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REPORT

2019

HEALTH TECHNOLOGY ASSESSMENT:

Transcatether aortic valve implantation (TAVI) as treatment of patients with severe aortic stenosis and intermediate surgical risk – Part 2. Health economic evaluation

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Key messages

The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway (Nye Metoder) commissioned the Norwegian Institute of Public Health (NIPH) to perform a health technology assessment evaluating Transcatheter aortic valve implantation (TAVI) as treatment for patients with severe aortic stenosis and intermediate surgical risk. The effect and safety aspects of the intervention are addressed by the rapid assessment published by EUnetHTA in December 2018 (1), co-authored by NIPH.
The aim of this report on health economic evaluation was to assess the cost-effectiveness of TAVI for patients with severe aortic stenosis and intermediate surgical risk compared with open surgery against the priority criteria applicable in Norway.

The key results are:

- The cost-utility analysis indicated that TAVI was slightly more effective (in terms of 0.07 quality-adjusted life-years (QALY) gain) and more costly (in terms of incremental costs of 71 000 Norwegian kroner) than the open surgery. These results were robust to variations in assumption about the time perspective.
- The incremental cost-effectivness ratio (ICER) was about 1.04 million Norwegian kroner per QALY in analysis with two-years perspective, falling to about 800 000 kroner per QALY in life time perspective.
- The results of sensitivity analysis of our model analysis showed that cost parameters related to the TAVI procedure had the greatest impact on the results (ICER).
- We have performed an analysis quantifying the severity criterion by calculating absolute shortfall for patients with severe aortic stenosis and intermediate surgical risk. The results show the absolute shortfall of 3.6 QALYs.
- The budget impact analysis based on the results of our cost-effectiveness analysis, and some conservative assumptions about expansion in the use of TAVI indicates that the incremental annual total cost of this expansion will reach 32.5 million Norwegian kroner in the course of five years.

Title:
Transcatether aortic valve implantation (TAVI) as treatment of patients with severe aortic stenosis and intermediate surgical risk – Part 2. Health economic evaluation

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Type of publication:

Health technology assessment

Health technology assessment (HTA) is a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the development of safe, effective health policies that are patient focused and that seek to achieve best value.

Doesn't answer everything:

- Excludes studies that fall outside of the inclusion criteria
- No recommendations

Publisher:

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Executive summary

Background

Transcatheter aortic valve implantation (TAVI), is the replacement of the aortic valve with a bioprosthesis delivered with use of a catheter in patients with severe aortic stenosis. TAVI has been in use in Norwegian hospitals for nearly a decade. Until recently the use was restricted to treatment of patients with severe symptomatic aortic valve stenosis that were inoperable or at high surgical risk of mortality or of complications from open surgery.

The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway (Nye Metoder) commissioned the National Institute of Public Health (NIPH) to perform a health technology assessment evaluating TAVI as treatment for patients with severe aortic stenosis and intermediate surgical risk. The effect and safety aspects of the intervention were assessed in the rapid assessment published by EUnetHTA in December 2018, which NIPH co-authored. The present report addresses health economics and organisational aspects of the intervention in the Norwegian settings.

Objective

The aim of this report is to assess the cost-effectiveness and budget impact of TAVI for patients with severe aortic stenosis and intermediate surgical risk compared with open surgery, and evaluate the intervention against the priority criteria (benefit, resource use and severity) applicable in Norway.

Methods

We performed a cost-utility analysis (CUA) comparing TAVI with open surgery, where all relevant cost and health outcomes related to both procedures were accounted for. The relevant costs were expressed in 2018 Norwegian kroner (NOK), and effects in quality-adjusted life-years (QALYs). The results were expressed as mean incremental cost-effectiveness ratio (ICER). The Markov model was developed and analysed in TreeAge Pro ® 2018. The uncertainty in model parameters were handled by performing probabilistic sensitivity analyses (PSA). The analyses were performed from the

healthcare perspective. Both costs and effects were discounted using an annual discount rate of 4%.

In accordance with the Government White Paper about priority setting, (Meld. St. 34 2015–2016)(2), and its recommendations related to quantification of the severity criterion, we estimated absolute shortfall for patients with severe aorta stenosis and intermediate surgical risk.

