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Protocols of antithrombotic therapy in a University Cardiocenter

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INFORMACE O ČLÁNKU

Historie článku:
Došel do redakce: 9. 1. 2013
Přijat: 19. 2. 2013
Dostupný online: 28. 2. 2013

Keywords:
Acute coronary syndrome
Antiaggregation drugs
Anticoagulant drugs
Antithrombotic therapy
Atrial fibrillation
Coronary artery bypass graft surgery
Percutaneous coronary intervention
Thromboembolic disease

Klíčová slova:
Akutní koronární syndromy
Antiagregancia
Antikoagulancia
Antitrombotická léčba
Aortokoronární bypass
Fibrilace síní
Perkutánní koronární intervence
Tromboembolická nemoc

ABSTRACT

This article presents local protocols for antithrombotic therapy used in a tertiary care institution – the cardiocenter of a university hospital. The protocols were discussed in detail among the whole team of physicians of the cardiocenter. This article addresses cardiac conditions requiring hospitalization whenever antithrombotic therapy is indicated. These protocols do not include antithrombotic therapy in other medicinal disciplines (e.g., orthopedics, surgery). These protocols are mostly based on the current guidelines of the European Society of Cardiology (ESC). The partial differences between the ESC guidelines and this text are usually based on the results of the latest clinical trials, which have not yet been included in the ESC guidelines.

SOUHRN

V článku jsou přehledně prezentovány postupy antitrombotické léčby, které se používají v univerzitním terciárním kardiocentru a které byly podrobně diskutovány celým týmem lékařů tohoto pracoviště. Text se zabývá těmi stavy, které vedou k hospitalizaci na kardiologickém či kardiochirurgickém oddělení, u nichž je indikována léčba ovlivňující krevní srážlivost. Práce se nezabývá užitím antitrombotik v jiných medicínských oborech (např. v ortopedii, chirurgii apod.). Postupy v naprosté většině vycházejí z platných doporučení Evropské kardiologické společnosti (ESC), v některých dílčích otázkách se od nich mírně odlišují – zpravidla na základě posledních výsledků klinických studií, které ještě nemohly být zohledněny v platných guidelines.

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DOI: 10.1016/j.crvasa.2013.02.006

Tento článek prosím citujte takto: P. Widimský, et al., Protocols of antithrombotic therapy in a University Cardiocenter, Cor et Vasa 55 (2013) e201–e206, jak vyšel v online verzi *Cor et Vasa* na http://www.sciencedirect.com/science/article/pii/S0010865013000295

Preamble

Adherence to these protocols by physicians in the Cardiocenter is not obligatory. These protocols are considered recommendations, not mandates. If a physician decides not to follow the protocols strictly in a particular case, he/she should write a short explanation of his/her decision in the medical documentation. These protocols are partially different from the official guidelines of the Czech Society of Cardiology (CKS) and the European Society of Cardiology (ESC). These partial differences are usually based on results of the latest clinical trials, which have not yet been included in the ESC or CKS guidelines.

Several modern and effective drugs included in these protocols are not yet fully covered by the Czech health insurance system, and patients need to pay part of their price (sometimes a significant amount). While prescribing these drugs, physicians are obliged to inform patients about differences in the effectiveness and safety in comparison with cheaper alternative drugs and also the amount the patient would be required to pay. The final decision whether to prescribe the cheaper or the more expensive drug must be based on the patient's wishes.

Positive list of used drugs (Table 1)

Table 1 – Positive list of used drugs.

Thrombolytics	Anticoagulants	Antiplatelet drugs
tPA (Alteplase®)	heparin (Heparin®)	acetylsalicylic acid, lysine salicylate (Anopyrin®, Kardegic®)
streptokinase (Streptase®)	enoxaparin (Clexane®)	clopidogrel (Trombex®)
		prasugrel (Efient®)
	warfarin (Warfarin®, Lawarin®)	ticagrelor (Brilique®)
	dabigatran (Pradaxa®)	
	rivaroxaban (Xarelto®)	eptifibatide (Integrilin®)

Maximal balance payment for outpatient prescribed drugs (status during 2012) (Table 2):
(Maximal balance payment for the patient according to the Czech Ministry of Health as of December 28, 2012; for details see www.mzcr.cz/leky.aspx)

1. Large myocardial infarction with an indication for urgent (right after admission) coronary angiography: acute ST elevation myocardial infarction (STEMI) or myocardial infarction with deep ST depressions (STDMI) or myocardial infarction with new-onset bundle branch block (RBBB-MI, LBBB-MI) or myocardial infarction causing cardiogenic shock or malignant arrhythmias [1,2]

Right after the diagnosis (in the ambulance, in the non-PCI-capable hospital, in the emergency admission department, upon arrival to the cathlab, etc.): Kardegic 0.5 g i.v. + Efient 60 mg p.o. + Heparin 70 IU/kg i.v.

