MC, Anker S, Rosano GMC. European Society of Cardiology/Heart Failure Association position paper on the role and safety of new glucose-lowering drugs in patients with heart failure. *Eur J Heart Fail* 2020;**22**:196–213.
103. Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, Charbonnel B, Frederich R, Gallo S, Cosentino F, Shih WJ, Gantz I, Terra SG, Cherney DZI, McGuire DK. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med* 2020;**383**:1425–1435.
104. Cosentino F, Cannon CP, Cherney DZI, Masiukiewicz U, Pratley R, Dagogo-Jack S, Frederich R, Charbonnel B, Mancuso J, Shih WJ, Terra SG, Cater NB, Gantz I, McGuire DK; on behalf of the VERTIS CV Investigators. Efficacy of ertugliflozin on heart failure-related events in patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease: results of the VERTIS CV trial. *Circulation* 2020;**142**:2205–2215.
105. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M, Chiang C-E, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde A-M. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**:1995–2008.
106. McMurray JJV, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, Martinez FA, Bengtsson O, Ponikowski P, Sabatine MS, Sjöstrand M, Solomon SD, McMurray JJ, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, Martinez FA, Ponikowski P, Sabatine MS, Sjöstrand M, Solomon SD, Diez M, Nicolau J, Katova T, O'Meara E, Howlett J, Verma S, Ge J, Belohlavek J, Schou M, Böhm M, Merkely B, Chopra V, Kitakaze M, de Boer RA, Drozdz J, Tereshchenko S, Dukat A, Ljungman C, Chiang C-E, Petrie M, Desai A, Anand I, Pham VN, Pfeffer MA, Pocock S, Swedberg K, Rouleau JL, Chaturvedi N, Ivanovich P, Levey AS, Christ-Schmidt H, Held C, Varenhorst C, Christersson C, Mann J, Holmgren P, Hallberg T, Langkilde A, Sjöstrand M, Denison H, Reicher B, Bengtsson O, Fox Y, Forsby M, Alenhag E-L, Nilsson A, Kazanowska K, Olofsson EL, Karup C, Ekedahl-Berggren M, Klockargård A-L, Kempe K, Selvén M; on behalf of the DAPA-HF Committees and Investigators. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). *Eur J Heart Fail* 2019;**21**:665–675.
107. Petrie MC, Verma S, Docherty KF, Inzucchi SE, Anand I, Belohlávek J, Böhm M, Chiang C-E, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett J, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Vinh PN, Schou M, Tereshchenko S, Køber L, Kosiborod MN, Langkilde AM, Martinez FA, Ponikowski P, Sabatine MS, Sjöstrand M, Solomon SD, Johanson P, Greasley PJ, Boulton D, Bengtsson O, Jhund PS, McMurray JJV. Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes. *JAMA* 2020;**323**:1353–1368.
108. Docherty KF, Jhund PS, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, DeMets DL, Sabatine MS, Bengtsson O, Sjöstrand M, Langkilde AM, Desai AS, Diez M, Howlett JG, Katova T, Ljungman CEA, O'Meara E, Petrie MC, Schou M, Verma S, Vinh PN, Solomon SD, McMurray JJV. Effects of dapagliflozin in DAPA-HF according to background heart failure therapy. *Eur Heart J* 2020;**41**:2379–2392.
109. Martinez FA, Serenelli M, Nicolau JC, Petrie MC, Chiang C-E, Tereshchenko S, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Ponikowski P, Sabatine MS, DeMets DL, Dutkiewicz-Piasecka M, Bengtsson O, Sjöstrand M, Langkilde AM, Jhund PS, McMurray JJV. Efficacy and safety of dapagliflozin in heart failure with reduced ejection fraction according to age: insights from DAPA-HF. *Circulation* 2020;**141**:100–111.
110. Serenelli M, Böhm M, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Solomon SD, DeMets DL, Bengtsson O, Sjöstrand M, Langkilde AM, Anand IS, Chiang C-E, Chopra VK, de Boer RA, Diez M, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Verma S, Docherty KF, Jhund PS, McMurray JJV. Effect of dapagliflozin according to baseline systolic blood pressure in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial (DAPA-HF). *Eur Heart J* 2020;**41**:3402–3418.
111. Jhund PS, Solomon SD, Docherty KF, Heerspink HJL, Anand IS, Böhm M, et al. Efficacy of dapagliflozin on renal function and outcomes in patients with heart failure with reduced ejection fraction: results of DAPA-HF. *Circulation* 2020. 10.1161/CIRCULATIONAHA.120.050391 (accessed 24 December 2020).
112. Kosiborod MN, Jhund PS, Docherty KF, Diez M, Petrie MC, Verma S, Nicolau JC, Merkely B, Kitakaze M, DeMets DL, Inzucchi SE, Køber L, Martinez FA, Ponikowski P, Sabatine MS, Solomon SD, Bengtsson O, Lindholm D, Niklasson A, Sjöstrand M, Langkilde AM, McMurray JJV. Effects of dapagliflozin on symptoms, function, and quality of life in patients with heart failure and reduced ejection fraction: results from the DAPA-HF trial. *Circulation* 2020;**141**:90–99.
113. McEwan P, Darlington O, McMurray JJV, Jhund PS, Docherty KF, Böhm M, Petrie MC, Bergenheim K, Qin L. Cost-effectiveness of dapagliflozin as a treatment for heart failure with reduced ejection fraction: a multinational health-economic analysis of DAPA-HF. *Eur J Heart Fail* 2020;**22**:2147–2156.
114. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F-F, Mann JFE, McMurray JJV, Lindberg M, Rossing P, Sjöström CD, Toto RD, Langkilde A-M, Wheeler DC.

Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;**383**:1436–1446.
115. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi D-J, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca H-P, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde M-F, Spinar J, Squire I, Taddei S, Wanner C, Zannad F. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;**383**:1413–1424.
116. Packer M, Anker SD, Butler J, Filippatos GS, Ferreira JP, Pocock S, et al. Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial. *Circulation* 2020. 10.1161/CIRCULATIONAHA.120.051783 (accessed 24 December 2020).
117. Packer M. Influence of neprilysin inhibition on the efficacy and safety of empagliflozin in patients with chronic heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial. *Eur Heart J* 2020, in press.
118. Anker SD, Butler J, Filippatos G, Khan MS, Marx N, Lam CSP, et al. Effect of empagliflozin on cardiovascular and renal outcomes in patients with heart failure by baseline diabetes status—results from the EMPEROR-Reduced trial. *Circulation* 2020. hhtps://doi.org/10.1161/CIRCULATIONAHA.120.051824.
119. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, Brueckmann M, Ofstad AP, Pfarr E, Jamal W, Packer M. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet (London, England)* 2020;**396**:819–829.
120. Lee MMY, Brooksbank KJM, Wetherall K, Mangion K, Roditi G, Campbell RT, et al. Effect of empagliflozin on left ventricular volumes in patients with type 2 diabetes, or prediabetes, and heart failure with reduced ejection fraction (SUGAR-DM-HF). *Circulation* 2020. 10.1161/CIRCULATIONAHA.120.052186 (accessed 24 December 2020).
121. Santos-Gallego CG, Vargas-Delgado AP, Requena JA, Garcia-Ropero A, Mancini D, Pinney S, et al. Randomized trial of empagliflozin in non-diabetic patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol* 2020. 10.1016/j.jacc.2020.11.008.
122. Butler J, Zannad F, Filippatos G, Anker SD, Packer M. Totality of evidence in trials of sodium-glucose co-transporter-2 inhibitors in the patients with heart failure with reduced ejection fraction: implications for clinical practice. *Eur Heart J* 2020;**41**:3398–3401.
123. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 2020. https:doi.org/10.1056/NEJMoa2030183 (accessed 24 December 2020).
124. Bhatt DL, Szarek M, Pitt B, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. *N Engl J Med* 2020. https://doi.org/10.1056/NEJMoa2030186 (accessed 24 December 2020).
125. Pieske B, Patel MJ, Westerhout CM, Anstrom KJ, Butler J, Ezekowitz J, Hernandez AF, Koglin J, Lam CSP, Ponikowski P, Roessig L, Voors AA, O'Connor CM, Armstrong PW, Abidin IZ, Atar D, Bahit MC, Benecke JLA, Bocchi EA, Bonderman D, Cho M-C, Chiang C-E, Cohen-Solal A, Cowie M, Edelmann F, Emdin M, Escobedo J, Ezekowitz JA, Givertz MM, Kaye DM, Lanas F, Lassus J, Lewis BS, Lopatin Y, López-Sendón J, Lund LH, McDonald K, Melenovský V, Mosterd A, Noori E, Oto MA, Palomino ALG, Piña IL, Ponikowski P, Pouleur A-C, Refsgaard J, Reyes E, Saldarriaga C, Senni M, Sim D, Siu D, Sliwa-Hähnle K, Sweitzer NK, Troughton RW, Tsutsui H, Tziakas DN, Vazquez-Tanus JB, Zhang J; on behalf of the VICTORIA Study Group. Baseline features of the VICTORIA (Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction) trial. *Eur J Heart Fail* 2019;21:1596–1604.
126. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, Lam CSP, Ponikowski P, Voors AA, Jia G, McNulty SE, Patel MJ, Roessig L, Koglin J, O'Connor CM. Vericiguat in patients with heart failure and reduced ejection fraction. *N* failure with reduced ejection fraction study. *JACC Heart Fail* 2020;**8**:931–939.
130. Armstrong PW, Lam CSP, Anstrom KJ, Ezekowitz J, Hernandez AF, O'Connor CM, Pieske B, Ponikowski P, Shah SJ, Solomon SD, Voors AA, She L, Vlajnic V, Carvalho F, Bamber L, Blaustein RO, Roessig L, Butler J; VITALITY-HFpEF Study Group. Effect of vericiguat vs placebo on quality of life in patients with heart failure and preserved ejection fraction: the VITALITY-HFpEF randomized clinical trial. *JAMA* 2020;**324**:1512–1521. Oct
131. Udelson JE, Lewis GD, Shah SJ, Zile MR, Redfield MM, Burnett J, Mittleman RS, Profy AT, Seferovic JP, Reasner D, Konstam MA. Rationale and design for a multicenter, randomized, double-blind, placebo-controlled, phase 2 study evaluating the safety and efficacy of the soluble guanylate cyclase stimulator praliciguat over 12 weeks in patients with heart failure with preserved eje. *Am Heart J* 2020;**222**:183–190.
132. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, et al. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. *N Engl J Med* 2020. 10.1056/NEJMoa2025797 (accessed 24 December 2020).
133. Voors AA, Tamby J-F, Cleland JG, Koren M, Forgosh LB, Gupta D, Lund LH, Camacho A, Karra R, Swart HP, Pellicori P, Wagner F, Hershberger RE, Prasad N, Anderson R, Anto A, Bell K, Edelberg JM, Fang L, Henze M, Kelly C, Kurio G, Li W, Wells K, Yang C, Teichman SL, Rio CL, Solomon SD. Effects of danicamtiv, a novel cardiac myosin activator, in heart failure with reduced ejection fraction: experimental data and clinical results from a phase 2a trial. *Eur J Heart Fail* 2020;**22**:1649–1658.
134. Olivotto I, Oreziak A, Barriales-Villa R, Abraham TP, Masri A, Garcia-Pavia P, Saberi S, Lakdawala NK, Wheeler MT, Owens A, Kubanek M, Wojakowski W, Jensen MK, Gimeno-Blanes J, Afshar K, Myers J, Hegde SM, Solomon SD, Sehnert AJ, Zhang D, Li W, Bhattacharya M, Edelberg JM, Waldman CB, Lester SJ, Wang A, Ho CY, Jacoby D, Bartunek J, Bondue A, Van Craenenbroeck E, Kubanek M, Zemanek D, Jensen M, Mogensen J, Thune JJ, Charron P, Hagege A, Lairez O, Trochu J-N, Axthelm C, Duengen H-D, Frey N, Mitrovic V, Preusch M, Schulz-Menger J, Seidler T, Arad M, Halabi M, Katz A, Monakier D, Paz O, Viskin S, Zwas D, Olivotto I, Brunner-La Rocca HP, Michels M, Dudek D, Oko-Sarnowska Z, Oreziak A, Wojakowski W, Cardim N, Pereira H, Barriales-Villa R, García Pavia P, Gimeno Blanes J, Hidalgo Urbano R, Rincón Diaz LM, Elliott P, Yousef Z, Abraham T, Afshar K, Alvarez P, Bach R, Becker R, Choudhury L, Fermin D, Jacoby D, Jefferies J, Kramer C, Lakdawala N, Lester S, Marian A, Masri A, Maurer M, Nagueh S, Owens A, Owens D, Rader F, Saberi S, Sherrid M, Shirani J, Symanski J, Turer A, Wang A, Wever-Pinzon O, Wheeler M, Wong T, Yamani M. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2020;**396**:759–769.
135. Ponikowski P, Kirwan B-A, Anker SD, Dorobantu M, Drozdz J, Fabien V, Filippatos G, Haboubi T, Keren A, Khintibidze I, Kragten H, Martinez FA, McDonagh T, Metra M, Milicic D, Nicolau JC, Ohlsson M, Parhomenko A, Pascual-Figal DA, Ruschitzka F, Sim D, Skouri H, Meer P, Jankowska EA. Rationale and design of the AFFIRM-AHF trial: a randomised, double-blind, placebo-controlled trial comparing the effect of intravenous ferric carboxymaltose on hospitalisations and mortality in iron-deficient patients admitted for acute heart failure. *Eur J Heart Fail* 2019;**21**:1651–1658.
136. Ponikowski P, Kirwan B-A, Anker SD, McDonagh T, Dorobantu M, Drozdz J, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet (London, England)* 2020. 10.1016/S0140-6736(20)32339-4 (accessed 24 December 2020).
137. Batkai S, Genschel C, Viereck J, Rump S, Bär C, Borchert T, et al. CDR132L improves systolic and diastolic function in a large animal model of chronic heart failure. *Eur Heart J* 2020. 10.1093/eurheartj/ehaa791 (accessed 24 December 2020).
138. Täubel J, Hauke W, Rump S, Viereck J, Batkai S, Poetzsch J, et al. Novel antisense therapy targeting microRNA-132 in patients with heart failure: results of a first-in-human Phase 1b randomized, double-blind, placebo-controlled study. *Eur Heart J* 2020. 10.1093/eurheartj/ehaa898 (accessed 24 December 2020).

139. Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Pedro Ferreira J, Zannad F, Packer M, Fonarow GC, McMurray JJV, Solomon SD. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. *Lancet (London, England)* 2020;**396**:121–128.
140. Reichart D, Kalbacher D, Rübsamen N, Tigges E, Thomas C, Schirmer J, Reichenspurner H, Blankenberg S, Conradi L, Schäfer U, Lubos E. The impact of residual mitral regurgitation after MitraClip therapy in functional mitral regurgitation. *Eur J Heart Fail* 2020;**22**:1840–1848.
141. Nijst P, Martens P, Dauw J, Tang WHW, Bertrand PB, Penders J, Bruckers L, Voros G, Willems R, Vandervoort PM, Dupont M, Mullens W. Withdrawal of neurohumoral blockade after cardiac resynchronization therapy. *J Am Coll Cardiol* 2020;**75**:1426–1438.
142. Zile MR, Lindenfeld JAnn, Weaver FA, Zannad F, Galle E, Rogers T, Abraham WT. Baroreflex activation therapy in patients with heart failure with reduced ejection fraction. *J Am Coll Cardiol* 2020;**76**:1–13.
143. Angermann CE, Assmus B, Anker SD, Asselbergs FW, Brachmann J, Brett M-E, Brugts JJ, Ertl G, Ginn G, Hilker L, Koehler F, Rosenkranz S, Zhou Q, Adamson PB, Böhm M; for the MEMS-HF Investigators. Pulmonary artery pressure-guided therapy in ambulatory patients with symptomatic heart failure: the CardioMEMS European Monitoring Study for Heart Failure (MEMS-HF). *Eur J Heart Fail* 2020;**22**:1891–1901.
144. Stehlik J, Schmalfuss C, Bozkurt B, Nativi-Nicolau J, Wohlfahrt P, Wegerich S, Rose K, Ray R, Schofield R, Deswal A, Sekaric J, Anand S, Richards D, Hanson H, Pipke M, Pham M. Continuous wearable monitoring analytics predict heart failure hospitalization: the LINK-HF multicenter study. *Circ Heart Fail* 2020;**13**:e006513.
145. Rahimi K, Nazarzadeh M, Pinho-Gomes A-C, Woodward M, Salimi-Khorshidi G, Ohkuma T, Fitzpatrick R, Tarassenko L, Denis M, Cleland J; SUPPORT-HF2 Study Group. Home monitoring with technology-supported management in chronic heart failure: a randomised trial. *Heart* 2020;**106**:1573–1578.
146. Galinier M, Roubille F, Berdague P, Brierre G, Cantie P, Dary P, Ferradou J-M, Fondard O, Labarre JP, Mansourati J, Picard F, Ricci J-E, Salvat M, Tartière L, Ruidavets J-B, Bongard V, Delval C, Lancman G, Pasche H, Ramirez-Gil JF, Pathak A; on behalf of the OSICAT Investigators. Telemonitoring versus standard care in heart failure: a randomised multicentre trial. *Eur J Heart Fail* 2020;**22**:985–994.
147. Zakeri R, Morgan JM, Phillips P, Kitt S, Ng GA, McComb JM, Williams S, Wright DJ, Gill JS, Seed A, Witte KK, Cowie MR; REM-HF Investigators. Impact of remote monitoring on clinical outcomes for patients with heart failure and atrial fibrillation: results from the REM-HF trial. *Eur J Heart Fail* 2020;**22**:543–553.
148. Abraham WT, Fiuzat M, Psotka MA, O'Connor CM. Heart failure collaboratory statement on remote monitoring and social distancing in the landscape of COVID-19. *JACC Heart Failure* 2020;**8**:692–694.
149. Jaarsma T, Hill L, Bayes-Genis A, Brunner La Rocca HP, Castiello T, Čelutkienė J, et al. Self-care of heart failure patients: practical management recommendations from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020. 10.1002/ejhf.2008 (accessed 24 December 2020).
150. Hill L, Geller TP, Baruah R, Beattie JM, Boyne J, De Stoutz N, et al. Integration of a palliative approach into heart failure care: a European Society of Cardiology Heart Failure Association position paper. *Eur J Heart Fail* 2020. 10.1002/ejhf.1994
151. Sobanski PZ, Alt-Epping B, Currow DC, Goodlin SJ, Grodzicki T, Hogg K, Janssen DJA, Johnson MJ, Krajnik M, Leget C, Martínez-Sellés M, Moroni M, Mueller PS, Ryder M, Simon ST, Stowe E, Larkin PJ. Palliative care for people living with heart failure: European Association for Palliative Care Task Force expert position statement. *Cardiovasc Res* 2020;**116**:12–27.
152. Sahlollbey N, Lee CKS, Shirin A, Joseph P. The impact of palliative care on clinical and patient-centred outcomes in patients with advanced heart failure: a systematic review of randomized controlled trials. *Eur J Heart Fail* 2020. https://doi.org/10.1002/ejhf.1783 (accessed 24 December 2020).

ESC European Society of Cardiology

Special article

The year in cardiovascular medicine 2020: epidemiology and prevention

Ramon Estruch[1,2*], Luis M. Ruilope[3,4,5], and Francesco Cosentino[6]

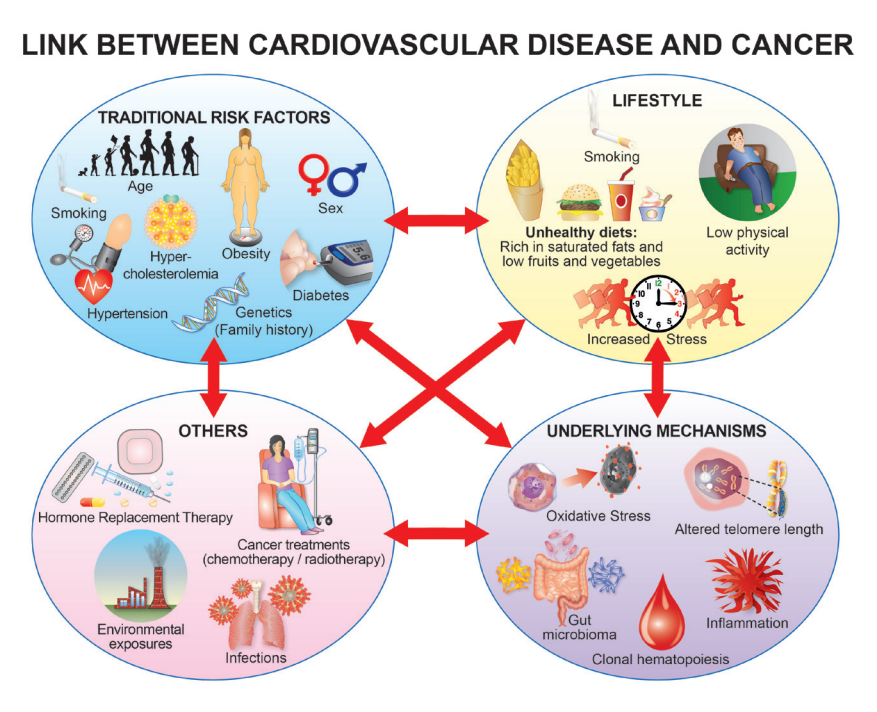
[1] Department of Internal Medicine, Hospital Clínic, IDIBAPS, University of Barcelona, Villarroel, 170. 08036 Barcelona, Spain; [2] CIBER Fisiopatología de la Obesidad y la Nutrición, CIBEROBN, Instituto de Salud Carlos III, Madrid, Spain; [3] Hypertension Unit and Cardiorenal Translational Laboratory, Research Institute, Hospital Universitario, 12 de Octubre, Madrid, Spain; [4] CIBER Enfermedades Cardiovasculares, CIBER-CV Hospital Universitario, 12 de Octubre, Avd. de Córdoba s/n. 28041 Madrid, Spain; [5] Faculty of Sport Sciences, Universidad Europea de Madrid, Madrid, Spain; and [6] Cardiology Unit, Department of Medicine, Karolinska Institutet and Karolinska University Hospital, FE 200, 171 77 Stockholm, Sweden

Received 23 October 2020; revised 1 December 2020; editorial decision 11 December 2020; accepted 12 December 2020

Reproduced from: Estruch R, Ruilope LM, Cosentino F. The year in cardiovascular medicine 2020: epidemiology and prevention. Eur Heart J. 2021 Feb 21;42(8):813-821. https://doi.org/10.1093/eurheartj/ehaa1062, by permission of Oxford University Press on behalf of the European Society of Cardiology

* Corresponding author: Tel: +34 93 227 55 39, Email: restruch@clinic.cat

Graphical Abstract



Cardiovascular disease and cancer continue to be the major causes of death worldwide and the two conditions have more in common than previously acknowledged. In fact, both diseases share many predisposing factors and mechanisms, with a common background of low-grade inflammation. Thus, both cardiologists and oncologists should score both cardiovascular and cancer risk factors and develop risk reduction strategies for their patients.

Keywords Cardiovascular prevention • Lifestyle • Nutrition • Exercise • Diabetes • Hypertension • Dyslipidemia • Cardio-renal syndrome • Cardio-oncology

Introduction

Cardiovascular disease (CVD) prevention has been classically divided into primary (aimed to asymptomatic subjects) and secondary (aimed to patients who have already suffered a cardiovascular event), but currently this classification is considered arbitrary given the overlap observed, for example in diabetic patients. Thus, prevention measures may be better divided into 'prevention at the population level' and 'prevention strategies in subjects with high vascular risk'.[1–3] *Figure 1* summarizes the role of different actors in the prevention of CVD.

In the current paper, we review relevant contributions to CVD prevention published in 2020. We have also included references to relevant articles related to cardio-renal syndrome and the common pathways of cancer and CVD, as well as new aspects of cardiac disease due to COVID-19 infection.

Lifestyle, behaviour, and environmental factors

Genetics

Both sex and gender have significant impact on the incidence and severity of cardiovascular events.[4] Compared to men, women disclose a higher incidence of some cardiovascular conditions such as heart failure with preserved ejection fraction[5] or Takotsubo syndrome,[6] but they also suffer from relevant differences in presenting symptoms of acute coronary syndrome (ACS).[7,8] Perhaps, different treatment protocols should be applied in men and women to avoid the differences observed.

New advances on precision nutrition occur every year. Although the relevance of dietary cholesterol on health has been questioned in the last years,[9,10] Helgadottir *et al.*[11] have found that sequence variants that decrease the function of ABC5/8 transporters increase the absorption of both dietary cholesterol and phytosterols, thereby increasing the risk of coronary artery disease (CAD).

Smoking and vaping

The use of electronic cigarettes (e-cigarettes) has dramatically increased, especially among young generations. Although e-cigarettes may be useful to save smokers or generate new addicts, the list of toxic compounds found in e-cigarette vapour is large, mainly nicotine, propylene glycol, and glycerine.[12] In fact, daily e-cigarette use has been associated with increased CVD morbidity and mor-

tality,[12] and various forms of pneumonitis.[13] Kuntic *et al*.[14] demonstrated that the e-cigarette use is associated with a marked impairment in endothelium-dependent flow-mediated vasodilatation and an increase in pulse wave velocity, a measurement of arterial stiffness. They also observed in mice that e-cigarette vapour raised blood pressure (BP) and increased superoxide production that reacts with nitric oxide in peripheral arteries and brain cortex. Thus, e-cigarettes are truly toxics and the recommendation should be to never start their use and for users to stop them.[15]

Nutrition

The most important strategy for the prevention of atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and atrial fibrillation (AF) is to promote a healthy lifestyle. Mediterranean diet is considered as one of the most cost-effective strategies to prevent CVD,[16] but individual responsiveness to compliance with this dietary pattern may vary due to differences in metabolic responses. Li *et al*.[17] identified a metabolic signature comprised of 67 metabolites that correlated with the Mediterranean diet adherence screener and also predicted future CVD risk independent of traditional risk factors in a Spanish (PREDIMED) and three US cohorts (NHS, NHSII, and HPFSP). Metabolomics profiling may allow stratifying individuals based on dietary response and disease risk, thus facilitating individualized approaches to dietary interventions.

In addition to CAD, diet may affect stroke risk. Tong *et al*.[18] examined the association between intake of major foods and fibre with risk of ischaemic and haemorrhagic stroke in 418 329 participants in the EPIC cohort. For ischaemic stroke, participants with high consumption of fruit and vegetables combined, dietary fibre, milk, yogurt, and cheese reduced risks by 13%, 23%, 5%, 9%, and 12%, respectively. Interestingly, for haemorrhagic stroke, higher risk was only associated with higher egg consumption, with a 25% increase per 20 g/day.

Notably, iron overload profoundly aggravated atherosclerotic damage in an APOE-deficient mouse model,[19] but iron deficiency was associated with a worse outcome in a cohort of 2357 patients with HF studied by van der Wal *et al*.[20] Depending on the context, iron excess and iron deficiency may both be harmful to cardiovascular health.

Excessive alcohol intake always affects the cardiovascular system, including induction of AF and adverse atrial remodelling. A randomized clinical trial (RCT) of continuous alcohol drinking vs. abstinence in patients with AF demonstrated reduced arrhythmia rates during a 6-month follow-up in the group assigned to abstinence,[21] emphasizing the present recommendation to abstain from alcohol in patients with recurrent AF.

Exercise

Physical activity is associated with a dose-dependent reduction in all-cause and CVD mortality.[22] This assertion was reconfirmed by a very large study of persons with and without CVD.[23] Physical activity should be promoted in young ages, since low levels of cardiorespiratory fitness (and obesity) in 1 078 685 male adolescents were associated with later cardiovascular disabilities.[24] Physical activity and cardiorespiratory fitness were also associated with lower long-term risk of CVD and all-cause mortality in patients with AF (HUNT study).[25] Likewise, incidence of AF and ventricular arrhythmias was lower among those who were physically active and remained relative stable over a broad range of activity levels.[26]

Finally, sport may favour healthy aging.[27] In this respect, a controlled trial (EXAMIN AGE) of high-intensity interval training in aged individuals reported restoration of retinal microvascular dysfunction, a clinical outcome associated with major adverse cardiovascular events (MACE), together with the reduction of other cardiovascular risk factors.[28,29]

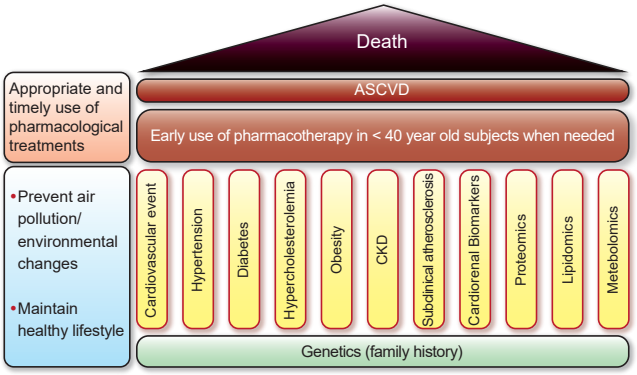


Figure 1 Different components involved in the lifetime genesis and evolution of cardiovascular risk. The three most important messages are: first, the need to prevent an unhealthy environment; second, the need to maintain an adequate lifestyle; and third, the use of appropriate pharmacotherapy when required. The first two have to be maintained for the lifetime, while pharmacological treatment should be started at an earlier age than was recommended a few years ago.

Obesity

Association between obesity and all-cause and CVD mortality follows a J-shaped curve.[30] Over two-thirds of deaths attributable to high body mass index (BMI) are due to CVD, mainly CAD,[31] but the causal role of adiposity for other CVD outcomes remains unclear. In a Mendelian randomization study, Larsson *et al*.[32] assessed the association of BMI-related genetic variants with 14 cardiovascular conditions among 367 703 UK Biobank participants and reported that higher BMI was associated with increased risk of aortic valve stenosis, AF, ischaemic stroke and abdominal aortic aneurisms.

Among diets used to lose weight,[30] intermittent fasting has gained increased popularity since it is purported to not only help reduce body weight, but also to reverse aging, increase lifespan, and improve several other chronic conditions, albeit most evidence is preclinical.[33] Concerning weight loss effects, Moussa *et al*.[34] evaluated the long-term effect of bariatric surgery on CVD outcomes in a UK nationwide nested cohort study. Occurrence of MACE (mainly myocardial infarction) and new HF diagnoses were reduced by nearly 60% in obese individuals who underwent the procedure compared to a matched control group.

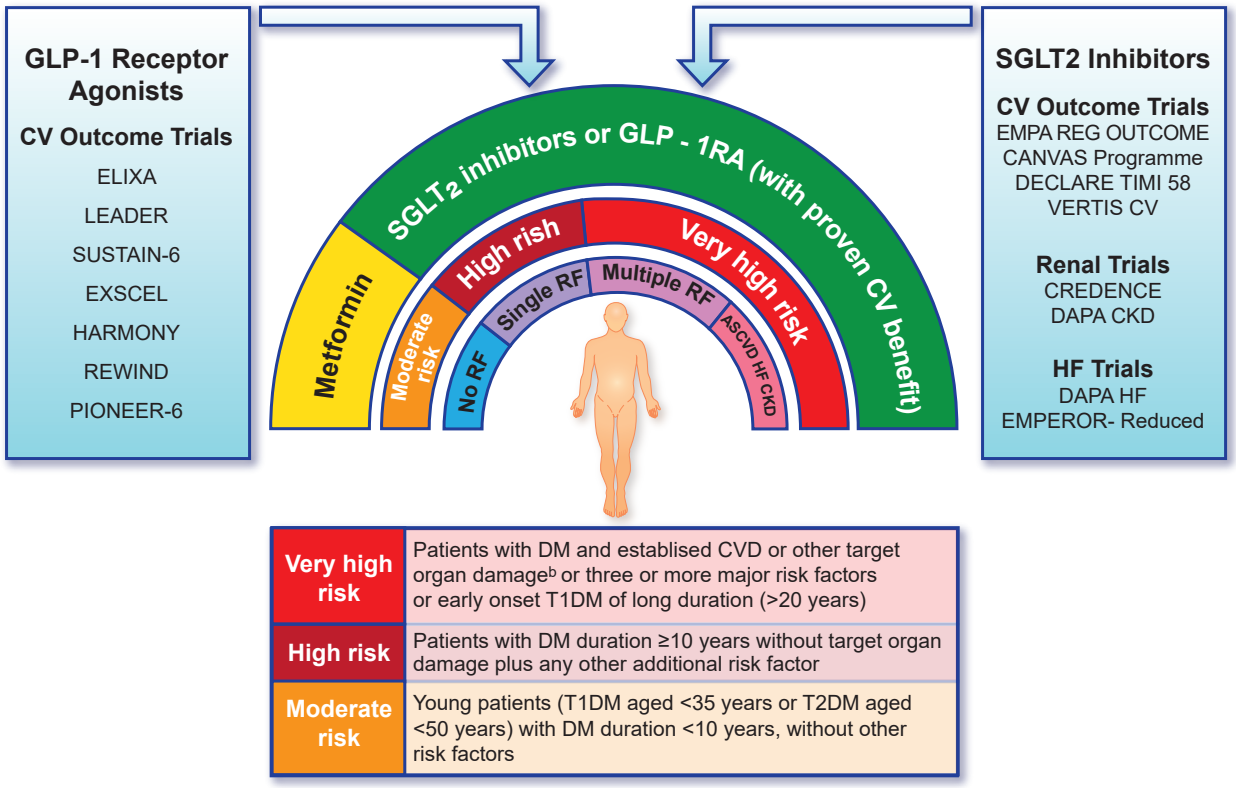


Figure 2 Cardiovascular risk classification and treatment recommendation to reduce cardiovascular outcomes in patients with T2D according to the 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; HF, heart failure; green, Class I/A recommendation; RF, risk factor; yellow, Class IIa/C recommendation (modified from Marx N, Eur Heart J 2020. doi:10.1093/eurheartj/ehaa174, by permission of OUP on behalf of ESC).

Other lifestyle factors

Emerging evidence has implicated sleep duration[35] and depression[36] as risk factors for CVD. Another study of 385 292 UK biobank participants[37] reported that ~10% CVD events could be attributed to disturbed sleep. By contrast, a healthy sleep pattern reduced risk of CAD and stroke by 34%. A position paper of the European Society of Cardiology (ESC) working group on coronary pathophysiology and microcirculation[38] concluded that depression is associated with a 30% increased risk for future CAD events.

Low education, low income, and work stress are also considered as risk factors for CVD.[39] In an analysis of a prospective cohort of 1.6 million Danish employees, Framke *et al*.[40] reported that low education was associated with higher risk of incident CVD and CVD mortality.

Diabetes

Over the last decade, large CVD outcome trials in patients with type-2 diabetes (T2D) have provided data on the efficacy of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium glucose cotransporter 2 inhibitors (SGLT2i) to reduce cardio-renal events. Today's awareness of the CVD continuum as a chain of pathophysiological events makes difficult to define risk in a binary manner using only primary and secondary prevention to drive management. Thus, the recent ESC guidelines on diabetes/prediabetes and CVD[2] recommend that patients with diabetes should be classified according to three levels of cardiovascular risk, into those at very high, high, or moderate risk (*Figure 2*).

The four available SGLT2 inhibitors have demonstrated to favourably affect a spectrum of CVD and kidney outcomes. Most recently, canagliflozin in the CREDENCE trial significantly reduced 3-point-MACE in a diabetes population with chronic kidney disease (CKD).[41] In DECLARE TIMI-58 trial, dapagliflozin vs. placebo did not significantly affect 3-point-MACE, possibly due to the lower-risk cohort recruited with ~60% of participants with only multiple risk factors without established ASCVD.[42] The VERTIS CV trial with ertugliflozin also did not show a reduction in MACE, despite the fact that people with established ASCVD were studied.[43] On the other hand, all the SGLT2 inhibitors investigated in the different trials showed a significant reduction in HF hospitalization. Most interestingly, dapagliflozin in DAPA-HF[44] and empagliflozin in EMPEROR-Reduced[45] showed a reduction in the combined endpoint of HF or CV death in patients with HFrEF with or without diabetes. A very recent meta-analysis representing the totality of CVD outcomes trial data for the four SGLT2 inhibitors available shows that reduction in risk for HF and CKD progression is the most consistent observation across the trials.[46]

Despite using different definitions of renal endpoints, all SGLT2-inhibitor RCTs also showed protection against progression of diabetic kidney disease. In most trials, these findings were secondary endpoints, but CREDENCE demonstrated a significant 30% reduction in the primary composite endpoint of CKD, doubling of serum creatinine, death from kidney causes or CV death in people with diabetes and CKD.[41]

A recent meta-analysis of RCTs concluded that also GLP-1 RAs lead to a significant reduction in the 3P-MACE as well as the risk of CV mortality, all-cause mortality, fatal and nonfatal stroke and heart failure hospitalization.[47] Moreover, based on data from five GLP-1 RA CVD outcome trials, which enrolled patients both with and without ASCVD, there were no between-group differences in GLP-1 RAs benefit on 3P-MACE, indicating consistent protective effects in patients with established ASCVD, as well as in those with multiple risk factors. The results of these RCTs and meta-analyses support the ESC guidelines to prioritize the use of SGLT2i and GLP-1 RAs in patients with T2D at high/very high risk to prevent CVD and kidney complications (*Figure 2*).

Of note, an analysis of the ORIGIN trial data assessing the relationship between body weight and CVD outcomes reported findings that contradict conventional wisdom on body weight and health outcomes.[48] In patients with DM/prediabetes, overweight/mild obesity was associated with lower all-cause and CV mortality compared to those with normal weight. Also, loss of weight related to higher all-cause and CV mortality compared to no weight loss, while weight gain was neutral. Further research is needed to clarify if recommendations on weight management should differentiate more clearly between moderate risk and patients with established ASCVD or elevated cardiovascular risk profiles.

Hypertension

The ESC in its 2020 publication on CVD statistics[49] described that in Europe the prevalence of major risk factors was higher in middle-income countries compared to high-income countries. In middle-income countries, the prevalence of hypertension was 23.8% compared with 15.7% in high-income countries. Prevention and control of arterial hypertension has then to be particularly intensive in middle-income countries. However, within the high-income countries after the improvement in hypertension awareness since the 1980s and 1990s, we have assisted to control figure rates with a plateau in the past decade.[50] This finding is probably due to an inadequate accomplishment of guidelines leading to an improper management of elevated BP that could depend on a delayed start of BP management.

How can we improve the control of BP and cardiovascular risk? Probably, risk assessment should start before age 40[51] due to the importance of early life exposure to risk factors and development of future CVD. The age of onset of hypertension correlates with CVD and mortality[52] and the BP trajectories exhibit sex differences that begin early and persist with aging, allowing the setting for later CVD.[53] Thus, an early control of BP and other cardiovascular risk factors, particularly cholesterol, has to be performed to obtain an adequate prevention of CVD and renal disease.

A recent publication has opened a new door to delimitate the definition of normal BP to start intervention. Performed with data from the Multi-Ethnic Study of Atherosclerosis,[54] the study[55] shows that beginning at a systolic BP (SBP) of 90 mmHg there is a progressive increase in coronary artery calcium and in ASCVD with progressing SBP. Hence, primordial prevention of BP elevation and other risk factors is necessary to improve cardiovascular prevention in subjects at risk of developing hypertension.

Intervention on BP at young ages is then needed and it must be considered that BP values will stay within the range of normalcy (SBP 90–129 mmHg) preventing the development of arterial hypertension in individuals with good cardiovascular health estimated as Life's Simple 7 metrics (adequate values and performance of BMI, diet, smoking, physical activity, BP, cholesterol, and glucose).[56]

Treatment and control of hypertension in 2020 requires a substantial improvement and one of the ways to accomplish it and thus diminish the burden of disease consists in ensuring an adequate control of BP and the other main cardiovascular risk factors since the early stages of life.

Dyslipidaemia

New guidelines for the management of dyslipidaemias from the ESC and the European Atherosclerosis Society have been published in 2020.[10] The treatment targets and goals for cardiovascular prevention defined in these guidelines are depicted in *Table 1*. The intensity of lipid-lowering treatment to accomplish approximate LDL-C

Table 1 Lipid treatment targets for cardiovascular disease prevention[54]

LDL-C. In patients with very high risk in primary or secondary prevention
A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline and an LDL-C goal of 1.4 mmol/L (<55 mg/dL)
No current statin use: this is likely to require high-intensity LDL-lowering therapy
Current LDL-lowering treatment: an increased treatment intensity is required
High risk
A therapeutic regimen that achieves ≥50% LDL-C reduction from baseline and an LDL-C goal of 1.8 mmol/L (<70 mg/dL)
Moderate risk
A goal of <2.6 mmol/L (<100 mg/dL)
Low risk
A goal of <3.0 mmol/L (<116 mg/dL)
Non-HDL-C
Non-HDL-C secondary goals are <2.2, 2.6, and 3.4 mmol/L (<85, 100, 130 mg/dL) for very-high-, high-, and moderate-risk people, respectively
ApoB
ApoB secondary goals are <65, 80, and 100 mg/dL, for very-high-, high-, and moderate-risk people, respectively
Triglycerides
No goal, but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors

targets relies on the use of moderate-intensity statin to reduce LDL-C by 30%, high-intensity statin (50% reduction), high-intensity statin plus ezetimibe (65% reduction), PCSK9 inhibitors (60% reduction), PCSK9 inhibitors plus high-intensity statin (75% reduction), and PCSK9 plus high-intensity statin plus ezetimibe (85% reduction).

The REDUCE-IT trial[57] has demonstrated profound reductions in first and total CVD events in patients treated with statins and well-controlled LDL-C presenting with elevated triglyceride levels with the administration of 4 g daily of icosapent ethyl. These findings should substantially change the management of patients with diabetes and/or metabolic syndrome presenting with hypertriglyceridemia whose lipid phenotype needs treatment beyond isolated LDL-C.[58]

Recently, a class of lipids termed ceramides has been demonstrated to be indices of cardiometabolic health.[59] The ceramide-based scores are simple and practical to be used in clinical practice to identify at-risk patients. In addition, new drugs to treat elevated LDL-C have been described[60,61] and soon will become part of the armamentarium. One of them is inclisiran, an inhibitor of hepatic synthesis of proprotein convertase subtilisin type 9 that reduces LDL-C by ~50% with subcutaneous administration every 6 months. Another is evinacumab, a monoclonal antibody against ANGPTL3 (Angiopoietin-like 3) that has been tested in homozygous familial hypercholesterolaemia with good results.

Cardio-renal syndrome

There is a clear linkage between cardiovascular and renal diseases characterized by an elevated prevalence of CVD in patients with CKD, and viceversa. Accordingly, RCTs addressing new therapies with the capacity to improve CVD outcomes in patients with CKD are needed.[62] Acute kidney injury, defined as an abrupt increase in serum creatinine, a fall in urinary volume, or both, is also a situation with relevant cardiovascular consequences mediated by cardiac inflammation and cellular apoptosis and necrosis rapidly developing and followed by cardiac fibrosis leading to CVD events, in particular HF.[63] Like in the case of CKD trials new studies aimed to find therapies improving CVD and renal outcomes in acute kidney injury are required.

Usually patients are diagnosed as having CKD when they present with albuminuria and/or an estimated Glomerular filtration rate [GFR (eGFR)] <60 mL/min/1.73 m^2. Detection of patients developing CKD before albuminuria develops or eGFR falls (early renal damage) actually is not clearly defined albeit some data indicate that certain interventions like control of adolescent hypertension can impede the future development of kidney failure.[64]

On the other hand, the clinical diagnosis of progressive CKD is usually based on the evolution of eGFR and the variation in albuminuria and it is accepted that actual management for cardiovascular protection translates into renal protection,[65] albeit CVD events, in particular HF, requiring hospitalization are associated with kidney failure independent of kidney risk factors.[66]

The use of new antidiabetic drugs sodium glucose cotransporter 2 and inhibitors of glucagon-like peptide-1 in patients with diabetes and CKD has provided evidence of simultaneous cardio-renal protection.[67] The results of similar trials using finerenone, a non-steroidal mineralocorticoid receptor antagonist, will be published soon.[68]

COVID-19 and cardiovascular disease

The novel coronavirus disease (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) initiated at the end of 2019. COVID-19 was shown initially to affect the lungs, causing interstitial pneumonitis and severe acute respiratory distress syndrome. Later it was observed that it also affects multiple organs, including the cardiovascular system. Advanced age and male sex are accompanied by severe infection and mortality that is promoted by accompanying comorbidities, particularly CVD, hypertension, diabetes, obesity, CKD, chronic pulmonary disease, and cancer.[69,70] Ultimately, a severe prognosis is the consequence of endothelial dysfunction and COVID-19 is finally considered an endotheliopathy.[71]

While waiting for adequate vaccines to prevent COVID-19 and specific medications counteracting the SARS-CoV-2, an array of medications, amply reviewed by Guzik *et al.*,[72] has been considered for the treatment of COVID-19 patients with variable effects. It has been established that the use of renin–angiotensin–aldosterone antagonists for the treatment of hypertension and/or heart diseases could be beneficial for COVID-19[73] as well as the use of anticoagulant therapy needed to diminish the risk of pulmonary embolism.[74]

Cancer and cardiovascular disease

CVD and cancer continue to be the leading causes of death worldwide. Interestingly, CVD and cancer share common pathways[75,76] and, in addition, an increasing number of cancer patients—successfully treated—show an increasing incidence of CVD mortality[77] and CVD events such as HF,[78] ACS,[79] and arrhythmias.[80]

Future perspectives in preventive cardiology

Probably in the next years, new advances on precision medicine will appear with the help of more useful genetic tests and better characterization patients according to their metabolomic profile.

