Commentary: The mid-life crisis of the meta-analysis

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The meta-analysis is 40 years old and having a mid-life crisis.¹ Conceived in the 1970s, the meta-analysis synthesizes studies to provide “best evidence” through systematic review, rigorous statistics, and formal protocols promoting reproducibility and reducing bias. However, success has not come without problems. A recent editorial in *Nature* observes: “One undesirable consequence of the growing recognition and high impact of meta-analysis is an increase in less-than-rigorous applications of these methods...Meta-analyses and systematic reviews can highlight areas in which evidence is deficient, but they cannot overcome these deficiencies—they are systematic and scientific techniques, not magical ones.”¹

Which brings us to the meta-analysis in this issue of the *Journal*, in which Diaz and colleagues² compare bioprosthetic with mechanical aortic valves in patients aged 50 to 70 years. The authors include 1 randomized and 4 observational studies encompassing 4686 patients, reporting a small survival advantage with mechanical valves.² Before recommending a mechanical aortic valve on the basis of these data, surgeons and cardiologists should consider these 3 points:

1. Current best evidence indicates no significant difference in long-term survival after bioprosthetic versus mechanical aortic valve replacement in patients aged 50 to 70 years.
2. Transcatheter valve-in-valve has lowered the risks associated with reintervention for bioprosthetic structural valve degeneration.
3. Stroke and bleeding carry substantial mortality and morbidity and remain commoner long term after mechanical than biological valve replacement.

The single randomized trial performed in this age-group showed no significant survival difference 15 years after bioprosthetic versus mechanical aortic valve replacement, findings confirmed by 2 large observational analyses in the *New England Journal of Medicine* and *JAMA* (Figure 1).³⁻⁵ These studies successfully address the inherent confounding bias arising when specific patient

Fifteen-year survival after bioprosthetic versus mechanical aortic valve replacement.

Central Message

In patients aged 50 to 70 years, either a bioprosthetic or mechanical valve replacement remains a reasonable choice.

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characteristics predict both the outcome and the choice of intervention—in this case shorter estimated life expectancy and noncompliance, both of which predict reduced survival and a bioprosthesis. Randomization is the most effective way of distributing these confounders evenly between comparison arms: consequently, a well-designed meta-analysis of randomized trials is “best evidence,” and synthesizing data from multiple randomized studies is a particularly valuable approach when the available trials are underpowered and inconclusive.

However, the study by Diaz and colleagues is a meta-analysis dominated by nonrandomized studies,

FIGURE 1. Fifteen-year survival in 2002 propensity-matched patients aged 50 to 69 years after bioprosthetic versus mechanical aortic valve replacement.⁴ HR, Hazard ratio; CI, confidence interval.

mostly limited by confounding bias favoring mechanical valves. In addition, the authors chose not to include relevant, well-designed studies such as the *New England Journal of Medicine* analysis. Consequently, their meta-analysis results are unreliable. Perhaps more importantly, these data no longer reflect contemporary practice, primarily because of the changing balance of risks associated with valve-related reoperation, bleeding, and embolic stroke. Transcatheter valve-in-valve has reduced mortality of reintervention for bioprosthetic degeneration for many patients, whereas the considerable mortality and morbidity associated with stroke and major bleeding (both more common after mechanical than bioprosthetic valve replacement) remain substantially unchanged.⁶

In summary, this meta-analysis provides no reason to deviate from clinical practice based on individual patient preference and risk factors, consensus guidelines, and best evidence. In patients aged 50 to 70 years, either a

bioprosthetic or mechanical valve replacement remains a reasonable choice.

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