Premised on assumptions based on registry data about adoption rates for TAVI as well as cost data derived from the Markov model, we calculated likely budgetary consequences of introduction of TAVI as a routine treatment for patients with severe aortic stenosis and intermediate surgical risk.

Results

The cost-utility analysis indicated that TAVI was slightly more effective (incremental effectiveness: 0.07 QALYs) and more costly (incremental costs: 71 000 Norwegian kroner) than the open surgery.
The incremental cost-effectiveness ratio (ICER) was about 1.04 million Norwegian kroner per QALY in analysis with two-years perspective, falling to about 800 000 kroner per QALY in life time perspective. The results of sensitivity analysis of our model analysis showed that cost parameters related to the TAVI procedure had the greatest impact on the results.
The calculated absolute shortfall for patients with severe aorta stenosis and intermediate surgical risk is equal to 3.6 QALYs. The budget impact analysis based on the results of the cost-effectiveness analysis, and some conservative assumptions about expansion in the use of TAVI indicates that the incremental annual total cost of this expansion will reach 32.5 million Norwegian kroner in the course of five years.

Discussion

The cost-utility analyses were based on the clinical data from a single randomized control multicentre trial (PARTNER 2A). For a number of outcomes, it was not possible to use pooled data from both studies included in EUnetHTA's relative effectiveness assessment, due to significant heterogeneity. Moreover, type of technology used in the included trial is in accordance with technology used most often in Norwegian clinical practice.
We used two-year perspective in the base case scenario in accordance with the time perspective for the efficacy data that informed the model. Mortality rates as well as valve function at two years follow-up were not significantly different between the treatment options. In addition, most of the complications occurred in the acute phase following aortic valve implantation and their rates were falling with time. We

considered the two-year perspective sufficient for capturing all relevant differences in outcomes. A separate scenario analysis, with lifetime time perspective showed similar results with ICER of about 800 000 kroner per QALY.
The results should be interpreted with caution as long-term effects on survival, complications, prostheses' longevity and need for future re-intervention remain to be established and documented.

Conclusion

The results of our cost-utility analysis indicate that TAVI for patients with aortic stenosis and intermediate surgical risk compared with open surgery offers modest health gains (incremental effectiveness: 0.07 QALYs), at higher costs (incremental costs: 71 000 Norwegian kroner). The calculated incremental cost-effectiveness ratio is equal to 1.04 million Norwegian kroner per QALY gained in the base case scenario.
The calculated absolute shortfall for patients with severe aortic stenosis and intermediate surgical risk receiving standard treatment is equal to 3.6 QALYs, categorising these patients into severity class 1, which is the least severe of the six classes suggested by the Magnussen group.
These findings can help decision makers appraise the intervention against the official priority setting criteria in health care sector applicable in Norway.

Hovedfunn (norsk)

Bestillerforum RHF i Nye Metoder ga Folkehelseinstituttet (FHI) i oppdrag å utføre en nasjonal metodevurdering om kateterbasert implantasjon av aortaklaffer (TAVI) for behandling av pasienter med alvorlig aorta stenose og intermediær risiko ved kirurgi. En rapport fra EUnetHTA publisert i desember 2018 (1) som FHI er medforfatter på, omfatter spørsmål om effekt og sikkerhet av TAVI. Målet med denne rapporten var å vurdere kostnadseffektiviteten av TAVI for pasienter med alvorlig aorta stenose og intermediær risiko sammenlignet med åpen kirurgi opp mot prioriteringskriteriene som gjelder i Norge.

De viktigste funnene er:

• Kostnadseffektivitetsanalysen viste at TAVI er noe mer effektiv (en gevinst på 0.07 kvalitetsjusterte leveår (QALY)) og dyrere (inkrementelle kostnader på 71 000 kroner) enn åpen kirurgi. Vi utførte flere scenarioanalyser, og resultatene var robuste for variasjoner i antagelser om tidsperspektivet.

