IMPULSE: the impact of gender on the presentation and management of aortic stenosis across Europe

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ABSTRACT

Aims There is an increasing awareness of gender-related differences in patients with severe aortic stenosis and their outcomes after surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI).

Methods Data from the IMPULSE registry were analysed. Patients with severe aortic stenosis (AS) were enrolled between March 2015 and April 2017 and stratified by gender. A subgroup analysis was performed to assess the impact of age.

Results Overall, 2171 patients were enrolled, and 48.0% were female. Women were characterised by a higher rate of renal impairment (31.7 vs 23.3%; p<0.001), were at higher surgical risk (EuroSCORE II: 4.5 vs 3.6%; p=0.001) and more often in a critical preoperative state (7.0 vs 4.7%; p<0.001). Men had an increased rate of previous cardiac surgery (9.4 vs 4.7%; p<0.001) and a reduced left ventricular ejection fraction (4.9 vs 1.3%; p<0.001). Concomitant mitral and tricuspid valve disease was substantially more common among women. Symptoms were highly prevalent in both women and men (83.6 vs 77.3%; p<0.001). AVR was planned in 1379 cases. Women were more frequently scheduled to undergo TAVI (49.3 vs 41.0%; p<0.001) and less frequently for SAVR (20.3 vs 27.5%; p<0.001).

Conclusions The present data show that female patients with severe AS have a distinct patient profile and are managed in a different way to males. Gender-based differences in the management of patients with severe AS need to be taken into account more systematically to improve outcomes, especially for women.

INTRODUCTION

Gender differences in the presentation and management of patients with severe aortic stenosis (AS) and their outcomes after an intervention have received increasing attention in recent years. At the time of diagnosis, women tend to be older, more frail, more often symptomatic, with lower glomerular filtration rates and at higher surgical risk than their male counterparts, while men are frequently affected by the consequences of ischaemic heart disease. Furthermore, female hearts and their aortic annuli tend to be smaller which may predispose them to procedure-related complications and poor surgical outcomes.

Key questions

What is already known about this subject?
► There is an increasing awareness of gender-related differences in the characteristics of patients diagnosed with severe aortic stenosis (AS) and their outcomes after surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI).

What does this study add?
► We investigated gender-related patient profiles at the time of diagnosis and the associated treatment decisions, leading to the provision of SAVR or TAVI. Both disease presentation and treatment approaches were found to differ between women and men with severe AS.
► Women were generally older and more symptomatic, despite a lesser degree of concentric LV remodelling. TAVI was more commonly assigned to women than to men, with the inverse true of SAVR.
► These decisions appear to be appropriate in principle given the increased risk for women undergoing surgery.

How might this impact on clinical practice?
► The findings of this study may help to guide treatment decisions for patients with severe AS.
► Future studies, such as RHEIA (NCT04160130), have been initiated to explore the benefits and risks of TAVI and SAVR in men versus women.
These gender differences translate into a differential risk profile for surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI). Indeed, recent large meta-analyses5,6 and a large retrospective study from the STS/ACC TVT registry7 demonstrated improved survival in female versus male patients with AS undergoing TAVI despite their advanced age and increased rates of major peri-procedural vascular complications, bleeding events and strokes. In the recent PARTNER 3 trial,8 which compared surgery with SAVR in low-risk patients, subgroup analyses of the primary endpoint at 1 year showed no heterogeneity of treatment effect by gender (p=0.27), but for women the endpoint rate for SAVR was 18.5% (men 13.8%) and 8.1% for TAVI (men 8.7%), showing a clear trend for an increased benefit of women undergoing TAVI instead of SAVR (rate difference −10.4%; 95% CI −18.3% to −2.5%).

These observations have triggered an investigation into gender-related patient profiles at the time of diagnosis and into the treatment decisions made, leading to the provision of SAVR or TAVI. The analyses are based on the prospective IMPULSE database,9 which enrolled patients at the time of diagnosis in the echo laboratory and followed them for 3 months.

METHODS

The design of the prospective IMPULSE database has been previously described.10 The European registry spanned 23 TAVI/SAVR-equipped centres across 9 countries (Austria, Czech Republic, France, Germany, Italy, the Netherlands, Spain, Switzerland and the UK) and was set up as part of a quality of care initiative for improving the management of patients with severe AS. Enrolment took place between March 2015 and April 2017, with each patient providing written informed consent to participate. Neither patients nor the public were not involved in the design, conduct, reporting or dissemination of our research.