If Efient is contraindicated, Trombex 600 mg should be used instead. In patients premedicated with Trombex, the use of Brilique 180 mg p.o. should be considered instead of Efient.

During urgent coronary angiography/PCI: If any of the three above-mentioned drugs were not administered before coronary angiography, administer them as soon as possible in the cathlab. The interventional cardiologist can decide whether to use an additional dose of heparin (until a total dose of 100 IU/kg) or alternatively whether to administer eptifibatide. The decision for eptifibatide use should be explained in documentation.

After primary PCI (regardless of the type of implanted stent): Anopyrin 100 mg daily indefinitely and Efient 10 mg daily for up to 12 months (or Brilique 2× 90 mg daily up to 12 months). In patients with weight < 60 kg or age > 75 years, an individual decision should be made (Trombex 75 mg daily or Efient 5 mg daily).

Clexane 0.4 ml s.c. daily should be considered during bed rest (last dose when the patient gets up from the bed). The first dose of Clexane should be administered after removing the compression over the site of puncture. The second dose (when the patient is still bed-rested) should be administered after 24 hours.

If the patient refuses to pay for Efient (or Brilique), the attending physician is obliged to replace, before discharge, Efient (or Brilique) with Trombex 2× 75 mg daily until day 14 after myocardial infarction, followed by 75 mg daily for up to 12 months.

2. Other forms of acute coronary syndrome (ACS) with coronary angiography indicated within 24 hours after admission: unstable angina (UA) with negative troponin, troponin-positive

Table 2 – Maximal balance payment for outpatient prescribed drugs (status during 2012).

Drug	Price (CZK)	Insurance company reimbursement (CZK)	Balance payment for patient (CZK)
Trombex 75 mg (30 tbl)	493,-	493,-	0,-
Efient 10 mg (28 tbl)	1520,-	384,-	1192,-
Efient 5 mg (28 tbl)			1192,-
Brilique 90 mg (56 tbl)	2123,-	383,-	1739,-
Warfarin 3 mg (100 tbl)	154,-	155,-	0,-
Warfarin 5 mg (100 tbl)	235,-	191,-	0–43,-; (according to the producer) 0,-
Pradaxa 110 mg (60 cps)	2200,-	2100,-	279,-
Pradaxa 150 mg (60 cps)	2200,-	2100,-	279,-
Xarelto 15 mg (28 tbl)	2242,-	1416,-	768,-
Xarelto 20 mg (28 tbl)	2242,-	1888,-	292,-

myocardial infarction without ST segment changes or without new bundle brunch block (trop-IM) [2]

On admission: Anopyrin 400 mg p.o. + Clexane at a therapeutic dose (1 mg/kg s.c. twice daily). The decision whether to use a $P2Y_{12}$ inhibitor will be made right after coronarography (in the case that coronarography is performed within 24 hours after admission). In patients with renal failure and GFR 30–60 ml/min/1.73 m^2, the dose of Clexane needs to be reduced (1 mg/kg s.c. once daily). Administration of Clexane before coronarography is not interrupted. In patients with GFR < 30 ml/min/1.73 m^2, Heparin (UFH) 60 IU/kg i.v. in a bolus dose and then by continual infusion of 15 IU/kg/h (maximally 1000 IU/h) is used instead of Clexane.

During coronarography ± PCI: If ad hoc PCI is indicated right after coronarography, Efient 60 mg p.o. is administered in the cathlab. In patients medicated early with Trombex, and/or with a history of TIA and/or ischemic stroke and/or weight < 60 kg and/or age >75 years, Brilique 180 mg p.o. should be used instead.

If ad hoc PCI is not indicated and the patient is stable, the decision about treatment with $P2Y_{12}$ inhibitors is made after exclusion of indication of CABG.

