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Přehledový článek | Review article

Novel TAVI designs

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ARTICLE INFO

Article history:
Received: 14. 12. 2016
Accepted: 12. 1. 2017
Available online: 20. 2. 2017

Klíčová slova:
Transkatétrová implantace aortální chlopně
Závažná aortální stenóza

SOUHRN

V současné době se stále objevují nová a nová technická řešení srdečních chlopní pro transkatétrovou implantaci aortální chlopně (TAVI). Od doby, kdy byla v randomizovaných studiích představena metoda TAVI s použitím chlopní první generace, byl zaznamenán obrovský technický pokrok s různými vylepšeními, jež umožnila dosáhnout vynikajících krátkodobých a střednědobých hemodynamických výsledků při – do velké míry – minimální aortální regurgitaci a většinou nulovém reziduálním gradientu, což umožnilo provádět u podstatné většiny pacientů výkon femorálním přístupem. Ve snaze zvýšit komfort operatéra umožňují nové konstrukce umělých chlopní vrátit je v případě dislokace do žádoucí polohy, případně je přesně umístit na první pokus, a zvýšit tak bezpečnost pacienta již bezprostředně po výkonu. Protože se s probíhajícími a budoucími studiemi tyto technické vymoženosti stanou dostupnými pro širší spektrum pacientů, je třeba věnovat maximální pozornost dlouhodobé trvanlivosti chlopní, snad i jejich další miniaturizaci (zvláště pro výkony s použitím jiného než femorálního přístupu), vývoji ještě „uživatelsky přátelštějších" zařízení pro instrumentální uzávěr (v jedné době), optimální antikoagulaci po výkonu, případně ochraně mozku a dalším zdokonalením, jež umožní dále snížit nutnost kardiostimulace.

Keywords:
Severe aortic stenosis
Transcatheter aortic valve implantation

ABSTRACT

"Novel" TAVI valves is a rapidly developing area. Since concept of TAVI was resolutely established in randomised trials with first generation valves, there was tremendous engineering development and finesse, enabling to achieve excellent acute and mid-term haemodynamic result with largely minimal aortic regurgitation, typically no residual gradient and miniaturisation enabling substantial majority of patients to be treated via transfemoral approach. To ease operator comfort designs enable reposionability or one attempt precision increasing acute safety. As current and future trials will bring this technology to broader spectrum of patients group, vigilance is required re long-term durability of valves, possibly further miniaturisation, especially for non transfemoral access, development of yet user friendly closure devices (single step), optimal anticoagulation post procedure, eventually cerebral protection and modification designs to further reduce requirement for cardiac pacing.

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DOI: 10.1016/j.crvasa.2017.01.014

Please cite this article as: J. Kovac, et al., Novel TAVI designs, Cor et Vasa 59 (2017) e42–e50 as published in the online version of *Cor et Vasa* available at http://www.sciencedirect.com/science/article/pii/S0010865016301588

Aortic stenosis is the most common valvular heart disease of adults in the Western world. When it is severe and symptomatic, it carries a poor prognosis. Conservative management of the condition has 5-year survival rates comparable to lung cancer [1,2]. Yet, a large cohort of patients – especially of older age – were denied surgical aortic valve replacement (SAVR) on the basis of their high predicted peri-procedural risks.

Trans-catheter aortic valve implantation (TAVI) has now matured to provide these patients with an effective treatment option. The technology has created a paradigm shift similar to that seen with the introduction of percutaneous coronary angioplasty in the late 1970s/early 1980s. Following the first reported implants (Cribier, 2002), TAVI devices have been used in patients with severe aortic stenosis deemed to be at high surgical risk, with suitably-sized aortic root anatomy and vascular access (femoral, subclavian, apical, aortic, carotic, caval).

The initial data from pivotal safety trials led to CE-mark approval and the world-wide marketing of the first two commercial devices (Medtronic-CoreValve and Edwards-Sapien) in 2007. The clinical results and long-term performance of these 2 devices and their later iterations (e.g. the Partner I and II Edwards and the CoreValve group of studies) formed the evidence base of current recommendations [3], and supported the initial use of TAVI for inoperable and high-risk surgical patients. Subsequently, newer TAVI technologies (Boston Scientific, St. Jude Medical, Symetis, Direct Flow Medical) have been shown to be safe and effective in industry-sponsored multi-centre observational studies, and national and international registries. There are also several novel designs that are predominantly used in the markets of Asia, predominantly in China (Lifetech-Venus and Microport).

