The Transcatheter Valve Revolution: Time for a Compensatory Pause

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Frederick G.P. Welt, MS, MD; Michael J. Davidson, MD; Andrew C. Eisenhauer, MD

Brigham and Women’s Hospital, Boston, MA

Address for Correspondence:
Frederick G.P. Welt, MD
Cardiovascular Division
Brigham and Women’s Hospital
Boston, MA 02115
Tel: 857-307-1986
Fax: 857-307-1955
E-mail: fwelt@partners.org

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The last 2 years have seen a torrent of information regarding transcatheter aortic valve replacement (TAVR), and it is no exaggeration to say that this compelling technology has revolutionized our approach to treatment of valvular aortic stenosis. High risk and inoperable patients heretofore relegated to minimally effective medical therapies have been offered a return to activity and in some cases, a longer life\textsuperscript{1, 2}.

Yet, not all the news is good. While the rate of vascular complications has subsided with lower profile tools and increased experience, they remain vexingly high. Similarly, stroke rates hover around 5% with some data suggesting they are higher than the risk associated with conventional surgery\textsuperscript{3}. Earlier this year, data emerged that even mild paravalvar leak (a common occurrence post-implantation) was associated with considerably worse outcome\textsuperscript{4}. Finally, the durability of these valves remains undetermined.

All of these issues gain additional import when seen in the context of the explosive growth of this procedure. An estimated 40,000 to 50,000 cases have been performed worldwide with the majority being in Europe. In Germany, where the most enthusiastic adoption has taken place, reports are that ~ 30% of valves implanted are via a transcatheter route. In the US, we have just seen the approval of the device for commercial use in inoperable patients. Adoption is much more conservative at present but growing.

In addition to the complications noted above, and germane to this editorial, there has been a well-recognized incidence of conduction system disturbance in patients post TAVR. While it has been assumed by many that this is a nuisance phenomena simply requiring the insertion of a permanent pacemaker in those with high degree AV block, evidence presented by Prinzen and colleagues in this issue of Circulation shows that new left bundle branch block (LBBB) induced by TAVR is associated with increased mortality with a hazard ratio of 1.54 and an absolute
increase in mortality of 13.8% at ~450 days. While this has prognostic significance, this finding also raises several fundamental questions about this specific condition and about the field in general that can only be answered by further investigation.

**Mechanistic questions**

That LBBB should be associated with higher mortality should be of little surprise to the clinician as there is abundant evidence that in a wide variety of clinical scenarios, including asymptomatic patients without known cardiovascular disease, LBBB is consistently found to be a potent risk factor for death. Whether this is simply a marker for increased risk or causative cannot be answered definitively by the current study. However, the authors found that the increased mortality is cardiac in nature and not sudden, suggesting that a possible mechanism is dyssynchrony-induced left ventricular dysfunction. A correlation between higher rate of LBBB following TAVR and of need for permanent pacemaker implantation has been documented in prior registries but a specific connection with mortality in this group has not been previously identified. Presumably, impingement of the prosthesis on the conduction system is the specific causative event.

Mechanistic insight is more than an academic question both in terms of the importance for patients currently being treated and the ramifications for device development moving forward. If brady-arrhythmias are the culprit for associated mortality, then it would be reasonable to assume that pacemaker therapy would be the solution. However, if cardiac dyssynchrony is responsible, it is much more problematic to assume that cardiac resynchronization therapy (CRT) would restore longevity. Current guidelines suggest that the greatest benefit of CRT is in patients with advanced heart failure, reduced (<35%) left ventricular ejection fraction (EF) and LBBB with a prolonged QRS (> 120 msec). Recent meta-analysis suggests that real benefit is
restricted to those patients with a QRS greater than 150 msec. The baseline EF of the population studied in the report of Prinzen and colleagues was less than 50% in only ~29% of patient developing new LBBB and the QRS length in those patients ranged from 140-162 msec suggesting that the majority of patients with new LBBB would not fall into a previously identified subgroup that would reasonably expect to achieve symptomatic or mortality benefit.

While case reports have suggested clinical improvement following CRT for LBBB post TAVI, this benefit cannot yet be generalized to this population. In addition, there are issues of both cost and incremental risk that would need to be taken into consideration for patients requiring an additional invasive procedure.

Device comparisons

Undoubtedly, what will receive the most interest is the fact that there was a much higher incidence of induced LBBB among patients treated with the Medtronic CoreValve® device compared to the Edwards Sapien® device. We do not have the benefit of head to head randomized trials to understand the relative strengths and weaknesses of the devices as they now exist. A recent meta-analysis of 3,519 patients from 16 studies utilizing both the Edwards and Medtronic devices found rates of permanent pacemaker implantation of 4.9% vs 28.9% respectively which was a statistically significant finding. The generally accepted reason for a higher rate of conduction system disorders with the Medtronic device is that it often extends deeper within the outflow tract and applies constant outward radial pressure due to its self-expanding platform.