Summary and conclusions

The current article summarizes relevant advances on CVD prevention in 2020.

We have highlighted the need for different protocols for men and women because of differences in presenting symptoms of ACS among sex, the truly toxic effects of e-cigarettes, and the usefulness of intermittent fasting to reduce body weight, improve several chronic conditions

and reverse aging. Four available SGLT2 inhibitors have demonstrated favourable effects on CVD and kidney outcomes. We have also underlined that CVD risk assessment should be started before age 40 given the importance of early life exposure to risk factors and development of future CVD events and that new treatment targets and goals have been defined in the new guidelines for the management of dyslipidaemias.

Finally, despite the striking consequences of COVID-19 pandemia, prevention of most prevalent and relevant chronic diseases worldwide, CVD and cancer, should continue to be promoted by all actors (governments, scientific societies and mass media) at both population and individual levels. In this setting, an adequate and joint prevention program should be useful to fight both CVD and cancer. Let us get going!

Conflict of interest: R.E. reports grants from Cerveza y Salud, Spain, and Fundacion Dieta Mediterranea, Spain; also, personal fees for given lectures from Brewers of Europe, Belgium, Fundacion Cerveza y Salud, Spain, Pernaud-Ricard, Mexico, Instituto Cervantes, Alburquerque, USA; Instituto Cervantes, Milan, Italy; Instituto Cervantes, Tokyo, Japan; Lilly Laboratories, Spain; and Wine and Culinary International Forum, Spain, and non-financial support to organize a National Congress on Nutrition; and also, feeding trials with product from Grand Fountain and Uriach Laboratories, Spain. L.R. has been speaker and advisor for Astra-Zeneca, Bayer, Novartis, Medtronic, Pfizer, Vifor and Menarini. F.C. reports personal fees from AstraZeneca, personal fees from Bayer, personal fees from Boehringer Ingelheim, personal fees from Bristol-Myers Squibb, personal fees from Merck Sharp & Dohme, personal fees from Mundipharma, personal fees from Novo Nordisk, personal fees from Pfizer, grants from King Gustav V and Queen Victoria Foundation, grants from Swedish Research Council, and grants from Swedish Heart & Lung Foundation, outside the submitted work. L.M.R. has nothing to declare.

References

1. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2020;doi:10.1093/eurheartj/ehaa575.
2. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV, Johansson I, Jüni P, Lettino M, Marx N, Mellbin LG, Östgren CJ, Rocca B, Roffi M, Sattar N, Seferović PM, Sousa-Uva M, Valensi P, Wheeler DC, Piepoli MF, Birkeland KI, Adamopoulos S, Ajjan R, Avogaro A, Baigent C, Brodmann M, Bueno H, Ceconi C, Chioncel O, Coats A, Collet J-P, Collins P, Cosyns B, Di Mario C, Fisher M, Fitzsimons D, Halvorsen S, Hansen D, Hoes A, Holt RIG, Home P, Katus HA, Khunti K, Komajda M, Lambrinou E, Landmesser U, Lewis BS, Linde C, Lorusso R, Mach F, Mueller C, Neumann F-J, Persson F, Petersen SE, Petronio AS, Richter DJ, Rosano GMC, Rossing P, Rydén L, Shlyakhto E, Simpson IA, Touyz RM, Wijns W, Wilhelm M, Williams B, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV, Johansson I, Jüni P, Lettino M, Marx N, Mellbin LG, Östgren CJ, Rocca B, Roffi M, Sattar N, Seferović PM, Sousa-Uva M, Valensi P, Wheeler DC, Windecker S, Aboyans V, Baigent C, Collet J-P, Dean V, Delgado V, Fitzsimons D, Gale CP, Grobbee DE, Halvorsen S, Hindricks G, Iung B, Jüni P, Katus HA, Landmesser U, Leclercq C, Lettino M, Lewis BS, Merkely B, Mueller C, Petersen SE, Petronio AS, Richter DJ, Roffi M, Shlyakhto E, Simpson IA, Sousa-Uva M, Touyz RM, Zelveian PH, Scherr D, Jahangirov T, Lazareva I, Shivalkar B, Naser N, Gruev I, Milicic D, Petrou PM, Linhart A, Hildebrandt P, Hasan-Ali H, Marandi T, Lehto S, Mansourati J, Kurashvili R, Siasos G, Lengyel C, Thrainsdottir IS, Aronson D, Di Lenarda A, Raissova A, Ibrahimi P, Abilova S, Trusinskis K, Saade G, Benlamin H, Petrulioniene Z, Banu C, Magri CJ, David L, Boskovic A, Alami M, Liem AH, Bosevski M, Svingen GFT, Janion M, Gavina C, Vinereanu D, Nedogoda S, Mancini T, Ilic MD, Fabryova L, Fras Z, Jiménez-Navarro MF, Norhammar A, Lehmann R, Mourali MS, Ural D, Nesukay E, Chowdhury TA; ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020;**41**:255–323.
3. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith SCJr, Virani SS, Williams KASr, Yeboah J, Ziaeian B. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *JACC* 2019;**74**:e177-232–e232.
4. Lam CSP, Arnott C, Beale AL, Chandramouli C, Hilfiker-Kleiner D, Kaye DM, Ky B, Santema BT, Sliwa K, Voors AA. Sex differences in heart failure. *Eur Heart J* 2019;**40**:3859–3868.
5. Gili S, Cammann VL, Schlossbauer SA, Kato K, D'Ascenzo F, Di Vece D, Jurisic S, Micek J, Obeid S, Bacchi B, Szawan KA, Famos F, Sarcon A, Levinson R, Ding KJ, Seifert B, Lenoir O, Bossone E, Citro R, Franke J, Napp LC, Jaguszewski M, Noutsias M, Münzel T, Knorr M, Heiner S, Katus HA, Burgdorf C, Schunkert H, Thiele H, Bauersachs J, Tschöpe C, Pieske BM, Rajan L, Michels G, Pfister R, Cuneo A, Jacobshagen C, Hasenfuß G, Karakas M, Koenig W, Rottbauer W, Said SM, Braun-Dullaeus RC, Banning A, Cuculi F, Kobza R, Fischer TA, Vasankari T, Airaksinen KEJ, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Crea F, Dichtl W, Empen K, Felix SB, Delmas C, Lairez O, El-Battrawy I, Akin I, Borggrefe M, Gilyarova E, Shilova A, Gilyarov M, Horowitz JD, Kozel M, Tousek P, Widimský P, Winchester DE, Ukena C, Gaita F, Di Mario C, Wischnewsky MB, Bax JJ, Prasad A, Böhm M, Ruschitzka F, Lüscher TF, Ghadri JR, Templin C. Cardiac arrest in Takotsubo syndrome: results from the Inter-TAK Registry. *Eur Heart J* 2019;**40**:2142–2151.
6. Lüscher TF. Sex and gender and cardiovascular medicine: impact in diabetes acute coronary syndromes and heart failure. *Eur Heart J* 2020;**41**:1311–1314.
7. Haider A, Bengs S, Luu J, Osto E, Siller-Matula JM, Muka T, Gebhard C. Sex and gender in cardiovascular medicine: presentation and outcomes of acute coronary syndrome. *Eur Heart J* 2020;**41**:1328–1336.
8. Blom MT, Oving I, Berdowski J, van Valkengoed IGM, Bardai A, Tan HL. Women have lower chances than men to be resuscitated and survive out-of-hospital cardiac arrest. *Eur Heart J* 2019;**40**:3824–3834.
9. Grundy SM. Does dietary cholesterol matter? *Curr Atheroscler Rep* 2016;**18**:68.
10. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen M-R, Tokgozoglu L, Wiklund O, Mueller C, Drexel H, Aboyans V, Corsini A, Doehner W, Farnier M, Gigante B, Kayikcioglu M, Krstacic G, Lambrinou E, Lewis BS, Masip J, Moulin P, Petersen S, Petronio AS, Piepoli MF, Pintó X, Räber L, Ray KK, Reiner Ž, Riesen WF, Roffi M, Schmid J-P, Shlyakhto E, Simpson IA, Stroes E, Sudano I, Tselepis AD, Viigimaa M, Vindis C, Vonbank A, Vrablik M, Vrsalovic M, Zamorano JL, Collet J-P, Koskinas KC, Casula M, Badimon L, John Chapman M, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine

MS, Taskinen M-R, Tokgozoglu L, Wiklund O, Windecker S, Aboyans V, Baigent C, Collet J-P, Dean V, Delgado V, Fitzsimons D, Gale CP, Grobbee D, Halvorsen S, Hindricks G, Iung B, Jüni P, Katus HA, Landmesser U, Leclercq C, Lettino M, Lewis BS, Merkely B, Mueller C, Petersen S, Petronio AS, Richter DJ, Roffi M, Shlyakhto E, Simpson IA, Sousa-Uva M, Touyz RM, Nibouche D, Zelveian PH, Siostrzonek P, Najafov R, van de Borne P, Pojskic B, Postadzhiyan A, Kypris L, Špinar J, Larsen ML, Eldin HS, Viigimaa M, Strandberg TE, Ferrières J, Agladze R, Laufs U, Rallidis L, Bajnok L, Gudjónsson T, Maher V, Henkin Y, Gulizia MM, Mussagaliyeva A, Bajraktari G, Kerimkulova A, Latkovskis G, Hamoui O, Slapikas R, Visser L, Dingli P, Ivanov V, Boskovic A, Nazzi M, Visseren F, Mitevska I, Retterstøl K, Jankowski P, Fontes-Carvalho R, Gaita D, Ezhov M, Foscoli M, Giga V, Pella D, Fras Z, de Isla LP, Hagström E, Lehmann R, Abid L, Ozdogan O, Mitchenko O, Patel RS, ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *Eur Heart J* 2020;**41**:111–188.

11. Helgadottir A, Thorleifsson G, Alexandersson KF, Tragante V, Thorsteinsdottir M, Eiriksson FF, Gretarsdottir S, Björnsson E, Magnusson O, Sveinbjornsson G, Jonsdottir I, Steinthorsdottir V, Ferkingstad E, Jensson BÖ, Stefansson H, Olafsson I, Christensen AH, Torp-Pedersen C, Køber L, Pedersen OB, Erikstrup C, Sørensen E, Brunak S, Banasik K, Hansen TF, Nyegaard M, Eyjolfssson GI, Sigurdardottir O, Thorarinsson BL, Matthiasson SE, Steingrimsdottir T, Bjornsson ES, Danielsen R, Asselbergs FW, Arnar DO, Ullum H, Bundgaard H, Sulem P, Thorsteinsdottir U, Thorgeirsson G, Holm H, Gudbjartsson DF, Stefansson K. Genetic variability in the absorption of dietary sterols affects the risk of coronary artery disease. *Eur Heart J* 2020;**41**:2618–2628.
12. Münzel T, Hahad O, Kuntic M, Keaney JF, Deanfield JE, Daiber A. Effects of tobacco cigarettes, e-cigarettes, and waterpipe smoking on endothelial function and clinical outcomes. *Eur Heart J* 2020;**41**:4057–4070.
13. Stanbrook MB, Drazen JM. Vaping-induced lung disease. A look forward by looking back. *N Engl J Med* 2020;**382**:1649–1650.
14. Kuntic M, Oelze M, Steven S, Kröller-Schön S, Stamm P, Kalinovic S, Frenis K, Vujacic-Mirski K, Bayo Jimenez MT, Kvandova M, Filippou K, Al Zuabi A, Brückl V, Hahad O, Daub S, Varveri F, Gori T, Huesmann R, Hoffmann T, Schmidt FP, Keaney JF, Daiber A, Münzel T. Short-term e-cigarette vapour exposure causes vascular oxidative stress and dysfunction: evidence for a close connection to brain damage and a key role of the phagocytic NADPH oxidase (NOX-2). *Eur Heart J* 2020;**41**:2472–2483.
15. Siedlinski M, Harrison DG, Guzik TJ. E-vaporating benefits of e-vaping. *Eur Heart J* 2020;**41**:2484–2486.
16. Estruch R, Ros E, Salas-Salvadó J, Covas M-I, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí JV, Martínez JA, Fitó M, Gea A, Hernán MA, Martínez-González MA, PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med* 2018;**378**:e34.
17. Li J, Guasch-Ferré M, Chung W, Ruiz-Canela M, Toledo E, Corella D, Bhupathiraju SN, Tobias DK, Tabung FK, Hu J, Zhao T, Turman C, Feng YA, Clish CB, Mucci L, Eliassen AH, Costenbader KH, Karlson EW, Wolpin BM, Ascherio A, Rimm EB, Manson JE, Qi L, Martínez-González MÁ, Salas-Salvadó J, Hu FB, Liang L. The Mediterranean diet, plasma metabolome, and cardiovascular disease risk. *Eur Heart J* 2020;**41**:2645–2656.
18. Tong TYN, Appleby PN, Key TJ, Dahm CC, Overvad K, Olsen A, Tjønneland A, Katzke V, Kühn T, Boeing H, Karakatsani A, Peppa E, Trichopoulou A, Weiderpass E, Masala G, Grioni S, Panico S, Tumino R, Boer JMA, Verschuren WMM, Quirós JR, Agudo A, Rodríguez-Barranco M, Imaz L, Chirlaque M-D, Moreno-Iribas C, Engström G, Sonestedt E, Lind M, Otten J, Khaw K-T, Aune D, Riboli E, Wareham NJ, Imamura F, Forouhi NG, di Angelantonio E, Wood AM, Butterworth AS, Perez-Cornago A. Perez-Cornago A. The associations of major foods and fibre with risks of ischaemic and haemorrhagic stroke: a prospective study of 418 329 participants in the EPIC cohort across nine European countries. *Eur Heart J* 2020;**41**:2632–2640.
19. Vinchi F, Porto G, Simmelbauer A, Altamura S, Passos ST, Garbowski M, Silva AMN, Spaich S, Seide SE, Sparla R, Hentze MW, Muckenthaler MU. Atherosclerosis is aggravated by iron overload and ameliorated by dietary and pharmacological iron restriction. *Eur Heart J* 2020;**41**:2681–2695.
20. van der Wal HH, Grote Beverborg N, Dickstein K, Anker SD, Lang CC, Ng LL, van Veldhuisen DJ, Voors AA, van der Meer P. Iron deficiency in worsening heart failure is associated with reduced estimated protein intake, fluid retention, inflammation, and antiplatelet use. *Eur Heart J* 2019;**40**:3616–3625.
21. Voskoboinik A, Kalman JM, De Silva A, Nicholls T, Costello B, Nanayakkara S, Prabhu S, Stub D, Azzopardi S, Vizi D, Wong G, Nalliah C, Sugumar H, Wong M, Kotschet E, Kaye D, Taylor AJ, Kistler PM. Alcohol abstinence in drinkers with atrial fibrillation. *N Engl J Med* 2020;**382**:20–28.
22. 2018 Physical Activity Guidelines Advisory Committee. 2018 Physical Activity Guidelines Advisory Committee Scientific Report. Washington, DC: US Department of Health and Human Services; 2018.
23. Jeong SW, Kim SH, Kang SH, Kim HJ, Yoon CH, Youn TJ, Chae IH. Mortality reduction with physical activity in patients with and without cardiovascular disease. *Eur Heart J* 2019;**40**:3547–3555.
24. Henriksson H, Henriksson P, Tynelius P, Ekstedt M, Berglind D, Labayen I, Ruiz JR, Lavie CJ, Ortega FB. Cardiorespiratory fitness, muscular strength, and obesity in adolescence and later chronic disability due to cardiovascular disease: a cohort study of 1 million men. *Eur Heart J* 2020;**41**:1503–1510.
25. Garnvik LE, Malmo V, Janszky I, Ellekjær H, Wisløff U, Loennechen JP, Nes BM. Physical activity, cardiorespiratory fitness, and cardiovascular outcomes in individuals with atrial fibrillation: the HUNT study. *Eur Heart J* 2020;**41**:1467–1475.
26. Elliott AD, Linz D, Mishima R, Kadhim K, Gallagher C, Middeldorp ME, Verdicchio CV, Hendriks JML, Lau DH, La Gerche A, Sanders P. Association between physical activity and risk of incident arrhythmias in 402 406 individuals: evidence from the UK Biobank cohort. *Eur Heart J* 2020;**41**:1479–1486.
27. Jenkin CR, Eime RM, Westerbeek H, O'Sullivan G, van Uffelen JGZ. Sport and ageing: a systematic review of the determinants and trend of participation in sport for older adults. *BMC Public Health* 2017;**17**:976.
28. Streese L, Khan AW, Deiseroth A, Hussain S, Suades R, Tiaden A, Kyburz D, Cosentino F, Hanssen H. High-intensity interval training modulates retinal microvascular phenotype and DNA methylation of p66Shc gene: a randomized controlled trial (EXAMIN AGE). *Eur Heart J* 2020;**41**:1514–1519.
29. Streese L, Khan AW, Deiseroth A, Hussain S, Suades R, Tiaden A, Kyburz D, Hanssen H, Cosentino F. Physical activity may drive healthy microvascular ageing via downregulation of p66Shc. *Eur J Prev Cardiol* 2020;**27**:168–176.
30. Estruch R, Ros E. Role of Mediterranean diet on weight loss and obesity-related diseases. *Rev Endocr Metab Disord* 2020;**21**:315–327.
31. Dale CE, Fatemifar G, Palmer TM, White J, Prieto-Merino D, Zabaneh D, Engmann JEL, Shah T, Wong A, Warren HR, McLachlan S, Trompet S, Moldovan M, Morris RW, Sofat R, Kumari M, Hypponen E, Jefferis BJ, Gaunt TR, Ben-Shlomo Y, Zhou A, Gentry-Maharaj A, Ryan A, Mutsert R, Noordam R, Caulfield MJ, Jukema JW, Worrall BB, Munroe PB, Menon U, Power C, Kuh D, Lawlor DA, Humphries SE, Mook-Kanamori DO, Sattar N, Kivimaki M, Price JF, Davey Smith G, Dudbridge F, Hingorani AD, Holmes MV, Casas JP. Causal associations of adiposity and body fat distribution with coronary heart disease, stroke subtypes, and type 2 diabetes mellitus: a Mendelian randomization analysis. *Circulation* 2017;**135**:2373–2388.
32. Larsson SC, Bäck M, Rees JMB, Mason AM, Burgess S. Body mass index and body composition in relation to 14

cardiovascular conditions in UK Biobank: a Mendelian randomization study. *Eur Heart J* 2020;**41**:221–226.
33. de Cabo R, Mattson MP. Effects of intermittent fasting on health, aging, and disease. *N Engl J Med* 2019;**381**:2541–2255.
34. Moussa O, Ardissino M, Heaton T, Tang A, Khan O, Ziprin P, Darzi A, Collins P, Purkayastha S. Effect of bariatric surgery on long-term cardiovascular outcomes: a nationwide nested cohort study. *Eur Heart J* 2020;**41**:2660–2667.
35. Wang C, Bangdiwala SI, Rangarajan S, Lear SA, AlHabib KF, Mohan V, Teo K, Poirier P, Tse LA, Liu Z, Rosengren A, Kumar R, Lopez-Jaramillo P, Yusoff K, Monsef N, Krishnapillai V, Ismail N, Seron P, Dans AL, Kruger L, Yeates K, Leach L, Yusuf R, Orlandini A, Wolyniec M, Bahonar A, Mohan I, Khatib R, Temizhan A, Li W, Yusuf S. Association of estimated sleep duration and naps with mortality and cardiovascular events: a study of 116 632 people from 21 countries. *Eur Heart J* 2019;**40**:1620–1629.
36. Carney RM, Freedland KE. Depression and coronary heart disease. *Nat Rev Cardiol* 2017;**14**:145–155.
37. Fan M, Sun D, Zhou T, Heianza Y, Lv J, Li L, Qi L. Sleep patterns, genetic susceptibility, and incident cardiovascular disease: a prospective study of 385 292 UK biobank participants. *Eur Heart J* 2020;**41**:1182–1189.
38. Vaccarino V, Badimon L, Bremner JD, Cenko E, Cubedo J, Dorobantu M, Duncker DJ, Koller A, Manfrini O, Milicic D, Padro T, Pries AR, Quyyumi AA, Tousoulis D, Trifunovic D, Vasiljevic Z, de Wit C, Bugiardini R, Lancellotti P, Carneiro AV; ESC Scientific Document Group Reviewers. Depression and coronary heart disease: 2018 position paper of the ESC working group on coronary pathophysiology and microcirculation. *Eur Heart J* 2020;**41**:1687–1696.
39. Tillmann T, Vaucher J, Okbay A, Pikhart H, Peasey A, Kubinova R, Pajak A, Tamosiunas A, Malyutina S, Hartwig FP, Fischer K, Veronesi G, Palmer T, Bowden J, Smith GD, Bobak M, Holmes MV. Education and coronary heart disease: Mendelian randomisation study. *BMJ* 2017;**358**:j3542.
40. Framke E, Sørensen JK, Andersen PK, Svane-Petersen AC, Alexanderson K, Bonde JP, Farrants K, Flachs EM, Hanson LLM, Nyberg ST, Villadsen E, Kivimäki M, Rugulies R, Madsen IEH. Contribution of income and job strain to the association between education and cardiovascular disease in 1.6 million Danish employees. *Eur Heart J* 2020;**41**:1164–1178.
41. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;**380**:2295–2306.
42. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde A-M, Sabatine MS; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;**380**:347–357.
43. Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, Charbonnel B, Frederich R, Gallo S, Cosentino F, Shih WJ, Gantz I, Terra SG, Cherney DZI, McGuire DK; McGuire DK for the VERTIS CV Investigators. Ertugliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2020;**383**:1425–1435.
44. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M, Chiang C-E, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjöstrand M, Langkilde A-M; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**:1995–2008.
45. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi D-J, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-La Rocca H-P, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde M-F, Spinar J, Squire I, Taddei S, Wanner C, Zannad F; EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;**383**:1413–1424.
46. McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, Pratley R, Greenberg M, Wang S, Huyck S, Gantz I, Terra SG, Masiukiewicz U, Cannon CP. Sodium-glucose cotransporter 2 inhibitors, cardiovascular and kidney outcomes in patients with type 2 diabetes: a systematic review and meta-analysis of outcomes trials. *JAMA Cardiol* 2020;doi: 10.1001/jamacardio.2020.4511.
47. Marsico F, Paolillo S, Gargiulo P, Bruzzese D, Dell'Aversana S, Esposito I, Renga F, Esposito L, Marciano C, Dellegrottaglie S, Iesu I, Perrone Filardi P. Effects of glucagon-like peptide-1 receptor agonists on major cardiovascular events in patients with Type 2 diabetes mellitus with or without established cardiovascular disease: a meta-analysis of randomized controlled trials. *Eur Heart J* 2020;**41**:3346–3358.
48. Doehner W, Gerstein HC, Ried J, Jung H, Asbrand C, Hess S, Anker SD. Obesity and weight loss are inversely related to mortality and cardiovascular outcome in prediabetes and type 2 diabetes: data from the ORIGIN trial. *Eur Heart J* 2020;**41**:2668–2677.
49. Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE, Mossialos EA, Maggioni AP, Kazakiewicz D, May HT, De Smedt D, Flather M, Zuhlke L, Beltrame JF, Huculeci R, Tavazzi L, Hindricks G, Bax J, Casadei B, Achenbach S, Wright L, Vardas P, Mimoza L, Artan G, Aurel D, Chettibi M, Hammoudi N, Sisakian H, Pepoyan S, Metzler B, Siostrzonek P, Weidinger F, Jahangirov T, Aliyev F, Rustamova Y, Manak N, Mrochak A, Lancellotti P, Pasquet A, Claeys M, Kušljugić Z, Dizdarević Hudić L, Smajić E, Tokmakova MP, Gatzov PM, Milicic D, Bergovec M, Christou C, Moustra HH, Christodoulides T, Linhart A, Taborsky M, Hansen HS, Holmvang L, Kristensen SD, Abdelhamid M, Shokry K, Kampus P, Viigimaa M, Ryödi E, Niemelä M, Rissanen TT, Le Heuzey J-Y, Gilard M, Aladashvili A, Gamkrelidze A, Kereselidze M, Zeiher A, Katus H, Bestehorn K, Tsioufis C, Goudevenos J, Csanádi Z, Becker D, Tóth K, Jóna Hrafnkelsdóttir Þ, Crowley J, Kearney P, Dalton B, Zahger D, Wolak A, Gabrielli D, Indolfi C, Urbinati S, Imantayeva G, Berkinbayev S, Bajraktari G, Ahmeti A, Berisha G, Erkin M, Saamay A, Erglis A, Bajare I, Jegere S, Mohammed M, Sarkis A, Saadeh G, Zvirblyte R, Sakalyte G, Slapikas R, Ellafi K, El Ghamari F, Banu C, Beissel J, Felice T, Buttigieg SC, Xuereb RG, Popovici M, Boskovic A, Rabrenovic M, Ztot S, Abir-Khalil S, van Rossum AC, Mulder BJM, Elsendoorn MW, Srbinovska-Kostovska E, Kostov J, Marjan B, Steigen T, Mjølstad OC, Ponikowski P, Witkowski A, Jankowski P, Gil VM, Mimoso J, Baptista S, Vinereanu D, Chioncel O, Popescu BA, Shlyakhto E, Oganov R, Foscoli M, Zavatta M, Dikic AD, Beleslin B, Radovanovic MR, Hlivák P, Hatala R, Kaliská G, Kenda M, Fras Z, Anguita M, Cequier Á, Muñiz J, James S, Johansson B, Platonov P, Zellweger MJ, Pedrazzini GB, Carballo D, Shebli HE, Kabbani S, Abid L, Addad F, Bozkurt E, Kayıkçıoğlu M, Erol MK, Kovalenko V, Nesukay E, Wragg A, Ludman P, Ray S, Kurbanov R, Boateng D, Daval G, de Benito Rubio V, Sebastiao D, de Courtelary PT, Bardinet I; European Society of Cardiology. European Society of Cardiology: cardiovascular disease statistics 2019. *Eur Heart J* 2020;**41**:12–85.
50. NCD Risk Factor Collaboration (NCD-RisC). Long-term and recent trends in hypertension awareness, treatment, and control in 12 high-income countries: an analysis of 123 nationally representative surveys. *Lancet* 2019;**394**:639–651.
51. Gidding SS, Robinson J. It is now time to focus on risk before age 40. *J Am Coll Cardiol* 2019;**74**:342–345.
52. Wang C, Yuan Y, Zheng M, Pan A, Wang M, Zhao M, Li Y, Yao S, Chen S, Wu S, Xue H. Association of age of onset of hypertension with cardiovascular diseases and mortality. *J Am Coll Cardiol* 2020;**75**:2921–2930.
53. Hongwei J, Kim A, Ebinger JE, Niiranen TJ, Claggett BL, Merz NB, Cheng S. Sex differences in blood pressure trajectories over the life course. *JAMA Cardiol* 2020;**5**:19–26.

54. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacobs DRJr, Kronmal R, Liu K, Nelson JK, O'Leary D, Saad MF, Shea F, Szklo S, Tracy RP. Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol* 2002;**156**:871–881.
55. Whelton SP, McEvoy JW, Shaw L, Psaty BM, Lima JAC, Budoff M, Nasir K, Szklo M, Blumenthal RS, Blaha MJ. Association of normal systolic blood pressure level with cardiovascular disease in the absence of risk factors. *JAMA Cardiol* 2020;**5**:1011–1018.
56. Plante TB, Koh I, Judd SE, Howard G, Howard VJ, Zakai NA, Booth JN, Safford MM, Muntner P, Cushman M. Life's Simple 7 and Incident Hypertension: the REGARDS study. *J Am Heart Assoc* 2020;**9**:e016482.
57. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT, Juliano RA, Jiao L, Granowitz C, Tardif J-C, Ballantyne CM; for the REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertrygliceridemia. *N Eng J Med* 2019;**380**:11–22.
58. Boden WE, Bhatt DL, Toth PP, Ray KK, Chapman MJ, Lüscher TF. Profound reductions in first and total cardiovascular events with icosapent ethyl in the REDUCE-IT trial: why these results usher in a new era in dyslipidemia therapeutics. *Eur Heart J* 2020;**41**:2304–2312.
59. Poss AM, Holland WL, Summers SA. Risky lipids: refining the ceramide score that measures cardiovascular health. *Eur Heart J* 2020;**41**:381–382.
60. Ray KK, Phil M, Wright RS, Kallend D, Koenig W, Leiter LA, Raal FJ, Bisch JA, Richardson T, Jaros M, Wijngaard PLJ, Kastelein JJP; for the ORION-10 and ORION 11 Investigators. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N Engl J Med* 2020;**382**:1507–1519.
61. Raal FJ, Rosenson RS, Reeskamp LF, Hovingh GK, Kastelein JJP, Rubba P, Ali S, Banerjee P, Chan KC, Gipe DA, Khilla N, Pordy R, Weinreich DM, Yancopoulos GD, Zhang Y, Gaudet D; for the Elipse HoFH Investigators. Evanicumab for homozygous familial hypercholesterolemia. *N Eng J Med* 2020;**383**:711–720.
62. Rossignol P, Agarwal R, Canaud B, Charney A, Chatellier G, Craig JC, Cushman WC, Gansevoort RT, Fellström B, Garza D, Guzman N, Holtkamp FA, London GM, Massy ZA, Mebazaa A, Mol PGM, Pfeffer MA, Rosenberg Y, Ruilope LM, Seltzer J, Shah AM, Shah S, Singh B, Stefánsson BV, Stockbridge N, Stough WG, Thygesen K, Walsh M, Wanner C, Warnock DG, Wilcox CS, Wittes J, Pitt B, Thompson A, Zannad F. Cardiovascular outcome trials in patients with chronic kidney disease: challenges associated with selection of patients and endpoints. *Eur Heart J* 2019;**40**:880–886.
63. Legrand M, Rossignol P. Cardiovascular consequences of acute kidney injury. *N Engl J Med* 2020;**382**:2238–2247.
64. Leiba A, Fishman B, Twig G, Gilad D, Derazne E, Shamiss A, Shohat T, Ron O, Grossman E. Association of adolescent hypertension with future end-stage renal disease. *JAMA Intern Med* 2019;**179**:517–523.
65. Ruiz-Hurtado G, Ruilope LM. Does cardiovascular protection translate into renal protection? *Nat Rev Cardiol* 2014;**11**:742–746.
66. Ishigami J, Cowan LT, Demmer RT, Grams ME, Lutsey PL, Carrero J-J, Coresh J, Matsushita K. Incident hospitalization with major cardiovascular diseases and subsequent risk of ESKD: implications for cardiorenal syndrome. *J Am Soc Nephrol* 2020;**31**:405–414.
67. Rangaswami J, Bhalla V, de Boer IH, Staruschenko A, Sharp JA, Singh RR, Lo KB, Tuttle K, Vaduganathan M, Ventura H, McCullough PA; American Heart Association Council on the Kidney in Cardiovascular Disease; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Lifestyle and Cardiometabolic Health. Cardiorenal protection with the newer antidiabetic agents in patients with diabetes and chronic kidney disease: a scientific statement from the American Heart Association. *Circulation* 2020;**142**:e265–e286.
68. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Nowack C, Kolkhof P, Ferreira AC, Schloemer P, Filippatos G; on behalf of the FIDELIO-DKD Study Investigators. Design and baseline characteristics of the finerenone in reducing kidney failure and disease progression in diabetic kidney disease trial. *Am J Nephrol* 2019;**50**:333–344.
69. Yang Y, Ding L, Zou X, Shen Y, Hu D, Hu X, Li Z, Kamel IR. Visceral adiposity and high intramuscular fat deposition independently predict critical illness in patients with SARS-CoV-2. *Obesity* 2020;**28**:2040–1002.
70. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, Li J, Yao Y, Ge S, Xu G. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int* 2020;**97**:829–838.
71. Libby P, Lüscher T, COVID-19 is, in the end, an endothelial disease. *Eur Heart J* 2020;**41**:3038–3044.
72. Guzik TJ, Mohiddin SA, Dimarco A, Patel V, Savvatis K, Marelli-Berg FM, Madhur MS, Tomaszewski M, Maffia P, D'Acquisto F, Nicklin SA, Marian AJ, Nosalski R, Murray EC, Guzik B, Berry C, Touyz RM, Kreutz R, Wang DW, Bhella D, Sagliocco O, Crea F, Thomson EC, McInnes IB. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. *Cardiovasc Res* 2020;**116**:1666–1687.
73. Ruilope LM, Tamargo J, Ruiz-Hurtado G. Reni-angiotensin system inhibitors in the COVID-19 pandemic: consequences of antihypertensive drugs. *Eur Heart J* 2020;**41**:2067–2069.
74. Fauvel C, Weizman O, Trimaille A, Mika D, Pommier T, Pace N, Douair A, Barbin E, Fraix A, Bouchot O, Benmansour O, Godeau G, Mecheri Y, Lebourdon R, Yvorel C, Massin M, Leblon T, Chabbi C, Cugney E, Benabou L, Aubry M, Chan C, Boufoula I, Barnaud C, Bothorel L, Duceau B, Sutter W, Waldmann V, Bonnet G, Cohen A, Pezel T; for the critical COVID-19 France Investigators. Pulmonary embolism in COVID-19 patients: a French multicentre cohort study. *Eur Heart J* 2020;**41**:3058–3068.
75. Vromman A, Ruvkun V, Shvartz E, Wojtkiewicz G, Santos Masson G, Tesmenitsky Y, Folco E, Gram H, Nahrendorf M, Swirski FK, Sukhova GK, Libby P. Stage-dependent differential effects of interleukin-1 isoforms on experimental atherosclerosis. *Eur Heart J* 2019;**40**:2482–2491.
76. van't Klooster CC, Ridker PM, Hjortnaes J, van der Graaf Y, Asselbergs FW, Westerink J, Aerts J, Visseren FLJ. The relation between systemic inflammation and incident cancer in patients with stable cardiovascular disease: a cohort study. *Eur Heart J* 2019;**40**:3901–3909.
77. Sturgeon KM, Deng L, Bluethmann SM, Zhou S, Trifiletti DM, Jiang C, Kelly SP, Zaorsky NG. A population-based study of cardiovascular disease mortality risk in US cancer patients. *Eur Heart J* 2019;**40**:3889–3897.
78. Potts JE, Iliescu CA, Lopez Mattei JC, Martinez SC, Holmvang L, Ludman P, De Belder MA, Kwok CS, Rashid M, Fischman DL, Mamas MA. Percutaneous coronary intervention in cancer patients: a report of the prevalence and outcomes in the United States. *Eur Heart J* 2019;**40**:1790–1800.
79. Guha A, Dey AK, Jneid H, Addison D. Acute coronary syndromes in cancer patients. *Eur Heart J* 2019;**40**:1487–1490.
80. Zamorano JL, Lancellotti PR, Munoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GYH, Lyon AR, Lopez Fernandez T, Mohty D, Piepoli MF, Tamargo J, Torbicki A, Suter TM. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**:2768–2801.

ESC European Society of Cardiology

Special article

The year in cardiovascular medicine 2020: acute coronary syndromes and intensive cardiac care

Borja Ibanez[1,2,3*], David Roque[4], and Susanna Price[5]

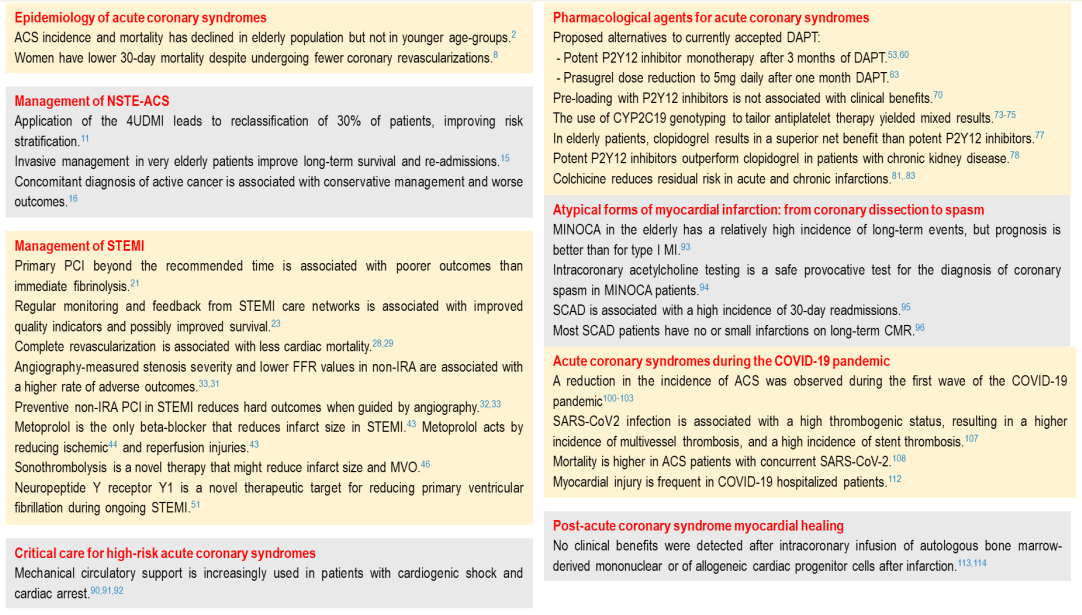
[1] Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid, Spain; [2] Cardiology Department, IIS-Fundación Jiménez Díaz University Hospital, Madrid, Spain; [3] CIBERCV, Madrid, Spain; [4] Cardiology Department, Prof. Dr. Fernando Fonseca Hospital, Amadora, Portugal; and [5] Department of Cardiology and Department of Adult Critical Care, Royal Brompton Hospital, London, UK

Received 22 October 2020; revised 7 December 2020; editorial decision 17 December 2020; accepted 17 December 2020

Reproduced from: Ibanez B, Roque D, Price S. The year in cardiovascular medicine 2020: acute coronary syndromes and intensive cardiac care. Eur Heart J. 2021 Mar 1;42(9):884-895, https://doi.org/10.1093/eurheartj/ehaa1090, by permission of Oxford University Press on behalf of the European Society of Cardiology

* Corresponding author. Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) & Cardiology Department, IIS-Fundación Jiménez Díaz University Hospital. c/Melchor Fernandez Almagro, 3. 28029 Madrid, Spain. Email: bibanez@cnic.es

Graphical Abstract



Highlights of 2020 publications on acute cardiac care–acute coronary syndromes. The statements in this figure are based on individual published articles and do not represent any kind of recommendation. ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; COVID-19, coronavirus disease 19; DAPT, dual antiplatelet therapy; FFR, fractional flow reserve; I/R, ischaemia–reperfusion; IRA, infarct-related artery; MI, myocardial infarction; MINOCA, myocardial infarction with non-obstructive coronary arteries; MVD, multivessel disease; MVO, microvascular obstruction; NSTE-ACS, non-ST segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCAD, spontaneous coronary artery dissection; STEMI, ST-segment elevation myocardial infarction; 4UDMI, fourth universal definition of myocardial infarction. Numbers correspond to the references in the text.

Keywords Acute coronary syndrome • Infarction • Acute cardiac care • Coronary artery disease • Intensive care

Introduction

Advancements in acute cardiac care have significantly contributed to prolonging life expectancy and improving quality of care. Acute cardiac care is an area of intense basic, translational, and clinical research. In particular, acute coronary syndrome (ACS) is one of the most frequent clinical presentations requiring acute cardiac care. Despite improvements in primary prevention, the incidence of ACS and its associated mortality and morbidity remains high, with an immense impact on patients and healthcare systems. This review presents the most relevant publications in 2020 that are likely to impact on the clinical management of patients presenting with ACS requiring intensive cardiac care.

Epidemiology of acute coronary syndromes

Identification of the association between risk factors and coronary heart disease allowed the implementation of preventive strategies. Poor control of modifiable risk factors is responsible for a large proportion of mortality and morbidity worldwide. The impact of risk factor modification was highlighted in a population analysis of 6518 men from the Seven Countries Study, in which participants were assessed over a 50-year follow-up.[1] Country cohorts showing long-term decreases in risk factors had a consistent decrease of coronary heart disease mortality during follow-up. In contrast, among participants whose risk factors increased, hazard rates also increased.[1] In a study of the MONICA population-based registries, all incidences of ACS in men and women aged 35–74 were recorded between 2006 and 2014.[2] Although event rates, incidence, and mortality all showed significant reductions, these were seen primarily in the 65–74 year age group, and there were no substantial declines in younger people except for mortality in young women, possibly brought about by reductions in smoking.

Racial disparities were explored in an observational cohort analysis of data from the multicentre National Cardiovascular Data Registry chest pain-MI Registry, which included 753 hospitals and 155 397 patients with acute myocardial infarction (MI).[3] Risk-adjusted 30-day readmission rates were higher in African-American patients, who had a higher prevalence of diabetes, hypertension,

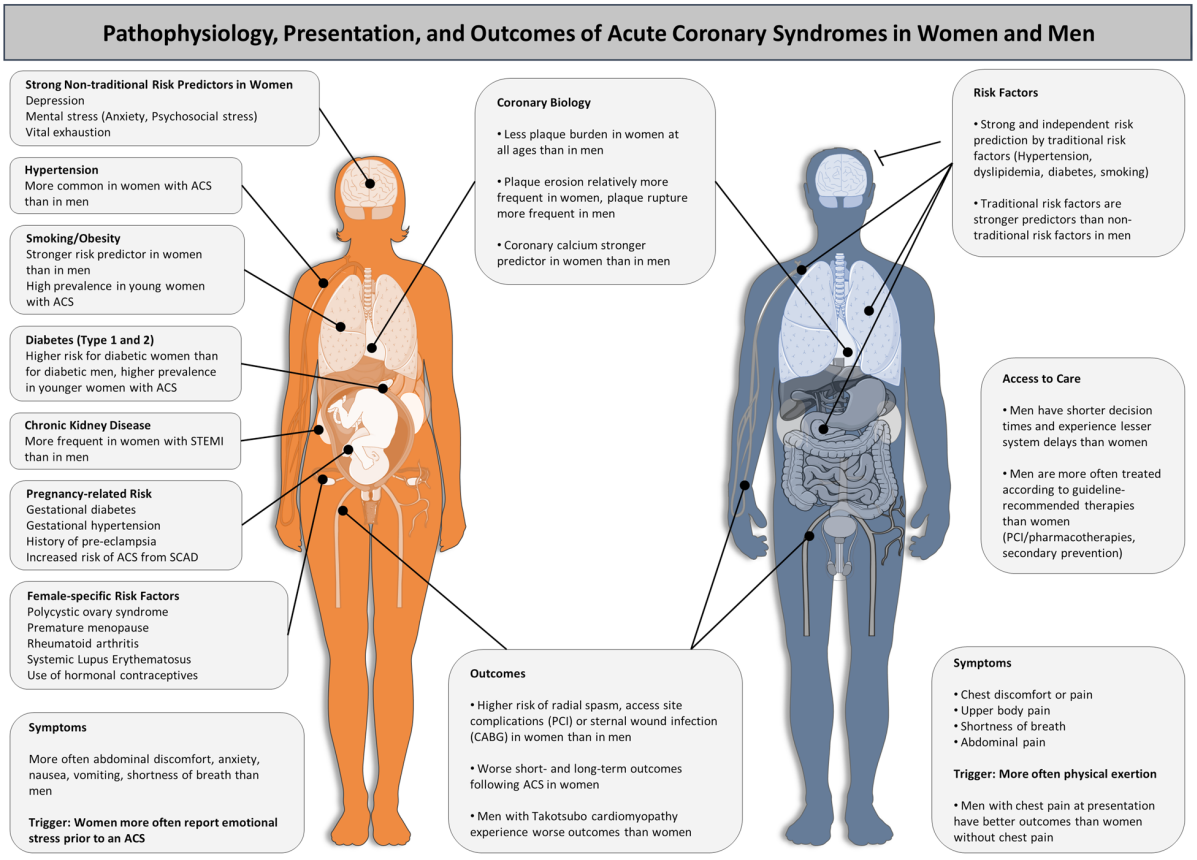


Figure 1 Sex differences in pathophysiology, presentation, and outcomes of acute coronary syndromes. ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; SCAD, spontaneous coronary artery dissection; STEMI, ST-elevation myocardial infarction. Reprinted from Haider *et al.*[4], by permission of OUP on behalf of the ESC.

heart failure, bleeding risk, stroke, and peripheral arterial disease. These findings speak to the need for a more personalized consideration of genotypic and phenotypic differences in ACS.

