10.1161/CIRCULATIONAHA.118.036606

Five-Year Clinical and Echocardiographic Outcomes from the Nordic Aortic Valve Intervention (NOTION) Randomized Clinical Trial in Lower Surgical Risk Patients

Running Title: *Thyregod et al.; NOTION 5-Year Outcomes*

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Abstract

Background: The Nordic Aortic Valve Intervention (NOTION) was designed to compare transcatheter aortic valve replacement (TAVR) to surgical aortic valve replacement (SAVR) in patients 70 years or older with isolated severe aortic valve stenosis. Clinical and echocardiographic outcomes are presented after 5 years.

Methods: Patients were enrolled at three Nordic centers and randomized 1:1 to TAVR using the self-expanding CoreValve prosthesis (n=145) or SAVR using any stented bio-prostheses (n=135). The primary composite outcome was the rate of all-cause mortality, stroke, or myocardial infarction at 1 year defined according to Valve Academic Research Consortium-2 criteria.

Results: Baseline characteristics were similar. The mean age was 79.1±4.8 years and mean STS-PROM score was 3.0%±1.7%. After 5 years, there were no differences between TAVR and SAVR in the composite outcome (Kaplan-Meier estimates 38.0% vs. 36.3%, log-rank test p=0.86) or any of its components. TAVR patients had larger prosthetic valve area (1.7 cm^2 vs. 1.2 cm^2, p<0.001) with a lower mean transprosthetic gradient (8.2 mm Hg vs. 13.7 mm Hg, p<0.001), both unchanged over time. More TAVR patients had moderate/severe total aortic regurgitation (8.2% vs. 0.0%, p<0.001) and a new pacemaker (43.7% vs. 8.7%, p<0.001). Four patients had prosthetic re-intervention and no difference was found for functional outcomes.

Conclusions: These are currently the longest follow-up data comparing TAVR and SAVR in lower risk patients, demonstrating no statistical difference for major clinical outcomes 5 years after TAVR with a self-expanding prosthesis compared to SAVR. Higher rates of prosthetic regurgitation and pacemaker implantation were seen after TAVR.

Clinical Trial Registration: URL: http://www.ClinicalTrials.gov. Unique identifier: NCT01057173.

Key Words: Aortic valve stenosis; transcatheter aortic valve implantation; surgical aortic valve replacement; long-term follow-up; surgical low-risk

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Clinical Perspective

What is new?

- The NOTION trial is the first to compare TAVR and SAVR in patients with severe isolated aortic valve stenosis and at lower surgical risk.
- The 5-year outcomes did not demonstrate a significant difference for all-cause death, stroke, or myocardial infarction.
- TAVR patients had a higher rate of new permanent pacemaker implantation and paravalvular leakage, whereas surgical patients experienced more new-onset or worsening atrial fibrillation during the immediate post-procedure course.

What are the clinical implications?

- The NOTION trial indicates, that TAVR could be a safe treatment alternative in patients with isolated severe aortic valve stenosis and at lower surgical risk.
- Improvements in TAVR valve prostheses and implantation techniques are warranted to avoid conduction abnormalities and paravalvular leakage.
- Larger scale clinical trials and long-term follow-up are needed to confirm these findings before the routine use of TAVR in this patient cohort.

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Introduction

Since 2002, transcatheter aortic valve replacement (TAVR) has been established as an effective treatment in patients with severe symptomatic aortic valve stenosis who are not candidates for surgical aortic valve replacement (SAVR), and the preferred treatment in those considered at high risk for mortality after surgery[1-3]. Furthermore, recent trials in intermediate-risk patients have demonstrated a similar rate of death or disabling stroke for TAVR compared to SAVR after two years[4, 5]. Although there are available data on the long-term performance of surgical bio-prosthetic aortic valves[6, 7], limited data past 5 years exist for TAVR patients[8-13]. Analysis of long-term outcomes for TAVR patients remains critical, as the therapy looks to extend to lower risk patients with longer life-expectancy.

The Nordic Aortic Valve Intervention (NOTION) trial was the first trial to randomize patients without a prespecified surgical risk profile and isolated severe aortic valve stenosis to TAVR or SAVR[14]. Outcomes after 1 and 2 years demonstrated the safety and effectiveness of TAVR in this population[15, 16]. The current analysis presents the 5-year clinical and echocardiographic outcomes in the NOTION trial.

Methods

Trial design

Details of the NOTION trial design have been previously described[14]. Briefly, the NOTION trial is an investigator-initiated, multi-center, non-blinded, superiority trial which randomized patients at age 70 years or older with isolated severe aortic valve stenosis to SAVR or TAVR in Denmark and Sweden. Follow-up was planned for 10 years. The local ethics committee at each site approved the protocol, the trial was conducted according to the Declaration of Helsinki, and all

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patients provided written informed consent. Data were collected and stored by the investigators and were fully monitored by independent monitors. The data, analytic methods, and trial materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. All authors had full access to all the data in the trial and take responsibility for its integrity and the data analysis.

Patient enrollment

All patients who were at least 70 years old, with isolated severe aortic valve stenosis, and no prespecified surgical risk profile were evaluated for enrollment by the Heart Team at each center. Furthermore, eligible patients were suitable for both SAVR, TAVR, and a bio-prosthesis as per guidelines at the time. Major exclusion criteria included need for acute treatment, severe coronary artery disease, severe non-aortic valvular disease, prior heart surgery, recent stroke or myocardial infarction (MI), severe lung or renal disease[14]. All eligible patients were consecutive enrolled from December 2009 to April 2013. In most patients, transthoracic echocardiography was used to determine trial eligibility and prosthesis size for TAVR patients.

Randomization and procedures

Patients were randomized 1:1 to either SAVR or TAVR. Randomization was stratified by trial center, patient age, and history of coronary artery disease. Patients randomized to SAVR received a stented bio-prosthetic aortic valve of size and type determined by the investigator during the procedure. Patients undergoing TAVR had a CoreValve self-expanding bio-prosthesis (Medtronic, Plc., Minneapolis, MN, USA) of size 23, 26, 29 or 31 mm via femoral or left subclavian artery access. General anesthesia was used for the majority of the TAVR procedures[17]. All TAVR and SAVR patients received similar peri-procedural prophylactic antibiotics and post-procedural anti-thrombotic therapy based on co-morbidities.

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Follow-up

Follow-up at 5 years consisted of a physical examination, assessment of protocol-specified clinical outcomes and adverse events, New York Heart Association (NYHA) classification, blood sampling, 12-lead electrocardiogram and transthoracic echocardiogram by a sonographist. Echocardiograms were evaluated by senior cardiologists at each site, and all clinical outcomes were confirmed by electronic medical records. An independent neurologist performed an evaluation on any patient with symptoms of stroke or transient ischemic attack (TIA) and relevant imaging was performed.