The most obvious conclusion, but potentially incorrect, is to assume that this represents a sign of superiority of one device over the other. This study cannot answer that question. Rather, we suggest that the study illustrates that there are likely significant differences in clinical
performance of the valves that follow from their different materials, design, and methods of insertion. Furthermore, the authors illustrate a phenomenon of a learning curve with the Medtronic CoreValve device in which the incidence of LBBB falls with increased experience. This observation, coupled with prior data showing that many patients develop LBBB prior to actual insertion of the valve\textsuperscript{12}, suggests that the valve itself may not be the predominant cause of conduction system defects but rather the method of insertion. It is certainly possible that there are other substantive differences in clinical performance between the two valves that would favor one over the other in certain clinical circumstances. An obvious comparison can be made with the decision regarding the selection of surgical aortic valve replacement between bioprosthetic and mechanical valves. While one of the few trials have showed a long term survival advantage of mechanical valves (due to earlier valve failure of bioprostheses), this came at a cost of a higher rate of bleeding\textsuperscript{13}. Thus, for older patients who have shorter expected survival and higher risks of bleeding, bioprosthetic valves, despite their lesser durability, are more commonly implanted.

**Lessons from the surgical experience**

There are few data in the surgical literature to shed light on the particular question of procedure-induced LBBB. Early experience with surgical valve replacement suggested that LBBB was a relatively frequent complication of surgery with an incidence as high as 32\%\textsuperscript{14}, whereas a more recent study by El-Khally et.al demonstrated a much lower rate at \textasciitilde 6\%\textsuperscript{15}. This single-center experience suggested that new LBBB after surgical AVR was associated with a high adverse event rate postoperatively. While a higher incidence of death has been associated with new LBBB, most of the reported deaths were sudden and presumed to be associated with high degree AV block\textsuperscript{14}. Only one study has compared new conduction delay rates following transcatheter
versus surgical AVR. While limited by its nonrandomized design and small sample size, this report suggested that new and persistent conduction delay rates are lower (12% vs 28%) in surgical versus transcatheter patients.

There is more to be learned from the surgical experience when the field is examined from a broader perspective. Prospective randomized trials of surgical valves are relatively few in number. In the early days of surgical valve replacement, it was assumed to be essentially unethical to randomize patients with severe AS to medical therapy given the dismal natural history of untreated critical AS. Accordingly, the “mortality advantage” conferred by surgical valve replacement has been studied only in non-randomized and retrospective studies. Even the randomized trials of mechanical vs bioprosthetic valves have been greeted by many with suspicion.. A rather remarkable discussion documented in the “Sounding Board” of the New England Journal of Medicine in 1979, suggested that randomized trials were of limited value in the realm of surgical procedures and that “the referring physician is … the surgeon’s Food and Drug Administration” as poor results would be greeted by fewer referrals. In the same piece and speaking of the Veterans Administration randomized study comparing the efficacy of different prosthetic valves, it was said that “one might question a plan to offer different prostheses to randomized patients who might best be served by a particular prosthesis” suggesting what could be called a proceduralist-knows-best policy. One could hardly imagine such a conversation in today’s highly regulated environment where we are increasingly being confronted with randomized data questioning the relative lack of benefit of many of the invasive procedures that have become so common in cardiology and cardiac surgery.

**The way forward**

So how should we react to the finding that acquired LBBB during TAVR is frequent and
associated with worse mortality? What are we to make of this finding, how should it inform our current practice, and what is needed to resolve uncertainty moving forward? The prognostic importance of a factor that is induced by the procedure is of inherently little value in patient selection unless there are other predictive features that can be identified and, unfortunately, none are suggested in this report. However, this study should spur further investigation into the patient characteristics that predict this outcome, to therapies that can mitigate the increased mortality, and to device design modifications that cause fewer conduction system disorders.

These issues are increasingly important in the era of commercialization and rapid increased use of this technology. The danger, of course, is that the spectacular results of the tightly controlled early randomized trials will fail to be reproduced when applied to a broader uncontrolled population. Findings such as those reported by Prinzen and colleagues are a constant reminder of the knowledge gaps present in this relatively nascent technology now being applied to an increasingly sick and complex patient population. This and other issues are unlikely to be resolved without eventually conducting further investigations including randomized, head-to-head trials of devices.

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**References:**


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