Death and Interventional Cardiology: A Tale of Two Trials

Running title: Dauerman; Death, Shock and Aortic Stenosis

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In this issue of *Circulation*, the 3 year follow up of the PARTNER B trial provides us with a sobering final word on the natural history of severe aortic stenosis \(^1\). As described 50 years ago, severe aortic stenosis is a terminal illness of the elderly with a progression from symptoms to death over an approximately 3 year period \(^2,3\). The current report of the 3 year follow up from the PARTNER B trial confirms this dismal natural history: among patients randomized to standard therapy in the initial trial and/or continued access study, 81% are dead after 3 years. Transcatheter aortic valve replacement (TAVR) alters this natural history significantly, providing a 47% reduction in the risk of death over 3 years (HR 0.53, 95% confidence interval 0.41-0.68, p < 0.001). Based upon this demonstration of effective therapy for even surgically inoperable patients, the natural history studies of untreated severe aortic stenosis are complete.

The PARTNER B control arm is not the only group with a concerning outcome: the majority of patients randomized to TAVR are also dead at 3 years follow up. These grim outcomes in both arms of the trial lead to two disturbing questions: 1) Was it necessary to perform a randomized trial in which the control group was already known to have an exceedingly high mortality rate? 2) Were elderly patients with multiple comorbidities unnecessarily included a randomized trial where any active intervention was predestined to be futile?

**Randomized Interventional Cardiology Trials and Death**

The last two decades of interventional cardiology clinical trials has been dominated by the combined endpoints, surrogate endpoints and goals of non-inferiority. The efficacy of PCI pharmacology is generally defined by peri-procedural elevations in myocardial biomarkers. The impact of coronary stents is demonstrated by either reduction or non-inferiority for a combined endpoint of death, myocardial infarction or target vessel revascularization. Trials of new
pathways, new technology and new pharmacology are rarely powered to show us that novelty leads to less death for the simple reason that death rates in the studied populations are too low to provide any realistic answers.

In this context, PARTNER B is an alarming trial defined by the highest imaginable rates of death. Alternative trial designs could have limited the number of deaths in this trial: PARTNER B could have used a combined surrogate primary endpoint (death, repeat hospitalization, and improvement in heart failure symptoms) to subject a smaller group to randomization. Or, PARTNER B could have favored a design similar to the Corevalve study which used a historical control group in place of a randomized medical therapy group. Finally, PARTNER B could have been limited to those patients with Society of Thoracic Surgery (STS) surgical risk scores less than 15% to decrease mortality rates in both arms of the study.

Before we discount the death driven design of PARTNER B, an alternative perspective on death in interventional cardiology trials is warranted: this counterpoint may be best illustrated by comparing the first TAVR trial to the first completed trial of early revascularization for cardiogenic shock. Similar to the challenge faced by the PARTNER investigators, the SHOCK trial investigators knew that patients with acute myocardial infarction complicated by cardiogenic shock had a terminal illness. Rather than look for a combined endpoint or a hemodynamic surrogate, the SHOCK investigators faced the certainty of death with a trial design that answered the essential question in a definitive manner: can we truly alter the natural history of a terminal illness?

There are numerous similarities between these two landmark trials (Table 1) beginning with a similar sample size (N= 300-350); neither of these trials is large in comparison to the surrogate endpoint driven trials of pharmacology and technology that dominate interventional
cardiology. In both of these trials, the expected benefit of the novel therapy (early revascularization in SHOCK, TAVR in PARTNER B) was not presumed to be miraculous: for both trials, the investigators hoped that the novel therapy would reduce death by approximately 33% thus leaving a clear expectation of plentiful death in both the control and active treatment arms. Both trials were multicenter national efforts requiring multiple years to complete enrollment; their subsequent influence on guidelines and clinical practice is clear. While the SHOCK trial may be the most influential trial in history to miss its primary endpoint, the benefit of early revascularization demonstrated in continuing follow up has had a lasting influence on practice and guidelines.

Did SHOCK need a death endpoint or a randomized control group with an expected mortality of 80%? The evidence supporting this design is quite clear from a subsequent story in this field: pathophysiologic observations and hemodynamic endpoint studies suggested that a novel nitric oxide synthase inhibitor, tilarginine, would clearly be superior to standard therapy for patients with acute myocardial infarction complicated by cardiogenic shock. When an international, multicenter mortality driven trial was performed, the surrogate endpoints proved useless and tilarginine had no effect on mortality. Similarly, the superiority of TAVR seems clear retrospectively, but the benefit was much less clear to patients and investigators during the trial: among patients randomized to standard therapy in PARTNER B, all were offered TAVR after the 12 months of initial follow up were completed. Yet, only a minority of patients and clinicians chose the novel therapy: of 58 eligible patients who were alive a 12 months in the standard therapy arm, only 20 patients crossed over to TAVR therapy. Now, we have clarity in both shock and aortic stenosis, and there will never be another control group randomized to medical therapy alone for these disease states. Based upon the history of the SHOCK trial and its
follow up studies, the PARTNER B investigators were right: they had to use a death defined randomized trial design to definitively prove that TAVR alters the natural history of a terminal illness.