Patients

Patients aged 18 years or older who were diagnosed with severe AS (symptomatic or asymptomatic; defined as aortic valve area (AVA) <1 cm², indexed AVA <0.6 cm²/m², maximum jet velocity (V_max) >4 m/s or mean transvalvular gradient >40 mmHg) after being referred for echocardiography at one of the participating sites were included in the registry. Recruitment was consecutive on a centre level based on the patient’s willingness to participate. For the purposes of the present analysis, the study population was divided into two groups according to gender. A subanalysis comparing males and females aged over 80 years was also carried out.

Data collection

An electronic case report form was used to collect data, which was entered by a dedicated study nurse. Patient demographics, echocardiographic parameters and medical history were recorded at baseline, alongside AS-attributed symptoms (chest pain, shortness of breath and dizziness on exertion/syncope). Surgical risk was calculated using logistic EuroSCORE I and EuroSCORE II risk-stratification tools, with frailty determined by the inability to walk 5 m in ≤6 s and/or to perform activities of daily living.10 Stroke volume and flow rate were not calculated. The decision on which treatment approach to take (TAVI, SAVR, balloon aortic valvuloplasty (BAV), watchful waiting or active decision not-to-treat) and the time between assignment to AVR and its performance were then documented. All data were subject to automatic checks for plausibility and completeness.

Statistics

Following descriptive analysis, continuous variables are presented as means with SDs, with categorical variables presented as absolute values with percentages (%). Comparisons between men and women were made using Pearson’s χ² or Fisher’s exact test for categorical variables and a t-test or Mann-Whitney-Wilcoxon U test for continuous variables. All statistical analysis was performed using SPSS V.24.0 and a p value of <0.05 was considered statistically significant.

RESULTS

A total of 2171 patients were enrolled in the registry of which 48.0% were women (n=1130) and 52.0% men (n=1130) (figure 1). Patient characteristics, symptoms, echocardiographic variables and treatment decisions were compared. As for many of these variables age was a potential confounder, analyses were repeated for the age group of patients over 80 years (women n=571, mean age 85.5 years; men n=435, mean age 85.5 years; p=0.256).

Patient characteristics

In patients diagnosed with severe AS (table 1), women were approximately 3 years older (79.5 vs 76.4 years; p<0.001), had a higher degree of renal impairment (31.7 vs 23.3%; p<0.001), had a higher surgical risk (EuroSCORE II: 4.5 vs 3.6%; p=0.001) and more often in a critical preoperative state (7.0 vs 4.2%; p=0.003). Men, on the other hand, had an increased rate of previous cardiac surgery (9.4 vs 4.7%; p<0.001) and a reduced left ventricular ejection fraction ((LVEF) EF <30% of 4.9 vs 1.3%; p<0.001). As many of these differences were potentially age related, we performed a sensitivity analysis for age. In patients older than 80 years, we essentially confirmed all of the observed differences between women and men, although the difference in haematological disorders and liver disease lost statistical significance. On the other hand, chronic obstructive pulmonary disease, which was borderline more frequent in men for the total population, became significantly more frequent in men versus women over 80 years (15.2 vs 9.2%; p=0.003).

Echocardiographic parameters

Aortic valve–related parameters, such as the indexed AVA and the mean AV gradient were largely identical
between women and men (table 2). While the p value for the mean AV gradient was below 0.05, the means did not show a potentially clinically relevant difference. The heart of women was, on the one hand, smaller (LV mass 128.9 g/m² vs 135.9 g/m²; p=0.001). On the other hand, there was an increased relative wall thickness (0.56 vs 0.50; p<0.001). Concomitant mitral and tricuspid valve disease was substantially more common among women than men, with increased rates of grade III/IV mitral (12.5 vs 9.0%; p=0.010) and tricuspid regurgitation (10.4 vs 5.5%; p<0.001). In a sensitivity analysis for age, the pattern of differences between women and men persisted, while the difference in the mean AV gradient as described earlier lost its statistical significance.

Symptom presentation
Symptoms were defined as any of chest pain, shortness of breath and dizziness/syncope in this registry (figure 2). Symptoms overall were common in both women and men but more frequent by approximately 6% in women (83.6 vs 77.3%; p<0.001). This was largely due to more frequent shortness of breath (77.4 vs 67.5%; p<0.001) and dizziness (27.4 vs 21.4%; p<0.01) in women, while chest pain was equally common in either gender. The sensitivity analysis revealed that the difference in the rate of dizziness/syncope was affected by age (resulting in no difference in patients over 80 years; 28.3 vs 28.2%), while other differences persisted.