Substantial progress has been made towards improving sex-specific ACS management.[4] The incidence of acute MI has declined in the last 20 years; however, declines in MI admission have slowed in women compared with men.[5] When hospitalized, women tend to be older and more deprived, and have a greater co-morbidity burden. Although more frequently managed with guideline-recommended therapy pre-admission, women less frequently receive coronary angiography and/or percutaneous coronary intervention (PCI) and are less comprehensively treated with evidence-based therapies post-MI.[6,7] An apparent paradox was revealed in the Prospective Urban Rural Epidemiological (PURE) study, which recruited 202 072 individuals aged 35–70 from 27 countries: although women less frequently received secondary prevention treatment, cardiac investigations, and coronary revascularization, they had lower 30-day mortality than men after a new cardiovascular event.[8] Sex differences in ACS pathophysiology, presentation, and outcomes are presented in *Figure 1*.

Overall, data published in 2020 illustrate that more refined strategies are needed to further reduce the burden of modifiable cardiac risk factors, with special attention to addressing sex and racial differences in the management and outcomes in ACS.

Management of non-ST segment elevation acute coronary syndrome

Diagnosis

Acute chest pain is one of the frequent reasons for attending the emergency department, and rapid diagnosis is vital.[9,10] The update of the Universal definition of MI (UDMI) has been shown to have prognostic value. Application of the fourth UDMI led to reclassification of 30% of 2302 patients presenting to the emergency department, mostly from type II MI to acute myocardial injury, and from type I MI to chronic myocardial injury.[11] Importantly, reclassified patients had significantly higher rates of subsequent cardiovascular events. In a stepped-wedge cluster trial in 48 282 consecutive patients, high-sensitivity cardiac troponin (hs-cTn) and the fourth UDMI identified patients at risk of cardiovascular or non-cardiovascular events but was not associated with improved outcomes.[12] Optimal management strategies and how to improve outcomes remain unknown for patients with type II MI.[13,14]

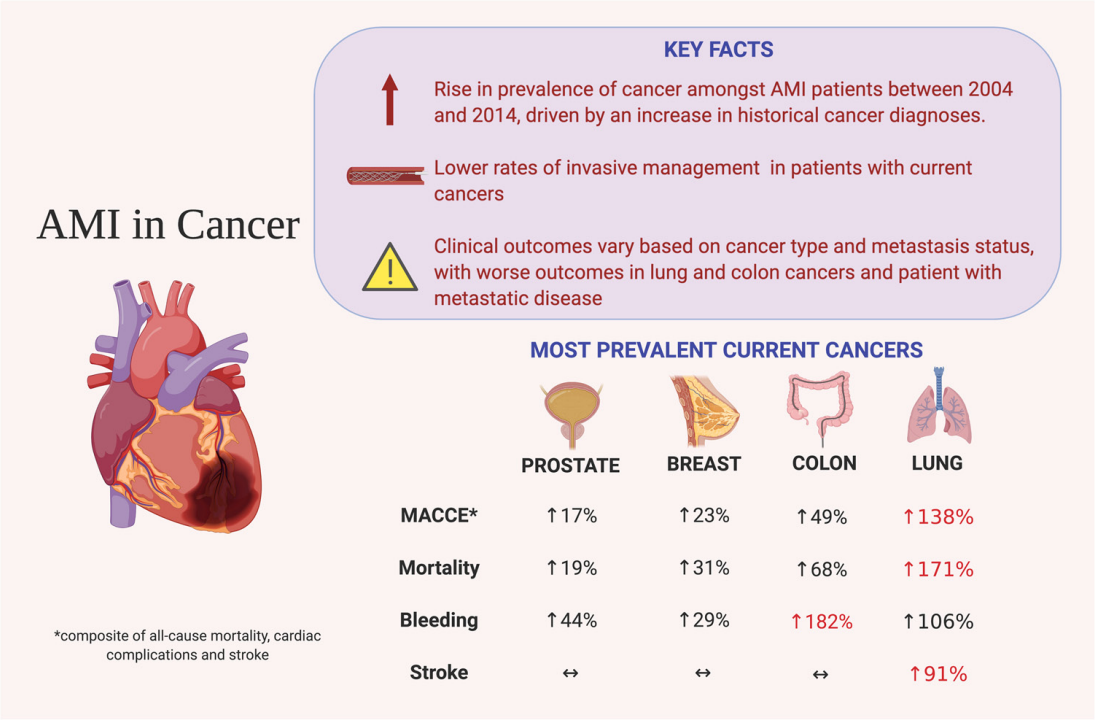


Figure 2 Management and outcomes of myocardial infarction patients with cancer. Reprinted from Bharadwaj *et al.*[16], by permission of OUP on behalf of the ESC.

Special populations

Management of special subpopulations, such as the elderly or those with cancer, is challenging. It is increasingly recognized that invasive intervention also benefits the elderly population. In a study of 1976 NSTE-ACS patients >80 years, the adjusted cumulative 5-year mortality was 35% for those managed with invasive intervention vs. 55% for those managed with non-invasive intervention.[15] A database analysis of 6 563 255 acute MI patients examined the effects of cancer on intervention and outcomes.[16] Marked differences were noted, with 43.9% of cancer-free patients undergoing PCI, compared with 21% with patients with lung cancer, which had the highest in-hospital mortality. Irrespective of cancer type, metastatic disease was associated with worse outcomes, whereas historical cancer had no impact on survival. Diagnosis of active cancer is associated with conservative management and worse outcomes; however, as these parameters vary significantly according to the type and extent of disease, an individualized approach is recommended (*Figure 2*).

Impact of bleeding

Historical data from the SWEDEHEART study demonstrated that although the introduction of antithrombotic therapies increased bleeding events during the first year following MI, this was accompanied by a substantially greater reduction in ischaemic events and an increased survival.[17] In contrast, analysis of a harmonized dataset from four multicentre randomized controlled trials (RCTs) comprising 45 011 participants found that post-discharge bleeding after an ACS was associated with a similar increase in subsequent all-cause mortality and had a similar prognostic impact to post-discharge MI.[18] These apparently conflicting data suggest that antithrombotic therapy overall has a clear benefit but bleeding identifies a population at higher risk of mortality.

Management of ST-segment elevation myocardial infarction

One of the most rapidly advancing areas of cardiology is STEMI. Since the 2017 ESC STEMI guidelines, important data with implications for patient management have continued to appear, and 2020 is a particularly prolific year in this regard.

Reperfusion strategies

The landmark DANAMI-2 and PRAGUE-2 trials demonstrated that transfer to the catheterization lab was superior to immediate fibrinolysis.[19] 2020 saw the publication of the very long-term follow-up of the DANAMI-2 RCT.[20] After 16 years of follow-up, the composite of death or MI remained significantly lower in patients transferred to PCI than in those undergoing on-site fibrinolysis. This is the first time that primary PCI has been shown to be associated with lower cardiac mortality than stand-alone fibrinolysis in a trial. The routine performance of angiography within 24 h after fibrinolysis has significantly reduced the rates of re-MI and future coronary revascularizations. Indeed, in the STREAM trial, which compared transfer to PCI vs. onsite fibrinolysis followed by routine angiography, cardiac mortality at 1 year was similar for both treatment strategies.[19] A new analysis of 2942 patients from the French FAST-MI registry found that the 5-year survival was lower in patients undergoing late PCI (>120 min) than in those undergoing timely PCI (within 120 min of diagnosis) or immediate fibrinolysis.[21]

Triage of patients to the appropriate reperfusion strategy requires the presence of well-trained healthcare providers on the scene and the integration of emergency medical services within an organized network. The creation of pan-European registries is critical to the acquisition of continuous information in this regard.[22] Clinical guidelines recommend regular monitoring and feedback in order to maintain a high quality of care, but there are few quantifiable data supporting this strategy. In a recent paper, the prospective, multicentre FITT-STEMI study assessed the long-term impact of formalized data assessment and systematic feedback on performance and mortality.[23] Over its 10-year evaluation, FITT-STEMI recorded significant improvement in all performance quality indicators used for feedback, and this feedback-informed continuous improvement in key quality indicators was linked to a significant reduction in mortality.[23]

Vascular access during primary percutaneous coronary intervention

The superiority of radial over femoral access seemed to be set in stone, and yet a recent RCT has shown intriguing results. The SAFARI-STEMI was a multicentre, open-label, RCT with blinded endpoint adjudication undertaken over 7 years (2011–2018) at five high-volume PCI centres in Canada.[24] STEMI patients were randomized 1:1 to radial vs. femoral access. The trial was stopped after enrolment of 2292 patients (47% of the original sample size) on the grounds of futility. In the trial, 30-day all-cause mortality was 1.5% vs. 1.3% in the radial and femoral access groups, respectively (P = 0.69). Intriguingly, bleeding outcomes (which were very few) did not differ between groups. It should be noted that a vascular closure device was used in 68% of patients assigned to femoral access. Whereas the SAFARI-STEMI trial assessed highly selected centres and operators, the pivotal MATRIX trial[25] was closer to the real-world clinical care, with 78 centres of different volumes in four countries. Therefore, while the SAFARI-STEMI trial shows that femoral access performed by operators experienced in the use of closure devices is a good alternative to radial access, these data should not modify the recommendation for radial access as the default vascular access route, as recommended in ESC guidelines.[10,26]

Management of non-culprit lesions

Clinical benefits of complete revascularization

Multivessel disease (MVD) is present in >50% of STEMI patients. Five major trials (*Figure 3*) published in recent years changed the therapeutic approach to severe stenosis in the non-infarct-related artery (IRA). The 2017 ESC STEMI guidelines introduced a major change, recommending that non-IRA preventive PCI should be considered before hospital discharge. Since then, this topic has been the subject of the large COMPLETE trial[27] and several meta-analyses. Two meta-analyses from 2020[28,29] clearly demonstrate that non-IRA preventive PCI, performed within weeks of the index STEMI, is associated with lower cardiovascular mortality. A pre-specified subanalysis of the COMPLETE trial concluded that complete revascularization reduced major cardiovascular outcomes to a greater extent in patients with more severe stenosis [≥60% on quantitative coronary angiography (QCA)].[30] A similar finding was recently reported after analysis of data from the Compare-acute trial.[31] The authors related events in patients allocated to medical treatment (IRA-only PCI) to the fractional flow reserve (FFR). Non-IRAs that required subsequent revascularization had a lower FFR than those without events. Increased risk of major adverse cardiovascular events (MACE) was significantly higher for lesions with FFR below 0.80.[31]

	PRAMI trial	CVLPRIT trial	DANAMI-3-PRIMULTI trial	Compare-Acute trial	COMPLETE trial
Reference	NEJM 2013; 369: 1115–1123	JACC 2015; 65: 963–972	Lancet 2015; 386: 665–671	NEJM 2017; 376: 1234–1244	NEJM 2019;381: 1411-1421
N	465	296	627	885	4041
Follow-up	23 months	12 months	27 months	12 months	12 months
Trigger for non-IRA PCI	Angio (>50%)	Angio (>70%)	FFR-guided	FFR-guided	Angio (>70%) or FFR in 50-70%
Timing of non-IRA PCI	immediate	Immediate (64%) or staged*	Staged* (2 days)	immediate	Staged (1 day (64%) 23 days (36%))
Primary outcome	Complete revasc superior	Complete revasc superior	Complete revasc superior	Complete revasc superior	Complete revasc superior
All cause death	NS	NS	NS	NS	NS
Re-infarction	Complete revasc superior	NS	NS	NS	Complete revasc superior
Repeat Revasc	Complete revasc superior	NS	Complete revasc superior	Complete revasc superior	Complete revasc superior

Figure 3 Major trials testing the clinical benefit of complete revascularization in STEMI patients with multivessel disease. IRA, infarct-related artery; PCI, percutaneous coronary intervention; Revasc, revascularization. * Before hospital discharge.

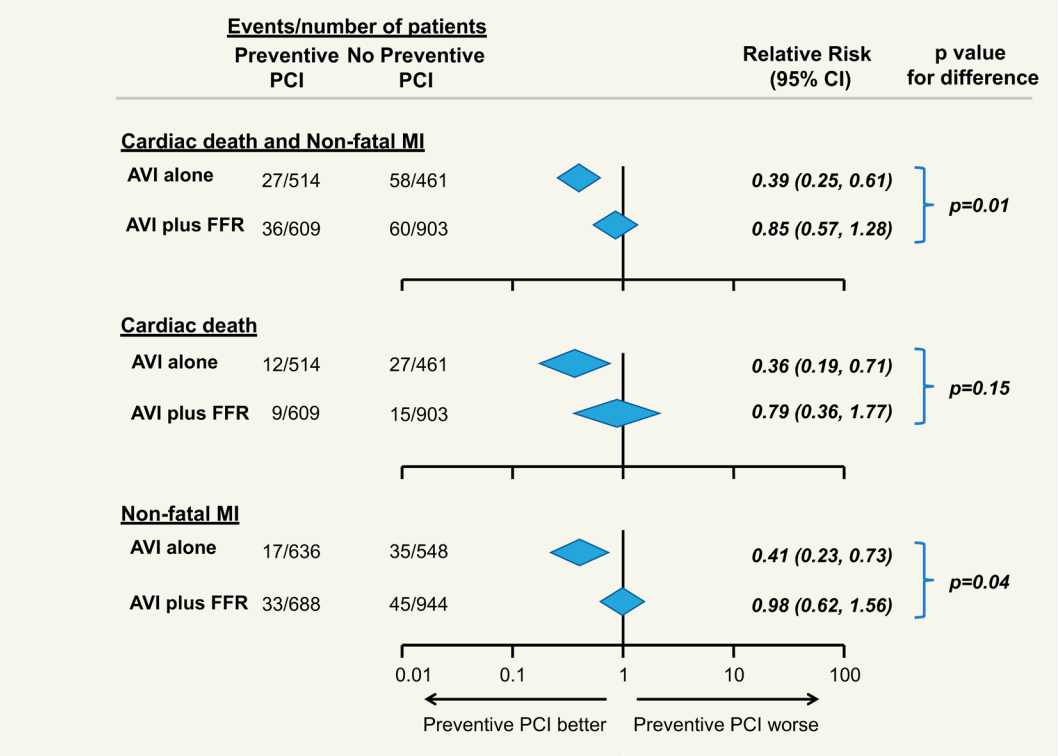


Figure 4 Role of fractional flow reserve in the assessment of non-infarct-related arteries with angiographic stenosis >50%. AVI, angiographic visual inspection; FFR, fractional flow reserve. Reprinted from Wald *et al.*[32], by permission of OUP on behalf of the ESC.

How to identify non-IRA severe lesions benefiting from PCI

There is no consensus about which method is more suitable for cataloguing a non-IRA as a candidate for preventive PCI in STEMI patients [angiography (visual inspection), FFR, or FFR after intermediate lesions on angiography]. Two recent studies intriguingly suggested that angiography-guided but not FFR-guided non-IRA PCI is associated with reduced major adverse events in STEMI patients with MVD.[32,33] Wald *et al.* performed a meta-analysis of 10 RCTs (3031 patients in total) and assessed outcomes in patients with complete revascularization vs. IRA-only PCI according to whether the decision to carry out non-IRA preventive PCI was based on angiography alone or on angiography plus FFR.[32] The authors concluded that preventive PCI of the non-IRA was associated with a significant reduction in cardiac death and non-fatal MI only when the decision to proceed with non-IRA PCI was based solely on angiography (*Figure 4*).[32] Similar findings were reported in an independent study by Gallone *et al*.[33] Here, the authors conducted an independent meta-analysis of seven RCTs, including a total of 6597 patients. The patients were stratified according to the strategy used to guide PCI of non-IRA lesions in the complete revascularization arm: angiography-guided (≥70% diameter stenosis) vs. FFR-guided (≤0.80 for lesions with ≤90% diameter stenosis). The authors found that angiography-guided but not FFR-guided complete revascularization was associated with less recurrent MI.[33] Conversely, both strategies were associated with fewer repeat revascularizations.[33] None of these studies evaluated the specific question on an ad hoc basis,[34] and these data should therefore be interpreted with caution; nevertheless, these two independent meta-analyses suggest that in STEMI patients with angiography-confirmed severe stenosis in a non-IRA, PCI should be performed regardless of the FFR result.

Ischaemia vs. vulnerable characteristics of non-IRA lesions

The accuracy of FFR to defer preventive PCI in arteries with severe angiography-detected stenosis has been questioned for patients with ACS. On one hand, coronary physiology in ACS might vary from that in stable patients, while, on the other hand, intermediate lesions with negative FFR in ACS patients might have vulnerable features that make them more prone to future rupture. Indeed, in a recently published study including data from 12 844 ACS patients from the TRITON-TIMI 38 study, spontaneous events in non-culprit lesions predominated 30 days after the index event.[35] Enlightening results from the Optical Coherence Tomography substudy of the COMPLETE trial show that 50% of assessed patients had at least one lesion in a non-IRA with features of a complex vulnerable plaque.[36]

In summary, a significant amount of data published in 2020 has increased our understanding of the implications of severe non-IRA lesions in STEMI patients and the best way to deal with them. Severe lesions on angiography seem to benefit from PCI without further FFR inspection. A more comprehensive description of the topic can be found in a major review recently published in the journal.[37]

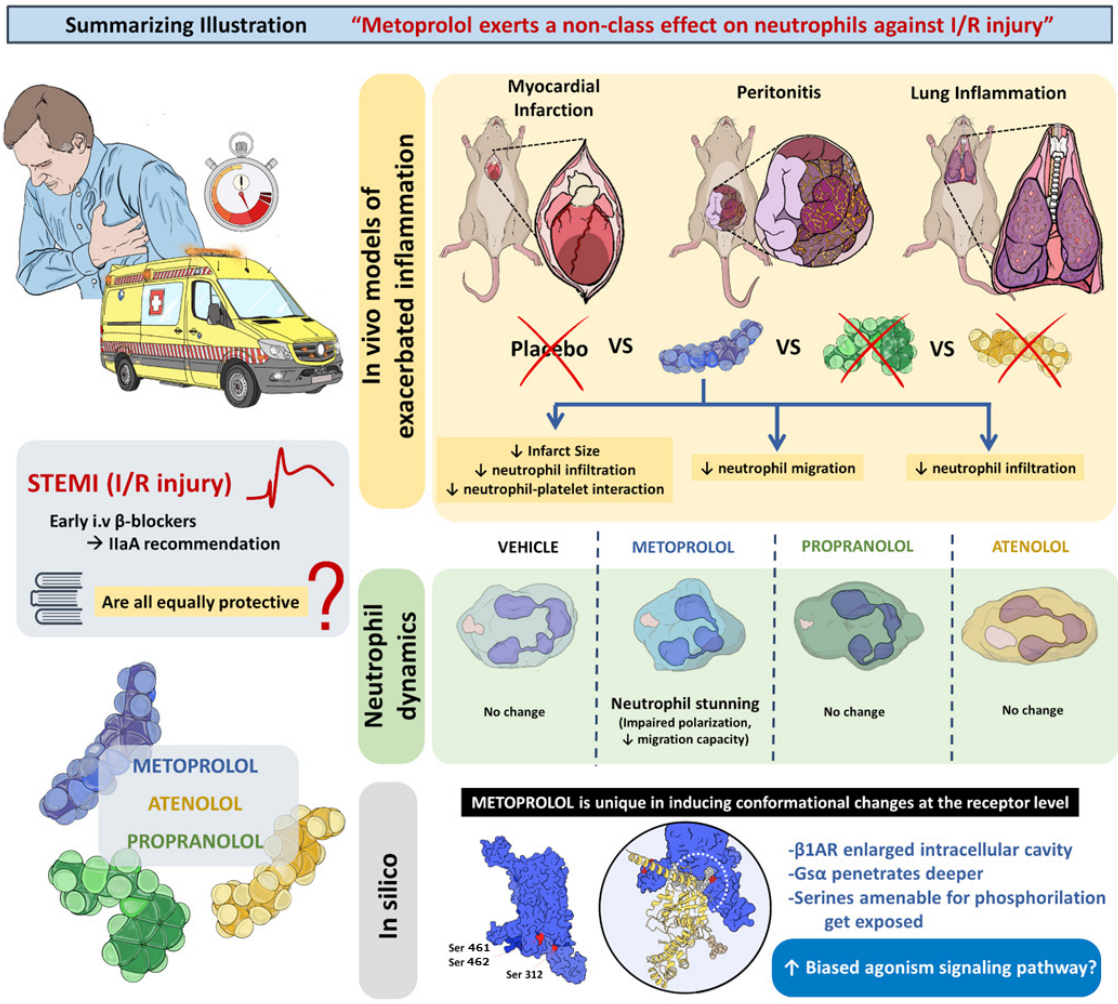


Figure 6 Metoprolol exerts a non-class effect against ischaemia–reperfusion injury by abrogating exacerbated inflammation. The cardioprotective properties of metoprolol derive from its particular ability to target neutrophils and reduce ischaemia–reperfusion injury. Atenolol and propranolol have no effect on this cell population or on infarct size. Conformational changes in the β1AR upon binding to metoprolol differ significantly from those induced by atenolol and propranolol, and this difference may underlie the neutrophil-stunning action of metoprolol. Reprinted from Clemente-Moragon *et al.*[43], by permission of OUP on behalf of the ESC.

Cardioprotection during STEMI

During ischaemia, necrosis progresses from the endocardium to the epicardium. A new cardiac magnetic resonance (CMR) clinical study this year demonstrated that the wave front of necrosis progression moves in both transmural and lateral directions (*Figure 5 – see in Lobo-Gonzalez et al.*[44] *and Lorca et al.*[38]). These data have important implications because cardioprotective strategies can salvage myocardium transmurally and laterally, potentially having a strong benefit in terms of global systolic function. Final infarct size is the result of several interconnected mechanisms.[39] There is growing evidence that these mechanisms are modified by ageing,[40] making the identification of therapeutic targets more challenging.

In >50% of patients, efficient myocardial perfusion is not achieved despite the unblocking of the epicardial coronary artery, and this is mostly due to severe microvascular obstruction (MVO).[41] Several interventions targeting MVO have been tested in experimental and clinical studies.[39] Among them, one of the strategies with more encouraging results is the early administration of the β1-selective blocker metoprolol.[42] Metoprolol injection in patients undergoing primary PCI is associated with less CMR-measured MVO.[42] A very recent experimental study demonstrated that this cardioprotective ability is not shared by other beta-blockers. Metoprolol, but not the other beta-blockers tested, reduces infarct size by stunning neutrophils during reperfusion, resulting in less MVO.[43] *In silico* modelling suggests that metoprolol induces a differential conformational change in the β1-adrenergic receptor that seems to trigger a biased agonistic effect (*Figure 6*).[43] In addition to reducing reperfusion injury, i.v. administration of metoprolol early in the course of ongoing MI is able to blunt the time-dependent progression of infarct size in a large animal model[44] (*Figure 5*). Reduced MVO was also the focus of a substudy of the small MRUSMI trial; 100 STEMI patients were randomized 1:1 to control or the novel intervention sonothrom-

bolysis (high mechanical index impulses from a diagnostic ultrasound transducer during an i.v. microbubble infusion). The primary report had already shown an association of sonothrombolysis with a smaller infarct size.[45] The new substudy shows that sonothrombolysis protected against MVO and improved global longitudinal strain in patients with an occluded artery on initial angiography.[46]

Reducing time to treatment is a central tenet of acute MI management that aims to limit mortality, infarct size, and the development of heart failure.[47] Following the pilot STEMI-DTU study, which suggested a role for left ventricular (LV) unloading in limiting infarct size,[48] a series of mechanistic studies in a pre-clinical pig model have examined LV unloading prior to revascularization. This analysis demonstrated that transvalve unloading [not extracorporeal membrane oxygenation (ECMO)] limits myocardial injury before reperfusion, reduces infarct size, and preserves myocardial energy substrate levels and mitochondrial structure and function in the infarct zone. While these findings need confirming in patient cohorts with clinical endpoints, they provide novel insights into ischaemia–reperfusion and serve as a salutary reminder that not all mechanical circulatory support devices are the same (see section below).

The cardioprotective strategy includes measures to reduce malignant arrhythmias during the acute phase of STEMI. The incidence of severe ventricular arrhythmia during STEMI is reduced by early i.v. administration of beta-blockers,[49] an effect mediated by epinephrine blockade not only in cardiomyocytes but also in cardiac-resident macrophages.[50] However, in some patients, malignant arrhythmias occur despite beta-blocker administration. A recent translational study demonstrated that patients developing primary ventricular fibrillation during an ongoing MI had higher circulating levels of the co-transmitter neuropeptide Y (NPY) than matched patients without malignant arrhythmias.[51] Experimental analysis in the same study demonstrated that NPY release from stimulation of stellate ganglia reduced the threshold for ventricular fibrillation despite the administration of beta-blockers. Pharmacological blockade of the NPY receptor Y1 prevented the development of malignant arrhythmias. These results identify Y1 as a novel therapeutic target for drugs acting in synergy with beta-blockers to prevent ventricular arrhythmias during ongoing STEMI.[51]

Pharmacological agents for acute coronary syndromes

The ever-growing maze of antiplatelet therapy

DAPT vs. $P2Y_{12}$ monotherapy after PCI

In the TICO trial, 3056 patients with ACS undergoing PCI were randomized 1:1 to ticagrelor monotherapy after 3 months of dual antiplatelet therapy (DAPT) vs. standard DAPT (aspirin + ticagrelor for 12 months). Ticagrelor monotherapy after 3 months was associated with a significant reduction in the composite primary endpoint of 1-year net adverse clinical events (2% absolute reduction).[52] In a pre-specified subanalysis of the diabetic cohort in the TWILIGHT study, ticagrelor monotherapy after 3 months was associated with a reduced risk of clinically relevant bleeding without any increase in ischaemic events, consistent with the main results of the trial.[53] Another pre-specified subanalysis of the TWILIGHT study showed that the benefits of shorter DAPT were also seen in the subpopulation undergoing complex PCI.[54] The benefits of ticagrelor monotherapy after 3 months are more pronounced in patients presenting with NSTEMI.[55] These results, suggesting a reduced risk of bleeding events with shorter DAPT without an increased risk of ischaemic events, are in line with other recently reported studies (including SMART-CHOICE,[56] STOPDAPT-2,[57] and GLOBAL-LEADERS[58]), and with a meta-analysis including trials in which aspirin was dropped 1–3 months after PCI.[59] Conversely, the RENAMI registry showed that prolonged DAPT (>12 months) with potent $P2Y_{12}$ inhibitors had a beneficial effect on ischaemic events (offsetting the increased risk of higher bleeding) except in patients older than 75 years and in women.[60] Moreover, a pre-specified subanalysis within the PEGASUS-TIMI 54 trial showed that patients with prior ACS (1–3 years before) benefitted from long-term ticagrelor on top of aspirin (fewer ischaemic events) regardless of whether they had prior coronary stenting.[61]

In the recent HOST-REDUCE-POLYTECH-ACS trial, 2338 ACS patients receiving DAPT with prasugrel for 1 month were randomized to half-dose prasugrel (5 mg daily) DAPT or full dose (10 mg) DAPT for an additional 11 months. Prasugrel-based dose de-escalation was associated with a net clinical benefit driven by a reduction in bleeding without an increase in ischaemic events.[62]

Prasugrel vs. ticagrelor in ACS patients

According to the new ESC NSTEMI guidelines,[10] prasugrel should be considered in preference to ticagrelor for NSTE-ACS patients who proceed to PCI. This notable recommendation change is mainly based on the results of the multicentre open-label ISAR-REACT 5 trial.[63] As the trial was designed to demonstrate that ticagrelor would be associated with fewer adverse events, the conclusion that prasugrel performed better generated some controversy. In a pre-specified subanalysis of the ISAR-REACT 5 trial STEMI population (41% of the sample), no significant differences in the primary endpoint (composite of 1-year death, MI, or stroke) were found between prasugrel and ticagrelor, albeit the latter was associated with a higher incidence of recurrent MI.[64] Conversely, in a post-hoc analysis of the trial undertaken in the NSTEMI population (59% of the sample), prasugrel was superior to ticagrelor in reducing the primary endpoint without increasing the risk of bleeding.[65]

In line with the ISAR-REACT 5 results, a small mechanistic study showed that, compared with ticagrelor and clopidogrel, prasugrel administered pre-PCI is associated with improved endothelial function, stronger platelet inhibition, and lower interleukin-6 (IL-6) levels, thus limiting stent-induced endothelial dysfunction and inflammation.[66] However, a recent meta-analysis of 12 trials found that of the three $P2Y_{12}$ receptor inhibitors, only ticagrelor was associated with decreased mortality.[67] A more recent large study of three databases including 31 290 ACS patients undergoing PCI found no differences in net adverse clinical events between patients taking ticagrelor or clopidogrel.[68]

Pre-loading strategies

Another new addition to the guidelines on NSTE-ACS is the recommendation against routine pre-treatment with a $P2Y_{12}$ receptor inhibitor in patients with unknown coronary anatomy who are scheduled for early invasive management.[10] In line with this recommendation, in the DUBIOUS trial, pre-loading with ticagrelor had no benefit in NSTE-ACS patients.[69] After an interim analysis of 1449 patients, the trial was prematurely interrupted for futility reasons (low incidence of the primary outcome and minimal differences between groups).[69]

Systemic platelet inhibition strategies

Although glycoprotein (GP) IIb/IIIa receptor inhibitors are now only recommended for bail-out situations, the small FABOLUS-FASTER trial randomized 122 $P2Y_{12}$-naive STEMI patients 1:1:1 to cangrelor infusion followed by prasugrel, tirofiban infusion followed by prasugrel, or prasugrel (chewed or integral). At 30 min, tirofiban yielded superior inhibition of platelet aggregation (primary endpoint) compared with cangrelor, and both were superior to chewed prasugrel (which did not provide superior platelet inhibition compared with the integral form).[70] The new kid on the block is selatogrel, a new highly selective, reversible $P2Y_{12}$ inhibitor with a fast onset of action. In a phase II trial, a single subcutaneous administration of selatogrel to MI patients reached maximum plasma concentration at ~1 h (with profound platelet inhibition as early as 15 min), without major bleeding complications.[71]

Overall, these data identify monotherapy with potent $P2Y_{12}$ inhibitors as a valid alternative to classical DAPT after the early post-MI period. While prasugrel is recommended over ticagrelor as the $P2Y_{12}$ inhibitor of choice after an MI, there are still contradictory data. De-escalation of prasugrel dose after 1 month appears as a valid alternative that can benefit patients at high bleeding risk. Cumulative evidence shows that pre-loading with $P2Y_{12}$ inhibitors in ACS patients undergoing early invasive management does not offer benefits. When fast platelet inhibition is needed, tirofiban seems a good option, with s.c. selatogrel being a promising alternative.

Personalized treatment after acute coronary syndrome

Genotyping

The GIANT study determined the CYP2C19 genotype in saliva samples from 1445 STEMI patients within 4 days after PCI to allow appropriate treatment adjustment.[72] Carriers of loss-of-function (LOF) alleles (22% of the study population) received prasugrel or a double dose of clopidogrel (potent thienopyridine strategy), while patients with wild-type or gain-of-function alleles were treated according to investigator preference. After genotyping, the potent strategy was prescribed to 99% of LOF carriers and to 55% of the other patients. Patients with LOF alleles showed no difference from the other patients in ischaemic or bleeding events at 1 year.[72] The larger TAILOR PCI trial (5302 patients undergoing PCI, 50% ACS) failed to show any ability of a CYP2C19 genotype-guided strategy to reduce adverse cardiovascular events.[73] Another study, in which a polygenic response score was derived from several CYP2C19 polymorphisms, showed that the number of alleles associated with increased platelet reactivity is a key determinant of clinical outcomes.[74]

Age and renal function

The POPular-AGE open-label trial randomized 1002 NSTE--ACS patients older than 70 years to clopidogrel or prasugrel/ticagrelor, and found that the trade-off between ischaemic and bleeding events favoured clopidogrel.[75] Similarly, in a SWEDEHEART registry report on ACS patients aged ≥80 years, ticagrelor was associated with a higher risk of bleeding and death, without providing any additional reduction in ischaemic outcomes.[76] Data from the RENAMI and BLEEMACS registries showed that prasugrel and ticagrelor performed better than clopidogrel at reducing the risk of all-cause mortality and recurrent MI, without an increase in major bleeding, in ACS patients with chronic kidney disease [estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2) treated by PCI.[77]

Altogether, these data show that while some patient subsets clearly benefit from potent $P2Y_{12}$ inhibitors (i.e. those with renal failure), others may not (i.e. the elderly). Tailored antithrombotic therapy based on genotype does not seem to offer clinical benefit yet.

Looking at old drugs with new eyes

Systemic inflammation is increasingly recognized as a therapeutic target for atherothrombosis. In a recent experimental study, colchicine was shown to stabilize atherosclerotic plaques.[78] In the landmark COLCOT trial of 4745 patients within 1 month after MI, low-dose colchicine (0.5 mg once daily) was associated with a significant reduction in the primary efficacy endpoint, mainly driven by significant reductions in stroke and urgent hospitalization for angina leading to coronary revascularization.[79] The benefit seems to be stronger when colchicine is initiated within the first 3 days after MI.[80] In the small COLCHICINE-PCI trial, acute oral colchicine (1.8 mg) before PCI had no effect on the risk of PCI-related myocardial injury, although it attenuated the increase in IL-6 and high-sensitivity C-reactive protein (hsCRP).[81] The benefits of colchicine have recently been shown to extend to patients with chronic coronary artery disease. In the LoDoCo2 trial enrolling 5522 patients (84% with prior ACS), 0.5 mg/day colchicine was associated with a reduced incidence in the composite primary endpoint (cardiovascular death, spontaneous MI, ischaemic stroke, or ischaemia-driven coronary revascularization) but did not significantly decrease cardiovascular deaths and was associated with a numerical increase in non-cardiovascular deaths.[82] The increase in non-cardiovascular deaths was also reported in the small Australian COPS trial, which randomized 795 ACS patients to placebo or colchicine (0.5 mg twice daily for the first month, then 0.5 mg daily for 11 months).[83] Colchicine was not associated with a reduction in the primary outcome of ischaemic events, but was associated with a higher rate of all-cause mortality, mainly non-cardiovascular.[83]

Altogether, these data identify colchicine as therapy that might be considered for post-MI patients with high residual ischaemic risk.

The benefits of chronic beta-blocker use in post-MI patients are well established for those with reduced LV

ejection fraction (LVEF), but the evidence is less firm for other patients. A recent study of the Korean national database followed 28 970 post-MI patients who were event-free after 1 year. Continuation with beta-blockers beyond 1 year was associated with a significantly lower rate of all-cause death than when therapy was discontinued before 1 year.[84] The benefits of beta-blockers were maintained beyond 2 years but not beyond 3 years.[84] Although this registry study was rigorous, it has important limitations that preclude a definitive answer to the question of post-MI beta-blocker therapy for patients with preserved EF.[85] In Europe, five ongoing trials are testing the role of beta-blockers in post-MI patients without reduced EF (REBOOT-CNIC, REDUCE-SWEDEHEART, BETAMI, DANBLOCK, and ABYSS). These trials will pool >20 000 properly randomized patients. The results of these trials will provide a definitive answer to this highly relevant question.

Critical care for high-risk acute coronary syndromes

The most lethal complications of MI remain cardiac arrest (CA) and cardiogenic shock (CS). CS complicates between 5% and 15% of STEMIs and is associated with in-hospital and 6-year mortality rates of 40–45% and 69%, respectively.[86] In a regional STEMI programme, CS and CA affected 9% and 11% of the 4511 patients, respectively, but represented 76% of in-hospital deaths.[87] The importance of CA as a disease modifier in CS is evident from comparison of in-hospital mortality data (CS+ and CA+, 44% vs. CS+ and CA–, 23%; $P < 0.001$). After discharge, the 5-year survival probability for CS patients was 0.69 and for CA patients was 0.89. The prognosis of CA patients was determined by the cardiac rhythm at presentation, and CS+ patients remained at high risk of lethal events.[87] A recent retrospective study has shown that young women with CS complicating an MI are treated less aggressively and experience higher in-hospital mortality than men.[88]

MI patients with concurrent CS are increasingly given mechanical circulatory support. This trend was explored in a controversy-provoking, registry-based retrospective cohort study of 168 propensity-matched patient pairs that compared the Impella heart pump with intra-aortic balloon pumps (IABPs).[89] The risks of in-hospital death and bleeding were significantly higher in patients supported with the Impella pump (45.0% vs. 34.1% and 31.3% vs. 16.0%, respectively). However, direct comparison of complication rates with different devices would require high-quality RCTs powered for hard clinical endpoints.

A recent observational study has shown that LV unloading with Impella is associated with lower mortality in patients with CS treated with venoarterial ECMO.[90]

In the very small phase II ARREST trial, 30 patients with out-of-hospital CA and refractory ventricular fibrillation were randomized to ECMO-facilitated resuscitation or standard treatment. Six-month survival was significantly better in the early ECMO group.[91]

Randomized clinical trials are needed to confirm the best strategy management for patients presenting with CS ± CA complicating an MI.

Atypical forms of myocardial infarction: from coronary dissection to spasm

The most typical form of STEMI is the formation of an occluding thrombus on a ruptured atherosclerotic plaque (type I MI). However, emergency angiography sometimes shows other findings, from MI with non-obstructive coronary arteries (MINOCA) to spontaneous coronary artery dissections (SCADs). Diagnosis, treatment, and prognosis of these patients is less well established. Of the 276 522 MI elderly patients (≥65 years old) in the US National Cardiovascular Data Registry CathPCI Registry, 16 849 (6%) fulfilled MINOCA criteria.[92] Compared with MI patients with obstructive coronary artery disease, patients with MINOCA had a lower 1-year rate of all-cause death (12% vs. 17%) and lower incidence rates of re-MI (1% vs. 6%) and heart failure (6% vs. 9%).[92] While this study shows that elderly patients with MINOCA have a relatively high incidence of 1-year MACE, this rate is significantly better than that of patients with typical MI.

MINOCA can also be caused by vasomotor dysfunction including epicardial and microvascular coronary spasm. Accurate diagnosis requires the execution of a provocative test (intracoronary acetylcholine testing), but the safety of this test in the acute MI setting has been questioned. A single-centre 10-year experience in performing provocative tests (80 MINOCA and 100 stable angina patients) has been reported.[93] Epicardial spasm was found more frequently in MINOCA patients than in stable angina patients (35% vs. 19%). Conversely, microvascular spasm was more frequent in stable angina patients (53% vs. 29% in MINOCA). Importantly, the rate of side effects was relatively low (15%), and that of complications (always reversible) was very low (2.2%) and did not differ between MINOCA and stable angina patients.[93]

SCAD is another entity that has gained attention in recent years. In the US Nationwide Readmissions Database, which included 2.5 million patients diagnosed with MI, 1386 (0.05%) were diagnosed with SCAD.[94] Compared with typical MI patients, patients with SCAD had a higher incidence of 30-day readmission (12% vs. 10%). In the SCAD population, 81% of readmissions were due to cardiac causes. The most frequent cardiac cause was reinfarction (45%), followed by chest pain (20%) and arrhythmia (13%). Half of SCAD readmissions occurred in the first week post-discharge, and more than half of reinfarctions occurred in the first 2 days post-discharge.[94] A recent report investigated the long-term impact of SCAD on CMR-measured myocardial function in 158 SCAD survivors (98% female).[95] The mode of presentation was NSTEMI in 60%, STEMI in 33%, and cardiac arrest in 7%. Most SCAD patients had no or small infarctions and preserved RF on CMR performed >1 year after the index event. Larger infarctions on CMR were associated with STEMI presentation, TIMI 0/1 flow, multivessel SCAD, and the presence of connective tissue disorders.[95]

In summary, recent publications add new information about the prognosis of elderly patients presenting MINOCA. Performance of provocative tests in MINOCA patients is safe and in a non-trivial proportion of them identify

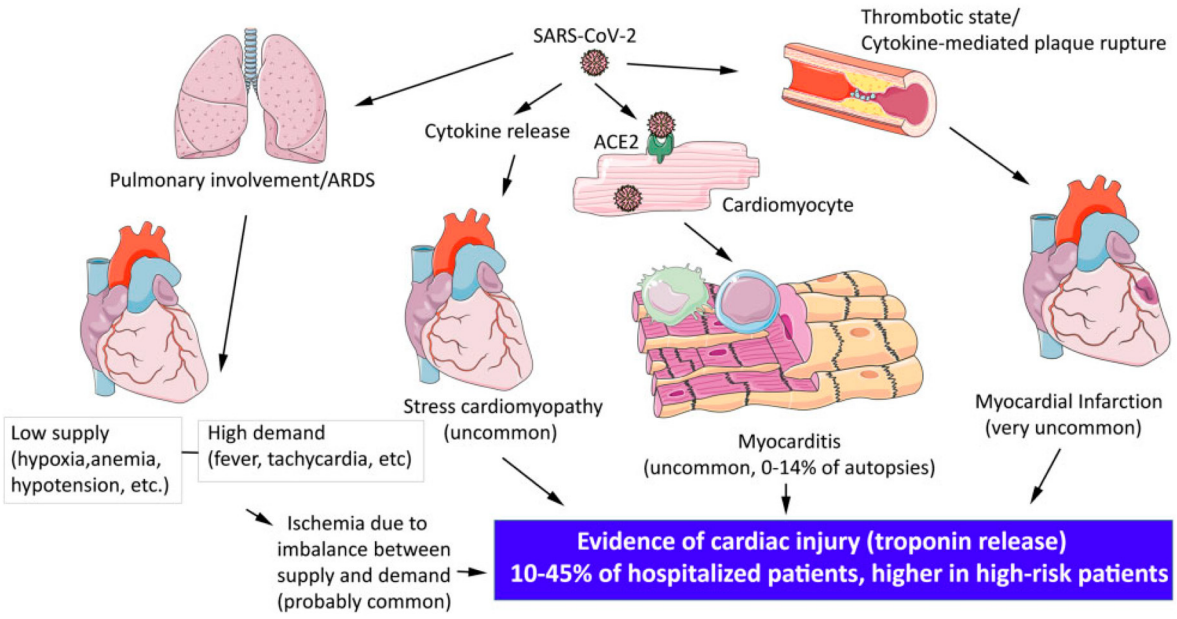


Figure 7 The causes of COVID-19-associated cardiac injury in adult patients. Reprinted from Frangogiannis *et al.*[111], by permission of OUP on behalf of the ESC.

epicardial spasm as its causal mechanism. Compared with typical MI, SCAD is associated with a high rate of early readmissions.

Acute coronary syndromes during the coronavirus disease 2019 pandemic

The year 2020 will be remembered as the year of the COVID-19 pandemic. The COVID-19 crisis has had a major impact on the management, treatment, and prognosis of ACS patients.[96] Dedicated reviews and position papers have detailed the impact of COVID-19 on cardiovascular disease in general. Here, we want to briefly highlight the most important data on the impact of COVID-19 on ACS. Most notably, the European Association of Percutaneous Cardiovascular Interventions and the Acute Cardiovascular Care Association published a dedicated joint position statement on the invasive management of ACS during the COVID-19 pandemic in May 2020.[97]

The first noticed impact of COVID-19 was the significant reduction in hospital admissions for ACS during the first wave of the COVID-19 crisis in Europe (March–April) compared with similar periods in previous years. This reduction was consistently reported in several European countries, including Spain,[98] Italy,[99] Austria,[100] the UK,[101] and others.[102] A recent ESC survey covering >140 countries worldwide showed that the COVID-19 crisis has had a major effect not only on the number of STEMI presentations (significantly reduced) but also on the rate of delayed presentations (significantly higher).[103]

During the first wave of the COVID-19 crisis, the entire healthcare system (hospitals, emergency medical services, etc.) underwent a massive reorganization to deal with the overwhelming number of infection-related admissions.[104] This reorganization involved rapid structural adaptations (networks, spoke, and hub centres) and therapeutic adjustments.[104]

SARS-CoV-2 infection is associated with a highly thrombogenic status. Autopsy studies show that COVID-19 patients frequently have thrombo-embolic disease.[105] This appears to be reflected in the apparent association of anticoagulation with better clinical outcomes in patients admitted for COVID-19.[105] Several studies have demonstrated that STEMI patients with COVID-19 have a significantly higher thrombus burden in culprit lesions[106,107] and a higher incidence of multivessel thrombosis.[106] This has resulted in higher heparin doses to achieve therapeutic activated clotting times and a higher use of GP IIb/IIIa receptor inhibitors. Importantly, STEMI patients with concurrent COVID-19 have a higher incidence of stent thrombosis.[106] Mortality of patients admitted for ACS with concurrent COVID-19 seems to be significantly higher than that of contemporaneous ACS patients without infection.[107]

Myocardial injury, evidenced as an elevation of troponins, is found in 10–35% of patients hospitalized with COVID-19.[108] In a study of 100 patients recovered from severe COVID-19, 60% had some evidence of myocardial inflammation on CMR.[109] While lymphocytic myocarditis has been shown in 14% of cases in a systematic evaluation of autopsies of COVID-19 patients,[110] current evidence suggests that SARS-CoV-2 cardiac infection is uncommon.[111] In most COVID-19 patients, myocardial injury is secondary to a myocardial oxygen supply/demand disbalance in the context of critical illness (especially in patients with pre-existing cardiovascular disease), and to a systemic cytokine storm.

