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EDITORIAL

Expansion of transcatheter aortic valve implantation: new indications and socio-economic considerations

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This editorial refers to 'Annual number of candidates for transcatheter aortic valve implantation per country: current estimates and future projections'[†], by A.P. Durko *et al.*, on page 2635.

Transcatheter aortic valve implantation (TAVI) entered the limelight more than a decade ago as a life-saving treatment option among inoperable patients with severe, symptomatic aortic stenosis.[1] Consistent data in terms of safety and efficacy of TAVI compared with surgical aortic valve replacement (SAVR) in several randomized controlled trials across the risk spectrum propelled the rapid expansion of TAVI to elderly patients at intermediate and high risk for SAVR. The innovation related to TAVI ignited an unprecedented interest in the field of valvular heart disease, created a momentum for transcatheter structural interventions, challenged cardiac surgery, and catalysed the formation of specialized heart teams.

Aortic stenosis is the most common valvular heart disease requiring intervention in high-income countries, ranging from 3.4% [95% confidence interval (CI) 1.1–5.7%] to 12.4% (95% CI 6.6–18.2%) in the elderly population ≥75 years of age according to severity of disease,[2] and accounts for the highest valve-related mortality in the USA.[3] In low- and middle-income countries, data on the prevalence of degenerative valvular heart disease in the ageing population are scarce and outnumbered by reports on the prevalence of rheumatic valvular disease at the opposite end of the age spectrum.[4] However, a shift in the age distribution towards the elderly and a transition from rheumatic to degenerative valvular heart disease in low- and middle-income countries let us anticipate a further increase in the global burden of aortic stenosis.[5]

In this issue of the *European Heart Journal*, Durko and colleagues present a systematic review and meta-analysis estimating the number of patients with severe, symptomatic aortic stenosis that may be potentially eligible for TAVI in the European Union and North America based on data from 37 studies including >26 000 patients.[6] The study refines the estimates reported in a previous publication by the same group of authors.[2] Interestingly, fewer than two-thirds of patients with severe, symptomatic aortic stenosis that were not eligible for SAVR actually underwent TAVI. The authors estimate that annually 180 000 patients in the European Union and North America may qualify for TAVI according to current guidelines, and anticipate an increase up to 270 000 patients per year with expansion of TAVI to low-risk patients.

Based on these data, it is of interest to analyse the forces that will lead to further expansion of TAVI in multiple directions at variable speed driven by different circumstances. First, a continuous improvement in procedural and long-term outcomes across all risk categories facilitated the dispersion of TAVI into the low-risk segment of elderly patients. This progress was related to the mitigation of the risk of paravalvular aortic regurgitation and the lower profile of newer generation transcatheter heart valves, as well as improved technique and the more frequent use of the transfemoral access site (*Figure 1*). Of note, while estimated risk in randomized controlled trials as assessed by the Society of Thoracic Surgeons (STS) score continuously decreased from 11.8% in the Placement of AoRTic TraNscathetER Valve (PARTNER) 1A trial to 2.9% in the Nordic Aortic Valve Intervention (NOTION) 1 trial, the mean age decreased only slightly, ranging from 83.6 years in PARTNER 1A to 79.2 years in NOTION I (*Figure 1*).[7,8] The ongoing PARTNER-3 (NCT02675114), NOTION-2 (NCT02825134), and the Evolut R low risk (NCT02701283) trials will cumulatively enrol ∼3500 patients with STS scores <4 (<3 for ELRT) into randomized controlled trials comparing TAVI with SAVR, and will provide a solid basis of evidence for the outcomes of TAVI among low-risk patients.

