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Cost-effectiveness of transcatheter versus surgical aortic valve replacement in patients at lower surgical risk: results from the NOTION trial

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KEYWORDS

- death
- miscellaneous
- no specific risk
- TAVI

Abstract

Aims: The aim of this study was to estimate the cost-effectiveness of transcatheter aortic valve implantation (TAVI) versus surgical aortic valve replacement (SAVR) in patients at lower surgical risk.

Methods and results: Discounted costs from a societal perspective and effectiveness as quality-adjusted life years (QALYs) were projected to lifetime via a decision-analytic model calibrated to 60-month data from the NOTION trial. The base case assumed a scenario in which any mortality benefit would gradually fade out over time, with other scenarios explored in sensitivity analyses. The incremental cost-effectiveness ratio (ICER) was compared to the country-specific willingness-to-pay (WTP) threshold of 1.13 million Danish kroner (DKK). The base case ICER was DKK 696,264/QALY (around €72,100/QALY via purchasing parity adjustment). Variation in long-term mortality beyond five years led to limited variation of incremental costs (DKK 64,200 to 64,600), but a more pronounced variation in incremental QALYs (0.07 to 0.19 QALYs for most conservative and optimistic assumptions, compared to base case of 0.09 QALYs). All resulting ICERs (range DKK 334,200 to DKK 904,100 per QALY gained) were below the WTP threshold.

Conclusions: TAVI in a cohort of primarily low surgical risk patients was found to be a cost-effective treatment strategy in the Danish healthcare system. Cost-effectiveness analyses in other settings are warranted as are registries given the sensitivity of the model to long-term mortality.

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Abbreviations

DKK	Danish kroner
ICER	incremental cost-effectiveness ratio
MI	myocardial infarction
NOTION	Nordic Aortic Valve Intervention Trial
NYHA	New York Heart Association
PPM	permanent pacemaker
PPP	purchasing power party
QALY	quality-adjusted life year
RR	relative risk
SAVR	surgical aortic valve replacement
TAVI	transcatheter aortic valve implantation
WTP	willingness-to-pay

Introduction

Transcatheter aortic valve implantation (TAVI) has experienced a remarkable uptake in patients with severe aortic stenosis and high surgical risk, with over 54,000 procedures between 2012 and 2015 in the USA alone[1]. Its cost-effectiveness in these populations has been established in various settings and for both balloon-expandable and self-expanding TAVI devices[2].

The Nordic Aortic Valve Intervention (NOTION) trial was the first trial in patients with severe aortic stenosis and lower surgical risk randomised to TAVI or surgical bioprosthetic aortic valve replacement (SAVR)[3,4]; four-year results were recently presented (Søndergaard L. Clinical, safety and echocardiographic outcomes from the Nordic Aortic Valve Intervention (NOTION) trial: Four-year follow-up data in all-comer patients with severe aortic valve stenosis. Presented at EuroPCR, Paris, France, 2017). The NOTION trial demonstrated no significant difference in the primary outcome, a composite of all-cause death, stroke, or myocardial infarction (MI), between TAVI and SAVR. Non-significant differences persisted after 24[4] and 48 months of follow-up, respectively (Søndergaard L. Clinical, safety and echocardiographic outcomes from the Nordic Aortic Valve Intervention (NOTION) trial: Four-year follow-up data in all-comer patients with severe aortic valve stenosis. Presented at EuroPCR, Paris, France, 2017).

Given that surgical candidates who are not at increased surgical risk might have fewer (or no) incremental benefits from TAVI compared to SAVR but potentially higher costs, the "real-world" value of TAVI outside carefully selected high or extreme surgical risk patient cohorts has been uncertain. The objective of the present study was therefore to estimate the long-term cost-effectiveness of TAVI compared to SAVR in the NOTION cohort.

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Methods

A Markov state transition model, nested in a decision tree **(Figure 1)**, was developed to compute long-term costs and effectiveness of TAVI versus SAVR from the NOTION trial, as well as to quantify the impact of variation in the following input parameters: trial-based efficacy and adverse events, procedure and event costs, and New York Heart Association (NYHA) class-stratified health-related

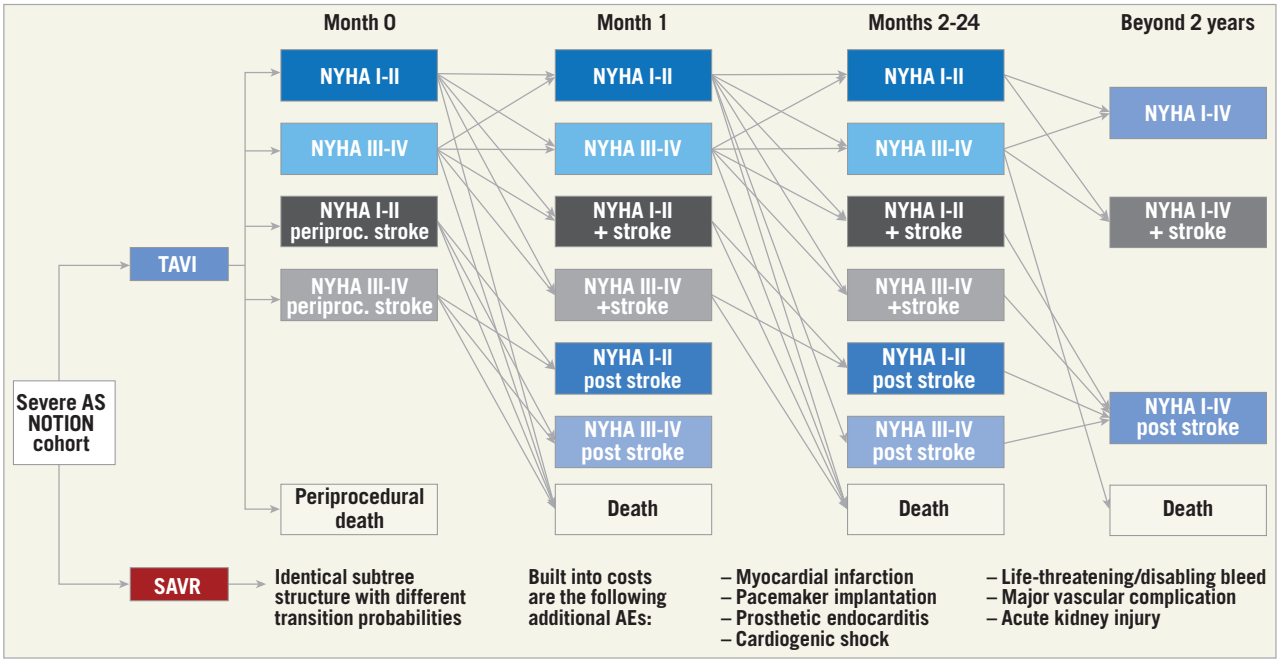

Figure 1. *Model structure. Patients start with the index procedure and associated risk of periprocedural adverse events (AE): death, stroke, MI, major or life-threatening bleeding, cardiogenic shock, acute kidney injury, major vascular complication, atrial fibrillation, permanent pacemaker implantation, prosthetic valve endocarditis, or the need for reintervention. Mortality, stroke, and MI probabilities and utilities were calculated separately for the following states: NYHA Class I/II, NYHA Class III/IV, NYHA Class I/II after an MI, NYHA Class III/IV after an MI, NYHA Class I/II after a stroke, and NYHA Class III/IV after a stroke. All other AE consequences were included in transition probabilities and utilities for these strata, but costs occurred separately as per the calculated event probabilities.*

quality of life estimates scored for the Danish population. Patient-level data from the six-year follow-up were analysed wherever possible. The study adheres to both the American College of Cardiology/American Heart Association Statement on Cost/Value Methodology in Clinical Practice Guidelines and Performance Measures as well as the Consolidated Health Economic Evaluation Reporting Standards statement[5,6]. The input parameters are shown in **Table 1** and **Supplementary Table 1-Supplementary Table 5**. The complete methods are described in **Supplementary Appendix 1-Supplementary Appendix 6**.

Results

MODEL CALIBRATION AND BASE CASE FINDINGS

After calibrating the available 60 months of data, the model output matched the actual trial results for the endpoints all-cause mortality, stroke, and MI **(Supplementary Figure 1-Supplementary Figure 3)**.

The model-projected life expectancy was 8.95 and 8.76 life years for TAVI and SAVR, respectively, a difference of 69 days. Consequently, TAVI and SAVR patients would have lived until 88.0 and 87.9 years of age, respectively.

Table 1. Key input parameters.

	TAVI	SAVR	Distribution	Source
Age (years)	79.1		Normal	[3]
Gender (female)	46.2%	47.4%	Beta	[3]
Immediate AEs				
Major/life-threatening bleeding	11.3%	20.9%	Beta	*post hoc* analysis
Cardiogenic shock	4.2%	10.4%	Beta	*post hoc* analysis
Acute kidney injury	0.7%	6.7%	Beta	*post hoc* analysis
Major vascular complications	5.6%	1.5%	Beta	*post hoc* analysis
30-day/1-year AEs				
All-cause mortality	2.1%/4.9%	3.7%/7.5%	Beta	[3]
Stroke	1.4%/2.9%	3.0%/4.6%	Beta	[3]
MI	2.8%/3.5%	6.0%/6.0%	Beta	[3]
Atrial fibrillation	16.9%/21.2%	57.8%/59.4%	Beta	[3]
PPM implantation	34.1%/38.0%	1.6%/2.4%	Beta	[3]
Prosthetic valve IE	0.7%/2.9%	0%/1.6%	Beta	[3]
Reintervention	0%/0%	0%/0%	n.a.	*post hoc* analysis
Outpatient costs				
Transthoracic echocardiography	DKK 1,150		Gamma	*
Coronary angiography	DKK 7,749			*
CTA chest	DKK 2,621			*
CV specialist visit	DKK 1,362			*
Procedure costs				
Procedure time (minutes)	90	177		*
Physician time	DKK 815	DKK 1,597		skin-to-skin time; wages *
Nursing time	DKK 415	DKK 813		skin-to-skin time; wages *
Tech time		DKK 813		skin-to-skin time; wages *
Valve costs	DKK 125,000	DKK 14,906		*
Heart-lung machine	n.a.	DKK 9,600		*
Concomitant CABG		DKK 25,000		*
Other materials	DKK 9,600	DKK 6,700		*
Blood products	DKK 227	DKK 866		*
Total procedure costs	DKK 136,057	DKK 31,189	Gamma	*
AE costs				
Major or life-threatening bleeding	DKK 4,752		Gamma	national price, *
Cardiogenic shock	DKK 29,638		Gamma	national price, *
Acute kidney injury	DKK 11,342		Gamma	national price, *
Major vascular complications	DKK 12,171		Gamma	national price, *
Stroke: first month	DKK 34,711		Gamma	[19,20]
Stroke: remaining months	DKK 3,192		Gamma	[19,20]
MI: first month	DKK 19,085		Gamma	[19,20]
MI: remaining months	DKK 136		Gamma	[19,20]
Atrial fibrillation	DKK 6,510		Gamma	national price, *
PPM implantation	DKK 15,500		Gamma	*
Prosthetic valve IE	DKK 80,586		Gamma	*
Atrial fibrillation	DKK 11,972		Gamma	national price, *
PPM implantation	DKK 15,000		Gamma	*
Prosthetic valve IE	DKK 80,586		Gamma	national price, *
LOS and related costs				
ICU LOS (days)	1.2	2.6	Gamma	*
Regular ward LOS (days)	7.7	10.3	Gamma	*
Costs per ICU day	DKK 22,915		Gamma	*
Costs per regular ward day	DKK 5,462		Gamma	*
Total index hospitalisation	DKK 76,109	DKK 132,330	Gamma	

*personal communication from the Financial Department, Heart Centre, Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark.

In the base case, TAVI was associated with total costs that were about DKK 65,000 higher than SAVR (276,142 vs 211,581), but TAVI patients also accumulated 0.09 additional quality-adjusted life years (QALYs; 5.39 vs 5.30). The resulting incremental cost-effectiveness ratio (ICER) of DKK 696,264/QALY (around €72,100/QALY using purchasing power party [PPP]-adjusted conversion via US dollars; 1 DKK=€0.1036) was below the willingness-to-pay (WTP) threshold for cost-effective (~DKK 1.1 million/QALY) and above the WTP threshold for highly cost-effective (DKK 375,489/QALY). The discounted ICER with quality-unadjusted, but still discounted, life years as effectiveness parameters was DKK 409,011/life year gained **(Table 2, Supplementary Table 6)**.

UNCERTAINTY ANALYSES

Sensitivity analyses revealed that the model projections were robust in terms of limited sensitivity to variation of short-term complications, except for the following parameters: relative mortality risks for TAVI and SAVR over 60 months, periprocedural TAVI mortality, and relative risk of mortality post stroke. **Figure 2** and **Supplementary Figure 4** display the results of a set of key deterministic one-way sensitivity analyses in a tornado diagram. As per a threshold analysis, large differences in mortality risk (e.g., initial mortality RR of 0.71 for SAVR – and assumed concurrent RR for TAVI of 1.23) would push the results above the WTP threshold for cost-effectiveness. Likewise, if the short-term absolute TAVI mortality was more than 1.7% higher than the SAVR mortality or if the relative risk of stroke was under 0.72, TAVI would not be cost-effective. Variation of all other input parameters across defined ranges did not change the decision; the largest impact was seen when assessing different TAVI procedure and SAVR index hospitalisation – in particular the length of the intensive care unit (ICU) stay, as well as the length of stay on the regular ward for both procedures.