Figure 7 summarizes the mechanisms leading to myocardial injury in patients with COVID-19.

Post-acute coronary syndrome myocardial healing

As discussed above, final infarct size (the extent of irreversible myocardial loss) is the main determinant of long-term mortality and morbidity, and infarct size can be limited by acute interventions during ongoing STEMI. However, there is a lack of therapies able to restore cardiac function after the acute episode, when the infarction is complete and necrotic myocardium is replaced by fibrotic tissue. The ability of cell therapy to improve outcomes in patients with large infarctions has been a matter of intense research over the past 15 years. This year, the results of two large cell therapy trials have been published. The BAMI trial enrolled 375 STEMI patients with low LVEF who were randomized to control or intracoronary infusion of autologous bone marrow-derived mononuclear cells 2–8 days after primary PCI.[112] The main outcome of this ambitious trial was all-cause death, which did not differ between groups (3.3% and 3.8%).[112] The incidence of 2-year mortality was overtly below that expected in the trial design (12%), and the results should thus be interpreted with caution. The ALLSTAR trial enrolled 142 patients 1–12 months after MI with low LVEF and a large scar. These patients were randomized 2:1 to placebo or intracoronary infusion of allogeneic cardiac progenitor cells (cardiosphere-derived cells; CDCs).[113] The primary efficacy endpoint (change in CMR-measured infarct size at 1 year) did not differ between groups. LV volume was reduced in the cell therapy group.[113]

Despite the disappointing results of both studies, they confirm the safety of intracoronary administration of cell therapy at different timings after MI. A crucial obstacle to moving this field forward is the identification of the target population that would benefit from these advanced therapies.

Outlook

In summary, 2020 has witnessed important studies that should have an impact on acute cardiac care management. Despite great advance in preventive strategies, the burden of modifiable risk factors is still very high, with sex and racial differences in the management and outcomes in ACS. Management of ACS patients with concurrent cancer is associated with a more conservative management and worse outcomes. The updated (fourth) UDMI results in a reclassification of a significant proportion of patients in a different MI type, coming with prognostic implications. 2020 observed the confirmation that complete revascularization is clearly the best strategy for stable STEMI patients with multivessel disease. The search of co-adjuvant therapies that might reduce infarct size in STEMI patients is still very active. Metoprolol has been shown to exert unique non-class cardioprotective effects and thus appears as the beta-blocker of choice in STEMI patients. The best antiplatelet regimen is a field of very active research. A more personalized approach results in better outcomes. The old and inexpensive drug colchicine has been revealed as a good candidate for post-MI patients with high residual risk. Myocardial injury has been shown to be frequent in patients with severe COVID-19, but this seems more related to the general condition of the patient than to direct cardiac viral infection. In addition, SARS-CoV-2 infection is associated with a high thrombotic burden. The very active clinical and translational research in the field of acute cardiac care will result in a continuous update on this topic.

Funding

B.I. is supported by the European Commission (ERC-CoG grant no. 819775, and European Regional Development Fund no. AC16/00021), the Spanish Ministry of Science and Innovation (MICINN; 'RETOS 2019' grant no. PID2019-107332RB-I00), the Instituto de Salud Carlos III (ISCIII; PI16/02110, and DTS17/00136), and the Comunidad de Madrid (S2017/BMD-3867 RENIM-CM). The CNIC is supported by the ISCIII, the MICINN, and the Pro CNIC Foundation.

Conflict of interest: none declared.

References

1. Menotti A, Puddu PE, Kromhout D, Kafatos A, Tolonen H. Coronary heart disease mortality trends during 50 years as explained by risk factor changes: the European cohorts of the Seven Countries Study. *Eur J Prev Cardiol* 2020;**27**:988–998.
2. Meirhaeghe A, Montaye M, Biasch K, Huo Yung Kai S, Moitry M, Amouyel P, Ferrieres J, Dallongeville J. Coronary heart disease incidence still decreased between 2006 and 2014 in France, except in young age groups: results from the French MONICA registries. *Eur J Prev Cardiol* 2020;**27**:1178–1186.
3. Pandey A, Keshvani N, Khera R, Lu D, Vaduganathan M, Joynt Maddox KE, Das SR, Kumbhani DJ, Goyal A, Girotra S, Chan P, Fonarow GC, Matsouaka R, Wang TY, de Lemos JA. Temporal trends in racial differences in 30-day readmission and mortality rates after acute myocardial infarction among Medicare beneficiaries. *JAMA Cardiol* 2020;**5**:136–145.
4. Haider A, Bengs S, Luu J, Osto E, Siller-Matula JM, Muka T, Gebhard C. Sex and gender in cardiovascular medicine: presentation and outcomes of acute coronary syndrome. *Eur Heart J* 2020;**41**:1328–1336.
5. Mefford MT, Li BH, Qian L, Reading SR, Harrison TN, Scott RD, Cavendish JJ, Jacobsen SJ, Kanter MH, Woodward M, Reynolds K. Sex-specific trends in acute myocardial infarction within an integrated healthcare network, 2000 through 2014. *Circulation* 2020;**141**:509–519.
6. Jackson AM, Zhang R, Findlay I, Robertson K, Lindsay M, Morris T, Forbes B, Papworth R, McConnachie A, Mangion K, Jhund PS, McCowan C, Berry C. Healthcare disparities for women hospitalized with myocardial infarction and angina. *Eur Heart J Qual Care Clin Outcomes* 2020;**6**:156–165.
7. DeFilippis EM, Collins BL, Singh A, Biery DW, Fatima A, Qamar A, Berman AN, Gupta A, Cawley M, Wood MJ, Klein J, Hainer J, Gulati M, Taqueti VR, Di Carli MF, Nasir K, Bhatt DL, Blankstein R. Women who experience a myocardial infarction at a young age have worse outcomes compared with men: the Mass General Brigham YOUNG-MI registry. *Eur Heart J* 2020;**41**:4127–4137.
8. Walli-Attaei M, Joseph P, Rosengren A, Chow CK, Rangarajan S, Lear SA, AlHabib KF, Davletov K, Dans A, Lanas F, Yeates K, Poirier P, Teo KK, Bahonar A, Camilo F, Chifamba J, Diaz R, Didkowska JA, Irazola V, Ismail R, Kaur M, Khatib R, Liu X, Manczuk M, Miranda JJ, Oguz A, Perez-Mayorga M, Szuba A, Tsolekile LP, Prasad Varma R, Yusufali A, Yusuf R, Wei L, Anand SS, Yusuf S. Variations between women and men in risk factors, treatments, cardiovascular disease incidence, and death in 27 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *Lancet* 2020;**396**:97–109.

9. Stepinska J, Lettino M, Ahrens I, Bueno H, Garcia-Castrillo L, Khoury A, Lancellotti P, Mueller C, Muenzel T, Oleksiak A, Petrino R, Guimenez MR, Zahger D, Vrints CJ, Halvorsen S, de Maria E, Lip GY, Rossini R, Claeys M, Huber K. Diagnosis and risk stratification of chest pain patients in the emergency department: focus on acute coronary syndromes. A position paper of the Acute Cardiovascular Care Association. *Eur Heart J Acute Cardiovasc Care* 2020;**9**:76–89.
10. Collet JP, Thiele H, Barbato E, Barthelemy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Juni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM, ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2020;doi: 10.1093/eurheartj/ehaa575.
11. Hartikainen TS, Sorensen NA, Haller PM, Gossling A, Lehmacher J, Zeller T, Blankenberg S, Westermann D, Neumann JT. Clinical application of the 4th Universal Definition of Myocardial Infarction. *Eur Heart J* 2020;**41**:2209–2216.
12. Chapman AR, Adamson PD, Shah ASV, Anand A, Strachan FE, Ferry AV, Ken Lee K, Berry C, Findlay I, Cruikshank A, Reid A, Gray A, Collinson PO, Apple F, McAllister DA, Maguire D, Fox KAA, Vallejos CA, Keerie C, Weir CJ, Newby DE, Mills NL, High SI. High-sensitivity cardiac troponin and the Universal Definition of Myocardial Infarction. *Circulation* 2020;**141**:161–171.
13. Thygesen K, Jaffe AS. Our nearly complete diagnostic trip of thousands of steps begets a new trip therapeutically. *Eur Heart J* 2020;**41**:2217–2219.
14. Lee KK, Shah ASV. High-sensitivity cardiac troponin: a double-edged sword. *Eur Heart J Qual Care Clin Outcomes* 2020;**6**:3–4.
15. Kaura A, Sterne JAC, Trickey A, Abbott S, Mulla A, Glampson B, Panoulas V, Davies J, Woods K, Omigie J, Shah AD, Channon KM, Weber JN, Thursz MR, Elliott P, Hemingway H, Williams B, Asselbergs FW, O'Sullivan M, Lord GM, Melikian N, Johnson T, Francis DP, Shah AM, Perera D, Kharbanda R, Patel RS, Mayet J. Invasive versus non-invasive management of older patients with non-ST elevation myocardial infarction (SENIOR-NSTEMI): a cohort study based on routine clinical data. *Lancet* 2020;**396**:623–634.
16. Bharadwaj A, Potts J, Mohamed MO, Parwani P, Swamy P, Lopez-Mattei JC, Rashid M, Kwok CS, Fischman DL, Vassiliou VS, Freeman P, Michos ED, Mamas MA. Acute myocardial infarction treatments and outcomes in 6.5 million patients with a current or historical diagnosis of cancer in the USA. *Eur Heart J* 2020;**41**:2183–2193.
17. Simonsson M, Wallentin L, Alfredsson J, Erlinge D, Hellstrom Angerud K, Hofmann R, Kellerth T, Lindhagen L, Ravn-Fischer A, Szummer K, Ueda P, Yndigegn T, Jernberg T. Temporal trends in bleeding events in acute myocardial infarction: insights from the SWEDEHEART registry. *Eur Heart J* 2020;**41**:833–843.
18. Marquis-Gravel G, Dalgaard F, Jones AD, Lokhnygina Y, James SK, Harrington RA, Wallentin L, Steg PG, Lopes RD, Storey RF, Goodman SG, Mahaffey KW, Tricoci P, White HD, Armstrong PW, Ohman EM, Alexander JH, Roe MT. Post-discharge bleeding and mortality following acute coronary syndromes with or without PCI. *J Am Coll Cardiol* 2020;**76**:162–171.
19. Ibanez B. And fibrinolysis became pharmacoinvasive. *Eur Heart J* 2020;**41**:855–857.
20. Thrane PG, Kristensen SD, Olesen KKW, Mortensen LS, Botker HE, Thuesen L, Hansen HS, Abildgaard U, Engstrom T, Andersen HR, Maeng M. 16-year follow-up of the Danish Acute Myocardial Infarction 2 (DANAMI-2) trial: primary percutaneous coronary intervention vs. fibrinolysis in ST-segment elevation myocardial infarction. *Eur Heart J* 2020;**41**:847–854.
21. Danchin N, Popovic B, Puymirat E, Goldstein P, Belle L, Cayla G, Roubille F, Lemesle G, Ferrieres J, Schiele F, Simon T, FAST-MI Investigators. Five-year outcomes following timely primary percutaneous intervention, late primary percutaneous intervention, or a pharmaco-invasive strategy in ST-segment elevation myocardial infarction: the FAST-MI programme. *Eur Heart J* 2020;**41**:858–866.
22. Zeymer U, Ludman P, Danchin N, Kala P, Maggioni AP, Weidinger F, ACS STEMI Investigators. The ESC ACCA EAPCI EORP acute coronary syndrome ST-elevation myocardial infarction registry. *Eur Heart J Qual Care Clin Outcomes* 2020;**6**:100–104.
23. Scholz KH, Lengenfelder B, Jacobshagen C, Fleischmann C, Moehlis H, Olbrich HG, Jung J, Maier LS, Maier SK, Bestehorn K, Friede T, Meyer T. Long-term effects of a standardized feedback-driven quality improvement program for timely reperfusion therapy in regional STEMI care networks. *Eur Heart J Acute Cardiovasc Care* 2020:2048872620907323.
24. Le May M, Wells G, So D, Chong AY, Dick A, Froeschl M, Glover C, Hibbert B, Marquis JF, Blondeau M, Osborne C, MacDougall A, Kass M, Paddock V, Quraishi A, Labinaz M. Safety and efficacy of femoral access vs radial access in ST-segment elevation myocardial infarction: the SAFARI-STEMI randomized clinical trial. *JAMA Cardiol* 2020;**5**:126–134.
25. Vranckx P, Frigoli E, Rothenbuhler M, Tomassini F, Garducci S, Ando G, Picchi A, Sganzerla P, Paggi A, Ugo F, Ausiello A, Sardella G, Franco N, Nazzaro M, de Cesare N, Tosi P, Falcone C, Vigna C, Mazzarotto P, Di Lorenzo E, Moretti C, Campo G, Penzo C, Pasquetto G, Heg D, Juni P, Windecker S, Valgimigli M, MATRIX Investigators. Radial versus femoral access in patients with acute coronary syndromes with or without ST-segment elevation. *Eur Heart J* 2017;**38**:1069–1080.
26. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P, ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**:119–177.
27. Mehta SR, Wood DA, Storey RF, Mehran R, Bainey KR, Nguyen H, Meeks B, Di Pasquale G, Lopez-Sendon J, Faxon DP, Mauri L, Rao SV, Feldman L, Steg PG, Avezum A, Sheth T, Pinilla-Echeverri N, Moreno R, Campo G, Wrigley B, Kedev S, Sutton A, Oliver R, Rodes-Cabau J, Stankovic G, Welsh R, Lavi S, Cantor WJ, Wang J, Nakamya J, Bangdiwala SI, Cairns JA, COMPLETE Trial Steering Committee and Investigators. Complete revascularization with multivessel PCI for myocardial infarction. *N Engl J Med* 2019;**381**:1411–1421.
28. Bainey KR, Engstrom T, Smits PC, Gershlick AH, James SK, Storey RF, Wood DA, Mehran R, Cairns JA, Mehta SR. Complete vs culprit-lesion-only revascularization for ST-segment elevation myocardial infarction: a systematic review and meta-analysis. *JAMA Cardiol* 2020;**5**:881–888.
29. Atti V, Gwon Y, Narayanan MA, Garcia S, Sandoval Y, Brilakis ES, Basir MB, Turagam MK, Khandelwal A, Mena-Hurtado C, Mamas MA, Abbott JD, Bhatt DL, Velagapudi P. Multivessel versus culprit-only revascularization in STEMI and multivessel coronary artery disease: meta-analysis of randomized trials. *JACC Cardiovasc Interv* 2020;**13**:1571–1582.
30. Sheth T, Pinilla-Echeverri N, Moreno R, Wang J, Wood DA, Storey RF, Mehran R, Bainey KR, Bossard M, Bangalore S, Schwalm JD, Velianou JL, Valettas N, Sibbald M, Rodes-Cabau J, Ducas J, Cohen EA, Bagai A, Rinfret S, Newby DE, Feldman L, Laster SB, Lang IM, Mills JD, Cairns JA, Mehta SR. Nonculprit lesion severity and outcome of revascularization in patients with STEMI and multivessel coronary disease. *J Am Coll Cardiol* 2020;**76**:1277–1286.
31. Piroth Z, Boxma-de Klerk BM, Omerovic E, Andreka P, Fontos G, Fulop G, Abdel-Wahab M, Neumann FJ, Richardt G, Abdelghani M, Smits PC. The natural history of nonculprit lesions in STEMI: an FFR substudy of the Compare-Acute Trial. *JACC Cardiovasc Interv* 2020;**13**:954–961.
32. Wald DS, Hadyanto S, Bestwick JP. Should fractional flow reserve follow angiographic visual inspection to guide preventive percutaneous coronary intervention in ST-elevation myocardial infarction? *Eur Heart J Qual Care Clin Outcomes* 2020;**6**:186–192.
33. Gallone G, Angelini F, Fortuni F, Gnecchi M, De Filippo O, Baldetti L, Giannini F, Colombo A, D'Ascenzo F, De Ferrari GM. Angiography- vs. physiology-guided complete revascularization in patients with ST-elevation myocardial infarction and

multivessel disease: who is the better gatekeeper in this setting? A meta-analysis of randomized controlled trials. *Eur Heart J Qual Care Clin Outcomes* 2020;**6**:199–200.
34. Henderson RA. Fractional flow reserve for non-culprit disease in ST-segment elevation myocardial infarction: first do no harm? *Eur Heart J Qual Care Clin Outcomes* 2020;**6**:181–183.
35. Scirica BM, Bergmark BA, Morrow DA, Antman EM, Bonaca MP, Murphy SA, Sabatine MS, Braunwald E, Wiviott SD. Nonculprit lesion myocardial infarction following percutaneous coronary intervention in patients with acute coronary syndrome. *J Am Coll Cardiol* 2020;**75**:1095–1106.
36. Pinilla-Echeverri N, Mehta SR, Wang J, Lavi S, Schampaert E, Cantor WJ, Bainey KR, Welsh RC, Kassam S, Mehran R, Storey RF, Nguyen H, Meeks B, Wood DA, Cairns JA, Sheth T. Nonculprit lesion plaque morphology in patients with ST-segment-elevation myocardial infarction: results from the COMPLETE trial optical coherence tomography substudys. *Circ Cardiovasc Interv* 2020;**13**:e008768.
37. Montone RA, Niccoli G, Crea F, Jang IK. Management of non-culprit coronary plaques in patients with acute coronary syndrome. *Eur Heart J* 2020;**41**:3579–3586.
38. Lorca R, Jimenez-Blanco M, Garcia-Ruiz JM, Pizarro G, Fernandez-Jimenez R, Garcia-Alvarez A, Fernandez-Friera L, Lobo-Gonzalez M, Fuster V, Rossello X, Ibanez B. Coexistence of transmural and lateral wavefront progression of myocardial infarction in the human heart. *Rev Esp Cardiol (Engl Ed)* 2020;doi: 10.1016/j.rec.2020.07.007.
39. Rossello X, Lobo-Gonzalez M, Ibanez B. Editor's Choice—Pathophysiology and therapy of myocardial ischaemia/reperfusion syndrome. *Eur Heart J Acute Cardiovasc Care* 2019;**8**:443–456.
40. Ruiz-Meana M, Bou-Teen D, Ferdinandy P, Gyongyosi M, Pesce M, Perrino C, Schulz R, Sluijter JPG, Tocchetti CG, Thum T, Madonna R. Cardiomyocyte ageing and cardioprotection: consensus document from the ESC working groups cell biology of the heart and myocardial function. *Cardiovasc Res* 2020;**116**:1835–1849.
41. Konijnenberg LSF, Damman P, Duncker DJ, Kloner RA, Nijveldt R, van Geuns RM, Berry C, Riksen NP, Escaned J, van Royen N. Pathophysiology and diagnosis of coronary microvascular dysfunction in ST-elevation myocardial infarction. *Cardiovasc Res* 2020;**116**:787–805.
42. Ibanez B. Intravenous beta-blockers in STEMI: what you are about to do, do it quickly. *Eur Heart J Acute Cardiovasc Care* 2020;**9**:459–461.
43. Clemente-Moragon A, Gomez M, Villena-Gutierrez R, Lalama DV, Garcia-Prieto J, Martinez F, Sanchez-Cabo F, Fuster V, Oliver E, Ibanez B. Metoprolol exerts a non-class effect against ischaemia–reperfusion injury by abrogating exacerbated inflammation. *Eur Heart J* 2020;**41**:4425–4440.
44. Lobo-Gonzalez M, Galan-Arriola C, Rossello X, Gonzalez-Del-Hoyo M, Vilchez JP, Higuero-Verdejo MI, Garcia-Ruiz JM, Lopez-Martin GJ, Sanchez-Gonzalez J, Oliver E, Pizarro G, Fuster V, Ibanez B. Metoprolol blunts the time-dependent progression of infarct size. *Basic Res Cardiol* 2020;**115**:55.
45. Mathias WJr, Tsutsui JM,, Tavares BG, Fava AM, Aguiar MOD, Borges BC, Oliveira MT Jr, Soeiro A, Nicolau JC, Ribeiro HB, Chiang HP, Sbano JCN, Morad A, Goldsweig A, Rochitte CE, Lopes BBC, Ramirez JAF, Kalil Filho R, Porter TR, MRUSMI Investigators. Sonothrombolysis in ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. *J Am Coll Cardiol* 2019;**73**:2832–2842.
46. Aguiar MOD, Tavares BG, Tsutsui JM, Fava AM, Borges BC, Oliveira MT Jr, Soeiro A, Nicolau JC, Ribeiro HB, Chiang HP, Sbano JCN, Goldsweig A, Rochitte CE, Lopes BBC, Ramirez JAF, Kalil Filho R, Porter TR, Mathias WJr. Sonothrombolysis improves myocardial dynamics and microvascular obstruction preventing left ventricular remodeling in patients with ST elevation myocardial infarction. *Circ Cardiovasc Imaging* 2020;**13**:e009536.
47. Swain L, Reyelt L, Bhave S, Qiao X, Thomas CJ, Zweck E, Crowley P, Boggins C, Esposito M, Chin M, Karas RH, O'Neill W, Kapur NK. Transvalvular ventricular unloading before reperfusion in acute myocardial infarction. *J Am Coll Cardiol* 2020;**76**:684–699.
48. Kapur NK, Alkhouli MA, DeMartini TJ, Faraz H, George ZH, Goodwin MJ, Hernandez-Montfort JA, Iyer VS, Josephy N,, Kalra S, Kaki A, Karas RH, Kimmelstiel CD, Koenig GC, Lau E, Lotun K, Madder RD, Mannino SF, Meraj PM, Moreland JA, Moses JW, Kim RL, Schreiber TL, Udelson JE, Witzke C, Wohns DHW, O'Neill WW. Unloading the left ventricle before reperfusion in patients with anterior ST-segment-elevation myocardial infarction. *Circulation* 2019;**139**:337–346.
49. Ibanez B. Intravenous β-blockers in STEMI: what you are about to do, do it quickly. *Eur Heart J Acute Cardiovasc Care* 2020;doi: 10.1177/2048872620950205.
50. Lyu J, Wang M, Kang X, Xu H, Cao Z, Yu T, Huang K, Wu J, Wei X, Lei Q. Macrophage-mediated regulation of catecholamines in sympathetic neural remodeling after myocardial infarction. *Basic Res Cardiol* 2020;**115**:56.
51. Kalla M, Hao G, Tapoulal N, Tomek J, Liu K, Woodward L, 'Oxford Acute Myocardial Infarction (OxAMI) Study', Dall'Armellina E, Banning AP, Choudhury RP, Neubauer S, Kharbanda RK, Channon KM, Ajijola OA, Shivkumar K, Paterson DJ, Herring N. The cardiac sympathetic co-transmitter neuropeptide Y is pro-arrhythmic following ST-elevation myocardial infarction despite beta-blockade. *Eur Heart J* 2020;**41**:2168–2179.
52. Kim BK, Hong SJ, Cho YH, Yun KH, Kim YH, Suh Y, Cho JY, Her AY, Cho S, Jeon DW, Yoo SY, Cho DK, Hong BK, Kwon H, Ahn CM, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Hong MK, Jang Y, TICO Investigators. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO randomized clinical trial. *JAMA* 2020;**323**:2407–2416.
53. Angiolillo DJ, Baber U, Sartori S, Briguori C, Dangas G, Cohen DJ, Mehta SR, Gibson CM, Chandiramani R, Huber K, Kornowski R, Weisz G, Kunadian V, Oldroyd KG, Ya-Ling H, Kaul U, Witzenbichler B, Dudek D, Sardella G, Escaned J, Sharma S, Shlofmitz RA, Collier T, Pocock S, Mehran R. Ticagrelor with or without aspirin in high-risk patients with diabetes mellitus undergoing percutaneous coronary intervention. *J Am Coll Cardiol* 2020;**75**:2403–2413.
54. Dangas G, Baber U, Sharma S, Giustino G, Mehta S, Cohen DJ, Angiolillo DJ, Sartori S, Chandiramani R, Briguori C, Dudek D, Escaned J, Huber K, Collier T, Kornowski R, Kunadian V, Kaul U, Oldroyd K, Sardella G, Shlofmitz R, Witzenbichler B, Ya-Ling H, Pocock S, Gibson CM, Mehran R. Ticagrelor with or without aspirin after complex PCI. *J Am Coll Cardiol* 2020;**75**:2414–2424.
55. Baber U, Dangas G, Angiolillo DJ, Cohen DJ, Sharma SK, Nicolas J, Briguori C, Cha JY, Collier T, Dudek D, Dzavik V, Escaned J, Gil R, Gurbel P, Hamm CW, Henry T, Huber K, Kastrati A, Kaul U, Kornowski R, Krucoff M, Kunadian V, Marx SO, Mehta S, Moliterno D, Ohman EM, Oldroyd K, Sardella G, Sartori S, Shlofmitz R, Steg PG, Weisz G, Witzenbichler B, Han YL, Pocock S, Gibson CM, Mehran R. Ticagrelor alone vs. ticagrelor plus aspirin following percutaneous coronary intervention in patients with non-ST-segment elevation acute coronary syndromes: TWILIGHT-ACS. *Eur Heart J* 2020;**41**:3533–3545.
56. Hahn JY, Song YB, Oh JH, Chun WJ, Park YH, Jang WJ, Im ES, Jeong JO, Cho BR, Oh SK, Yun KH, Cho DK, Lee JY, Koh YY, Bae JW, Choi JW, Lee WS, Yoon HJ, Lee SU, Cho JH, Choi WG, Rha SW, Lee JM, Park TK, Yang JH, Choi JH, Choi SH, Lee SH, Gwon HC, SMART-CHOICE Investigators. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. *JAMA* 2019;**321**:2428–2437.
57. Watanabe H, Domei T, Morimoto T, Natsuaki M, Shiomi H, Toyota T, Ohya M, Suwa S, Takagi K, Nanasato M, Hata Y, Yagi M, Suematsu N, Yokomatsu T, Takamisawa I, Doi M, Noda T, Okayama H, Seino Y, Tada T, Sakamoto H, Hibi K, Abe M, Kawai K, Nakao K, Ando K, Tanabe K,, Ikari Y, Hanaoka KI, Morino Y, Kozuma K, Kadota K, Furukawa Y, Nakagawa Y, Kimura T, STOPDAPT-2 Investigators. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. *JAMA* 2019;**321**:2414–2427.

58. Vranckx P, Valgimigli M, Juni P, Hamm C, Steg PG, Heg D, van Es GA, McFadden EP, Onuma Y, van Meijeren C, Chichareon P, Benit E, Mollmann H, Janssens L, Ferrario M, Moschovitis A, Zurakowski A, Dominici M, Van Geuns RJ, Huber K, Slagboom T, Serruys PW, Windecker S, GLOBAL LEADERS Investigators. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. *Lancet* 2018;**392**:940–949.
59. O'Donoghue ML, Murphy SA, Sabatine MS. The safety and efficacy of aspirin discontinuation on a background of a P2Y12 inhibitor in patients after percutaneous coronary intervention: a systematic review and meta-analysis. *Circulation* 2020;**142**:538–545.
60. D'Ascenzo F, Bertaina M, Fioravanti F, Bongiovanni F, Raposeiras-Roubin S, Abu-Assi E, Kinnaird T, Ariza-Sole A, Manzano-Fernandez S, Templin C, Velicki L, Xanthopoulou I, Cerrato E, Rognoni A, Boccuzzi G, Omede P, Montabone A, Taha S, Durante A, Gili S, Magnani G, Autelli M, Grosso A, Blanco PF, Garay A, Quadri G, Varbella F, Queija BC, Paz RC, Fernandez MC, Pousa IM, Gallo D, Morbiducci U, Dominguez-Rodriguez A, Valdes M, Cequier A, Alexopoulos D, Iniguez-Romo A, Gaita F, Rinaldi M, Luscher TF. Long versus short dual antiplatelet therapy in acute coronary syndrome patients treated with prasugrel or ticagrelor and coronary revascularization: insights from the RENAMI registry. *Eur J Prev Cardiol* 2020;**27**:696–705.
61. Furtado RHM, Nicolau JC, Magnani G, Im K, Bhatt DL, Storey RF, Steg PG, Spinar J, Budaj A, Kontny F, Corbalan R, Kiss RG, Abola MT, Johanson P, Jensen EC, Braunwald E, Sabatine MS, Bonaca MP. Long-term ticagrelor for secondary prevention in patients with prior myocardial infarction and no history of coronary stenting: insights from PEGASUS-TIMI 54. *Eur Heart J* 2020;**41**:1625–1632.
62. Kim HS, Kang J, Hwang D, Han JK, Yang HM, Kang HJ,, Koo BK, Rhew JY, Chun KJ, Lim YH, Bong JM, Bae JW, Lee BK, Park KW, HOST-REDUCE-POLYTECH-ACS investigators. Prasugrel-based de-escalation of dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (HOST-REDUCE-POLYTECH-ACS): an open-label, multicentre, non-inferiority randomised trial. *Lancet* 2020;**396**:1079–1089.
63. Schupke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wohrle J, Richardt G, Liebetrau C,, Witzenbichler B, Antoniucci D, Akin I, Bott-Flugel L, Fischer M, Landmesser U, Katus HA, Sibbing D, Seyfarth M, Janisch M, Boncompagni D, Hilz R, Rottbauer W, Okrojek R, Mollmann H, Hochholzer W, Migliorini A, Cassese S, Mollo P, Xhepa E, Kufner S, Strehle A, Leggewie S, Allali A, Ndrepepa G, Schuhlen H,, Angiolillo DJ, Hamm CW, Hapfelmeier A, Tolg R, Trenk D, Schunkert H, Laugwitz KL, Kastrati A, ISAR-REACT 5 Trial Investigators. Ticagrelor or prasugrel in patients with acute coronary syndromes. *N Engl J Med* 2019;**381**:1524–1534.
64. Aytekin A, Ndrepepa G, Neumann FJ, Menichelli M, Mayer K, Wohrle J, Bernlochner I, Lahu S, Richardt G, Witzenbichler B, Sibbing D, Cassese S, Angiolillo DJ, Valina C, Kufner S, Liebetrau C, Hamm CW, Xhepa E, Hapfelmeier A, Sager HB, Wustrow I, Joner M, Trenk D, Fusaro M, Laugwitz KL, Schunkert H, Schupke S, Kastrati A. Ticagrelor or prasugrel in patients with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Circulation* 2020;**142**:2329–2337.
65. Valina C, Neumann FJ, Menichelli M, Mayer K, Wohrle J, Bernlochner I, Aytekin A, Richardt G, Witzenbichler B, Sibbing D, Cassese S, Angiolillo DJ, Kufner S, Liebetrau C, Hamm CW, Xhepa E, Hapfelmeier A, Sager HB, Wustrow I, Joner M, Trenk D, Laugwitz KL, Schunkert H, Schupke S, Kastrati A. Ticagrelor or prasugrel in patients with non-ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol* 2020;**76**:2436–2446.
66. Schnorbus B, Daiber A, Jurk K, Warnke S, Koenig J, Lackner KJ, Munzel T, Gori T. Effects of clopidogrel vs. prasugrel vs. ticagrelor on endothelial function, inflammatory parameters, and platelet function in patients with acute coronary syndrome undergoing coronary artery stenting: a randomized, blinded, parallel study. *Eur Heart J* 2020;**41**:3144–3152.
67. Navarese EP, Khan SU, Kolodziejczak M, Kubica J, Buccheri S, Cannon CP, Gurbel PA, De Servi S, Budaj A, Bartorelli A, Trabattoni D, Ohman EM, Wallentin L, Roe MT, James S. Comparative efficacy and safety of oral P2Y12 inhibitors in acute coronary syndrome: network meta-analysis of 52 816 patients from 12 randomized trials. *Circulation* 2020;**142**:150–160.
68. You SC, Rho Y, Bikdeli B, Kim J, Siapos A, Weaver J, Londhe A, Cho J, Park J, Schuemie M, Suchard MA, Madigan D, Hripcsak G, Gupta A, Reich CG, Ryan PB, Park RW, Krumholz HM. Association of ticagrelor vs clopidogrel with net adverse clinical events in patients with acute coronary syndrome undergoing percutaneous coronary intervention. *JAMA* 2020;**324**:1640–1650.
69. Tarantini G, Mojoli M, Varbella F, Caporale R, Rigattieri S, Ando G, Cirillo P, Pierini S, Santarelli A, Sganzerla P, Cacciavillani L, Babuin L, De Cesare N, Limbruno U, Massoni A, Rognoni A, Pavan D, Belloni F, Cernetti C, Favero L, Saia F, Fovino LN, Masiero G, Roncon L, Gasparetto V, Ferlini M, Ronco F, Rossini R, Canova P, Trabattoni D, Russo A, Guiducci V, Penzo C, Tarantino F, Mauro C, Corrada E, Esposito G, Berti S, Martinato M, Azzolina D, Gregori D, Angiolillo DJ, Musumeci G, DUBIUS Investigators; Italian Society of Interventional Cardiology. Timing of oral P2Y12 inhibitor administration in non-ST elevation acute coronary syndrome. *J Am Coll Cardiol* 2020;**76**:2450–2459.
70. Gargiulo G, Esposito G, Avvedimento M, Nagler M, Minuz P, Campo G, Gragnano F, Manavifar N, Piccolo R, Tebaldi M, Cirillo P, Hunziker L, Vranckx P, Leonardi S, Heg D, Windecker S, Valgimigli M. Cangrelor, tirofiban, and chewed or standard prasugrel regimens in patients with ST-segment-elevation myocardial infarction: primary results of the FABOLUS-FASTER trial. *Circulation* 2020;**142**:441–454.
71. Sinnaeve P, Fahrni G, Schelfaut D, Spirito A, Mueller C, Frenoux JM, Hmissi A, Bernaud C, Ufer M, Moccetti T, Atar S, Valgimigli M. Subcutaneous selatogrel inhibits platelet aggregation in patients with acute myocardial infarction. *J Am Coll Cardiol* 2020;**75**:2588–2597.
72. Hulot JS, Chevalier B, Belle L, Cayla G, Khalife K, Funck F, Berthier R, Piot C, Tafflet M, Montalescot G, GIANT Investigators. Routine CYP2C19 genotyping to adjust thienopyridine treatment after primary PCI for STEMI: results of the GIANT study. *JACC Cardiovasc Interv* 2020;**13**:621–630.
73. Pereira NL, Farkouh ME, So D, Lennon R, Geller N, Mathew V, Bell M, Bae JH, Jeong MH, Chavez I, Gordon P, Abbott JD, Cagin C, Baudhuin L, Fu YP, Goodman SG, Hasan A, Iturriaga E, Lerman A, Sidhu M, Tanguay JF, Wang L, Weinshilboum R, Welsh R, Rosenberg Y, Bailey K, Rihal C. Effect of genotype-guided oral P2Y12 inhibitor selection vs conventional clopidogrel therapy on ischemic outcomes after percutaneous coronary intervention: the TAILOR-PCI randomized clinical trial. *JAMA* 2020;**324**:761–771.
74. Lewis JP, Backman JD, Reny JL, Bergmeijer TO, Mitchell BD, Ritchie MD, Dery JP, Pakyz RE, Gong L, Ryan K, Kim EY, Aradi D, Fernandez-Cadenas I, Lee MTM, Whaley RM, Montaner J,, Gensini GF, Cleator JH, Chang K, Holmvang L, Hochholzer W, Roden DM, Winter S, Altman RB, Alexopoulos D, Kim HS, Gawaz M, Bliden KP, Valgimigli M, Marcucci R, Campo G, Schaeffeler E, Dridi NP, Wen MS, Shin JG,, Fontana P, Giusti B, Geisler T, Kubo M, Trenk D, Siller-Matula JM, Ten Berg JM, Gurbel PA, Schwab M, Klein TE, Shuldiner AR, ICPC Investigators. Pharmacogenomic polygenic response score predicts ischaemic events and cardiovascular mortality in clopidogrel-treated patients. *Eur Heart J Cardiovasc Pharmacother* 2020;**6**:203–210.
75. Gimbel M, Qaderdan K, Willemsen L, Hermanides R, Bergmeijer T, de Vrey E, Heestermans T, Tjon Joe Gin M, Waalewijn R, Hofma S, den Hartog F, Jukema W, von Birgelen C, Voskuil M, Kelder J, Deneer V, Ten Berg J. Clopidogrel versus ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome (POPular AGE): the randomised, open-label, non-inferiority trial. *Lancet* 2020;**395**:1374–1381.

76. Szummer K, Montez-Rath ME, Alfredsson J, Erlinge D, Lindahl B, Hofmann R, Ravn-Fischer A, Svensson P, Jernberg T. Comparison between ticagrelor and clopidogrel in elderly patients with an acute coronary syndrome: insights from the SWEDEHEART registry. *Circulation* 2020;**142**:1700–1708.
77. De Filippo O, D'Ascenzo F, Raposeiras-Roubin S, Abu-Assi E, Peyracchia M, Bocchino PP, Kinnaird T, Ariza-Sole A, Liebetrau C, Manzano-Fernandez S, Boccuzzi G, Henriques JPS, Templin C, Wilton SB, Omede P, Velicki L, Xanthopoulou I, Correia L, Cerrato E, Rognoni A, Fabrizio U, Nunez-Gil I, Iannaccone M, Montabone A, Taha S, Fujii T, Durante A, Song X, Gili S, Magnani G, Varbella F, Kawaji T, Blanco PF, Garay A, Quadri G, Alexopoulos D, Caneiro Queija B, Huczek Z, Cobas Paz R, Gonzalez Juanatey JR, Cespon Fernandez M, Nie SP, Munoz Pousa I, Kawashiri MA, Gallo D, Morbiducci U, Conrotto F, Montefusco A, Dominguez-Rodriguez A, Lopez-Cuenca A, Cequier A, Iniguez-Romo A, Usmiani T, Rinaldi M, De Ferrari GM. P2Y12 inhibitors in acute coronary syndrome patients with renal dysfunction: an analysis from the RENAMI and BleeMACS projects. *Eur Heart J Cardiovasc Pharmacother* 2020;**6**:31–42.
78. Cecconi A, Vilchez-Tschischke JP, Mateo J, Sanchez-Gonzalez J, Espana S, Fernandez-Jimenez R, Lopez-Melgar B, Fernandez Friera L, Lopez-Martin GJ, Fuster V, Ruiz-Cabello J, Ibanez B. Effects of colchicine on atherosclerotic plaque stabilization: a multimodality imaging study in an animal model. *J Cardiovasc Transl Res* 2020;doi: 10.1007/s12265-020-09974-7.
79. Tardif JC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, Berry C, Lopez-Sendon J, Ostadal P, Koenig W, Angoulvant D, Gregoire JC, Lavoie MA, Dube MP, Rhainds D, Provencher M, Blondeau L, Orfanos A, L'Allier PL, Guertin MC, Roubille F. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med* 2019;**381**:2497–2505.
80. Bouabdallaoui N, Tardif JC, Waters DD, Pinto FJ, Maggioni AP, Diaz R, Berry C, Koenig W, Lopez-Sendon J, Gamra H, Kiwan GS, Blondeau L, Orfanos A, Ibrahim R, Gregoire JC, Dube MP, Samuel M, Morel O, Lim P, Bertrand OF, Kouz S, Guertin MC, L'Allier PL, Roubille F. Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT). *Eur Heart J* 2020;**41**:4092–4099.
81. Shah B, Pillinger M, Zhong H, Cronstein B, Xia Y, Lorin JD, Smilowitz NR, Feit F, Ratnapala N, Keller NM, Katz SD. Effects of acute colchicine administration prior to percutaneous coronary intervention: COLCHICINE-PCI randomized trial. *Circ Cardiovasc Interv* 2020;**13**:e008717.
82. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, The SHK, Xu XF, Ireland MA, Lenderink T, Latchem D, Hoogslag P, Jerzewski A, Nierop P, Whelan A, Hendriks R, Swart H, Schaap J, Kuijper AFM, van Hessen MWJ, Saklani P, Tan I, Thompson AG, Morton A, Judkins C, Bax WA, Dirksen M,, Alings M, Hankey GJ, Budgeon CA, Tijssen JGP, Cornel JH, Thompson PL, LoDoCo2 Trial Investigators. Colchicine in patients with chronic coronary disease. *N Engl J Med* 2020;**383**:1838–1847.
83. Tong DC, Quinn S, Nasis A, Hiew C, Roberts-Thomson P, Adams H, Sriamareswaran R, Htun NM, Wilson W, Stub D, van Gaal W, Howes L, Collins N, Yong AS, Bhindi R, Whitbourn R, Lee A, Hengel C, Asrress K, Freeman M, Amerena J, Wilson A, Layland J. Colchicine in patients with acute coronary syndrome: the Australian COPS randomized clinical trial. *Circulation* 2020;**142**:1890–1900.
84. Kim J, Kang D, Park H, Kang M, Park TK, Lee JM, Yang JH, Song YB, Choi JH,, Choi SH, Gwon HC, Guallar E, Cho J, Hahn JY. Long-term beta-blocker therapy and clinical outcomes after acute myocardial infarction in patients without heart failure: nationwide cohort study. *Eur Heart J* 2020;**41**:3521–3529.
85. Harari R, Bangalore S. Beta-blockers after acute myocardial infarction: an old drug in urgent need of new evidence! *Eur Heart J* 2020;**41**:3530–3532.
86. Zeymer U, Bueno H, Granger CB, Hochman J, Huber K, Lettino M, Price S, Schiele F, Tubaro M, Vranckx P, Zahger D, Thiele H. Acute cardiovascular care association position statement for the diagnosis and treatment of patients with acute myocardial infarction complicated by cardiogenic shock: a document of the Acute Cardiovascular Care Association of the European Society of Cardiology. *Eur Heart J Acute Cardiovasc Care* 2020;**9**:183–197.
87. Omer MA, Tyler JM, Henry TD, Garberich R, Sharkey SW, Schmidt CW, Henry JT, Eckman P, Megaly M, Brilakis ES, Chavez I, Burke N, Gossl M, Mooney M, Sorajja P, Traverse JH, Wang Y, Hryniewicz K, Garcia S. Clinical characteristics and outcomes of STEMI patients with cardiogenic shock and cardiac arrest. *JACC Cardiovasc Interv* 2020;**13**:1211–1219.
88. Vallabhajosyula S, Ya'Qoub L, Singh M, Bell MR, Gulati R, Cheungpasitporn W, Sundaragiri PR, Miller VM, Jaffe AS, Gersh BJ, Holmes DR Jr, Barsness GW. Sex disparities in the management and outcomes of cardiogenic shock complicating acute myocardial infarction in the young. *Circ Heart Fail* 2020;**13**:e007154.
89. Dhruva SS, Ross JS, Mortazavi BJ, Hurley NC, Krumholz HM, Curtis JP, Berkowitz A, Masoudi FA, Messenger JC, Parzynski CS, Ngufor C, Girotra S, Amin AP, Shah ND, Desai NR. Association of use of an intravascular microaxial left ventricular assist device vs intra-aortic balloon pump with in-hospital mortality and major bleeding among patients with acute myocardial infarction complicated by cardiogenic shock. *JAMA* 2020;**323**:734–745.
90. Schrage B, Becher PM, Bernhardt A, Bezerra H, Blankenberg S, Brunner S, Colson P, Cudemus Deseda G, Dabboura S, Eckner D, Eden M, Eitel I, Frank D, Frey N, Funamoto M, Gossling A, Graf T, Hagl C, Kirchhof P, Kupka D, Landmesser U, Lipinski J, Lopes M, Majunke N, Maniuc O, McGrath D, Mobius-Winkler S,, Morrow DA, Mourad M, Noel C, Nordbeck P, Orban M, Pappalardo F, Patel SM, Pauschinger M, Pazzanese V, Reichenspurner H, Sandri M, Schulze PC, Schwinger RHG, Sinning JM, Aksoy A, Skurk C, Szczanowicz L, Thiele H, Tietz F, Varshney A, Wechsler L, Westermann D. Left ventricular unloading is associated with lower mortality in patients with cardiogenic shock treated with venoarterial extracorporeal membrane oxygenation: results from an international, multicenter cohort study. *Circulation* 2020;**142**:2095–2106.
91. Yannopoulos D, Bartos J, Raveendran G, Walser E, Connett J, Murray TA, Collins G, Zhang L, Kalra R, Kosmopoulos M, John R, Shaffer A, Frascone RJ, Wesley K, Conterato M, Biros M, Tolar J, Aufderheide TP. Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single centre, open-label, randomised controlled trial. *Lancet* 2020;**396**:1807–1816.
92. Dreyer RP, Tavella R, Curtis JP, Wang Y, Pauspathy S, Messenger J, Rumsfeld JS, Maddox TM, Krumholz HM, Spertus JA, Beltrame JF. Myocardial infarction with non-obstructive coronary arteries as compared with myocardial infarction and obstructive coronary disease: outcomes in a Medicare population. *Eur Heart J* 2020;**41**:870–878.
93. Probst S, Seitz A, Martinez Pereyra V, Hubert A, Becker A, Storm K, Bekeredjian R, Sechtem U, Ong P. Safety assessment and results of coronary spasm provocation testing in patients with myocardial infarction with unobstructed coronary arteries compared to patients with stable angina and unobstructed coronary arteries. *Eur Heart J Acute Cardiovasc Care* 2020:2048872620932422.
94. Gad MM, Mahmoud AN, Saad AM, Bazarbashi N, Ahuja KR, Karrthik AK, Elgendy IY, Elgendy AY, Don CW, Hira RS, Massoomi MR, Saw J, Anderson RD, Kapadia SR. Incidence, clinical presentation, and causes of 30-day readmission following hospitalization with spontaneous coronary artery dissection. *JACC Cardiovasc Interv* 2020;**13**:921–932.
95. Al-Hussaini A, Abdelaty A, Gulsin GS, Arnold JR, Garcia-Guimaraes M, Premawardhana D, Budgeon C, Wood A, Natarajan N, Mangion K, Rakhit R, Hoole SP, Johnson TW, Berry C, Hudson I, Gershlick AH, Ladwiniec A, Kovac J, Squire I, Samani NJ, Plein S, McCann GP, Adlam D. Chronic infarct size after spontaneous coronary artery dissection: implications for pathophysiology and clinical management. *Eur Heart J* 2020;**41**:2197–2205.
96. Ibanez B. [Myocardial infarction in times of COVID-19]. *Rev Esp Cardiol* 2020;**73**:975–977.
97. Chieffo A, Stefanini GG, Price S, Barbato E, Tarantini G, Karam N, Moreno R, Buchanan GL, Gilard M, Halvorsen S, Huber K,

James S, Neumann FJ, Mollmann H, Roffi M, Tavazzi G, Mauri Ferre J, Windecker S, Dudek D, Baumbach A. EAPCI Position Statement on Invasive Management of Acute Coronary Syndromes during the COVID-19 pandemic. *Eur Heart J* 2020;**41**:1839–1851.