Secondly, TAVI is increasingly performed among patients with off-label indications such as bicuspid aortic valve anatomy,[9] failed surgical bioprostheses,[10] and pure native aortic valve regurgitation.[11] In a

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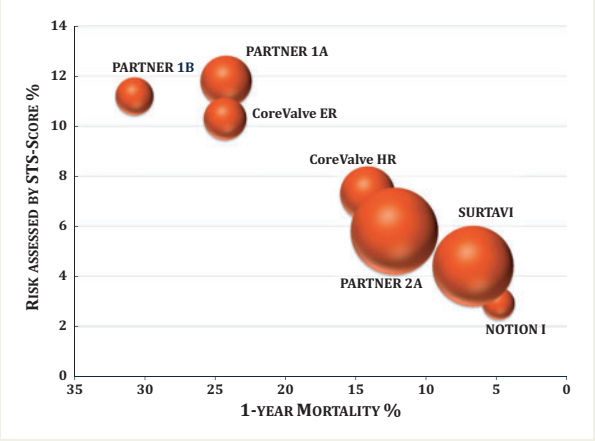


Figure 1 Expansion of TAVI towards the low-risk spectrum in randomized controlled trials. Risk as assessed by the STS score is shown on the *y*-axis and observed 1-year mortality is shown on the *x*-axis. The size of the circles correlates with the number of patients included in the randomized controlled trial.

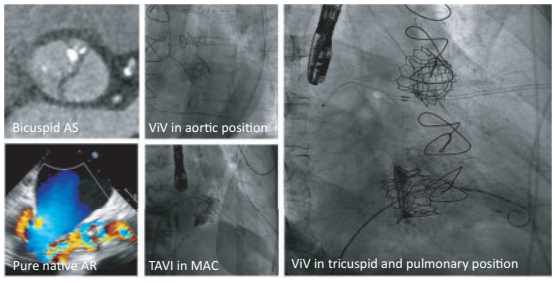
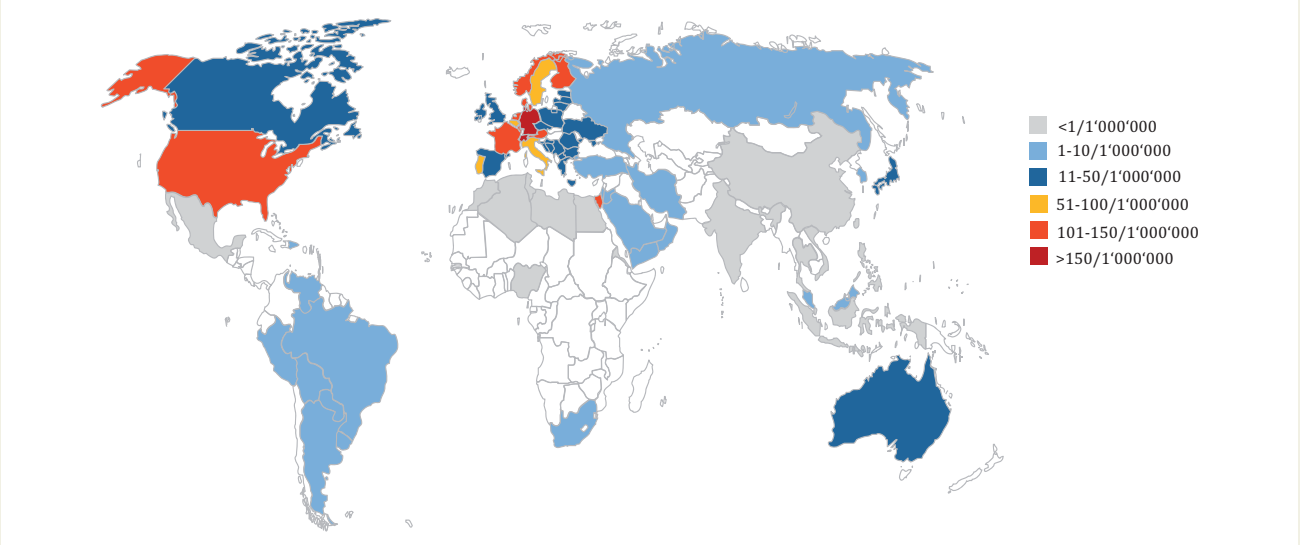


Figure 2 Expansion of TAVI towards off-label indications: bicuspid aortic stenosis, valve-in-valve in aortic position, pure native aortic regurgitation, TAVR in mitral annular calcification, and valve-in-valve in the tricuspid and pulmonary position.

