AUTHOR(S) Jørgensen TH, Thyregod HGH, Savontaus M, Willemen Y, Bleie Ø, Tang M, Niemela M, Angerås O, Gudmundsdóttir IJ, Sartipy U, Dagnegaard H, Laine M, Rück A, Piuhola J, Petursson P, Christiansen EH, Malmberg M, Olsen PS, Haaverstad R, Sondergaard L, De Backer O; NOTION-2 investigators.

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Transcatheter Aortic Valve Implantation in Low-Risk Tricuspid or Bicuspid Aortic Stenosis: The NOTION-2 Trial

Troels Højsgaard Jørgensen, MD, PhD[1], Hans Gustav Hørsted Thyregod, MD, PhD[1], Mikko Savontaus, MD, PhD[2], Yannick Willemen, MD, PhD[1], Øyvind Bleie, MD, PhD[3], Mariann Tang, MD; PhD[4], Matti Niemela, MD, PhD[5], Oskar Angerås, MD, PhD[6], Ingibjörg J. Gudmundsdóttir, MD, DM[7], Ulrik Sartipy, Md, PhD[9] Hanna Dagnegaard, MD, PhD[1], Mika Laine, MD, PhD[8], Andreas Rück, MD, PhD[9], Jarkko Piuhola, MD, PhD[5], Petur Petursson, MD, PhD[6], Evald H Christiansen MD, PhD[4], Markus Malmberg, MD, PhD[2], Peter Skov Olsen, MD, DMSc[1], Rune Haaverstad, MD, PhD[3], Lars Sondergaard, MD, DMSc[10], Ole De Backer, MD, PhD[1], for the NOTION-2 investigators

[1] Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

[2] Turku University Hospital, Turku, Finland

[3] Haukeland University Hospital, Bergen, Norway

[4] Skejby, Aarhus University hospital, Aarhus, Denmark

[5] Department of Cardiology, Medical Research Center, Oulu University Hospital, Oulu, Finland

[6] Sahlgrenska University Hospital, Göteborg, Sweden

[7] Landspitali, Reykjavík, Iceland

[8] Helsinki University Central Hospital, Helsinki, Finland

[9] Karolinska University Hospital, Stockholm, Sweden

[10]Abbott Structural Heart, Santa Clara, California, US

The complete list of NOTION-2 Investigators is provided in the Supplementary Appendix.

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Corresponding author

Ole De Backer, MD, PhD

The Heart Center - Rigshospitalet

University of Copenhagen
Inge Lehmanns Vej 7
Copenhagen, Denmark
Tel: +45-3545 7086
E-mail: ole.de.backer@regionh.dk

ABSTRACT

Background and Aims. Transcatheter aortic valve implantation (TAVI) has become the first choice to treat older patients with severe symptomatic aortic stenosis (AS). This study aimed to compare TAVI with surgery in low-risk patients ≤ 75 years of age, including both tricuspid and bicuspid AS.

Methods. The NOTION-2 trial enrolled and 1:1 randomized low-risk patients aged ≤ 75 years with severe symptomatic AS to TAVI or surgery. The primary endpoint was a composite of all-cause mortality, stroke or rehospitalization (related to the procedure, valve or heart failure) at 12 months.

Results. A total of 370 patients were enrolled with a mean age of 71.1 years and a median Society of Thoracic Surgeons risk score of 1.1%. A total of 100 patients had bicuspid AS. The 1-year incidence of the primary endpoint was 10.2% in the TAVI group and 7.1% in the surgery group (absolute risk difference 3.1%; 95% confidence interval [CI], −2.7% to 8.8%; hazard ratio (HR) 1.4, 95% CI: 0.7 to 2.9; p=0.3). Patients with TAVI, when compared to surgery, had lower risk of major bleeding and new-onset atrial fibrillation and higher risk of non-disabling stroke, permanent pacemaker implantation and moderate-or-greater paravalvular regurgitation. The risk of the primary composite endpoint was 8.7% and 8.3% in patients with tricuspid AS (HR 1.0, 95% CI: 0.5 to 2.3) and 14.3% and 3.9% in patients with bicuspid AS (HR 3.8, 95% CI: 0.8 to 18.5) treated with TAVI or surgery, respectively (P for interaction=0.1).

Conclusions. Among low-risk patients aged ≤ 75 years with severe symptomatic AS, the rate of the composite of death, stroke, or rehospitalization at one year was similar between TAVI and surgery. TAVI outcomes in young bicuspid AS patients warrant caution and should be further investigated. (NOTION-2, ClinicalTrials.gov, NCT02825134).

INTRODUCTION

The role of transcatheter aortic valve implantation (TAVI) in the treatment of patients with severe, symptomatic aortic stenosis (AS) has evolved on the basis of evidence from clinical trials (1–11). This resulted in a steady expansion of indications for TAVI in both the European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) and the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of valvular heart disease (12,13). Both guidelines highlight patient age and life expectancy as major considerations when deciding on surgical aortic valve replacement (SAVR) or TAVI. The European guidelines recommend SAVR for low surgical risk patients <75 years of age and TAVI for patients ≥75 years of age. The American guidelines use an age threshold of <65 years or a life expectancy >20 years to recommend SAVR and an age >80 years or a life expectancy <10 years to recommend TAVI. In addition, the American guidelines recommend SAVR for patients with a bicuspid aortic valve, whereas the European guidelines offer no formal recommendation but note that SAVR is more appropriate in case of bicuspid AS and associated aortopathy.

Despite insufficient evidence regarding the comparison of TAVI with SAVR in patients younger than 75 years, there is already a strong adoption of TAVI to treat younger low-risk patients, especially in the United States (14,15). In this study, we report the findings of the Nordic Aortic Valve Intervention (NOTION)-2 trial, in which TAVI was compared with surgery in low-risk patients ≤75 years of age and including both tricuspid and bicuspid AS.

METHODS

Trial design

The NOTION-2 trial was an investigator-initiated and -driven, multicenter, randomized trial in which transfemoral TAVI was compared with standard SAVR in patients ≤75 years of age with severe symptomatic aortic AS and a low surgical risk (Society of Thoracic Surgeons [STS] mortality risk score <4%). Patients were enrolled across nine centers in Denmark, Norway, Sweden, Finland and Iceland with the first patient enrolled June 30th, 2016 and enrollment ended February 2023. The regional ethical review boards approved the study protocol at each site and the trial was conducted according to the principles of the Declaration of Helsinki. The trial sponsor was The Heart Center, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. All data were collected and stored by the investigators and externally monitored (Supplementary Appendix, Section A-B).

Patients

Eligible patients were ≤75 years of age with a severe tricuspid or bicuspid AS (aortic valve area <1.0 cm^2 or <0.6 cm^2/m^2 and mean transvalvular gradient >40 mmHg or peak jet velocity >4.0m/s), with an estimated low 30-day mortality risk after surgery (STS score <4%) and suitable to undergo both transfemoral TAVI or SAVR. Patients with an ascending aorta ≥45 mm or coronary artery disease not suitable for both percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery were excluded. A list of all in- and exclusion criteria can be found in the Supplementary Appendix, Section D.

Study procedures

Patients were randomized in a 1:1 ratio; the randomization was stratified for gender, the need for coronary revascularization and valve morphology (bicuspid vs. tricuspid) as assessed by cardiac computed tomography scan. Screening and enrollment were performed by the local Heart Teams and investigators. The choice of type and size of transcatheter or surgical aortic bioprosthesis was left at the discretion of the treating physician. In case of need for coronary artery revascularization in the TAVI arm, PCI was performed prior to or concomitant with TAVI. The choice of post-procedural antithrombotic therapy was as per local protocol. Patients were followed with registration of clinical status, New York Heart Association (NYHA) class, Kansas City Cardiomyopathy Questionnaire (KCCQ) and echocardiography at baseline, discharge, one month and one year, and then yearly up to ten years after the procedure.

Study endpoints

The primary endpoint was a composite risk of death of any cause, stroke or rehospitalization (related to the procedure, valve or heart failure) at one year after the procedure.

The list of secondary endpoints includes death of any cause, stroke (disabling and non-disabling), major or life-threatening bleeding, new-onset atrial fibrillation, need for permanent pacemaker implantation, valve endocarditis, valve thrombosis, need for valve re-intervention and valve performance as assessed by transthoracic echocardiographic at one month and one year after the procedure (Supplementary Appendix, Sections F-G).

The NOTION-2 trial has been an externally monitored study and all primary events were assessed and revalidated by an independent Clinical Event Adjudication Committee.

Statistical analyses

For the study sample size calculation, it was estimated that a sample of 372 patients would provide the trial 90% power to show the non-inferiority of TAVI to surgery with regard to the primary endpoint at 1 year, assuming a Kaplan–Meier estimate of the primary endpoint of 10% in the TAVI group and 15% in the surgery group. To test for non-inferiority, we determined whether the upper boundary of the 95% confidence interval (CI) for the difference in the rate of the primary endpoint between the TAVI and surgery group was less than the prespecified non-inferiority margin of 5 percentage points.

The primary analysis was calculated and compared in the intention-to-treat (ITT) population. Further sub-analyses should be considered exploratory and were calculated for the as-treated population, as well as for the tricuspid and bicuspid AS populations separately.

Categorical values were presented as counts and percentages and compared with a Chi-square or Fisher's exact test. Continuous variables were presented as mean and standard deviation or median and interquartile range (IQR) and respectively compared with a Student's *t*-test or Wilcoxon signed-rank test. Time-to-event analyses were performed with Kaplan-Meier estimates and comparisons with a log-rank test. The cumulative incidence of stroke, rehospitalization, bleeding, vascular complications, acute kidney injury, new-onset atrial fibrillation, permanent pacemaker, endocarditis, myocardial infarction, valve thrombosis and aortic reintervention was estimated with the Aalen-Johansen method with death as competing risk and groups were compared using a Gray's test. Patients with atrial fibrillation or a permanent pacemaker at baseline were excluded from the respective analyses to calculate the cumulative incidence of new-onset atrial fibrillation and need for a permanent pacemaker implantation. The association between exposure and the primary and

secondary endpoints were analyzed with Cox regression and reported as hazard ratio (HR) with a 95% CI. Sub-analyses of the association between exposure and primary and secondary endpoints in patients with bicuspid and tricuspid AS were performed with calculation of risk differences in percentage points. All tests used a 2-sided significance level of 5%. All statistical analyses were performed by means of SAS Guide 8.3 (SAS Institute, Cary, NC, USA).

RESULTS

Patients

A total of 376 patients were enrolled, five patients withdrew consent, and one patient was a screening failure, resulting in 187 and 183 patients randomized to TAVI and surgery in the ITT population (N = 370), respectively. Two patients crossed over from TAVI to surgery and 9 patients crossed over from surgery to TAVI prior to intervention, resulting in 194 patients in the TAVI and 176 patients in the surgery group in the as-treated population (Figure S1, Figure 1).

Baseline characteristics were balanced between the two groups. The mean age of the patients was 71.1 years, with 42.7% of patients being 70 years or younger and the median STS score was 1.1%. A total of 100 patients (27%) had a native bicuspid aortic valve verified by cardiac computed tomography (Table 1).

In the TAVI group, self-expanding and balloon-expandable transcatheter aortic valves were used to treat 72.7% and 25.7% of patients, respectively, and 5.9% of patients were revascularized prior to or during TAVI. A cerebral embolic protection device was used in 15.5% of TAVI patients. In the surgery group, 68.8% of patients were treated with a CE Magna or Perimount bioprosthesis and 9.8% underwent concomitant CABG (Table S4).

Primary endpoint

At one year, data regarding the primary endpoint were available for 100% of the patients. In the ITT population, the risk of death from any cause, stroke or rehospitalization at 1 year was 10.2% in the TAVI group and 7.1% in the surgery group, with an absolute risk difference between the TAVI and surgery group of 3.1% (95% CI, -2.7% to 8.8%; P=0.3) and a HR of 1.4 (95% CI, 0.7 to 2.9; P=0.3). The risk estimates of the individual components are also shown in Figure 2 and Table 2.

The results were similar in the as-treated population with a primary endpoint risk of 9.8% in the TAVI group and 7.4% in the surgery group; resulting in an absolute risk difference of 2.4% (95% CI, -3.3% to 8.1%; P=0.4) and a HR of 1.3 (95% CI, 0.7 to 2.7; P=0.4) (Figure S3; Table S9).

Secondary clinical endpoints

At one year, the cumulative incidence rates in the TAVI group compared with the surgery group were lower for major or life-threatening bleeding (4.8% vs. 17.5%; HR 0.3; 95% CI, 0.1 to 0.5) and new-onset atrial fibrillation (3.2% vs. 41.7%; HR 0.06; 95% CI: 0.03 to 0.2) and higher for non-disabling stroke (3.7 vs. 0.5%; HR 7.0; 95% CI 0.9 to 56.5) and permanent pacemaker implantation (15.1% vs. 8.0%; HR 2.0; 95% CI, 1.1 to 3.8). The risk of major vascular complications and myocardial infarction were similar between the two groups. A similar trend in outcomes was observed after just one month of follow-up (Table S8). Finally, the length of index hospitalization was significantly shorter in the TAVI group as compared to the surgery group (median: 3 days vs. 7 days; P<0.001; Table 2).

Valve performance

At 30 days, the mean trans-prosthetic gradient was 12.0 mmHg in the TAVI group and 12.9 mmHg in the surgery group. The mean aortic valve orifice area was 1.8 cm^2 and 1.7 cm^2, respectively (Figure 3A). The TAVI group had a higher risk of moderate or greater paravalvular regurgitation (PVR) as compared to the surgery group (4.7% vs. 0%; P<0.01) (Figure S9), a lower risk of severe patient-prosthesis mismatch (10.1% vs. 19.4%; P=0.02) and a similar risk of aortic valve re-intervention (1.1 vs. 2.2; P=0.4) at 1 year of follow-up (Table 2). Analyses in the as-treated population showed similar results and can be found in Figure S6 and Table S9.

Functional outcomes

Dyspnea as measured by NYHA class II-IV was experienced at one month and one year of follow-up in 28% and 22% of patients in the TAVI group and 42% and 29% in the surgery group, respectively (Figure 3B). The KCCQ overall summary score improved from baseline to one month by 16% in the TAVI group and 4% in the surgery group and improved by 17% in both groups at one year of follow-up (Figure 3C). At one year of follow-up, 85% of patients in both groups had a KCCQ overall summary score ≥ 50 points (fair or greater health status) and avoided a decline of > 10 points (equivalent to a moderate deterioration). Analyses for the as-treated population showed similar results and are shown in Figure S6.

Outcomes in tricuspid vs. bicuspid AS

In the overall study population, 270 patients had a tricuspid AS and 100 patients a bicuspid AS. Patients in the tricuspid cohort had a mean age of 71.5 years, whereas patients with a bicuspid AS had a mean age of 69.9 years. Baseline characteristics were balanced between the two treatment groups in both patient cohorts (Tables S2-S3 and S6-S7).

In the tricuspid cohort, the risk of the primary endpoint was 8.7% in the TAVI and 8.3% in the surgery group, resulting in an absolute risk difference of 0.4% (95% CI, -6.3% to 7.0%) and a HR of 1.0 (95% CI, 0.5 to 2.3; P=0.9). The risk of death or disabling stroke at 1 year was 2.2% in the TAVI and 1.5% in the surgery group, resulting in an absolute risk difference of 0.7% (95% CI, -2.5% to 3.9%) and a HR of 1.4 (95% CI, 0.2 to 8.5; P=0.7) (Figure 4, Figure S4, Table S10).

In the bicuspid cohort, the risk of the primary endpoint was 14.3% in the TAVI and 3.9% in the surgery group, resulting in an absolute risk difference of 10.4% (95% CI, -0.8% to 21.5%) and a HR of 3.8 (95% CI, 0.8 to 18.5; P=0.07). The risk of death or disabling stroke at 1 year was 6.1% in the TAVI and 2.0% in the surgery group, resulting in an absolute risk difference of 4.1% (95% CI, -3.6% to 11.9%) and a HR of 3.1 (95% CI, 0.3 to 30.0; P=0.3) (Figure 4, Figure S5, Table S11). The P-value for interaction between TAVI and surgery as well as bicuspid and tricuspid AS was 0.1.

Regarding valve performance, there was a markedly higher rate of moderate or greater PVR in the bicuspid TAVI cohort as compared to the bicuspid surgery cohort, resulting in an absolute risk difference of 9.1% (95% CI, 0.6% to 17.6%); this is a 3-fold higher risk as observed in the tricuspid cohort. Finally, the risk for a permanent pacemaker between treatment groups was not markedly different in the tricuspid vs. bicuspid cohorts (Figure 4C).

DISCUSSION

There are three main findings of the NOTION-2 trial. First, there was clinical equipoise for TAVI vs. surgery in the overall study cohort with regard to the primary composite endpoint of death, stroke, or rehospitalization at one year, although the underpowered sample size complicates a definitive assessment of the study hypothesis. Second, analysis of key secondary endpoints showed that TAVI was associated with a significantly higher rate of non-disabling stroke, PVR and new pacemaker implantation, but also a significantly lower rate of new-onset atrial fibrillation and major bleeding than surgery. The between-group differences in non-disabling stroke and PVR can mainly be ascribed to a higher rate of these events in the bicuspid TAVI cohort (Structured Graphical Abstract). Third, patients who underwent TAVI had a more rapid improvement in NYHA class and KCCQ than those who underwent surgery.

TAVI has revolutionized the treatment of patients with severe, symptomatic AS. Initially limited to high surgical risk patients, indications for TAVI have expanded to intermediate- and low-risk patients through a rigorous series of clinical trials comparing TAVI with SAVR (1–11). Currently, there are three randomized clinical trials - NOTION, PARTNER 3, and Evolut Low-Risk - which evaluated TAVI in low surgical risk patients (3,7,10,16). All three trials showed that TAVI was non-inferior to surgery and this with 4-year to 10-year follow-up data available. An important limitation of these low-risk TAVI trials is that patients were in their mid-70s or older when enrolled in the trial and bicuspid aortic valves were excluded.

The NOTION-2 trial is the first-ever trial comparing TAVI with surgery in patients ≤75 years of age and not excluding bicuspid aortic valves. As bicuspid AS is more commonly

diagnosed in young patients, it is highly relevant to include bicuspid AS in a trial comparing both treatment modalities in a young population (17). The NOTION-2 study population has a mean age of 71.1 years with a median STS score of 1.1% (18). In comparison, the mean age of the PARTNER 3 and Evolut Low-Risk study populations was 73.9 and 73.5 years, respectively, with a mean STS score of 1.9% in both populations (19,20).