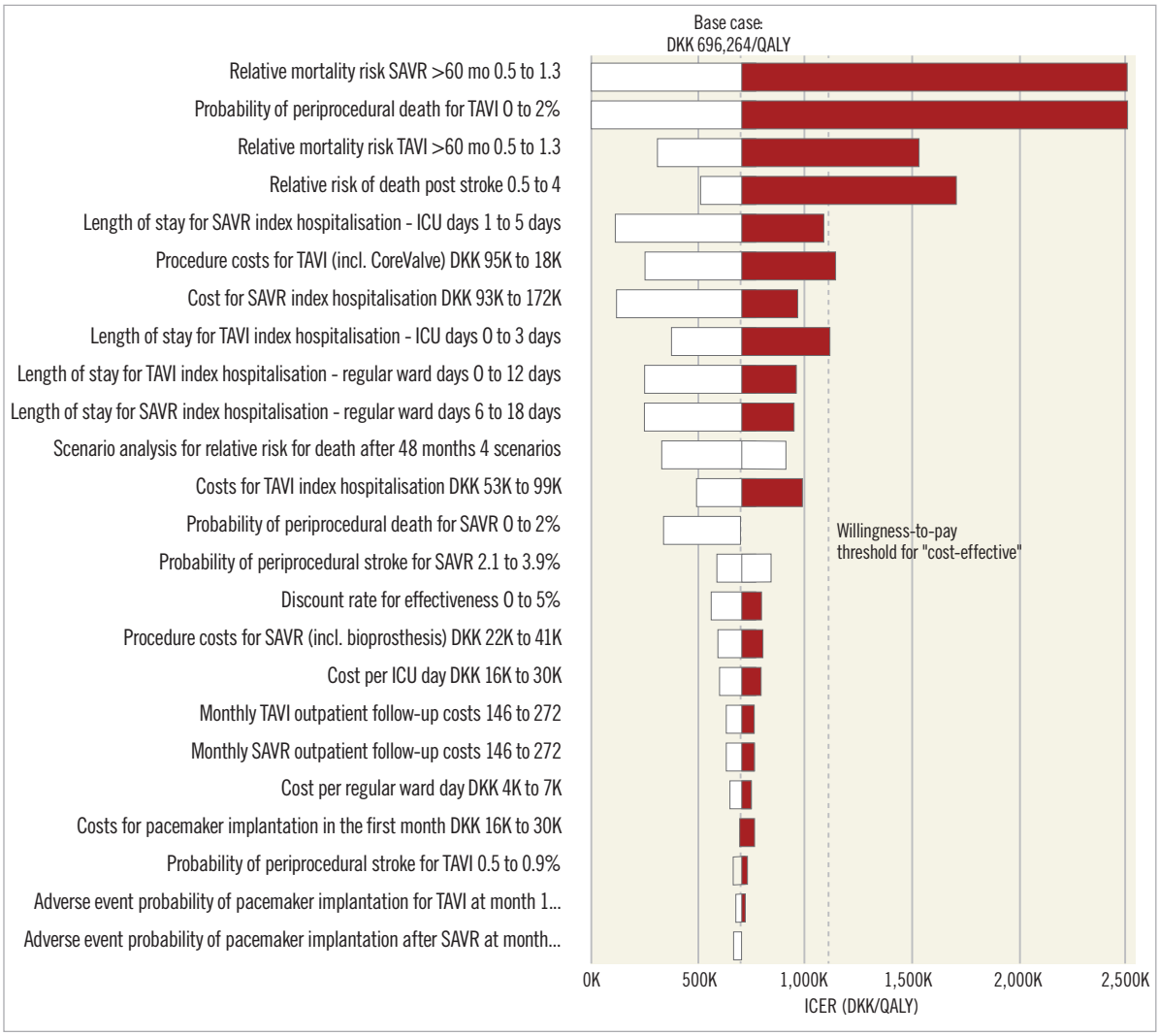

Figure 2. *One-way sensitivity analyses in the form of a tornado diagram. Data categories are listed vertically instead of the standard horizontal presentation, and the categories are ordered so that the largest bar (based on the largest spread of the ICER) appears at the top of the chart, the second largest appears second from the top, and so on. A black bar represents the ICER for the high value of the varied input parameter and a white bar the low value. The base case and the willingness-to-pay threshold for "cost-effective" are marked with dashed lines.*

Table 2. Results of the base case and other long-term mortality scenarios.

		Costs (DKK)	Incremental costs (DKK)	QALYs	Incremental QALYs	ICER (DKK/QALY)
Realistic scenario I (base case - fade out over 24 months to life tables [RR=1])	SAVR	211,581		5.30		
	TAVI	276,142	64,561	5.39	0.09	696,264
Realistic scenario II (fade out over 24 months to weighted RR [1.10] - then continues lifelong)	SAVR	210,826		5.19		
	TAVI	275,329	64,503	5.28	0.09	712,188
Best case scenario I (group-specific RRs [1.05/1.15] continue lifelong)	SAVR	210,484		5.14		
	TAVI	275,722	64,238	5.33	0.19	334,166
Worst case scenario I (immediate drop to life tables [RR=1.0])	SAVR	211,881		5.33		
	TAVI	276,238	64,357	5.40	0.07	892,000
Worst case scenario II (immediate drop to weighted RR [1.10] – but continues lifelong)	SAVR	210,920		5.20		
	TAVI	275,239	64,319	5.27	0.07	904,070

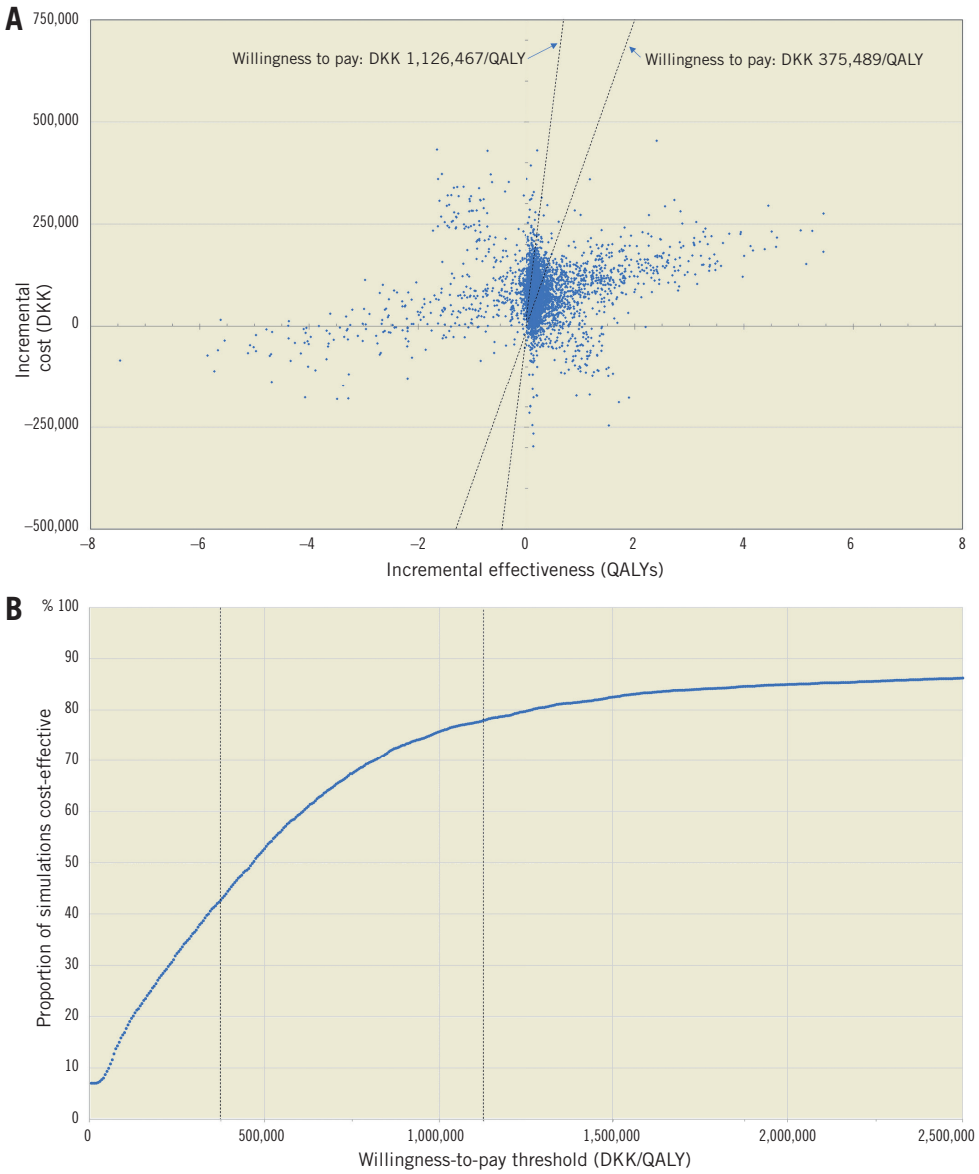

Figure 3. *Probabilistic sensitivity analysis. Panel A shows a scatter plot containing the 5,000 simulation results as sets of incremental costs (y-axis) and incremental effectiveness in QALYs (x-axis). The two willingness-to-pay (WTP) thresholds of DKK 375,489 and DKK 1,126,467 are marked as dashed lines. Panel B contains the corresponding WTP threshold where the y-axis depicts the percentage of simulations that are cost-effective at the given WTP threshold on the x-axis.*

Figure 3 depicts the results of the probabilistic sensitivity analysis. About 42% of the 5,000 simulations resulted in an ICER under DKK 375,489 whereas 78% of the simulations were below DKK 1,126,467 **(Supplementary Figure 5-Supplementary Figure 7)**.

Mortality was singled out as the most important driver for cost-effectiveness. Therefore, the RR for long-term mortality (i.e., beyond the observed 60-month period) was assessed further in sensitivity and scenario analyses **(Table 2, Supplementary Figure 8-Supplementary Figure 16)**. As expected, the continued benefit scenario as the most optimistic scenario provided the lowest ICER (DKK 334,166/QALY), while the stop-and-drop scenarios as the most conservative scenarios provided the most pessimistic results (ICERs of DKK 892,000/QALY and DKK 904,070/QALY for the stop-and-drop scenario with an immediate drop to life tables and with a drop to the weighted relative risk, respectively). The fade-out scenarios, which were considered the most realistic, resulted in ICERs between those two extreme scenarios (DKK 696,264/QALY and DKK 712,188/QALY for fading out to life tables and to weighted relative risk, respectively). Importantly, the two-way sensitivity analyses **(Supplementary Figure 10, Supplementary Figure 14)** indicate that the width of the "corridor" where TAVI (compared to SAVR) is highly cost-effective and not just cost-effective or is dominated by SAVR depends on which scenario is analysed, as evidenced by the difference of the blue shapes in those figures: while the corridor for the realistic scenario is relatively broad, the best case scenario was more susceptible to changes to the long-term mortality.

Discussion

The present study is the first economic evaluation to compare first-line TAVI with SAVR in a cohort comprised primarily of patients at low surgical risk. Its results indicate that the additional resources spent on TAVI are, on average, well spent given that there were no statistical differences in the underlying clinical trial[3] and the health economic profile is favourable. While TAVI is not an economically dominant or cost-saving procedure in this setting, all examined scenarios fell below the cost-effective WTP threshold set by the World Health Organization, and in one scenario TAVI was highly cost-effective.

The reason for this perhaps initially counterintuitive result – that TAVI is cost-effective – is that the higher TAVI device price is partially compensated for by the lower procedural and hospitalisation costs, as well as the slightly lower major adverse event rates. The only exception for this is permanent pacemaker (PPM) implantation due to a high risk of conduction abnormalities such as complete heart block among TAVI patients. The incidence of PPM placement was 34.1% at 30 days compared with 1.6% in patients treated with SAVR[3], a value that was higher than rates found in contemporary trials or registries that have studied self-expanding TAVI devices[7-9]. Given the costs of only around DKK 15,500 (excluding hospital stay) for PPM implantation in the Danish setting (personal communication from the Financial Department, Heart Centre, Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark), this difference in PPM rates did not have a greater impact on the results. This might be different in other healthcare systems where PPM implantation is associated with higher costs. However, data from newer studies of self-expanding TAVI devices, including Evolut™ R (Medtronic, Minneapolis, MN, USA), suggest a reduction in observed PPM rates that can be expected to improve the cost-effectiveness of TAVI[10].

On the other hand, the largest drivers of the value of TAVI in the NOTION trial were associated with periprocedural and long-term mortality risk, as well as the costs for the procedure itself and the index hospitalisation.