98. Rodriguez-Leor O, Cid-Alvarez B, Perez de Prado A, Rossello X, Ojeda S, Serrador A, Lopez-Palop R, Martin-Moreiras J,, Rumoroso JR, Cequier A, Ibanez B, Cruz-Gonzalez I, Romaguera R, Moreno R en representacion de los investigadores del Grupo de Trabajo sobre Codigo Infarto de la Asociacion de Cardiologia Intervencionista de la Sociedad Espanola de CVilla M, Ruiz-Salmeron R, Molano F, Sanchez C, Munoz-Garcia E, Inigo L, Herrador J, Gomez-Menchero A, Gomez-Menchero A, Caballero J, Ojeda S, Cardenas M, Gheorghe L, Oneto J, Morales F, Valencia F, Ruiz JR, Diarte JA, Avanzas P, Rondan J, Peral V, Pernasetti LV, Hernandez J, Bosa F, Lorenzo PLM, Jimenez F, Hernandez JMT, Jimenez-Mazuecos J, Lozano F, Moreu J, Novo E, Robles J, Moreiras JM, Fernandez-Vazquez F, Amat-Santos IJ, Gomez-Hospital JA, Garcia-Picart J, Blanco BGD, Regueiro A, Carrillo-Suarez X, Tizon H, Mohandes M, Casanova J,, Agudelo-Montanez V, Munoz JF, Franco J, Del Castillo R, Salinas P, Elizaga J, Sarnago F, Jimenez-Valero S, Rivero F, Oteo JF, Alegria-Barrero E, Sanchez-Recalde A, Ruiz V, Pinar E, Pinar E, Planas A, Ledesma BL, Berenguer A, Fernandez-Cisnal A, Aguar P, Pomar F, Jerez M, Torres F, Garcia R, Frutos A, Nodar JMR, Garcia K, Saez R, Torres A, Telleria M, Sadaba M, Minguez JRL, Merchan JCR, Portales J, Trillo R, Aldama G, Fernandez S, Santas M, Perez MPP. [Impact of COVID-19 on ST-segment elevation myocardial infarction care. The Spanish experience]. *Rev Esp Cardiol* 2020;**73**:994–1002.
99. De Rosa S, Spaccarotella C, Basso C, Calabro MP, Curcio A, Filardi PP, Mancone M, Mercuro G, Muscoli S, Nodari S, Pedrinelli R, Sinagra G, Indolfi C, De Rosa S, Spaccarotella C, Basso C, Calabro MP, Curcio A, Filardi PP, Mancone M, Mercuro G, Muscoli S, Nodari S, Pedrinelli R, Sinagra G, Indolfi C. Reduction of hospitalizations for myocardial infarction in Italy in the COVID-19 era. *Eur Heart J* 2020;**41**:2083–2088.
100. Metzler B, Siostrzonek P, Binder RK, Bauer A, Reinstadler SJ. Decline of acute coronary syndrome admissions in Austria since the outbreak of COVID-19: the pandemic response causes cardiac collateral damage. *Eur Heart J* 2020;**41**:1852–1853.
101. Mafham MM, Spata E, Goldacre R, Gair D, Curnow P, Bray M, Hollings S, Roebuck C, Gale CP, Mamas MA, Deanfield JE, de Belder MA, Luescher TF, Denwood T, Landray MJ,, Emberson JR, Collins R, Morris EJA, Casadei B, Baigent C. COVID-19 pandemic and admission rates for and management of acute coronary syndromes in England. *Lancet* 2020;**396**:381–389.
102. Niccoli G, Luescher TF, Crea F. Decreased myocardial infarction admissions during COVID times: what can we learn? *Cardiovasc Res* 2020;**116**:e126–e128.
103. Pessoa-Amorim G, Camm CF, Gajendragadkar P, De Maria GL, Arsac C, Laroche C, Zamorano JL, Weidinger F, Achenbach S, Maggioni AP, Gale CP, Poppas A, Casadei B. Admission of patients with STEMI since the outbreak of the COVID-19 pandemic: a survey by the European Society of Cardiology. *Eur Heart J Qual Care Clin Outcomes* 2020;**6**:210–216.
104. Huber K, Goldstein P. Covid-19: implications for prehospital, emergency and hospital care in patients with acute coronary syndromes. *Eur Heart J Acute Cardiovasc Care* 2020;**9**:222–228.
105. Nadkarni GN, Lala A, Bagiella E, Chang HL, Moreno P, Pujadas E, Arvind V, Bose S, Charney AW, Chen MD, Cordon-Cardo C, Dunn AS, Farkouh ME, Glicksberg B, Kia A, Kohli-Seth R, Levin MA, Timsina P, Zhao S, Fayad ZA, Fuster V. Anticoagulation, mortality, bleeding and pathology among patients hospitalized with COVID-19: a single health system study. *J Am Coll Cardiol* 2020;**76**:1815–1826.
106. Choudry FA, Hamshere SM, Rathod KS, Akhtar MM, Archbold RA, Guttmann OP, Woldman S, Jain AK, Knight CJ, Baumbach A, Mathur A, Jones DA. High thrombus burden in patients with COVID-19 presenting with ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2020;**76**:1168–1176.
107. Solano-Lopez J, Zamorano JL, Pardo Sanz A, Amat-Santos I, Sarnago F, Gutierrez Ibanes E, Sanchis J, Rey Blas JR, Gomez-Hospital JA, Santos Martinez S, Maneiro-Melon NM, Mateos Gaitan R, Gonzalez D'Gregorio J, Salido L, Mestre JL, Sanmartin M, Sanchez-Recalde A. [Risk factors for in-hospital mortality in patients with acute myocardial infarction during the COVID-19 outbreak]. *Rev Esp Cardiol* 2020;**73**:985–993.
108. Lala A, Johnson KW, Januzzi JL, Russak AJ, Paranjpe I, Richter F, Zhao S, Somani S, Van Vleck T, Vaid A, Chaudhry F, De Freitas JK, Fayad ZA, Pinney SP, Levin M, Charney A, Bagiella E, Narula J, Glicksberg BS, Nadkarni G, Mancini DM, Fuster V, Mount Sinai COVID Informatics Center. Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection. *J Am Coll Cardiol* 2020;**76**:533–546.
109. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, Shchendrygina A, Escher F, Vasa-Nicotera M, Zeiher AM, Vehreschild M, Nagel E. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;**5**:1265–1273.
110. Basso C, Leone O, Rizzo S, De Gaspari M, van der Wal AC, Aubry MC, Bois MC, Lin PT, Maleszewski JJ, Stone JR. Pathological features of COVID-19-associated myocardial injury: a multicentre cardiovascular pathology study. *Eur Heart J* 2020;**41**:3827–3835.
111. Frangogiannis NG. The significance of COVID-19-associated myocardial injury: how overinterpretation of scientific findings can fuel media sensationalism and spread misinformation. *Eur Heart J* 2020;**41**:3836–3838.
112. Mathur A, Fernandez-Aviles F, Bartunek J, Belmans A, Crea F, Dowlut S, Galinanes M, Good MC, Hartikainen J, Hauskeller C, Janssens S, Kala P, Kastrup J, Martin J, Menasche P, Sanz-Ruiz R, Yla-Herttuala S, Zeiher A, BAMI Group. The effect of intracoronary infusion of bone marrow-derived mononuclear cells on all-cause mortality in acute myocardial infarction: the BAMI trial. *Eur Heart J* 2020;**41**:3702–3710.
113. Makkar RR, Kereiakes DJ, Aguirre F, Kowalchuk G, Chakravarty T, Malliaras K, Francis GS, Povsic TJ, Schatz R, Traverse JH, Pogoda JM, Smith RR, Marban L, Ascheim DD, Ostovaneh MR, Lima JAC, DeMaria A, Marban E, Henry TD. Intracoronary ALLogeneic heart STem cells to Achieve myocardial Regeneration (ALLSTAR): a randomized, placebo-controlled, double-blinded trial. *Eur Heart J* 2020;**41**:3451–3458.

ESC European Society of Cardiology

Special article

The year in cardiovascular medicine 2020: interventional cardiology

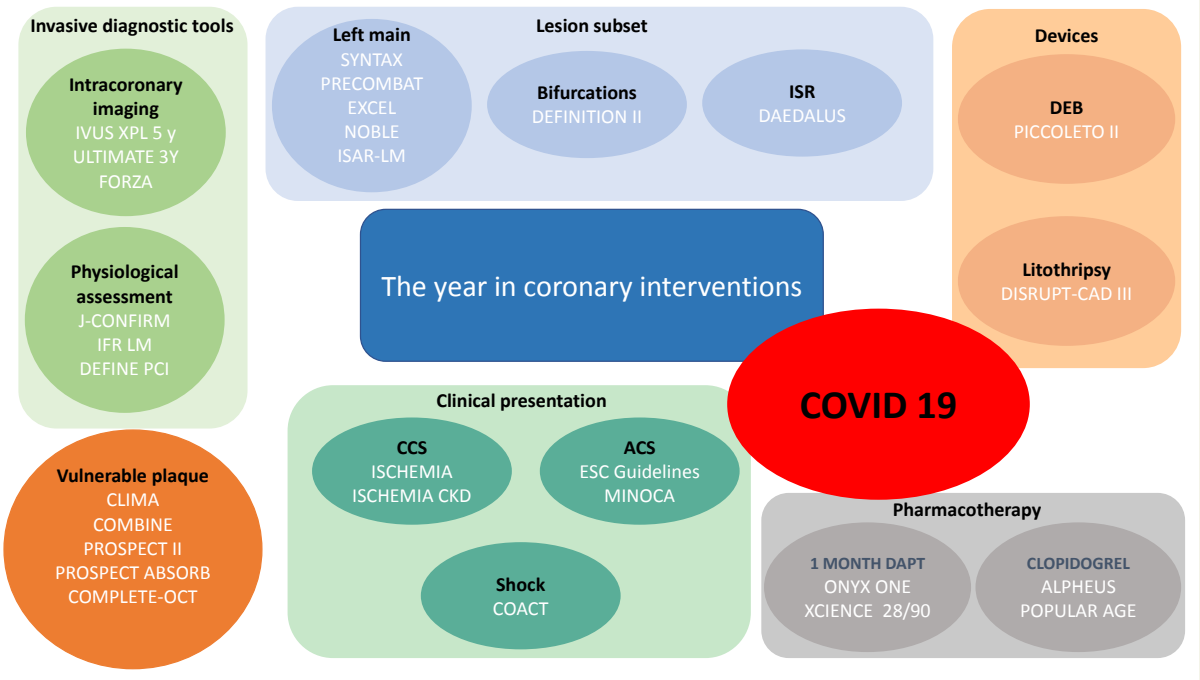
Fernando Alfonso[1]*, Nieves Gonzalo[2], Fernando Rivero[1], and Javier Escaned[2]

[1] Cardiology Department, Hospital Universitario de la Princesa, Instituto de Investigación Sanitaria IIS-IP, Universidad Autónoma de Madrid, CIBERCV, C/Diego de León 62, Madrid 28006, Spain; and [2] Cardiology Department, Hospital Clinico San Carlos, IdISSC, Universidad Complutense de Madrid. C/ Martín Lagos s/n 28042 Madrid, Spain

Received 11 November 2020; revised 11 December 2020; editorial decision 23 December 2020; accepted 23 December 2020

Reproduced from: Alfonso F, Gonzalo N, Rivero F, Escaned J. The year in cardiovascular medicine 2020: interventional cardiology. Eur Heart J. 2021 Mar 7;42(10):985-1003, https://doi.org/10.1093/eurheartj/ehaa1096, by permission of Oxford University Press on behalf of the European Society of Cardiology

* Corresponding author. Tel: +34 680483165, Email: falf@hotmail.com



The year in coronary interventions. ACS, acute coronary syndrome; CCS, chronic coronary syndrome; COVID-19: coronavirus disease-19; DEB, drug-eluting balloon; DAPT, dual antiplatelet therapy; ISR, in-stent restenosis.

Keywords
Acute coronary syndromes • Chronic coronary syndromes • Myocardial infarction • Coronavirus disease 19 • Clinical practice guidelines • Drug-eluting stents • Drug-coated balloons • Antiplatelet drugs • Coronary revascularization • Stent thrombosis • Left main coronary artery • In-stent restenosis • Intravascular ultrasound • Optical coherence tomography • Cardiogenic shock • Vulnerable plaque • Coronary physiology • Myocardial ischaemia

Introduction

Percutaneous coronary interventions (PCI) constitute the most widely used revascularization modality in patients with coronary artery disease (CAD). The past year witnessed major advances in the treatment of patients with acute coronary syndromes (ACS) and acute myocardial infarction (MI), including both ST-segment elevation (STEMI) and non-ST-segment elevation (NSTEMI), together with the presentation of a new clinical practice guideline (CPG). Management of patients with chronic coronary syndrome with demonstrable ischaemia has been specifically addressed by a new pivotal randomized trial. Significant advancements in the treatment specific lesion subsets together with novel data on long-term results of interventional devices have been published. Moreover, the value of physiological assessment before and after PCI has been consolidated, whereas new coronary imaging trials shed new light on the never-ending quest of the vulnerable plaque. Finally, advances in antithrombotic management, particularly addressing very short duration regimens, have been presented.

However, without any doubt, 2020 will be remembered as the year of the pandemic. Indeed, coronavirus disease-19 (COVID-19) drastically disrupted health care around the world, posing unprecedented challenges in the care of patients with cardiovascular diseases and CAD in particular (*Graphical abstract*).

COVID-19

Myocardial damage related to COVID-19 has been a subject of major clinical interest due to its prognostic implications. Non-ischaemic myocardial injury and myocarditis have been demonstrated in severe cases with this condition.[1–5] In addition, the intense inflammatory and prothrombotic milieu found in patients with severe COVID-19 disease has been considered a potential trigger of MI as a result of plaque rupture. Likewise, cases associated with severe coronary spasm, Takotsubo syndrome, spontaneous coronary artery dissection, and stent thrombosis have been reported.[6–8] A series from New York of COVID-19 patients with STEMI demonstrated a heterogeneous clinical presentation with a high prevalence (one-third of patients) of non-obstructive CAD and a poor prognosis (72% hospital mortality). In some patients, myocardial injury, rather than MI, was considered secondary to the cytokine

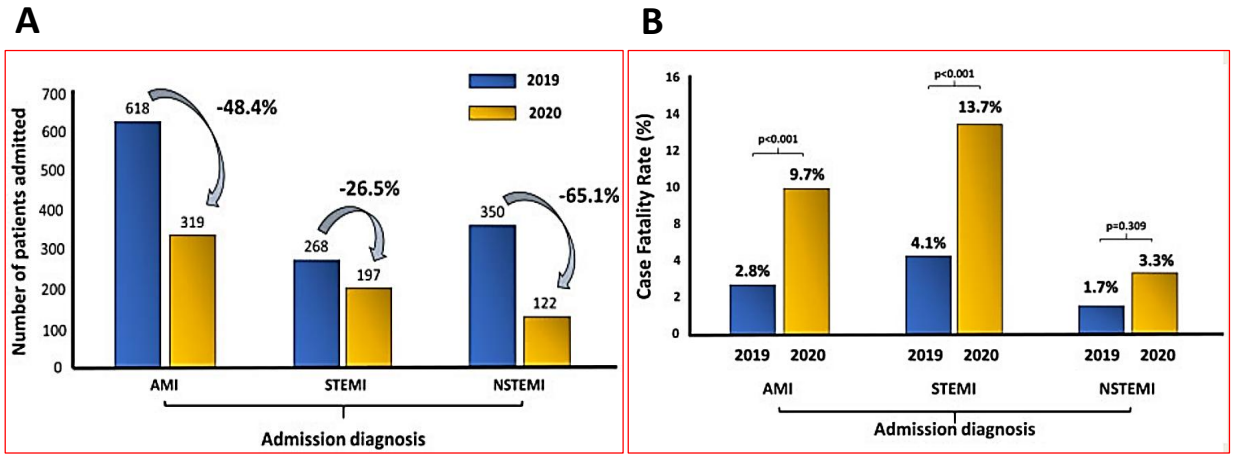


Figure 1 (*A*) Admissions for acute myocardial infarction across Italy. Number of admissions registered among Italian cardiac care units (CCUs) during the week 12–19 March 2020, in the midst of the COVID-19 emergency (yellow bars) and during the same week of the previous year (blue bars) for comparison. (*B*) Case fatality rates for acute myocardial infarction. Image obtained with permission from De Rosa *et al*.[18], by permission of OUP on behalf of the ESC.

storm, hypoxic injury, coronary spasm, microthrombi or, endothelial damage.[9] Furthermore, several studies demonstrated a prominent role of systemic thrombotic complications (both arterial and venous) in COVID-19 patients with some observational data suggesting a benefit of anticoagulation therapy in selected patients.[10] Notably, STEMI patients with concurrent COVID-19 infection appear to have larger thrombus burden and poorer outcomes. An observational study compared the characteristics and results of STEMI patients with and without concurrent COVID-19 infection. STEMI patients with COVID-19 had higher levels of troponin T, D-dimer, C-reactive protein, and lower lymphocyte counts. These patients had higher thrombus grade, more frequent multivessel thrombosis and stent thrombosis, needed more often the use of glycoprotein IIb/IIIa inhibitors and thrombus aspiration, but, eventually, had a poorer left ventricular ejection fraction (LVEF).[11]

COVID-19 had also a striking and unexpected effect on PCI activity around the world. A question was ubiquitously asked at the beginning of the pandemic: where have all the patients with acute MI gone? A significantly delayed hospital presentation after symptoms onset was consistently noticed.[12,13] Some have suggested increasing use of fibrinolytic therapy rather than primary PCI for patients with STEMI, given delays to catheterization laboratory arrival, and to avoid exposing staff to COVID. However, studies have confirmed that in spite of the logistic challenges, primary PCI remains the therapy of choice for STEMI during the pandemic.[14–16] Subsequently, cardiovascular mortality was found to play a major role in the 'excess in mortality' seen during the pandemic. A significant decrease in ACS-related hospitalization in northern Italy during the early days of the COVID-19 outbreak suggested that the total increase in mortality (not fully explained by COVID-19 cases alone) would be the result of ACS patients dying without seeking medical attention[15–18] (*Figure 1*). A study from England confirmed the reduced number of admissions and PCI for ACS during the pandemic, particularly among NSTEMI patients.[19] The risk for an increase in out-of-hospital death and long-term complications of MI was a cause of major concern. Another study from the Lombardia region demonstrated a strong correlation between the cumulative incidence of out of hospital cardiac arrest and the COVID-19 cumulative incidence per 100 000 inhabitants.[15] Accordingly, modified diagnostic and treatment algorithms were rapidly developed to adapt classical protocols to this unprecedented sanitary challenge. The need for drastic reorganization of catheterization laboratories, including protection measures for healthcare providers, ACS networks (with redistribution of hub and spoke hospitals), and reshaping of emergency rooms and cardiac units, soon became apparent worldwide.[20]

Chronic coronary syndromes

The long-awaited results of the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial were published in 2020.[21] The trial investigated in a 1:1 randomized fashion if, in patients with stable CAD and moderate or severe ischaemia, an initial invasive strategy of cardiac catheterization and optimal revascularization, in addition to optimal medical treatment (OMT), would improve clinical outcomes compared with an initial conservative strategy of OMT alone with coronary angiography reserved for failure of medical therapy. In total, 5179 patients were enrolled in the trial. Importantly, cardiac computed tomography was required before randomization in patients without severe kidney disease to exclude the presence of left main coronary artery disease (LMCAD) or non-obstructive CAD. At 5-year follow-up, no superiority of the invasive over the medical strategy was documented. The estimated cumulative event rate of the primary endpoint (a composite of death from cardiovascular causes, MI, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest) was 16.4% in the invasive-strategy group and 18.2% in the conservative-strategy group [difference, –1.8 percentage

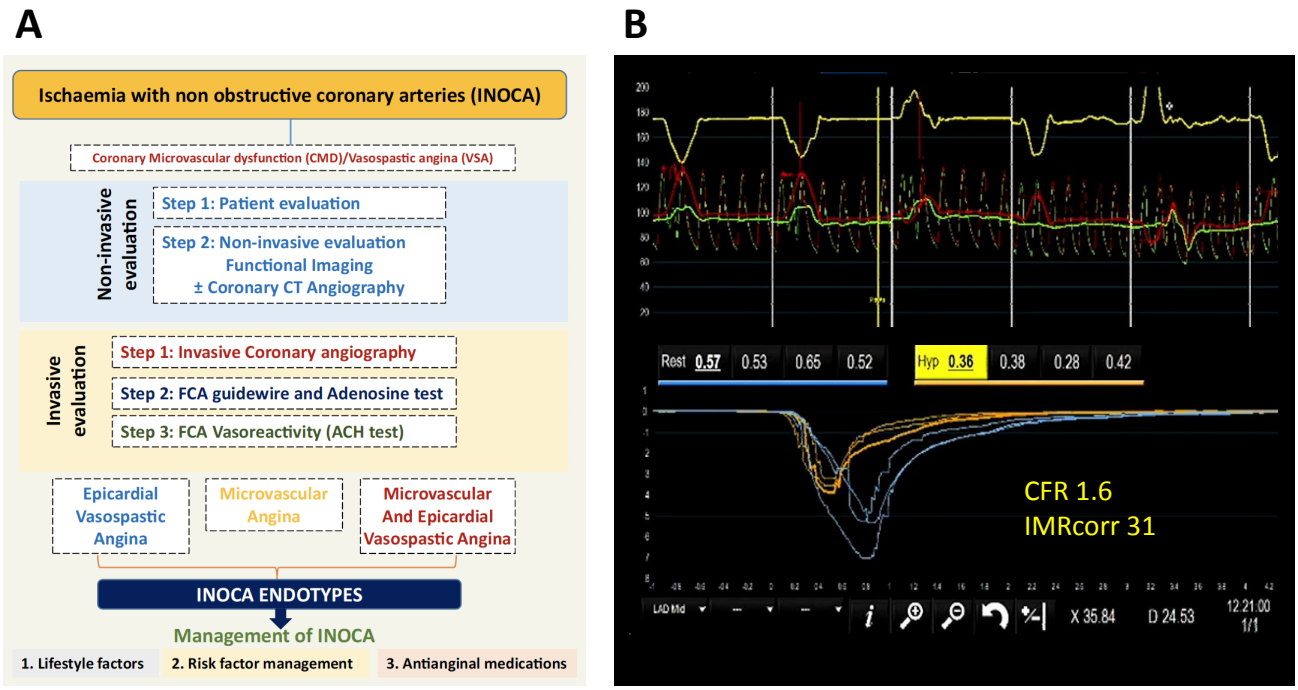


Figure 3 (*A*) Management of patients with ischaemia and normal coronary arteries (INOCA). (*B*) Case example of a patient with angiographically normal coronary arteries in whom microvascular dysfunction was invasively studied using coronary flow reserve (CFR) and the index of myocardial resistance (IMR). (*A*) Image obtained with permission from Kunadian *et al*.[27], by permission of OUP on behalf of the ESC.

points; 95% confidence interval (CI) –4.7 to 1.0] (*Figure 2A – see Spertus et al.[22]*). In terms of mortality, there was no significant difference in all-cause mortality in the two study groups. Of note, while associated with more procedural MI, in the long term, the invasive strategy demonstrated to be superior to the conservative one in terms of spontaneous MI (*Figure 2B and 2C – see Spertus et al.[22]*). Furthermore, the invasive strategy leads to greater improvement in angina-related health status than the conservative strategy, with a sustained improvement in quality of life that was maintained through 3 years.[22] Due to the study exclusion criteria, the findings of the ISCHEMIA trial do not apply to patients with ACS, LMCAD, reduced LVEF, heart failure (class III or IV), or severe angina despite maximal medical therapy. Among a more complex population of patients with chronic kidney disease, the ISCHEMIA-CKD randomized trial failed to detect any benefit (primary endpoint mortality and MI) in the invasive compared with the conservative strategy.[23]

A study-level meta-analysis of 14 randomized clinical trials (RCT) (14 877 patients) comparing routine revascularization vs. an initial conservative strategy in patients with stable ischaemic heart disease including also the two ISCHEMIA trials reported that, despite similar rates of all-cause death, cardiovascular death, MI, heart failure, or stroke in the invasive and conservative approaches, an invasive strategy is associated with reduced risks of non-procedural MI, unstable angina, and superior rates of freedom from angina, at the cost of an increased risk of procedural MI.[24]

The 2019 European Society of Cardiology (ESC) CPG on the Diagnosis and Management of Chronic Coronary Syndromes introduced several new recommendations of particular interest for interventional cardiologists.[25] Invasive angiography was recommended as an alternative test to diagnose CAD in patients with a high clinical likelihood and severe symptoms refractory to medical therapy, or typical angina at a low level of exercise and clinical evaluation that indicates high event risk (IA class and level of recommendation). The recommendation specifies that invasive functional assessment must be available and used to evaluate stenosis before revascularization, unless very high grade (>90% diameter stenosis), providing an important support to the use of physiology in the catheterization laboratory. The coronary sinus reducer device received an IIb recommendation to ameliorate symptoms of debilitating angina refractory to OMT and revascularization strategies.[26] Of note, the diagnosis of microvascular angina in the catheterization laboratory is strongly supported by these CPG. New recommendations include the use of intracoronary measurements of coronary flow reserve and microvascular resistance (IIa B), as well as the use of acetylcholine testing (IIb B), in patients with persistent symptoms but coronary arteries that are either angiographically normal or have moderate stenoses with preserved instantaneous wave-free ratio (iwFR) or fractional flow reserve (FFR). Ample information on how to outline vascular dysfunction pathways in patients with ischaemia with non-obstructive coronary arteries, and on how to set stratified treatment on the grounds of the obtained information, has been put together into a dedicated, expert document published by the European Association of Percutaneous Coronary Interventions (EAPCI) in conjunction with scientific working groups (*Figure 3*).[27]

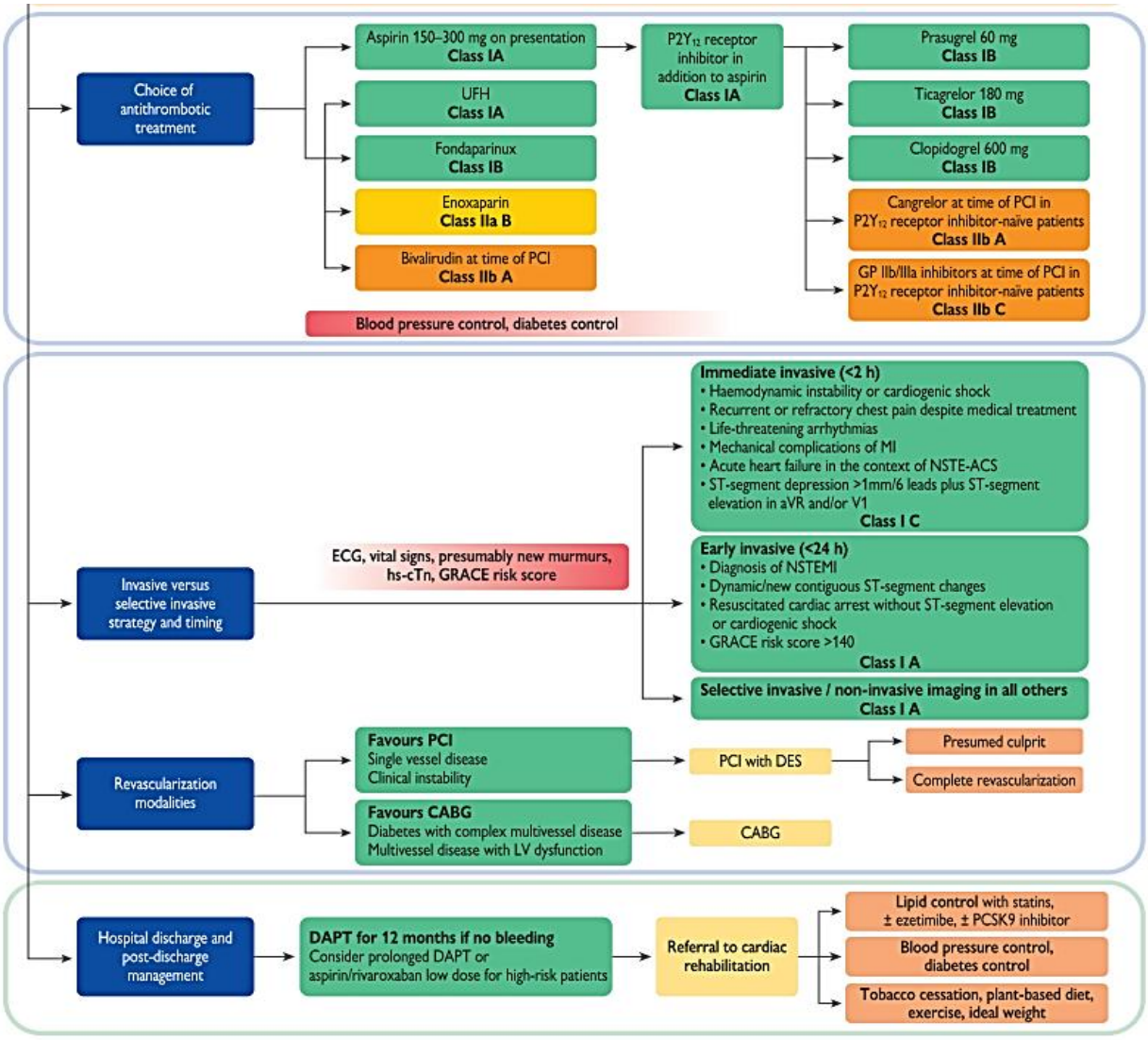


Figure 4 Management strategy for non-ST-segment elevation acute coronary syndrome patients according to the new ESC CPG. CABG, coronary artery bypass graft(ing); DAPT, dual antiplatelet therapy; DES, drug-eluting stent; ECG, electrocardiogram/electrocardiography; GP, glycoprotein; GRACE, Global Registry of Acute Coronary Events; hs-cTn, high-sensitivity cardiac troponin; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PCSK9, protein convertase subtilisin kexin 9; UFH, unfractionated heparin. Image obtained with permission from Collet *et al*.[29], by permission of OUP on behalf of the ESC.

Finally, a recent study on women ($n=301$) presenting with MI and angiographically non-obstructed coronary arteries demonstrated the value of optical coherence tomography (OCT) and cardiac magnetic resonance imaging (CMR) to identify a potential mechanism for the acute event in 84.5% of patients (63.8% had a ischaemic- and 20.7% a non-ischaemic aetiology).[28]

Acute coronary syndromes

Non-ST-segment elevation myocardial infarction

This year, a new ESC CPG on the management of ACS patients without persistent STEMI was issued.[29] This guideline facilitates decision-making in daily practice and includes a set of quality indicators to assess the level of implementation and clinical outcomes. New recommendations for these patients regarding diagnosis and medical treatment included the ESC high-sensitive cardiac troponin T (hs-cTnT) blood sampling 0 h/2 h algorithm as an alternative to the 0 h/1 h algorithm (I), no need for other biomarkers in addition to hs-cTnT for diagnostic purposes (III), use of B-type natriuretic peptide (BNP)/N-terminal pro-B-type natriuretic peptide for risk stratification (IIa), prasugrel preferred to ticagrelor for patients proceeding to PCI (IIa), P2Y12 pre-treatment for patients who cannot undergo early invasive management (IIb) but not for patients with unknown anatomy planned for early invasive management (III), de-escalation of P2Y12 for patients unsuitable for potent platelet inhibition (IIb), use of novel oral anticoagulants and a single antiplatelet agent after 1 week of triple therapy in patients with

atrial fibrillation with embolic risk (I), and discontinuation of antiplatelet therapy at 1 year in patients requiring oral anticoagulation (I).[29] Alternatively, new recommendations regarding invasive treatment included an early invasive strategy (<24 h) for high-risk patients (I), selective invasive strategy for low-risk patients following non-invasive imaging/ischaemia detection tests (I), delayed (rather than immediate) coronary angiography for cardiac arrest survivors without STEMI (IIa), complete revascularization for patients without cardiogenic shock (IIa) (IIb to be accomplished during index procedure), FFR-guided complete revascularization during index procedure (IIb).[29] A summary of management recommendations is presented in *Figure 4*.

ST-segment elevation myocardial infarction (STEMI)

The very long-term safety and efficacy of drug-eluting stents (DES) in STEMI patients were recently confirmed. The 10-year results of the EXAMINATION trial demonstrated the superiority of everolimus-DES compared with bare-metal stents (BMS) regarding the primary efficacy endpoint.[30] Interestingly, the landmark analysis beyond 5 years showed identical and very low event rates with the two strategies.[30] In asymptomatic patients with 'transient' STEMI, an immediate invasive strategy was unable to reduce CMR-assessed infarct size compared to an early invasive strategy.[31] A large cohort study using routine clinical data from tertiary UK centres suggested that less than half of octogenarians with STEMI/NSTEMI underwent invasive management. Interestingly, the adjusted cumulative 5-year mortality rate was 36% in the invasive management group and 55% in the non-invasive management group.[32] Several new meta-analyses, including data from the COMPLETE trial, comparing complete vs. culprit-only revascularization in STEMI patients supported the value of complete revascularization to reduce rates of re-infarction, cardiovascular mortality, and repeat revascularization with no difference in all-cause mortality.[33] Likewise, in patients with NSTEMI, an observational study suggested that multivessel revascularization reduced 3-year rates of major adverse cardiac events (MACE) (total death, MI, any revascularization) compared with culprit-vessel-only revascularization.[34] However, in this study, 1-stage multivessel revascularization was not superior to multistage revascularization except in low-to-intermediate risk patients.[34]

Cardiac arrest/shock

The Coronary Angiography after Cardiac Arrest (COACT) randomized trial enrolled 552 patients successfully resuscitated after out-of-hospital cardiac arrest without electrocardiographic signs of STEMI.[35] The 1-year survival (61.4% vs. 64.0%) and MACE rates were similar in the immediate vs. delayed angiography strategies.[35] In a population-based registry from Paris, 4% of out-of-hospital cardiac arrests were treated with extracorporeal-cardiopulmonary resuscitation (CPR), which was not associated with increased hospital survival.[36] However, in the extracorporeal-CPR group, initial shockable rhythm and pre-hospital extra-corporeal membrane oxygenation (ECMO) implantation improved clinical outcomes. The value of routine mechanical circulatory support in patients with cardiogenic shock remains controversial even though these devices are increasingly used as the ultimate option for these critically ill patients. A meta-analysis of randomized trials suggested no reduction in mortality with the use of Impella or intra-aortic balloon in patients undergoing high-risk PCI or cardiogenic shock, but a significant increase in vascular complications.[37] However, another concurrent meta-analysis of observational studies suggested the potential value of the new generations of the Impella device in selected patients in cardiogenic shock.[38] Finally, data from a large nationwide administrative database in patients with acute MI and cardiogenic shock suggested that the adjusted mortality rate was lower in patients no-electively treated with Impella than in those receiving venoarterial (VA)-ECMO.[39] Finally, in a large (686 patients) multicentre cohort study, left ventricular unloading with Impella reduced mortality in patients in cardiogenic shock treated with VA-ECMO despite higher complication rates (mainly access site-related and renal replacement therapy).[40] Many studies on this field are currently limited by a retrospective design, observational nature, and reduced sample size. Accordingly, controlled studies are required to further elucidate the value of mechanical circulatory support in patients undergoing high--risk interventions and in those with cardiogenic shock.

Lesion subsets

Left main and multivessel disease

The last year provided significant information on long--term outcomes of patients with LMCAD treated with PCI vs. coronary artery bypass grafting (CABG). One of the sources for such evidence is the SYNTAX trial, which randomized patients with LMCAD or 3-vessel disease to PCI with first-generation paclitaxel-eluting stent ($n=903$) vs. CABG ($n=897$).[41] Information on vital status at 10 years was obtained for 841 (93%) patients in the PCI group and 848 (95%) patients in the CABG group showing no significant differences in all-cause death between the two treatment modalities. At 10 years, 248 (28%) patients had died in the PCI and 212 (24%) in the CABG study groups [hazard ratio (HR) 1.19 (95% CI 0.99–1.43), $P=0.066$]. When analysed separately, all-cause mortality was higher in the PCI group in patients with 3-vessel disease, but not in patients with LMCAD.[41] These data should be interpreted taking into consideration that PCI in this trial was performed using a first-generation DES (Taxus™) with rates of late stent thrombosis superior to current generation DES and not currently available for clinical practice.

The PRECOMBAT trial (Premier of Randomized Comparison of Bypass Surgery vs. Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease), randomized 600 patients with LMCAD to PCI with sirolimus-eluting stents or CABG. The extended 10-year follow-up published this year showed no differences between the two groups in the primary outcome (composite of all-cause death, MI, stroke, or ischaemia-driven target-vessel revascularization). Ischaemia-driven target-vessel revascularization (TVR) was more frequent after PCI than after CABG [16.1% vs. 8.0%; HR 1.98 (95%

CI 1.21–3.21)].[42] Two RCT comparing PCI vs. CABG for LMCAD treatment have reported their 5-year follow-up results. The EXCEL study that randomized 1905 patients with LMCAD to be treated with PCI (with everolimus-DES) or CABG showed no differences between groups for the combined endpoint of all-cause death, MI, or stroke (22.0% for PCI and 19.2% for CABG).[43] Patients treated with PCI showed an increased all-cause mortality (13.0% vs. 9.9%) and higher rates of revascularization (16.9% vs. 10.0%) while cerebrovascular events were more frequent in patients treated with CABG (3.3% vs. 5.2%). There were no differences between PCI and CABG in cardiovascular death (5.0% vs. 4.5%) or MI (10.6% and 9.1%, respectively). The 5-year follow-up of the NOBLE study that randomized 1201 patients with LMCAD to PCI with DES (88% biolimus-DES) or CABG showed a higher incidence of MACE (composite of all-cause mortality, non-procedural MI, repeat revascularisation, and stroke) in patients treated with PCI (28% for PCI and 19% for CABG). Interestingly, there were no differences in all-cause mortality (9% for both groups), but patients treated with PCI had higher rates of non-procedural MI (8% vs. 3%) and repeat revascularisation (17% vs. 10%).[44] Table 1 presents the results of the RCT comparing PCI vs. CABG for the treatment of LMCAD with long-term clinical follow-up. To summarize the long-term results of LMCAD revascularization, a meta-analysis of the four RCT comparing PCI and CABG for the treatment of LMCAD with >5 years follow-up reported no differences in all-cause death and cardiovascular death between the two types of revascularization. MACE was higher in the PCI group mainly in relation with an increase in MI and revascularizations.[45] A second meta-analysis including 4595 patients with LMCAD from five RCT showed no differences in all-cause mortality or MI between CABG and PCI with higher rates of revascularization in the PCI group at 5 years' follow-up.[46] Finally, the most recent meta-analysis comparing the two types of revascularization included 4612 patients from five trials.[47] No differences were found between PCI and CABG regarding all-cause mortality or cardiac death. No significant differences were observed between therapies in the risk of stroke or MI but PCI was associated with an increased risk of revascularization.

Several sub-studies of the EXCEL trial have been reported in the past year. One of them evaluated the impact of periprocedural MI on mortality. Periprocedural MI [defined as creatinine kinase-MB (CK-MB) elevation >10× the upper reference limit (URL) within 72 h post-procedure, or >5× URL with new Q-waves, angiographic vessel occlusion, or loss of myocardium on imaging] was more frequent after CABG and was associated with 3-year all-cause death and cardiovascular death for both modalities of revascularization. Only increases of biomarkers indicating large necrosis (CK-MB > 10× URL) were related to mortality.[48] A second sub-analysis of the EXCEL trial explored the influence of repeat revascularizations on mortality. PCI was associated with higher rates of any repeat revascularization, and the need for repeat revascularization by CABG (but not by PCI) was independently associated with increased risk for 3-year all-cause and cardiovascular mortality after both CABG and PCI.[49] Another sub-analysis of the EXCEL trial showed that a reduced LVEF (<40%) was associated with an increased 3-year rate of the composite of death, stroke, and MI driven mainly by an increased rate of all-cause death.[50] However, this study did not show any significant differences between PCI and CABG irrespective of the underlying LVEF.[50]

A patient-level pooled analysis of the randomized ISAR-LEFT-MAIN and ISAR-LEFT-MAIN-2 trials, in which patients underwent treatment of LMCAD with DES, was reported. The 5-year mortality rate was higher in patients with target lesion revascularization (TLR) compared with those without. In this analysis, severe renal dysfunction, COPD, and body mass index were independent predictors of mortality while type of stent and type of repeat revascularization did not influence mortality.[51] Other studies published this year evaluated the influence of the LVEF on LMCAD revascularisation. A study performed in South Korea evaluated a total of 3488 patients with LMCAD who underwent CABG ($n = 1355$) or PCI ($n = 2133$) from the IRIS-MAIN (Interventional Research Incorporation Society-Left MAIN Revascularization) registry.[52] The authors found no differences in the composite of death, MI, or stroke between the two treatment strategies when the patients had normal or mildly reduced LVEF. However, as compared with CABG, PCI was associated with a higher adjusted risk of the primary outcome in patients with reduced LVEF.[52]

Regarding strategies of revascularization in patients with multivessel disease, a registry from Canada analysing with propensity match diabetic patients with 2- or 3-vessel disease who underwent PCI or CABG showed a higher mortality and MACE rates in patients treated percutaneously at a median follow-up of 5.5 years.[53] These results should, however, be interpreted with caution as this study suffers from limitations (e.g. significant differences in the rates of complete revascularization between the two groups even after propensity score matching).