Treatment decisions
Of the 2000 patients with a documented treatment decision, AVR was planned in 1379 cases (69%), with BAV, medical management or watchful waiting planned in the remaining 621 patients (31%). This split was uniform across genders (69.5% in women vs 68.5% in men; p=0.614). However, the type of AVR planned differed significantly, with women more frequently being scheduled to undergo TAVI (49.3 vs 41.0%; p<0.001) and less frequently for SAVR (20.3 vs 27.5%; p<0.001) (figure 3; table 3). A higher proportion of women also underwent TAVI within 3 months of the treatment decision (41.3 vs 35.0%; p=0.004). Conversely, a higher proportion of men underwent SAVR within 3 months compared with women (19.9 vs 16.5%; p=0.047). The mean time to AVR (33.0±34.7 days) was comparable between gender groups, with the same true for TAVI (29.2±34.2) and SAVR (40.7±34.5 days) considered separately. The gender-related trends observed in the overall population were also seen in the subset of patients aged >80 years (figure 3; table 3).

**DISCUSSION**
In the present analysis, both disease presentation and treatment approach were found to differ between women and men with severe AS. Women were generally older and more symptomatic, despite a lesser degree of concentric LV remodelling. Although the proportion of patients...
scheduled for AVR was largely comparable between genders, TAVI was more commonly assigned to females than to males, with the inverse true of SAVR. While these decisions appear to be appropriate in principle given the increased risk for women undergoing surgery, the degree of this location shift may be questioned in the absence of additional benefit of TAVI in women compared with men.

Gender and symptomatic presentation

Cardiac symptoms were more common in women compared with men. This trend is consistent with the observations of prior studies, and was primarily driven by shortness of breath and dizziness/syncope. Nevertheless, a lesser degree of concentric remodelling was seen in women at echocardiography. A similar trend was recently observed by Singh et al in their study into the relationship between LV remodelling and AS symptom onset in men and women, with other studies also reporting women to have a higher relative wall thickness, a smaller LV cavity and a lower LV mass index than men in the context of AS chronic pressure overload. Singh et al have suggested that, in the context of these diverse pathophysiological profiles, the higher symptomatic burden in women may be due to higher wall stress and filling pressures. Alternatively, it may be partly reflective of differences in physical activity levels, which are reportedly higher in men than in women. As such, women could describe or be perceived to have more shortness of breath due to a naturally lower exercise tolerance. Indeed, dyspnoea but not dizziness/syncope remained significantly more common in women than men aged over 80 years, despite comparable mean ages. Activity-dependent gender subjectivity may thus be a driver for the apparently higher frequency of symptoms in women. Finally, the higher frequency of concomitant tricuspid/mitral valvular disease in women may have impacted on symptoms, given that shortness of breath is also a manifestation of both of these valvular conditions. Regardless of the underlying explanation, our data support the previously reported trend towards a greater likelihood of symptomatic presentation in women compared with men with severe AS. Considering that symptomatic onset is a key consideration when determining the timing of AVR, this difference has important implications for treatment decisions.

Gender and treatment decision

Early AVR is strongly recommended in all severe symptomatic patients with AS, unless the intervention is unlikely to improve quality of life/survival or the patient has a
life expectancy of less than 1 year. Therefore, given that symptomatic presentation was more common in women, it is surprising that the proportion of patients assigned to AVR did not differ according to gender. This may be partly explained by the counterbalancing effect of a more severely reduced LVEF in men, which is an independent indication for AVR in asymptomatic patients. Regardless, nearly two-thirds of the present study population were denied a life-saving AVR intervention. This rate is similar to that reported by the Euro Heart Survey prior to the widespread diffusion of TAVI. Consequently, it would appear that this minimally invasive alternative to SAVR is being used as an approach to risk reduction in patients previously considered for surgery, but not as a novel option in those considered inoperable. As such, there may be considerable scope for increasing the rate of AVR in clinical practice.

The type of AVR planned differed significantly between genders. In line with previous studies, women were less frequently assigned to SAVR; however, contrary to the existing literature suggesting that comparable proportions of men and women undergo TAVI, a higher rate of TAVI was observed in the latter. This reciprocal trend may be partly explained by the slightly higher surgical risk scores, the older age of our female patients and a smaller valvular anatomy/aortic annulus which are favouring patient prosthesis mismatch in women. The factors are also favouring TAVI over SAVR according to European guidelines. More specifically, the higher prevalence of renal impairment in women (apparent both overall and in the elderly subgroup) is likely to have been a strong deterrent for cardiac surgery, given that it has been previously associated with increased in-hospital mortality and length of hospital/ICU stay in individuals undergoing SAVR. A further consideration is the higher prevalence of coronary artery disease generally seen in men compared with women, which may have resulted in a tendency towards the performance of more AVR/coronary artery bypass graft hybrid interventions in men, increasing the overall proportion undergoing SAVR. Unfortunately, data to support this speculation were not available in the present analysis. Finally, assuming that the physicians responsible for treatment decisions were familiar with contemporary real-world AVR studies, they may have been aware of data suggesting women to have

