Editorial

The timing of elective ascending aortic aneurysm replacement for non-syndromic patients and the implication of bicuspid aortic valve-related aortopathy

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"*There is no disease more conductive to clinical humility than aneurysm of the aorta.*"—Sir William Osler.

The outcome of patients with acute type A aortic dissection, or rupture, remains bleak. Based upon a recent report from International Registry of Acute Aortic Dissection (IRAD), the early mortality for patients undergoing surgical repair is 18% in experienced aortic centers (1). This represent a drop of only 7% over a 17-year span despite significant improvements in surgical techniques, perioperative care and pharmacotherapy (1,2).

In order to circumvent this high-risk surgery, patients are offered an elective aortic replacement operation. Proper and optimal timing of this elective operation is of the utmost importance, as an early or delayed operative date puts the patient at unnecessary risk of morbidity and mortality. Most significantly, delaying the operation beyond the optimal "sweet spot" increases the risk of acute aortic syndrome, with its long associated risk of high mortality. Optimal timing of surgical intervention occurs when the annual risk of conservative management begins to exceed the risk of operative intervention. According to IRAD in an article published in *Circulation*, a surprising 59% of type A aortic dissections occur in patients with aortic diameter actually below 5.5 cm (3). This article, along with others, has been used to make the case for a lower elective threshold for ascending aortic replacement, especially when diagnosing patients with a bicuspid aortic valve (3,4). Aside from maximum aortic diameter, the surgeon also has to take in account a multitude of other factors. These include the presence of aortic risk factors such as rate of aortic growth, aortic wall thickness, systemic hypertension and the patient's compliance to medical therapy. Genetic factors include the patient's family history of aortic complications and the phenotype of the aortic valve, along with other inherited traits such as aortic coarctation and connective tissue disorders. Common cardiac surgical risk factors also play a role including advanced age, frailty, decreased left ventricular ejection fraction, renal dysfunction, redo surgery and a high STS-score. And, as always, concomitant indications for cardiac surgery must be weighed, including coronary artery disease, atrial fibrillation, valvular dysfunction, the experience and expertise of the surgeon and team, and the hospital's infra-structure, including ICU care.

In the November 2016 edition of the *Journal of American College of Cardiology*, Kim and co-authors present the risk of acute aortic syndrome (rupture and dissection) in a cohort of patients with moderately enlarged aortas, followed with echocardiography, in the outpatient clinic at Massachusetts General Hospital (5). In 3,825 patients with medial follow-ups of 40.1 months, aortic dissection occurred in 13 patients and rupture occurred in one. It is important to note that 12.6% of the patients had bicuspid aortic valves. Elective ascending aortic replacement was performed in 176 individuals

during the follow-up. However, in multivariable analyses, independent predictors of adverse events were age and baseline aortic diameters, but not bicuspid aortic valves. Not surprisingly, the risks of aortic dissection and/or rupture increased in proportion to aortic diameter. The incidences of dissection and/or ruptures were measured at 0.4%, 1.1%, and 2.9% with corresponding baseline aortic diameters of 45, 50, and 55 mm within 5 years.

Overall, Kim and colleagues' manuscript adds to the body of literature supporting the current conservative approach to elective ascending aortic aneurysm replacement (5). Based upon the findings of this study, the incidence of aortic dissection or rupture was only one per 1,000 patient-years. This correlates well with a recent study by Michelena and co-authors, on aortic dissection risks in patients with bicuspid aortic valves with an incidence of 3.1 patients per 10,000 patient years (6). Of note, while the growth rate of bicuspid aortic patients was greater than non-bicuspid aortic patients, the incidence of dissection between patients with bicuspid versus tricuspid aortic valves was similar (5). In other words, more rapid aortic expansion did not translate into a higher incidence of adverse events. This finding is also consistent with data presented in some other recent studies (6,7).

Furthermore, increased age was associated with a higher rate of dissection in this study, while the risk of dissection in young patients remained low (5). Most aortic experts agree that bicuspid aortic valve patients seem to have substantially lower rates of aortic dissection than previously determined, especially in younger patients. Based upon the aforementioned newer data, the writing committee of the American Association for Thoracic Surgery has gathered up-to-date literature related to bicuspid aortic valve-aortopathy, and published new evidence-based guidelines for treatment. This has resulted in increased thresholds for ascending aortic replacement in this patient cohort. Based upon these guidelines, repair of an ascending aorta or aortic root is recommended, when aortic diameter is 5.5 cm or greater in patients without risk factors (class I/level of evidence B). The authors recommend replacing the aorta at 5 cm or larger diameter, if the patient is a low risk surgical candidate or has certain risk factors. Related morbidities include predominant aortic insufficiency, uncontrolled hypertension, family history of aortic dissection and sudden death, and documented significant aortic growth in 1 year (class II/level of evidence B). Surgery can also be elected at 5 cm with an experienced aortic team with established surgical results (class II/level of evidence B).