MORTALITY

Even though four-year results have recently been made available for the NOTION trial (Søndergaard L. Clinical, safety and echocardiographic outcomes from the Nordic Aortic Valve Intervention (NOTION) trial: Four-year follow-up data in all-comer patients with severe aortic valve stenosis. Presented at EuroPCR, Paris, France, 2017), the impact of just changing the relative all-cause mortality risk of 0.05 to 0.1 (compared to the general population) beyond those four years resulted in significant changes in the incremental QALYs; while the worst case scenarios resulted in a difference of only 0.07 QALYs, the best case scenario showed a benefit of around 0.19 additional QALYs for TAVI patients. It was these incremental QALY differences that drove the somewhat different ICERs, and the base care that we chose, one of the fade-out scenarios (termed "realistic" scenario), was a middle ground between the possibly too conservative stop-and-drop scenarios and the possibly too optimistic continuous-benefit scenarios.

While we varied the RRs for the long-term mortality in a large range of parameters, the one-way analyses should be interpreted with caution. For example, the ICER of nearly DKK 2.8 million/QALY gained for a SAVR RR of 0.5 would only have an effect if the TAVI RR stayed at 1.05, which is unrealistic based on the four-year follow-up results from NOTION (Søndergaard L. Clinical, safety and echocardiographic outcomes from the Nordic Aortic Valve Intervention (NOTION) trial: Four-year follow-up data in all-comer patients with severe aortic valve stenosis. Presented at EuroPCR, Paris, France, 2017). Therefore, the two-way sensitivity analyses can be helpful, providing reassurance that even when increasing or decreasing the RR for SAVR a bit more than the one for TAVI would still result in a similar ICER range; in particular, the two-way sensitivity analysis for the realistic scenario contained a broad cost-effectiveness "corridor".

Most importantly, a difference in periprocedural mortality between TAVI and SAVR of 2% will render the procedure cost-ineffective. However, it is not likely that the periprocedural mortality of TAVI in other cohorts will exceed that of SAVR given that there was no statistically significant difference in the low-risk NOTION cohort[3,4] (Søndergaard L. Clinical, safety and echocardiographic outcomes from the Nordic Aortic Valve Intervention (NOTION) trial: Four-year follow-up data in all-comer patients with severe aortic valve stenosis. Presented at EuroPCR, Paris, France, 2017) and the intermediate-risk SURTAVI cohort[8], and that it was superior at the initial follow-up of the CoreValve High

Risk cohort[7]. The same holds true for data observed in previous trials of balloon-expandable TAVI devices[11,12].

TAVI PROCEDURE COSTS

While comments about future device price developments would be speculative, it is not just possible but seems highly likely that, with increasing procedural experience, procedures and discharge processes will be streamlined, and other costs associated with TAVI will decrease further[13,14].

HOSPITALISATION COSTS

The costs for the index hospitalisation are considerable - DKK 132,330 after SAVR, not including additional costs for various procedure-related adverse events. SAVR has been performed for decades, and discharge from both the ICU and regular floors can be considered to have little possible room for efficiency gains given the maturity of the procedure, even though performance might vary between surgeons and centres[15]. In particular, length of stay might be slightly longer in the Nordic countries compared to the USA and certain other European countries. What seems sensible to point out is that, after these long hospitalisations and procedure-related adverse events, old and frail patients will have a harder time recovering from "post-hospital syndrome"[16] – so every day less spent in the hospital, and in particular in ICU settings, might be even more meaningful for the relatively old patients with severe aortic stenosis and their relatives than can be gathered in these data. On the other hand, fast-track hospital stay and even next-day discharge have been developed for selected patients after TAVI[13], and the length of stay after TAVI in the NOTION trial might have improved since the patients for this study were recruited between 2009 and 2014.

SURGICAL RISK

Compared with cost-effectiveness analyses in high or extreme surgical risk cohorts[2], the additional benefit associated with TAVI that was found in the present study is smaller. Given that the NOTION trial was a low surgical risk cohort, different results are to be expected. The relatively small effectiveness gain is in line with the clinical results from the low-[3,4] (Søndergaard L. Clinical, safety and echocardiographic outcomes from the Nordic Aortic Valve Intervention (NOTION) trial: Four-year follow-up data in all-comer patients with severe aortic valve stenosis. Presented at EuroPCR, Paris, France, 2017) and intermediate-risk[8] cohorts and underscores that the additional expenditures for TAVI are partially compensated for by other cost-saving mechanisms, including the lower procedure costs apart from the device costs, the lower index hospitalisation costs, and somewhat lower complication costs apart from PPM.

Limitations

Our study is subject to several limitations. First, the present analyses apply only to Denmark as different cost structures in different healthcare systems might lead to different results. Nevertheless, if potentially different cost structures were applied in a U.S. setting, then this would translate to a PPP-adjusted ICER of around $102,000/QALY gained which, per the ACC/AHA guidelines on costs and value[17], can be considered a cost-effective intervention of an intermediate value. Second, a decision-analytic model is just a representation of the reality and will never be perfect. However, modelling might help to inform decision makers better, and it highlights areas in which uncertainty exists and possibly even quantifies this uncertainty. Third, the long-term mortality of TAVI and SAVR beyond four years is unclear. However, we have conducted extensive sensitivity and scenario analyses. Fourth, it is unclear whether the outcomes of the NOTION trial are applicable to other settings, for example in patients with another distribution of access routes, surgical risks, and comorbidities. However, the NOTION trial was the first to study TAVI in a low surgical risk cohort, and insights from the Danish setting provided valuable insight for other trials and observational studies in either low or intermediate surgical risk cohorts. Fifth, cost structures and absolute costs, in particular for the procedure itself and for the index hospitalisation, tend to vary dramatically between the USA and other countries[18]; consequently, predictions about the cost-effectiveness of self-expanding TAVI devices in other settings may prove difficult. Sixth, while some cost estimates were derived from national prices on a near-cost basis, other costs and prices were taken from a single Danish institution. However, TAVI and SAVR are performed in only four Danish centres, and costs are likely to be relatively similar among them. Finally, the results herein might be applicable only to self-expanding and not to balloon-expandable TAVI devices.

Conclusions

TAVI was shown to be cost-effective in a low surgical risk cohort. However, the results are highly dependent on the long-term mortality and are applicable only to Denmark or to countries with similarly structured direct medical costs. While model-based analyses can help to facilitate an appreciation of the cost and effectiveness drivers, long-term registries should be pursued to decrease the uncertainty around long-term mortality. Likewise, cost-effectiveness analyses should be conducted in other countries to prove or disprove the cost-effectiveness of TAVI in other low-risk settings.

Impact on daily practice

TAVI might not just be an option for all patients (regardless of their surgical risk) with severe aortic stenosis in that its results are clinically not different from SAVR, but could also be cost-effective, depending on the setting. The suitability of individual patients for a transcatheter procedure should ultimately be decided on and the actual procedure performed by a dedicated service as both outcomes and costs might depend on the experience and procedural skill of that service. While the cost-effectiveness of TAVI has been demonstrated for low-risk patients in Denmark, different cost structures or long-term mortality in other countries and settings, e.g., in patients at other surgical risks, in newer self-expanding or in balloon-expandable devices, might result in other conclusions regarding their health economic profiles.

Guest Editor

This paper was guest edited by Alec Vahanian, MD, PhD; Department of Cardiology, Hôpital Bichat-Claude Bernard, and University Paris VII, Paris, France.

Conflict of interest statement

J.B. Pietzsch and B.P. Geisler (Wing Tech Inc.) provided health-economic consulting services to Medtronic plc. L. Søndergaard was the principal investigator for the NOTION trial and has received a consultant fee and institutional research grants from Medtronic plc. H.G.H. Thyregod was the other principal investigator for the NOTION trial and has no conflicts of interest to declare. The other author has no conflicts of interest to declare. The Guest Editor is a consultant for Edwards Lifesciences.

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Supplementary Table 1. Complete list of input parameters.

Supplementary Table 2. SF-6D and NYHA class at one-month visit.

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The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-18-00847

Supplementary data

Supplementary Appendix 1. Methods

Model structure and decision-analytic framework

The decision-analytic model was constructed in TreeAge 2019 R1.1 (TreeAge Software, Inc., Waltham, MA, USA) to forecast long-term societal costs and effectiveness and to compute an incremental cost-effectiveness ratio (ICER). The model was a combination of a decision tree and a state transition or Markov model where the patients' disease progression through defined, mutually exclusive health states is tracked at monthly intervals [21]. The model was run with half-cycle correction until the entire cohort was deceased (lifetime horizon).

All patients started off with the index procedure, TAVI or SAVR, where they could experience the following Valve Academic Research Consortium-2-defined periprocedural events [22]: all-cause death, fatal and non-fatal stroke, fatal and non-fatal MI, major or life-threatening bleeding, cardiogenic shock, stage 2-3 acute kidney injury, major vascular complication, atrial fibrillation, permanent pacemaker (PPM) implantation, prosthetic valve infective endocarditis, or the need for reintervention. These events were accounted for in terms of costs and mortality. Utilities, derived from trial-collected SF-6D data, were estimated to adjust life expectancy for health-related quality of life [23].

For modelling purposes, the study population was stratified into the following subgroups: NYHA Class I/II or Class III/IV without stroke or MI, with stroke, or with MI, respectively, based on the assumption that these events would impact on both costs and health-related quality of life [24]. If the patients did not die during the procedure, we calculated their monthly probability of experiencing NYHA Class I/II vs Class III/IV symptoms and either an MI or a stroke (see below and **Figure 1** in the main manuscript for details). In addition, we also accounted for the following one-year adverse events in terms of costs: atrial fibrillation, PPM, and infective endocarditis. For the long-term mortality beyond the observed trial period, we defined as a reference the Danish life tables [25]. This means that a relative risk (RR) of 1.0 corresponds to

the mortality of the general population. On top of this background mortality derived from the life tables, various scenarios analysing different combinations of RRs for TAVI and SAVR were modelled (see below for details). A simplified representation of the model structure is shown in **Figure 1** in the main manuscript.

In the absence of other clear recommendations for Denmark [26], the main decision criterion to evaluate cost-effectiveness was whether the ICER was below the willingness-to-pay thresholds established by the World Health Organization [27]. These thresholds stipulate that an intervention is "cost-effective" if the ICER is less than three times the gross domestic product per capita of the respective country and "highly cost-effective" if below the per-capita gross domestic product. All costs in this analysis are expressed in 2016 Danish kroner (DKK) and hence used the nominal 2016 gross domestic product per capita of DKK 375,489 [28]. The discount rate was 3% for costs and effectiveness.

Patient characteristics and other input parameters

Patient characteristics were based on the only available trial of TAVR vs SAVR in low-risk patients, NOTION 3; at baseline, there were 280 patients, mean age at the time of the procedure was 79.1±4.8 years, 46.8% of the cohort were female, and their mean Society of Thoracic Surgeons Predicted Risk of Mortality and logistic EuroSCORE II were 3.0% and 2.0%, respectively. 96.5% of patients had transfemoral access. Preoperative test and consults included transthoracic echocardiography, coronary angiography, and visits to a cardiologist and/or a cardiothoracic surgeon (the latter for SAVR patients only). Computed tomography for sizing of the aortic valve annulus was not routinely performed. For TAVI, only the CoreValve® self-expanding bioprosthesis was used (Medtronic, Minneapolis, MN, USA), whereas surgical patients received any commercially available bioprosthetic aortic valve at the discretion of the surgeon. In 2.8% of patients, two valve kits with the corresponding costs were assumed. The 30-day mortality in NOTION was 2.1% vs 3.7% for TAVI vs SAVR, respectively; 1.4% and 3.0% experienced a stroke, and 2.8% and 6.0% an MI. At one year, 92.4% vs 96.4% of the patients, respectively, had NYHA Class I/II symptoms. A TAVI device cost of DKK 125,000 was assumed (personal communication from the Financial Department, Heart Centre, Rigshospitalet,

University Hospital of Copenhagen, Copenhagen, Denmark), and for SAVR a bioprosthetic and not a mechanical valve at DKK 14,906 without the need for systemic anticoagulation for all patients given their age; all device costs were subsumed in the procedure costs. In the NOTION trial, patients had a mean intensive care unit length of stay of 1.3 vs 2.6 days after TAVI and SAVR and remained on a general ward for 8.9 and 12.9 days, respectively [3]. Amid these lengths of stay, none of the patients was assumed to have been transferred from the hospital to a free-standing physical rehabilitation centre at the time of discharge.

Monthly probabilities of experiencing all-cause death, stroke, or MI in the remaining patients at risk were computed from the patient-level NOTION five-year data set [4] (Søndergaard L. Clinical, safety and echocardiographic outcomes from the Nordic Aortic Valve Intervention (NOTION) trial: Four-year follow-up data in all-comer patients with severe aortic valve stenosis. Presented at EuroPCR, Paris, France, 2017). All statistical analyses were conducted in SAS 9.4 (SAS Institute, Cary, NC, USA). Resulting key input parameters for the model can be found in **Supplementary Table 1**.

Model calibration and uncertainty analyses

To achieve concordance with the actual trial results, the present model was calibrated with regard to the following endpoints: all-cause mortality, stroke, or MI. See below for details on the calibration.