As evidence in initial clinical trials has been very favourable (in comparison to medical/conservative therapy in inoperable patients, and also in comparison to surgery in high risk surgical candidates), TAVI was accepted and widely adopted as the therapy of choice in such patients groups.

Current clinical trials have since moved to studies comparing TAVI to SAVR in "medium" risk patients (Partner III, Surtavi, UKTAVI), and there are also studies designed investigating lower risk groups (Medtronic), as well as several studies comparing valves between each other (e.g. CoreValve vs Lotus, CoreValve, SAPIEN vs Direct Flow).

From the early development of TAVI technology, engineering and manufacturer challenges concentrated on the technical capability of implanting a preloaded biological valve through the arterial vasculature, ideally via a transfemoral approach. Leading centres, in collaboration with manufacturers and regulators, gained practical experience in the technique of implantation through various anatomies, acquiring "tips and tricks" with accumulated experience to overcome the limits of technology, as well as maximising safety of the procedure. Manufacturers developed the size ranges to cater for majority of anatomies.

Throughout developing these prostheses, all parameters and standards were derived from industry standards for surgical bioprosthetic valves (Fig. 1).

Fig. 1 – Accelerated wear testing

Key 4 principles for aortic valve prostheses [3]:
- predictable procedure,
- low rate of complications,
- optimal haemodynamics,
- durability.

- **Allow optimal forward flow**
  - **Minimize transvalvular gradient**
  - **Avoid turbulance**
  - **Obtain largest possible functional valve diameter**
- **Avoid back flow**
  - **Optimal leaflet coaptation**
  - **Consistent leaflet coaptation**
- **Cope with back slam**
  - **Optimize load absorption**

Fig. 2 – Surgical tissue valve design challenges

- Valve compression
- Valve expansion
- Sutureless anchoring
- Avoid migration
- Mitigate para-valvular leak
- Rotational valve orientation (avoiding coronaries)
- Dynamic valve positioning and placement
- Space saving challenge

Fig. 3 – Additional TAVI valve design challenges

All valves undergo testing based on CE mark requirements (5 million cycles during accelerated wear testing – Figs. 2, 3).

There are additional engineering challenges resulting from the requirements for valve preparation/loading, valve leaflet exposure during travel through challenging anatomies. There are broad sizing requirements (to match population sizes of annuli), whilst minimizing delivery catheter diameter to enable utilisation of a transfemoral approach wherever possible, which has proven to be the safest one (Fig. 4). Furthermore there might be additional testing of the frame (up to equivalent of 10 years *in vivo*).

- Medtronic Evolut R
- Medtronic CoreValve
- Edwards SAPIEN XT
- Edwards SAPIEN S3
- Boston Scientific Lotus
- Boston Scientific Lotus Edge
- Direct Flow Medical
- Symetis Accurate
- Symetis Accurate Neo
- Abbott/St. Jude Medical Portico

Fig. 4 – TAVI valves commercialised in Europe 2016

Since the first commercial exploitation of TAVI procedures (following first CE marking approval, subsequently FDA and Japan approval), there have been a few important factors contributing to improvement of outcomes and widespread safe and effective application of this therapy worldwide.

Challenges observed in "first generation" valves were at least partially addressed in further generations of TAVI valves, as well as through accumulated confidence and experience of operators.

1. Engineering (miniaturization or ingenious ways of valve loading such as within-body loading of balloon expandable valves, reposionability, ease and stability of implant to improve accuracy of positioning, skirts to prevent paravalvular leak, broadening of valve size range enabling treating large as well as small anatomies [valve in valve]), development of dedicated wires, closure devices).
2. Industry standards in heart teams training unification, patient selection and proctoring.
3. Individual operator and implant team experience.
4. Heart/TAVI team experience in patient selection, procedural performance and post procedural care, surgical standard in outcome measurement and complication standardisation.