In the NOTION-2 trial, surgical outcomes were favorable; the rate of death at 30 days was 1.1%, and the rate of a composite of death or disabling stroke at one year was 1.6%. In the TAVI group, the rate of death at 30 days was even lower (0.5%), whereas the rate of death or disabling stroke at one year was 3.2% in the overall TAVI cohort - however, with a striking difference in this outcome between the tricuspid (2.2%) vs. bicuspid (6.1%) TAVI cohort. In comparison, the 1-year incidence of death or disabling stroke has been reported to be 1.0%, 2.9% and 3.8% in the TAVI cohorts of the PARTNER 3, Evolut Low-Risk and DEDICATE trials, respectively (9, 19, 20). Unfortunately, the reported outcomes in these trials are difficult to compare as different in- and exclusion criteria were applied.

Three disabling strokes were noted in the NOTION-2 TAVI cohort: one haemorrhagic stroke (day 9), one infective endocarditis-related stroke (day 107), and one ischemic stroke (day 181). In addition, seven non-disabling strokes were noted. Complete symptom resolution was noted after few days/weeks in five patients. In two patients, there was only partial or no resolution of the neurological symptoms; these were two bicuspid AS patients treated with TAVI and without use of cerebral embolic protection. Remarkably, 5 out of 10 strokes in the TAVI cohort occurred beyond 30 days (all in the tricuspid cohort); whether this is related to (a) specific transcatheter aortic valve type(s), valve under-expansion or the

prescribed anti-thrombotic therapy should be investigated in future properly-powered studies.

In line with these observations, reported stroke rates at one year after TAVI in bicuspid AS in the non-randomized prospective BIVOLUTX (5.3%), Low-Risk TAVI Bicuspid (1.6%) and Evolut Low-Risk Bicuspid (4%) registries have been higher than in contemporary low-risk TAVI trials in patients with tricuspid AS (21–23). Higher stroke rates with TAVI in bicuspid AS were also observed in registry studies with intermediate- and high-risk patients (24–26). Excessive aortic valve calcification, more need for balloon pre- and post-dilation, and more frequent valve repositioning may be reasons for an increased stroke risk in bicuspid AS patients treated with TAVI (26,27).

Contrarily, the primary event rate in the surgery group was lower in patients with a bicuspid (3.9%) as compared a tricuspid (8.3%) aortic valve. This may be related to a slightly younger age and better cardiovascular risk profile of the bicuspid AS cohort. Similar differences in baseline characteristics and outcomes in bicuspid vs. tricuspid AS patients undergoing SAVR have recently been reported by Hirji et al. (2023) (28). On the other hand, we also have to be humble and aware of that this may simply be a play of chance, taking into account the relatively small bicuspid AS cohort in this trial.

Similar to previous trials, new-onset atrial fibrillation and major bleeding occurred less frequently with TAVI than with surgery. Results of other secondary endpoints, including new pacemaker implantation and PVR, favored surgery (1–11). The rates of new pacemaker implantation were not different in TAVI patients with a native bicuspid (14.6%) vs. tricuspid AS (15.2%). However, there was a marked difference in moderate or greater PVR rates in TAVI patients with a bicuspid (9.1%) vs. tricuspid AS (3.1%). Finally, the trial results indicate that TAVI patients had a more rapid improvement in NYHA class and

KCCQ score than those who underwent surgery. Importantly, patients reached a similar clinical and functional status at one-year post-procedure in both groups. This is in line with previous TAVI vs. SAVR trials including high-, intermediate-, or low surgical risk patients (1-11).

The most important limitations of this trial and report are the underpowered sample size and the fact that current results only reflect one-year outcomes. The small sample size complicates a definitive assessment of the study hypothesis, with an absolute risk difference between both groups for the primary endpoint of 3.1%, but also surpassing the pre-specified non-inferiority margin of 5% with the upper limit of the 95% CI. This one-year study report also does not address long-term clinical or valvular aspects. Definitive conclusions regarding the possible (dis)advantages of TAVI and surgery when treating a young AS population should depend on long-term outcomes.

Besides the limited sample size and follow-up time, this trial has several other limitations. First, the results apply only to the defined trial population. Second, the outcomes obtained in this trial are the result of a valve choice which was left at the physician's discretion; results cannot be extrapolated to one particular valve type and further research is needed to investigate whether some transcatheter valve types may be associated with better clinical outcomes than others, in particular when treating bicuspid AS. Third, a bias in the diagnosis of all stroke cannot be excluded, as most TAVI were performed in local anesthesia with immediate hospitalization at the regular ward post-procedure vs. cardiac surgery which was performed in general anesthesia and with a minimum 24-hour hospitalization at the intensive care unit. This may have led to a bias in diagnosis of early post-procedural non-disabling stroke. Fourth, this study did not discriminate different types of bicuspid AS. This issue will be examined in a sub-study, in which clinical outcomes and valve performance

will be studied in relation to the underlying bicuspid AS phenotype and implanted valve type. Fifth, echocardiography was performed as per local protocol without core lab adjudication.

Previous low-risk TAVI trials have shown equipoise between TAVI and surgery when treating patients with severe tricuspid AS (18–20). The findings in this trial suggest that TAVI may be a valuable option to treat low-risk patients aged 65 to 75 years with a tricuspid AS. However, long-term clinical outcomes and valve durability are still unknown and lifetime management aspects should be considered when treating this patient group. Although this trial was not powered to study and compare outcomes between TAVI and surgery in young bicuspid AS patients, the study findings urge caution for a (too) liberal use of TAVI in this specific patient population and indicate that SAVR should be the first-line recommendation.

Dedicated randomized trials comparing TAVI with surgery in young bicuspid patients are needed to provide a final answer to this clinical question. In the meantime, when opting for TAVI in younger bicuspid patients, one should consider the risk of stroke and PVR, with a higher vigilance to prevent cerebral embolic events and a careful selection of bicuspid aortic valve morphologies, linked with a lower risk of PVR.

In conclusion, in this randomized trial involving low-risk patients aged ≤75 years with severe AS, the risk of death from any cause, stroke or rehospitalization at one year was similar between TAVI and surgery. However, TAVI outcomes in young bicuspid AS patients warrant caution with respect to non-disabling stroke and paravalvular regurgitation.

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FIGURE LEGENDS

Figure 1. Flow chart of study population selection and treatment. AT, As-Treated; ITT, Intention-To-Treat; TAVI, transcatheter aortic valve implantation. ^Patients enrolled in the study, excluding 1 screen failure and 5 consent withdrawals. §A detailed overview of the reasons for cross-over are reported in Figure S1 in the Supplementary Appendix.

Figure 2. Time-to-Event Curves for the Primary Composite Endpoint and Key Secondary Endpoints. Shown are Kaplan–Meier estimates of the rate of the primary composite endpoint (Panel A), the rate of death from any cause or disabling stroke (Panel B), and the rate of death from any cause (Panel C), cumulative incidence of all stroke (Panel D), rehospitalization (Panel E), and disabling stroke (Panel F) in patients who underwent transcatheter aortic valve implantation (TAVI) and surgical aortic valve replacement. The inserts show the same data on an enlarged y axis, also including the 95% confidence intervals.

Figure 3. Hemodynamic Valve Performance, Functional Status and Quality of Life at 30 Days and 1 Year. In Panel A, the effective aortic valve orifice area (solid lines, cm^2) and transvalvular mean gradient (dashed lines, mmHg) are shown for the TAVI group and the surgery group at all time points after the procedure until one-year follow-up. Panel B shows the functional status (New York Heart Association functional class) at 30 days and one year, respectively. Panel C shows the mean relative change (%) from baseline in KCCQ overall summary score as a measure of quality of life in both groups.

Figure 4. Primary Composite Endpoint and Key Secondary Endpoints in the Tricuspid and Bicuspid Cohorts. Shown are Kaplan–Meier estimates of the rate of death or disabling stroke in the tricuspid (Panel A) and bicuspid (Panel B) cohorts. Panel C shows subgroup analyses for the primary composite endpoint and key secondary endpoints in the tricuspid and bicuspid cohorts comparing TAVI and surgery. All percentages are Kaplan–Meier estimates or cumulative incidence at one year, except for moderate or greater paravalvular regurgitation rates which are the 30-day incidence rates (§). The risk differences with 95% confidence intervals between TAVI and surgery are shown in percentage points per subgroup (tricuspid vs. bicuspid cohorts).

Structured Graphical Abstract. The NOTION-2 trial is the first randomised controlled trial comparing transcatheter aortic valve implantation (TAVI) with surgical aortic valve replacement in young, low surgical risk patients with severe tricuspid or bicuspid aortic stenosis (AS). One year after aortic valve replacement, the risk of all-cause death, stroke or rehospitalisation was 10.2% in the TAVI group and 7.1% in the surgery group. Important differences in outcomes are observed in the tricuspid versus bicuspid AS cohorts. CI, confidence interval.

1

Table 1. Characteristics of the Patients at Baseline*		
Characteristic	**TAVI (N = 187)**	**Surgery (N = 183)**
Age – years	71.1±3.1	71.0±3.2
Male sex – no. (%)	119 (63.6)	113 (61.7)
STS-PROM score – %†	1.1 (0.9–1.5)	1.1 (0.8–1.5)
EuroSCORE II score – %‡	1.0 (0.8–1.3)	1.1 (0.8–1.4)
Arterial hypertension – no. (%)	128 (68.4)	131 (71.6)
Diabetes mellitus – no. (%)	37 (19.8)	41 (22.4)
Body mass index – kg/m²§	28.0±4.4	27.5±4.3
Coronary artery disease – no. (%)^	25 (13.4)	18 (9.8)
Previous myocardial infarction – no. (%)	13 (7.0)	5 (2.7)
Previous percutaneous coronary intervention – no. (%)	23 (12.3)	18 (9.8)
Atrial fibrillation – no. (%)	32 (17.1)	27 (14.8)
Previous stroke – no. (%)	12 (6.4)	14 (7.7)
Peripheral arterial disease – no. (%)	2 (1.1)	4 (2.2)
Estimated glomerular filtration rate < 45 ml/min/1.73m² – no. (%)	5 (2.7)	2 (1.1)
Chronic obstructive pulmonary disease – no. (%)	21 (11.2)	19 (10.4)
NYHA class III or IV – no. (%)	51 (27.3)	40 (21.9)
Moderate pulmonary hypertension – no. (%)¶	9 (4.8)	6 (3.3)
Left bundle branch block – no. (%)	4 (2.1)	3 (1.6)
Right bundle branch block – no. (%)	8 (4.3)	8 (4.4)
Pre-existing pacemaker or defibrillator – no. (%)	7 (3.7)	8 (4.4)
Echocardiography		
Aortic valve area – cm²	0.7±0.2	0.7±0.2
Mean aortic valve gradient – mmHg	50.4±13.8	51.6±14.1
Left ventricular ejection fraction – %	58.9±6.6	58.9±8.5
Moderate or severe aortic regurgitation – no./total no. (%)	26/177 (14.7)	18/172 (10.5)
Moderate or severe mitral regurgitation – no./total no. (%)	7/173 (4.0)	3/172 (1.7)
Cardiac computed tomography		
Systolic annular perimeter – mm	79.5±9.4	78.9±11.4
Systolic annular area – mm²	495±97	498±78
Bicuspid aortic valve – no. (%)	49 (26.2)	51 (27.9)
Type 0 – no. (%)	3 (1.6)	4 (2.2)
Type 1 – no. (%)	45 (24.1)	47 (25.7)
Type 2 – no. (%)	1 (0.5)	0 (0)

* Plus–minus values are means ± SD. There were no significant between-group differences in baseline characteristics. Data on aortic valve area were available for 185 patients in the TAVI group and 178 patients in the surgery group; mean aortic valve gradient, 184 and 176, respectively; left ventricular ejection fraction, 186 and 183; and systolic annular perimeter and area on cardiac computed tomography (CT), 185 and 174. TAVI denotes transcatheter aortic valve implantation and NYHA New York Heart Association.

† Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) scores range from 0 to 100% and provide an estimate of the risk of death at 30 days among patients undergoing surgical aortic valve replacement on the basis of several demographic and procedural variables.

‡ Scores on the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II range from 0 to 100%, with higher scores indicating a greater risk of death within 30 days after the procedure.

§ The body mass index is the weight in kilograms divided by the square of the height in meters.

^ Coronary artery disease defined as previous myocardial infarction or coronary revascularization.
¶ Moderate pulmonary hypertension defined as an echocardiographic tricuspid regurgitation gradient ≥ 40 mmHg.

Table 2. Primary and Key Secondary Endpoints at 1 year*

End Point	TAVI	Surgery	TAVI vs. Surgery HR (95% CI)†	P Value‡
	% of patients			
Death from any cause, stroke, or rehospitalization	10.2	7.1	1.4 (0.7 to 2.9)	0.3
Death from any cause, disabling stroke or rehospitalization	6.4	6.6	1.0 (0.4 to 2.1)	0.9
Death from any cause or disabling stroke	3.2	1.6	2.0 (0.5 to 7.8)	0.3
Death from any cause	2.1	1.1	2.0 (0.4 to 10.7)	0.4
Death from cardiovascular cause	2.1	1.1	2.0 (0.4 to 10.7)	0.4
Stroke	5.4	1.6	3.3 (0.9 to 12.0)	0.05
Disabling stroke	1.6	1.1	1.5 (0.2 to 8.8)	0.7
Non-disabling stroke	3.7	0.5	7.0 (0.9 to 56.5)	0.03
Transient ischemic attack	2.7	1.6	1.6 (0.4 to 6.8)	0.5
Rehospitalization - procedure-, valve- or heart failure-related	3.7	4.9	0.7 (0.3 to 2.0)	0.6
Rehospitalization - procedure-related	1.1	4.0	0.3 (0.06 to 1.3)	0.09
Rehospitalization - valve-related	2.2	1.1	1.9 (0.3 to 10.3)	0.5
Rehospitalization - heart failure-related	0.6	0	-	0.3
Major or life-threatening bleeding	4.8	17.5	0.3 (0.1 to 0.5)	<0.001
Life-threatening bleeding	1.1	3.3	0.3 (0.1 to 1.6)	0.2
Major vascular complication	1.6	1.6	1.0 (0.2 to 4.8)	1.0
Acute kidney injury stage 2 or 3	0.5	0.5	1.0 (0.1 to 15.5)	1.0
Length of index hospitalization – median no. of days (IQR)	3 (2 to 4)	7 (6 to 9)	4 (4 to 5)	<0.001
New-onset atrial fibrillation^	3.2	41.7	0.06 (0.03 to 0.2)	<0.001
New permanent pacemaker implantation^^	15.1	8.0	2.0 (1.1 to 3.8)	0.03
Endocarditis	1.1	1.6	0.6 (0.1 to 3.9)	0.6
Myocardial infarction	2.1	1.6	1.3 (0.3 to 5.9)	0.7
Valve thrombosis	1.1	0	-	0.2
Moderate or greater paravalvular regurgitation§	4.7	0	-	0.005
Severe patient-prosthesis mismatch#	10.1	19.4	0.5 (0.3 to 0.9)	0.02
Aortic reintervention	1.1	2.2	0.5 (0.1 to 2.7)	0.4

* The percentages are Kaplan-Meier estimates. Except for the length of index hospitalization, the values are median and interquartile range. TAVI denotes transcatheter aortic valve replacement and IQR interquartile range.
† The reported TAVI vs. Surgery difference values are hazard ratios. Except for the length of index hospitalization, the value is a difference in medians estimated.
‡ The P values are based on the log-rank test (for the primary endpoint and death from any cause) and Gray's test (for other endpoints). Except for the length of index hospitalization, the P value is based on the Wilcoxon rank-sum test. Caution should be exercised regarding drawing inferences about absolute treatment effects, owing to the fact that these are secondary endpoint comparisons.
^ Patients who had atrial fibrillation before the procedure were excluded from the analysis.
^^ Patients with a pre-existing permanent pacemaker or defibrillator were excluded from the analysis.
§ Moderate or greater paravalvular regurgitation rate at 30 days.
# Severe patient-prosthesis mismatch rate at 30 days.