To evaluate the effects of uncertainty in input parameters, we conducted the following analyses. For all input parameters, one-way sensitivity analyses were performed by changing the input parameter by at least ±30%. The input parameters to which the model was most sensitive (as judged by the spread of net monetary benefit) were summarised in tornado diagrams. We also performed a probabilistic sensitivity analysis with 5,000 random draws in a second-order Monte Carlo simulation (see below). Extensive sensitivity analyses were performed regarding the long-term mortality as this was *a posteriori* judged to be one of the most important parameters for a low-risk cohort (see **Results** in the main manuscript and below). The RRs were analysed in

separate one-way sensitivity analyses and in a two-way analysis. Several scenarios were created in accordance with established standards on how to extrapolate along-the-trial results [29]. First, two "stop-and-drop" scenarios (most conservative scenarios), one involving dropping the RRs to 1.0 (i.e., applying the mortality from the life tables of the general population to both TAVI and SAVR arms) and one dropping it to the weighted mortality observed in the second two-year interval of the trial (combined RR: 1.10, applied to both arms). Second, the most optimistic scenario was a "continued-benefit" scenario where the mortality benefit of TAVI over SAVR observed in the last two years of the trial continued for the remainder of the patients' lifetime. Third, for the base case, we used a "fade-out" scenario, where the relative risks of TAVI and SAVR were both subject to a linear fading out over 24 months towards an RR of 1.0, i.e., the mortality of the two groups was approaching the life tables of the general population over this time. A second fade-out scenario examined the effect of a fade-out from the observed RRs (RR for TAVI: 1.05; RR for SAVR: 1.15) towards the weighted combined RR of 1.10 as compared to general population life tables. In addition, selected threshold analyses were conducted.

Complete list of input parameters

In **Supplementary Table 1**, we list all input parameters used in the decision-analytic model. The parameters are distributed into the following categories (as they are in all sections below):

- Patient characteristics
- Probability of immediate adverse events
- Probability of 30-day adverse events
- Probability of one-year adverse events
- Preoperative costs
- Procedure costs
- Costs per immediate adverse event
- Length of stay and hospitalisation-related costs
- Costs per 30-day adverse events
- Costs of follow-up care
- Costs per one-year adverse events

Some parameters are different for the TAVI and SAVR arms and are listed in the respective column. The values in the brackets correspond to the ranges for the deterministic sensitivity analyses. The second row lists the distribution assumed in the probabilistic sensitivity analysis with the corresponding parameters.

Supplementary Appendix 2. Trial-based mortality, stroke, and MI incidence, and model calibration

This section shows a set of figures with an overlay of the calibrated model output (all-cause mortality, stroke, and myocardial infarction) over the actual trial outcome with the corresponding patients at risk in the TAVI and SAVR groups, respectively. The trial outcomes were taken from the publications and presentations describing the outcomes of the NOTION study [3,4] (Søndergaard L. Clinical, safety and echocardiographic outcomes from the Nordic Aortic Valve Intervention (NOTION) trial: Four-year follow-up data in all-comer patients with severe aortic valve stenosis. Presented at EuroPCR, Paris, France, 2017) as well as the five-year outcomes which are currently in print. The model output was generated via Markov traces for each treatment strategy separately.

All-cause mortality

Supplementary Figure 1 depicts all-cause mortality. The actual TAVI trial outcome is represented by the orange line and the TAVI model output by the red circles. The actual SAVR trial outcome is represented by the turquoise line and the SAVR model output by the green circles.

Of note, these model results match the actual trial because we manually calibrated the transition probabilities to the actual trial results.

Stroke

Supplementary Figure 2 depicts the incidence of stroke. The actual TAVI trial outcome is represented by the orange line and the calibrated model output by the red circles. The actual

SAVR trial outcome is represented by the turquoise line, and the green circles represent the model output.

Of note, these model results match the actual trial because we manually calibrated the transition probabilities to the actual trial results.

Myocardial infarction

Supplementary Figure 3 depicts the incidence of myocardial infarction. The actual TAVI trial outcome is represented by the orange line and the calibrated model output by the red circles. The actual SAVR trial outcome is represented by the turquoise line, and the green circles represent the model output.

Of note, these model results match the actual trial because we manually calibrated the transition probabilities to the actual trial results.

Supplementary Appendix 3. Utilities

Supplementary Table 2-Supplementary Table 5 summarise the utilities used in the model, based on scored SF-6D questionnaires collected in NOTION.

Supplementary Appendix 4. Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was performed to quantify the overall uncertainty. We used 54 distributions for the input parameters (**Table 1** in the main manuscript). In a second-order Monte Carlo simulation, 5,000 random draws from these distributions were performed, and the model was run to estimate a cost/effectiveness data point for TAVI and SAVR, which are depicted on the two subsequent incremental cost-effectiveness (ICE) scatter plots. The ellipse on each represents the area where 95% of the simulations are located.

Supplementary Figure 4 demonstrates the results of the probabilistic sensitivity analysis with a willingness-to-pay threshold of DKK 375,489/QALY which is equivalent to "highly cost-effective".

Supplementary Figure 5 demonstrates the results of the probabilistic sensitivity analysis with a willingness-to-pay threshold of DKK 1,126,467/QALY which is equivalent to "cost-effective".

Supplementary Figure 6 is a cost-effectiveness acceptability curve. About 32% of the 5,000 simulations resulted in an ICER under DKK 375,489 (corresponding to the WHO definition of "highly cost-effective") whereas 56% of the simulations were below DKK 1,126,467 ("cost-effective").

Supplementary Appendix 5. Tornado diagram

Supplementary Figure 4 shows a slightly more comprehensive tornado diagram compared to the Figure in the manuscript. However, as can be seen and as discussed in the manuscript, the main drivers of the ICER are (in descending order) the following.

1. Relative mortality risk for SAVR beyond the 48-month trial observation period (and, to a lesser degree, for the relative risk for TAVI and for the five scenarios [as discussed in extensive detail below]).
2. Periprocedural mortality during TAVI (and, to a lesser degree, for corresponding periprocedural mortality of SAVR).
3. Procedure costs for TAVI (and, to a lesser degree, for SAVR procedural costs).
4. Length of stay for SAVR and TAVI index hospitalisation, in particular for the ICU component of the SAVR and the regular ward component of the TAVI index hospitalisations, respectively – or costs *in toto* for the entire hospitalisation or per ICU day.
5. Discount rates for effectiveness.

Again, we discuss these factors in the manuscript. However, a more extensive discussion on the relative mortality risks and the scenarios created from varying these in different ways can be found below.

Supplementary Appendix 6. Sensitivity analyses on long-term mortality

As discussed in the main manuscript and in line with the health economic literature [21], we analysed several scenarios for the long-term mortality beyond the observed 48 months.

1. Base case: fade-out scenario I (fade out over 12 months to life tables [RR=1]).
2. Fade-out scenario II (fade out over 12 months to weighted RR [1.10] – then continues lifelong).
3. Continuous benefit scenario I (group-specific RRs [1.05/1.15] continue lifelong).
4. Stop-and-drop scenario I (immediate drop to life tables [RR=1.0]).
5. Stop-and-drop scenario II (immediate drop to weighted RR [1.10] – but continues lifelong).

What might be perceived as slightly different from the standard approach [21] is that we have two fade-out and two stop-and-drop scenarios. The reason for this is that we consider the relative risks to fade out – or drop immediately – to different values: one, to the background mortality of the general population (i.e., a relative risk of 1.0), and two, to a weighted RR of 1.1, which corresponds to a slightly worse mortality than the general population. This relative risk was derived from the weighted relative risks from the second two years of the NOTION trial [3]. To explain, we obtained the "weighted" relative risk of 1.1 from the second two years of the trial (months 24 to 47), which was 12.0% for TAVI and 13.2% for SAVR. This compared to a gender-adjusted mortality over the corresponding two years from the Danish life tables (ages 81 and 82, based on the mean age of around 79 at baseline) of 11.48%. Hence, the relative risks of TAVI and SAVR are 1.05 and 1.15. Weighing these two with the patients at risk at month 24 (n=75 and 72, respectively) results in a relative risk of 1.15.

Fade-out scenarios – base case

In the first fade-out scenario, we let the relative mortality risk of TAVI and SAVR that was observed in the second two years of the trial "fade out" of 12 months to the background mortality (Danish life tables).

In the second fade-out scenario, we let the relative mortality risk of TAVI and SAVR that was observed in the second two years of the trial "fade out" of 24 months – as explained above.

Supplementary Figure 8 contains an illustration of the fade-out of the relative mortality risk (reference: life tables) over the first year after the observed trial period.

The sensitivity analyses regarding the long-term mortality RR for the fade-out scenario are displayed in **Supplementary Figure 9** and **Supplementary Figure 10**. Of note, we only analysed these for the first fade-out scenario, where the relative risk fades out to the background mortality as this had been chosen as the base case.

- **Supplementary Figure 9** contains two one-way sensitivity analyses with the outcome undiscounted (and quality-unadjusted) life years. The first curve, in orange, analyses the relative mortality risk (with life tables of the general population as a reference) of TAVI after the trial observation period of 48 months, the other curve, in green, the respective relative mortality risk of SAVR. Each relative risk corresponds to the x-axis, and the y-axis represents the outcome undiscounted life years. The base case is marked with a red circle (TAVI) and a yellow diamond (SAVR).

- **Supplementary Figure 10** contains a two-way sensitivity analysis of the same relative risks but, instead of each relative risk being on the same axis (as in **Supplementary Figure 9**), they are represented by the x and y axes, and the colour or the area corresponds to the category that the result for that respective pair of x and y values belongs to (red for TAVI being highly cost-effective, blue for TAVI being cost-effective

[but not highly cost-effective], and purple for not cost-effective, i.e., TAVI is economically dominated by SAVR). It is important to note that, when varying one RR in these sensitivity analyses, the other is fixed. For example, when assuming a SAVR RR of 0.9 in **Supplementary Figure 13**, the TAVI RR is kept at 1.05. Hence, these graphs represent extreme cases.

Continuous benefit scenario

In the continuous benefit scenario, the estimated relative mortality risks (RRs, see above for definitions) continue lifelong. Since we observed a slightly more favourable relative risk for TAVI compared to SAVR (1.05 vs 1.1), we call this scenario "continuous benefit," although the relative risk over 1.0 (reference: life tables) indicates that the mortality is slightly worse compared to the general population. Given that the benefit of TAVI over SAVR was observed in the last two years of the trial, we chose to analyse this scenario even though it might be the least conservative assumption – and is hence not the base case.

Below are several graphs that analyse the RRs as one-way sensitivity analyses between the extremes of 0.5 and 1.3 (the extremes observed in individual 12-month periods in the trial):

- Analogous to **Supplementary Figure 10**, **Supplementary Figure 9** (please see above for an explanation) contains two one-way sensitivity analyses with the outcome undiscounted (and quality-unadjusted) life years. What can be gathered immediately is that the curves are much less flat than in the fade-out scenario I.
- **Supplementary Figure 12** and **Supplementary Figure 13** show separate one-way sensitivity analyses on the RRs for the outcome discounted incremental cost-effectiveness ratio (ICER). Again, it is important to note that, when varying one RR in these sensitivity analyses, the other is fixed. For example, when assuming a SAVR RR of 0.9 in **Supplementary Figure 13**, the TAVI RR is kept at 1.05. Hence, these graphs represent extreme cases.

  Supplementary Figure 14 contains a two-way sensitivity analysis of the same relative risks but, instead of each relative risk being on the same axis (as in **Supplementary**

Figure 11), they are represented by the x and y axes, and the colour or the area corresponds to the category that the result for that respective pair of x and y values belongs to (red for TAVI being highly cost-effective, blue for TAVI being cost-effective [but not highly cost-effective], and purple for not cost-effective, i.e., TAVI is economically dominated by SAVR).

Summary and comparison of the base case scenarios

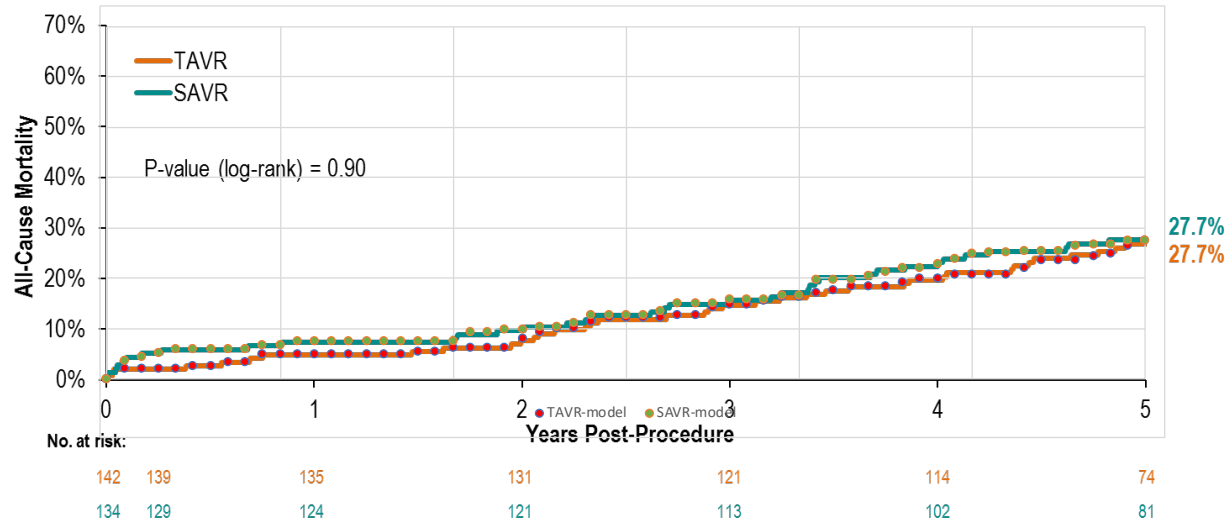
Reproduced in **Supplementary Table 6** are the results for the various scenarios. Below, please find the description of several charts to compare the different scenarios graphically.