1. Engineering
a. novel generations/iterations of established TAVI prosthesis (CoreValve Evolut, Edwards SAPIEN);
b. early generation designs (Portico, St. Jude);
c. novel designs – Boston Scientific – Lotus, Lotus Edge, Direct Flow Medical and Symetis)
d. adjacent procedural devices (femoral closure devices – Proglide, Prostar, cerebral protection devices, trialled apical closure devices).

2. Stringent criteria were applied by companies for clinical and anatomical selection of suitable patient anatomies for these implants. Adherence to these, inclusive of validation by the company specialists, was/is a prerequisite for implantation in an individual centre, at least during the training and proctorship phase.

3. Individual operator and TAVI team experience--strict adherence to surgical criteria for success [4]. Complications were defined in a standardised way (VARC2) [5].

4. While there is convincing evidence of TAVI utility in inoperable and high risk surgical group, there is still limited longer term follow-up. Therefore emphasis is on a multispeciality team assessment of the patient and his anatomy, as well as on performance of these procedures. Selection criteria are twofold; there are 1. clinical aspects and 2. anatomical aspects for patient selection. This multidisciplinary group should consist of multiple specialities – cardiac surgeons, imaging and interventional cardiologists and a cardiac anaesthetist. For frailty and general patient assessment a geriatrician is also desirable.

Currently marketed (CE mark) valves in Europe are summarised in Figure 4.

Direct Flow Medical (DFM)

Direct Flow is a non-metallic expandable valve with an implant technique somewhat different from other mainstream TAVI valves (Figs. 5, 6). Following good balloon aortic valvuloplasty (mandatory prerequisite), the loaded valve is passed inside the delivery sheath, placing its distal end beyond the aortic annulus. The sheath is then retracted to free the rings. Both rings are inflated with saline/contrast to verify that whole valve is below the native annulus. The aortic (upper) ring is then deflated. While the bottom ring remains inflated in the ventricle, the valve is

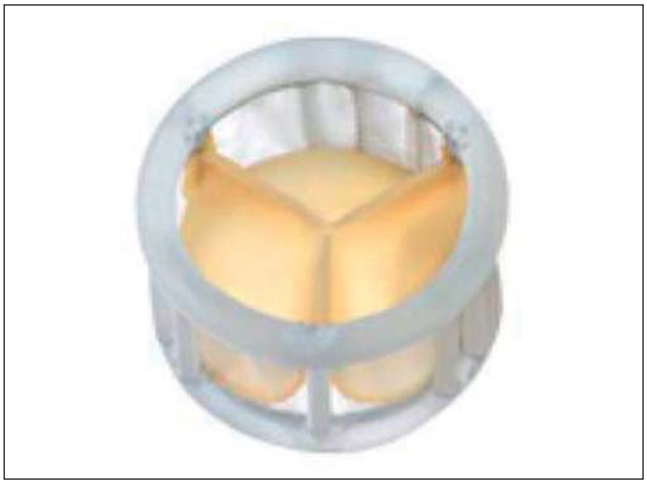


Fig. 5 – Direct Flow Medical

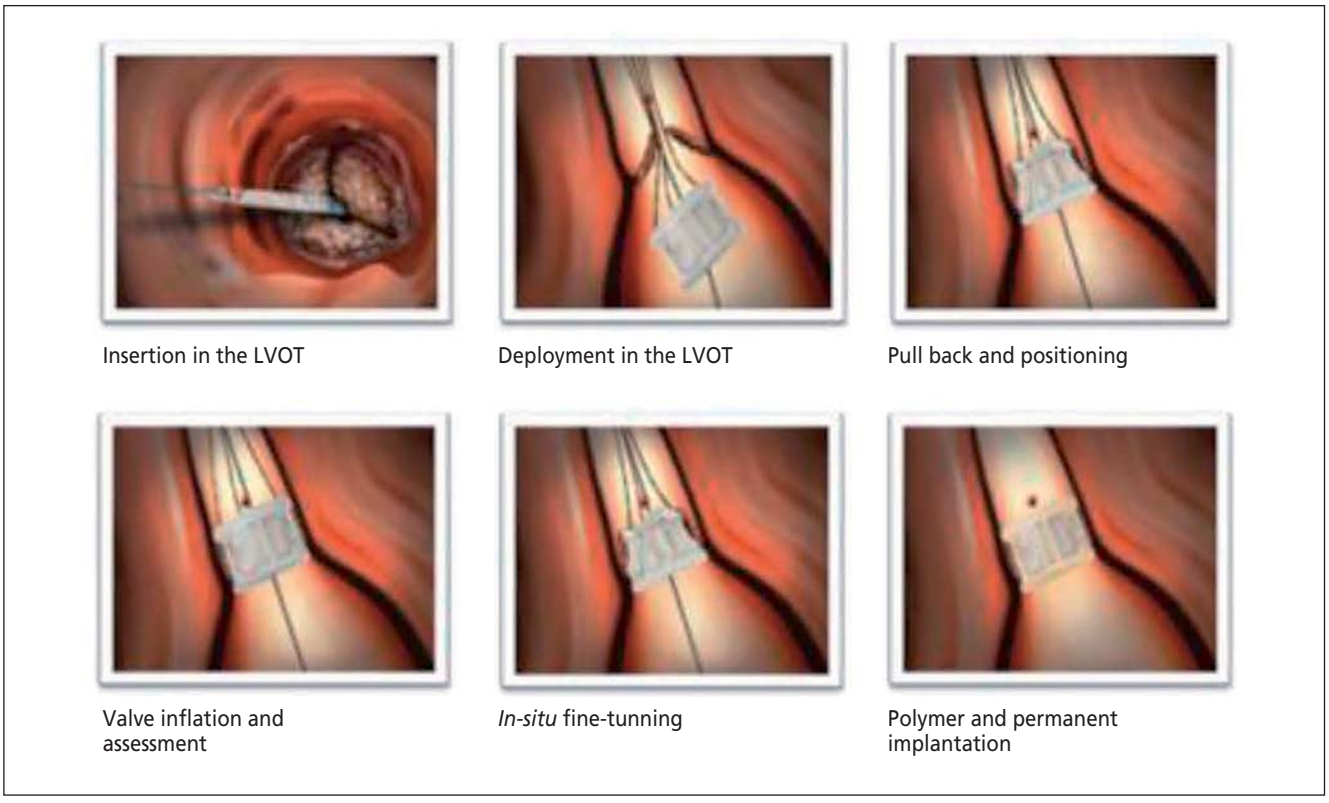


Fig. 6 – Direct Flow Medical Valve implant procedure

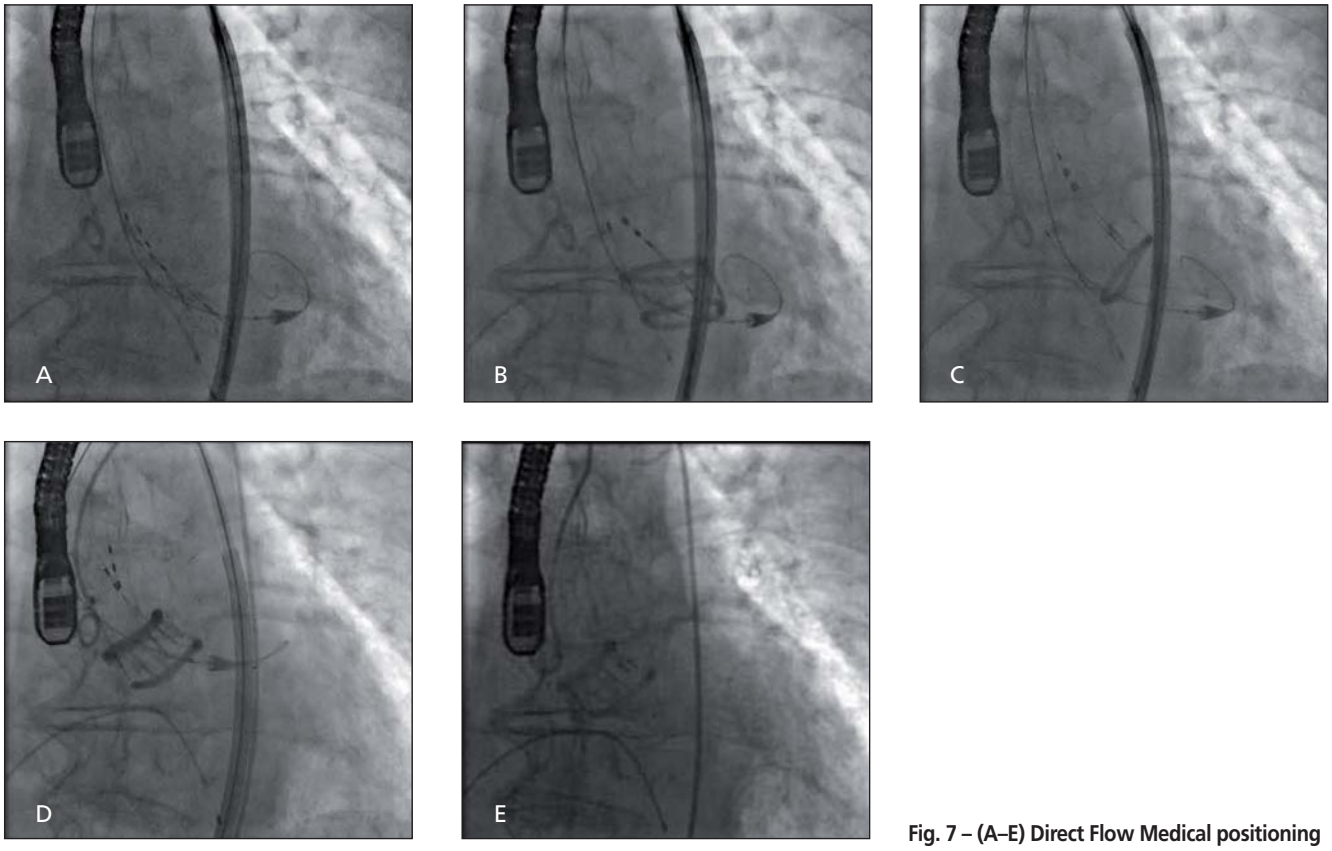
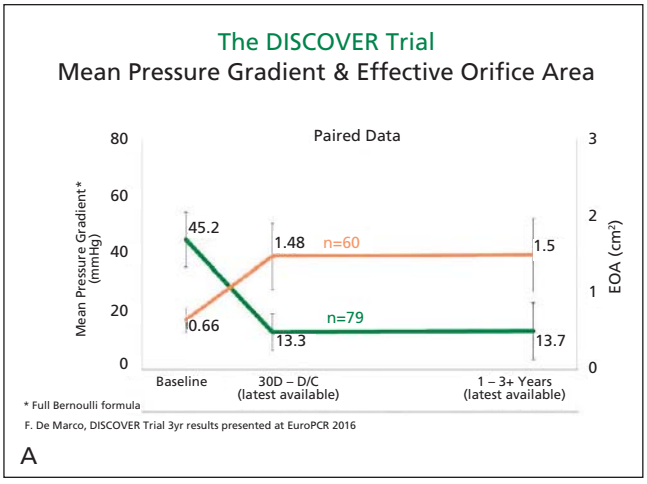


Fig. 7 – (A–E) Direct Flow Medical positioning

then pulled via 3 wires/rods using the inner curve technique, where the inner part of the ring is pulled first (pic). The distal ring is gradually pulled back with a careful pull of the 3 delivery wires in succession to maintain a good alignment into a good sub annular position. Once the ventricular ring is snugly against the aortic valve, the ring in the supra annular position is inflated with the saline/contrast mixture (Figs 7A–7E). While the valve is still attached to its delivery system, angio, echo and haemodynamic assessment (via nosecone lumen) is possible to verify the correct position (ventricular pressure is obtained, so simultaneous haemodynamic is possible while valve is still attached to the delivery catheter). A polymer syringe and relief valve are then attached and the polymer replaces the radiopaque solution. This fixes the valve (by the rings hardening) immediately. Following that rings are detached by unscrewing the positioning wires. Attention must be paid during implantation that the inflated bottom ring does not slip above the annulus, as the valve would need to be retrieved. One advantage of this design is typically no interruption of cardiac output there and implantation itself does not require rapid pacing. Process of inflation/deflation of the rings with saline/contrast can be repeated (as long as bottom ring remains below the annulus) until optimal position is achieved.



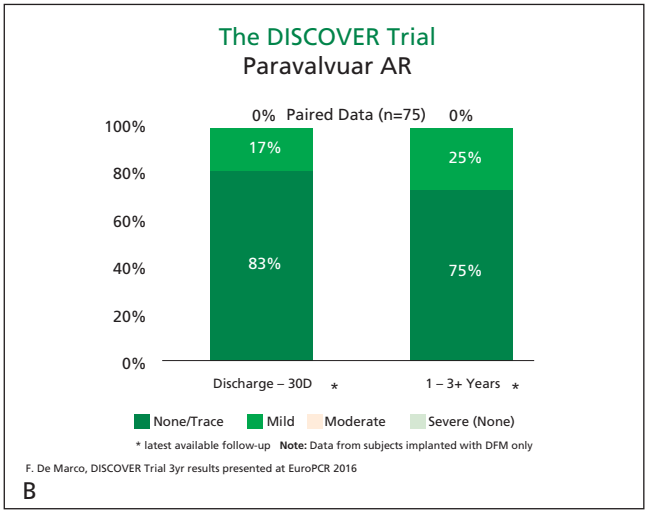


Fig. 8 – (A,B) Direct Flow Medical DISCOVER Trial

Fig. 9 – Symetis valve family

Typically a potential advantage of this valve design is no interruption of cardiac output and implantation itself doesn't require rapid pacing.

DFM evidence [6,7]

Summary of acute haemodynamic results from pivotal trial is shown in Figures 8A, 8B.

Direct Flow initial single arm feasibility trial in Europe called DISCOVERY included 100 patients in single arm [7]. The principal clinical characteristic was a EuroSCORE more than 20. This was followed by the EU DISCOVERY registry, which enrolled 503 patients in a single arm. Currently enrolling is the US pivotal trial SALUS, which randomizes 2:1 DFM vs S3 and Corevalve Evolut R, with planned enrolment of 648 patients. There is established on-site training and a proctor led certification programme in Europe and around the world.

Symetis Accurate and Accurate Neo [9]

Symetis group of valves is self-expandable bioprosthetic valve with a specific feature of release from top (aortic portion, Fig. 10) to bottom-annular/subannular portion as fundamental difference to other self-expanding valves.

Valve is produced in 2 designs – 1. for transapical delivery (Symetis Accurate, with CE mark received in 2011)

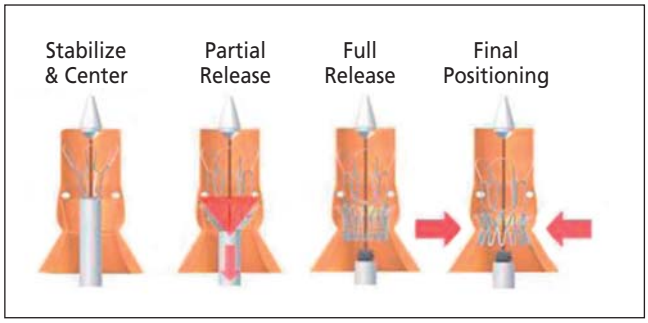


Fig. 10 – Symetis release concept (TA)