propensity score-matched analysis of 546 matched pairs of patients with bicuspid and tricuspid aortic stenosis, bicuspid aortic stenosis conferred a higher risk of conversion to surgery (2.0% vs. 0.2%, P = 0.006) and a lower device success rate (85.3% vs 91.4%, P = 0.002); however, among the subgroup of patients treated with newer generation devices, clinical event rates were comparable with those with tricuspid valve anatomy.[9] The multinational valve-in-valve registry including 459 patients with degenerated surgical bioprostheses reported a 1-year survival rate of 83.2% after valve-in-valve TAVI. Bioprosthetic valve stenosis was associated with a three-fold increased risk of mortality as compared with regurgitation, and small surgical bioprostheses (≤21 mm) doubled the risk of mortality at 1 year.[10] In a multicentre registry of 331 patients with pure native aortic valve regurgitation undergoing TAVI, all-cause mortality at 1 year amounted to 24.1% and was determined by the extent of residual aortic regurgitation (AR ≥moderate 46.1% vs. AR ≤mild 21.8%, log-rank P = 0.001). The risk of device embolization was significantly lower in patients treated with newer as compared with early generation devices (12.7% vs. 24.4%, P = 0.007).[11] In addition to the above-mentioned indications, transcatheter aortic valve devices have been successfully used for the treatment of degenerated mitral valve prostheses and failed annuloplasty rings,[12] as well as mitral annular calcification (*Figure 2*). At the same time, optimal timing of TAVI is re-evaluated in randomized controlled trials. The EARLY TAVR trial investigates TAVI for asymptomatic severe aortic stenosis compared with watchful waiting (NCT03042104), while the TAVR UNLOAD trial (NCT02661451) assesses the impact of TAVI in patients with moderate aortic stenosis and heart failure with reduced ejection fraction as compared with optimal heart failure therapy alone.

Thirdly, the projections provided by Durko and colleagues raise the question of geographical and socio-economic inequalities in access to and utilization of TAVI worldwide. An analysis from 11 European countries in 2011 showed a variation in TAVI procedures between 6.1 in Portugal and 88.7 per million in Germany, and suggested a significant correlation between TAVI use and healthcare spending per capita.[13] TAVI expansion seems to follow a gradient of



Take home figure Geographical dispersion of TAVI. TAVI implantation per 1 000 000 inhabitants. Estimates for Q1–Q4 2017 (Western Europe) or Q4 2016–Q3 2017 (all other regions) including moving annual total (MAT) data. Data are subject to end of year adjustment. Source: BIBA Medical.

prosperity and healthcare spending, while remaining inaccessible to the majority of patients with severe, symptomatic aortic stenosis worldwide. The rapid expansion of TAVI into the low-risk patient population and off-label indications in selected countries contrast with the low penetration of TAVI outside of North America and Western Europe (*Take home figure*). Differences in the access to medical innovation result from economic constraints, social values, and political processes.[14] More than half of all surgical procedures globally are performed in high-income countries, whereas four out of five deaths from cardiovascular disease occur in low- and middle-income countries.[15,16] Challenges in the expansion of valvular interventions to less privileged regions of the world include awareness and education, absence of resources for diagnosis and referral, lack of infrastructure, competing health priorities, and extortionate costs.[14] Strategies to advance TAVI in these settings need to respect the local context and include the education of physicians and healthcare personnel, the access to affordable devices, and promotion of a minimalistic strategy.[14] Disparities in the implementation of TAVI inspired the 'valve for life' initiative launched by the European Association of Percutaneous Cardiovascular Intervention of the ESC in 2015. The initiative aims to raise awareness of valvular heart disease, improve educational standards for healthcare professionals and specialists, and attenuate disparities in access to care across Europe.[17]

Geographic dissemination of valvular heart disease treatment to less privileged regions of the world and strategies for equitable access and utilization to commensurate treatment may in fact represent yet another frontier of the TAVI revolution.

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