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DOUBLE EDITORIAL

Transcatheter aortic valve implantation: the evidence is catching up with reality

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This editorial refers to 'Transcatheter aortic valve implantation: early results of the FRANCE (FRench Aortic National CoreValve and Edwards) registry'†, by H. Eltchaninoff *et al.* on page 191 and 'Transcatheter aortic valve implantation: first results from a multi-centre real-world registry'‡, by R. Zahn *et al.* on page 198

Degenerative aortic stenosis has become the most common valve disease in Europe and the USA due to prolonged life expectancy and associated degenerative effects on cardiac structures. It is caused by an active pathobiological process which entails chronic inflammation with lipoprotein deposition, osteoblast activation, and extracellular calcification with bone formation.[1] Progressive valve obstruction due to immobilized leaflets results in pressure overload, which in turn leads to left ventricular hypertrophy, collagen deposition, relative ischaemia, and diastolic dysfunction with pulmonary congestion (*Figure 1*). For several decades, surgical aortic valve replacement (SAVR) has been considered the gold standard in the treatment of symptomatic patients, resulting in effective symptom relief and near normalization of prognosis.[2]

In the search for less invasive treatment modalities, the concept of transcatheter implantation of heart valves was pioneered in experimental models by Henning Andersen[3] for the aortic and Philipp Bonhoeffer[4] for the pulmonary position, followed by the first percutaneous human implant of an aortic valve prosthesis by Alain Cribier[5] in 2002. Since then, transcatheter aortic valve implantation (TAVI) has revolutionized the management of patients with severe aortic stenosis, with >10 000 implants performed to date. The enthusiasm generated by TAVI relates to the simple but convincing concept, a technique easily adopted by interventional cardiologists, and a large unmet clinical need. While SAVR, in analogy to most other medical procedures (i.e. percutaneous coronary interventions), slowly progressed from low to higher risk patient populations, the evolution of TAVI took the opposite course, with early candidates being high risk surgical patients with relevant co-morbidities judged to be 'inoperable'. The reproducible safety and efficacy data in published series of these unfavourable patient populations (*Table 1*) not only increased confidence in the technique but also established a novel, valuable treatment option in the sizeable group of symptomatic patients with severe aortic stenosis previously denied access to treatment. Against this background, it is natural that indications will be tested in less complex patient populations in the future, and TAVI enters into competition with SAVR. In response to these developments, the scientific community takes on the responsibility of defining the framework, including unified clinical outcome definitions, rules of data collection and validation, standardized echocardiographic assessment, and design of appropriate registries and randomized trials.

Eltchaninoff *et al.*[6] and Zahn *et al.*[7] publish the results of two moderate to large-scale national registries on TAVI in Europe in this issue. Somewhat different in size, both registries have an almost similar enrolment period starting in early 2009, are industry independent, report data on both commercially available devices, the Edwards Sapien balloon-expandable prosthesis (23 and 26 mm prosthesis with 22–24 F delivery sheath) and the Medtronic CoreValve self-expanding device (26 and 29 mm prosthesis with 18 F delivery sheath), and include all presently established access options, namely the transfemoral, transapical, and trans-subclavian access sites. Patients included in the registries were mainly octogenarians with a high prevalence of coronary and peripheral vascular disease, previous cardiac surgery in a quarter of patients, and a history of stroke in every 10th patient. Both studies corroborate the results of previous reports (*Table 1*) in a real-world population of consecutive patients within their respective countries, demonstrating a technical success rate of 98–99%, similar 30-day mortality of 12%, and an incidence of stroke of 3–4%.