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Echocardiographic parameters</th>
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<tr>
<td></td>
<td>Total population</td>
</tr>
<tr>
<td></td>
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<tr>
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<td>Mean AV gradient (mm Hg)</td>
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<td>LVEF (%)</td>
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<td>Left ventricle parameters</td>
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<td>LV-ESD (mm)</td>
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<td>Indexed LV mass (g/m²)</td>
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<td>Mitral stenosis III/IV</td>
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<tr>
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Values are reported as mean with SD or as percentage.
*Defined as LV wall thickness >12 mm.
†Calculated as 2×PW/LV−EDD.
AV, aortic valve; AVA, aortic valve area; LVEF, left ventricular ejection fraction; LV, left ventricular; ESD, end-systolic dimension; EDD, end-diastolic dimension; IVS, interventricular septal thickness at end-diastole; PW, posterior wall thickness at end diastole; RWT, relative wall thickness.
superior long-term outcomes and achieve a greater clinical benefit after TAVI compared with SAVR, with greater survival compared with men undergoing this minimally invasive procedure. This may also have contributed to the gender-related disparity in preferred AVR type. Interestingly, several of the factors highlighted in contemporary guidelines as instrumental for choosing between TAVI and SAVR were significantly different between gender groups, but appeared to have little influence on clinical decision-making. For example, significantly more men than women had previously undergone cardiac surgery, which is a characteristic in favour of TAVI, yet fewer men underwent this intervention. Furthermore, age >75 years is another guideline-recommended factor favouring TAVI. Although there was a nominally higher rate of TAVI and lower rate of SAVR in elderly compared with all patients, the sex-dependent differences in treatment decision persisted, with relatively fewer men undergoing TAVI, despite comparable mean ages. Thus, the observed differences in TAVI/SAVR assignment cannot be explained purely as a function of age.

Gender and time to intervention

The waiting time between referral for AVR and its performance appeared to be unrelated to gender, averaging at approximately 30 days in both males and females. This is longer than the 20.3 days reported by a 2014 study, perhaps reflecting the temporal trend towards an increasing prevalence of severe AS in the ageing population, which in turn places a higher burden on healthcare providers.

TAVI waiting times were shorter than SAVR waiting times in both males and females, with no significant differences between gender groups. This suggests that the urgency of the intervention is not sex dependent and largely is restricted by procedure availability. The differences in

Figure 2  Cardiac symptoms at baseline in (A) all patients and (B) those aged >80 years. **p<0.01, ***p<0.001. NYHA class III or IV: female 441/1024 (43.1) vs male 418/1118 (37.4); p=0.007. Angina class III or IV: female 43/909 (4.7) vs male 48/992 (4.8); p=0.912.

Figure 3  Treatment decision in (A) all patients and (B) those aged >80 years. AVR, aortic valve replacement; M, months; SAVR, surgical aortic valve implantation; TAVI, transcatheter aortic valve implantation. *p<0.05, **p<0.001. †Balloon aortic valvuloplasty, medical management or watchful waiting planned. Values are proportional to the number of patients with known treatment decisions.
the proportions of male and female patients who underwent TAVI and SAVR within 3 months of the treatment decision are likely to reflect general differences in AVR assignment. Indeed, when expressed as a proportion of patients initially assigned to the procedure, the rate of TAVI performance within 3 months was the same in men and women. A slight sex-dependent disparity may exist in terms of SAVR, with only 72% of the assigned males undergoing the procedure within 3 months compared with 81% of the assigned females \((p=0.026)\). Speculatively, this may be related to the lower rate of symptoms in males, making them lower priority for such an invasive procedure. This merits further investigation.

**Limitations**

The principal limitation in the present analysis is the lack of adjustment for confounding variables when comparing genders. This means that it is difficult to determine sex-specific trends from those influenced by the particular characteristics of male and female patients with AS. On the other hand, adjustment for gender-specific variables would abolish the clear difference between both gender, making conclusions of the gender impact impossible. As the two are closely linked, the present data provide an overview of the multifactorial gender-related influences that are relevant to clinical practice. While the wide range of countries included is a strength of the registry, our findings may not be generalisable to regions outside of Europe. The interventional portion of the quality of care initiative did not take place until month 3, so did not influence the data presented.