Clinical and echocardiographic outcomes

The primary outcome was the composite rate of all-cause mortality, stroke, or MI at 1 year. This composite outcome was also assessed at 5 years, in addition to the pre-specified clinical outcomes of all-cause mortality, cardiovascular mortality, stroke, and myocardial infarction (MI).

Echocardiographic outcomes evaluated at five years included aortic valve effective orifice area, transprosthetic mean pressure gradient, degree of total aortic valve regurgitation (AR) (combined paravalvular (PVL) and central regurgitation) and left ventricular ejection fraction (LVEF). Potential baseline and postprocedural predictors of mortality were examined. All outcomes were defined according to Valve Academic Research Consortium-2 definitions[18].

Statistical analyses

For clinical outcomes, a time-to-event analysis was conducted using Kaplan-Meier estimates and comparisons between treatment groups were done using the log-rank test for the composite outcome and all-cause mortality outcome. The analysis adjusted for competing risks of death for nonfatal outcomes, and cumulative incidence functions were compared between treatment

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groups using Gray's test. Results for the intention-to-treat population are reported, and results for the as-treated population are found in the supplemental material. The as-treated population was defined as patients in whom one of the two trial procedures was attempted. If a patient was converted to the other treatment arm, then the patient would be included in that group for the echocardiographic outcomes. Categorical variables were compared using the Fisher's exact test or the chi-square test, as appropriate. Continuous variables were presented as means (±SD) and compared with the use of Student's t-test. Ordinal variables were compared using the Mantel-Haenszel test. In order to examine selected potentially relevant baseline characteristics' effect on 5-year mortality, a Cox-proportional-hazards model was constructed. All testing used a two-sided alpha level of 0.05. No adjustment for multiple comparisons was performed. The current analysis is a secondary analysis, and the sample size estimate was based on the primary outcome after one year. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

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Results

Patients

The Heart Team at each center pre-screened a total of 1,576 consecutive patients. Almost 80% of patients did not meet inclusion criteria. Baseline patient characteristics have been described previously (**Supplemental Table 1**)[15], and there were no significant baseline differences between patients in the intention-to-treat TAVR (n=145) and SAVR (n=135) groups, nor in the as-treated population (TAVR n=142, 3 died and 1 crossed-over before attempted intervention, and SAVR n=134, 1 died and 1 crossed-over before intervention). Of note, the mean age was 79.1±4.8 years, Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score

was 3.0% ± 1.7%, and logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) I was 8.6% ± 4.8% for the entire cohort, highlighting the lower risk nature of this population. Patient follow-up compliance out to 5 years was 100% for both patient groups. Echocardiograms were performed in 81% TAVR and 92% SAVR patients alive after 5 years. More TAVR patients received aspirin at 5 years (TAVR 71.6% vs. SAVR 47.6%, p=0.001) while other antiplatelets were more often used in SAVR patient (TAVR 10.1% vs. SAVR 21.4%, p=0.04). All other cardiac medications were similar between the two groups.

Clinical outcomes

The primary composite outcome of all-cause mortality, stroke, or MI at 30 days and 1 year, was not statistically different between TAVR and SAVR groups[15] and remained not different between groups at 5 years with 38.0% for TAVR and 36.3% for SAVR (p = 0.86), **Figure 1**. Components of the primary composite outcome were also not statistically different for TAVR and SAVR groups, respectively: all-cause mortality 27.6% vs. 28.9% (p=0.75), stroke 9.0% vs. 7.4% (p=0.65), and MI 7.7% vs. 7.4% (p=0.96), **Table 1**. In patients with an STS-PROM score below 4%, no difference was found for the composite outcome (TAVR 32.3% vs. SAVR 35.2%, p=0.67).

Additional clinical outcomes at 5 years are given in **Table 1** (for outcomes in the as-treated population see **Supplemental Table 2**). Cumulative incidence for TAVR and SAVR were not statistically different for cardiovascular mortality (20.8% vs. 23.0%, p=0.62) and definite prosthetic valve endocarditis (6.2% vs. 4.4%, p=0.51) at 5 years, respectively. A higher cumulative rate of new-onset or worsening atrial fibrillation was found in the SAVR group (60.8% vs. 23.4% for TAVR, p<0.001), and there was a higher incidence of new pacemaker implants for the TAVR group (41.7% vs. 7.8%, p<0.001). These significant differences were

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sustained from 30-days after the procedures. The 30-day rates of new-onset or worsening atrial fibrillation was 16.9% for TAVR and 57.8% for SAVR, and for new pacemaker implantation 34.1% for TAVR and 1.6% for SAVR (**Supplemental Table 3**)[15]. The difference in new pacemaker implants was no longer significant with a total of 12 TAVR patients and 8 SAVR patients receiving a new pacemaker from 30 days to 5 years (p=0.077). Rate of re-intervention for prosthetic valve dysfunction, all transcatheter valve-in-valve procedures, was low (3 in the TAVR group for symptomatic PVL and 1 in the SAVR group for symptomatic re-stenosis). There were no significant differences in NYHA functional class between groups after 5 years, but there was a decline in functional class for both groups over time (**Supplemental Figure 1**).

Echocardiographic outcomes

Improvement in aortic valve effective orifice area and transprosthetic mean pressure gradient for patients treated with TAVR and SAVR patients were maintained out to 5 years and were significantly better (p<0.001) for TAVR than for SAVR patients at all time points **(Figure 2).** There was a significant difference in the degree of total AR measured between TAVR and SAVR groups post-procedure (**Figure 3**) using the Mantel-Haenszel test: at 5 years, 38.8% (TAVR) vs. 77.4% (SAVR) patients had none/trace total AR, and 52.9% vs. 22.6% patients had mild AR (p<0.001). The difference was driven by the degree of PVL: at 5 years, 47.0% (TAVR) vs. 83.3% (SAVR) had none/trace PVL and 45.9% vs. 16.7% had mild PVL. Moderate PVL was seen in 7.1% of TAVR patients, none in the SAVR group. The median change in LVEF after 5 years from baseline was -3.6% (95% CI: -8.2%, - 3.0%) for TAVR vs. 0.0% (-1.1% - 3.3%) for SAVR (p<0.001).

Association between all-cause mortality at 5 years, baseline characteristics, new pacemaker implantation, and aortic valve regurgitation

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In the univariable subgroup analysis, no difference was demonstrated between TAVR and SAVR for any of the potentially relevant subgroups (**Figure 4**). TAVR patients with new pacemaker implantation within 30 days after the procedure (n=45) had a numerically higher, but not statistically significant, all-cause mortality rate after 5 years compared to those without (n=88) (38.2% vs. 21.7%, p=0.07). Three patients without a pacemaker died within 30 days (2 related to conduction abnormalities), and 12 patients received a pacemaker during follow-up in the no pacemaker group. The all-cause mortality rate at 5 years was not significantly different for patients in the TAVR group with moderate total AR three months after the procedure (n=20) compared to those with none-mild (n=104) (30.8% vs. 22.2%, p=0.43) (**Figure 5**).