Bifurcations

The DEFINITION II trial randomized 653 patients with complex bifurcation lesions according to DEFINITION criteria to provisional stenting vs. a systematic 2-stent technique. Target lesion failure (TLF) at 1-year follow-up was significantly higher in the provisional group mainly driven by an increase in target vessel MI and TLR without differences in cardiac death. No differences in stent thrombosis were observed between the two groups.[54]

A network meta-analysis published this year evaluated outcomes of five different PCI techniques (provisional stenting, T stenting/T and protrusion, crush, culotte, and DK-crush) in patients with lesions involving coronary bifurcations. The study evaluated 21 RCT including 5711 patients. At a median follow-up of 12 months, DK-crush was associated with fewer MACE, driven by lower rates of repeat revascularization. Rates of cardiac death, MI, and stent thrombosis were not significantly different among techniques.[55] In the context of LMCAD involving the bifurcation, the need for final kissing balloon inflation is still debated. A large registry including 2742 patients treated with ultra-thin strut DES showed no differences in the composite endpoint (all-cause death, MI, TLR, and stent thrombosis) between patients treated with final kissing balloon or not. However, in LMCAD involving the bifur-

Table 1 Randomized controlled trials comparing coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) for the treatment of left main coronary artery disease

	n	Type of stent used	Primary endpoint definition	FU	Primary endpoint	All-cause death	Cardiovascular death	MI	Repeat revascularization	Stroke
EXCEL[43]	CABG 957 PCI 948	Everolimus--eluting stent	Composite of death, stroke, or myocardial infarction	5 years	CABG 19.2% PCI 22.0% *P*=0.13 OR 1.19 (95% CI 0.95–1.50)	CABG 9.9% PCI 13.0% OR 1.38 (95% CI 1.03–1.85)	CABG 4.5% PCI 5% OR 1.13 (95% CI 0.73–1.74)	CABG 9.1% PCI 10.6% OR 1.14 (95% CI 0.84–1.55)	CABG 10% PCI 16.9% OR 1.84 (95% CI 1.39–2.44)	CABG 3.7% PCI 2.9% OR 0.78 (95% CI 0.46–1.31)
NOBLE[44]	CABG 592 PCI 592	88% Biolimus-eluting stent	Composite of all--cause mortality, non-procedural MI, repeat revascularisation, and stroke	5 years	CABG 19% PCI 28.0% HR 1.58 (95% CI 1.24–2.01) *P*=0.0002	CABG 9% PCI 9% HR 1.08 (95% CI 0.74–1.59); *P*=0.68	CABG 4% PCI 4% HR 0.99 (95% CI 0.57–1.73) *P*=0.99	CABG 3% PCI 8% HR 2.99 (95% CI 1.66–5.39) *P*=0.0002	CABG 10% PCI 17% HR 1.73 (95% CI 1.25–2.40) *P*=0.0009	CABG 2% PCI 4% HR 1.75 (0.86–3.55) *P*=0.11
SYNTAXES (LM subgroup)[41]	CABG 348 PCI 357	First generation paclitaxel eluting stent	10-year all-cause death	10 years	CABG 28% PCI 26% HR 0.90 (95% CI 0.68–1.20)	CABG 28% PCI 26% HR 0.90 (95% CI 0.68–1.20)	NA	NA	NA	NA
PRECOMBAT 10 years[42]	CABG 300 PCI 300	First generation sirolimus eluting stents	Composite of death from any cause, MI, stroke, or ischaemia--driven target-vessel revascularization	10 years	CABG 24.7% PCI 29.8% HR 1.25 (95% CI 0.93–1.69)	CABG 13.8% PCI 14.5% HR 1.13 (95% CI 0.75–1.70)	CABG 8.7% PCI 7.8% HR 0.96 (95% CI 0.56–1.65)	CABG 2.8% PCI 3.2% HR 0.76 (95% CI 0.32–1.82)	CABG 8% PCI 16.1% HR 1.98 (95% CI 1.21–3.21)	CABG 2.2% PCI 1.9% HR 0.71 (95% CI 0.22–2.23)

CI, confidence interval; FU, follow-up; HR, hazard ratio; MI, myocardial infarction.

cation treated with two stents, the use of final kissing balloon was associated with less restenosis and TVR.[56] In contrast, a sub-analysis of the EXCEL trial showed no differences in events at 4-year follow-up between patients treated with and patients treated without final kissing balloon inflation in both one and two stent groups.[57]

Restenosis and small vessel disease

Several studies have focused on the treatment of small coronary vessels assessing the performance of different devices in this lesion subset. A study from the SCAAR registry including 14 788 patients with small vessels (<2.5 mm) treated with DES or drug-coated balloons (DCB) showed a higher rate of restenosis in the DCB group at 3-year follow-up with no differences in death, MI, or target lesion thrombosis.[58] A pooled analysis from the BIOFLOW II, IV, and VI trials compared the performance of an ultrathin-strut bioresorbable-polymer sirolimus-DES vs. durable-polymer everolimus-DES in small vessels (<2.75 mm) showing lower rates of TLF and target vessel MI in the biodegradable polymer sirolimus-DES group.[59]

In the field of restenosis, the DAEDALUS study, a patient-level meta-analysis including 10 RCT, showed that treatment of in-stent restenosis (ISR) with DCB was associated with a higher risk of TLR at 3 years, with no differences in the safety outcome (death, MI, or target lesion thrombosis).[60] A sub-analysis of this study, comparing BMS-ISR and DES-ISR, demonstrated that both treatment strategies (DCB and new DES implantation) were similarly effective and safe in patients with BMS-ISR. However, in patients with DES-ISR, treatment with DCB was associated with a higher rate of TLR at 3 years and non-significant differences in safety outcomes.[61]

Chronic total occlusions

Research in the field of chronic total occlusions (CTO) has focused largely on technical aspects and clinical benefit. The impact of CTO PCI on ischaemic burden was evaluated in a study in which patients underwent [15O]H_2O positron emission tomography prior to and 3 months after successful CTO PCI. Results demonstrated a significant reduction in perfusion defect size after CTO PCI with significant improvement of the hyperaemic myocardial blood flow and coronary flow reserve within the CTO area.[62] The efficacy and safety of using saphenous vein grafts (SVG) for retrograde crossing during CTO PCI was explored in a study including 1615 retrograde CTO PCI. The use of the SVG for retrograde access was associated with higher rates of procedural success without differences in in-hospital MACE.[63] A comparison of available scores to predict CTO PCI success showed comparable capacity of the EuroCTO (CASTLE) and JCTO scores with a superior discriminatory capacity for CASTLE score as complexity increased.[64] A Japanese score to predict successful guidewire crossing through collaterals identified small vessel, reverse bend, and continuous bends as predictors of failure in septal collaterals, and small vessel, reverse bend, and corkscrew as predictors of failure in epicardial collaterals.[65]

In the field of complex PCI, a registry from the British Cardiovascular Intervention Society demonstrated that patients who had PCI to their last remaining patent vessel had a higher risk profile (older age, more comorbidities, and higher prevalence of reduced LVEF) and had more clinical events than patients with more than one patent vessel. This was independent of the vessel treated.[66]

Interventional devices

Durable-polymer, biodegradable-polymer, and polymer-free drug-eluting stents

The 10-year results of the ISAR-TEST-5 trial, including the 64% surviving patients of the initial 3000 patients enrolled, did not find any difference in outcomes between patients treated with polymer-free vs. durable polymer DES.[67] The incidence of stent thrombosis was low and comparable in both groups (1.6% vs. 1.9%) but, unfortunately, high rates of overall adverse clinical events were observed during this very long clinical follow-up. In the SORT-OUT 9 trial, 3151 patients were randomized to treatment with the Biofreedom™ stent (stainless steel drug-coated polymer-free stent) or the Orsiro™ stent (ultrathin strut, biodegradable polymer, cobalt-chromium sirolimus-eluting).[68] The Biofreedom™ polymer-free stent did not meet the criteria for non-inferiority regarding major adverse cardiovascular events at 12 months in this all-comers population. The HOST-Reduce-Polytech-ACS trial randomized over 3400 patients with ACS, known to carry a heightened risk of thrombosis and delayed healing after PCI, to a durable-polymer DES or a biodegradable-polymer stent.[69] There was no significant difference between the groups on the primary outcome measure (patient-oriented clinical outcome at 1 year). Nevertheless, the device-oriented clinical endpoint at 1-year was significantly lower in patients treated with the durable--polymer device. The PIONEER III trial tested the Supreme 'healing-targeted' HT-DES [a thin-strut (80 µg) DES with rapid sirolimus delivery and polymer degradation (4–6 weeks), plus a base layer that promotes endothelial migration] against the Xience™/Promus™ durable-polymer DES in 1632 all-comer patients.[70] At 12 months, TLF occurred in 5.4% of the HT-DES patients and on 5.1% of the durable-polymer DES patients, meting the trial criteria for non-inferiority. The secondary endpoint of target--vessel MI was not significantly different between groups, although it tended to be lower for the HT-DES (3.4% vs. 4.1%; $P=0.45$). These findings suggest that among the three components of DES, the platform (strut thickness and the stent design) might at least be as important as the drug and the polymer.

Drug-coated balloons

Despite the initial alarm created by the publication of a meta-analysis that suggested an increased mortality risk associated with paclitaxel-containing devices in patients with peripheral arterial disease, another meta-analysis with patient-level data dissipated these safety concerns.[71] A meta-analysis focused on the coronary space including 4590 patients treated for either coronary ISR or *de novo* lesions did not find an increase in mortality in patients treated with paclitaxel-DCB.[72] In fact, at a 3-year follow-up, the risk of both all-cause (RR 0.73, 95% CI 0.53–1.00) and cardiac mortality (RR 0.53, 95% CI 0.33–0.85) was significantly lower in those patients treated with DCB compared

with alternative treatments. Likewise, another meta-analysis, which included 14 RCT with 2483 patients treated for '*de novo*' lesions found no differences between DCB and alternative therapeutic modalities in terms of MACE, vessel thrombosis, or cardiovascular mortality.[73] However, DCB were associated with a lower incidence of MI (RR 0.48, 95% CI 0.25–0.90) and all-cause mortality (RR 0.45, 95% CI 0.22–0.94). Finally, the PICCOLETO II RCT recently compared DCB with everolimus-DES in 118 stable patients with *de novo* lesions in small vessels.[74] At 6 months, in-lesion late lumen loss (primary endpoint) was 0.17 ± 0.39 mm in the everolimus-DES group and 0.04 ± 0.28 mm in the DCB group, meeting the pre-defined non-inferiority criteria ($P = 0.03$).

Thin-struts drug-eluting stents

At 3 years, the ultrathin-strut Orsiro™ stent maintained an advantage over the durable-polymer Xience™, according to the new data from the BIOFLOW V study. This study showed a 40% relative reduction in TLF as well as significantly lower rates of target-vessel MI, ischaemia-driven TLR, and late/very late stent thrombosis in the Orsiro™ arm.[75] The 3-year clinical follow-up of the DESSOLVE III RCT confirmed the efficacy and safety of the ultrathin-strut biodegradable polymer MiStent sirolimus-eluting stent as compared to thin-strut permanent polymer Xience™ stent.[76] The primary endpoint (a device-oriented composite endpoint) occurred in 10.5% for MiStent™ sirolimus-eluting stent and 11.5% for Xience™ stent ($P = 0.55$). A pooled analysis including 2337 patients with more complex coronary artery disease (moderate-to-severe calcification or small vessels) showed a reduction in TLF at 1 year favouring the ultrathin-strut Orsiro™ stent in the small vessels cohort (8.0% vs. 12.4%; $P < 0.01$).[59]

Coronary intravascular lithotripsy

Intravascular lithotripsy (IVL) showed its usefulness to optimize PCI results in severely calcified lesions, with good safety and efficacy results at 30 days in the DISRUPT-CAD III study.[77] This single-arm prospective registry included 431 patients with severely calcified lesions (mean calcified segment length 47.9 ± 18.8 mm, calcium angle 292.5 ± 76.5° and calcium thickness 0.96 ± 0.25 mm), treated with IVL. Procedural success was 92.4% and a residual diameter stenosis <30% was obtained in 99.5% of lesions (*Figure 5 – see Hill et al.[77]*). The primary safety endpoint, freedom from 30-day MACE, was observed in 92.2% of patients. Therefore, this technique emerges as a new attractive (easy-to-use) therapeutic modality for patients with heavily calcified lesions.

Bare-metal stents

In patients with ACS, cobalt–chromium-based TiNO-coated stents were non-inferior to platinum–chromium-based biodegradable polymer everolimus-DES for major cardiac events at 12 months (HR 0.93, 95% CI 0.71–1.22, $P < 0.001$ for non-inferiority), and were superior for the co-primary endpoint of cardiac death, MI, and bleeding at 18 months, as shown in the TIDES-ACS randomized trial.[78] Despite the early superiority of everolimus-DES over BMS in STEMI patients, the 10-year results of the EXAMINATION trial demonstrated that, beyond 5 years, event rates were very low and similar with both stents.[30] No differences were found between everolimus-DES and BMS in terms of TLR and definite stent thrombosis between 5 and 10 years (1.2% vs. 1.2%; $P = 0.962$; 0.5% vs. 0.1%; $P = 0.177$, respectively).

Bioresorbable scaffolds

The MAGSTEMI trial compared the in-stent/scaffold vasomotion (primary endpoint) between the magnesium-based bioresorbable scaffold (MgBRS) and a sirolimus-DES at 12-month follow-up in patients with STEMI.[79] Although MgBRS demonstrated a larger vasomotor response to pharmacological agents, they were associated with a lower angiographic efficacy and a higher need for TLR at 1 year (16.2% vs. 5.2%; $P = 0.030$). The OCT sub-study of this trial showed that at 1-year follow-up, both the minimal lumen area (MLA) (3.92 vs. 6.31 mm^2; $P < 0.001$) and the expansion index (0.58 vs. 0.86; $P < 0.001$) were smaller in patients treated with MgBRS.[80] Interestingly, half of the MgBRS restenosis was caused by scaffold collapse (*Figure 6 – see Gomez-Lara et al.[80]*). In another OCT study that included 70 patients with MgBRS failure, the presence of late collapse was found as the main cause of late lumen loss, and device collapse was seen significantly more frequently in patients with fibrotic lesions.[81] These data suggest that future developments of MgBRS should focus on maintaining the radial force of the device for a longer period.

Invasive diagnostic tools

Intracoronary imaging

The long-term clinical follow-up of two large randomized trials evaluating the benefit of intravascular ultrasound (IVUS) use for PCI optimization was published this year. The IVUS-XPL trial randomized 1400 patients with long coronary lesions (implanted stent length ≥28 mm) to receive IVUS-guided or angiography-guided everolimus-DES. At 1 year, IVUS-guided stent implantation was associated with a significantly lower rate of MACE, mainly driven by the reduced risk for TVR. The trial showed a sustained benefit of the IVUS-guided strategy for up to 5 years and a landmark analysis demonstrated that differences in events between the two strategies not only accrued in the first year but also between the first and fifth year.[82] These results are in line with the 3-year follow-up of ULTIMATE, another RCT comparing angio and IVUS-guided second-generation DES implantation in an all-comer's population (1448 patients). At 3 years, the target vessel failure (TVF) rate was lower in the IVUS-guided group, mainly driven by a reduction in the need for repeated revascularisations.[83] A patient-level meta-analysis of four randomised clinical trials of angiographic vs. IVUS-guided DES implantation (including 1396 patients) evaluated the effect of using IVUS *before* stent implantation on late outcomes. All patients underwent final IVUS-guided optimization after stent deployment. The authors demonstrated that the use of IVUS pre-intervention was associated with better procedural outcomes (larger minimum stent area), although no differences in clinical events were observed at 1-year follow-up.[84]

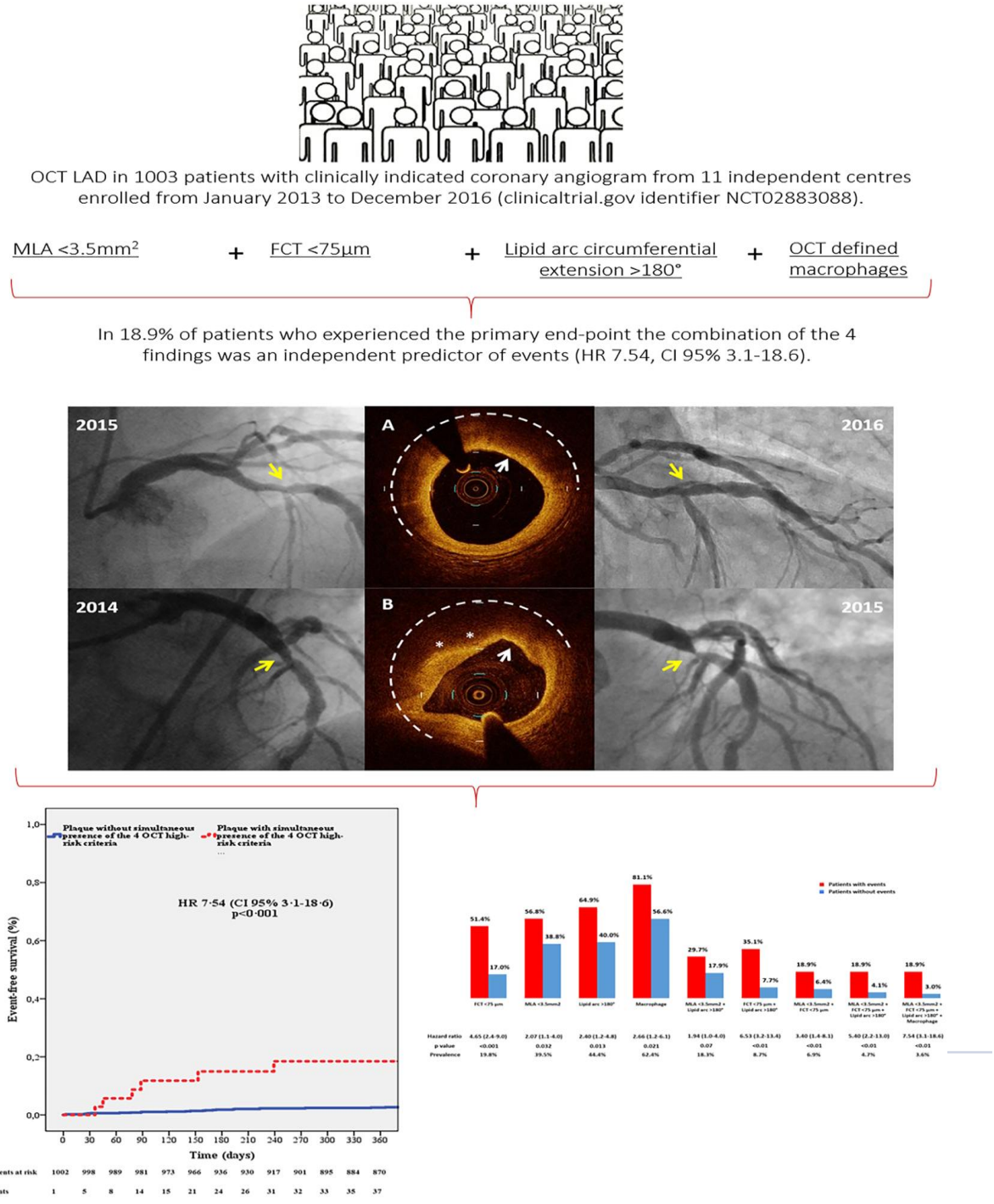


Figure 7 The CLIMA study. This prospective study explored the predictive value of multiple high-risk plaque features in the same coronary lesion [minimum lumen area (MLA), fibrous cap thickness (FCT), lipid arc circumferential extension, and presence of macrophages] as detected by optical coherence tomography (OCT) in 1003 patients undergoing OCT evaluation of the untreated proximal left anterior descending coronary artery. At 1 year, the pre-specified combination of plaque vulnerability features was an independent predictor of events. Image obtained with permission from Prati *et al*.[86], by permission of OUP on behalf of the ESC.

The value of OCT to guide the management of angiographically intermediate coronary stenosis was assessed in a single-centre study that randomized patients to FFR or OCT imaging management. Criteria for treatment were FFR < 0.80 in the physiology arm, and area stenosis ≥75%, or 50–75% with minimal luminal area <2.5 mm² or plaque rupture, in the imaging arm. A total of 350 patients were randomized. The primary endpoint (composite of MACE or significant angina at 13 months) occurred significantly less frequently in the OCT-guided group. In the FFR arm, the rate of patients medically managed was higher and the total costs were lower.[85]

The identification of vulnerable plaques still remains elusive and highly controversial. Several studies have been presented this year analysing the value of OCT to identify plaque characteristics related to the appearance of subsequent clinical events. The CLIMA study evaluated the predictive value of four high-risk plaque features as assessed by OCT, namely MLA <3.5 mm^2, fibrous cap thickness <75 µm, lipid arc circumferential extension >180°, and presence of macrophages. A total of 1003 patients with an OCT pullback performed in the left anterior descending coronary artery were included. The primary endpoint was a composite of cardiac death and target segment MI at 1 year. The simultaneous presence of the four high-risk features in the same plaque was an independent predictor of adverse events in this population (*Figure 7*).[86] The predictive value of OCT has been also assessed in the COMBINE trial, a natural history prospective study evaluating the incidence of MACE at 18 months in diabetic patients with FFR negative lesions according to the presence of a thin-cap fibroatheroma (TCFA) vs. non-TCFA morphology. OCT-defined TCFA was present in ~25% of the FFR negative lesions and was a predictor of events at follow-up.[87] The OCT sub-study of the COMPLETE trial evaluated the morphological characteristics of non-culprit plaques in STEMI patients. The authors found that nearly half of the patients had an obstructive plaque with high-risk features. Interestingly, the presence of TCFA was more frequent in obstructive than in non-obstructive lesions. The association of lesion obstruction and vulnerability features might explain the better outcomes observed in patients randomized to the treatment of the non-culprit obstructive stenosis in the COMPLETE trial.[88]

Regarding the use of other intracoronary imaging techniques to assess plaque characteristics, the PROSPECT II was a natural history study evaluating the predictive value of near infrared spectroscopy IVUS (IVUS-NIRS) in patients after an ACS. Following treatment of the culprit lesion, the proximal segments of the three coronary arteries were systematically assessed with IVUS-NIRS. Plaque burden >70%, MLA <4.0 mm^2, and a high lipid core burden index were predictors of events at follow-up (median 3.7 years).[89] A total of 182 patients (with angiographically mild and non-flow-limiting lesions and a plaque burden >65%), included in PROSPECT II were further randomized to medical treatment or bioresorbable vascular scaffold (BVS) implantation (in the PROSPECT ABSORB trial). At 25-month IVUS follow-up, the MLA was larger in lesions treated with BVS vs. those managed medically. Scaffold implantation in these lesions was safe with only one reported case of thrombosis and 1 case showing scaffold discontinuities. A favourable but non-significant trend towards 1-year plaque-related events was observed. The trial was, however, not powered for clinical endpoints and this concept needs to be examined in a larger study.[89]

Coronary physiology

New data published this year have confirmed the safety of PCI deferral based on FFR. The J-CONFIRM Registry, from Japan, prospectively enrolled 1263 patients with 1447 lesions and showed a 2-year TVF rate of 5.5% in deferred lesions, highlighting the safety of this strategy.[90] A large registry evaluating patients with stable angina who underwent angiography between 2009 and 2017 demonstrated a progressive increase in the use of FFR and a lower risk of mortality at 1-year follow-up in patients with FFR-guided treatment vs. those managed based only on angiography.[91] In specific lesions subsets, a multicentre observational study evaluated the safety of LMCAD revascularization deferral based on iwFR. The study included 314 patients in whom LMCAD treatment was deferred [n = 163 (51.9%)] or performed [n = 151 (48.1%)] according to the iwFR cut-off ≤0.89. There were no differences between the two groups in the composite of all-cause death, nonfatal MI, and ischaemia-driven TLR during a median follow-up of 30 months, suggesting the safety of using iwFR to determine the need for revascularization in patients with LMCAD.[92]

Another field of intense research has been the use of physiology *after* PCI. The DEFINE PCI was a multicentre, prospective study in which a blinded iwFR pull-back was performed after an angiographically successful PCI. A total of 500 patients were evaluated showing an iwFR <0.90 after PCI in 24% of them. Of those with an abnormal iwFR post-PCI, 81.6% had focal stenosis potentially treatable with stent optimization or new stent implantation.[93] The 1-year follow-up results demonstrated that patients with iwFR <0.95 post-PCI had more events at follow-up (a composite of death, spontaneous MI, or clinically driven TVR) (HR 3.38; 95% CI 0.99–11.6; log-rank P = 0.04) and less improvement in anginal symptoms.[94]

Adjunctive pharmacotherapy and high bleeding risk patients

Two trials explored the effect of ticagrelor monotherapy on bleeding and ischaemic events in ACS patients undergoing PCI. TWILIGHT-ACS confirmed that dropping aspirin after 3 months of dual antiplatelet therapy (DAPT) with ticagrelor reduced bleeding risk by 53% without increasing the rate of ischaemic events.[95] Along the same line, the TICO randomized trial showed that switching to ticagrelor monotherapy after 3 months of DAPT reduced major bleeding without increasing ischaemic risk compared with 12 months of DAPT in ACS patients.[96] These findings indicate that ticagrelor monotherapy could be an optimal strategy, balancing both ischaemic and bleeding risks, for patients with ACS treated by PCI with second-generation DES. However, neither trial was powered to detect a difference in ischaemic events.

Results of two large prospective studies have consolidated the concept of a reduced DAPT duration with current-generation DES among patients at high risk for bleeding. In the ONYX-ONE trial, 1996 patients at high bleeding risk were randomly assigned to receive zotarolimus-DES or polymer-free DES.[97] After PCI, patients were treated with 1-month DAPT, followed by single antiplatelet therapy. At 1 year, the primary outcome was observed in 17% of patients in the zotarolimus-DES group and in 17% in the polymer-free DES group, suggesting that among patients at high bleeding risk who received 1-month DAPT, use of polymer-based zotarolimus-DES was non-inferior to the use of polymer-free DES. Likewise, the XIENCE Short DAPT program, including ~3600 patients, tested antiplate-

let treatment duration of 1 month and 3 months. XIENCE 90, using 3-month DAPT, enrolled 2047 patients, and XIENCE 28, using 1-month DAPT, included 963 patients.[98] For XIENCE 28, the primary analysis period was between months 1 and 6. For XIENCE 90, outcomes were analysed between months 3 and 12. For comparative purposes, historical controls were drawn from the XIENCE V all-comers study, in which 91% of patients were on DAPT at 6 months and 85.6% at 1 year. XIENCE 90 participants had similar rates of all death or MI between 3 and 12 months compared with controls (5.4% vs. 5.4%; P for non-inferiority = 0.0063). XIENCE 28 also used controls for death/MI in the test group between 1 and 6 months (3.5% vs. 4.5%; *P* for non-inferiority: 0.0005). Interestingly, major bleeding (BARC type 3 to 5) was less common in both XIENCE 90 and XIENCE 28, than in the XIENCE V historic cohort.

A network meta-analysis including 52 816 patients with ACS observed that prasugrel and ticagrelor reduced ischaemic events and increased bleeding in comparison with clopidogrel. There was no efficacy or safety difference between prasugrel and ticagrelor.[99] A Korean randomized trial in ACS patients undergoing PCI showed that a prasugrel-based dose de-escalation strategy, starting 1 month after PCI, reduced the risk of net clinical outcomes up to 1 year, mainly driven by a reduction in bleeding without an increase in ischaemic events.[100] Regarding the optimal timing of P2Y12 inhibitors administration, an RCT including 1449 ACS patients found no differences in clinical outcomes between a downstream and an upstream antiplatelet treatment strategy.[101] In the COMPARE CRUSH trial, 727 patients with STEMI were randomly assigned to 60 mg crushed or whole prasugrel in addition to 500 mg IV aspirin.[102] There were no differences, in TIMI 3 flow either in the infarct-related artery before PCI, or in the rates of complete ST-segment resolution at 1 hour after PCI. Although an enhanced degree of platelet inhibition was demonstrated in the group receiving crushed pills before primary PCI, this theoretical benefit failed to translate into clinically detectable reperfusion effects.

In patients aged 70 years or older presenting with NSTEMI-ACS, clopidogrel is a favourable alternative to ticagrelor, because it leads to fewer bleeding events without an increase in the combined endpoint of all-cause death, MI, stroke, and bleeding, as observed in POPULAR AGE trial.[103] Moreover, an observational analysis of 14 005 MI patients 80 years or older enrolled in the SWEDEHEART registry showed that, compared to clopidogrel, ticagrelor was associated with 17% and 48% higher risks of death (1.17, 95% CI 1.03–1.32) and bleeding (1.48, 95% CI 1.25–1.76), but a lower risk of MI (0.80, 95% CI 0.70–0.92) and stroke (0.72, 95% CI 0.56–0.93).[104] Therefore, clopidogrel appears to be an interesting P2Y12 inhibitor alternative for elderly patients with a higher bleeding risk. The One-Month DAPT randomized trial tested if 1 month of aspirin plus a P2Y12 inhibitor followed by aspirin monotherapy would be non-inferior to the standard regimen of 6–12 months of DAPT for the composite endpoint of cardiovascular events or major bleeding at 1 year.[105] In the 1-month DAPT group, composite events occurred in 5.9% of patients vs. 6.5% of the 6- to 12-month DAPT group. The HR for the 1-month DAPT therapy followed by aspirin monotherapy was 0.9, $P<0.001$ for non-inferiority compared to the recommended 6–12 months of DAPT therapy. The COMPASS-PCI, a sub-study of COMPASS trial, included 9862 patients who underwent PCI for chronic coronary syndrome >1 year earlier (average time 5.4 years) to aspirin plus rivaroxaban vs. aspirin alone. The study demonstrated that rivaroxaban 2.5 mg twice daily plus aspirin reduced MACE rate (cardiovascular death, MI, or stroke) and all-cause mortality, but increased major bleeding as compared with aspirin alone.[106] Interestingly, among those patients with previous PCI, the effects on MACE and mortality were consistent irrespective of the time elapsed since the last PCI. Finally, the ALPHEUS trial found that ticagrelor was not superior to clopidogrel in reducing periprocedural myocardial necrosis in stable coronary patients undergoing high-risk elective PCI but caused an increase in minor bleeding at 30 days.[107]

Conclusions

Last year, the first report from the ESC/EAPCI ATLAS project disclosed considerable international heterogeneity in PCI volumes that was closely related to gross national income per capita.[108,109] Major efforts should be made by scientific societies (including ESC and EAPCI) focusing on all implicated stakeholders to address these equity gaps. Likewise, in the year 2020, the pandemic strikingly disrupted clinical care of patients with cardiovascular diseases and, particularly, those with CAD. Currently, we are enduring the 'third wave' of COVID-19 while getting ready for future threats. Resilience will remain paramount to face these complex novel scenarios. This paper highlights that the field of interventional cardiology continues to evolve each year. However, major care should be taken to preserve academic endeavour in these challenging times and to ensure that continuous scientific research efforts, as those reported in this review, will be maintained in order to advance our knowledge on prevention, diagnosis, and management of patients with CAD, eventually leading to improved clinical outcomes.

Conflict of interest: Nieves Gonzalo: speaker at educational events for Abbott and Boston Scientific. Other authors have nothing to declare.

References

1. Lombardi CM, Carubelli V, Iorio A, Inciardi RM, Bellasi A, Canale C, Camporotondo R, Catagnano F, Dalla Vecchia LA, Giovinazzo S, Maccagni G, Mapelli M, Margonato D, Monzo L, Nuzzi V, Oriecuia C, Peveri G, Pozzi A, Provenzale G, Sarullo F, Tomasoni D, Ameri P, Gnecchi M, Leonardi S, Merlo M, Agostoni P, Carugo S, Danzi GB, Guazzi M, La Rovere MT, Mortara A, Piepoli M, Porto I, Sinagra G, Volterrani M, Specchia C, Metra M, Senni M. Association of troponin levels with mortality in Italian patients hospitalized with coronavirus disease 2019: results of a multicenter study. *JAMA Cardiol* 2020;**5**:1274–1280.
2. Shi S, Qin M, Cai Y, Liu T, Shen B, Yang F, Cao S, Liu X, Xiang Y, Zhao Q, Huang H, Yang B, Huang C. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *Eur Heart J* 2020;**41**:2070–2079.
3. Peretto G, Sala S, Caforio ALP. Acute myocardial injury, MINOCA, or myocarditis? Improving characterization of coronavirus-associated myocardial involvement. *Eur Heart J* 2020;**41**:2124–2125.

4. Basso C, Leone O, Rizzo S, De Gaspari M, van der Wal AC, Aubry MC, Bois MC, Lin PT, Maleszewski JJ, Stone JR. Pathological features of COVID-19-associated myocardial injury: a multicentre cardiovascular pathology study. *Eur Heart J* 2020;**41**:3827–3835.
5. Inciardi RM, Adamo M, Lupi L, Cani DS, Di Pasquale M, Tomasoni D, Italia L, Zaccone G, Tedino C, Fabbricatore D, Curnis A, Faggiano P, Gorga E, Lombardi CM, Milesi G, Vizzardi E, Volpini M, Nodari S, Specchia C, Maroldi R, Bezzi M, Metra M. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. *Eur Heart J* 2020;**41**:1821–1829.
6. Fernandez Gasso L, Maneiro Melon NM, Sarnago Cebada F, Solis J, Garcia Tejada J. Multivessel spontaneous coronary artery dissection presenting in a patient with severe acute SARS-CoV-2 respiratory infection. *Eur Heart J* 2020;**41**:3100–3101.
7. Meyer P, Degrauwe S, Van Delden C, Ghadri JR, Templin C. Typical takotsubo syndrome triggered by SARS-CoV-2 infection. *Eur Heart J* 2020;**41**:1860–1860.
8. Rivero F, Antuña P, Cuesta J, Alfonso F. Severe coronary spasm in a COVID-19 patient. *Catheter Cardiovasc Interv* 2020;doi:10.1002/ccd.29056.
9. Bangalore S, Sharma A, Slotwiner A, Yatskar L, Harari R, Shah B, Ibrahim H, Friedman GH, Thompson C, Alviar CL, Chadow HL, Fishman GI, Reynolds HR, Keller N, Hochman JS. ST-segment elevation in patients with COVID-19—a case series. *N Engl J Med* 2020;**382**:2478–2480.
10. Nadkarni GN, Lala A, Bagiella E, Chang HL, Moreno PR, Pujadas E, Arvind V, Bose S, Charney AW, Chen MD, Cordon-Cardo C, Dunn AS, Farkouh ME, Glicksberg BS, Kia A, Kohli-Seth R, Levin MA, Timsina P, Zhao S, Fayad ZA, Fuster V. Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19. *J Am Coll Cardiol* 2020;**76**:1815–1826.
11. Choudry FA, Hamshere SM, Rathod KS, Akhtar MM, Archbold RA, Guttmann OP, Woldman S, Jain AK, Knight CJ, Baumbach A, Mathur A, Jones DA. High thrombus burden in patients with COVID-19 presenting with ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2020;**76**:1168–1176.
12. Said K, El-Baghdady Y, Abdel-Ghany M. Acute coronary syndromes in developing countries during the COVID-19 pandemic. *Eur Heart J* 2020;**41**:2518–2521.
13. Pessoa-Amorim G, Camm CF, Gajendragadkar P, De Maria GL, Arsac C, Laroche C, Zamorano JL, Weidinger F, Achenbach S, Maggioni AP, Gale CP, Poppas A, Casadei B. Admission of patients with STEMI since the outbreak of the COVID-19 pandemic: a survey by the European Society of Cardiology. *Eur Heart J Qual Care Clin Outcomes* 2020;**6**:210–216.
14. Mahmud E, Dauerman HL, Welt FGP, Messenger JC, Rao SV, Grines C, Mattu A, Kirtane AJ, Jauhar R, Meraj P, Rokos IC, Rumsfeld JS, Henry TD. Management of acute myocardial infarction during the COVID-19 pandemic: a position statement from the Society for Cardiovascular Angiography and Interventions (SCAI), the American College of Cardiology (ACC), and the American College of Emergency Physicians (ACEP). *J Am Coll Cardiol* 2020;**76**:1375–1384.
15. Baldi E, Sechi GM, Mare C, Canevari F, Brancaglione A, Primi R, Klersy C, Palo A, Contri E, Ronchi V, Beretta G, Reali F, Parogni P, Facchin F, Rizzi U, Bussi D, Ruggeri S, Oltrona Visconti L, Savastano S; Lombardia CARe researchers. COVID-19 kills at home: the close relationship between the epidemic and the increase of out-of-hospital cardiac arrests. *Eur Heart J* 2020;**41**:3045–3054.
16. Rodriguez-Leor O, Cid-Alvarez B, Ojeda S, Martin-Moreiras J, Rumoroso JR, Lopez-Palop R, Serrador A, Cequier A, Romaguera R, Cruz I, Perez e Prado A, Moreno R. Impact of the COVID-19 pandemic on interventional cardiology activity in Spain. *REC Interv Cardiol* 2020;**2**:82–89.
17. De Luca G, Verdoia M, Cercek M, Jensen LO, Vavlukis M, Calmac L, Johnson T, Ferrer GR, Ganyukov V, Wojakowski W, Kinnaird T, van Birgelen C, Cottin Y, IJsselmuiden A, Tuccillo B, Versaci F, Royaards KJ, Berg JT, Laine M, Dirksen M, Siviglia M, Casella G, Kala P, Díez Gil JL, Banning A, Becerra V, De Simone C, Santucci A, Carrillo X, Scoccia A, Amoroso G, Lux A, Kovarnik T, Davlouros P, Mehilli J, Gabrielli G, Rios XF, Bakraceski N, Levesque S, Cirrincione G, Guiducci V, Kidawa M, Spedicato L, Marinucci L, Ludman P, Zilio F, Galasso G, Fabris E, Menichelli M, Garcia-Touchard A, Manzo S, Caiazzo G, Moreu J, Forés JS, Donazzan L, Vignali L, Teles R, Benit E, Agostoni P, Bosa Ojeda F, Lehtola H, Camacho-Freiere S, Kraaijeveld A, Antti Y, Boccalatte M, Deharo P, Martínez-Luengas IL, Scheller B, Alexopoulos D, Moreno R, Kedhi E, Uccello G, Faurie B, Gutierrez Barrios A, Di Uccio FS, Wilbert B, Smits P, Cortese G, Parodi G, Dudek D. Impact of COVID-19 pandemic on mechanical reperfusion for patients with STEMI. *J Am Coll Cardiol* 2020;**76**:2321–2330.
18. De Rosa S, Spaccarotella C, Basso C, Calabrò MP, Curcio A, Filardi PP, Mancone M, Mercuro G, Muscoli S, Nodari S, Pedrinelli R, Sinagra G, Indolfi C; Società Italiana di Cardiologia and the CCU Academy investigators group. Reduction of hospitalizations for myocardial infarction in Italy in the COVID-19 era. *Eur Heart J* 2020;**41**:2083–2088.
19. Mafham MM, Spata E, Goldacre R, Gair D, Curnow P, Bray M, Hollings S, Roebuck C, Gale CP, Mamas MA, Deanfield JE, de Belder MA, Luescher TF, Denwood T, Landray MJ, Emberson JR, Collins R, Morris EJA, Casadei B, Baigent C. COVID-19 pandemic and admission rates for and management of acute coronary syndromes in England. *Lancet* 2020;**396**:381–389.
20. Chieffo A, Stefanini GG, Price S, Barbato E, Tarantini G, Karam N, Moreno R, Buchanan GL, Gilard M, Halvorsen S, Huber K, James S, Neumann FJ, Möllmann H, Roffi M, Tavazzi G, Mauri Ferré J, Windecker S, Dudek D, Baumbach A. EAPCI position statement on invasive management of acute coronary syndromes during the COVID-19 pandemic. *Eur Heart J* 2020;**41**:1839–1851.
21. Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, Chaitman BR, Senior R, López-Sendón J, Alexander KP, Lopes RD, Shaw LJ, Berger JS, Newman JD, Sidhu MS, Goodman SG, Ruzyllo W, Gosselin G, Maggioni AP, White HD, Bhargava B, Min JK, Mancini GBJ, Berman DS, Picard MH, Kwong RY, Ali ZA, Mark DB, Spertus JA, Krishnan MN, Elghamaz A, Moorthy N, Hueb WA, Demkow M, Mavromatis K, Bockeria O, Peteiro J, Miller TD, Szwed H, Doerr R, Keltai M, Selvanayagam JB, Steg PG, Held C, Kohsaka S, Mavromichalis S, Kirby R, Jeffries NO, Harrell FE, Rockhold FW, Broderick S, Ferguson TB, Williams DO, Harrington RA, Stone GW, Rosenberg Y. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med* 2020;**382**:1395–1407.
22. Spertus JA, Jones PG, Maron DJ, O'Brien SM, Reynolds HR, Rosenberg Y, Stone GW, Harrell FE, Boden WE, Weintraub WS, Baloch K, Mavromatis K, Diaz A, Gosselin G, Newman JD, Mavromichalis S, Alexander KP, Cohen DJ, Bangalore S, Hochman JS, Mark DB. Health-status outcomes with invasive or conservative care in coronary disease. *N Engl J Med* 2020;**382**:1408–1419.
23. Bangalore S, Maron DJ, O'Brien SM, Fleg JL, Kretov EI, Briguori C, Kaul U, Reynolds HR, Mazurek T, Sidhu MS, Berger JS, Mathew RO, Bockeria O, Broderick S, Pracon R, Herzog CA, Huang Z, Stone GW, Boden WE, Newman JD, Ali ZA, Mark DB, Spertus JA, Alexander KP, Chaitman BR, Chertow GM, Hochman JS; ISCHEMIA-CKD Research Group. Management of coronary disease in patients with advanced kidney disease. *N Engl J Med* 2020;**382**:1608–1618.
24. Bangalore S, Maron DJ, Stone GW, Hochman JS. Routine revascularization versus initial medical therapy for stable ischemic heart disease: a systematic review and meta-analysis of randomized trials. *Circulation* 2020;**142**:841–857.
25. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**:407–477.
26. Konigstein M, Giannini F, Banai S. The Reducer device in patients with angina pectoris: mechanisms, indications, and perspectives. *Eur Heart J* 2018;**39**:925–933.
27. Kunadian V, Chieffo A, Camici PG, Berry C, Escaned J, Maas AHEM, Prescott E, Karam N, Appelman Y, Fraccaro C, Louise Buchanan G, Manzo-Silberman S, Al-Lamee R, Regar E, Lansky A, Abbott JD, Badimon L, Duncker DJ, Mehran R, Capodanno D,

