A heart valve is no stronger than its weakest link: The need to improve durability of pericardial leaflets

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Central Message

Innovative anticalcification treatments can improve the durability of surgical and transcatheter valve bioprostheses.

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The durability of bioprosthetic heart valves continues to increase with each decade, with improved patient selection, better protocols for tissue fixation, and the availability of various anticalcification treatments. Despite these encouraging outcomes, calcification of bioprosthetic valves continues to remain a challenge, with reoperation rates at 10 years after implantation ranging from 3% to 20%.^{1,2}

The advent of transcatheter aortic valve replacement (TAVR) and the ability to perform valve-in-valve replacements has shifted focus slightly from investing in strategies to improve material durability toward an approach to develop low-profile valves that can be implanted into the failing original bioprosthetic valve. Although this is an alluring idea, the fact that TAVR valves are manufactured from thinner leaflets of the same material indicates the potential for these secondary replacements to calcify and deteriorate with time. This risk becomes higher as TAVR valves are used in patients at lower risk with several decades of expected survival after the procedure. Dvir and colleagues³ studied 378 patients who received a TAVR valve and observed a 50% structural valve deterioration rate between 5 and 7 years after the implantation.

Calcification of bioprosthetic heart valves could occur from external patient-specific factors (eg, hyperlipidemia, chronic kidney disease, young age) or from internal valve material-specific factors (eg cellular remnants, calcium entrenchment into phospholipids in the cellular remnants, traces of free glutaraldehyde), or from unknown interactions between both types of factor. In their publication in this issue of the *Journal*, Meuris and colleagues⁴ report the efficacy of the LivaNova FREE treatment (LivaNova PLC, London, United Kingdom), which involves octanediol-ethanol to remove phospholipids in the cellular remnants, a taurine wash to neutralize unbound aldehydes left after glutaraldehyde fixation, and storage in an aldehyde-free solution containing preservatives such as

parabens. The logic behind this treatment strategy is sound. Plasma membranes and membrane organelles in the cellular remnants of the bovine pericardium are rich in phospholipids, which are a source of phosphorus that favors calcium phosphate crystallization in the tissue. Vyavahare and associates⁵ pioneered a high-concentration ethanol (a short chain alcohol) anticalcification treatment for bovine pericardium to remove phospholipids⁵; others have extended this to long-chain alcohols like octanediol, which are structurally like phospholipids⁶. Because the solubility of octanediol in water is limited, buffered ethanolic solution improves solubility and tissue penetrance. Pathak and associates⁷ demonstrated the benefit of such a treatment in reducing tissue calcification, with possibly better outcomes with use of octanediol in an ethanol solution than with ethanol alone. Meuris and colleagues⁴ used this technique reported by Pathak and associates,⁷ and as such are not innovative in this regard. In the next step, Meuris and colleagues⁴ detoxify the tissue with taurine (also known as aminoethane sulfonic acid), which has an amine group (NH₂) to bond with the aldehyde group of any unconjugated glutaraldehyde left after tissue fixation. It is possible that the combination of phospholipid repletion and subsequent treatment with taurine, may allow better penetration of the taurine into the tissue and aid in better outcomes. Finally, the tissue is preserved in aldehyde-free solution with parabens, which is a common preservative used in foods and cosmetic products. By addressing these different components contributing to calcification, the

FREE treatment is theoretically an effective strategy to improve durability of bioprosthetic heart valves.

The results of Meuris and colleagues,⁴ however, fall short in validating this theoretic excitement, as I shall elucidate. The phospholipid content in the tissue treated with FREE treatment was equivalent to that of Linx (>60% volume ethanol treatment to remove phospholipids, marketed by St Jude Medical and used in Trifecta [St Jude Medical Inc, St Paul, Minn]) and Thermafix (heat treatment to denature proteins and phospholipids, marketed by Edwards Lifesciences and used in Perimount [Irvine, Calif]). This observation makes one wonder whether the theoretic benefit of treating with long-chain octanediol was realized at all, because treatment with ethanol alone (Linx) seems to have the same effect. Extractable aldehydes were significantly lower in the FREE treatment compared to tissues treated with Linx or Thermafix, but at day 6 the levels were comparable between Thermafix and FREE. The calcium content after subcutaneous implantation in rats were equivalent among the 3 treatments, and the preclinical implants are too underpowered to deduce any conclusions. Bringing together these results, it would be reasonable to deduce that the FREE treatment may be noninferior to Linx and Thermafix, but for reasons unknown the theoretic benefits laid out from FREE treatment relative to other treatments are lost in translation.

Despite the theoretic benefits and noninferiority of the FREE treatment strategy, the longer term outcomes in human patients can only be assessed with longitudinal observational studies. Most anticalcification strategies

have succeeded in the subcutaneous rat and juvenile sheep models, but those favorable results could not be replicated in human patients, probably because of individual patient risk factors. Research to improve tissue durability should therefore continue, and probably accelerate, because of the rapid proliferation of TAVR. Ultimately, lack of tissue durability is the weakest link, whether a valve is deployed surgically or through a catheter, and the current fervor surrounding the delivery mode should not mask research in this area. I therefore congratulate Meuris and colleagues⁴ for their study.

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