The interventional cardiologist can decide whether to administer eptifibatide. This decision must be later explained in documentation.

Patients treated with Clexane who did not receive the latest dose within 8 h before PCI should be treated with a bolus dose of Clexane 0.3 mg/kg i.v. before PCI.

After PCI (regardless of the type of implanted stent): Anopyrin 100 mg daily indefinitely. Efient 10 mg daily for up to 12 months (or Brilique 2× 90 mg daily up to 12 months). In patients with weight < 60 kg and/or age > 75 (see commentary at the end of the article), give Trombex 75 mg daily or Efient 5 mg daily. The sheath can be removed 6 h after the latest i.v./s.c. dose of Clexane. Clexane 0.4 ml s.c. daily should be considered during bed rest (last dose when the patient gets up from the bed). The first dose of Clexane should be administered after removing the compression over the site of puncture. The second dose should not be administered earlier than 24 hours later.

If the patient refuses to pay for Efient (or Brilique), the attending physician is obliged to replace, before discharge, Efient (or Brilique) with Trombex 75 mg daily.

3. PCI with implantation of a drug-eluting stent (DES) in patients with chronic forms of coronary artery disease

Patients with chronic coronary artery disease are usually treated with Anopyrin 100 mg daily. This treatment remains the same before and after PCI.

In cathlab: Heparin 25 IU/kg is usually administered before coronarography (the interventional cardiologist can decide not to use this treatment if a short duration of coronarography is expected, especially in females). In case of ad hoc PCI after coronarography, an additional dose of Heparin up to a total dose of 70–100 IU/kg is administered. Other anticoagulation after PCI is not indicated (except when there is a separate indication).

If ***PCI is performed ad hoc*** after coronarography, no specific preparation of the patient before coronarography is necessary. The patient is treated with Trombex 600 mg p.o. right after coronarography (before PCI).

If ***PCI is scheduled*** (coronarography is already known), the patient receives 600 mg of Trombex p.o. any time between 24 and 2 hours before PCI.

After PCI: Trombex 75 mg daily is indicated for up to 6 months (in individual patients with increased bleeding risk and use of a XIENCE® or RESOLUTE® stent, dual antiplatelet therapy can extend for up to 3 months). In high-risk patients (increased risk of stent thrombosis, a single last patent conduit, PCI of left main or multiple-vessel PCI), the interventional cardiologist can decide to administer dual antiplatelet therapy for up to 12 months (possibly even longer). In these high-risk patients, the platelet response to clopidogrel should be assessed. If resistance to clopidogrel is verified, Trombex is switched to Efient 10/5 mg daily (if there are no contraindications and the patient gives consent).

4. PCI with implantation of bare-metal stent (BMS) or PCI without implantation of stent in patients with chronic coronary artery disease

The operating procedure is the same as in previous case [3], only the period of treatment with Trombex is up to 1 month. Efient is not indicated in this case. If no stent was implanted, treatment with Trombex is not indicated, and only Anopyrin 100 mg daily is administered.

5. Chronic forms of coronary artery disease without recently implanted stent

Anopyrin 100 mg daily is used indefinitely. Patients intolerant to aspirin can receive Trombex 75 mg daily.

6. Recently implanted stent (any indication, including ACS) in combination with any other condition (e.g., atrial fibrillation), which is an indication for oral anticoagulation (including patients already treated by anticoagulants)

Radial access is preferred. If INR ≥ 2.0, no periprocedural treatment with heparin is necessary. The interventional cardiologist can decide whether to administer eptifibatide. If there is a known indication for chronic anticoagulation, the patient should receive a bare-metal stent (not DES). The only exception (i.e., when DES can be implanted) is the case of PCI for in-stent restenosis in patients without known bleeding risks. The bleeding/thromboembolic risk ratio must be assessed.

If any type of stent is implanted and the indication to PCI is ACS, 6 months of dual therapy with Warfarin (INR 2.0–2.5) + Trombex 75 mg daily followed by monotherapy with Warfarin (INR 2.0–3.0) is indicated. If the indication for a bare-metal stent was chronic coronary artery disease, dual therapy of Warfarin + Trombex is indicated for up to 1 month, followed by monotherapy with Warfarin [4].

In patients taking chronic oral anticoagulation with a DES implant, the management of antiplatelet therapy is the same as in an ACS (6 months dual therapy with Trombex + Warfarin, followed by monotherapy with Warfarin).