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Discussion

The NOTION trial was the first to randomize patients 70 years or older with isolated severe aortic valve stenosis and no prespecified surgical risk profile to TAVR using only the CoreValve self-expanding prosthesis or SAVR. The majority of patients had a STS-PROM score below 4% and were considered as surgical low-risk patients. The current analysis demonstrates no difference in rates of all-cause mortality, stroke, MI, or these combined between TAVR and SAVR out to 5 years. The differences seen shortly after the procedure with more pacemaker implantations after TAVR and more new-onset or worsening atrial fibrillation after SAVR remained out to 5 years. Furthermore, patients who underwent TAVR continued to have unchanged lower transprosthetic pressure gradient and larger prosthetic effective orifice area, but more PVL compared to the SAVR group. This did not result in differences in functional class. Only 3 TAVR and 1 SAVR patient required prosthetic re-intervention due to bio-prosthetic valve failure.

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As expected for a trial including primarily (80%) patients at low surgical risk, although with a mean age close to 80 years, the 5-year rate of all-cause (27.6%) and cardiovascular (20.8%) mortality for patients randomized to TAVR after 5 years is the lowest ever reported. Only 7.1% of patients died from non-cardiovascular causes, primarily cancer. The risk of death after 5 years in the PARTNER 1 trial including high-risk patients (mean age 84 and STS-PROM score 11.8%) and using a balloon-expanding prosthesis for TAVR was also similar after TAVR 67.8% compared to SAVR 62.4%[9]. In the CoreValve High Risk Trial using only the self-expanding prosthesis (mean age 85 and STS-PROM score 7.4%), 5-year all-cause mortality rate was 55.3% for TAVR and 55.4% for SAVR[10]. Five-year observational data for TAVR and high-risk patients have also been reported. Mean STS-PROM score in the ADVANCE registry was 6.4% and all-cause mortality rate was 50.7%[8]. In the Italian and German registries, the 5-year all-cause mortality rate was 55.0% and 59.1%, respectively[11, 12]. Intermediate-risk patients were included in the SURTAVI trial (mean STS-PROM score 4.4% for TAVR) comparing a self-expanding prosthesis to SAVR[4] and in the PARTNER 2 trial (mean STS-PROM score 5.8% for TAVR) using a balloon-expanding prosthesis[5]. The all-cause mortality rate for TAVR after 2 years in SURTAVI and the PARTNER 2 trial was 11.4% and 16.3%, respectively, with no difference compared to SAVR. The 2-year TAVR all-cause mortality rate was 8.0% for TAVR and 9.8% for SAVR in the NOTION trial[16]. A study using propensity score matching in low-risk patients has reported worse survival for TAVR after 3 years compared to SAVR (72.0% vs. 83.4%, p=0.002)[19]. When examining only patients with a STS-PROM score below 4%, no difference between the TAVR and SAVR groups was found for the composite outcome. Thus, the 5-year mortality from the NOTION trial support the conduction of trials comparing TAVR and SAVR in patients at low surgical risk (PARTNER 3, NCT02675114 and Medtronic low-risk

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trial, NCT02701283) as well as younger patients (NOTION II, NCT02825134). Due to the low mortality rate, the NOTION trial may for the first time achieve long-term outcomes including durability data for TAVR compared to SAVR bio-prostheses.

The differences in secondary outcomes observed after 5 years already existed after 30 days. As described in other trials, the rate of new-onset or worsening atrial fibrillation was higher after SAVR and more patients received a new permanent pacemaker after TAVR[3, 4]. The increase in new pacemaker rate from 30 days to 5 years was not statistically different between groups, and probably reflect the natural course of conduction disturbances in treated severe aortic valve stenosis rather than prosthesis specific complications. The new pacemaker rate of 34.1% 30 days after TAVR was higher compared to the more contemporary SURTAVI trial, 25.9%[4], and FORWARD registry, 17.5%, using the next generation self-expanding prosthesis[20]. The NOTION trial used a self-expanding prosthesis without the possibility for re-positioning. This combined with the relatively early stage of TAVR development at the time of trial procedures, with no firmly established indications for pacemaker after TAVR, may partly explain the higher pacemaker rate[21]. However, all trials have found a higher new pacemaker rate for TAVR using a self-expanding prosthesis compared to SAVR[3, 4]. There was a trend for a higher all-cause mortality rate in those TAVR patients with a new pacemaker 30 days after the procedure, compared to those without. Right ventricular pacing induces mechanical dyssynchrony and may decrease ventricular function. This has also been demonstrated in TAVR patients, but the suggested association with increased mortality has been less clear[8, 22-24]. However, chronic pacing dependency in the NOTION trial was unknown, patients who died within 30 days and those who received a pacemaker during follow-up were all included in the no pacemaker group, and finally, we did not adjust for potential pre-procedural confounders in that specific analysis

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within the TAVR group. All of these factors could affect the association. Furthermore, the relative adverse effect of new bundle branch block, atrio-ventricular block, and chronic pacing is unknown. On the other hand, a pacemaker protects against sudden cardiac death from severe brady-arrhythmia. Although the rate of new pacemaker is lower when using newer generation TAVR prostheses, the potential adverse long-term effect of chronic pacing should be explored before disseminating the treatment for younger low-risk patients.

Echocardiographic outcomes demonstrated maintenance of prosthetic performance at 5 years for both groups and no signs of concerning structural valve deterioration (e.g. calcification, cusp fibrosis, tears or flail), thrombosis or endocarditis. As demonstrated in all other trials using both self- and balloon-expanding prostheses, TAVR prostheses have superior forward hemodynamics compared to surgical stented prostheses with larger effective orifice area and lower transprosthetic pressure gradients, but more prosthetic AR particularly PVL. When the NOTION trial was initiated, echocardiography was standard for sizing of the aortic annulus, which has later been proven to be inferior to the current standard computed tomography imaging[21]. While 5-year data are not sufficient to determine prosthesis longevity, it is reassuring to observe favorable and unchanged hemodynamics since TAVR is increasingly being used in younger patients with longer life-expectancies[25]. The higher incidence of severe patient-prosthesis mismatch after SAVR compared to TAVR (33.9% vs. 14.0%; P<0.001) has not been associated with higher mortality in the NOTION trial[26], but this has been observed by others[27]. Also, the incidence of even mild AR has been associated with increased admissions for heart failure and mortality[28], but this association was not observed in the NOTION trial perhaps due to the small number of patients. However, AR seemed to impair left ventricular mass regression after the first year[29].

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There was a general decline in functional class for both treatment groups over time, but as in other trials, the observed differences in secondary clinical and echocardiographic outcomes did not result in significant functional differences between groups[2-5]. The subgroup analysis for the treatment interaction between baseline characteristics and 5-year all-cause mortality could not identify any significant variables. Others have found SAVR to be favored over TAVR in patients with peripheral artery disease or no pulmonary hypertension[9]. Sufficiently reliable estimates of pulmonary artery pressures were not available for the current analysis.

