Aortic valve replacement in younger adults: a biological valve is not the logical choice

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This editorial refers to ‘Aortic valve replacement with mechanical vs. biological prostheses in patients aged 50–69 years’, by N. Glaser et al. on page 2658.

Since the Veterans Affairs landmark randomized trial on heart valve replacement with mechanical vs. bioprosthetic valves reported their long-term results, guidelines for aortic valve replacement (AVR) have recommended the use of mechanical valves in patients younger than 60 years of age and the use of bioprosthetic valves in patients above the age of 65 or 70 years, depending on the European or North American guidelines, respectively, with a grey area from 60 to 65–70 years in which both valves can be considered. However, despite these recommendations, studies on trends of mechanical and bioprosthetic valve implantations have found increasingly higher usage of bioprosthetic valves, particularly in patients aged 55–70 years. The evidence base to support lowering of the age cut-off for implanting bioprosthetic valves is limited and this increase is therefore potentially concerning. The susceptibility for bioprosthetic valve failure is particularly prominent in younger patients and may be related to higher rates of mortality during long-term follow-up.

There is a constant debate regarding whether mechanical or bioprosthetic valves should be used in patients aged 50–70 years. The choice of implanting a bioprosthetic over a mechanical valve is particularly influenced by (i) the risk of stroke and bleeding related to the thrombogenicity of mechanical valves and the use of oral anticoagulation; (ii) the perceived lower risk of valve dysfunction with newer bioprosthetic valves as compared with older ones; and (iii) reductions in operative complications, including mortality, of reoperations that renders such procedures a less important outcome to consider. However, although these arguments hold true, strong evidence favouring use of bioprosthetic over mechanical valves in younger patients is not available. An analysis of nearly 40 000 patients from the Society of Thoracic Surgeons database in the USA clearly demonstrated that survival was better with bioprosthetic valves in patients aged 75–80 years, but patients with mechanical valves had improved survival if aged 65–75. As a matter of fact, there are no studies that report a benefit in terms of survival with bioprosthetic valves, while there are several studies showing a survival benefit with mechanical valves. Only one randomized trial was performed with 310 patients aged 55–70, which found no difference in the rate of mortality at a mean follow-up of 13 years.

In addition to this underpowered analysis, several conflicting reports from observational studies have been published. Two very recent propensity-matched analyses found that survival was comparable between the types of valves. McClure et al. reported a single-centre analysis of 722 propensity-matched patients younger that 65 years and a mean age of 53 who were followed for a median of 6–7 years. Survival after bioprosthetic and mechanical valve implantation was 78% vs. 79% at 10 years, respectively, and 65% vs. 75% at 15 years, respectively (P = 0.75). Chiang et al. analysed 2002 patients aged 50–69 years from the New York State registry and followed these patients for a median of 10.8 years. At 15 years, survival was 60.6% in the bioprosthetic valve group and 62.1% in the mechanical group (P = 0.74). Unfortunately, these studies did not include a propensity-matched analysis according to age groups.

In the current issue of the journal, Glaser et al. report an analysis of the Swedish national SWEDEHEART registry with 4545 patients aged 50–70 who underwent isolated AVR between 1997 and 2013. The authors were able to report 15-year follow-up and demonstrated that unadjusted survival was significantly improved in patients receiving a mechanical vs. a bioprosthetic valve (16% vs. 20%, respectively; hazard ratio (HR) 1.67, 95% confidence interval (CI) 1.44–1.94). Because of severely different baseline characteristics between the groups, the authors performed more rigorous analyses and found that the results were consistent in a multivariable propensity score-adjusted model (HR 1.30, 95% CI 1.09–1.56) as well as in an analysis of 2198 propensity-matched patients (HR 1.34, 95% CI 1.09–1.66). Further propensity-matched analyses provide important information to substantiate risk–benefit ratios of mechanical vs. bioprosthetic valves by reporting a similar risk of stroke (5.8% vs. 6.1%, respectively; HR 1.04, 95% CI 0.71–1.50), a higher risk of aortic valve reoperation for patients with a bioprosthetic valve (2.2% vs. 5.2%, respectively; HR 2.36, 95% CI 1.42–3.94), and a...
higher risk of major bleeding for patients with a mechanical valve (9.6% vs. 4.9%, respectively; HR 0.49, 95% CI 0.34–0.70).