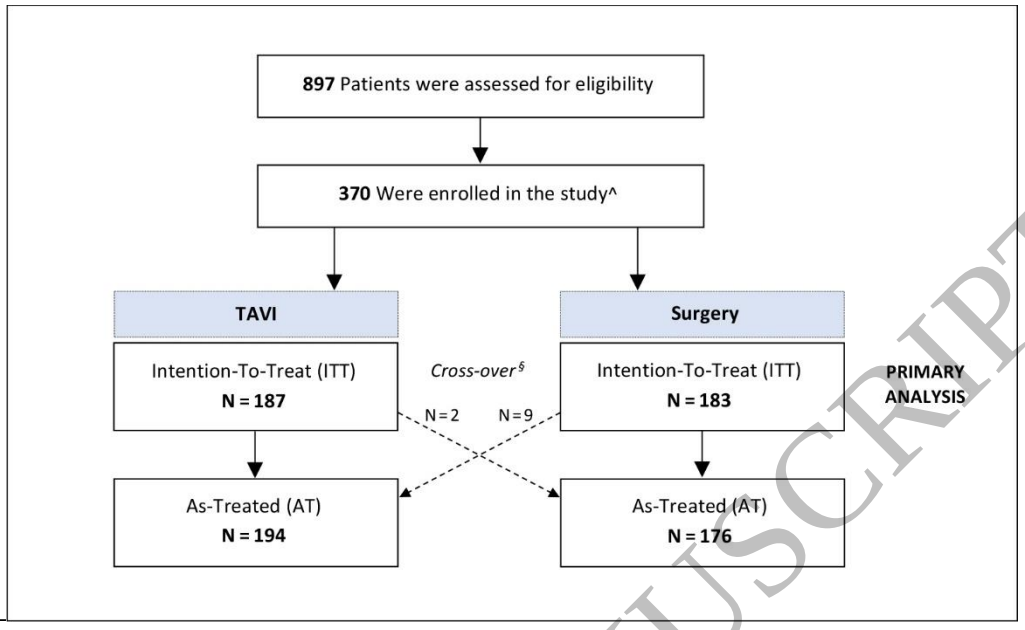

Figure 1
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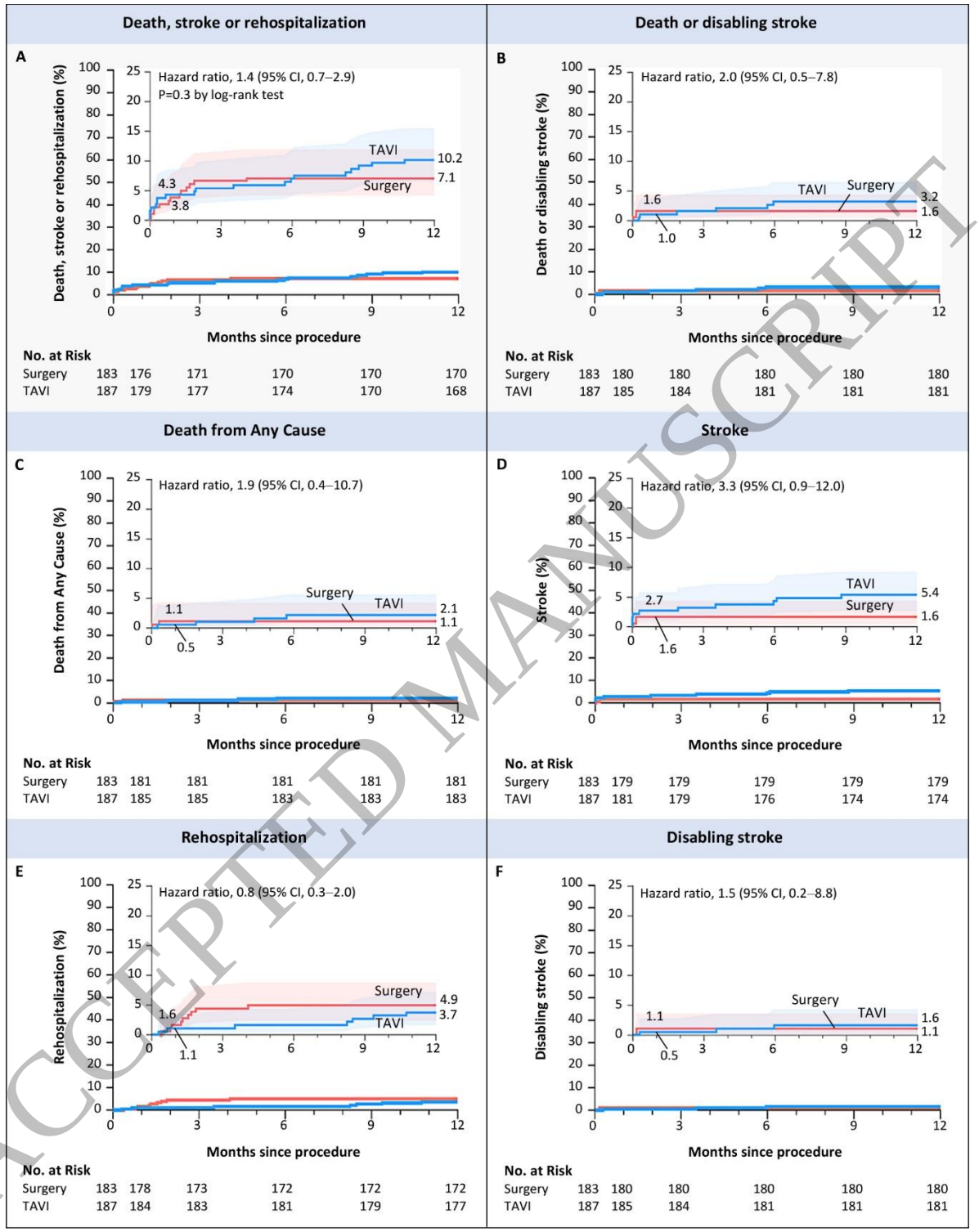

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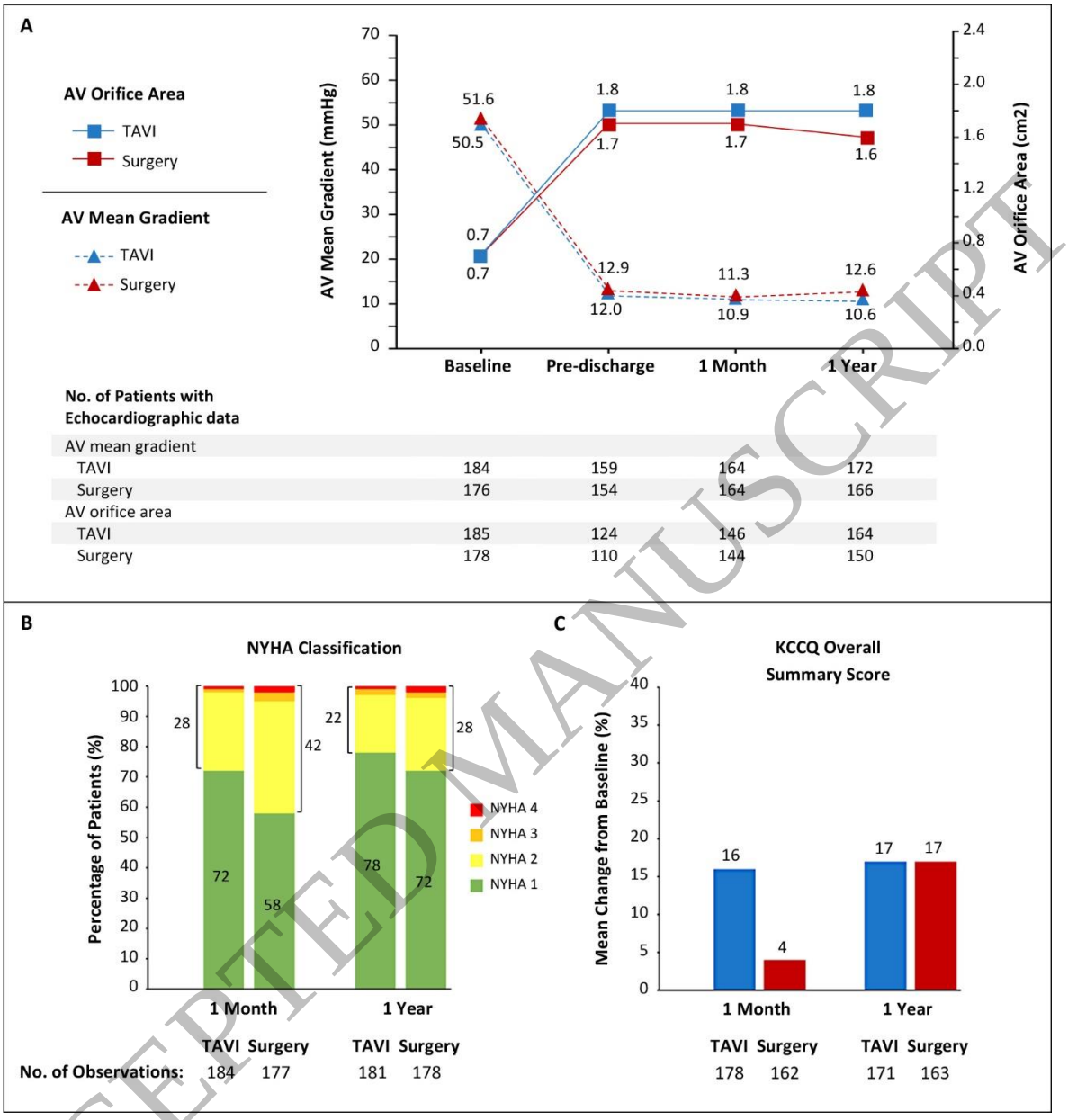

