The INvestigation of STEnt Grafts in Aortic Dissection (INSTEAD) Trial
The Need for Ongoing Analysis

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In the present issue of Circulation, Nienaber et al report the results of a randomized comparison of strategies for type B dissection: the INvestigation of STEnt grafts in Aortic Dissection (INSTEAD) trial. This trial represents the first prospective randomized study of elective stent graft placement in survivors of uncomplicated chronic type B aortic dissection. The results have been eagerly anticipated by clinicians, particularly in light of recent analyses of the benefits of endovascular repair for abdominal aortic aneurysms and thoracic endovascular aneurysm repair (TEVAR) for the treatment of degenerative thoracic aneurysms. The authors are to be commended on providing Level 1 evidence to assist us in the management of chronic aortic dissection. The INSTEAD trial demonstrates that thoracic stent graft (TEVAR) placement failed to improve the rates of 2-year survival and adverse events when compared with optimal medical therapy (OMT). Although considerable attention to detail was paid by the authors in the design of this trial, several limitations exist that may preclude using these results to determine the final role of stent grafts in the management of chronic aortic dissection.

Of major concern is the fact that the study was underpowered to evaluate the mortality end point, as was pointed out by the authors in their article. For the study to have adequate power, 28 events needed to be observed, but only 11 events were observed. Thus, the significance of the negative results of this study must be called into question. Extending the follow-up of these patients would potentially provide further time points to allow for a more meaningful analysis of the data.

Furthermore, when the 11 observed deaths were analyzed in detail (Table 4 in Nienaber et al1), the authors reported that 4 patients received OMT alone and 7 patients received OMT plus TEVAR. Of the 4 patients in the OMT group, 2 aneurysm-related deaths occurred (50%), and all 4 patients met the inclusion criteria for the INSTEAD trial. However, of the 7 patients who received OMT plus TEVAR, 4 patients violated an inclusion criterion and should not have been enrolled in the trial: 1 patient had acute malperfusion and renal insufficiency, 1 had a ruptured thoracic aorta, and 2 patients had acute lower-extremity ischemia.

The inclusion of these patients in the trial is problematic because this study was designed to evaluate the elective management of stable uncomplicated Type B dissection. If these 4 deaths are eliminated from the analysis, then no aneurysm-related deaths were associated with OMT plus TEVAR. The remaining deaths in the OMT plus TEVAR group resulted from pulmonary embolism, ventricular fibrillation, and fatal hemorrhagic stroke associated with severe hypertension. The inclusion of these patients further emphasizes the fact that the study was underpowered to make conclusions about likelihood of death, and the results must be considered in this light.

In addition, the study design included patients whose dissections were present between 2 and 52 weeks. Given such a wide time frame for inclusion of patients in this trial, one might conclude that the pathological conditions of the individuals being treated in the latter part of the study may have been different from those of the patients enrolled 2 weeks into the course of their aortic dissection. Although the time interval between onset of dissection and randomization was reported as identical in both groups, with medians of 45 (OMT) and 39 (OMT plus TEVAR) days, stratifying these patients into different time periods might provide us with more information about the efficacy of TEVAR in the treatment of these patients.

Finally, although there was no difference in death rate between the TEVAR plus OMT group and the OMT group, this analysis demonstrated that aortic expansion (>60 mm) occurred more frequently with medical treatment, whereas the process of false lumen thrombosis was enhanced after stent graft placement (91.3% false lumen thrombosis and significant aortic remodeling, as shown in their Figure 4). In Table 6 of Nienaber et al, the authors report that OMT failed to demonstrate significant true lumen recovery or false lumen shrinkage. These findings underscore the potential ability of TEVAR to modulate late death related to type B dissection by creating favorable aortic remodeling. Unfavorable aortic remodeling is thought to contribute to late death after type B dissection. Although many late deaths are related to comorbid conditions, subsequent complications such as aneurysm development and late rupture have been estimated to occur in 20% to 50% of patients by 5 years.12-14

In this study, crossover to TEVAR occurred in 16.2% of patients. All crossover cases from OMT to OMT plus
TEVAR had uneventful outcomes, with no deaths and documented aortic remodeling. However, we do not know the outcomes of TEVAR in patients undergoing delayed stent grafting at time points >12 months. Although some of these patients may be amenable to treatment with TEVAR, others may require conversion to complex open aortic repair. Thus, the continued evaluation of these patients’ conditions for at least 5 years will allow the authors to analyze the effects of TEVAR and OMT on long-term aortic remodeling and death rate.15

Disclosures
Dr Kwolek has been a clinical investigator involved with the following companies within the past year: Bolton, Cook, Medtronic, and W.L. Gore. He does not have equity interest and does not currently sit on any advisory boards for these companies. He has not received funds for any speaking engagements for these companies within the past year. Dr Watkins reports no conflicts of interest.

References

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