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INVITED COMMENTARY

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Critical appraisal of a registry study: aortic valve replacement in patients aged 50–69 years

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Life expectancy in patients after surgical aortic valve replacement (SAVR) is lower compared with the general population, and the loss of life expectancy is more pronounced in younger age groups [1]. Efforts to improve prognosis in these patients are therefore needed and welcome.

The optimal choice between mechanical and biological aortic valve prostheses in patients aged 50–69 has been debated [2], and results from prior studies investigating outcomes after SAVR in this age group showed contradictory results [3–5]. Some found no difference in mortality between the 2 groups [3] while others found a higher survival for patients with mechanical valve prostheses [4]. The results regarding bleeding and cerebrovascular outcomes have been more consistent. In previous studies, the rate of reoperation was higher in patients who received biological valve prostheses, whereas the rate of bleeding was higher in patients with mechanical valve prostheses; both expected findings [3–5]. Similarly, the rate of stroke was comparable in patients with mechanical and biological valve prostheses in previous studies [3, 4]. The ESC/EACTS and ACC/AHA guidelines recommend a mechanical valve prosthesis in patients aged <60 and <50 years, respectively, and a biological valve in patients aged >65 years [6, 7].

In this issue of the *EJCTS*, Vogt *et al.* [8] compared 5-year survival, the rate of reintervention and stroke in patients aged 50–69 years who underwent SAVR with either a biological ($n = 2239$) or a mechanical ($n = 807$) valve prosthesis between 2011 and 2012 with data from the German Aortic valve RegistrY. They used propensity score matching to control for differences between the groups (610 patient-pairs) and found a similar 5-year survival and rate of reoperation between the groups but a higher rate of disabling stroke in patients who underwent SAVR with a mechanical valve prosthesis.

The unexpected finding of a higher rate of disabling stroke in patients who had mechanical valves prompted the authors to highlight these results in their 'Take home message' and 'Central Illustration'. To critically assess the robustness of the conclusion made by Vogt *et al.* [8] that 'Patients with a mechanical prosthesis have a higher risk of immediate, short and midterm term stroke', several study aspects must be considered.

First, the way in which outcomes were measured affects the reliability and validity of a study. The authors state that stroke was self-reported by patients or their family members. The validity of the described procedure for outcome ascertainment was unknown or at least not reported. Therefore, the reader cannot assess the magnitude of measurement error or misclassification of outcome. Another limitation, acknowledged by the authors, was that it was not possible to distinguish between ischaemic and haemorrhagic stroke.

Second, the number of events (strokes), particularly in the propensity score-matched analysis, was low (3 vs 11 at 1 year and 9 vs 20 at 5 years in patients with biological and mechanical valves, respectively). From a statistical standpoint, this is an important weakness that readers should take into account when assessing the findings of the study.

Third, to better understand the underlying mechanism causing a stroke, it is important to consider the time point in relation to surgery. According to the 'Central Illustration', a large proportion of the strokes in the mechanical group occurred very early (intra- or perioperatively). Indeed, Table 3 shows the number of in-hospital strokes, 2 vs 8 in patients with biological and mechanical valves, respectively. This strongly suggests that surgical or perioperative factors, rather than the type of prosthesis, were the explanation for the higher stroke rate in patients with mechanical valves.

Based on the Kaplan–Meier estimation of cumulative survival and a stratified log-rank test in the propensity score-matched sample (Fig. 2), the authors conclude that there was no difference in survival (90.8% vs 87.9%; $P = 0.05$) between the 2 groups at 5 years of follow-up. Another way of looking at these data is to consider the trend that results in a survival difference of 3% at 5 years in favour of mechanical valves, a difference that may be clinically relevant in patients with an expected mean survival of

20–25 years [1]. To be clear, we do not believe that weak evidence suddenly becomes credible just because a *P*-value passes a certain threshold. Also, we do not advocate a superficial interpretation of a single statistic (i.e., the *P*-value) to assess a potential causal relationship by categorizing results into 'statistically significant' and 'statistically non-significant'.

Because study exposure (i.e. type of valve) was not allocated randomly, a major challenge in the process of estimating the association between valve group and outcomes was to control for the effects of other factors that simultaneously affect treatment choice and the outcomes. To address confounding, the authors used conventional methods involving propensity scores and matching. Table 1 indicates an acceptable balance on measured variables after matching. However, Fig. 2 shows that the 2 survival curves start to diverge already from the beginning, and at ∼3 months, there is a clear difference between the curves. This is a notable observation because no difference between the groups is expected that early after surgery. The very early separation of the curves in Fig. 2 is an indication of possible differences between the groups at baseline in terms of comorbidity or other factors associated with lower survival. The results may thus be unreliable or biased due to extensive residual or unmeasured confounding. For causal inference, it is crucial for researchers to navigate a wide range of phenomena to ultimately account for potential confounding when the aim is to provide patients and surgeons with evidence-based guidance before treatment decisions. For example, it is well recognized that there are differences in performance between different types of bioprostheses [9], and factors that affect the quality of the anticoagulation treatment may differ in patients with mechanical valves [10].

As all scientific papers, the study by Vogt *et al.* [8] has strengths and limitations, some of which are discussed in this commentary. The study findings must be interpreted with those weaknesses in mind, and based on these new data, changes in clinical practice are not justified in our opinion. We agree with current clinical guidelines that valve choice in this age group should be guided by individual patient factors and patient preference rather than by chronological age.

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