In **Supplementary Figure 15,** the absolute QALYs for TAVI and SAVR are graphed by scenario. As can be seen, the stop-and-drop I scenario (to life tables) had the highest TAVI and SAVR QALY gains, followed by the fade-out I scenario (to life tables). This can of course be explained by the fact that the relative risk drops the soonest to the background mortality of the general population in the stop-and-drop scenario, but the fade-out scenario I achieves this relative risk after just 60 months. However, and more importantly, the continuous benefit scenario offers the greatest incremental benefit.

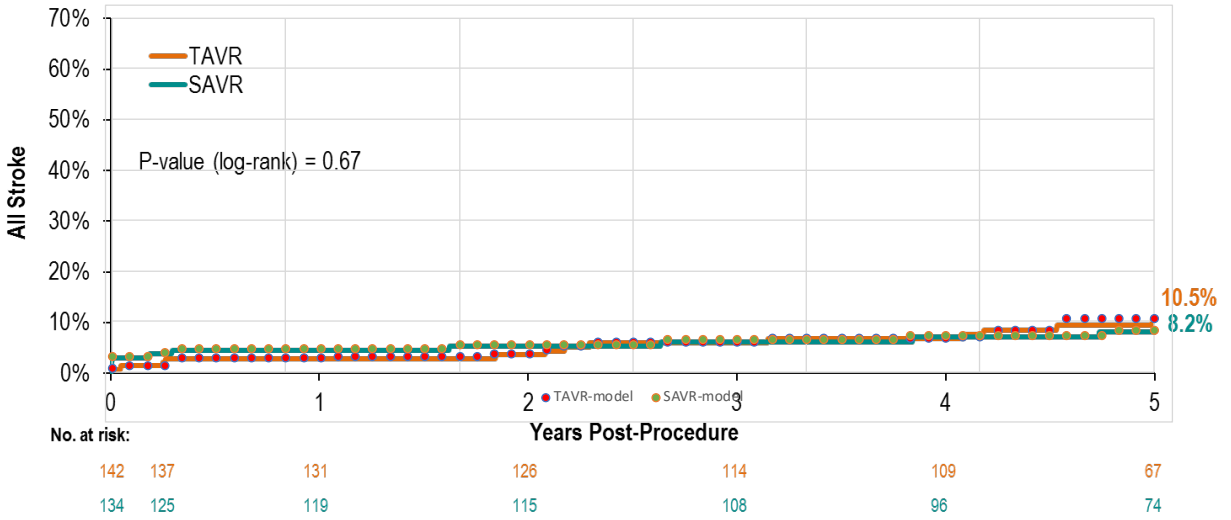
As can be seen in **Supplementary Figure 16**, the continuous benefit, which was also *a priori* believed to be the least conservative scenario, has the highest QALY gain and the lowest ICER. Noteworthy are three points:-

1. The ICER largely depends on the incremental QALY difference and not on the incremental costs (these are largely the same for the different scenarios). This is probably due to the effect that, four months out from the procedure, the most important costs are the outpatient follow-up costs, which are similar between the strategies if survival is not much different.

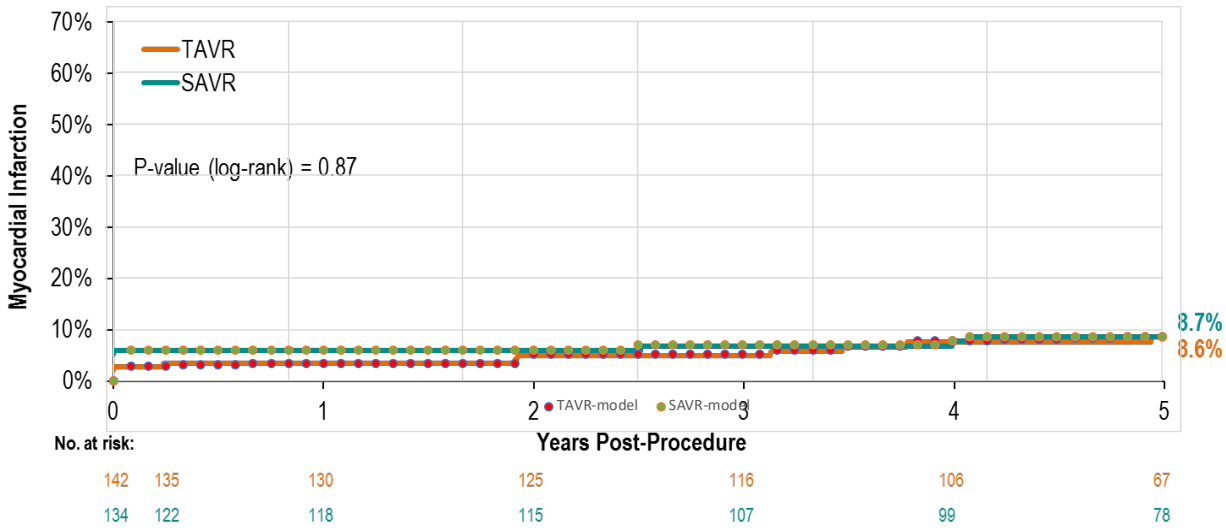
2. The difference between the continuous benefit and the fade-out scenarios (which lie in the “middle”) is much greater than between the fade-out scenarios and the stop-and drop scenarios.
3. The difference between the two fade-out scenarios and the two stop-and-drop scenarios is relatively small. This is despite the higher/lower QALYs that the two strategies achieve **(Supplementary Figure 15)** but *because* of similar incremental QALY gains, as can be gathered from **Supplementary Figure 16**.



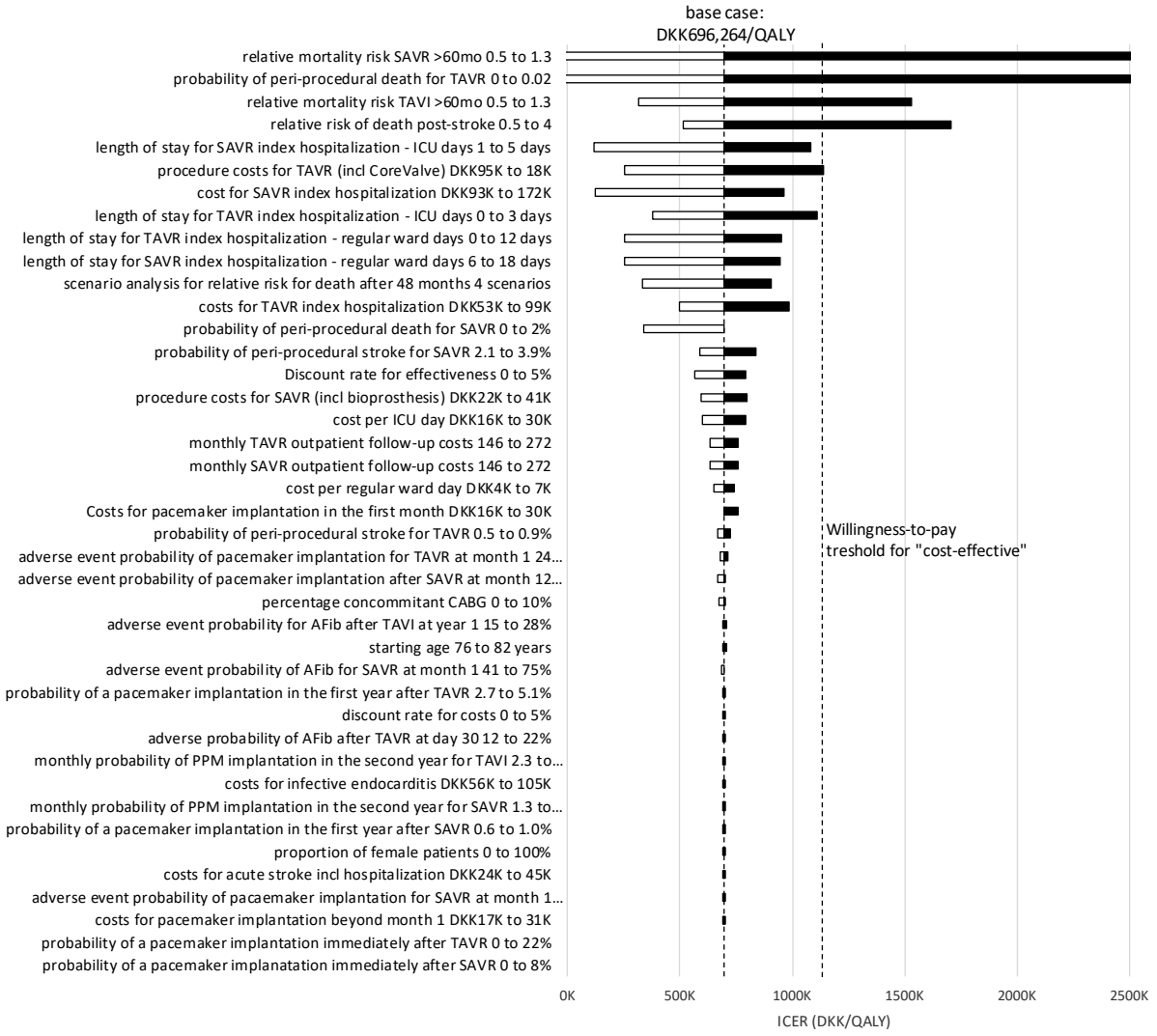
Supplementary Figure 1. 60-month mortality data with calibrated model output.



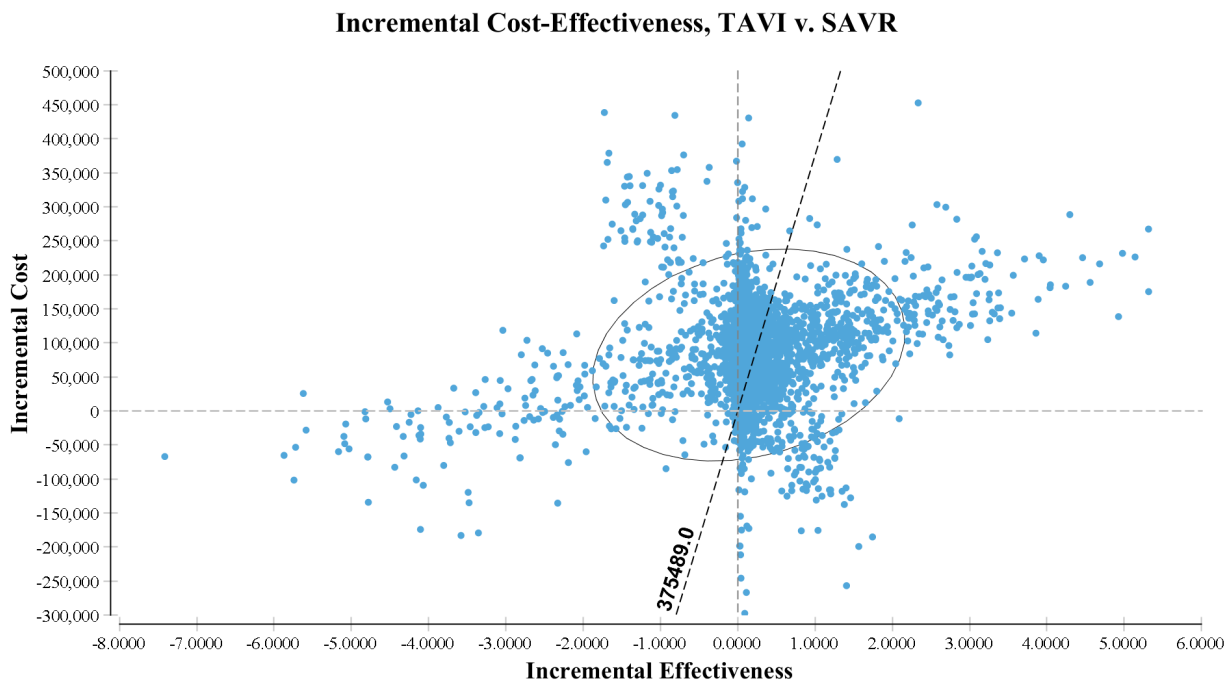
Supplementary Figure 2. 60-month stroke incidence with calibrated model output.