Cave: In patients treated with combination Warfarin + antiplatelet drug, prevention of gastrointestinal bleeding using proton pump inhibitors is important. Omeprazole is less appropriate. Lansoprazole (Lanzul) or pantoprazole

(Nolpaza) is recommended; both drugs are approved in the Czech Republic.

7. Chronic coronary artery disease without recently implanted stent or other condition requiring oral anticoagulation

Warfarin, target INR 2.0–3.0. Anopyrin is not required.

8. Atrial fibrillation (AF) [3]

Thromboembolic risk (CHA_2DS_2-VASc – see http://www.mdcalc.com/cha2ds2-vasc-score-for-atrial-fibrillation-stroke-risk/) and bleeding risk (HAS-BLED – see http://www.mdcalc.com/has-bled-score-for-major-bleeding-risk/) should be assessed in every patient with atrial fibrillation. Decisions about long-term oral anticoagulation are based on these scoring systems – (see Table 3).

Table 3 – Long-term oral anticoagulation based on scoring systems for thromboembolic and bleeding risk calculation.

	HAS-BLED < 3	HAS-BLED ≥ 3
CHA_2DS_2-VASc 0	Without therapy or Anopyrin	Without therapy
CHA_2DS_2-VASc 1	Pradaxa or Xarelto or Warfarin	Anopyrin
CHA_2DS_2-VASc ≥ 2	Pradaxa or Xarelto or Warfarin	Individual decision

The patient needs to be informed about all issues (Warfarin vs. new anticoagulants), including practical aspects (INR, prices of drugs). The final decision of the patient has to be respected.

Dosing: Warfarin with target INR 2.5–3.5 (valve prosthesis in mitral position, recent pulmonary embolism and other high-risk conditions) or target INR 2.0–3.0 (most of the conditions when therapy with Warfarin is indicated) or target INR 2.0–2.5 (combination of Warfarin with an antiplatelet drug, low-risk atrial fibrillation, prior history of bleeding). Pradaxa 150 mg twice daily (most of the patients with atrial fibrillation indicated for treatment with Pradaxa) or 110 mg twice daily (patients with higher bleeding risk, – age over 80 years, use of verapamil, HAS-BLED score ≥ 3, creatinine clearance 30–49 ml/min). Xarelto 20 mg once daily or 15 mg once daily in higher-bleeding-risk patients (HAS-BLED score ≥ 3 and/or creatinine clearance 30–49 ml/min.). Pradaxa and Xarelto are not recommended in patients with creatinine clearance < 30 ml/min.

9. Acute pulmonary embolism

Thrombolysis administered in one dose t-PA 100 mg i.v. for 30–120 min is indicated in massive pulmonary embolism (severe dyspnea with hemodynamic instability, right ventricle larger than left ventricle by echocardiography). The speed of infusion is regulated by the clinical condition of the patient: patients in most critical conditions require a faster infusion. This form of one-dose thrombolysis needs to be considered also in situations when primary anticoagulation treatment with heparin (UFH/Clexane) does not lead to remission of dyspnea, tachycardia, and hypoxemia and to normalization of right ventricle size. ***Prolonged thrombolysis:*** Streptokinase 500,000 IU bolus dose + subsequent infusion at 100,000 IU/h for 12–72 h should be considered in patients with unambiguously diagnosed (CT or pulmonary angiography) subacute (estimated time of duration: a few weeks) and very large pulmonary embolism (persisting dilatation of right ventricle). ***Parenteral anticoagulation***: Heparin or Clexane is indicated either after thrombolysis in case of massive pulmonary embolism or as a primary treatment in other forms of pulmonary embolism. The duration of parenteral treatment depends on the clinical condition of the patient: switching to Warfarin can be started after remission of all symptoms (complete relief from dyspnea), full hemodynamic stabilization and normalization of right ventricle size (in cases where the right ventricle was not dilated before the recent episode of pulmonary embolism). Dosage of Clexane: 1 mg/kg s.c. twice daily (12 h). Dosage of heparin: bolus dose 80 IU/kg (bolus dose is not administered after thrombolysis), followed by infusion of 18 IU/kg/h, with the dose titration speed according to aPTT (target values 65–85 s).