Limitations

In the NOTION trial almost 80% of those prescreened for trial enrollment were excluded mostly due to significant coronary artery disease, prohibitive high surgical risk, or technical unsuitability, and therefore the results are not applicable for these subgroups. Furthermore, we did not collect data on procedural risk factors not captured in the STS score, e.g. porcelain aorta, frailty, hostile chest etc., for further patient risk-stratification. All eligible patients were consecutively enrolled. Trial eligibility and prosthesis sizing was determined by transthoracic echocardiography instead of computed tomography imaging and this most likely compromised measurements of the aortic root[21]. Also, only the non-re-positioning self-expanding CoreValve prosthesis was used for TAVR, and this may have negatively influenced patient outcomes compared to other and newer types of prostheses[20, 30, 31]. Surgical annular enlargement techniques were not applied and could potentially have improved the surgical outcomes. Echocardiographic data were site-reported, and no core lab was available for verification of echocardiographic outcomes, but experienced imaging cardiologists evaluated all echocardiograms. Lastly, the trial sample size was not based on expected 5-year outcomes, and consequently patient numbers could be too small to detect clinical differences.

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Conclusions

In the NOTION trial including elderly patients with isolated severe aortic valve stenosis, who were mainly at low surgical risk, the rate of all-cause mortality, stroke, or MI after 5 years was not statistically different for TAVR compared to SAVR. The hemodynamic performance of the TAVR prosthesis was unchanged up to 5 years, with larger opening area and lower gradients but more regurgitation. Longer term follow-up and larger trials are needed to confirm these results and to examine the impact of permanent pacing before expanding treatment indications for TAVR.

Acknowledgments

The authors wish to acknowledge research nurses Line M. Kristensen, Lisette L. Larsen, Ane L. Johansen, Ida Rosenlund, and Eva-Lena Pommer; medical writers Colleen Gilbert and Jessica Dries-Devlin of Medtronic, for developing figures and tables and providing copyediting assistance; and all patients participating in the trial.

Sources of Funding

This work was financially supported by the Danish Heart Foundation (grant numbers: 09-10-AR76-A2733-25400, 12-04-R90-A3879-22733 and 13-04-R94-A4473-22762). Author Y.C. of Medtronic provided statistical support.

Disclosures

Dr. Thyregod has no financial relationships to disclose. Dr. Ihlemann has received speaker fees from Medtronic. Dr. Jørgensen and Dr. Nissen have no financial relationships to disclose. Dr.

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Kjeldsen is a proctor for Edwards Lifesciences. Dr. Petursson has no financial relationships to disclose. Ms. Chang is an employee and shareholder of Medtronic. Dr. Franzen has received research contracts from Abbott Vascular and St. Jude Medical, and consulting fees from Edwards Lifesciences. Dr. Engstrøm has received fees from St. Jude Medical, Bayer, Boston Scientific, and AstraZeneca. Dr. Clemmensen has received research contracts and speaker fees from Medtronic, Eli-Lilly, Daichii-Sankyo, AstraZeneca, Bayer, Boehringer-Ingelheim, Sanofi, Pfizer, and BMS. Dr. Hansen has received speaker fees from Medtronic. Dr. Andersen has no financial relationships to disclose. Dr. Steinbrüchel has received research contracts from Medtronic and St. Jude Medical. Dr. Olsen has received research contracts from Medtronic, St. Jude Medical, and Abbott Vascular. Dr. Søndergaard has received consultant fees and institutional research grants Medtronic, St. Jude Medical, Abbott Vascular, Boston Scientific, Edwards Lifesciences and Symetis.

American Heart Association.

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Presented at American College of Cardiology's Annual Meeting, March 10th, 2018, Orlando, Florida, USA.

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References

1. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S and Investigators PT. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363:1597-1607.
2. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ and Investigators PT. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364:2187-2198.
3. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J, Jr., Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P,

Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK and Investigators USCC. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014;370:1790-1798.
4. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Sondergaard L, Mumtaz M, Adams DH, Deeb GM, Maini B, Gada H, Chetcuti S, Gleason T, Heiser J, Lange R, Merhi W, Oh JK, Olsen PS, Piazza N, Williams M, Windecker S, Yakubov SJ, Grube E, Makkar R, Lee JS, Conte J, Vang E, Nguyen H, Chang Y, Mugglin AS, Serruys PW, Kappetein AP and Investigators S. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. *N Engl J Med*. 2017;376:1321-1331.
5. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG and Investigators P. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. *N Engl J Med*. 2016;374:1609-1620.
6. Sharabiani MT, Fiorentino F, Angelini GD and Patel NN. Long-term survival after surgical aortic valve replacement among patients over 65 years of age. *Open Heart*. 2016;3:e000338.
7. Thourani VH, Myung R, Kilgo P, Thompson K, Puskas JD, Lattouf OM, Cooper WA, Vega JD, Chen EP and Guyton RA. Long-term outcomes after isolated aortic valve replacement in octogenarians: a modern perspective. *Ann Thorac Surg*. 2008;86:1458-1464; discussion 1464-1465.
8. Gerckens U, Tamburino C, Bleiziffer S, Bosmans J, Wenaweser P, Brecker S, Guo J and Linke A. Final 5-year clinical and echocardiographic results for treatment of severe aortic stenosis with a self-expanding bioprosthesis from the ADVANCE Study. *Eur Heart J*. 2017;38:2729-2738.
9. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, Webb JG, Douglas PS, Anderson WN, Blackstone EH, Kodali SK, Makkar RR, Fontana GP, Kapadia S, Bavaria J, Hahn RT, Thourani VH, Babaliaros V, Pichard A, Herrmann HC, Brown DL, Williams M, Akin J, Davidson MJ, Svensson LG and investigators Pt. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. *Lancet*. 2015;385:2477-2484.
10. Gleason TG, Reardon MJ, Popma JJ, Deeb GM, Yakubov SJ, Lee JS, Kleiman NS, Chetcuti S, Hermiller JB, Jr., Heiser J, Merhi W, Zorn GL, 3rd, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte JV, Mumtaz M, Oh JK, Huang J, Adams DH and CoreValve USPHRTCI. 5-Year Outcomes of Self-Expanding Transcatheter Versus Surgical Aortic Valve Replacement in High-Risk Patients. *J Am Coll Cardiol*. 2018;72:2687-2696.
11. Barbanti M, Petronio AS, Ettori F, Latib A, Bedogni F, De Marco F, Poli A, Boschetti C, De Carlo M, Fiorina C, Colombo A, Brambilla N, Bruschi G, Martina P, Pandolfi C, Giannini C, Curello S, Sgroi C, Gulino S, Patane M, Ohno Y, Tamburino C, Attizzani GF, Imme S, Gentili A and Tamburino C. 5-Year Outcomes After Transcatheter Aortic Valve Implantation With CoreValve Prosthesis. *JACC Cardiovasc Interv*. 2015;8:1084-1091.
12. Zahn R, Werner N, Gerckens U, Linke A, Sievert H, Kahlert P, Hambrecht R, Sack S, Abdel-Wahab M, Hoffmann E, Zeymer U, Schneider S and German Transcatheter Aortic Valve Interventions-Registry i. Five-year follow-up after transcatheter aortic valve implantation for symptomatic aortic stenosis. *Heart*. 2017;103:1970-1976.