Overall, the manuscript by Kim and co-workers further substantiates our current thresholds for ascending aortic aneurysms both in bicuspid and non-bicuspid aortic patients. However, there are several limitations, some of which have been discussed by the authors (5). One weakness of this study is that the primary lesion (i.e., stenosis *vs.* regurgitation *vs.* mixed lesion) of the bicuspid aortic valve is not captured. Based upon retrospective data, we know that aortic dissection is less frequent in patients with bicuspid aortic stenosis compared to aortic regurgitation (8). Also, the phenotype of bicuspid aortic valve (i.e., Sievert classification) is not collected. This is of importance, as right/left cups fusion morphology in bicuspid aortic valves has been linked with increased diameters of the sinuses of Valsalva (9-11). In contrast, right/noncoronary cusp fusion morphology is associated with smaller dimension of the aortic root and in some studies, larger aortic arch diameters (9-11). Furthermore, the body size of patients is not evaluated. Body size must be considered to help with indexing the aortic diameter to patient's habitus, and correcting the absolute diameters for patients with smaller height. Socio-economic factors also weigh in, for while the number of adverse outcomes was low in this study, this could also be explained by patients having easy access to good medical care. All of these considerations can improve outcomes in addition to conservative follow-up methods for patients, and reduce the dissection or rupture rates. But they may not be available, or statistically representative, for patients in rural areas or less developed countries. In addition, declared institutional bias favoring operations at lower aortic diameters for bicuspid aortic valve patients, can further reduce the incidence of adverse events (i.e., dissection or rupture).

Last but not least, the follow-up was complete in only 82% of patients with an average of 40 months. This is not ideal, but nonetheless is the reality of most aortic outpatient clinics. A significant rate of dissection, rupture or death cannot be excluded in the patients lost from the follow-up process. A statistically complete, 100% follow-up would have likely increased the number of adverse events captured, thereby potentially making a meaningful, multivariate analysis of risk factors possible. This latter point brings us to the importance of the denominator neglect phenomenon. While most studies (including the paper by Kim and co-authors) report the complications, such as dissection or rupture of the ascending aortic aneurysm, there is a paucity of data on the risk of development of these complications (e.g., denominator). Kim and co-workers provide the incidence

of dissection or rupture (numerator) in the cohort, but the patients followed in the aortic clinic hardly represent the entire population at risk for aneurysm formation (denominator).

Aortic diameter and age were the only factors correlated with adverse events in this study (5). Other potential morbidities were chosen. But while aortic diameter should not be the only way to make a decision for recommending surgery, it represents the best measure currently available in clinical practice. As we face the future, we need to incorporate newer diagnostic modalities such as genetics, aortic compliance, rheological forces at the aorta wall, and blood markers of inflammation. All of these methodologies may provide us prognostically more valuable information in achieving more accurate diagnoses in the years ahead.

Last, but not least, reducing morbidity and mortality in patients treated with type A dissection may change (possibly increase) the threshold for elective surgical treatment. While the outcome has just slightly improved with open repair (1,2), endovascular therapy in anatomically suitable high-risk patients may become a viable alternative for these challenging patients (12). Acute type A aortic dissection represents the low hanging fruit for endovascular therapy: it is more feasible for endovascular therapy to cut down on a double-digit mortality in type A aortic dissection, than a low single-digit mortality reduction for elective proximal aortic operations (13). Within next decade, endovascular repair has a high potential for becoming a viable alternative to open repair in high risk patients. It may also become a bridge to definitive open repair, allowing the postponement of open repair to an elective session with significantly lower mortality, a concept that has been used successfully in Marfan patients with acute complicated type B aortic dissection. Of course, many challenges need to be addressed before this could happen. There is need for better, trackable, more conformable, and lower profile devices that are ideally bio-absorbable. Limitations will likely remain patients with diffusely enlarged proximal aortas, where there is no room for a proximal or distal landing zone (12-14).

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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