Figure 3
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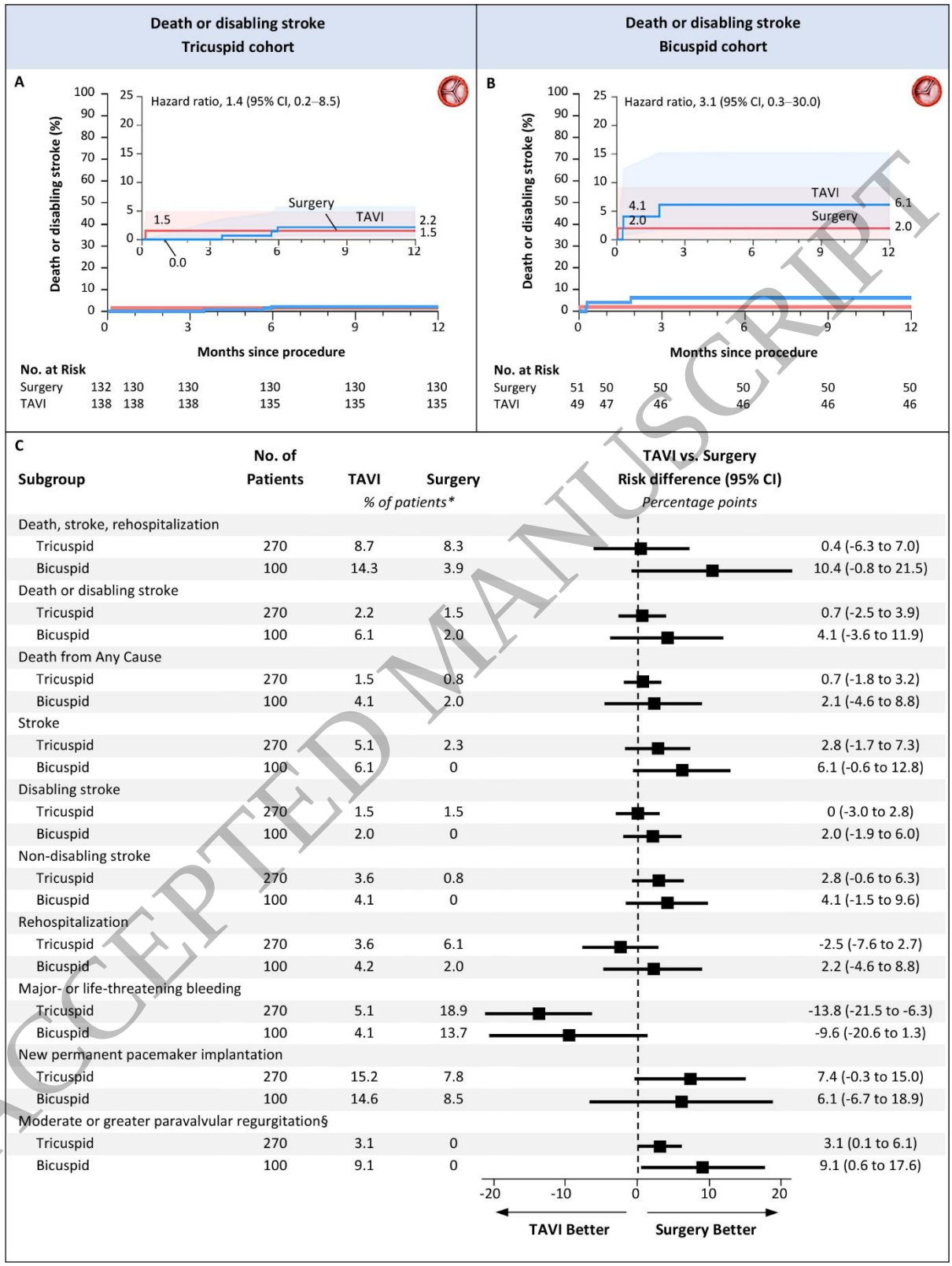

Figure 4
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Key Question

A randomised comparison of transcatheter aortic valve implantation (TAVI) with surgical aortic valve replacement in young, low surgical risk patients with severe tricuspid or bicuspid aortic valve stenosis (AS) is missing.

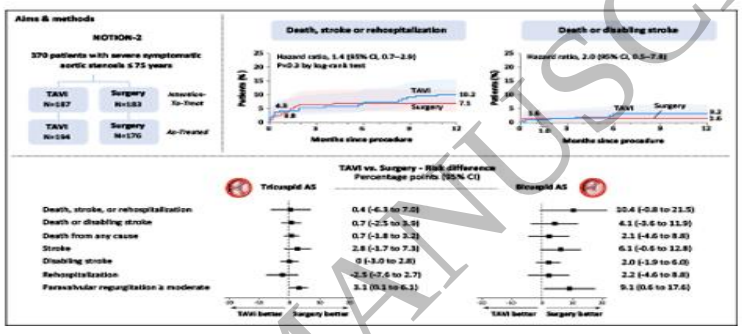
Key Finding

In the NOTION-2 trial at one year after aortic valve replacement, the risk of all-cause death, stroke or rehospitalisation (procedure-, valve- or heart failure-related) was 10.2% in the TAVI group and 7.1% in the surgery group (absolute risk difference 3.1%; 95% CI - 2.7% to 8.8%). Of note, the risk of this same endpoint was 8.7% and 8.3% in patients with tricuspid AS and 14.3% and 3.9% in patients with bicuspid AS treated with TAVI or surgery, respectively (P for interaction=0.1)

Take-home message

For low-risk patients =75 years of age with severe AS, one-year outcomes are comparable between TAVI and surgery. However, in patients with bicuspid AS, TAVI outcomes should be further investigated due to higher rates of non-disabling stroke and paravalvular leak.

Graphical abstract



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