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13. Duncan A, Ludman P, Banya W, Cunningham D, Marlee D, Davies S, Mullen M, Kovac J, Spyt T and Moat N. Long-term outcomes after transcatheter aortic valve replacement in high-risk patients with severe aortic stenosis: the U.K. Transcatheter Aortic Valve Implantation Registry. *JACC Cardiovasc Interv*. 2015;8:645-653.
14. Thyregod HG, Sondergaard L, Ihlemann N, Franzen O, Andersen LW, Hansen PB, Olsen PS, Nissen H, Winkel P, Gluud C and Steinbruchel DA. The Nordic aortic valve intervention (NOTION) trial comparing transcatheter versus surgical valve implantation: study protocol for a randomised controlled trial. *Trials*. 2013;14:11.
15. Thyregod HG, Steinbruchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, Chang Y, Franzen OW, Engstrom T, Clemmensen P, Hansen PB, Andersen LW, Olsen PS and Sondergaard L. Transcatheter Versus Surgical Aortic Valve Replacement in Patients With Severe Aortic Valve Stenosis: 1-Year Results From the All-Comers NOTION Randomized Clinical Trial. *J Am Coll Cardiol*. 2015;65:2184-2194.
16. Sondergaard L, Steinbruchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, Ngo AT, Olsen NT, Chang Y, Franzen OW, Engstrom T, Clemmensen P, Olsen PS and Thyregod HG. Two-Year Outcomes in Patients With Severe Aortic Valve Stenosis Randomized to Transcatheter Versus Surgical Aortic Valve Replacement: The All-Comers Nordic Aortic Valve Intervention Randomized Clinical Trial. *Circ Cardiovasc Interv*. 2016;9:e003665.
17. Grube E, Schuler G, Buellesfeld L, Gerckens U, Linke A, Wenaweser P, Sauren B, Mohr FW, Walther T, Zickmann B, Iversen S, Felderhoff T, Cartier R and Bonan R. Percutaneous aortic valve replacement for severe aortic stenosis in high-risk patients using the second- and current third-generation self-expanding CoreValve prosthesis: device success and 30-day clinical outcome. *J Am Coll Cardiol*. 2007;50:69-76.
18. Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodes-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW and Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol*. 2012;60:1438-1454.
19. Rosato S, Santini F, Barbanti M, Biancari F, D'Errigo P, Onorati F, Tamburino C, Ranucci M, Covello RD, Santoro G, Grossi C, Ventura M, Fusco D, Seccareccia F and Group OR. Transcatheter Aortic Valve Implantation Compared With Surgical Aortic Valve Replacement in Low-Risk Patients. *Circ Cardiovasc Interv*. 2016;9:e003326.
20. Grube E, Van Mieghem NM, Bleiziffer S, Modine T, Bosmans J, Manoharan G, Linke A, Scholtz W, Tchetche D, Finkelstein A, Trillo R, Fiorina C, Walton A, Malkin CJ, Oh JK, Qiao H, Windecker S and Investigators FS. Clinical Outcomes With a Repositionable Self-Expanding Transcatheter Aortic Valve Prosthesis: The International FORWARD Study. *J Am Coll Cardiol*. 2017;70:845-853.
21. Casset C, Jankowski A, Bertrand B, Saunier C, Piliero N, Rodiere M, Ferretti G, Quesada JL, Broisat A, Riou L, Fagret D, Ghezzi C, Vanzetto G and Barone-Rochette G. Evaluation of Imaging Strategy to Optimize and Improve Outcome of Transcatheter Aortic Valvular Implantation. *Am J Cardiol*. 2017;120:1633-1638.
22. Regueiro A, Abdul-Jawad Altisent O, Del Trigo M, Campelo-Parada F, Puri R, Urena M, Philippon F and Rodes-Cabau J. Impact of New-Onset Left Bundle Branch Block and Periprocedural Permanent Pacemaker Implantation on Clinical Outcomes in Patients Undergoing Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis. *Circ Cardiovasc Interv*. 2016;9:e003635.

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23. Fadahunsi OO, Olowoyeye A, Ukaigwe A, Li Z, Vora AN, Vemulapalli S, Elgin E and Donato A. Incidence, Predictors, and Outcomes of Permanent Pacemaker Implantation Following Transcatheter Aortic Valve Replacement: Analysis From the U.S. Society of Thoracic Surgeons/American College of Cardiology TVT Registry. *JACC Cardiovasc Interv*. 2016;9:2189-2199.
24. Dizon JM, Nazif TM, Hess PL, Biviano A, Garan H, Douglas PS, Kapadia S, Babaliaros V, Herrmann HC, Szeto WY, Jilaihawi H, Fearon WF, Tuzcu EM, Pichard AD, Makkar R, Williams M, Hahn RT, Xu K, Smith CR, Leon MB, Kodali SK and Office PP. Chronic pacing and adverse outcomes after transcatheter aortic valve implantation. *Heart*. 2015;101:1665-71.
25. Gaede L, Blumenstein J, Kim WK, Liebetrau C, Dorr O, Nef H, Hamm C, Elsasser A and Mollmann H. Trends in aortic valve replacement in Germany in 2015: transcatheter versus isolated surgical aortic valve repair. *Clin Res Cardiol*. 2017;106:411-419.
26. Thyregod HG, Steinbruchel DA, Ihlemann N, Ngo TA, Nissen H, Kjeldsen BJ, Chang Y, Hansen PB, Olsen PS and Sondergaard L. No clinical effect of prosthesis-patient mismatch after transcatheter versus surgical aortic valve replacement in intermediate- and low-risk patients with severe aortic valve stenosis at mid-term follow-up: an analysis from the NOTION trial. *Eur J Cardiothorac Surg*. 2016;50:721-728.
27. Head SJ, Mokhles MM, Osnabrugge RL, Pibarot P, Mack MJ, Takkenberg JJ, Bogers AJ and Kappetein AP. The impact of prosthesis-patient mismatch on long-term survival after aortic valve replacement: a systematic review and meta-analysis of 34 observational studies comprising 27 186 patients with 133 141 patient-years. *Eur Heart J*. 2012;33:1518-1529.
28. Athappan G, Patvardhan E, Tuzcu EM, Svensson LG, Lemos PA, Fraccaro C, Tarantini G, Sinning JM, Nickenig G, Capodanno D, Tamburino C, Latib A, Colombo A and Kapadia SR. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: meta-analysis and systematic review of literature. *J Am Coll Cardiol*. 2013;61:1585-1595.
29. Ngo A, Hassager C, Thyregod HGH, Sondergaard L, Olsen PS, Steinbruchel D, Hansen PB, Kjaergaard J, Winther-Jensen M and Ihlemann N. Differences in left ventricular remodelling in patients with aortic stenosis treated with transcatheter aortic valve replacement with corevalve prostheses compared to surgery with porcine or bovine biological prostheses. *Eur Heart J Cardiovasc Imaging*. 2018;19:39-46.
30. Abdel-Wahab M, Mehilli J, Frerker C, Neumann FJ, Kurz T, Tolg R, Zachow D, Guerra E, Massberg S, Schafer U, El-Mawardy M, Richardt G and investigators C. Comparison of balloon-expandable vs self-expandable valves in patients undergoing transcatheter aortic valve replacement: the CHOICE randomized clinical trial. *JAMA*. 2014;311:1503-1514.
31. Kodali S, Thourani VH, White J, Malaisrie SC, Lim S, Greason KL, Williams M, Guerrero M, Eisenhauer AC, Kapadia S, Kereiakes DJ, Herrmann HC, Babaliaros V, Szeto WY, Hahn RT, Pibarot P, Weissman NJ, Leipsic J, Blanke P, Whisenant BK, Suri RM, Makkar RR, Ayele GM, Svensson LG, Webb JG, Mack MJ, Smith CR and Leon MB. Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis. *Eur Heart J*. 2016;37:2252-2262.