What can we learn from these two studies? First, TAVI is associated with a high technical success rate using both devices in appropriately selected patients, and conversion to open surgery is exceedingly rare. However, it would be misleading to conclude that these procedures can be performed safely at sites without cardiac surgery. A collaborative approach between invasive

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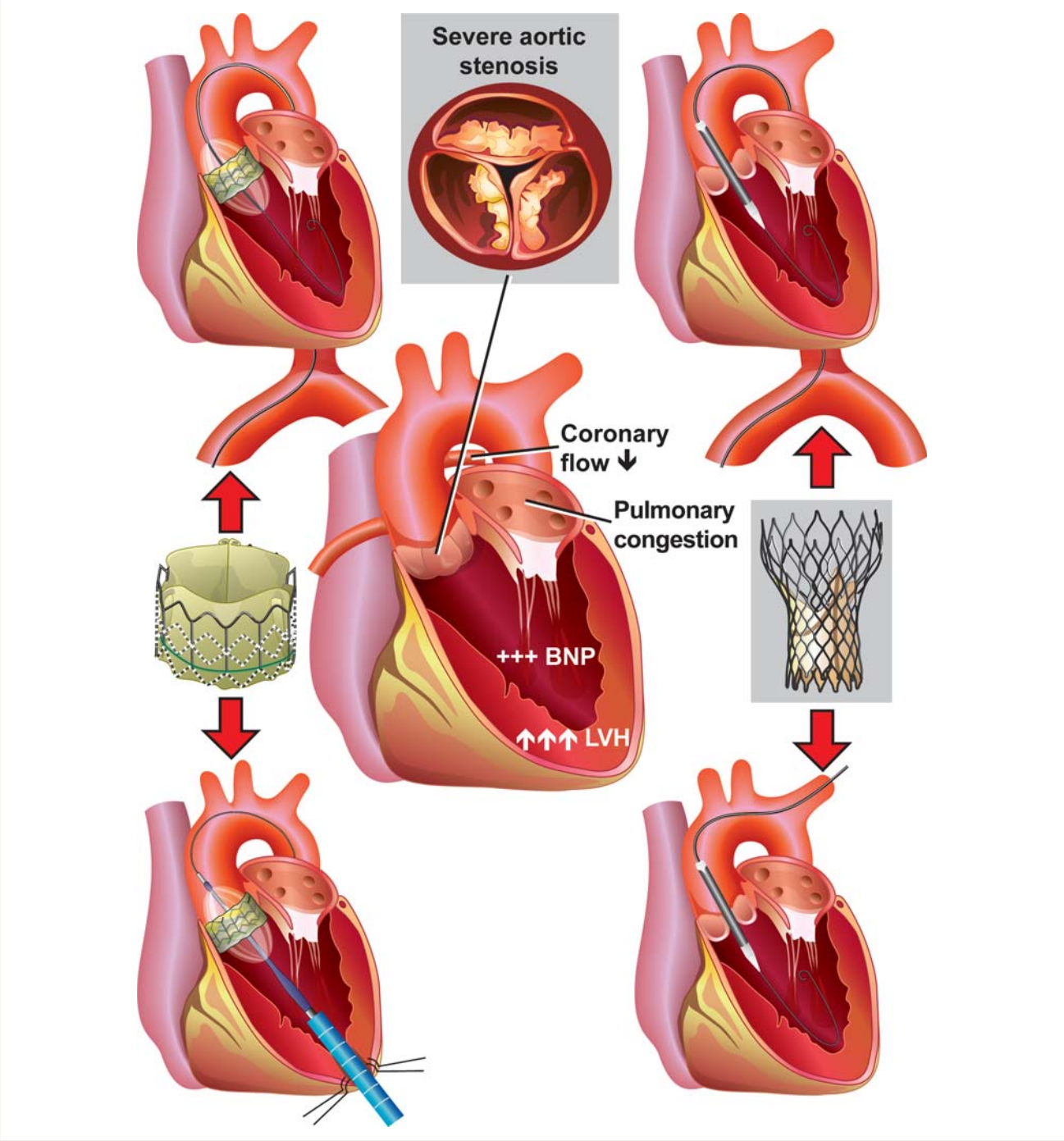

Figure 1 Centre: severe calcific aortic stenosis causes pressure overload followed by left ventricular hypertrophy, collagen deposition, relative ischaemia, and diastolic dysfunction with pulmonary congestion. Left top: transfemoral TAVI with implantation of the Edwards Sapien prosthesis. Left bottom: transapical TAVI with implantation of the Edwards Sapien prosthesis. Right top: transfemoral TAVI with implantation of the Medtronic CoreValve prosthesis. Right bottom: transsubclavian TAVI with implantation of the Medtronic CoreValve prosthesis.

cardiologists and cardiac surgeons is of paramount importance for the overall success of any TAVI programme. It not only provides a safety net, but also safeguards against inappropriate patient selection and promotes discussion within the heart team, adds the tremendous expertise of cardiac surgeons to the treatment of complex patients with non-isolated aortic stenosis, and frequently involves a team approach during the procedure itself. In addition, the full exploitation of various access routes including the transapical and transsubclavian sites makes the involvement of cardiac surgeons invaluable. Secondly, the 30-day mortality of 12% in both registries remains high. Although these figures may compare favourably with expected mortality derived from the EuroScore

Table 1 Demographics and outcome data of published single- and multicentre registries of TAVI using the Edwards Sapien and Medtronic CoreValve prostheses

	Year of publication	Type of TAVI	Study design	Device	Total patients, *n*	Age, years	Logistic EuroScore, %	Procedural success, %	Procedural mortality, %	30-day mortality, %	30-day stroke, %
Lichtenstein *et al.*	2006	TA	Single centre	Edwards	7	80 ± 7	35	100	–	14	0
Cribier *et al.*	2006	TF	Single centre	Edwards	36	80 ± 7	~27	75	7.4	22.2	3.7
Webb *et al.*	2006	TF	Single centre	Edwards	18	80 ± 7	26.2 ± 13.1	77.8	0	11.1	–
Grube *et al.*	2006	TF/TS	Single centre	CoreValve	25	80 ± 7	11	84	–	20	12
Walther *et al.*	2007	TA	Multicentre	Edwards	59	80 ± 7	27	93.2	13.6	13.6	3.4
Webb *et al.*	2007	TF	Single centre	Edwards	50	82 ± 7	28	86	2	12	4
Grube *et al.*	2007	TF/TS	Multicentre (2)	CoreValve	86	82 ± 6	21.7 ± 12.6	88	6	12	10
Svensson *et al.*	2008	TA	Multicentre	Edwards	40	80 ± 7	35.5	90	22.5	17.5	0
Piazza *et al.*	2008	TF/TS	Multicentre	CoreValve	646	81 ± 7	23.1 ± 13.8	97	1.5	8	1.9
Grube *et al.*	2008	TF/TS	Single centre	CoreValve	136	82 ± 7	23.1 ± 13.8	–	0	10.8	2.9
Walther *et al.*	2008	TA	Single centre	Edwards	50	82 ± 5	27.6 ± 12.2	94	0	8	0
Webb *et al.*	2009	TF/TA	Single centre	Edwards	168	84	28.6	94.1	1.2	11.3	4.2
Himbert *et al.*	2009	TF/TA	Single centre	Edwards	75	82 ± 8	26 ± 13	93.3	–	10	4
Osten *et al.*	2009	TF/TA	Single centre	Edwards	46	80 ± 7	25.3	91	2.2	6.5	6.5
Thielmann *et al.*	2009	TF/TA	Single centre	Edwards	39	81 ± 5	44.2 ± 12.6	97	2.6	17.9	–
Bleiziffer *et al.*	2009	TF/TA/TS	Single centre	Edwards/CoreValve	203	81 ± 7	22 ± 14	–	–	11.2	7
Buellesfeld *et al.*	2010	TF/TS	Multicentre (2)	CoreValve	168	80 ± 7	23.8 ± 15.4	90.5	–	11.9[a]	–
Thomas *et al.*	2010	TF/TA	Multicentre (34)	Edwards	1038	80 ± 7	25.7 (TF)/29.1 (TA)	93.8	–	8.5	2.5
Rodés-Cabau *et al.*	2010	TF/TA	Multicentre (6)	Edwards	339	80 ± 7	–	93.3	1.7	10.4	2.3
Petronio *et al.*	2010	TF/TS	Multicentre (13)	CoreValve	514	83	20.1	98.6	0.8	5.4	1.8
Tchetche *et al.*	2010	TF	Multicentre (2)	Edwards/CoreValve	45	81.8 ± 4.2	25.2 ± 8.4	97.8	2.2	4.4	0

[a]In hospital.
TA, transapical; TAVI, transcatheter aortic valve implantation; TF, transfemoral; TS, transsubclavian.

and STS score as well as relative to the spontaneous clinical course in untreated patients, clearly efforts to reduce mortality further are needed. More than 80% of all reported deaths in these series occurred during the first week and were largely related to severe vascular complications. The advent of smaller introducer and delivery systems will undoubtedly reduce the incidence of these complications and the associated morbidity and mortality. As both registries included a considerable number of sites with no previous TAVI experience, it is likely that results will improve further in experienced centres with high procedural volume. The importance of the learning curve in reducing mortality has been previously shown in single-centre series using both the Edwards Sapien[8] and the Medtronic CoreValve prosthesis.[9] Thirdly, the incidence of atrioventricular conduction disturbances and the need for pacemaker implantation in 12–39% of patients is notable. The anatomic proximity of the AV node and His bundle to the valvular apparatus in conjunction with balloon- and device-mediated injury and inflammation explain the occurrence of this adverse event. In addition, device-specific differences come into play, with a higher incidence of conduction disturbances encountered with the Medtronic CoreValve prosthesis possibly related to a deeper extension into the left ventricular outflow tract as well as the self-expanding nature of its frame,[10] which may apply a higher radial force and tissue stress in the subannular region, particularly in the case of device–annulus mismatch. Notwithstanding, the threshold for pacemaker implantation varies widely according to clinical practice, as exemplified by a pacemaker rate of 5% in the French and 21% in the German registry following implantation of the Edwards Sapien prosthesis, which shows the need for widely accepted and uniform criteria on pacemaker indications after TAVI procedures. In addition, precautionary measures such as the depth of the implantation of the prosthesis, a less aggressive pre-dilatation regimen, and adequately sized devices will help to reduce the rate of permanent pacemakers. Fourthly, the haemodynamic short-term profiles of both prostheses are excellent and similar to surgically implanted valves in terms of transvalvular gradient as well as effective orifice area, and accompanied by symptomatic improvement and improved left ventricular function. Conversely, TAVI remains associated with more frequent paravalvular regurgitation as compared with SAVR whose long-term sequelae require careful study.[11] Fifthly, TAVI is a catheterization laboratory-based technique with more than two-thirds of procedures performed in this environment in the French registry. While some advocate hybrid operating suites as the optimal location to perform TAVI, reality as reflected in the French registry and future developments with smaller delivery systems may outpace institutional hurdles and cost-related delays in the timely establishment of other settings. Finally, TAVI is a highly versatile technique, which, by means of various access routes including the transfemoral, transapical, and transsubclavian site, allows for a broad clinical applicability in the majority of patients (*Figure 1*). Both devices play a complementary role and currently accommodate a valve annulus ranging from 19 to 27 mm largely independent of the take-off of the coronary arteries, and a wider range of device sizes will allow the indications to be extended to even smaller and larger aortic annuli in the near future.

There are several limitations which should be considered when interpreting the presented data. In both registries, the two devices as well as the access routes have been used according to the discretion of the operator, rendering the results of multiple fairly small subgroups less meaningful. Moreover, both registries report only short-term clinical outcome data at 1 month, which are important to define device safety, but are clearly insufficient to delineate the efficacy profile of this technology. In addition, the data assembled in both registries become outdated with the advent of new device iterations. The newest generation Edwards SAPIEN XT prosthesis has a lower profile (NovaFlex delivery system) and is delivered through 18/19 F sheaths. The next iteration of the Medtronic CoreValve device uses the Accutrak feature for improved stability upon device placement. Finally, the lack of data monitoring, independent event adjudication, differences in event reporting as well as inconsistent outcome definitions provide additional sources of relevant bias. Future studies in the field of TAVI will benefit from the consensus on standardized outcome definitions, the results of which are published in this issue by Leon and colleagues[12] and have been assembled under the umbrella of the Valve Academic Research Consortium (VARC) representing several Academic Research Organizations, Surgical and Cardiological Professional Societies, members of the US Food & Drug Administration, and independent experts. This achievement must be followed by properly conducted randomized clinical trials comparing TAVI with the established gold standard therapy of SAVR before further expanding the indications for TAVI towards lower risk patient populations.

