BIOPROSTHETIC VALVE DURABILITY: AN INDUSTRIAL PUDDING?

To the Editor:

In his Editorial Commentary¹ on our recent article on a new tissue preservation technology tested in juvenile sheep,² Schmoker found it necessary to warn the readership to interpret the conclusions in the setting of industry sponsorship. Readers are intelligent enough to realize that industry sponsorship is frequently needed to perform expensive and demanding translational research in qualified university laboratories. When new technologies are introduced, they need to be tested, and it is the task of independent laboratories to do so in an objective manner. The methods, design, and results of these studies are reviewed seriously by many, and when the final results are written down in an article, editors and their boards of highly specialized reviewers decide on publication. It is therefore questionable that “gimmicks” and “new industrial selling points” would pass these selection processes.

Translational research on bioprosthetic valve durability is quite a challenge. Structural valve degeneration in human beings is a process that takes years to develop, so accelerated animal models are needed. Juvenile sheep are known to be an acceptable model in this respect, and it was possible to demonstrate that antimineralization treatments tested in this model can adequately model prosthetic valve degeneration in human beings.^{3,4} In these studies, we tested most of the commercially available bioprosthetic valves from almost all valve companies worldwide.

Schmoker¹ states that “it remains unclear how this new treatment differs from the second-generation ThermaFix process” and “why the experimental design did not include the newer ThermaFix valves as controls.” Our article describes some of the basic elements in the new technology (free aldehyde capping, storage in a nonglutaraldehyde solution, glycerolization, etc). Of course, none of the valve companies ever reveal the ultimate production details of their antimineralization technologies. This is something we have to live with. Nobody knows how to make Coca-Cola except the company. This does not mean, however, that the basic principles, mode of action, and components remain undisclosed as they are described in the product and application patents. Concerning the control group, we chose a control valve

with several decades of clinical data so that we could assess this novel technology against a well-established, clinically proven valve. Finally, on a technical note, Schmoker¹ asks whether “calcium content was different in the leaflets before implantation.” This was tested, and there was no difference.

Schmoker¹ concludes that the ultimate proof is in the pudding. This is true, as we are all well aware that the ultimate result can only be seen after 15 years of patient follow-up. But if we have to wait for that, progress will hardly ever be made. In the evaluation of new treatments, we must use our best experimental methods to study their performance in comparison to established technologies. In the meantime, when you don’t like the pudding, nobody forces you to eat it.

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CHOOSING FROM THE MENU

Reply to the Editor:

Participation with industry on device design and testing is vital to our specialty. We partner with industry with the hope of advancing technology that will have direct benefit to our patients. In doing so, we must constantly reevaluate our relationship in terms of what Mack and Sade describe as the “universal human trait of self-deception in ourselves.”¹ In this regard, when I evaluate a study financed by industry, I tend to look more deeply at study design and look for clues of potential bias, introduced intentionally or not, by the investigators. In their Letter to the Editor regarding my Editorial Commentary,² Flameng and Meuris have taken issue with this approach. I have no argument that their animal model³ is an important translational step toward human valve testing, and I concur that the device company has no obligation to release proprietary information about their product; however, I see potential for loss of objectivity with some aspects of the study design of Flameng and colleagues.³ For example, much of the data analysis of the explanted valves is subjective. The only quantifiable datum described is the calcium content of the leaflets. Subjective data analysis is vulnerable to unintentional bias. Effort should have been made to objectify the

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analysis better, such as with the use of image analysis for semi-quantitative assessment of the interpretation of the radiographic and histologic results, and with blinded assessment of the explanted valves as was done for the echocardiographic data. Flameng and colleagues³ should also clearly state that the explanted valve analysis was performed at their institution, and not by industry scientists. Unfortunately, they show bias toward the funding manufacturer's products, as witness by the unsubstantiated statement of "standard of care" when discussing the company's valves, both at the beginning and at the end of their discussion section.³

The authors are correct that if this technology is approved for commercial human use, there will be no long-term longitudinal studies of durability available initially for assessment, and we will have to go by studies such as theirs to make a decision on use. When the industry representative arrives at my office door with a brochure of research papers promoting this novel treatment relative to their second generation anticalcification product, I would hope that they will include studies with better objective design. Otherwise, I may suggest to them that this is just a *gimmick* or *new selling point*, and not choose the pudding. Rather, I may ask, "Where's the beef?"

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STATE-OF-THE-ART SURGICAL CORONARY REVASCULARIZATION: MULTIPLE ARTERIAL CONDUITS, MINIMAL AORTIC MANIPULATION To the Editor:

In a recent issue, the Danish On-Pump Versus Off-Pump Randomization Study (DOORS) investigators reported a statistically significant

7% decrement in overall graft patency (defined as open and nonstenotic) assessed by angiography 6 months after off-pump coronary artery bypass graft (OPCAB) versus on-pump coronary artery bypass graft (ONCAB).¹ In the same issue, Takagi and colleagues² offer a meta-analysis of long-term survival after OPCAB versus ONCAB, reporting an adjusted hazard ratio of 1.07 (95% confidence interval, 1.03-1.11) for death $\geq$ 5 years following OPCAB compared with ONCAB. Smith³ and Lazar⁴ offered separate editorial commentaries, adding their clinical perspectives. They identified several important weaknesses and limitations of the DOORS trial¹ and the meta-analysis by Takagi and colleagues.²

Smith³ noted that the experience threshold for surgeons in the DOORS trial was relatively meager (at least 25 OPCAB cases with circumflex territory grafts) and that the predominance of single internal thoracic artery (ITA) plus saphenous vein grafts (SVGs) suggests something less than cutting-edge coronary surgery. Importantly, 57 of 446 (12.8%) OPCAB cases in the DOORS trial were converted to ONCAB, approximately 5-fold the rate of conversion reported in the Society of Thoracic Surgeons database (2.2%),⁵ perhaps suggesting an incomplete comfort level with OPCAB among some of the operating surgeons. Inexplicably, more perioperative bleeding was found in OPCAB patients than in ONCAB patients in the DOORS study, contrary to many previous reports.

The reported difference in occluded grafts did not reach significance ($P = .20$). Both OPCAB and ONCAB had 95% non-occluded left ITA grafts; the differences were in SVG, radial artery, and right ITA conduits. Moreover, in the 250 stenotic or occluded grafts, the obstruction was located at proximal anastomoses ($n = 121$), shaft lesions ($n = 65$), and distal anastomoses ($n = 96$). As Smith noted,³ in 74% of occluded/stenotic grafts, the problem was seen in sites (proximal anastomosis and midshaft lesions) that might not be expected to differ greatly between the 2 operative techniques.

Importantly, "The propensity to attend the follow-up angiography was unevenly distributed among groups."¹ Post-hoc adjustment for the propensity to attend the follow-up angiography suggested that the groups that had angiography were similar to their respective preoperative groups, but it is unclear whether sampling/selection bias at follow-up angiography could have confounded the study. Caution should be exercised in generalizing from this trial in which no primary end point was reported for almost half of enrolled patients.

We respectfully disagree with Smith's statement that OPCAB behaves like percutaneous coronary intervention (PCI) in multivessel disease or diabetes without the benefits of a truly noninvasive procedure. Indeed, it is important to note that when comparisons have been made between OPCAB and multivessel PCI, they have uniformly and strongly favored OPCAB over PCI.⁶⁻⁸ However, it is certainly true that the widespread use of SVG conduits, with their inevitable attrition, makes coronary artery bypass