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Table 1. Clinical outcomes at 5 years for TAVR and SAVR patients.

Outcome (%)	TAVR N=145	SAVR N=135	P-value
All-cause mortality, stroke, or MI*	55 (38.0%)	49 (36.3%)	0.86
All-cause mortality*	40 (27.6%)	39 (28.9%)	0.75
Cardiovascular mortality	30 (20.8%)	31 (23.0%)	0.62
Stroke	13 (9.0%)	10 (7.4%)	0.65
TIA	9 (6.2%)	5 (3.7%)	0.33
MI	11 (7.7%)	10 (7.4%)	0.96
Atrial fibrillation	34 (23.4%)	82 (60.8%)	<0.0001
Pacemaker†	58 (41.7%)	10 (7.8%)	<0.0001
Aortic valve re-intervention	3 (2.1%)	1 (0.7%)	0.35
Valve endocarditis‡	9 (6.2%)	6 (4.4%)	0.51

TAVR indicates transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement; TIA, transient ischemic attack; and MI, myocardial infarction

*Percentages are Kaplan-Meier estimates and *P* values were calculated from log-rank tests in the intention-to-treat population. Other rows report cumulative incidence function estimates and *P* values from Grey's tests.

†Baseline pacemakers are not included.

‡Confirmed definite cases according to modified Duke criteria.

Circulation

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Figure Legends

Figure 1. Kaplan-Meier estimates at 5 years for transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) patients. MI indicates myocardial infarction.

Figure 2. Effective orifice area measurements and mean transprosthetic pressure gradients from baseline to 5 years for transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) patients. At baseline, both measurements were similar for TAVR and SAVR (effective orifice area, p=0.28; mean pressure gradient, p=0.54). At all follow-up time-points, for both effective orifice area and mean gradient, p<0.001 for TAVR vs. SAVR. Data are site-reported.

Figure 3. Degree of total aortic valve regurgitation from baseline to 5 years for transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) patients. Data are site-reported.

Figure 4. Univariable subgroup analysis for 5-year mortality in transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) patients. BMI indicates body mass index; STS, Society of Thoracic Surgeons; and LVEF, left ventricular ejection fraction.

Figure 5. Association between all-cause mortality and aortic valve regurgitation at 3 months in transcatheter aortic valve replacement (TAVR) patients.

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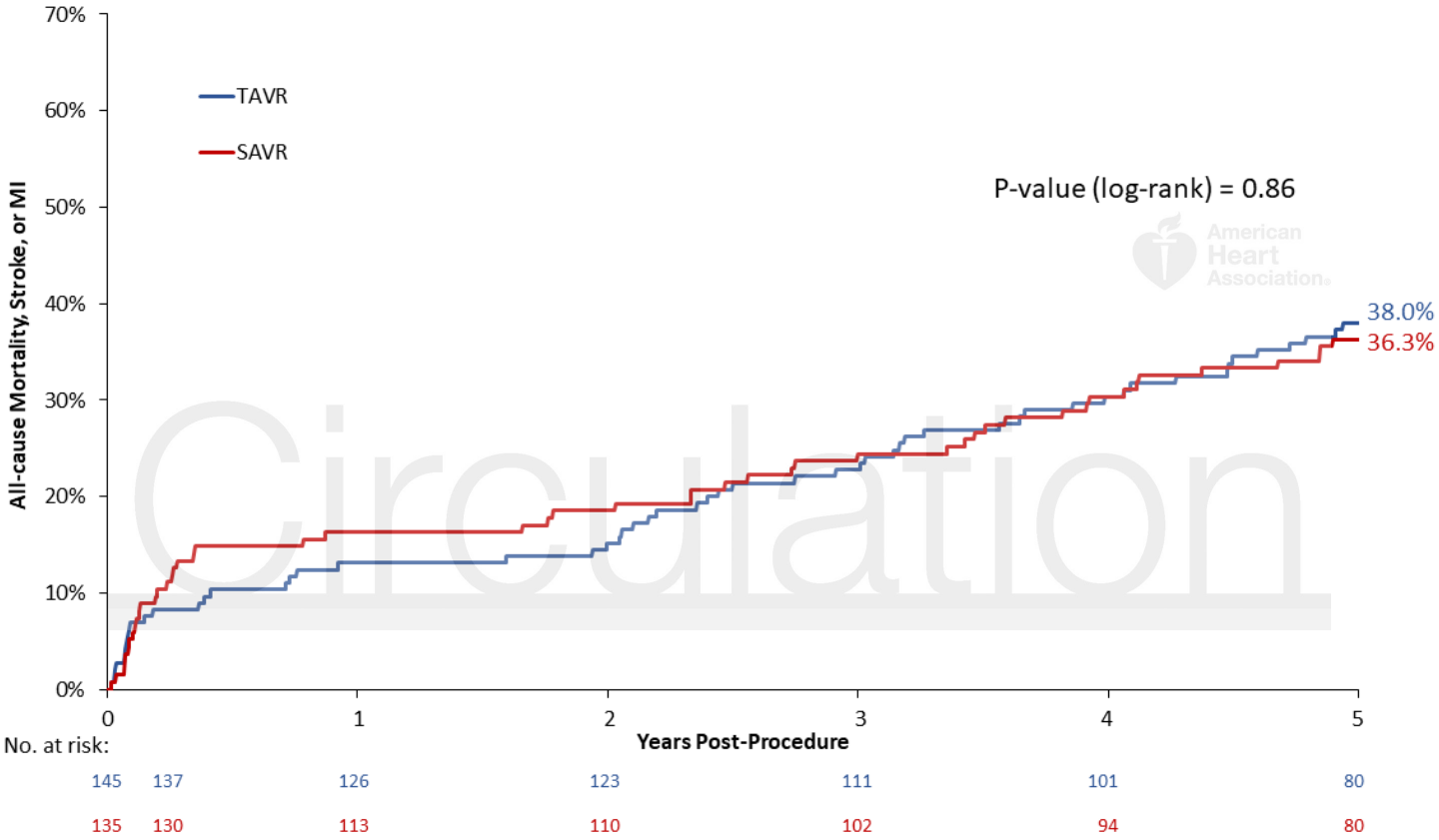

