In this issue of Circulation, the 3-year follow-up of the Placement of Aortic Transcatheter Valves Cohort B (PARTNER B) trial provides us with a sobering final word on the natural history of severe aortic stenosis. As described 50 years ago, severe aortic stenosis is a terminal illness of the elderly with a progression from symptoms to death over an ≈3-year period. The present 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 or continued-access study, 81% were 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 (hazard ratio, 0.53; 95% confidence interval, 0.41–0.68; P<0.001). As a result of 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 the 3-year follow-up. These grim outcomes in both arms of the trial lead to 2 disturbing questions: Was it necessary to perform a randomized trial in which the control group was already known to have an exceedingly high mortality rate? And were elderly patients with multiple comorbidities unnecessarily included a randomized trial in which any active intervention was predestined to be futile?

Interventional Cardiology

Trials and Death

The last 2 decades of interventional cardiology clinical trials have been dominated by combined end points, surrogate end points, and goals of noninferiority. The efficacy of percutaneous coronary intervention pharmacology is generally defined by periprocedural elevations in myocardial biomarkers. The impact of coronary stents is demonstrated by either a reduction in or noninferiority for a combined end point 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 fewer deaths 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 primary end point (death, repeat hospitalization, and improvement in heart failure symptoms) to subject a smaller group to randomization. Alternatively, PARTNER B could have favored a design similar to that of 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 <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 and the first completed trial of early revascularization for cardiogenic shock. Similar to the challenge faced by the PARTNER investigators, the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial investigators knew that patients with acute myocardial infarction complicated by cardiogenic shock had a terminal illness. Rather than look for a combined end point 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 2 landmark trials (Table), beginning with a similar sample size (n=300–350); neither of these trials is large compared with the surrogate end point–driven trials of pharmacology and technology that dominate interventional cardiology. In both 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 ≈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. Although the SHOCK trial may be the most influential trial in history to miss its primary end point, the benefit of early revascularization demonstrated in continuing follow-up has had a lasting influence on practice and guidelines.

Did SHOCK need a death end point 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. Pathophysiological observations and hemodynamic end-point 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.8 When an international, multicenter, mortality-driven trial was performed, the surrogate end points proved useless, and tilarginine had no effect on mortality.9 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. However, 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.10 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. On the basis of 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 al1 report a 54% mortality at the 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 comorbidities.” 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 much less impressive absolute reductions in mortality (21%) among patients with STS scores >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 >15% may represent the cohort C of the PARTNER trials, the group who should never have been randomized in PARTNER A or B trials because of the futility of any aggressive therapy. Other risk scores have similarly been calculated to help guide clinicians with better selection of patients for TAVR.11

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 >75 years of age, the benefit of an early revascularization approach was not seen.5 In fact, there was a 41% increased risk of death among elderly patients undergoing early revascularization compared with 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 therapy proven to affect mortality.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; 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 toward clinical judgment rather than subgroup analysis as a means of patient selection.12–14

The analogy with PARTNER reminds us to go slowly in applying the findings of subgroup analysis to our clinical practice. Although improved selection of patients for TAVR is clearly warranted, the temptation to exclude any single subgroup on the basis of the PARTNER B analysis should be avoided. Like SHOCK, randomizing ≈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 >11, and at the 3-year follow up, the P value for interaction between STS score and mortality was strikingly nonsignificant (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 patients with a higher STS score. Although 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.13 Thus, both SHOCK and PARTNER B subgroup analyses should be used primarily to guide future investigations. We cannot definitively conclude from underpowered trials focusing on improving selection, pharmacology, and death, and we have hypotheses to generate the future clinical trial. As a result of 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.16,17

Disclosures
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References


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