Peroral anticoagulation is initiated after complete stabilization of the patient and normalization of echocardiography findings. If Warfarin is used, its initial dose is 10 mg daily, followed by 5 mg daily. Daily control of INR should be performed. As soon as INR reaches 2.5, Heparin or Clexane is discontinued. Patients with a primary history of pulmonary embolism are treated with Warfarin for up to 6 months (in patients with high bleeding risk, 3 months is satisfactory) with target INR 2.0–3.0. If the patient has a history of pulmonary embolism, or the patient has a thrombophilic condition and high risk of thromboembolic events and does not have a high bleeding risk, Warfarin should be administered indefinitely. After discontinuation of Warfarin, treatment with Anopyrin should be considered for the next 3–6 months.

10. Deep vein thrombosis without pulmonary embolism

Initial treatment with UFH 80 IU/kg i.v. bolus dose followed by continuous infusion of UFH 18 IU/kg/h (target aPTT 60–80 s), or Clexane 1 mg/kg s.c. every 12 h. Treatment with Warfarin can be started 1 or 2 days after initiation of parenteral anticoagulation. Principles of peroral anticoagulation are the same as in the case of pulmonary embolism. If Xarelto is used, the initial dose for the treatment of deep vein thrombosis is 15 mg 2× daily for the first 3 weeks, followed by 20 mg once daily. The duration of anticoagulation therapy in deep vein thrombosis is based on the same principles as in pulmonary embolism. After discontinuation of treatment with Warfarin, treatment with Anopyrin should be considered for the next 3–6 months (Table 4).

Table 4 – Absolute contraindications of thrombolysis in massive pulmonary embolism.

Prior history of hemorrhagic stroke or stroke of unknown etiology
History of ischemic stroke in previous 6 months
CNS damage or neoplasia
Large surgery/injury/cranial injury in previous 3 weeks
History of gastrointestinal bleeding in previous month
Known bleeding

11. Stroke (including TIA)

Treatment of stroke is managed by the neurologist. In case of hemorrhagic stroke, it is managed in cooperation with the neurosurgeon. Severe or moderate acute ischemic stroke (NIHSS ≥ 8) is treated depending on CT findings and the time interval between the onset of stroke and execution of CT. Ischemic strokes lasting less than 3 h are treated by catheterization intervention (thrombectomy or angioplasty), or in the case of immediate inaccessibility of catheterization (less than 30 min from CT), strokes are treated by thrombolysis (0,9 mg/kg rt-PA in an infusion lasting 60 min). Upon appropriate CT findings (judged by the neurologist), catheterization intervention can be performed up to 6 h after the start of the stroke. In severe strokes affecting the catchment area of the vertebral artery or the basilar artery, intervention can be considered up to 8 h after the start of the symptoms. In the case that stroke occurs during cardiac or other vessel catheterization as an unexpected complication of the procedure, immediate angiography is indicated (with no previous CT examination), and if thromboembolic obstruction is confirmed, urgent intervention for the obstruction follows. Mild strokes (NIHSS < 8) are usually treated conservatively – always after consultation with the neurologist. Secondary prevention after stroke is individual and depends on CT findings and on the probable etiology of the ischemic stroke (cardioembolization vs. arterial thrombosis). Anopyrin, Aggrenox, Trombex and Warfarin (alternatively Xarelto or Pradaxa) are the drugs of choice. The particular therapy and dosage is always indicated by the neurologist.

12. Coronary artery bypass graft surgery with no further indication for anticoagulation therapy

Administration of acetylsalicylic acid (100 mg daily) can be initiated 12–24 h after a surgery and should continue indefinitely. Patients intolerant to ASA can receive Trombex 75 mg daily. In a case the indication for CABG was acute coronary syndrome, dual antiplatelet therapy (acetylsalicylic acid 100 mg/day and Trombex 75 mg/day) is indicated for up to 12 months.

13. Coronary artery bypass graft surgery with indication for anticoagulation therapy

Clexane s.c. should be administered starting 1 day after surgery at a maximal dose of 0.5 mg/kg 2× daily (e.g., 60 kg = 2× 0.3 ml). Starting 2 days after surgery, Warfarin is added (men 5 mg/day, women 3 mg/day). When Warfarin is at an effective level (INR > 2.0), Clexane is discontinued. Simultaneous treatment with acetylsalicylic acid 100 mg/day can be considered.