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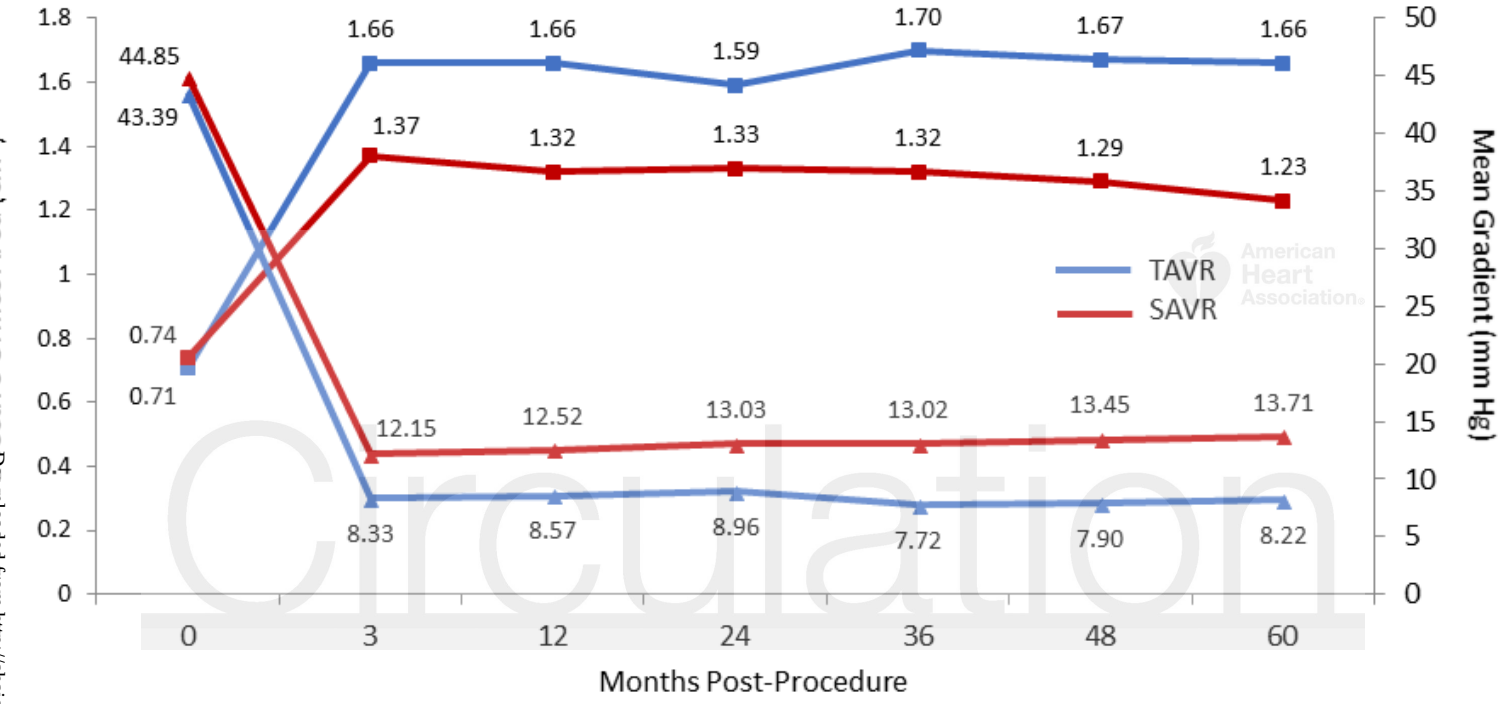

EOA N=	125	121	116	119	88	83	76
MG N=	124	123	120	105	108	99	80
EOA N=	118	110	112	110	96	78	84
MG N=	117	111	112	108	107	98	85

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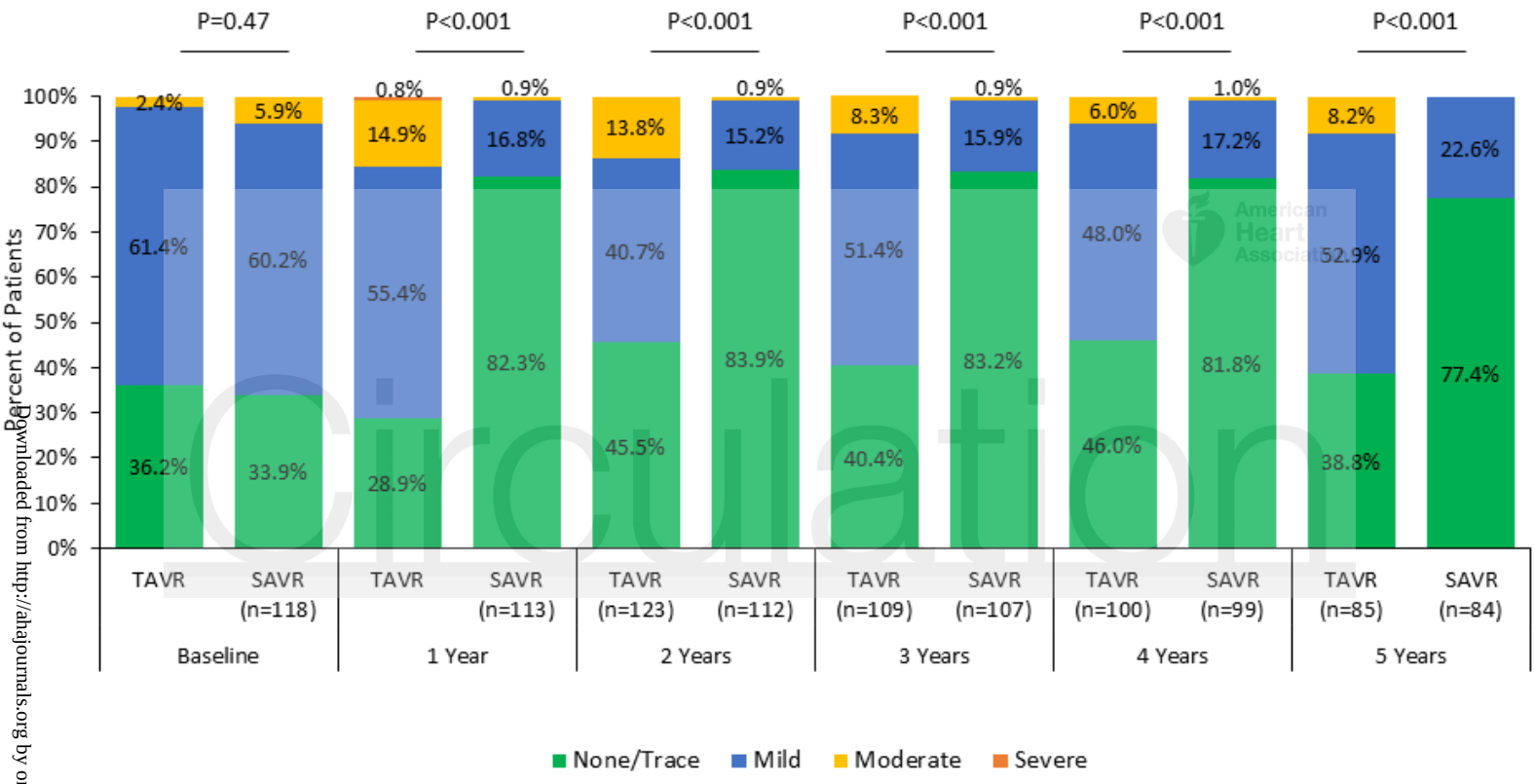