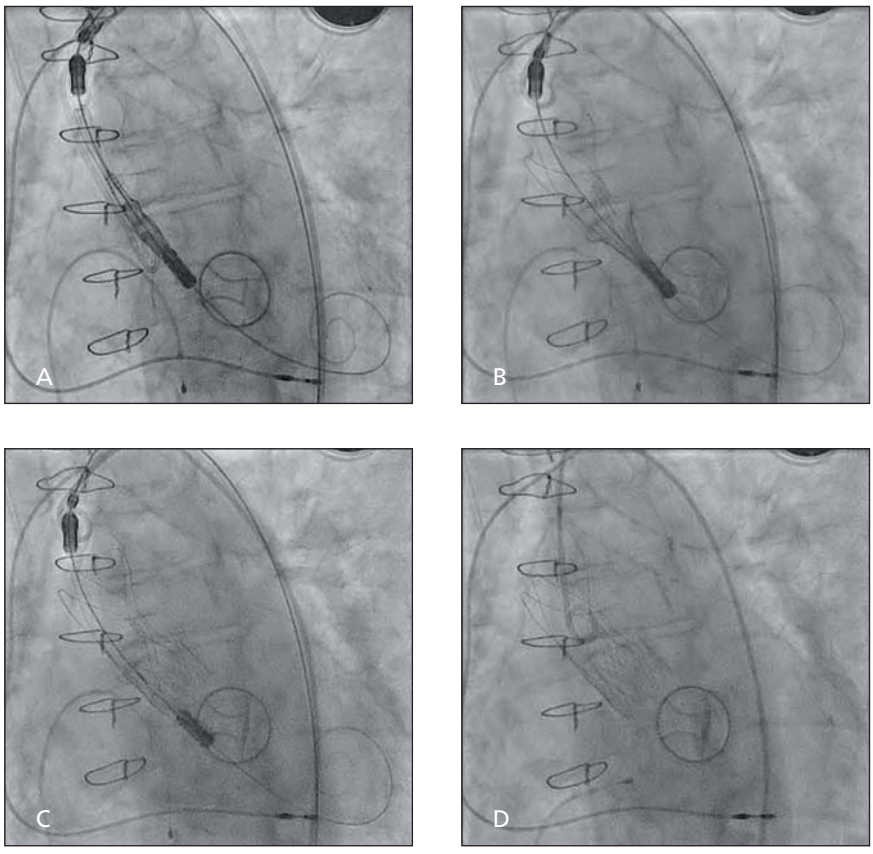


Fig. 11 – (A–D) Gradual Symetis Accurate TF release (top to bottom)

and 2. Symetis Accurate Neo for transfemoral implant, CE mark received in 2014.

A self-expanding nitinol stent, a valve made of three non-coronary native porcine leaflets and a polyethylene terephthalate (PET) skirt sutured onto the inner and the outer surface of the nitinol stent.

The stent geometry allows for anatomically aligned intra-annular fixation in a subcoronary position. Each of the three stent segments presents a distinctive function. The distal stent segment is made of three connected stabilization arches to facilitate commissural alignment and to prevent tilting. In a two-step deployment technique, the second stent segment – the upper crown – is deployed above the annular plain and during gentle retraction pulled until the upper crown hooks into the distal annulus. Aided by tactile feedback, the lower skirt is released. The central stent segment with a waist geometry 'sandwiches' the aortic valve annulus and anchors the valve safely at the intended target location (Figs. 11A–11D).

Currently exists in 3 sizes (marked S, M, L) and can be implanted into annuli sizes 21 mm to 27 mm. The most characteristic aspects of the bioprosthesis design are the self-alignment and self-centring features that allow for optimal positioning of the valve, better sealing and reduction of the paravalvular leak rate. Potential advantage is the possibility to implant the device in highly calcified annuli without paravalvular regurgitation and an extremely low risk of annular rupture as well as to safely anchor the device in annuli without or with minimal calcium load.

Another advantage is the downward encroachment of the calcified leaflets that may better prevent coronary ostia occlusion through the calcified leaflets.

Symetis Evidence

Principal Haemodynamics acute results are shown in Figures 12A, 12B.

Transapical version has been used extensively and published data shown [9,10].

Transfemoral version is evidenced in published registries, (1000 patients enrolled in SAVI TF [Symetis ACURATE neo™ Valve Implantation using TransFemoral Access]). The registry was presented at PCR 2016 [11].

Implant success was 98.7%, 30-day mortality 1.3%, 30-day stroke 1.9%, post procedural mean EOA 1.8 cm^2, 95.9% of implants had aortic regurgitation grade 1 and less. One-year data are expected at next year meetings.