14. Discontinuation of antiplatelet or anticoagulation therapy before coronary artery bypass graft surgery

Elective indication (code C): All antithrombotic drugs (Warfarin, clopidogrel, acetylsalicylic acid) are discontinued 7 days before surgery. Indication during the same hospitalization as coronary angiography (code B): Warfarin and clopidogrel are discontinued at the moment of indication for surgery; acetylsalicylic acid is discontinued if the patient is free of chest pain for more than 3 days. Urgent indication (code A): Warfarin and clopidogrel are discontinued at the moment of indication; treatment with acetylsalicylic acid can continue until surgery. In patients with an effective level of antiaggregation therapy, administration of tranexamic acid (and thrombocyte concentrate) is indicated before surgery. If the indication for operation is acute coronary syndrome, treatment with Heparin or Clexane continues until surgery. Importantly, Heparin cannot be discontinued in unstable patients – there is a risk of rebound phenomenon and myocardial infarction right before surgery.

15. Aortic valvuloplasty or aortic valve replacement using bioprosthesis

Patients with no risk factors (atrial fibrillation, history of thromboembolic event, left ventricle dysfunction, thrombophilia) are treated only with antiplatelet therapy: acetylsalicylic acid (100 mg daily). In case of the presence of risk factor(s), Clexane + Warfarin are indicated [5].

16. Mitral valvuloplasty or mitral valve replacement using bioprosthesis

Anticoagulation therapy using Warfarin up to 3 months with target INR 2.0–3.0 is indicated [5].

17. Valve replacement using metallic valve prosthesis

Clexane s.c. is administered starting 1 day after surgery with a maximal dose of 0.5 mg/kg 2× daily (e.g., 60 kg = 2× 0.3 ml). Starting 2 days after surgery, Warfarin is added (men 5 mg/day, women 3 mg/day). When Warfarin is at an effective level (INR > 2.5), Clexane is discontinued. Target values of INR are 2.5–3.5 [5].

18. TAVI

ASA 100–200 mg/day indefinitely and Trombex 75 mg/day up to 6 months after the procedure. Trombex 300 mg loading dose 1 day before the procedure.

Notes on the new antithrombotics

Prasugrel (Efient) is contraindicated in patients with prior history of stroke or TIA and in patients with severe hepatic damage (Child-Pugh C). Prasugrel is not recommended in patients ≥ 75 years old. The dose of Efient in the maintenance phase of treatment in patients with weight < 60 kg is reduced to 5 mg daily. The recommended time of discontinuation of Efient before elective surgery is 7 days.

Ticagrelor (Brilique) is contraindicated in patients with prior history of intracranial bleeding and in patients with moderate and severe hepatic damage. The recommended time of discontinuation of Brilique before elective surgery is 7 days.

Dabigatran (Pradaxa) is not recommended in patients with severe renal failure (CrCL < 30 ml/min). Patients with elevation of liver enzymes to more than twice the upper limit of normal have been excluded from clinical trials investigating the prevention of stroke and systemic embolization in patients with atrial fibrillation. This lack of ex-

perience with treatment of this subpopulation is a reason why Pradaxa is not recommended in this case.

Rivaroxaban (Xarelto) is not recommended in patients with severe renal failure (CrCL < 30 ml/min). This drug is contraindicated in patients with liver disease connected with coagulopathy and clinically relevant bleeding, including patients with liver cirrhosis (Child-Pugh B and C).

References

[1] P.G. Steg, S.K. James, D. Atar, et al., ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation, European Heart Journal 33 (2012) 2569–2619.

[2] C.W. Hamm, J.P. Bassand, S. Agewall, et al., ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation, European Heart Journal 32 (2011) 2999–3054.

[3] A.J. Camm, P. Kirchhof, G.Y.H. Lipp, et al., Guidelines for the management of atrial fibrillation, European Heart Journal 31 (2010) 2369–2429.

[4] W. DeWilde, T. Oirbans, F. Verheugt, et al., WOEST: first randomised trial that compares two different regimens with and without aspirin in patients on oral anticoagulant therapy (OAC) undergoing coronary stent placement (PCI). http://www.escardio.org/congresses/esc-2012/congress-reports/Pages/708-2-WOEST.aspx

[5] A. Vahanian, O. Alfieri, F. Andreotti, et al., Guidelines on the management of valvular heart disease (version 2012), European Heart Journal 33 (2012) 2451–2496.