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Commentary: The X and Y of Zero Gender Gap in outcomes of Aortic Dissection

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Central message: Meta-analytic data are encouraging towards closing gender gap after surgery for aortic dissection, but registries still marking worse outcomes for women and call for concerted action to close the gap.

Central Picture Legend: Christoph A. Nienaber, MD, PhD

Acute aortic dissection is a disruptive event changing life dramatically, with complex phenotypic presentation ranging from non-specific chest or back pain to severe neurological complications, syncope, or even sudden death.

In this issue of JTCVS, sex-based outcomes in acute type A Aortic Dissection derived from meta-analysis and meta-regression of 9,317 patients are reported. On the background of conflicting data on gender differences in perioperative outcomes of aortic surgery in acute dissection meta-information was collected using the Newcastle-Ottawa Quality Assessment scale (NOS) for bias in non-randomized studies. Only 9 publications met criteria to analyse the primary endpoint of in-hospital 30-day mortality, and the secondary cluster endpoint of post-operative stroke, renal failure requiring dialysis, or reoperation for bleeding, and expressed in relation to the outcome of male counterparts. In addition, meta-regression analysis showed female sex was not associated with higher 30-day mortality (RR=1.05; P=0.67), at low publication bias and medium data heterogeneity. Even the secondary cluster endpoint (RR=1.07; P=0.43), need for dialysis (RR=0.84; P=0.32) and reoperation for bleeding (0.84; P=0.003) was similar to men; only preoperative shock was associated with the first endpoint (RR1.1; P=0.04), but not female sex.¹

These results sound reassuring but somewhat surprising, as different from our traditional experience that women are diagnosed later with acute aortic dissection and treated less
extensively than their male counterparts\textsuperscript{2,3} along these lines a closing gender gap was recently confirmed in Germany, Japan and Taiwan\textsuperscript{4-6}. Accordingly, decision making for surgery should not depend on gender, but other risk factors\textsuperscript{4}, while a Japanese single centre study quoted similar early and long-term mortality in female and male patients with a higher rate of reoperations in men\textsuperscript{5}. Finally, population-based cohort studies\textsuperscript{6,7} confirmed no significant gender differences with open repair (type A) and endovascular management (type B) in oriental patients, with a trend for better long-term outcome in males\textsuperscript{7}. So, is it time to say the gap is closed?

The problem with this meta-analysis and meta-regression is that the underlying reasons for equal outcomes in women could not be analysed properly with only 30 days of follow-up. Moreover, type and extent of surgery has not been specified, length of stay and managed complications are not reported; in addition, the percentage of women in those 9 studies was consistently lower that expected which may be related to lower diagnostic yield of dissection in women, or later presentation to emergency care due to atypical symptoms and possibly higher mortality prior to hospital admission; thus, an element of selection bias is difficult to exclude. Underrepresentation of women could reflect biological selection, as admitted cases have declared themselves as likely survivors.

When looking at established registries the in-hospital mortality remains higher among women with acute Type A aortic dissection with some improvement over the last decade\textsuperscript{8}. The International Registry of Acute Aortic Dissection (IRAD) found differences in clinical presentation in women, including older age, distinct imaging features, greater evidence of malperfusion, all suggesting a tailored surgical approach to reduce sex disparities and improve early outcomes\textsuperscript{9}. Despite more frequent complex operations in men including Bentall, complete arch and elephant trunk procedures, early mortality remained higher in women with 16.7\% versus 13.8\%; P=0.039); with adjustment differences between female and
male mortality tapered off over the last decade.\textsuperscript{8} The National Patient Register and Cause of Death Register in Sweden recently published population-based figures with overall incidence of aortic dissection higher than in previous reports, but decreasing in men;\textsuperscript{10} surgical therapy was increasingly used in both sexes with more favourable outcomes, but less frequently offered to elderly patients with sustained difference in both incidence and outcomes among 8,057 individuals of which 3,035 (38\%) were women. Remarkably, the proportion of women was higher among patients dying before admission than in hospitalized women (42\% versus 36\%; P=0.001); those women were 5 years older than men at diagnosis with a 30-day mortality of 26\% versus 21\% in men (P<0.001), and 17\% versus 12\% in men after surgery.\textsuperscript{10} It may be revealing that both analyses from IRAD showed consistently in 2004 and 2011 that women present later as a result of less typical, or less severe symptoms causing delays to diagnosis and treatment, and subsequently, at least in the elderly subgroup, worse prognosis than men.\textsuperscript{2, 3} It appears absolutely justified to question, where we stand and what is true - are we indeed inching towards closing gender gap of surgical outcomes in acute type A aortic dissection? From an aerial view there is room for improvement to ensure equal treatment and better outcomes in both sexes. Delays to diagnosis and subsequent specialist treatment need to be minimised using standardised protocols and swift transportation to specialist centres. Better public awareness for typical symptoms and risk constellations, as well as ongoing education of our junior colleagues in emergency departments are of utmost importance considering that aortic dissection is a relatively rare event. The threshold for CT imaging in the emergency department should be lower.

When it comes to surgery in proximal dissection, a strategic approach is probably the better option with less aggressive surgery in women due to aortic size and fragility to improve survival rather than replacing the entire arch and even parts of the descending aorta at once.\textsuperscript{9} Staged strategies with a deferred endovascular component may minimise the surgical risk;
other potential explanations for differences in surgical outcome may be increased fragility of the aorta in women of older age, hormone deficiency, greater atherosclerotic burden and long-lasting hypertension. While the message is encouraging, I take it with a pinch of salt as meta-analytic approaches and meta-regression calculation provide powerful numbers but lose detail and granularity to explain observations. Conversely, IRAD and the Swedish registry provide detailed analysis of clinical comorbidity, temporal trends and surgical technique applied over the years to male and female patients, showing us that gender gap is still reality although with a trend to narrow. A multifaceted approach is needed, to make sure that women are equally well diagnosed and treated in acute aortic dissection.

Campaigns by the Society of Thoracic and Cardiovascular Surgery, the European Society of Cardiology and the American College of Cardiology/American Heart Association are focussing on public awareness and teaching. Untreated hypertension needs to be understood as a serious risk factor for aortic dissection with recognition of a “new normal” blood pressure\textsuperscript{11}. For the actual treatment of aortic dissection, no matter whether proximal or distal, an expert team of cardiologists, imaging specialists and surgeons should be in place to optimise swift and relevant treatment according to standardised protocols. Finally, lifelong follow-up should be offered in specialised outpatient clinics even reaching out to family members of patients detected and treated with dissection, to teach prevention, smoking cessation, as well as screening for hypertension. Patients with additional risk conditions such as connective tissue disorders should be informed of their elevated risk of dissection in later life and should be made aware of potential symptoms and signs of acute aortic syndrome. Only concerted efforts in our medical community may finally close the narrowing gender gap in aortic dissection.
References:
