Transcatheter or surgical aortic valve replacement in patients with severe aortic stenosis aged 70 years or younger: A NOTION-2 substudy

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ABSTRACT This NOTION-2 sub-study revealed distinct outcomes for transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) in low surgical risk patients aged ≤ 70 years with a tricuspid or bicuspid aortic valve stenosis (AS). One year after intervention, the risk of death, stroke or rehospitalization in patients with tricuspid AS was similar after TAVR when compared to SAVR (absolute risk difference: −2.0%; 95% confidence interval (CI): −11.8% to 7.7%) Conversely, in patients with bicuspid AS, TAVR was associated with a significantly higher risk of adverse outcomes (absolute risk difference: 13.8%; 95% CI: 1.2% to 26.3%). These analyses are exploratory, but highlight the importance of tailoring the intervention to the patient's clinical risk profile, life expectancy, native aortic valve morphology and the anticipated risks associated with TAVR or SAVR. (Am Heart J 2025;284:67–70.)

Background

On the basis of evidence from large clinical trials, transcatheter aortic valve replacement (TAVR) has evolved into an alternative strategy to treat patients with severe symptomatic aortic stenosis (AS) across the spectrum of surgical risk.[1-9] In Europe, TAVR is the first-choice therapy for patients aged ≥75 years, whilst the procedure is now used widely to treat younger patients in the USA.[1,10] As TAVR is increasingly adopted, critical appraisal of its safety and efficacy relative to surgical aortic valve replacement (SAVR) in younger low-risk patients remains essential. Herein, we report a sub-study of the NOTION-2 randomised clinical trial, aiming to investigate and report the clinical outcomes of TAVR compared to SAVR in low-risk AS patients aged ≤ 70 years.

Methods

NOTION-2 was an investigator-driven, multicentre, randomised clinical trial that compared transfemoral TAVR with standard SAVR in low surgical risk patients aged ≤ 75 years with severe symptomatic AS. Uniquely, patients with bicuspid AS were not excluded (ClinicalTrials.gov Identifier: NCT02825134).[11] Only patients aged 70 years or younger were included in the current sub-study, resulting in 158 subjects randomised to TAVR ($n = 81$) or SAVR ($n = 77$) (Figure 1A). The primary endpoint was defined as a composite risk of death, stroke, or rehospitalization (related to the procedure, valve, or heart failure). Statistical analyses were conducted on the intention-to-treat (ITT) population and sub-analyses performed for patients with native bicuspid and tricuspid aortic valves. The trial was funded by Abbott (MN, USA); Boston Scientific (MA; USA) and Edwards Lifesciences (CA, USA). The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final content.

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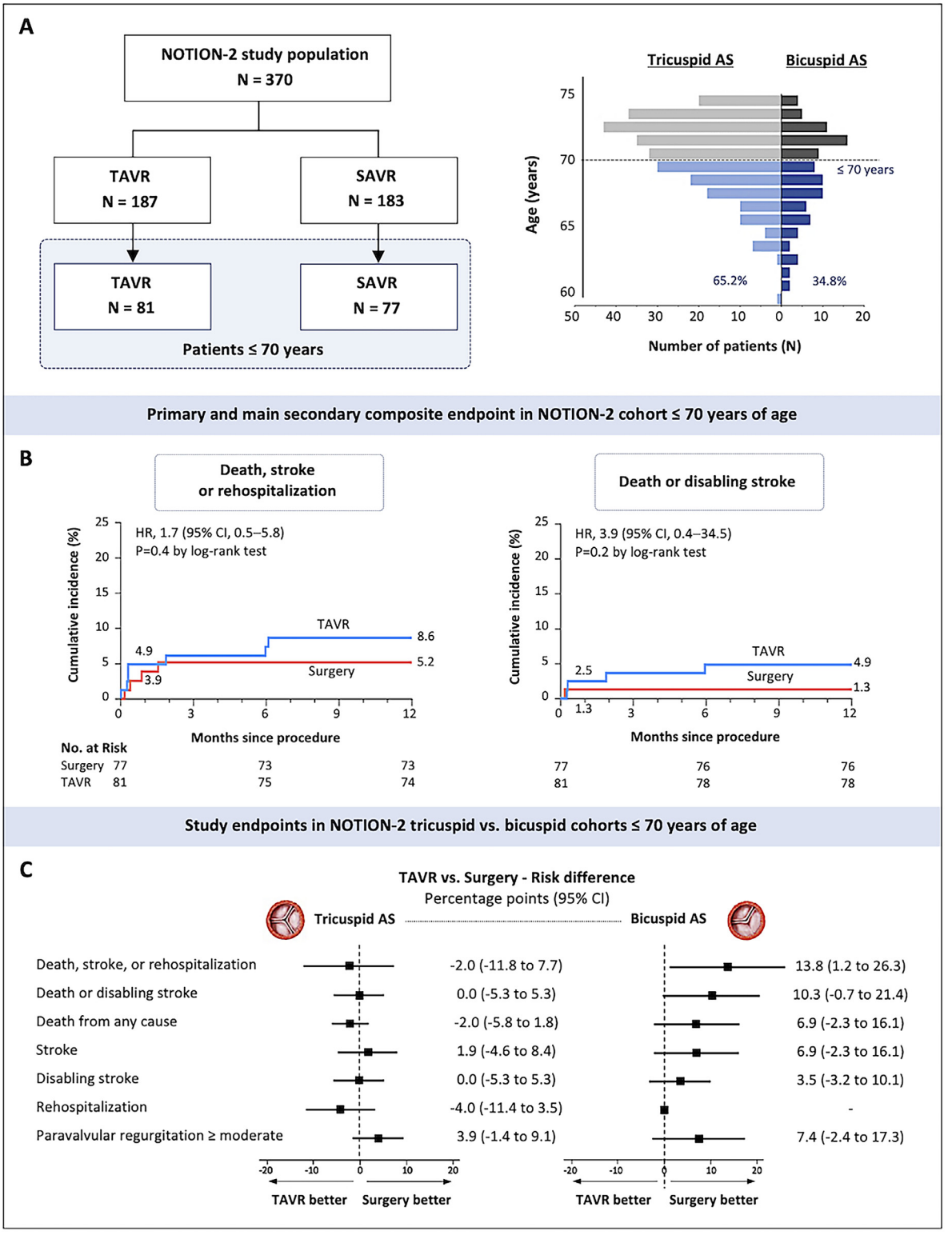
Figure 1. TAVR vs SAVR in low-risk patients aged 70 years or younger. SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.



Results

The study population had a median age of 68 years, 71% were male and the median STS-PROM score was 1.0 (IQR: 0.8-1.2). Baseline characteristics were balanced between the 2 treatment groups and a total of 55 patients (35%) had a native bicuspid aortic valve.

The primary endpoint was observed at 12 months in 8.6% and 5.2% (HR 1.7; 95% CI: 0.5-5.8) of patients in the TAVR and SAVR cohorts, respectively (Figure 1B). The risk of the individual components was 2.5% and 1.3% (HR: 1.9; 95% CI: 0.2-21.0) for death, 4.9% and 1.3% (HR: 3.9; 95% CI: 0.4-34.8) for stroke, and 1.2% and 3.9% (HR 0.3; 95% CI: 0.03-3.1) for rehospitalization after TAVR and SAVR, respectively. At discharge, 9.0% of TAVR patients and 15.5% of SAVR patients had measured severe prosthesis-patient mismatch; whereas 5.1% and 0.0% of TAVR and SAVR patients had a moderate or greater aortic regurgitation (which was solely paravalvular regurgitation [PVR]) at 1 year. The rate of moderate or greater PVR was 3.9% and 7.4% in the tricuspid and bicuspid TAVR cohorts, respectively. After 1 year of follow-up the risk of permanent pacemaker was 16.3% and 8.3% (HR: 2.1; 95% CI: 0.8-5.5) in the TAVR and SAVR groups, respectively, with no significant differences between tricuspid and bicuspid AS cohorts.

In patients with tricuspid AS, the incidence of the hard combined endpoint of death or disabling stroke was 2.0% at 12 months in both treatment arms (risk difference 0.0%; Figure 1C). Patients with bicuspid AS exhibited a markedly higher risk of death or disabling stroke after TAVR (10.3%) compared to SAVR (0%; risk difference 10.3%; Figure 1C).

Discussion

Consistent with the main study analysis, the primary endpoint of all-cause mortality, stroke and rehospitalization at one year was similar in the TAVR and SAVR cohorts (8.6% and 5.2%, respectively) in this low-risk AS population aged 70 years or younger. Of note, there was a relatively high rate of prosthesis-patient mismatch (15%) in the NOTION-2 SAVR cohort, which was higher than in other low-risk TAVR vs. SAVR trials.[5,6] Although reflecting contemporary SAVR practice in the Northern European countries, the question could be raised whether aortic root enlargement could have been applied more often, especially when intervening on young AS patients with a long life-expectancy. However, aortic root enlargement can come at a cost of longer aortic cross clamp times and increased risk of operative mortality, which could have had a negative impact on the short-term SAVR outcomes in this trial.[12]

Importantly, there were strikingly different outcomes with TAVR and SAVR in the tricuspid and bicuspid AS cohorts. In patients with tricuspid AS, the incidence of the hard combined endpoint of death or disabling stroke was 2.0% in the TAVR and SAVR cohorts in this analysis, which is in line with the rate of death or disabling stroke at one year in the PARTNER-3[5] (TAVR: 1.0%, SAVR: 2.9%) and Evolut Low-Risk[6] (TAVR: 2.9%; SAVR: 4.6%) trials. The findings of this NOTION-2 sub-study therefore contribute to the growing body of evidence supporting TAVR as a viable alternative to SAVR in younger low-risk patients with native tricuspid AS.

However, a different picture emerged for the bicuspid AS cohort. Notably, 35% of enrolled patients had a native bicuspid AS and exhibited worse than expected outcomes. This is possibly related to the fact that cases were not assessed by a selection committee, resulting in the inclusion of bicuspid AS patients with an unfavourable anatomy for TAVR and, hence, a higher risk of procedural complications and significant PVR than observed in the SAVR or tricuspid TAVR cohorts. Conversely, the absence of any primary endpoint in the bicuspid cohort that underwent SAVR may be explained by their low mean age (66.8 years) and low surgical risk (STS-PROM 0.8), lower than in any other low-risk TAVR trial. Regardless, caution is warranted when expanding the use of TAVR in young bicuspid AS patients, particularly those who have a low surgical risk.

The limitations of this NOTION-2 sub-study are numerous. Firstly, the population sample was small and all analyses were exploratory. Secondly, we are currently only able to address one-year clinical outcomes and longer-term follow-up will be necessary to demonstrate improved prognosis in this subset of younger low-risk patients.

In conclusion, this analysis was exploratory and found the risk of death, stroke or rehospitalization at one year to be similar in low-risk AS patients aged $\leq$ 70 years treated with TAVR or SAVR. However, this risk was higher with TAVR compared to SAVR in the bicuspid AS cohort. Hence, the mode of intervention should be tailored to the patient's clinical risk profile, life expectancy, native aortic valve morphology and the anticipated risks associated with TAVR or SAVR.

Conflict of interest

Savontaus, M. received honoaria from Medtronic, Boston Scientific and Edwards LifeSciences; Angerås, O. received honoraria from Medtronic, Abbott, Meril and support for attending meeting and travel from Meril, Abbott; Rück, A. received grants, consulting fees and participated in data safety monitoring board with Boston Scientific; Christiansen, E. received honoaraia from Meril; Predergast, B is in advisory Board Anteris, Trial Steering Committee Medtronic and Data Safety Monitoring Committee Valvosoft; Leon M has recieved grant from Edwards Lifesciences, Abbott Vascular and Medtronic, consultant fees from Foldax and Anteris, is in data saftemonitoring board with Medtronic, have leadership role

in Heart Valve Collaboratory and stocks in Pi-Cardia; Søndergaard, L. is employee at Abbott; De Baclker, O. received consulting fees from Abott, Boston Scientific, Medtronic.

CRediT authorship contribution statement

Troels Højsgaard Jørgensen: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Hans Gustav Hørsted Thyregod:** Conceptualization, Methodology, Writing – original draft. **Mikko Savontaus:** Investigation, Data curation. **Öjvind Bleie:** Investigation, Data curation. **Evald H Christiansen:** Investigation, Data curation. **Matti Niemela:** Investigation, Data curation. **Oskar Angerås:** Investigation, Data curation. **Ingibjörg J. Gudmundsdóttir:** Investigation, Data curation. **Mika Laine:** Investigation, Data curation. **Andreas Rück:** Investigation, Data curation. **Bernard Prendergast:** Writing – review & editing, Conceptualization. **Martin Leon:** Writing – review & editing, Conceptualization. **Lars Søndergaard:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ole De Backer:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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