**Clinical implications and perspectives**

There is an ever growing number of patients for whom TAVI is preferred over SAVR, which is due to growing body of evidence for a benefit of TAVI over SAVR in high and prohibitive surgical risk, and also intermediate and even risk patients. This trend is even more important in women than in men, as the benefits of TAVI are pronounced in women: A meta-analysis of randomised trials compared TAVI with SAVR and found that TAVI was associated with a survival benefit compared with SAVR in women but not men.\(^{37,38}\) A further meta-analysis found TAVI to be associated with reduced mortality compared with SAVR in women at both 1 (OR 0.68, 95% CI 0.50 to 0.94) and 2 years of follow-up (OR 0.74, 95% CI 0.58 to 0.95), whereas there was no difference among men at either time point.\(^{38}\) The difference in treatment effect between the sexes was significant at both 1 (\(p=0.02\)) and 2 years (\(p=0.04\)). In the recent PARTNER 3 trial,\(^{10}\) which is pivotal in showing the benefits of TAVI over SAVR in low-risk patients, subgroup analyses of the primary endpoint at 1 year showed no heterogeneity of treatment effect by gender (\(p=0.27\)). However, apart from this non-significant \(p\) value, the endpoint rate in SAVR-treated women was 18.5% (vs 13.8% in men) and 8.1% for TAVI (vs 8.7% in men), showing a clear trend for an increased benefit of women undergoing TAVI instead of SAVR (rate difference −10.4%; 95% CI −18.3% to −2.5%). To shed further light on the potential benefits of TAVI in women, there is an ongoing clinical trial (ClinicalTrials.gov: NCT04160130), which compares either strategy in women undergoing TAVI. Women with severe symptomatic aortic stenosis, with any but prohibitive surgical risk status, will be randomised 1:1 to undergo aortic valve intervention with either transfemoral TAVR with the SAPIEN 3 or SAPIEN 3 Ultra device or SAVR and followed up for 1 year. The authors pursue non-inferiority, but the trial is also powered to show superiority of this approach in women.\(^{39}\)

### Table 3  Treatment decision and time to intervention

<table>
<thead>
<tr>
<th></th>
<th>Total population</th>
<th>Population &gt;80 years</th>
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<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>Decision to perform AVR</td>
<td>69.5</td>
<td>68.5</td>
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<tr>
<td>AVR performed in 3 months</td>
<td>57.8</td>
<td>54.9</td>
</tr>
<tr>
<td>Time to intervention (days)</td>
<td>33.3±34.1</td>
<td>32.8±35.2</td>
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<tr>
<td>Decision made for TAVI</td>
<td>49.3</td>
<td>41.0</td>
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<tr>
<td>TAVI performed in 3 months</td>
<td>41.3</td>
<td>35.0</td>
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<tr>
<td>Time to intervention (days)</td>
<td>30.2±34.2</td>
<td>28.1±34.1</td>
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<tr>
<td>Decision made for SAVR</td>
<td>20.3</td>
<td>27.5</td>
</tr>
<tr>
<td>SAVR performed in 3 months</td>
<td>16.5</td>
<td>19.9</td>
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<tr>
<td>Time to intervention (days)</td>
<td>40.8±32.8</td>
<td>40.7±35.8</td>
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<tr>
<td>Decision not to perform AVR*</td>
<td>30.5</td>
<td>31.5</td>
</tr>
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</table>

Values are reported as mean with SD or as percentage. *Balloon aortic valvuloplasty, medical management or watchful waiting planned instead.

AVR, aortic valve replacement; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve replacement.
CONCLUSION
The present contemporary data from major treatment centres across Europe show that female patients with severe AS have a distinct patient profile and are managed in a different way to males with the same condition. Gender-based differences in the management of patients with severe AS need to be taken into account more systematically to improve outcomes, especially for women.

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Acknowledgements Data were captured using the #trials Software provided by Software for Trials Europe GmbH, Berlin, Germany.

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Funding This work was supported by a research grant from Edwards Lifesciences (Nyon, Switzerland), awarded to the Sponsor, the Institute for Pharmacology and Preventive Medicine (IPPMed, Cloppenburg, Germany).

Competing interests PB is the representative of the IPPMed, Cloppenburg, Germany. NF, RPS and DM-Z have received honoraria for advisory board meetings and TBK speakers’ honoraria from Edwards Lifesciences. The institutions of those three and those of the remaining authors representing study centres have received funding for employing a study nurse. JK and MT are employees of the funder of this registry. As this is a disease registry, neither the type of intervention (SAVR, TAVI or medical management) nor on the valves to be used was pre-specified.

Patient consent for publication Not required.

Ethics approval The study was carried out in accordance with the Declaration of Helsinki and was approved by the independent ethical review board at each participating institution.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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