Baumbach AA. EAPCI expert consensus document on ischaemia with non-obstructive coronary arteries in collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders Internati. *Eur Heart J* 2020;**41**:3504–3520.
28. Reynolds HR, Maehara A, Kwong Ry Sedlak T, Saw J, Smilowitz Nr ME, Wei J, Marzo K, Matsumura M, Seno A, Hausvater A, Giesler C, Jhalani N, Toma C, Har B, Thomas D, Mehta LS, Trost J, Mehta PK, Ahmed B, Bainey KR, Xia Y, Shah B, Attubato M, Bangalore S, Razzouk L, Ali ZA, Bairey-Merz CN, Park K, Hada E, Zhong H, Hochman JS. Coronary optical coherence tomography and cardiac magnetic resonance imaging to determine underlying causes of MINOCA in women. *Circulation* 2020; doi: 10.1161/CIRCULATIONAHA.120.052008.
29. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt Dl Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2020;doi:10.1093/eurheartj/ehaa575.
30. Brugaletta S. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction: 10-year follow-up of the multicenter randomized controlled EXAMINATION trial. Cardiovascular Therapeutics annual scientific symposium 2020. 15 October 2020.
31. Lemkes JS, Janssens GN, van der Hoeven NW, van de Ven PM, Marques KMJ, Nap A, van Leeuwen MAH, Appelman YEA, Knaapen P, Verouden NJW, Allaart CP, Brinckman SL, Saraber CE, Plomp KJ, Timmer JR, Kedhi E, Hermanides RS, Meuwissen M, Schaap J, van der Weerdt AP, van Rossum AC, Nijveldt R, van Royen N. Timing of revascularization in patients with transient ST-segment elevation myocardial infarction: a randomized clinical trial. *Eur Heart J* 2019;**40**:283–291.
32. Kaura A, Sterne JAC, Trickey A, Abbott S, Mulla A, Glampson B, Panoulas V, Davies J, Woods K, Omigie J, Shah AD, Channon KM, Weber JN, Thursz MR, Elliott P, Hemingway H, Williams B, Asselbergs FW, O'Sullivan M, Lord GM, Melikian N, Johnson T, Francis DP, Shah AM, Perera D, Kharbanda R, Patel RS, Mayet J. Invasive versus non-invasive management of older patients with non-ST elevation myocardial infarction (SENIOR-NSTEMI): a cohort study based on routine clinical data. *Lancet* 2020;**396**:623–634.
33. Atti V, Gwon Y, Narayanan MA, Garcia S, Sandoval Y, Brilakis ES, Basir MB, Turagam MK, Khandelwal A, Mena-Hurtado C, Mamas MA, Abbott JD, Bhatt DL, Velagapudi P. Multivessel versus culprit-only revascularization in STEMI and multivessel coronary artery disease: meta-analysis of randomized trials. *JACC Cardiovasc Interv* 2020;**13**:1571–1582.
34. Kim MC, Hyun JY, Ahn Y, Bae S, Hyun DY, Cho KH, Sim DS, Hong YJ, Kim JH, Jeong MH, Kim HS, Gwon HC, Seong IW, Hwang KK, Chae SC, Hur SH, Cha KS, Oh SK. Optimal revascularization strategy in non-ST-segment-elevation myocardial infarction with multivessel coronary artery disease: culprit-only versus one-stage versus multistage revascularization. *J Am Heart Assoc* 2020;**9**:e016575.
35. Lemkes JS, Janssens GN, van der Hoeven NW, Jewbali LSD, Dubois EA, Meuwissen MM, Rijpstra TA, Bosker HA, Blans MJ, Bleeker GB, Baak RR, Vlachojannis GJ, Eikemans BJW, van der Harst P, van der Horst ICC, Voskuil M, van der Heijden JJ, Beishuizen A, Stoel M, Camaro C, van der Hoeven H, Henriques JP, Vlaar APJ, Vink Ma van den Bogaard B, Heestermans TACM, de Ruijter W, Delnoij TSR, Crijns HJGM, Jessurun GAJ, Oemrawsingh PV, Gosselink MTM, Plomp K, Magro M, Elbers PWG, Spoormans EM, van de Ven PM, Oudemans-van Straaten HM, van Royen N. Coronary angiography after cardiac arrest without ST segment elevation: one-year outcomes of the COACT randomized clinical trial. *JAMA Cardiol* 2020;**5**:1–8.
36. Bougouin W, Dumas F, Lamhaut L, Marijon E, Carli P, Combes A, Pirracchio R, Aissaoui N, Karam N, Deye N, Sideris G, Beganton F, Jost D, Cariou A, Jouven X; the Sudden Death Expertise Center investigators. Extracorporeal cardiopulmonary resuscitation in out-of-hospital cardiac arrest: a registry study. *Eur Heart J* 2020;**41**:1961–1971.
37. Kuno T, Takagi H, Ando T, Kodaira M, Numasawa Y, Fox J, Bangalore S, Kuno T. Safety and efficacy of mechanical circulatory support with Impella or intra-aortic balloon pump for high-risk percutaneous coronary intervention and/or cardiogenic shock: Insights from a network meta-analysis of randomized trials. *Catheter Cardiovasc Interv* 2020;doi: 10.1002/ccd.29236.
38. Siannaccone M, Albani S, Giannini F, Colangelo S, Boccuzzi GG, Garbo R, Brilakis ES, D'ascenzo F, de Ferrari GM, Colombo A, Iannaccone M. Short term outcomes of Impella in cardiogenic shock: a review and meta-analysis of observational studies. *Int J Cardiol* 2020;doi: 10.1016/j.ijcard.2020.09.044.
39. Lemor A, Hosseini Dehkordi SH, Basir MB, Villablanca PA, Jain T, Koenig GC, Alaswad K, Moses JW, Kapur NK, O'Neill W, Lemor A. Impella versus extracorporeal membrane oxygenation for acute myocardial infarction cardiogenic shock. *Cardiovasc Revasc Med* 2020;**21**:1465–1471.
40. Schrage B, Becher PM, Bernhardt A, Bezerra H, Blankenberg S, Brunner S, Colson P, Cudemus Deseda G, Dabboura S, Eckner D, Eden M, Eitel I, Frank D, Frey N, Funamoto M, Goßling A, Graf T, Hagl C, Kirchhof P, Kupka D, Landmesser U, Lipinski J, Lopes M, Majunke N, Maniuc O, McGrath D, Möbius-Winkler S, Morrow DA, Mourad M, Noel C, Nordbeck P, Orban M, Pappalardo F, Patel SM, Pauschinger M, Pazzanese V, Reichenspurner H, Sandri M, Schulze PC, Schwinger RHG, Sinning JM, Aksoy A, Skurk C, Szczanowicz L, Thiele H, Tietz F, Varshney A, Wechsler L, Westermann D, Schrage B. Left ventricular unloading is associated with lower mortality in cardiogenic shock patients treated with veno-arterial extracorporeal membrane oxygenation: results from an international, multicenter cohort study. *Circulation* 2020;**142**:2095–2106.
41. Thuijs DJFM, Kappetein AP, Serruys PW, Mohr F-W, Morice M-C, Mack MJ, Holmes DR, Curzen N, Davierwala P, Noack T, Milojevic M, Dawkins KD, da Costa BR, Jüni P, Head SJ, Casselman F, de Bruyne B, Høj Christiansen E, Ruiz-Nodar JM, Vermeersch P, Schultz W, Sabaté M, Guagliumi G, Grubitzsch H, Stangl K, Darremont O, Bentala M, den Heijer P, Preda I, Stoler R, Mack MJ, Szerafin T, Buckner JK, Guber MS, Verberkmoes N, Akca F, Feldman T, Beyersdorf F, Drieghe B, Oldroyd K, Berg G, Jeppsson A, Barber K, Wolschleger K, Heiser J, van der Harst P, Mariani MA, Reichenspurner H, Stark C, Laine M, Ho PC, Chen JC, Zelman R, Horwitz PA, Bochenek A, Krauze A, Grothusen C, Dudek D, Heyrich G, Davierwala P, Noack T, Kolh P, LeGrand V, Coelho P, Ensminger S, Nasseri B, Ingemansson R, Olivecrona G, Escaned J, Guera R, Berti S, Morice M-C, Chieffo A, Burke N, Mooney M, Spolaor A, Hagl C, Näbauer M, Suttorp MJ, Stine RA, McGarry T, Lucas S, Endresen K, Taussig A, Accola K, Canosi U, Horvath I, Cannon L, Talbott JD, Akins CW, Kramer R, Aschermann M, Killinger W, Narbute I, Holmes DR, Burzotta F, Bogers A, Zijlstra F, Eltchaninoff H, Berland J, Stefanini G, Cruz Gonzalez I, Hoppe U, Kiesz S, Gora B, Ahlsson A, Corbascio M, Bilfinger T, Carrie D, Tchétché D, Hauptman K-E, Stahle E, James S, Sandner S, Laufer G, Lang I, Witkowski A, Thourani V, Suryapranata H, Redwood S, Knight C, MacCarthy P, Curzen N, de Belder A, Banning A, Gershlick A. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. *Lancet* 2019;**394**:1325–1334.
42. Park D-W, Ahn J-M, Park H, Yun S-C, Kang D-Y, Lee PH, Kim Y-H, Lim D-S, Rha S-W, Park G-M, Gwon H-C, Kim H-S, Chae I-H, Jang Y, Jeong M-H, Tahk S-J, Seung KB, Park S-J; On behalf of the PRECOMBAT Investigators. Ten-year outcomes after drug-eluting stents versus coronary artery bypass grafting for left main coronary disease: extended follow-up of the PRECOMBAT trial. *Circulation* 2020;**141**:1437–1446.
43. Stone GW, Kappetein AP, Sabik JF, Pocock SJ, Morice M-C, Puskas J, Kandzari DE, Karmpaliotis D, Brown WM, Lembo NJ, Banning A, Merkely B, Horkay F, Boonstra PW, van Boven AJ, Ungi I, Bogáts G, Mansour S, Noiseux N, Sabaté M, Pomar J, Hickey M, Gershlick A, Buszman PE, Bochenek A, Schampaert E, Pagé P, Modolo R, Gregson J, Simonton CA, Mehran R, Kosmidou I, Généreux P, Crowley A, Dressler O, Serruys PW; EXCEL Trial Investigators. Five-year outcomes after PCI or CABG

for left main coronary disease. *N Engl J Med* 2019;**381**:1820–1830.
44. Holm NR, Mäkikallio T, Lindsay MM, Spence MS, Erglis A, Menown IBA, Trovik T, Kellerth T, Kalinauskas G, Mogensen LJH, Nielsen PH, Niemelä M, Lassen JF, Oldroyd K, Berg G, Stradins P, Walsh SJ, Graham ANJ, Endresen PC, Fröbert O, Trivedi U, Anttila V, Hildick-Smith D, Thuesen L, Christiansen EH, Holm NR, Mäkikallio T, Lindsay M, Spence MS, Erglis A, Menown IBA, Trovik T, Eskola M, Romppanen H, Kellerth T, Jensen LO, Kalinauskas G, Linder RBA, Pentikainen M, Hervold A, Banning A, Zaman A, Cotton J, Eriksen E, Margus S, Mogensen LJH, Nielsen PH, Niemelä M, Kervinen K, Lassen JF, Oldroyd K, Berg G, Walsh SJ, Hanratty CG, Kumsars I, Stradins P, Steigen TK, Fröbert O, Graham AN, Endresen PC, Corbascio M, Kajander O, Trivedi U, Hartikainen J, Anttila V, Hildick-Smith D, Thuesen L, Christiansen EH. Percutaneous coronary angioplasty versus coronary artery bypass grafting in the treatment of unprotected left main stenosis: updated 5-year outcomes from the randomised, non-inferiority NOBLE trial. *Lancet* 2020;**395**:191–199.
45. D'Ascenzo F, De Filippo O, Elia E, Doronzo MP, Omedè P, Montefusco A, Pennone M, Salizzoni S, Conrotto F, Gallone G, Angelini F, Franchin L, Bruno F, Boffini M, Gaudino M, Rinaldi M, De Ferrari GM. Percutaneous vs. surgical revascularization for patients with unprotected left main stenosis: a meta-analysis of 5-year follow-up randomized controlled trials. *Eur Heart J Qual Care Clin Outcomes* 2020;doi: 10.1093/ehjqcco/qcaa041.
46. Gallo M, Blitzer D, Laforgia PL, Doulamis IP, Perrin N, Bortolussi G, Guariento A, Putzu A. Percutaneous coronary intervention versus coronary artery bypass graft for left main coronary artery disease: a meta-analysis. *J Thorac Cardiovasc Surg* 2020;doi: 10.1016/j.jtcvs.2020.04.010.
47. Ahmad Y, Howard JP, Arnold AD, Cook CM, Prasad M, Ali ZA, Parikh MA, Kosmidou I, Francis DP, Moses JW, Leon MB, Kirtane AJ, Stone GW, Karmpaliotis D. Mortality after drug-eluting stents vs. coronary artery bypass grafting for left main coronary artery disease: a meta-analysis of randomized controlled trials. *Eur Heart J* 2020;**41**:3228–3235.
48. Gregson J, Stone GW, Ben-Yehuda O, Redfors B, Kandzari DE, Morice MC, Leon MB, Kosmidou I, Lembo NJ, Brown WM3rd, Karmpaliotis D, Banning AP, Pomar J, Sabaté M, Simonton CA, Dressler O, Kappetein AP, Sabik JF3rd, Serruys PW, Pocock SJ. Implications of alternative definitions of peri-procedural myocardial infarction after coronary revascularization. *J Am Coll Cardiol* 2020;**76**:1609–1621.
49. Giustino G, Serruys PW, Sabik JF, Mehran R, Maehara A, Puskas JD, Simonton CA, Lembo NJ, Kandzari DE, Morice M-C, Taggart DP, Gershlick AH, Ragosta M, Kron IL, Liu Y, Zhang Z, McAndrew T, Dressler O, Généreux P, Ben-Yehuda O, Pocock SJ, Kappetein AP, Stone GW. Mortality after repeat revascularization following PCI or CABG for left main disease: the EXCEL trial. *JACC Cardiovasc Interv* 2020;**13**:375–387.
50. Thuijs DJFM, Milojevic M, Stone GW, Puskas JD, Serruys PW, Sabik JF, Dressler O, Crowley A, Head SJ, Kappetein AP. Impact of left ventricular ejection fraction on clinical outcomes after left main coronary artery revascularization: results from the randomized EXCEL trial. *Eur J Heart Fail* 2020;**22**:871–879.
51. Wiebe J, Kuna C, Ibrahim T, Lösl M, Cassese S, Kufner S, Schunkert H, Byrne RA, Laugwitz K-L, Valgimigli M, Richardt G, Mehilli J, Kastrati A. Long-term prognostic impact of restenosis of the unprotected left main coronary artery requiring repeat revascularization. *JACC Cardiovasc Interv* 2020;**13**:2266–2274.
52. Park S, Ahn J-M, Kim TO, Park H, Kang D-Y, Lee PH, Jeong YJ, Hyun J, Lee J, Kim JH, Yang Y, Choe K, Park S-J, Park D-W. Revascularization in patients with left main coronary artery disease and left ventricular dysfunction. *J Am Coll Cardiol* 2020;**76**:1395–1406.
53. Tam DY, Dharma C, Rocha R, Farkouh ME, Abdel-Qadir H, Sun LY, Wijeysundera HC, Austin PC, Udell JA, Gaudino M, Fremes SE, Lee DS. Long-term survival after surgical or percutaneous revascularization in patients with diabetes and multivessel coronary disease. *J Am Coll Cardiol* 2020;**76**:1153–1164.
54. Zhang JJ, Ye F, Xu K, Kan J, Tao L, Santoso T, Munawar M, Tresukosol D, Li L, Sheiban I, Li F, Tian NL, Rodríguez AE, Paiboon C, Lavarra F, Lu S, Vichairuangthum K, Zeng H, Chen L, Zhang R, Ding S, Gao F, Jin Z, Hong L, Ma L, Wen S, Wu X, Yang S, Yin WH, Zhang J, Wang Y, Zheng Y, Zhou L, Zhou L, Zhu Y, Xu T, Wang X, Qu H, Tian Y, Lin S, Liu L, Lu Q, Li Q, Li B, Jiang Q, Han L, Gan G, Yu M, Pan D, Shang Z, Zhao Y, Liu Z, Yuan Y, Chen C, Stone GW, Han Y, Chen SL. Multicentre, randomized comparison of two-stent and provisional stenting techniques in patients with complex coronary bifurcation lesions: the DEFINITION II trial. *Eur Heart J* 2020;**41**:2523–2536.
55. Gioia G, Di Sonck J, Ferenc M, Chen S-L, Colaiori I, Gallinoro E, Mizukami T, Kodeboina M, Nagumo S, Franco D, Bartunek J, Vanderheyden M, Wyffels E, Bruyne B, De Lassen JF, Bennett J, Vassilev D, Serruys PW, Stankovic G, Louvard Y, Barbato E, Collet C. Clinical outcomes following coronary bifurcation PCI techniques: a systematic review and network meta-analysis comprising 5,711 patients. *JACC Cardiovasc Interv* 2020;**13**:1432–1444.
56. Gaido L, D'Ascenzo F, Imori Y, Wojakowski W, Saglietto A, Figini F, Mattesini A, Trabattoni D, Rognoni A, Tomassini F, Bernardi A, Ryan N, Muscoli S, Helft G, Filippo O, De Parma R, Luca L, De Ugo F, Cerrato E, Montefusco A, Pennacchi M, Wańha W, Smolka G, Lio G, de Bruno F, Huczek Z, Boccuzzi G, Cortese B, Capodanno D, Omedè P. Impact of kissing balloon in patients treated with ultrathin stents for left main lesions and bifurcations: an analysis from the RAIN-CARDIOGROUP VII study. *Circ Cardiovasc Interv* 2020;**13**:e008325.
57. Kini AS, Dangas GD, Baber U, Vengrenyuk Y, Kandzari DE, Leon MB, Morice M-C, Serruys PW, Kappetein AP, Sabik JF3rd, Dressler O, Mehran R, Sharma SK, Stone GW. Influence of final kissing balloon inflation on long-term outcomes after PCI of distal left main bifurcation lesions in the EXCEL trial. *EuroIntervention* 2020;**16**:218–224.
58. Silverio A, Buccheri S, Venetsanos D, Alfredsson J, Lagerqvist B, Persson J, Witt N, James S, Sarno G. Percutaneous treatment and outcomes of small coronary vessels: a SCAAR report. *JACC Cardiovasc Interv* 2020;**13**:793–804.
59. Dan K, Garcia-Garcia HM, Kolm P, Windecker S, Saito S, Kandzari DE, Waksman R. Comparison of ultrathin, bioresorbable-polymer sirolimus-eluting stents and thin, durable-polymer everolimus-eluting stents in calcified or small vessel lesions. *Circ Cardiovasc Interv* 2020;**13**:e009189.
60. Giacoppo D, Alfonso F, Xu B, Claessen BEPM, Adriaenssens T, Jensen C, Pérez-Vizcayno MJ, Kang D-Y, Degenhardt R, Pleva L, Baan J, Cuesta J, Park D-W, Schunkert H, Colleran R, Kukla P, Jiménez-Quevedo P, Unverdorben M, Gao R, Naber CK, Park S-J, Henriques JPS, Kastrati A, Byrne RA. Paclitaxel-coated balloon angioplasty vs. drug-eluting stenting for the treatment of coronary in-stent restenosis: a comprehensive, collaborative, individual patient data meta-analysis of 10 randomized clinical trials (DAEDALUS study). *Eur Heart J* 2020;**41**:3715–3728.
61. Giacoppo D, Alfonso F, Xu B, Claessen BEPM, Adriaenssens T, Jensen C, Pérez-Vizcayno MJ, Kang D-Y, Degenhardt R, Pleva L, Baan J, Cuesta J, Park D-W, Kukla P, Jiménez-Quevedo P, Unverdorben M, Gao R, Naber CK, Park S-J, Henriques JPS, Kastrati A, Byrne RA. Drug-coated balloon angioplasty versus drug-eluting stent implantation in patients with coronary stent restenosis. *J Am Coll Cardiol* 2020;**75**:2664–2678.
62. Schumacher SP, Kockx M, Stuijfzand WJ, Driessen RS, Diemen PA, van Bom MJ, Everaars H, Raijmakers PG, Boellaard R, Rossum AC, van Opolski MP, Nap A, Knaapen P. Ischaemic burden and changes in absolute myocardial perfusion after chronic total occlusion percutaneous coronary intervention. *EuroIntervention* 2020;**16**:e462–e471.
63. Xenogiannis I, Gkargkoulas F, Karmpaliotis D, Krestyaninov O, Khelimskii D, Jaffer FA, Khatri JJ, Kandzari DE, Wyman RM, Doing AH, Dattilo P, Toma C, Yeh RW, Tamez H, Choi JW, Jaber W, Samady H, Sheikh AM, Potluri S, Patel M, Mahmud E, Elbaruni B, Love MP, Koutouzis M, Tsiafoutis I, Jefferson BK, Patel T, Uretsky B, Moses JW, Lembo NJ, Parikh M, Kirtane AJ, Ali ZA, Hall AB, Megaly MS, Vemmou E, Nikolakopoulos I, Rangan BV, Morley PW, Bou Dargham B, Abdullah S, Garcia S, Banerjee S, Burke MN, Brilakis ES, Alaswad K. Retrograde chronic total occlusion percutaneous coronary intervention via saphenous vein graft. *JACC Cardiovasc Interv* 2020;**13**:517–526.

64. Kalogeropoulos AS, Alsanjari O, Keeble TR, Tang KH, Konstantinou K, Katsikis A, Jagathesan R, Aggarwal RK, Clesham GJ, Kelly PA, Werner GS, Hildick-Smith D, Davies JR, Karamasis G. CASTLE score versus J-CTO score for the prediction of technical success in chronic total occlusion percutaneous revascularisation. *EuroIntervention* 2020;**15**:e1615–e1623.
65. Nagamatsu W, Tsuchikane E, Oikawa Y, Sumitsuji S, Igarashi Y, Yoshikawa R, Muto M, Okada H, Katoh O. Successful guidewire crossing via collateral channel at retrograde percutaneous coronary intervention for chronic total occlusion: the J-Channel score. *EuroIntervention* 2020;**15**:e1624–e1632.
66. Shoaib A, Rashid M, Kontopantelis E, Sharp A, Fahy EF, Nolan J, Townend J, Ludman P, Ratib K, Azam ZA, Ahmad A, McEntegart M, Mohamed M, Kinnaird T, Mamas MA. Clinical characteristics and outcomes from percutaneous coronary intervention of last remaining coronary artery: an analysis from the British Cardiovascular Intervention Society Database. *Circ Cardiovasc Interv* 2020;**13**:e009049.
67. Kufner S, Ernst M, Cassese S, Joner M, Mayer K, Colleran R, Koppara T, Xhepa E, Koch T, Wiebe J, Ibrahim T, Fusaro M, Laugwitz KL, Schunkert H, Kastrati A, Byrne RA; ISAR-TEST-5 Investigators. 10-year outcomes from a randomized trial of polymer-free versus durable polymer drug-eluting coronary stents. *J Am Coll Cardiol* 2020;**76**:146–158.
68. Jensen LO, Maeng M, Raungaard B, Kahlert J, Ellert J, Jakobsen L, Villadsen AB, Veien KT, Kristensen SD, Ahlehoff O, Carstensen S, Christensen MK, Terkelsen CJ, Engstroem T, Hansen KN, Bøtker HE, Aaroe J, Thim T, Thuesen L, Freeman P, Aziz A, Eftekhari A, Junker A, Jensen SE, Lassen JF, Hansen HS, Christiansen EH, Thygesen K, Sørensen JT, Andersen HR; Sort Out IX Study Group. Randomized comparison of the polymer-free biolimus-coated biofreedom stent with the ultrathin strut biodegradable polymer sirolimus-eluting orsiro stent in an all-comers population treated with percutaneous coronary intervention: the SORT OUT IX trial. *Circulation* 2020;**141**:2052–2063.
69. Kim HS, Kang J, Hwang D, Han JK, Yang HM, Kang HJ, Koo BK, Kim SY, Park KH, Rha SW, Shin WY, Lim HS, Park K, Park KW; HOST-REDUCE-POLYTECH-ACS Randomized Clinical Trial Investigators. Durable polymer versus biodegradable polymer drug-eluting stents after percutaneous coronary intervention in patients with acute coronary syndrome: the HOST-REDUCE-POLYTECH-ACS trial. *Circulation* 2020;doi: 10.1161/CIRCULATIONAHA.120.051700.
70. DES with synchronized antiproliferative drug delivery to target smooth muscle cell proliferation after DES implantation in coronary artery disease. Primary results of the PIONEER III Trial. American Heart Association Scientific Sessions 2020. 15 November 2020.
71. Rocha-Singh KJ, Duval S, Jaff MR, Schneider PA, Ansel GM, Lyden SP, Mullin CM, Ioannidis JPA, Misra S, Tzafriri AR, Edelman ER, Granada JF, White CJ, Beckman JA; On behalf of VIVA Physicians, Inc. Mortality and paclitaxel-coated devices: an individual patient data meta-analysis. *Circulation* 2020;**141**:1859–1869.
72. Scheller B, Vukadinovic D, Jeger R, Rissanen TT, Scholz SS, Byrne R, Kleber FX, Latib A, Clever YP, Ewen S, Böhm M, Yang Y, Lansky A, Mahfoud F. Survival after coronary revascularization with paclitaxel-coated balloons. *J Am Coll Cardiol* 2020;**75**:1017–1028.
73. Elgendy IY, Gad MM, Elgendy AY, Mahmoud A, Mahmoud AN, Cuesta J, Rivero F, Alfonso F. Clinical and angiographic outcomes with drug-coated balloons for de novo coronary lesions: a meta-analysis of randomized clinical trials. *J Am Heart Assoc* 2020;**9**:e016224.
74. Cortese B, Di Palma G, Guimaraes MG, Piraino D, Orrego PS, Buccheri D, Rivero F, Perotto A, Zambelli G, Alfonso F. Drug-coated balloon versus drug-eluting stent for small coronary vessel disease: PICCOLETO II randomized clinical trial. *JACC Cardiovasc Interv* 2020;**13**:2840–2849.
75. Kandzari DE, Koolen JJ, Doros G, Garcia-Garcia HM, Bennett J, Roguin A, Gharib EG, Cutlip DE, Waksman R; BIOFLOW V Investigators. Ultrathin bioresorbable-polymer sirolimus-eluting stents versus thin durable-polymer everolimus-eluting stents for coronary revascularization: 3-year outcomes from the randomized BIOFLOW V trial. *JACC Cardiovasc Interv* 2020;**13**:1343–1353.
76. Takahashi K, Serruys PW, Kogame N, Buszman P, Lurz P, Jessurun GAJ, Koch KT, Troquay RPT, Hamer BJB, Ophuis Milewski OT, Hofma KP, Wykrzykowska SH, Onuma JJ, de Winter RJ, Wijns W. Final 3-year outcomes of MiStent Biodegradable Polymer Crystalline Sirolimus-Eluting Stent Versus Xience Permanent Polymer Everolimus-Eluting Stent: insights from the DESSOLVE III All-Comers Randomized Trial. *Circ Cardiovasc Interv* 2020;**13**:e008737.
77. Hill JM, Kereiakes DJ, Shlofmitz RA, Klein AJ, Riley RF, Price MJ, Herrmann HC, Bachinsky W, Waksman R, Stone GW. Intravascular lithotripsy for treatment of severely calcified coronary artery disease: the Disrupt CAD III study. *J Am Coll Cardiol* 2020;**76**:2635–2646.
78. Tonino PAL, Pijls NHJ, Collet C, Nammas W, Van der Heyden J, Romppanen H, Kervinen K, Airaksinen JKE, Sia J, Lalmand J, Frambach P, Penaranda AS, De Bruyne B, Karjalainen PP; TIDES-ACS Study Group. Titanium-nitride-oxide-coated versus everolimus-eluting stents in acute coronary syndrome: the Randomized TIDES-ACS trial. *JACC Cardiovasc Interv* 2020;**13**:1697–1705.
79. Sabaté M, Alfonso F, Cequier A, Romaní S, Bordes P, Serra A, Iñiguez A, Salinas P, García Del Blanco B, Goicolea J, Hernández-Antolín R, Cuesta J, Gómez-Hospital JA, Ortega-Paz L, Gomez-Lara J, Brugaletta S. Magnesium-based resorbable scaffold versus permanent metallic sirolimus-eluting stent in patients with ST-segment elevation myocardial infarction: the MAGSTEMI Randomized Clinical Trial. *Circulation* 2019;**140**:1904–1916.
80. Gomez-Lara J, Ortega-Paz L, Brugaletta S, Cuesta J, Romaní S, Serra A, Salinas P, García Del Blanco B, Goicolea J, Hernandez-Antolín R, Antuña P, Romaguera R, Regueiro A, Rivero F, Cequier À, Alfonso F, Gómez-Hospital JA, Sabaté M, Collaborators. Bioresorbable scaffolds versus permanent sirolimus-eluting stents in patients with ST-Segment Elevation Myocardial Infarction: vascular healing outcomes from the MAGSTEMI trial. *EuroIntervention* 2020;**16**:e913–e921.
81. Ueki Y, Räber L, Otsuka T, Rai H, Losdat S, Windecker S, Garcia-Garcia HM, Landmesser U, Koolen J, Byrne R, Haude M, Joner M. Mechanism of drug-eluting absorbable metal scaffold restenosis: a serial optical coherence tomography study. *Circ Cardiovasc Interv* 2020;**13**:e008657.
82. Hong S-J, Mintz GS, Ahn C-M, Kim J-S, Kim B-K, Ko Y-G, Kang T-S, Kang W-C, Kim YH, Hur S-H, Hong B-K, Choi D, Kwon H, Jang Y, Hong M-K. Effect of intravascular ultrasound-guided drug-eluting stent implantation: 5-year follow-up of the IVUS-XPL Randomized trial. *JACC Cardiovasc Interv* 2020;**13**:62–71.
83. Gao X-F, Ge Z, Kong X-Q, Kan J, Han L, Lu S, Tian N-L, Lin S, Lu Q-H, Wang X-Y, Li Q-H, Liu Z-Z, Chen Y, Qian X-S, Wang J, Chai D-Y, Chen C-H, Pan T, Ye F, Zhang J-J, Chen S-L; ULTIMATE Investigators. Three-year outcomes of the ULTIMATE trial comparing intravascular ultrasound versus angiography-guided drug-eluting stent implantation. *J Am Coll Cardiol Cardiovasc Interv* 2020;doi: 10.1016/j.jcin.2020.10.001.
84. Hong SJ, Kim D, Kim BK, Ahn CM, Kim JS, Ko YG, Choi D, Hong MK, Jang Y. Acute and one-year clinical outcomes of pre-stenting intravascular ultrasound: a patient-level meta-analysis of randomised clinical trials. *EuroIntervention* 2020;doi: 10.4244/EIJ-D-20-00276.
85. Burzotta F, Leone AM, Aurigemma C, Zambrano A, Zimbardo G, Arioti M, Vergallo R, Maria GL, De Cerracchio E, Romagnoli E, Trani C, Crea F. Fractional flow reserve or optical coherence tomography to guide management of angiographically intermediate coronary stenosis: a single-center trial. *JACC Cardiovasc Interv* 2020;**13**:49–58.
86. Prati F, Romagnoli E, Gatto L, Manna A, La Burzotta F, Ozaki Y, Marco V, Boi A, Fineschi M, Fabbiocchi F, Taglieri N, Niccoli G, Trani C, Versaci F, Calligaris G, Ruscica G, Giorgio A, Di Vergallo R, Albertucci M, Biondi-Zoccai G, Tamburino C, Crea F, Alfonso F, Arbustini E. Relationship between coronary plaque morphology of the left anterior descending artery and 12 months clinical outcome: the CLIMA study. *Eur Heart J* 2020;**41**:383–391.
87. Kedhi E. Combined optical coherence tomography and fractional flow reserve assessment to better predict adverse event outcomes in DM patients. Presented at: TCT 2020. 14 October 2020.

88. Pinilla-Echeverri N, Mehta SR, Wang J, Lavi S, Schampaert E, Cantor WJ, Bainey KR, Welsh RC, Kassam S, Mehran R, Storey RF, Nguyen H, Meeks B, Wood DA, Cairns JA, Sheth T. Nonculprit lesion plaque morphology in patients with ST-segment-elevation myocardial infarction: results from the COMPLETE Trial Optical Coherence Tomography Substudys. *Circ Cardiovasc Interv* 2020;**13**:e008768.
89. Stone GW, Maehara A, Ali ZA, Held C, Matsumura M, Kjøller-Hansen L, Bøtker HE, Maeng M, Engstrøm T, Wiseth R, Persson J, Trovik T, Jensen U, James SK, Mintz GS, Dressler O, Crowley A, Ben-Yehuda O, Erlinge D; PROSPECT ABSORB Investigators. Percutaneous coronary intervention for vulnerable coronary atherosclerotic plaque. *J Am Coll Cardiol* 2020;**76**:2289–2301.
90. Kuramitsu S, Matsuo H, Shinozaki T, Horie K, Takashima H, Terai H, Kikuta Y, Ishihara T, Saigusa T, Sakamoto T, Suematsu N, Shiono Y, Mizuno A, Tsujita K, Masamura K, Yokoi H, Tanaka N. Two-year outcomes after deferral of revascularization based on fractional flow reserve: the J-CONFIRM Registry. *Circ Cardiovasc Interv* 2020;**13**:e009049.
91. Parikh RV, Liu G, Plomondon ME, Sehested TSG, Hlatky MA, Waldo SW, Fearon WF. Utilization and outcomes of measuring fractional flow reserve in patients with stable ischemic heart disease. *J Am Coll Cardiol* 2020;**75**:409–419.
92. Warisawa T, Cook CM, Rajkumar C, Howard JP, Seligman H, Ahmad Y, El Hajj S, Doi S, Nakajima A, Nakayama M, Goto S, Vera-Urquiza R, Sato T, Kikuta Y, Kawase Y, Nishina H, Petraco R, Al-Lamee R, Nijjer S, Sen S, Nakamura S, Lerman A, Matsuo H, Francis DP, Akashi YJ, Escaned J, Davies JE. Safety of revascularization deferral of left main stenosis based on instantaneous wave-free ratio evaluation. *JACC Cardiovasc Interv* 2020;**13**:1655–1664.
93. Jeremias A, Davies JE, Maehara A, Matsumura M, Schneider J, Tang K, Talwar S, Marques K, Shammas NW, Gruberg L, Seto A, Samady H, Sharp A, Ali ZA, Mintz G, Patel M, Stone GW. Blinded physiological assessment of residual ischemia after successful angiographic percutaneous coronary intervention: the DEFINE PCI study. *JACC Cardiovasc Interv* 2019;**12**:1991–2001.
94. Patel M, Jeremias A, Davies J. One-year outcomes of patients with residual physiologic ischemia after percutaneous coronary intervention: the DEFINE PCI trial. Cardiovascular Therapeutics annual scientific symposium 2020. 15 October 2020.
95. Baber U, Dangas G, Angiolillo DJ, Cohen DJ, Sharma SK, Nicolas J, Briguori C, Cha JY, Collier T, Dudek D, Džavik V, Escaned J, Gil R, Gurbel P, Hamm CW, Henry T, Huber K, Kastrati A, Kaul U, Kornowski R, Krucoff M, Kunadian V, Marx SO, Mehta S, Moliterno D, Ohman EM, Oldroyd K, Sardella G, Sartori S, Shlofmitz R, Steg PG, Weisz G, Witzenbichler B, Han YL, Pocock S, Gibson CM, Mehran R. Ticagrelor alone vs. ticagrelor plus aspirin following percutaneous coronary intervention in patients with non-ST-segment elevation acute coronary syndromes: TWILIGHT-ACS. *Eur Heart J* 2020;**41**:3533–3545.
96. Kim BK, Hong SJ, Cho YH, Yun KH, Kim YH, Suh Y, Cho JY, Her AY, Cho S, Jeon DW, Yoo SY, Cho DK, Hong BK, Kwon H, Ahn CM, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Hong MK, Jang Y; TICO Investigators. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome: the TICO Randomized Clinical Trial. *JAMA* 2020;**323**:2407–2416.
97. Windecker S, Latib A, Kedhi E, Kirtane AJ, Kandzari DE, Mehran R, Price MJ, Abizaid A, Simon DI, Worthley SG, Zaman A, Hudec M, Poliacikova P, Abdul Ghapar AKB, Selvaraj K, Petrov I, Mylotte D, Pinar E, Moreno R, Fabbiocchi F, Pasupati S, Kim HS, Aminian A, Tie C, Wlodarczak A, Hur SH, Marx SO, Jankovic I, Brar S, Bousquette L, Liu M, Stone GW; ONYX ONE Investigators. Polymer-based or polymer-free stents in patients at high bleeding risk. *N Engl J Med* 2020;**382**:1208–1218.
98. Mehran R. The XIENCE Short DAPT Program: XIENCE 90/28 evaluating the safety of 3- and 1-month DAPT in HBR patients. Transcatheter Cardiovascular Therapeutics annual scientific symposium 2020. 15 October 2020.
99. Navarese EP, Khan SU, Kołodziejczak M, Kubica J, Buccheri S, Cannon CP, Gurbel PA, De Servi S, Budaj A, Bartorelli A, Trabattoni D, Ohman EM, Wallentin L, Roe MT, James S. Comparative efficacy and safety of oral P2Y12 inhibitors in acute coronary syndrome: network meta-analysis of 52 816 patients from 12 randomized trials. *Circulation* 2020;**142**:150–160.
100. Kim HS, Kang J, Hwang D, Han JK, Yang HM, Kang HJ, Koo BK, Rhew JY, Chun KJ, Lim YH, Bong JM, Bae JW, Lee BK, Park KW; HOST-REDUCE-POLYTECH-ACS investigators. Prasugrel-based de-escalation of dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (HOST-REDUCE-POLYTECH-ACS): an open-label, multicentre, non-inferiority randomised trial. *Lancet* 2020;**396**:1079–1089.
101. Tarantini G, Mojoli M, Varbella F, Caporale R, Rigattieri S, Andò G, Cirillo P, Pierini S, Santarelli A, Sganzerla P, Cacciavillani L, Babuin L, De Cesare N, Limbruno U, Massoni A, Rognoni A, Pavan D, Belloni F, Cernetti C, Favero L, Saia F, Fovino LN, Masiero G, Roncon L, Gasparetto V, Ferlini M, Ronco F, Rossini R, Canova P, Trabattoni D, Russo A, Guiducci V, Penzo C, Tarantino F, Mauro C, Corrada E, Esposito G, Berti S, Martinato M, Azzolina D, Gregori D, Angiolillo DJ, Musumeci G; DUBIUS Investigators, on behalf of the Italian Society of Interventional Cardiology (SICI-GISE). Timing of oral P2Y12 inhibitor administration in non-ST elevation acute coronary syndrome. *J Am Coll Cardiol* 2020;**76**:2450–2459.
102. Vlachojannis GJ,, Wilschut JM,, Vogel RF,, Lemmert ME,, Delewi R,, Diletti Nancy R,, van der Waarden WPL,, Nuis R-J, Paradies V, Alexopoulos D, Zijlstra F, Montalescot G, Angiolillo DJ, Krucoff MW, Van Mieghem NM, Smits PC. COMPARE CRUSH: a randomized trial of prehospital crushed vs uncrushed prasugrel in STEMI. *Circulation* 2020;**142**:2316–2328.
103. Gimbel M, Qaderdan K, Willemsen L, Hermanides R, Bergmeijer T, de Vrey E, Heestermans T, Tjon Joe Gin M, Waalewijn R, Hofma S, den Hartog F, Jukema W, von Birgelen C, Voskuil M, Kelder J, Deneer V, Ten Berg J. Clopidogrel versus ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome (POPular AGE): the randomised, open-label, non-inferiority trial. *Lancet* 2020;**395**:1374–1381.
104. Szummer K, Montez-Rath ME, Alfredsson J, Erlinge D, Lindahl B, Hofmann R, Ravn-Fischer A, Svensson P, Jernberg T. Comparison between ticagrelor and clopidogrel in elderly patients with an acute coronary syndrome: insights from the SWEDEHEART Registry. *Circulation* 2020;**142**:1700–1708.
105. Hong MK. One-month dual antiplatelet therapy followed by aspirin monotherapy after drug-eluting stent implantation: randomized One-Month DAPT trial. American Heart Association Scientific Sessions 2020. 15 November 2020.
106. Bainey KR, Welsh RC, Connolly SJ, Marsden T, Bosch J, Fox KAA, Steg PG, Vinereanu D, Connolly DL, Berkowitz SD, Foody JM, Probstfield JL, Branch KR, Lewis BS, Diaz R, Muehlhofer E, Widimsky P, Yusuf S, Eikelboom JW, Bhatt DL; On behalf of the COMPASS Investigators. Rivaroxaban plus aspirin versus aspirin alone in patients with prior percutaneous coronary intervention (COMPASS-PCI). *Circulation* 2020;**141**:1141–1151.
107. Silvain J, Lattuca B, Beygui F, Rangé G, Motovska Z, Dillinger J-G, Boueri Z, Brunel P, Lhermusier T, Pouillot C, Larrieu-Ardilouze E, Boccara F, Labeque J-N, Guedeney P, El Kasty M, Laredo M, Dumaine R, Ducrocq G, Collet J-P, Cayla G, Blanchart K, Kala P, Vicaut E, Montalescot G; ALPHEUS investigators. Ticagrelor versus clopidogrel in elective percutaneous coronary intervention (ALPHEUS): a randomised, open-label, phase 3b trial. *Lancet* 2020;**396**:1737–1744.
108. Barbato E, Noc M, Baumbach A, Dudek D, Bunc M, Skalidis E, Banning A, Legutko J, Witt N, Pan M, Tilsted HH, Nef H, Tarantini G, Kazakiewicz D, Huculeci R, Cook S, Magdy A, Desmet W, Cayla G, Vinereanu D, Voskuil M, Goktekin O, Vardas P, Timmis A, Haude M. Mapping interventional cardiology in Europe: the European Association of Percutaneous Cardiovascular Interventions (EAPCI) Atlas Project. *Eur Heart J* 2020;**41**:2579–2588.
109. Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE, Mossialos EA, Maggioni AP, Kazakiewicz D, May HT, De Smedt D, Flather M, Zuhlke L, Beltrame JF, Huculeci R, Tavazzi L, Hindricks G, Bax J, Casadei B, Achenbach S, Wright L, Vardas P; European Society of Cardiology. European Society of Cardiology: cardiovascular disease statistics 2019. *Eur Heart J* 2020;**41**:12–85.

ESC European Society of Cardiology

Special article

The year in cardiovascular medicine 2020: digital health and innovation

Charalambos Antoniades[1,2]*, Folkert W. Asselbergs[3,4], and Panos Vardas[5,6]

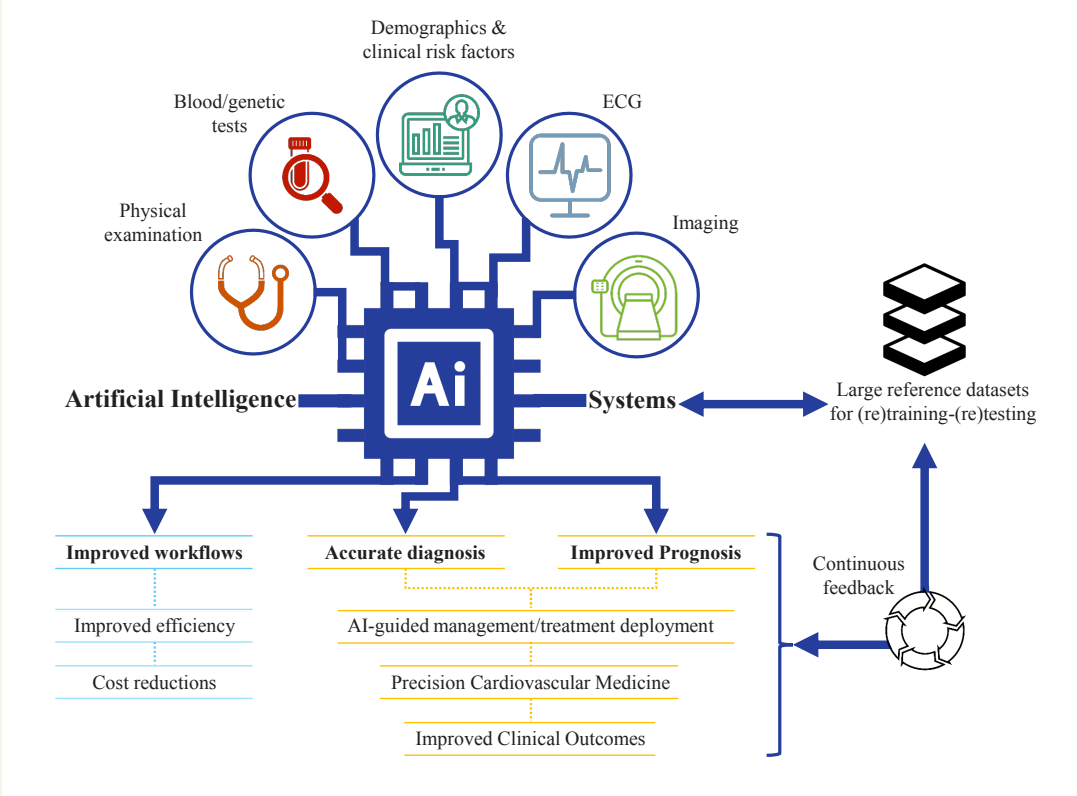
[1] Acute Vascular Imaging Centre, University of Oxford, John Radcliffe Hospital, Headley Way, Oxford OX39DU, UK; [2] Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, L6 West Wing, John Radcliffe Hospital, Headley Way, Oxford OX39DU, UK; [3] Department of Cardiology, Division Heart & Lungs, University Medical Center Utrecht, Utrecht University, Heidelberglaan 8, 3584 CX, Utrecht, the Netherlands; [4] Institute of Cardiovascular Science and Institute of Health Informatics, Faculty of Population Health Sciences, University College London, 222 Euston Road, NW1 2DA, London, UK; [5] Heart Sector, Hygeia Hospitals Groups, Erithrou Stavrou 4, Marousi 151 23, Athens, Greece; and [6] Cardiology Department, Medical School, University of Crete, University Campus of Voutes, 700 13, Heraclion, Greece

Received 6 October 2020; revised 26 November 2020; editorial decision 14 December 2020; accepted 18 December 2020

Reproduced from: Antoniades C, Asselbergs FW, Vardas P. The year in cardiovascular medicine 2020: digital health and innovation. Eur Heart J. 2021 Feb 14;42(7):732-739. https://doi.org/10.1093/eurheartj/ehaa1065, by permission of Oxford University Press on behalf of the European Society of Cardiology

* Corresponding author. Tel: +44 1865228340, Email: charalambos.antoniades@cardiov.ox.ac.uk

Graphical Abstract



Keywords
Artificial intelligence • Deep learning • Atherosclerosis • Cardiovascular diseases • Machine learning • Digital health • Big Data

Introduction

Advances in digital health and particularly in artificial intelligence (AI) have led us very close to the true implementation of personalized medicine. The year 2020 has brought an exponential increase of studies using various forms of AI, from supervised machine learning to unsupervised deep learning, with applications across all domains of cardiovascular medicine. AI is now moving from research to implementation, affecting all aspects of clinical cardiology. The studies bringing AI close to clinical practice span from fast clinical and biochemical data analysis and interpretation of results to image analysis, electrocardiogram (ECG) interpretation, arrhythmia detection, or even the use of face recognition to diagnose cardiovascular diseases. We review some of the most exciting development if the field of AI in cardiology, published from fall of 2019 up until now. The studies highlighted in this article give only a small glimpse into this booming field, creating more anticipation for what will come to clinical practice in the coming years.