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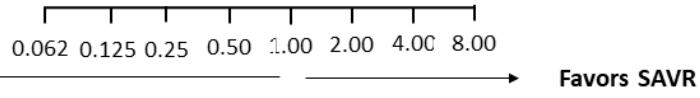
	All-Cause Mortality 5-Year KM Rates		Hazard Ratio (95% CI)	P for interaction
Variable	TAVR (n/N)	SAVR (n/N)		
Age (years)				0.63
<75y	12.9 (4/31)	18.5 (5/27)	0.69 (0.19-2.58)	
≥75y	31.6 (36/114)	31.5 (34/108)	0.97 (0.61-1.56)	
Gender				0.63
Male	33.4 (26/78)	32.5 (23/71)	1.01 (0.58-1.77)	
Female	20.9 (14/67)	25.0 (16/64)	0.81 (0.39-1.65)	
BMI (kg/m²)				0.83
≤30	29.2 (35/120)	29.7 (35/118)	0.96 (0.60-1.54)	
>30	20.0 (5/25)	23.5 (4/17)	0.83 (0.22-3.07)	
STS (%)				0.11
<4	22.3 (27/121)	27.8 (30/108)	0.77 (0.46-1.30)	
≥4	54.2 (13/24)	33.3 (9/27)	1.73 (0.74-4.04)	
Peripheral Vascular Disease				0.90
No	28.1 39/139)	29.4 (37/126)	0.92 (0.59-1.45)	
Yes	16.7 (1/6)	22.2 (2/9)	0.80 (0.07-8.77)	
Diabetes				0.52
No	26.1 (31/119)	29.0 (31/107)	0.87 (0.53-1.43)	
Yes	35.0 (9/26)	28.6 (8/28)	1.23 (0.48-3.20)	
LVEF (%)				0.45
≤40	22.2 (2/9)	40.0 (4/10)	0.53 (0.10-2.88)	
>40	20.5 (24/117)	19.2 (20/104)	1.05 (0.58-1.90)	



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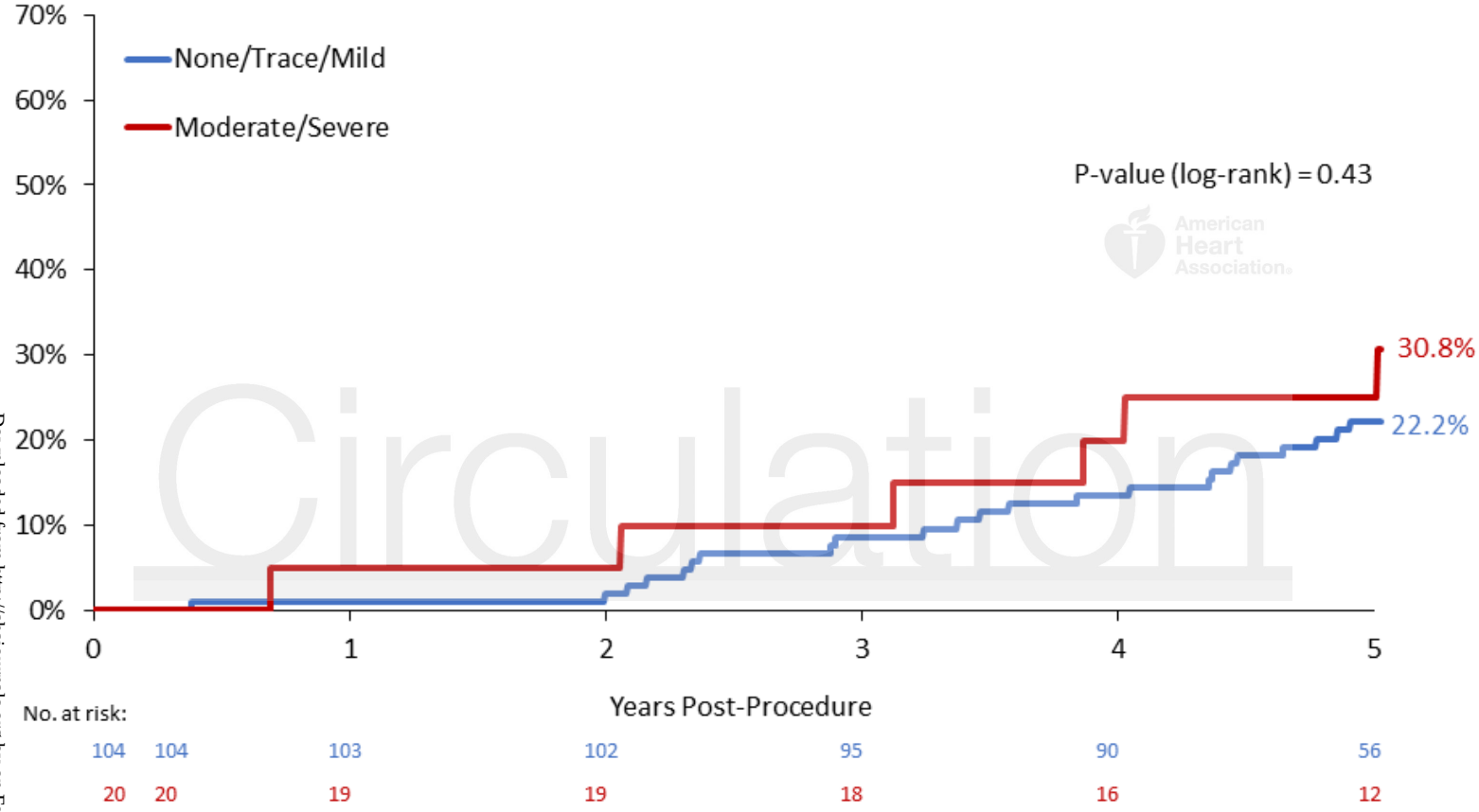

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