The findings of Glaser et al. have several important implications for everyday clinical practice by producing evidence that may have a significant impact on decision-making. They stress the importance of age by reporting a propensity-matched subgroup analysis that is unprecedented in other studies. The analysis showed a significant interaction ($P = 0.04$), with patients aged 50–59 years having an improved survival with mechanical valves (HR 1.67, 95% CI 1.06–2.61), while patients aged 60–69 years had no survival difference between mechanical and bioprosthetic valves (HR 1.08, 95% CI 0.85–1.36). Although there may well be a treatment–age interaction for secondary adverse events as well, no data on secondary endpoints were available in these age categories; therefore it is not possible to produce substantiated risk–benefit ratios beyond mortality.

One of the strengths of this study is that it is a nationwide analysis that reflects a true real-world experience with diverging treatment and follow-up strategies among centres, increasing the generalizability of the data. Furthermore, the study spans a long inclusion of patients up to 2013 during which contemporary valve designs were used, although follow-up with the latest valves is relatively short. An additional strength is the reliability of the data that were collected using multiple nationwide databases for all the necessary information, providing a high rate of complete clinical follow-up and ensuring that few events were missed. Unfortunately, no data on the cause of death were available from these databases. The finding that mechanical valves were only shown to have a survival benefit in terms of all-cause death but not cardiovascular death raises some doubts about the definition of cardiovascular death that was applied in the database. There is no clear rationale for higher rates of non-cardiovascular death in patients with mechanical valves, and a previous study showed that the distribution of causes of death is similar for patients receiving mechanical and bioprosthetic valves. Therefore, all-cause death as the primary endpoint remains the least biased endpoint and should be considered the leading analysis of the study.

Despite these convincing data, the final chapter on mechanical vs. bioprosthetic valves for young adults has not yet been written. In the era of transcatheter aortic valve implantation (TAVI) in which the number of implants is exponentially growing, it will be interesting to see how valve-in-valve procedures in degenerated bioprosthetic valves will change long-term mortality after initial AVR. Many surgeons will become more reluctant to perform high-risk reoperations when patients can undergo TAVI with lower procedural complications and excellent long-term results. However, the interest in TAVI has recently taught us that anticoagulation therapy also significantly reduces the risk of stroke in patients with bioprosthetic valves who have reduced leaflet motion, potentially warranting more routine use of anticoagulation associated with major bleeding, diminishing the major benefit of bioprosthetic over mechanical valves. A large observational study demonstrated that patients with bioprosthetic valves had improved outcomes if anticoagulation therapy was prolonged. On the other hand, new oral anticoagulants may also change the long-term risks associated with mechanical valves, although recent efforts have not yet been successful in reducing the risk of bleeding and stroke. Until these drugs do succeed, newly designed mechanical valves demanding lower international normalized ratio (INR) targets can be implemented to reduce the risk of bleeding at a comparable risk of thrombo-embolic complications. Alternatively, an INR target range of 1.6–2.1 via telemedicine-guided self-control has demonstrated a reduction of complications as compared with an INR target range of 1.8–2.8 in a large randomized trial. With lower INR targets, major bleeding events will probably have a less significant impact than the 30-day mortality rate of 13.2% in the study of Chiang et al. Considering an increasing life expectancy of patients, these

**Figure 1** Simplified decision-making based on age and the potential impact of new developments on the age threshold for implanting bioprosthetic valves. The age threshold should be 60 years of age as determined by Glaser et al., although a black-and-white cut-off is inadvisable, reflected by the overlapping grey arrows. The threshold may change by new developments for mechanical valves (left within green) and bioprosthetic valves (right within blue). With an increasing life expectancy of patients, the need for long-term anticoagulation therapy after bioprosthetic valve implantation may change the threshold to a higher age as the benefit of lower major bleeding may be diminished. INR, international normalized ratio; TAVI, transcatheter aortic valve implantation.
developments may potentially have an impact on the threshold for implanting bioprosthetic valves (Figure 1).

In conclusion, the study of Glaser et al. contributes significantly to the existing literature on mechanical vs. bioprosthetic valves by showing that patients above the age of 60 years may benefit from receiving a bioprosthetic valve, but supporting the notion that lowering the age for implantation of bioprosthetic valves to below 60 years is premature. New advancements may reduce the risk of adverse events and potentially mortality after both mechanical and bioprosthetic valve implantation. However, before significantly altering treatment strategies, an evidence base from randomized clinical trials is essential. Although recruitment in a trial comparing mechanical and bioprosthetic valves would be cumbersome because of strong patient preferences in favour of bioprosthetic valves, it is our duty as individual physicians as well as Heart Team members to provide full information to patients regarding their long-term risk—benefit ratio, which should include evidence of a survival benefit of mechanical valves in patients below 60 years of age.

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References