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REPLY: RANDOMIZED CONTROLLED TRIALS IN AORTIC SURGERY: A CALL TO ACTION

Reply to the Editor:

The article by Saeyeldin and colleagues¹ on decision making for patients presenting with ascending aortic aneurysm has stirred a lot of interest in the surgical community. Although the letter to the Editor by Bugan and colleagues² is primarily directed toward the original article, we have been asked by the Editors of the *Journal* to comment on the letter in question.

In their letter to the Editor, Bugan and colleagues² point out significant differences in the baseline characteristics of those patients who underwent a watchful waiting strategy relative to those who were recommended to undergo surgery but did not for a variety of reasons. The study by Saeyeldin and colleagues¹ is not a randomized controlled trial; it is a retrospective, observational study. Although the concerns raised by Bugan and colleagues² are important, they can only be addressed by a prospective, randomized trial. We think that instead of further discussing the current article published by the Yale group, we should direct our efforts toward defining the framework requirements for a randomized trial in the treatment of ascending aortic aneurysm.

Elefteriades and Farkas³ have shown that 9 of 10 patients with thoracic aortic aneurysms are symptom free until the first event. We therefore already know that even a randomized trial will represent only a minority of patients with thoracic aortic disease. Furthermore, we know that by including the patient in a structured follow-up program, we alter the natural history of the disease even if the patient does not undergo surgery.⁴ When following the discussions at meetings, it becomes apparent that indications for surgery vary widely among centers. The current guidelines^{5,6} do not take into account basic but important factors such as age and the general condition of the patient, factors that certainly affect decision making for the individual patient. Furthermore, it will be difficult to design a trial that randomizes patients into a

watchful waiting strategy if they already have an indication for surgery according to the current guidelines.

Some obstacles seem almost insurmountable; for example, strictly speaking, every patient would have to undergo genetic testing to make sure that he or she is not harboring a mutation that increases the risk for dissection at smaller diameters. Furthermore, there is a large group of patients with mutations associated with thoracic aortic disease, but we do not know whether they have an increased risk for aortic dissection (or surgery, by the way). And then there is probably an even larger group of patients for whom we do not know yet whether the genetic variant they harbor is indeed associated with thoracic aortic disease.

In our mind, an ideal population to include in a randomized trial comparing best medical treatment and watchful-waiting with best medical treatment and surgery would be symptom-free, young, active patients with a low surgical risk who present with ascending aortic diameters between 4.5 and 4.9 cm. If they do not have Loeys-Dietz syndrome or Marfan syndrome with additional risk factors, these patients do not qualify for elective surgery according to the current guidelines. Nevertheless, the aorta is certainly too large, and it can be expected that they will fulfill the criteria for elective surgery in the future. Furthermore, most of these patients have very active professional and private lives, and the effect of an active lifestyle on the risk of aortic events at this diameter is unclear. This is the patient population for whom a randomized trial could affect the way we treat these patients.

It is unlikely that one center alone would have sufficient numbers to make these efforts worthwhile. But if everybody who has read the article by Saeyeldin and colleagues¹ would invest a little bit of time and energy toward setting up a randomized trial, we could actually move a step forward in the treatment of patients with thoracic aortic disease. Furthermore, only a randomized trial will eliminate the problem that Sundt⁷ highlighted in his recent letter to the Editor regarding the article in question, that just because we can perform an operation safely does not mean that every patient will benefit from it.

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REPLY: YOU CAN'T ALWAYS GET WHAT YOU WANT

Reply to the Editor:

For patients with aortic dilatation who are free of symptoms, establishing the timing of aortic repair is the most crucial health decision they will likely face in their lifetimes.¹ For their clinicians, the timing of repair is almost universally based on the aortic diameter. For most symptom-free patients with an aortic aneurysm, the threshold of repair is set at 5.5 cm or larger by contemporary practice guidelines.^{2,3} Depending on patient circumstances, the hinge point of repair may be lowered to between 4.0 cm and 5.0 cm. For patients with symptoms, surgery is warranted regardless of aortic diameter.

In the study in this issue of the *Journal* by Saeyeldin and colleagues⁴ (including the senior author, Dr Elefteriades), 781 patients with ascending aortic aneurysms were reviewed. In this study, they evaluated the impact of lowering the 5.5 cm diameter-based threshold for surgery to 5.0 cm or larger, in addition to further lowering that threshold to 4.0 cm in the presence of unexplained chest pain, strong family history, severe connective tissue disorder, or disease of a bicuspid aortic valve. Saeyeldin and colleagues⁴ found that when their algorithm was followed, the risk of 30-day death after ascending aortic replacement was an outstanding 1%. They

found, however, that when their algorithm could not be followed (if comorbidities ruled out surgery or if the patient refused surgery), the risk of late aortic death or an aortic event was 12% or 13%, respectively. In addition, Saeyeldin and colleagues⁴ noted that in patients with aortic diameters between 4.0 cm and 4.9 cm who were without the specified risk factors, the likelihood of a late aortic risk factor dropped to 1% to 2%.

The recent letter by Bugan and colleagues⁵ touches on the continuing controversy of how far to lower diameter-based thresholds of repair. The primary concern of Bugan and colleagues⁵ is how to treat the group of patients within the space between the existing (5.5 cm) and suggested (5.0 cm) hinge points. Further, Bugan and colleagues⁵ argue that the study conducted by Saeyeldin and colleagues⁴ could have evaluated their existing data better by using a different grouping strategy for patients in the study; Rather than analyze their triage algorithm, Saeyeldin and colleagues⁴ should have narrowed the study's focus, the better to examine the hinge point.

Should existing guidelines drop the threshold of repair from 5.5 to 5.0 cm in symptom-free patients who are without additional risk factors? Bugan and coauthors⁵ state that Saeyeldin and colleagues⁴ have missed an opportunity to evaluate their data in terms of a practical, evidence-based recommendation to support lowering the threshold of repair to 5.0 cm. It is very likely that when aortic practice guidelines are updated, the guidelines authors will reconsider the hinge point for repair. The quest for a definitive diameter continues.

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