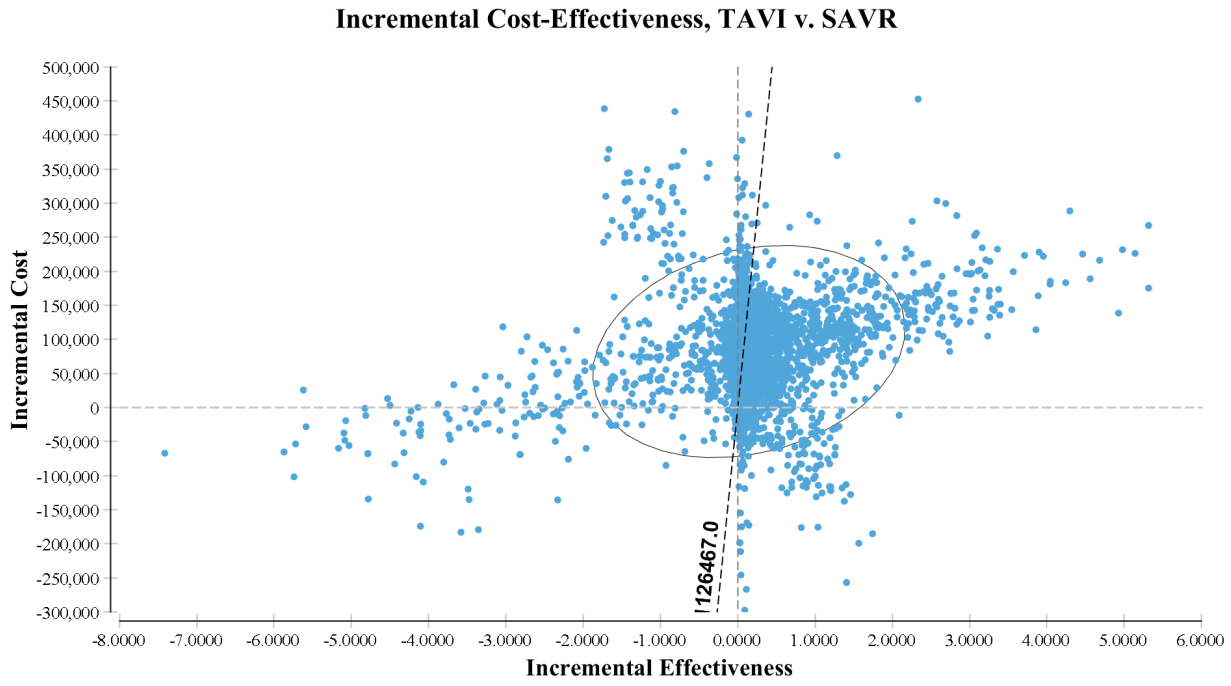
Supplementary Figure 3. 60-month myocardial infarction incidence with calibrated model output.



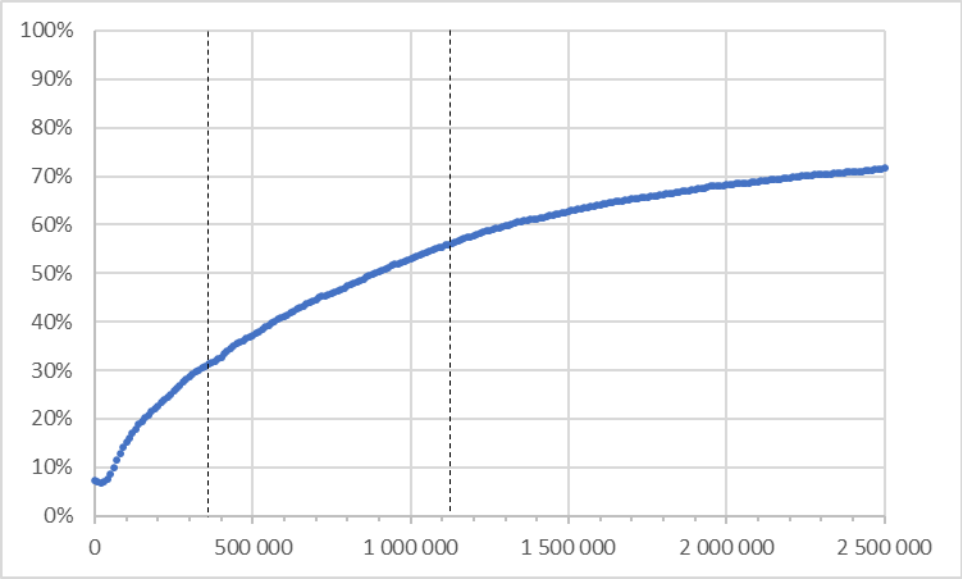
Supplementary Figure 4. Tornado diagram.



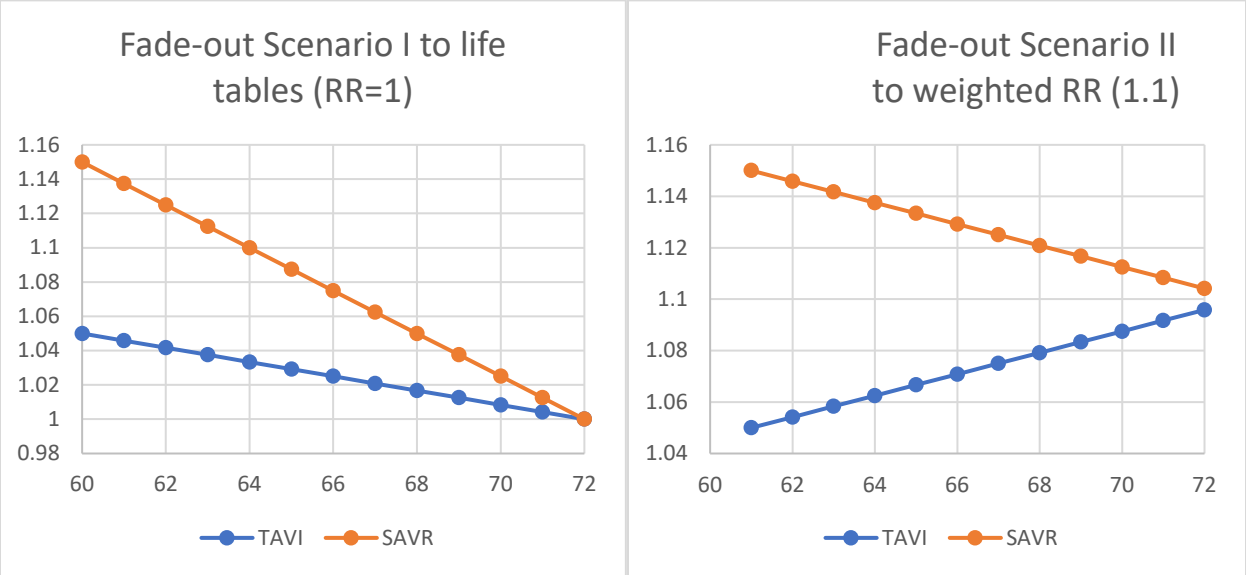
Supplementary Figure 5. Incremental cost-effectiveness (ICE) scatter plot with a willingness-to-pay threshold of DKK 375,489.



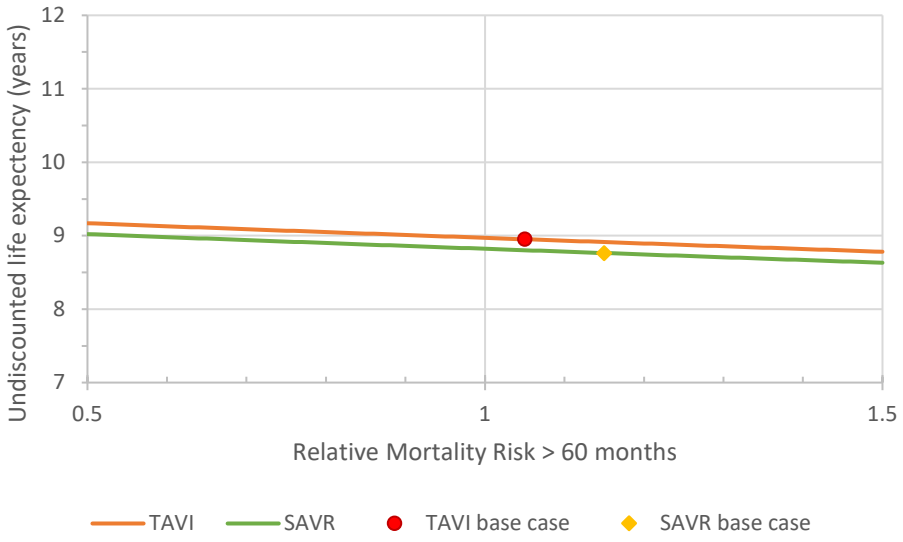
Supplementary Figure 6. Incremental cost-effectiveness (ICE) scatter plot with a willingness-to-pay threshold of DKK 1,126,467.



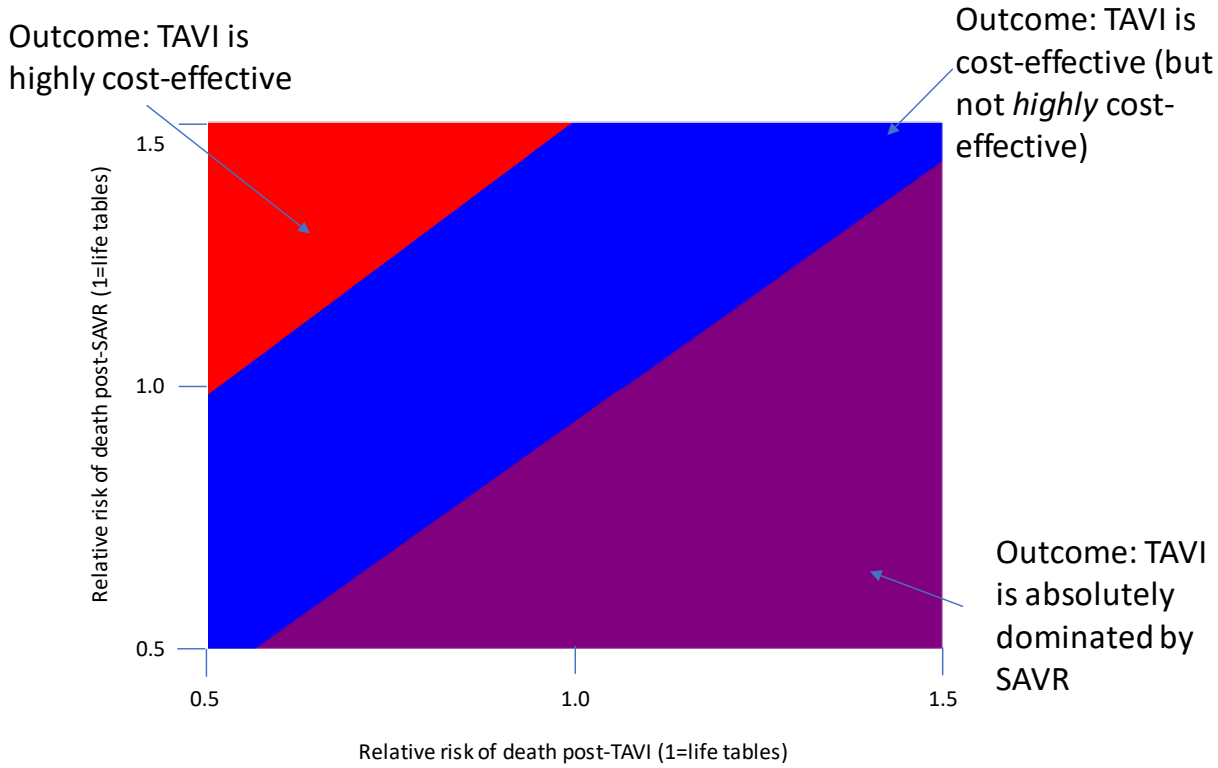
Supplementary Figure 7. Cost-effectiveness acceptability curve.



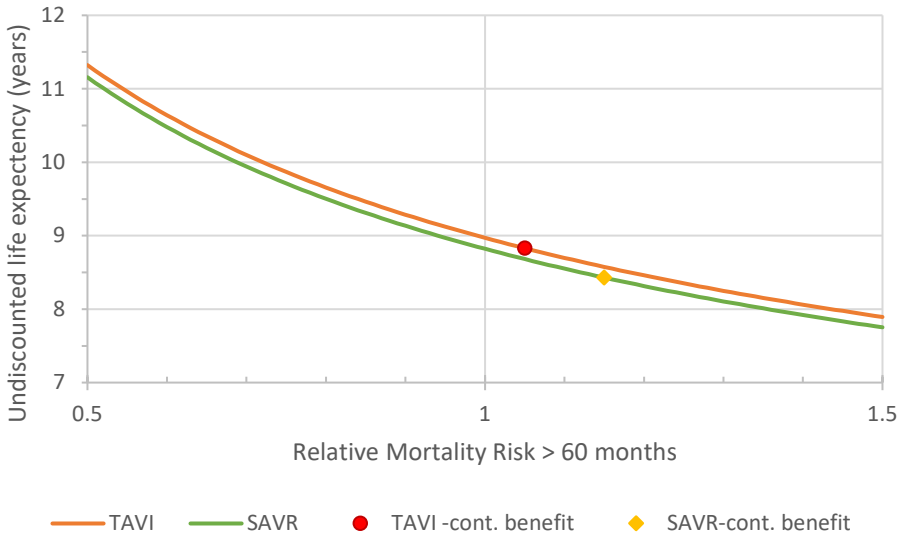
Supplementary Figure 8. Illustration of the relative mortality risk fading out over time.