Patient Inclusion and Subgroup Analysis

Kapadia et al report a 54% mortality at 3 year follow up of the TAVR arm of PARTNER B. The authors speculate that this high mortality in the novel treatment arm “highlights the need for better case selection, especially in those with multiple co-morbidities”. Support for this concept comes from subgroup analysis demonstrating the interaction of TAVR effectiveness with baseline assessment of surgical risk. When patients are stratified according to 3 tertiles of STS scores, the greatest absolute reduction in all-cause mortality (67%) is in the lowest STS (estimated risk < 5.0%) group with a much less impressive absolute reductions in mortality (21%) among patients with STS scores over 15%. Thus, it is tempting to conclude that our selection process for TAVR extreme risk patients should begin with the STS score; elderly patients with STS scores over 15% may represent the cohort C of the PARTNER trials—the group which should never have been randomized in PARTNER A or B trials due to futility of any aggressive therapy. Other risk scores have similarly been calculated to help guide clinicians with better selection of patients for TAVR.

Once again, the SHOCK trial may provide an alternative perspective on this conclusion. Like PARTNER, SHOCK had prespecified subgroup analyses, generally intended to determine the consistency of a novel treatment effect. In SHOCK, there was a glaring inconsistency: among patients over age 75, the benefit of an early revascularization approach was not seen. In fact, there was a 41% increased risk of death among elderly patients undergoing early revascularization as compared to intensive medical therapy (p=0.01). This subgroup analysis
had an impact: initial guideline statements restricted the Class I recommendation for early revascularization in the setting of shock to only those patients who were not elderly\(^7\). The scope of this restricted recommendation was not small: like aortic stenosis, cardiogenic shock is a disease of the elderly and older age is the strongest predictor of shock complicating acute myocardial infarction. Thus, withholding the SHOCK early revascularization strategy among elderly patients could eliminate nearly 40\% of affected patients with the disease from qualifying for the only proven therapy to impact mortality\(^\text{12}\). If one looks carefully at the SHOCK elderly subgroup analysis, caution is clearly warranted: there were only 56 randomized elderly patients in the SHOCK trial and thus any conclusions from this subgroup analysis are necessarily ambiguous. Furthermore, subsequent large registry studies failed to demonstrate any clear harm of early revascularization (and suggested potential benefit) in the elderly shock patient thus calling into question a restricted guideline and pointing towards clinical judgement rather than subgroup analysis as a means of patient selection\(^\text{12-14}\).

The analogy with PARTNER reminds us to go slow in applying the findings of subgroup analysis to our clinical practice: while improved selection of patients for TAVR is clearly warranted, the temptation to exclude any single subgroup based upon the PARTNER B analysis should be avoided. Like SHOCK, randomizing approximately 350 patients means that each subgroup of the novel treatment group consisted of a small number of patients. Only 104 patients in PARTNER B had an STS score over 11 and at three year follow up, the p value for interaction between STS score and mortality was strikingly non-significant (p=0.74)\(^1\) : similar to the 56 elderly patients in SHOCK, this small sample size makes it hard to be certain of the futility of TAVR in higher STS score patients. While we may be concerned with application of TAVR to elderly patients in whom it may be futile, the European experience suggests that the
opposite has occurred: inoperable and high risk patients with terminal aortic stenosis appear to be undertreated and these untreated extreme risk patients are repeating a potentially unnecessary natural history study. Thus, both SHOCK and PARTNER B subgroup analyses should be used primarily to guide future investigations; we cannot definitively conclude from underpowered subgroup observations that the trial or our clinical practice would be better off excluding the patients who are older, sicker and have more extensive coronary artery disease.

**Conclusion**

The 3 year follow up of PARTNER B is a disturbing final reminder of the natural history of severe aortic stenosis. Even with the implementation of an exciting new technology, we are still facing death: in this extreme risk population, the majority of TAVR patients will be dead at 3 years. In the face of so much death, we are indebted to the PARTNER investigators for providing us with a definitive trial design that makes a final statement: the conclusions of PARTNER B, like SHOCK, require no further proof in subsequent trials. These conclusions from the 358 patients in PARTNER B (and the subsequent continued access study) are both narrow and powerful: TAVR saves lives in extreme risk patients with severe symptomatic aortic stenosis.

Due to PARTNER B, we have a good therapy for a patient group at extreme risk for death and we have hypotheses to generate the future clinical trials focusing on improving selection, pharmacology and technology to guide our therapy.

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### Table 1. Interventional Cardiology Trials at the Extreme of Mortality.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SHOCK</th>
<th>PARTNER B*</th>
</tr>
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<tbody>
<tr>
<td>Study Design</td>
<td>Randomized Clinical Trial</td>
<td>Randomized Clinical Trial</td>
</tr>
<tr>
<td>Randomized Sample Size</td>
<td>N=302</td>
<td>N=358</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Death at 30 days</td>
<td>Death at 1 year</td>
</tr>
<tr>
<td>Expected Mortality in Control Group</td>
<td>75% at 30 days</td>
<td>37.5% at 1 year</td>
</tr>
<tr>
<td>Expected Impact of Novel Therapy</td>
<td>20% Absolute Reduction in Death at</td>
<td>12.5% Absolute Reduction in Death at</td>
</tr>
<tr>
<td></td>
<td>30 Days</td>
<td>1 Year</td>
</tr>
<tr>
<td>Achieved Mortality in the Novel Treatment Arm</td>
<td>47% at 30 Days</td>
<td>31% at 1 Year</td>
</tr>
<tr>
<td>Primary Endpoint Achieved</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Key Secondary Endpoint</td>
<td>Significant Mortality Reduction with TAVR Persisting for 3 Years</td>
<td></td>
</tr>
<tr>
<td>Exploratory Subgroup Analyses</td>
<td>No Benefit of Early Revascularization in the Elderly</td>
<td>No Benefit of TAVR in Patients with STS Score &gt; 15%</td>
</tr>
<tr>
<td>Subsequent or Planned Confirmatory Trials</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*PARTNER B: 91 Additional Patients Were Enrolled During the Continued Access Phase
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