Digital health and particularly artificial intelligence (AI) are getting fast ground during the last few years in cardiovascular diagnostics and therapeutics. Indeed, the number of publications using various AI techniques has been increased by >20-fold from 2010 to 2020. Since last year's European Society of Cardiology (ESC) congress, the role of AI in cardiovascular medicine had been highlighted as the next frontier in cardiovascular diagnostics, paving the way to the implementation of personalized strategies in cardiovascular therapeutics.[1] In a similar line, the last American Heart Association 2020 meeting also had a session entitled 'Hype or Hope? Artificial Intelligence and Machine Learning in Imaging', reminding us the importance paid by the major clinical cardiovascular medicine societies in this field. Indeed, issues like algorithm transparency and data open access transparency were key issues introduced. The concept of using digital innovation and particularly AI and Big Data to optimize treatments in clinical trials and eventually in clinical practice was brought up as a fundamental aspect of digital health of the future.

The introduction of AI in research but also in clinical practice is mainly driven by the technological advances in the handling and analysis of big data. AI is referred to the ability of a machine to execute tasks characteristic of human intelligence, such as problem solving or pattern recognition, and it is typically characterized by the element of positive or negative reinforcement as part of the

learning process, similar to what typically happens with human learning. Indeed, machine learning refers to the ability of computers to improve their knowledge without being explicitly programmed to do so; so the machines can identify patterns in digital data and make generalizations, learning from their observations.[2] Unsupervised deep learning is used to build convolutional neuronal networks (CNNs) that recognize features in digital data, not visible to the human eye. These data can be clinical information, images, ECGs or even standard 'selfies' taken using smartphone cameras.

AI as a tool for arrhythmias' prediction and management

Management of arrhythmias has always been a challenge, especially when we have to deal with subclinical conditions such as paroxysmal atrial fibrillation, which often have stroke as their first presentation. Indeed, including clinical risk factors into a machine-learning algorithm was recently found to identify patients at risk for atrial fibrillation in a primary care population of >600k individuals in the DISCOVER registry in the UK.[3] That algorithm could achieve negative predictive value of 96.7% and sensitivity to detect atrial fibrillation of 91.8%. In another landmark study published by the Mayo Clinic last year,[4] it seems now possible that, by using a CNN to screen standard 12 lead ECGs for characteristics not visible to the eye of the clinician, we can detect subclinical paroxysmal atrial fibrillation from sinus rhythm ECGs, achieving AUC as high as 0.9. This study was conducted in a population of >180k individuals with >450k ECGs included in the training set, >64k ECGs in the internal validation dataset, and >130k in the testing dataset. Algorithms like this could completely transform population screening for atrial fibrillation and will most likely enable timely administration of anticoagulant treatment to prevent cardioembolic stroke. The astonishing size of this dataset gives a clear example of how deep learning should be performed, to yield reproducible, practice-changing tools. Algorithms like this will soon be available on our portable ECGs in the clinic. One of the major problems of deep learning algorithms used for ECG interpretation is their susceptibility to adversarial examples, leading to consistently wrong classification of the test by detecting false patterns undetectable to the human eye. An elegant study by Han *et al.*[5] has provided recently the tools needed to study the impact of these adversarial patterns in automated ECG classification and provides new opportunities to develop appropriate mitigation measures.

The recent release of large, publically available ECG databases such as the PTB-XL (that includes ~21k records from ~19k patients)[6] or the one from the Shaoxing Hospital Zhejiang University School of Medicine (~10k patients)[7] brings further optimism that, by increasing the variability and ethnic diversity of the training and validation datasets, these ECG applications are not far from clinical implementation. Further to the use of AI to detect atrial fibrillation, a recent study built a deep neural network to classify various types of ECGs using >2.3 m ECGs from >1.6 m patients, demonstrating a remarkable ability of these networks to provide accurate interpretation of these tests.[8] Finally, in the Apple Heart Study,[9] the use of smartphones was demonstrated to be a very effective way to detect patients with subclinical paroxysmal atrial fibrillation. That was a large study that included ~420k participants followed up for a median of 117 days through their smartphones. The technology developed by apple identified 0.5% with potentially irregular pulse (34% of which were proven to have atrial fibrillation confirmed by ECG). Although the exact nature of the technology used in the smartphone is not available, this study demonstrates that large volumes of data can be collected even using standard smartphones or portable devices like apple watches, opening new opportunities for big data research and development of AI algorithms for timely detection of cardiac arrhythmias in asymptomatic individuals.

AI for the management of heart failure

Risk stratification plays a key role in designing the therapeutic strategies in heart failure, given that the expected survival inevitably affects the decision for device implantation.[10] Currently, decision of implanting a defibrillator and/or applying cardiac resynchronization therapy (CRT) in patients with heart failure relies on well-defined clinical, electrophysiological and imaging characteristics.[10,11] However, a recent study published in *European Heart Journal* (EHJ) earlier this year[12] came to remind us that the prediction of responsiveness to CRT focused on mid- or long-term outcomes should be a key driver in decision-making. Indeed, Tokodi *et al.*[12] used machine learning to help them build a risk score for the prediction of mortality following CRT. The score used information from medical history, physical examination, medication records, ECG, echocardiographic and laboratory data commonly obtained as part of routine hospital visits of patients with heart failure, and after it was trained in 1510 patients using a random forest algorithm, it has achieved a remarkable prognostic value for all-cause mortality, with AUC in ROC analysis ranging from 0.77 (in 1-year prediction) to 0.8 (in 5-year prediction). The risk calculator is now available for use (SEMMELWEIS-CRT Score, https://arguscognitive.com/crt, *Figure 1*).[12] As the authors mention, this score could facilitate the prompt recognition of high-risk patients, guiding deployment of the appropriate prophylactic measures.[13] It could also assist the patients and the families in making advance care decisions,[13] while it could assist clinicians in deciding which patients are most suitable for CRT.

The results of that study were in line with another recent study showing that the use of machine learning to integrate clinical data together with imaging characteristics can provide meaningful information about the future responsiveness of heart failure patients to CRT in a population of >1.1k patients from the MADIT-CRT study.[14]

CRT would have meaningful impact in patient's prognosis. Before we reach at that stage though, it seems important to understand how to manage the high-risk individuals identified through such algorithms, given that most of the factors included into these models are non-modifiable.[15] Randomized clinical trials are needed,

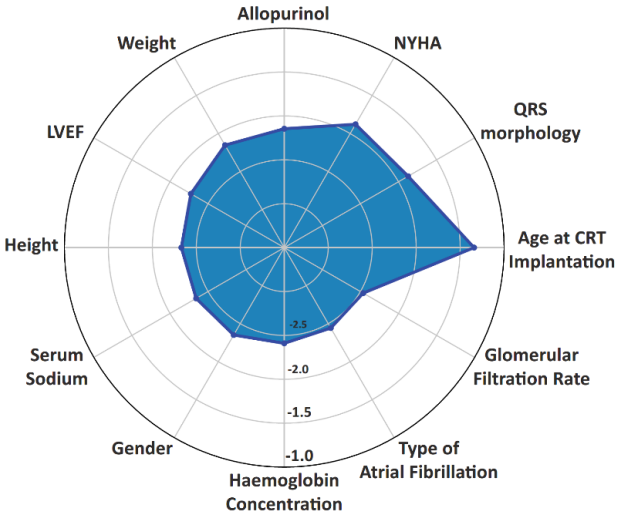


Figure 1 The 12 most important predictors of all-cause mortality as assessed by the SEMMELWEIS-CRT score. The importance of each feature was quantified by calculating the decrease in the model's performance (area under the receiver operating characteristic curve) after permuting its values (permutation feature importance method). The higher its value, the more important the feature is. As the values of feature importance were spread over a wide range (more orders of magnitude), base-10 logarithmic transformation was performed to facilitate plotting. CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; NYHA, New York Heart Failure Association functional class. (Reprinted from Tokodi *et al.*[12], by permission of OUP on behalf of the ESC.)

to evaluate the clinical benefit and cost-effectiveness of applying such algorithms in clinical practice.

The last year brought also new advances in the use of AI for the diagnosis of heart failure. Indeed, a CNN was trained based on paired ECGs and transthoracic echocardiograms from ~45k patients and validated in an independent cohort of >52k patients.[16] The ROC for detection of systolic dysfunction using this AI-enhanced ECG interpretation reached an AUC of 0.93. This impressive result confirms the notion that AI could extract invaluable information even from simple, low-cost tests like ECG, which could even be used as screening tests for the detection of subclinical heart failure in the community.

AI in cardiac imaging

This year has been extraordinary for medical imaging, as a wide range of AI-powered algorithms has been introduced in clinical care by the hardware vendors and software manufacturers. These algorithms range from image reconstruction, to automated segmentation and improvement of workflows, or even to the detection of imaging characteristics not visible to the human eye assisting diagnosis.[17,18] The year 2020 is considered by many as the year of cardiac computed tomography angiography (CTA), as this has just been incorporated into the recent ESC guidelines as a first-line investigation for the management of chest pain.[19] This approach came a few years after a similar recommendation was published in the UK NICE guidelines, but it is still more advanced compared to the US standard of care.[20] Given the standardized way by which computed tomography (CT) images are captured, the modality is particularly attractive to machine-learning methods to improve segmentation and interpretation. Indeed, in a study by Al'Aref *et al.*[21] from the CONFIRM registry, a population of >13k patients undergoing coronary calcium score measurements (CCS) was used to examine whether including CCS in a machine-learning model together with clinical risk factors could improve risk stratification. Indeed, adding CCS in a baseline model that included clinical risk factors resulted in ~9% improvement in the ability to estimate the pre-test probability of obstructive coronary artery disease, with remarkable diagnostic accuracy. Particularly in the young patients (<65 years old), the algorithm improved the ability to detect coronary artery disease by ~17%. However, it remains to be proven that machine learning performs better than simple statistical regression models, when risk factors are combined with results from tests like CCS.[22] Further to the use of machine learning to integrate imaging with other datasets, the practical value of AI lies with the improvement of image analysis workflows.[18] Automated segmentation of coronary atherosclerotic plaques, coronary calcification or even epicardial fat in CT makes image interpretation faster and more accurate and eliminates user-dependent variability.[23]

The true power of AI though comes from its ability to 'see the invisible'. The field of radiomics allows extraction of thousands of different pieces of information from images, which provide information on the texture and composition of the tissue visualized (*Figure 2*). Indeed, further to the analysis of the composition and volume of coronary atherosclerotic plaques, it is now widely accepted that vascular inflammation causes changes in the composition and texture of perivascular fat, which activates lipolysis and increases its hydrophilic content around inflamed vascular structures.[24] Visualizing perivascular fat using standard CTA allows the calculation of a metric of these changes, driven by the 3D changes in perivascular fat attenuation. An AI-derived biomarker that captures that biology, the fat attenuation index (FAI), has striking prognostic value[25] that goes beyond atherosclerotic plaque characteristics,[26] as demonstrated in ~4000 patients from the CRISP-CT outcomes study. In a recent paper published by Oikonomou *et al.*[27] published in EHJ, the same principle, i.e. the ability of perivascular fat to change its texture and composition in response to inflammatory signals coming from the vascular wall, was transferred in the field of radiomics. The concept of radiotranscriptomics has been introduced in the cardiovascular dictionary, as by using the gene expression profile of adipose tissue in fat biopsies obtained from 167 patients undergoing cardiac surgery, they created molecular classifiers for inflammation, fibrosis, and angiogenesis, all features characterizing perivascular fat after prolonged exposure to vascular inflammation. Then, they extracted the radiomic features from the CT images of the same adipose tissue, and by using machine learning they built a radiomic signature to detect chronic vascular inflammation (capturing perivascular fibrosis, angiogenesis,

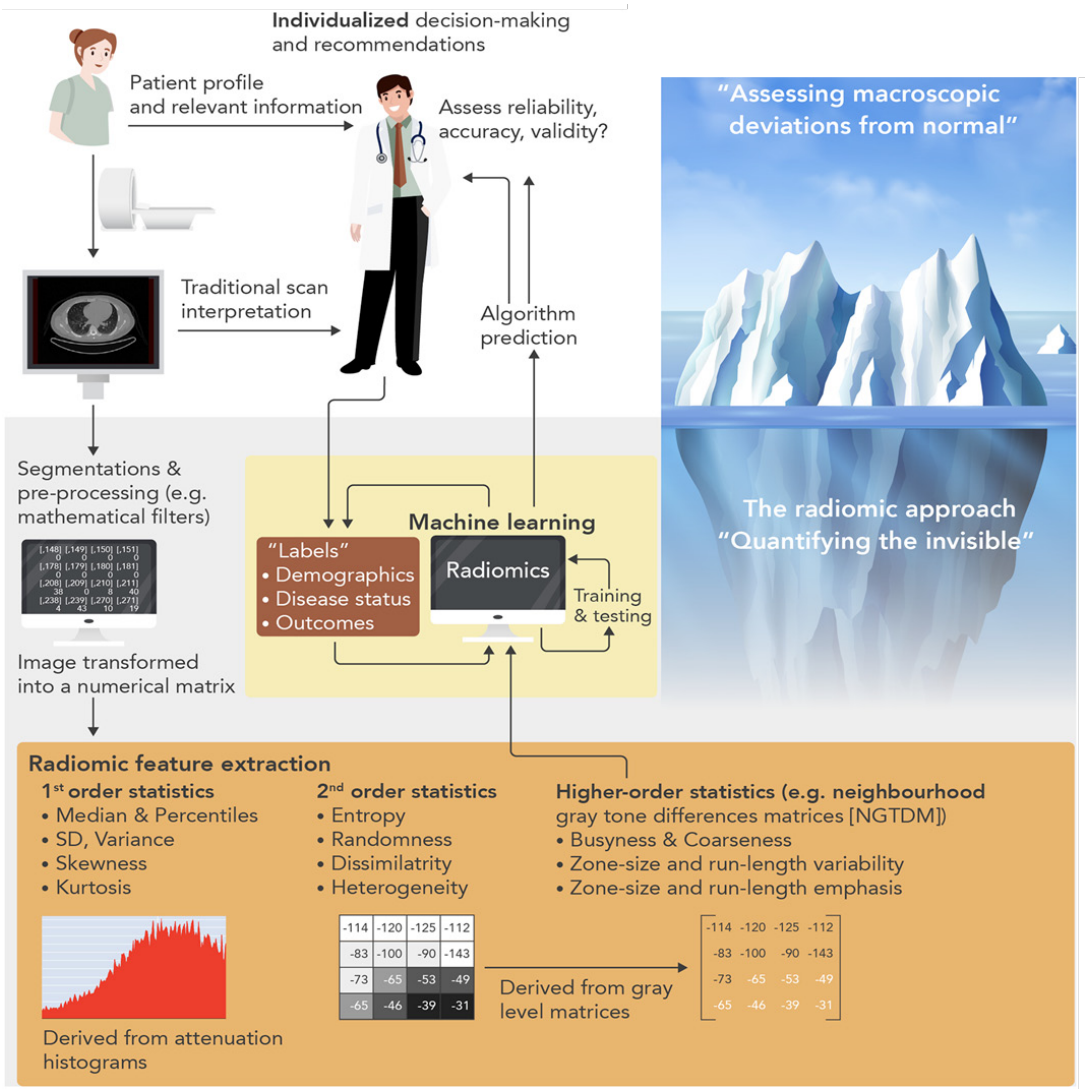


Figure 2 Artificial intelligence can be used to combine different types of information, from clinical and laboratory data, to imaging or any other type of information, to assist clinical diagnosis and decision-making. (Reprinted from Oikonomou *et al.*[18], by permission of OUP on behalf of the ESC.)

and inflammation). The new radiotranscriptomic metric generated, the Fat Radiomic Profile (FRP) index (*Figure 3*), was then tested for its performance in 1575 patients from the SCOTHEART trial, who were followed up for 5 years after their CTA.[26,28] Indeed, FRP had a remarkable prognostic value, as those people with abnormal FRP had >10 times higher risk for a fatal or non-fatal cardiac event, with an AUC to detect those who will have the event, of 0.88. When abnormal FRP was combined with the presence of high risk plaque, the patient's relative risk for cardiac event was >43 times higher than the reference group (*Figure 3*). As it was discussed in the associated editorial,[29] this technology could guide therapeutic interventions; this could be done in the future either in the form of a companion diagnostic to allow targeted deployment of expensive treatments, or as an enrichment tool for clinical trials. Other papers published this year[30] seem to confirm the validity of this approach, while the strategies for Imaging residual inflammatory risk have been presented in a recent state of the art review published in EHJ.[31] This method needs further validation in non-Caucasian ethnic groups, while its translation into a clinically applicable tool is challenging due to the complexity of the analysis, which makes it difficult to perform on standard clinical workstations onsite.

From an ultrasound point of view, 2020 has been a year for the consolidation of earlier technical developments in how to train neural networks to handle raw images and video loops from echocardiograms to segment and extract useful metrics such as ejection fraction and myocardial strain.[32] The study by Ouyang *et al.*[33] is probably the most significant advancement in the field, driven by AI in 2020. In that study, they took echocardiography analysis from still frame segmentation to a video-based deep learning approach through development of a specific EchoNet-Dynamic algorithm that combines temporal and spatial information within the neural network. Training networks for the evaluation of segmentation and quantification achieve an acceptable accuracy for the estimation of ejection fraction on a beat-to-beat

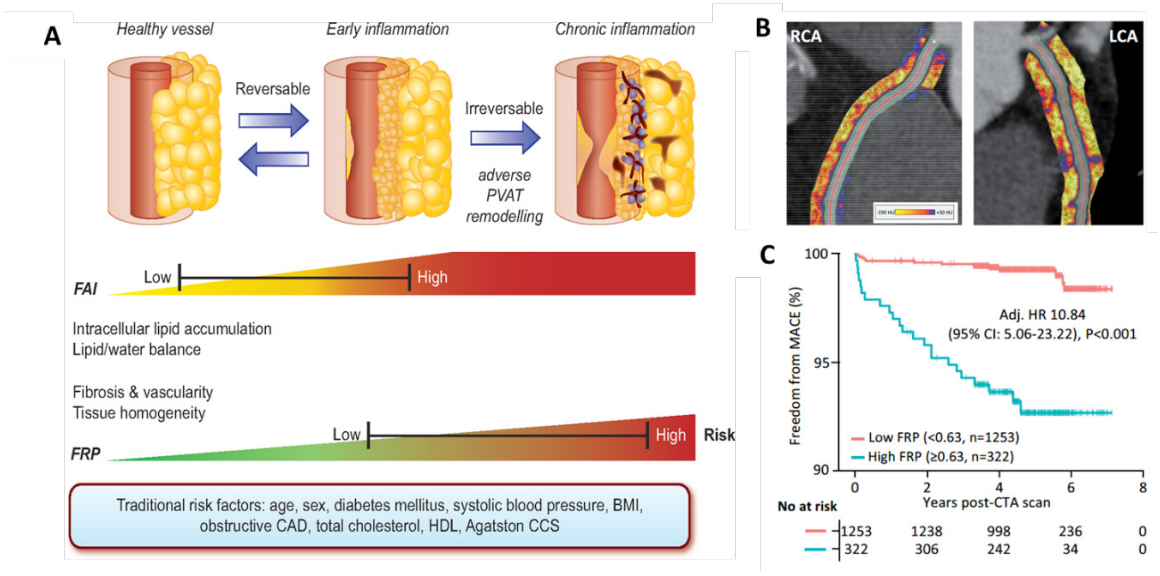


Figure 3 (*A*) Coronary inflammation first drives changes in peri-coronary adipocyte size, while at a later stage it leads to perivascular fibrosis and angiogenesis. (*B*) These changes can be visualised in standard coronary CT angiography by a method called Fat Attenuation Indexing. By using a radiotranscriptomic approach, Oikonomou *et al.*[27] have built an imaging signature that captures these changes (Fat Radiomic Profile). (*C*) That signature has striking prognostic value over and above risk factors including coronary calcium score, as it was validated in the SCOTHEART population. CAD, coronary artery disease; BMI, body mass index; FAI, Fat attenuation index; MACE, Major Adverse Cardiac Events. (Reprinted from Bartelt *et al.*[29], by permission of OUP on behalf of the ESC.)

basis that can help in identification of heart failure. The next interesting phase is going to be the application of these approaches to larger scale datasets to improve accuracy of disease prediction, in large databases like the UK Biobank.[34] This approach could open new horizons in applying deep learning in image interpretation for risk prediction. Indeed, this year the outputs of the UK-Biobank confirmed its potential to drive innovation for years to come. In a study just published,[35] >26k cardiac MRI scans were used in machine-learning algorithms to allow the detection of >2k interactions between imaging phenotypes and non-imaging phenotypes in the UK-Biobank, providing new insights into the influence of early-life factors and diabetes on cardiac and aortic structure and function, linking them also with cognitive phenotypes.

AI and COVID-19

Above all, 2020 will be remembered as the year when COVID-19 brought the world upside down.[36] As our knowledge accumulates about the disease, it becomes clear that COVID-19 is, in the end, a vascular endothelial disease.[37,38] The need for rapid integration of large volumes of data collected from around the world to facilitate the urgent development of treatments to combat the disease brought to the surface the power of AI to give solutions fast and accurately.[39] Indeed, fast and accurate data collection has been in the centre of the efforts to combat the disease. European registries like the CAPACITY-COVID[40] are actively collecting data around the disease, working together with international efforts from the International Severe Acute Respiratory and Emerging Infection Consortium and World Health Organization. The use of AI to interrogate these datasets is expected to improve our understanding on the incidence and pattern of cardiovascular complications in patients with COVID-19 and evaluate the vulnerability and clinical course of patients with underlying cardiovascular diseases. In addition, AI algorithms have been used to integrate chest CT findings with clinical symptoms, laboratory testing and exposure history to rapidly diagnose COVID-19. In a very recent study[41] that included 905 patients tested with (419 of which tested positive for SARS-CoV-2), the AI system achieved an area under the curve of 0.92 to diagnose the disease without the need of a PCR method, having sensitivity comparable to a senior thoracic radiologist.[41] The use of computational learning methods to integrate biomarkers of inflammation and myocardial injury (e.g. C-reactive protein, N-terminus pro B type natriuretic peptide, myoglobin, D-dimer, procalcitonin, creatine kinase-myocardial band and cardiac troponin I) in COVID-19 was recently found to predict mortality with AUC 0.94.[42] These initial models could lead to point-of-care Severity Score systems and could have major impact in clinical decision-making, in the coming months. In the post-COVID-19 period, the expertise gained in applying machine learning to integrate multi-omic and clinical data[43] is expected to revolutionise cardiac diagnostics.

AI: from pattern recognition to analysis of 'selfies'!

AI and particular convolutional neural networks are being accused as 'black boxes' that combine features that

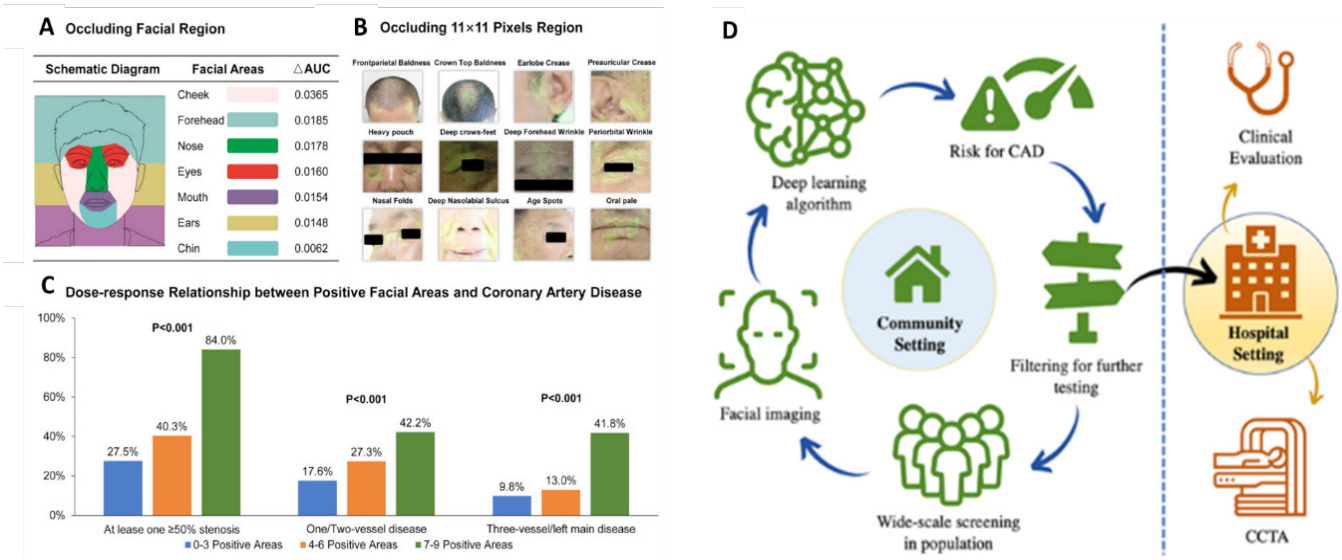


Figure 4 Areas in the face with information useful in face pattern recognition, involved in prediction of coronary artery disease. In tests occluding facial regions (*A*), AUC was defined as the decrease in algorithm performance after occluding a specific facial region. In tests occluding regions of 11 × 11 pixels (*B*), the green regions were highlighted by the algorithm as important for detecting CAD. In the dose–response relationship test (*C*), the positive facial areas were judged based on the change in algorithm performance after occlusion. Having 7–9 positive areas was related with presence of coronary artery disease in 84% of the cases, while there was >1 vessel disease in ~42% of the cases (*C*). (Reprinted from Lin *et al.*[44], by permission of OUP on behalf of the ESC.) This technology can be used for screening in the community (*D*). (Reprinted from Kotanidis and Antoniades[45], by permission of OUP on behalf of the ESC.)

are individually meaningless into algorithms that give meaningful predictions. Indeed, in a landmark study just published in the EHJ,[44] a Chinese group of scientist has developed a deep convolutional neural network that detects coronary artery disease (with stenosis >50% documented by angiography), by analysing the patient's facial photos (*Figure 4*). They included >5k patients in their training dataset and 580 in the test dataset. The algorithm had sensitivity 80% and specificity 54% to detect significant coronary artery disease from the faces of the patients, with an AUC 0.73. Could this be demonstrating genetic predisposition to atherosclerosis? Could it demonstrate secondary effects on the skin and structure of the face due to risk factors or the disease itself? Or is it just the result of training the algorithm in an ethnically homogenous population that will not survive the test of time?[45] If the concept behind this study is confirmed, then medical confidentiality may be at risk; walking into a train station or walking through the doors of an insurance company (where CCTV is in operation) may already give away health problems that you would like to keep private (breaching individual confidentiality), or inform you about health issues you are not aware of (saving your life). These issues will definitely spark extensive debates in the coming years.

Challenges of AI application in clinical practice

Further to the great opportunities presented by AI, these technologies also generate significant scepticism. The results generated by most machine-learning algorithms often fail to generalize in different populations. Since these algorithms are often in the form of a 'black box', it is hard to understand (and therefore criticize and edit) their content, and this generates unavoidable bias. Such bias could lead to results applicable only to specific populations, specific technical equipment, or specific clinical practices included into the training datasets. Many deep learning algorithms are also susceptible to adversarial examples, leading to consistently wrong classification of the measured parameter(s) by detecting false patterns undetectable to the human eye.

The limited generalizability in machine learning (i.e. the poor adaptability of these models to previously unseen data) comes to limit the applicability of these algorithms to clinical practice. This issue is mitigated by applying beyond training and internal validation (which inevitably leads to overestimation of the model's performance), also independent testing. For the proper generalizability assessment, independent test dataset should represent the population of interest, but in a dataset totally independent of the training dataset (typically from independent institutions and/or geographically distant populations). The training part should be used for dimension reduction, development of the model and for hyperparameter tuning (and can use methods like cross-validation, random sampling or nested cross-validation). To prevent bias in performance evaluation, the model should be locked before the independent testing. The lack of transparency on the true links between the training and the independent validation dataset often makes it hard to evaluate the quality of the published literature. Transparent reporting can be ensured by following specific principles,[46] while open data sharing would allow independent reproducibility tests, securing high standards in publishing in the field.

Conclusions

There is no doubt that 2020 has been an extraordinary year, dominated by the COVID-19 pandemic. Under these difficult circumstances for humanity, and with most areas of cardiovascular research compromised due to national lockdowns, the data science endured. The ability of AI to extract and analyse large volumes of data remotely allowed this field of cardiovascular medicine to continue its evolution, and we have seen major discoveries transforming many aspects of clinical care. From workflow improvements to automated image segmentation, accurate cardiovascular risk prediction or event facial recognition to screen for cardiac diseases, AI is now major part of cardiovascular medicine. The studies highlighted in this article give only a small glimpse into this booming field, creating more anticipation for what will come to clinical practice in the coming years.

The European Society of Cardiology has early recognized the importance of the fast evolving field of digital health technologies and has prioritized it as a strategic domain of cardiovascular medicine. The *European Heart Journal* family is at the forefront of the international effort to set high standards in publishing AI studies, actively promoting the translation of AI technologies into clinical applications. A new section on digital health has recently been included in the EHJ, aiming to cultivate the culture of digitization in the full spectrum of cardiovascular medicine. In addition, a new journal (EHJ Digital Health) has been added into the EHJ family. Finally, the European Union has recently launched an effort to regulate the use of AI algorithms as medical devices, especially for risk prediction. AI algorithms will need to receive CE mark as medical devices from May next year.[47] This approach is being adopted by both Food and Drugs Administration and European Medicines Authority and will have direct implications on the clinical implementation of newly developed AI cardiovascular risk calculators that will be included in the clinical guidelines in the future.

Conflict of interest: C.A. is Founder, shareholder and director of Caristo Diagnostics, an Oxford Spinout company; he is also head of Oxford Academic Cardiovascular CT Core lab, and is inventor of intellectual property relevant to this work (GB2015/052359, GB2016/ 1620494.3, GB2018/1818049.9, GR2018/0100490, GR2018/0100510).

Acknowledgements

The authors are grateful to Dr Christos Kotanidis for his technical contribution in drafting the graphical abstract.

Funding

C.A. is supported by the British Heart Foundation (FS/16/15/32047 and TG/19/2/34831), the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre and Innovate UK. F.W.A. is supported by UCL Hospitals NIHR Biomedical Research Centre and the EU/EFPIA Innovative Medicines Initiative 2 Joint Undertaking BigData@Heart grant n° 116074. P.V. is supported by the Hygeia Hospitals Group, Athens, Greece. P.V. is supported by the Hygeia Hospitals Group, Athens, Greece

References

1. Nicholls M. Machine learning-state of the art. *Eur Heart J* 2019;**40**:3668–3669.
2. Lamata P. Teaching cardiovascular medicine to machines. *Cardiovascular Research* 2018;**114**:e62–e64. 10.1093/cvr/cvy127
3. Sekelj S, Sandler B, Johnston E, Pollock KG, Hill NR, Gordon J, Tsang C, Khan S, Ng FS, Farooqui U. Detecting undiagnosed atrial fibrillation in UK primary care: validation of a machine learning prediction algorithm in a retrospective cohort study. *Eur J Prev Cardiol* 2020.
4. Attia ZI, Noseworthy PA, Lopez-Jimenez F, Asirvatham SJ, Deshmukh AJ, Gersh BJ, Carter RE, Yao X, Rabinstein AA, Erickson BJ, Kapa S, Friedman PA. An artificial intelligence-enabled ECG algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction. *Lancet* 2019;**394**:861–867.
5. Han X, Hu Y, Foschini L, Chinitz L, Jankelson L, Ranganath R. Deep learning models for electrocardiograms are susceptible to adversarial attack. *Nat Med* 2020;**26**:360–363.
6. Wagner P, Strodthoff N, Bousseljot RD, Kreiseler D, Lunze FI, Samek W, Schaeffter T. PTB-XL, a large publicly available electrocardiography dataset. *Sci Data* 2020;**7**:154.
7. Zheng J, Zhang J, Danioko S, Yao H, Guo H, Rakovski C. A 12-lead electrocardiogram database for arrhythmia research covering more than 10,000 patients. *Sci Data* 2020;**7**:48.
8. Ribeiro AH, Ribeiro MH, Paixao GMM, Oliveira DM, Gomes PR, Canazart JA, Ferreira MPS, Andersson CR, Macfarlane PW, Meira W Jr., Schon TB, Ribeiro ALP. Automatic diagnosis of the 12-lead ECG using a deep neural network. *Nat Commun* 2020;**11**:1760.
9. Perez MV, Mahaffey KW, Hedlin H, Rumsfeld JS, Garcia A, Ferris T, Balasubramanian V, Russo AM, Rajmane A, Cheung L, Hung G, Lee J, Kowey P, Talati N, Nag D, Gummidipundi SE, Beatty A, Hills MT, Desai S, Granger CB, Desai M, Turakhia MP; Apple Heart Study I. Large-scale assessment of a smartwatch to identify atrial fibrillation. *N Engl J Med* 2019;**381**:1909–1917.
10. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Group ESCSD. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–2200.
11. Gutman SJ, Costello BT, Papapostolou S, Voskoboinik A, Iles L, Ja J, Hare JL, Ellims A, Kistler PM, Marwick TH, Taylor AJ. Reduction in mortality from implantable cardioverter-defibrillators in non-ischaemic cardiomyopathy patients is dependent on the presence of left ventricular scar. *Eur Heart J* 2019;**40**:542–550.
12. Tokodi M, Schwertner WR, Kovács A, Tősér Z, Staub L, Sárkány A, Lakatos BK, Behon A, Boros AM, Perge P, Kutyifa V, Széplaki G, Gellér L, Merkely B, Kosztin A. Machine learning-based mortality prediction of patients undergoing cardiac resynchronization therapy: the SEMMELWEIS-CRT score. *Eur Heart J* 2020;**41**:1747–1756.
13. Tokodi M, Schwertner WR, Kosztin A, Merkely B. The ongoing quest for improving machine learning-based risk stratification. *Eur Heart J* 2020;**41**:2914–2915.
14. Cikes M, Sanchez-Martinez S, Claggett B, Duchateau N, Piella G, Butakoff C, Pouleur AC, Knappe D, Biering-Sorensen T, Kutyifa V, Moss A, Stein K, Solomon SD, Bijnens B. Machine learning-based phenogrouping in heart failure to identify responders to cardiac resynchronization therapy. *Eur J Heart Fail* 2019;**21**:74–85.

15. Kim WH, Kim JT. Machine learning-based mortality prediction: how to be connected to daily clinical practice? *Eur Heart J* 2020;**41**:2913–2913.
16. Attia ZI, Kapa S, Lopez-Jimenez F, McKie PM, Ladewig DJ, Satam G, Pellikka PA, Enriquez-Sarano M, Noseworthy PA, Munger TM, Asirvatham SJ, Scott CG, Carter RE, Friedman PA. Screening for cardiac contractile dysfunction using an artificial intelligence-enabled electrocardiogram. *Nat Med* 2019;**25**:70–74.
17. Commandeur F, Slomka PJ, Goeller M, Chen X, Cadet S, Razipour A, McElhinney P, Gransar H, Cantu S, Miller RJH, Rozanski A, Achenbach S, Tamarappoo BK, Berman DS, Dey D. Machine learning to predict the long-term risk of myocardial infarction and cardiac death based on clinical risk, coronary calcium, and epicardial adipose tissue: a prospective study. *Cardiovasc Res* 2019.
18. Oikonomou EK, Siddique M, Antoniades C. Artificial intelligence in medical imaging: a radiomic guide to precision phenotyping of cardiovascular disease. *Cardiovasc Res* 2020.
19. Collet JP, Thiele H, Barbato E, Barthelemy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Juni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM; Group ESCSD. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2020.
20. Taylor A, Yang E. Comparing American and European guidelines for the initial diagnosis of stable ischaemic heart disease. *Eur Heart J* 2020;**41**:811–815.
21. Al'Aref SJ, Maliakal G, Singh G, van Rosendael AR, Ma X, Xu Z, Alawamlh OAH, Lee B, Pandey M, Achenbach S, Al-Mallah MH, Andreini D, Bax JJ, Berman DS, Budoff MJ, Cademartiri F, Callister TQ, Chang HJ, Chinnaiyan K, Chow BJW, Cury RC, DeLago A, Feuchtner G, Hadamitzky M, Hausleiter J, Kaufmann PA, Kim YJ, Leipsic JA, Maffei E, Marques H, Goncalves PA, Pontone G, Raff GL, Rubinshtein R, Villines TC, Gransar H, Lu Y, Jones EC, Pena JM, Lin FY, Min JK, Shaw LJ. Machine learning of clinical variables and coronary artery calcium scoring for the prediction of obstructive coronary artery disease on coronary computed tomography angiography: analysis from the CONFIRM registry. *Eur Heart J* 2020;**41**:359–367.
22. Sengupta PP, Shrestha S, Zeb I. Solving coronary risk: time to feed machines some calcium (score) supplements. *Eur Heart J* 2020;**41**:368–370.
23. Pennell D, Delgado V, Knuuti J, Maurovich-Horvat P, Bax JJ. The year in cardiology: imaging. *Eur Heart J* 2020;**41**:739–747.
24. Antonopoulos AS, Sanna F, Sabharwal N, Thomas S, Oikonomou EK, Herdman L, Margaritis M, Shirodaria C, Kampoli AM, Akoumianakis I, Petrou M, Sayeed R, Krasopoulos G, Psarros C, Ciccone P, Brophy CM, Digby J, Kelion A, Uberoi R, Anthony S, Alexopoulos N, Tousoulis D, Achenbach S, Neubauer S, Channon KM, Antoniades C. Detecting human coronary inflammation by imaging perivascular fat. *Sci Transl Med* 2017;**9**(398):eaal2658.
25. Oikonomou EK, Marwan M, Desai MY, Mancio J, Alashi A, Hutt Centeno E, Thomas S, Herdman L, Kotanidis CP, Thomas KE, Griffin BP, Flamm SD, Antonopoulos AS, Shirodaria C, Sabharwal N, Deanfield J, Neubauer S, Hopewell JC, Channon KM, Achenbach S, Antoniades C. Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): a post-hoc analysis of prospective outcome data. *Lancet* 2018;**392**:929–939.
26. Oikonomou EK, Desai MY, Marwan M, Kotanidis CP, Antonopoulos AS, Schottlander D, Channon KM, Neubauer S, Achenbach S, Antoniades C. Perivascular fat attenuation index stratifies cardiac risk associated with high-risk plaques in the CRISP-CT study. *J Am Coll Cardiol* 2020;**76**:755–757.
27. Oikonomou EK, Williams MC, Kotanidis CP, Desai MY, Marwan M, Antonopoulos AS, Thomas KE, Thomas S, Akoumianakis I, Fan LM, Kesavan S, Herdman L, Alashi A, Centeno EH, Lyasheva M, Griffin BP, Flamm SD, Shirodaria C, Sabharwal N, Kelion A, Dweck MR, Van Beek EJR, Deanfield J, Hopewell JC, Neubauer S, Channon KM, Achenbach S, Newby DE, Antoniades C. A novel machine learning-derived radiotranscriptomic signature of perivascular fat improves cardiac risk prediction using coronary CT angiography. *Eur Heart J* 2019;**40**:3529–3543.
28. Investigators S-H, Newby DE, Adamson PD, Berry C, Boon NA, Dweck MR, Flather M, Forbes J, Hunter A, Lewis S, MacLean S, Mills NL, Norrie J, Roditi G, Shah ASV, Timmis AD, van Beek EJR, Williams MC. Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med* 2018;**379**:924–933.
29. Bartelt A, Leipsic J, Weber C. The new age of radiomic risk profiling: perivascular fat at the heart of the matter. *Eur Heart J* 2019;**40**:3544–3546.
30. Lin A Kolossváry M Yuvaraj J Cadet S Mcelhinney P A Jiang C Nerlekar N Nicholls S J Slomka P J Maurovich-Horvat P Wong D T Dey D. Myocardial Infarction Associates With a Distinct Pericoronary Adipose Tissue Radiomic Phenotype. *JACC: Cardiovascular Imaging* 2020;**13**:2371–2383. 10.1016/j.jcmg.2020.06.033
31. Antoniades C, Antonopoulos AS, Deanfield J. Imaging residual inflammatory cardiovascular risk. *Eur Heart J* 2020;**41**:748–758.
32. Leeson P, Fletcher AJ. Combining artificial intelligence with human insight to automate echocardiography. *Circ Cardiovasc Imaging* 2019;**12**:e009727.
33. Ouyang D, He B, Ghorbani A, Yuan N, Ebinger J, Langlotz CP, Heidenreich PA, Harrington RA, Liang DH, Ashley EA, Zou JY. Video-based AI for beat-to-beat assessment of cardiac function. *Nature* 2020;**580**:252–256.
34. Littlejohns TJ, Holliday J, Gibson LM, Garratt S, Oesingmann N, Alfaro-Almagro F, Bell JD, Boultwood C, Collins R, Conroy MC, Crabtree N, Doherty N, Frangi AF, Harvey NC, Leeson P, Miller KL, Neubauer S, Petersen SE, Sellors J, Sheard S, Smith SM, Sudlow CLM, Matthews PM, Allen NE. The UK Biobank imaging enhancement of 100,000 participants: rationale, data collection, management and future directions. *Nat Commun* 2020;**11**:2624.
35. Bai W, Suzuki H, Huang J, Francis C, Wang S, Tarroni G, Guitton F, Aung N, Fung K, Petersen SE, Piechnik SK, Neubauer S, Evangelou E, Dehghan A, O'Regan DP, Wilkins MR, Guo Y, Matthews PM, Rueckert D. A population-based phenome-wide association study of cardiac and aortic structure and function. *Nat Med* 2020;**26**:1654–1662.
36. Adao R, Guzik TJ. Inside the heart of COVID-19. Cardiovasc Res 2020;**116**:e59–e61.
37. Libby P, Luscher T. COVID-19 is, in the end, an endothelial disease. *Eur Heart J* 2020;**41**:3038–3044.
38. Evans PC, Rainger G, Mason JC, Guzik TJ, Osto E, Stamataki Z, Neil D, Hoefer IE, Fragiadaki M, Waltenberger J, Weber C, Bochaton-Piallat ML, Back M. Endothelial dysfunction in COVID-19: a position paper of the ESC Working Group for Atherosclerosis and Vascular Biology, and the ESC Council of Basic Cardiovascular Science. *Cardiovasc Res* 2020.
39. Bachtiger P, Peters NS, Walsh SL. Machine learning for COVID-19-asking the right questions. *Lancet Digit Health* 2020;**2**:e391–e392.
40. Linschoten M, Asselbergs FW. CAPACITY-COVID: a European Registry to determine the role of cardiovascular disease in the COVID-19 pandemic. *Eur Heart J* 2020;**41**:1795–1796.
41. Mei X, Lee HC, Diao KY, Huang M, Lin B, Liu C, Xie Z, Ma Y, Robson PM, Chung M, Bernheim A, Mani V, Calcagno C, Li K, Li S, Shan H, Lv J, Zhao T, Xia J, Long Q, Steinberger S, Jacobi A, Deyer T, Luksza M, Liu F, Little BP, Fayad ZA, Yang Y. Artificial intelligence-enabled rapid diagnosis of patients with COVID-19. *Nat Med* 2020;**26**:1224–1228.
42. McRae MP, Simmons GW, Christodoulides NJ, Lu Z, Kang SK, Fenyo D, Alcorn T, Dapkins IP, Sharif I, Vurmaz D, Modak SS, Srinivasan K, Warhadpande S, Shrivastav R, McDevitt JT. Clinical decision support tool and rapid point-of-care platform for determining disease severity in patients with COVID-19. *Lab Chip* 2020;**20**:2075–2085.
43. Olin JW, Di Narzo AF, d'Escamard V, Kadian-Dodov D, Cheng H, Georges A, King A, Thomas A, Barwari T, Michelis KC,

Bouchareb R, Bander E, Anyanwu A, Stelzer P, Filsoufi F, Florman S, Civelek M, Debette S, Jeunemaitre X, Björkegren JLM, Mayr M, Bouatia-Naji N, Hao K, Kovacic JC. A plasma proteogenomic signature for fibromuscular dysplasia. *Cardiovasc Res* 2020;**116**:63–77.

44. Lin S, Li Z, Fu B, Chen S, Li X, Wang Y, Wang X, Lv B, Xu B, Song X, Zhang Yj Cheng X, Huang W, Pu J, Zhang Q, Xia Y, Du B, Ji X, Zheng Z. Feasibility of using deep learning to detect coronary artery disease based on facial photo. *Eur Heart J* 2020;**41**:4400–4411.
45. Kotanidis CP, Antoniades C. Selfies in cardiovascular medicine: welcome to a new era of medical diagnostics. *Eur Heart J* 2020;**41**:4412–4414.
46. Collins GS, Moons KGM. Reporting of artificial intelligence prediction models. *Lancet* 2019;**393**:1577–1579.
47. Minssen T, Gerke S, Aboy M, Price N, Cohen G. Regulatory responses to medical machine learning. *J Law Biosci* 2020;**46**:1–18.