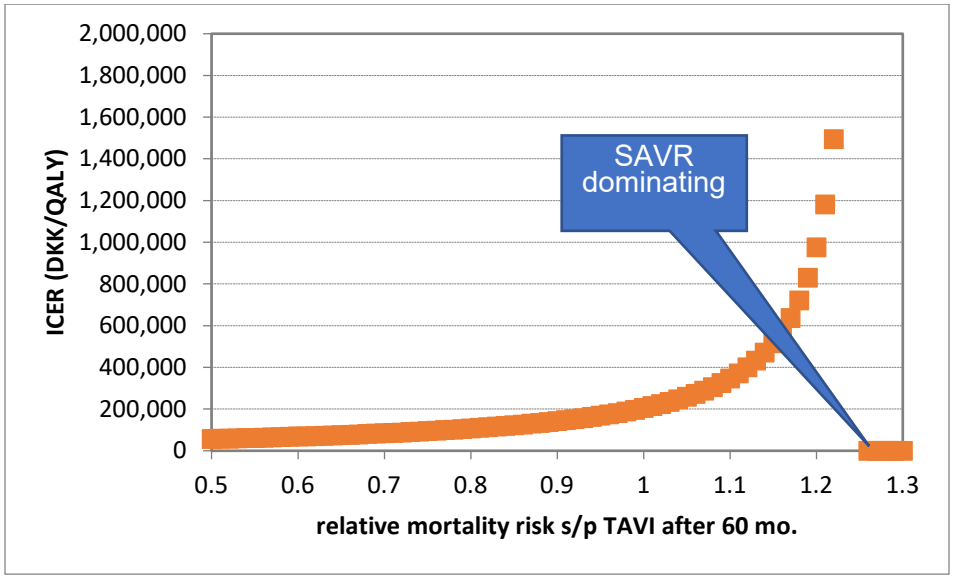
Supplementary Figure 9. One-way sensitivity analyses of relative mortality risk after TAVI and SAVR in the fade-out I scenario (base case, outcome: undiscounted life years).



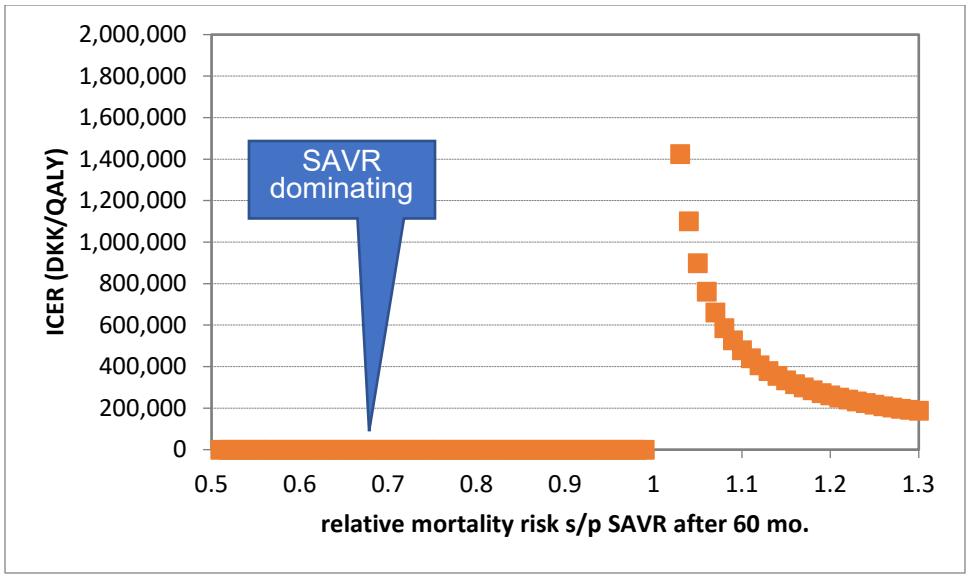
Supplementary Figure 10. Two-way sensitivity analysis on relative mortality risk after SAVR over relative mortality risk after TAVI (fade-out scenario).



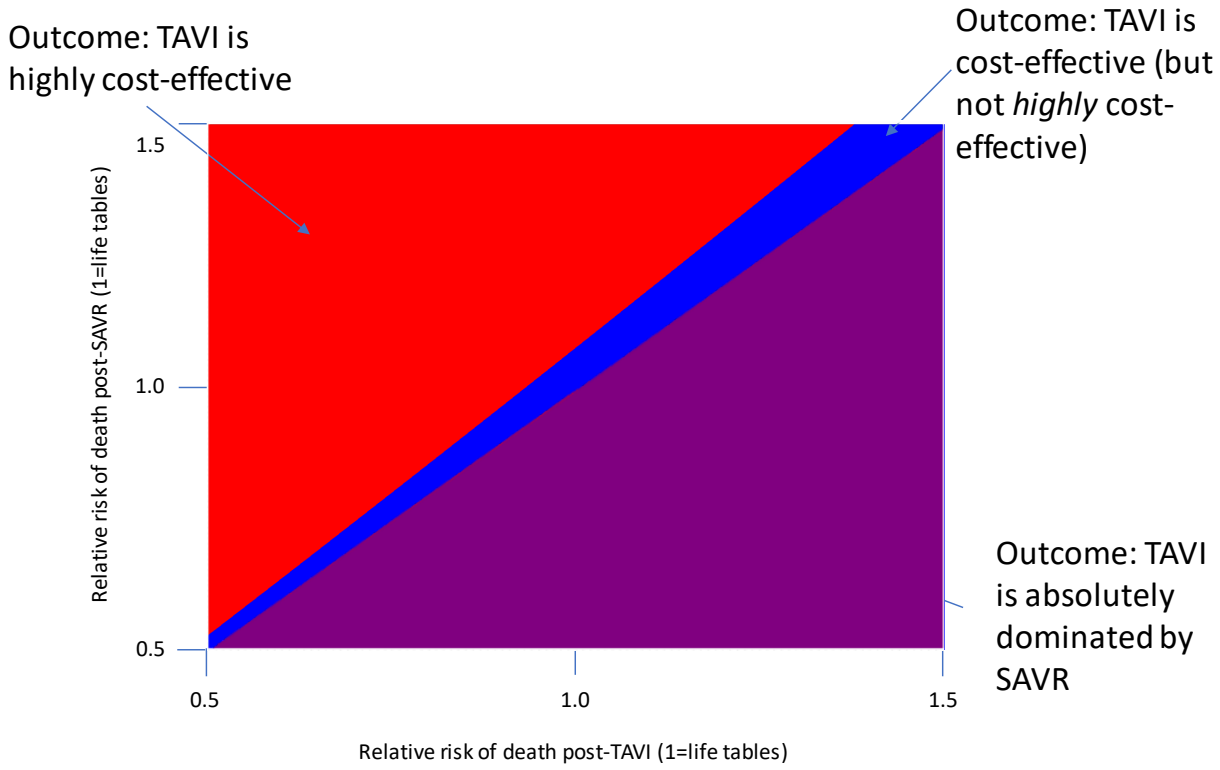
Supplementary Figure 11. One-way sensitivity analyses of relative mortality risk after TAVI and SAVR in the continuous benefit scenario (outcome: undiscounted life years).



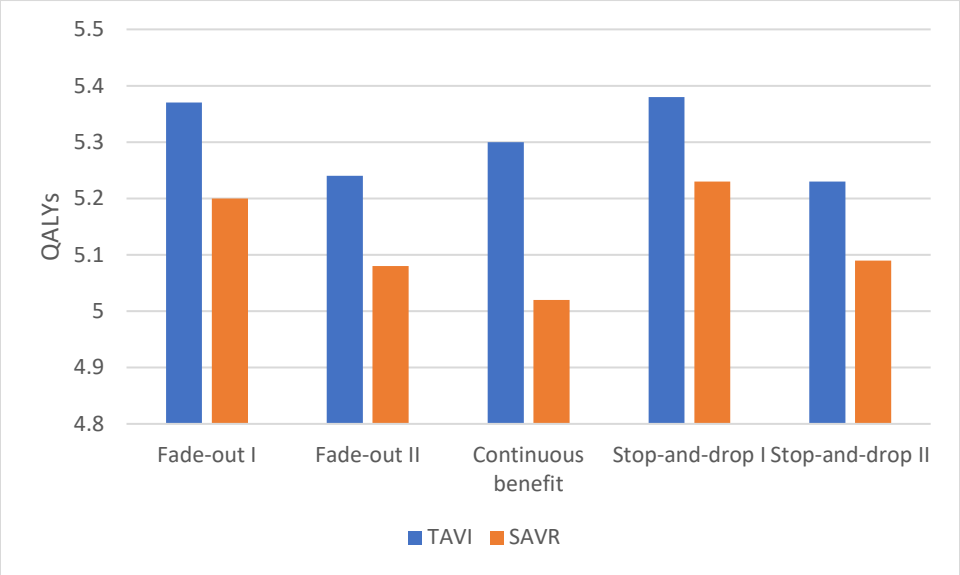
Supplementary Figure 12. One-way sensitivity analysis over relative mortality risk after TAVI (continuous benefit scenario).



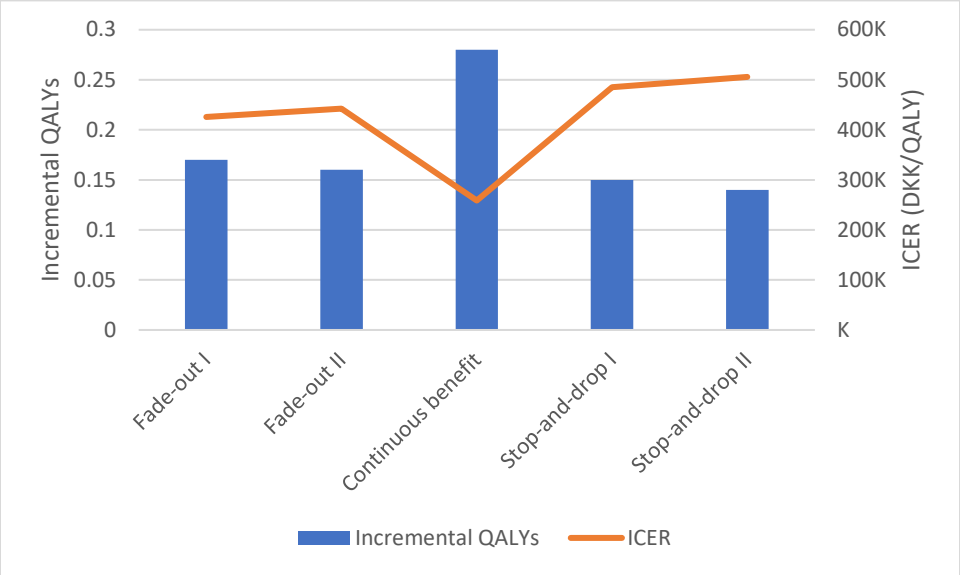
Supplementary Figure 13. One-way sensitivity analysis over relative mortality risk after SAVR (continuous benefit scenario).



Supplementary Figure 14. Two-way sensitivity analysis on relative mortality risk after SAVR over relative mortality risk after TAVI (continuous benefit scenario).



Supplementary Figure 15. Bar chart comparing the QALYs incurred by TAVI and SAVR.



Supplementary Figure 16. Combined bar and line chart comparing the incremental QALYs (blue bars) and corresponding ICERs (orange line).

Supplementary Table 1. Complete list of input parameters.