TAVI has led to a paradigm shift in the management of patients with aortic stenosis at high risk for SAVR. Its full potential will unfold during the upcoming years of continued technical refinements and clinical investigation. The intense research activities including numerous TAVI registries, ongoing randomized clinical trials, and efforts such as VARC are taking place during a period where this technology is still in its infancy. They are the foundation of what may evolve into a field of unprecedented wealth and quality of clinical research, guiding physicians in the selection of the most appropriate treatment for their patients.

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CARDIOVASCULAR FLASHLIGHT

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Double orifice mitral valve with normal function: an echocardiography and MRI study of a rare finding

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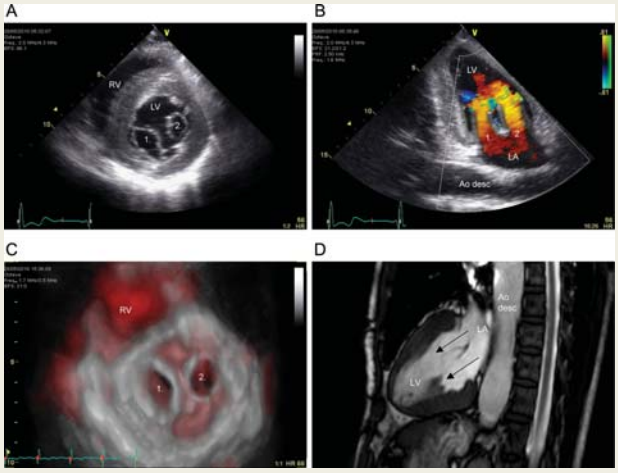

Double orifice mitral valve (DOMV) is a rare congenital lesion often associated with other abnormalities such as bicuspid aortic valve or aortic coarctation. Also abnormalities of the subvalvular apparatus such as malformation of chordae tendineae (abnormal attachment, parachute type, etc.) and papillary muscles are found frequently. The atrio-ventricular connection consists of two anatomically distinct orifices separated by accessory fibrous tissue. In about 50% of DOMV cases, valvular function is normal, others present with stenosis or regurgitation. In most cases (~85%), a larger orifice is accompanied by a small eccentric accessory orifice, 15% (see our case) show duplicated mitral valves (MVs). Embryologically, the lesion results from abnormal leaflet fusion and persistence of the left part of the common atrio-ventricular canal.

We present a 59-year-old male patient with DOMV and coexisting stenotic bicuspid aortic valve, a low gradient aortic coarctation, and normal MV function. Parasternal 2D cross-sectional echocardiography (*Panel A*) demonstrates two MV orifices (1./2.), a modified apical four-chamber view shows four leaflets and two separated diastolic left ventricular inflow jets (*Panel B*). Three-dimensional echocardiography (*Panel C*) and MRI imaging in the two-chamber view (*Panel D*, Supplementary material online, *Video S1*) confirmed the central fibrous bridge dividing the atrio-ventricular orifice. The mild aortic coarctation is demonstrated in Supplementary material online, *Video S2*.

In cases of severely dysfunctional DOMV with stenosis or regurgitation, surgical intervention is recommended. In cases with normal MV function, surgical therapy is eventually necessary to repair the associated cardiac lesion. In our patient, aortic valve replacement and closure of a coexisting ASD were performed uneventfully.

RV, right ventricle; LV, left ventricle; LA, left atrium; Ao desc, aorta descendens.

Supplementary material

Supplementary material is available at *European Heart Journal* online.