Venus Medtech (Venus-A valve/ Venibri-A valve)

Originating in China, Venus Medtech has produced a self-expanding nitinol frame porcine pericardial leaflet prosthesis (Fig. 13) for emerging markets and completed in 2015 the first pivotal trial for TAVI in China. The platform is based on a self-expanding hour-glass morphology stent frame design with some key differences to other designs

A **SAVI TF 1 000**

Acute outcomes	Post-implant
Population [n]	1 000
Procedure success [n]	987 (98.7 %)
VinV	9 (0.9 %)
Conversion to surgery	3 (0.3 %)
Aborted procedure	1 (0.1 %)
* Device usage time [min:sec, mean ± SD]	6:34 ± 6.0
Deployed with rapid pacing [n]	487 (48.7%)

* Delivery system into sheath to delivery system removal post-implant

B **SAVI TF 1 000**

Performance	7 days
Population [n]	999*
Mean BP gradient [mmHg] *(n = 919)*	8.3 ± 4.0
Mean EOA [cm^2] *(n = 546)*	1.81 ± 0.5
PVL grade	*n = 966*
≤ Grade 1 (none to mild) [n]	926 (95,9 %)
Grade 2 (moderate) [n]	39 (4.0 %)
> Grade 2 [n]	1 (0.1%)

* One patient withdrew consent after treatment.

Fig. 12 – (A, B) Symetis Registry results

employed in Western countries; it has 3 markers 6 mm aortic to the device inflow, it has a higher radial force that was designed to address the excess calcification noted in the Chinese aortic stenosis population, its four sizes are presently 23 mm, 26 mm, 29 mm and 32 mm and it has a reinforced delivery capsule with a smoother inner wall designed for easier loading and more stable device deployment; the device profile is 19 Fr but is performed sheathless which often facilitates device delivery in femoral vessels below 6 mm in the absence of significant calcification.

A recent iteration has been facilitated by a joint venture collaboration with Colibri (a company specializing in dry leaflet technology) and the resultant product (Venibri-A) has the same frame, leaflet and delivery system design as Venus-A but dry leaflets which facilitates a pre-crimped, packaged and sterilized system. The dry tissue technology has no residual gluaraldehyde residue and is hoped to improve device durability but currently facilitates an immediate off-the-shelf product that requires no device loading and a few seconds of device preparation (comprising only flushing of the delivery system). The device has been deployed in a first-in-human in South America recently with 2 successful implants with deployment time only 15 and 16 minutes respectively from device opening.

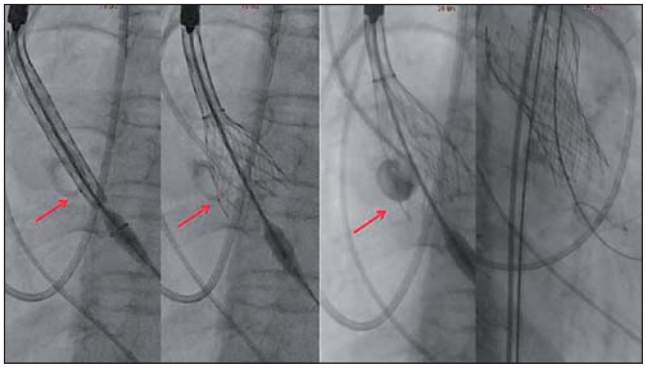


Fig. 13 – Venus valve implant

Venus evidence

The Venus A trial recently completed 1-year follow-up and the data has been submitted for publication and for device approval with the Chinese FDA. Between September 2012 and January 2015, 101 patients were treated in China. The study included a large proportion of bicuspid aortic valve (BAV) disease (almost a half), an anatomy that was observed frequently in China [12]; other differences noted in the Chinese TAVI population relative to the Western TAVI populations included smaller iliofemoral access, more frequent BAV anatomy (although this may be driven by age, non-raphe, also known as Sievers type 0 morphology predominated in contrast to the raphe-type morphology that dominates in the West) and considerable excess of valvular calcium volume in both tricuspid and BAV morphologies [12].

In the Venus-A trial employed 86.1% transfemoral and 13.9% transaortic approach. At 30 days, mortality was 5.3% and stroke/TIA 0%. Valve function and cumulative survival at 6 months was similar in tricuspid and BAV morphologies (6-month survival 96.2% with tricuspid and 90.9% with BAV, p=0.29).

Conflict of interest

Jan Kovac is a proctor to Direct Flow, Medtronic, Boston Scientific, Edwards Lifesciences. D. Chin is a proctor to Boston Scientific. J. Baron has no conflict of interest. H. Jilaihawi is a consultant to Venus Lifetech.

Funding

No funding provided for this article.

Ethical statement

Authors adhered to institutional ethical standards.

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