	TAVI	SAVR	Source
Patient characteristics			
Age (years)	79.1 (76; 82) Normal; 79.1; 4.9		[3]
Gender (female)	46.8% (0%; 100%) Beta; 11.18; 12.71		[3]
Immediate AEs			
Major/life-threatening bleeding	11.3% (7.9%; 14.7%) Beta; 1.02; 8.00	20.9% (14.6%; 27.2%) Beta; 3.25; 12.29	Post hoc analysis
Cardiogenic shock	4.2% (2.9%; 5.5%) Beta; 0.13; 2.90	10.4% (7.3%; 13.5%) Beta; 3.25; 12.29	Post hoc analysis
Acute kidney injury	0.7% (0.5%; 0.9%) Beta; $6.03 \cdot 10^{-4}$; $8.55 \cdot 10^{-2}$	6.7% (4.7%; 8.7%) Beta; 0.59; 8.18	Post hoc analysis
Major vascular complications	5.6% (3.9%; 7.3%) Beta; 0.24; 4.05	1.5% (1.1%; 2.0%) Beta; $7.16 \cdot 10^{-3}$; 0.47	Post hoc analysis
30-day AEs			
All-cause mortality	2.1% Beta; $2.22 \cdot 10^{-2}$; 1.03	3.7% Beta; $9.48 \cdot 10^{-2}$; 2.47	[3]
Stroke	1.4% Beta; $5.33 \cdot 10^{-3}$; 0.38	3.0% Beta; $5.73 \cdot 10^{-2}$; 1.85	[3]
Myocardial infarction	2.8% Beta; $4.82 \cdot 10^{-2}$; 1.67	6.0% Beta; 0.28; 4.36	[3]
Atrial fibrillation	16.9% (11.8%; 22.0%) Beta; 0.42; 2.09	57.8% (40.5%; 75.1%) Beta; 2.95; 2.15	[3]
PPM implantation	34.1% (24.0%; 44.3%) Beta; 1.57; 3.04	1.6% (1.1%; 2.1%) Beta; $9.19 \cdot 10^{-3}$; 0.57	[3]
Prosthetic valve IE	0% (0.5%; 0.9%) Beta; $6.03 \cdot 10^{-4}$; $8.55 \cdot 10^{-2}$	0% (0%; 0.9%) Beta; $1.55 \cdot 10^{-2}$; 155.2	[3]
Reintervention	0% (0%; 5%)	0% (0%; 5%)	Post hoc analysis
1-year AEs			
All-cause mortality	4.9%	7.5%	[3]
Stroke	2.9%	4.6%	[3]
Myocardial infarction	3.5%	6.0%	[3]
Atrial fibrillation	21.2% (14.8%; 27.6%)	59.4% (41.6%; 77.2%)	[3]

	Beta; 3.33; 12.38	Beta; 13.73; 9.39	
PPM implantation	3.9% (2.7%; 5.1%)* +34.1% (at month 1) Beta; 8.57; 13.99	0.8% (0.6%; 1.0%)* +1.6% (at month 1) Beta; $3.22 \cdot 10^{-2}$; 1.31	[3]
Prosthetic valve IE	2.9% (2.0%; 3.7%) Beta; 0.10; 3.30	1.6% (1.1%; 2.1%) Beta; $2.34 \cdot 10^{-2}$; 1.44	[3]
Preoperative costs			
Transthoracic echo	DKK 1,150		[16]
Coronary angiography	DKK 7,749		[16]
CTA chest		DK 2,621	[16]
Cardiologist visit	DKK 1,362		[16]
Cardiothoracic surgeon visit		DKK 1,362	[16]
Total preoperative costs	DKK 14,244 (9,971; 18,517) Gamma; 32.46; $2.28 \cdot 10^{-3}$	DKK 11,623 (8,136; 15,110) Gamma; 21.62; $1.86 \cdot 10^{-3}$	
Procedure costs			
Procedure time	90 minutes	177 minutes	[16]
Physician time	DKK 815	DKK 1,597	Skin-to-skin time; wages [16]
Nursing time	DKK 415	DKK 813	Skin-to-skin time; wages [16]
Tech time		DKK 813	Skin-to-skin time; wages [16]
Valve costs	DKK 125,000	DKK 14,500	[16]
Heart-lung machine	n.a.	DKK 9,600	[16]
Concomitant CABG		DKK 25,000**	[16]
Other materials	DKK 9,600	DKK 6,700	[16]
PRBC transfusions	DKK 172	DKK 455	[16]
FFP transfusions	DKK 18	DKK 63	[16]
Platelet transfusions	DKK 37	DKK 348	[16]
Total procedure costs	DKK 136,057*** (95,240; 176,874) Gamma; 185.12; $1.36 \cdot 10^{-3}$	DKK 31,189**** (21,832; 40,546); Gamma; 155.64; $4.99 \cdot 10^{-3}$	[16]
AE costs during index hospitalisation			
Stroke	see below		[31, 32]
Myocardial infarct	see below		[31, 32]
Major or life-threatening bleeding	DKK 4,752 (3,326; 6,178) Gamma; 3.61; $7.60 \cdot 10^{-4}$		[16]
Cardiogenic shock	DKK 29,638 (20,747; 38,529) Gamma; 0.98; $3.29 \cdot 10^{-5}$		[16]

Acute kidney injury	DKK 11,342 (7,939; 14,745) Gamma; 0.57; $5.04 \cdot 10^{-5}$		[16]
Major vascular complications	DKK 12,171 (8,520; 15,822) Gamma; 5.93; $4.87 \cdot 10^{-4}$		[16]
Stroke: first month	DKK 34,711 (24,298; 45,124) Gamma; 5.35; $1.54 \cdot 10^{-4}$		[31, 32]
Stroke: monthly costs for remaining lifetime	DKK 3,192 (2,234; 4,150) Gamma 40.76; $1.28 \cdot 10^{-4}$		[31, 32]
MI: first month	DKK 64,200 (44,940; 83,460) Gamma; 3.64; $1.91 \cdot 10^{-4}$		[31, 32]
MI: monthly costs for remaining lifetime	DKK 136 (95; 176) Gamma; 29.59; 0.22		[31, 32]
Atrial fibrillation	DKK 6,510 (4,577; 8,463) plus 1.5 days LOS Gamma; 18.84; $2.89 \cdot 10^{-3}$		
PPM implantation	DKK 15,500 (21,830; 40,541) Gamma; 2.40; $1.55 \cdot 10^{-4}$		Rigshospitalet 2016
LOS and related costs			
ICU LOS	1.2 days (0; 3) Gamma 6.76; 5.20	2.6 days (1; 5) 6.76; 2.60	Rigshospitalet 2016
Regular ward LOS	7.7 days (0; 10.8) Gamma; 6.59; 0.86	10.3 days (3.4; 15.4) Gamma; 16.97; 1.65	Rigshospitalet, 2016
Costs per ICU day	DKK 22,915 (16,041; 29,790) Gamma; 84.02; $3.67 \cdot 10^{-3}$		Rigshospitalet 2016
Costs per regular ward day	DKK 5,462 (3,823; 7,101) Gamma; 13.26; $2.43 \cdot 10^{-3}$		Rigshospitalet 2016
AE costs after index hospitalisation			
Major or life-threatening bleeding	DKK 15,676 (10,973; 20,379) Gamma; 39.32; $2.51 \cdot 10^{-3}$		[16]
Major vascular complications	DKK 12,171 (8,520; 15,822) Gamma; 31.47; $5.61 \cdot 10^{-4}$		[16]
Stroke: first month	DKK 34,711 (24,298; 45,124) Gamma; 5.35; $1.54 \cdot 10^{-4}$		[31, 32]
Stroke: monthly costs for remaining lifetime	DKK 3,192 (2,234; 4,150) Gamma; 40.76; $1.28 \cdot 10^{-4}$		[31, 32]
MI: first month	DKK 64,200 (44,940; 83,460) Gamma; 3.64, $1.91 \cdot 10^{-4}$		[31, 32]
MI: monthly costs for remaining lifetime	DKK 136 (95; 176) Gamma; 29.59; 0.22		[31, 32]
Atrial fibrillation	DKK 6,510 (4,577; 8,463) Gamma; 18.84; $2.89 \cdot 10^{-3}$		
PPM implantation	DKK 15,500 plus 1.5 days LOS on a regular ward (21,830; 40,541) Gamma; 2.40; $1.55 \cdot 10^{-4}$		Rigshospitalet 2016
Prosthetic valve IE	DKK 80,586 (56,410; 104,762)		

	Gamma; 10.39; $1.29 \cdot 10^{-4}$		
Reintervention	DKK 11,057 (7,740; 14,374)	DKK 31,189 (21,832; 40,546)	Calculation
Follow-up care costs			
Cardiologist visit	DKK 1,362		
Transthoracic echo	DKK 1,150		
Total monthly cost	DKK 209 (147; 272) Gamma; 17.47; 0.08		
Long-term mortality			
Relative risk, compared to baseline mortality per life tables	1.05 Log normal; $3.92 \cdot 10^{-2}$; 0.14	1.15 Log normal; 0.12; 0.19	

Listed are base case values and ranges for sensitivity analyses.

AEs: adverse events; angio: angiography; CTA: computed tomography angiography; echo: echocardiography; IE: infective endocarditis; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation

* These probabilities are the differences between the absolute 1-month and 1-year probabilities.

** Event probability was 0.7%.

*** Includes costs for the CoreValve device.

**** Cost does not include concomitant CABG costs (DKK 187 per case).

Supplementary Table 2. SF-6D and NYHA at one-month visit.

	NYHA I-II				NYHA III-IV			
	Major/minor stroke before 1 month		No stroke before 1 month		Major/minor stroke before 1 month		No stroke before 1 month	
SF-6D	TAVR (N=1)	SAVR (N=2)	TAVR (N=121)	SAVR (N=106)	TAVR (N=0)	SAVR (N=0)	TAVR (N=10)	SAVR (N=4)
n	1	2	102	78	0	0	8	3
Mean±SD	0.60	0.44±0.17	0.70±0.12	0.66±0.10	NA	NA	0.57±0.11	0.56±0.08
Median	0.60	0.44	0.70	0.66	NA	NA	0.59	0.60
Min, max	0.6, 0.6	0.3, 0.6	0.4, 1.0	0.4, 0.9	NA	NA	0.4, 0.7	0.5, 0.6
Q1, Q3	0.60, 0.60	0.32, 0.57	0.62, 0.78	0.59, 0.74	NA	NA	0.49, 0.63	0.47, 0.61

Supplementary Table 3. SF-6D and NYHA class at 6-month visit.

	NYHA I-II				NYHA III-IV			
	Major/minor stroke before 6 months		No stroke before 6 months		Major/minor stroke before 6 months		No stroke before 6 months	
SF-6D	TAVR (N=3)	SAVR (N=5)	TAVR (N=119)	SAVR (N=108)	TAVR (N=0)	SAVR (N=0)	TAVR (N=10)	SAVR (N=4)
n	1	2	90	86	0	0	7	3
Mean±SD	0.57	0.60±0.00	0.72±0.13	0.76±0.12	NA	NA	0.66±0.12	0.51±0.20
Median	0.57	0.60	0.72	0.74	NA	NA	0.62	0.40
Min, max	0.6, 0.6	0.6, 0.6	0.3, 1.0	0.5, 1.0	NA	NA	0.5, 0.8	0.4, 0.7
Q1, Q3	0.57, 0.57	0.60, 0.61	0.64, 0.80	0.67, 0.85	NA	NA	0.56, 0.81	0.39, 0.74

Supplementary Table 4. SF-6D and NYHA class at 12-month visit.

	NYHA I-II				NYHA III-IV			
	Major/minor stroke before 12 months		No stroke before 12 months		Major/minor stroke before 12 months		No stroke before 12 months	
SF-6D	TAVR (N=3)	SAVR (N=5)	TAVR (N=125)	SAVR (N=111)	TAVR (N=0)	SAVR (N=0)	TAVR (N=4)	SAVR (N=4)
N	3	3	102	90	0	0	3	4
Mean±SD	0.63±0.04	0.69±0.10	0.71±0.12	0.75±0.14	NA	NA	0.61±0.12	0.57±0.12
Median	0.63	0.66	0.73	0.74	NA	NA	0.63	0.53
Min, max	0.6, 0.7	0.6, 0.8	0.3, 1.0	0.4, 1.0	NA	NA	0.5, 0.7	0.5, 0.7
Q1, Q3	0.60, 0.67	0.62, 0.80	0.64, 0.79	0.66, 0.85	NA	NA	0.47, 0.72	0.48, 0.65

Supplementary Table 5. SF-6D and NYHA class at 24-month visit.

	NYHA I-II				NYHA III-IV			
	Major/minor stroke before 24 months		No stroke before 24 months		Major/minor stroke before 24 months		No stroke before 24 months	
SF-6D	TAVR (N=4)	SAVR (N=5)	TAVR (N=115)	SAVR (N=105)	TAVR (N=0)	SAVR (N=0)	TAVR (N=4)	SAVR (N=4)
n	1	4	83	79	0	0	4	4
Mean±SD	0.62	0.66±0.25	0.72±0.12	0.73±0.14	NA	NA	0.63±0.17	0.60±0.05
Median	0.62	0.61	0.73	0.74	NA	NA	0.68	0.59
Min, max	0.6, 0.6	0.4, 1.0	0.4, 1.0	0.3, 1.0	NA	NA	0.4, 0.8	0.6, 0.7
Q1, Q3	0.62, 0.62	0.51, 0.81	0.66, 0.81	0.62, 0.84	NA	NA	0.51, 0.76	0.56, 0.64

Supplementary Table 6. Results of the base case and other long-term mortality scenarios.

	Costs (DKK)	Incremental costs (DKK)	QALYs	Incremental QALYs	ICER (DKK/QALY)
Fade-out scenario I (proposed base case – fade out over 24 months to life tables [RR=1])					
SAVR	211,581		5.30		
TAVI	276,142	64,561	5.39	0.09	696,264
Fade-out scenario II (fade out over 24 months to weighted RR [1.10] – then continues lifelong)					
SAVR	210,826		5.19		
TAVI	275,329	64,503	5.28	0.09	712,188
Continuous benefit scenario I (group-specific RRs [1.05/1.15] continue lifelong)					
SAVR	210,484		5.14		
TAVI	275,722	64,238	5.33	0.19	334,166
Stop-and-drop scenario I (immediate drop to life tables [RR=1.0])					
SAVR	211,881		5.33		
TAVI	276,238	64,357	5.40	0.07	892,000
Stop-and-drop scenario II (immediate drop to weighted RR [1.10] – but continues lifelong)					
SAVR	210,920		5.20		
TAVI	275,239	64,319	5.27	0.07	904,070