• Den inkrementelle kostnadseffektivitets ratioen (ICER) var omtrent 1,04 millioner norske kroner per kvalitetsjusterte leveår i analysen med et to års perspektiv, og sank ned til rundt 800 000 kroner per QALY i livstidsperspektivet.

• Resultatene av sensitivitetsanalysen viste at kostnads parameter relatert til TAVI-prosedyren hadde størst effekt på resultatene (ICER).

• For å kvantifisere alvorlighetsgradkriteriet, beregnet vi et absolutt prognosetapp for pasienter med alvorlig aorta stenose og intermediær risiko. Resultatene viser absolutt prognosetapp på 3.6 QALYs.

• Analysen av budsjettetsvirkninger basert på resultatene fra kostnadseffektivitetsanalysen samt konservative antagelser om utvidelse av bruk av TAVI, viser at den inkrementelle årlige totalkostnaden for utvidelsen vil utgjøre 32,5 millioner norske kroner i løpet av fem år.

Tittel:
Kateterbasert implantasjon av aortaklaffer (TAVI/TAVR) i behandling av pasienter med alvorlig aortastenose og intermediær operativ risiko. Del 2 – Helseøkonomisk vurdering

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Publikasjonstype:

Metodevurdering

En metodevurdering er resultatet av å
- innhente
- kritisk vurdere og
- sammenfatte

relevante forskningsresultater ved hjelp av forhåndsdefinerte og eksplisitte metoder.

Minst ett av følgende tillegg er også med:
helseøkonomisk evaluering, vurdering av konsekvenser for etikk, jus, organisasjon eller sosiale forhold

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Svarer ikke på alt:

- Ingen studier utenfor de eksplisitte inklusjonskriteriene
- Ingen anbefalinger

Hvem står bak denne rapporten?

Folkehelseinstituttet har skrevet rapporten på oppdrag fra Nye Metoder.

Sammendrag (norsk)

Kateterbasert implantasjon av aortaklaffer (TAVI/TAVR) i behandling av pasienter med alvorlig aortastenose og intermediær operativ risiko

Bakgrunn

Kateterbasert implantasjon av aortaklaffer (TAVI), er erstatning av aortaklaffen med en biologisk protese satt inn ved bruk av et kateter hos pasienter med alvorlig aortastenose. TAVI har vært i bruk på norske sykehus i et tiår. Inntil nylig var bruken begrenset til behandling av aortastenose hos pasienter som enten er uegnet for åpen klaffekirurgi eller har høy risiko for dødelighet eller komplikasjoner ved åpen kirurgi.
Bestillerforum RHF i Nye Metoder ga Folkehelseinstituttet (FHI) i oppdrag å utføre en nasjonal fullstendig metodevurdering av TAVI for pasienter med alvorlig aortastenose og intermediær risiko ved kirurgi. Effekt- og sikkerhetsaspekter ved tiltaket er vurdert i den europeiske metodevurderingen som ble publisert av EUnetHTA i desember 2018, der FHI bidro som medforfattere.
Denne rapporten omhandler helseøkonomi og organisatoriske aspekter ved intervensjonen i den norske konteksten.

Problemstilling

Formålet med denne rapporten er å vurdere kostnadseffektivitet av TAVI for pasienter med alvorlig aortastenose og intermediær operativ risiko mot prioriteringskriteriene (nytte, ressursbruk og alvorlighetsgrad) som gjelder i Norge, samt å beregne budsjettmessige konsekvenser av en eventuell innføring av tiltaket som rutinebehandling.

Metode

Vi utførte en kostnadseffektivitetsanalyse (CUA) som sammenlignet TAVI med åpen kirurgi, hvor alle relevante kostnader og helserelaterte utfall knyttet til begge prosedyrene var tatt hensyn til. Kostnadene ble uttrykt i 2018 kroner, og helserelaterte effekter var uttrykt i kvalitetsjusterte leveår (QALYs). Resultatene er presentert som

den gjennomsnittlige inkrementelle kostnadseffektivitets ratioen (ICER). En Markov modell ble utviklet og analysert i TreeAge Pro ® 2018. Usikkerhet i modellparametere ble håndtert ved å utføre probabilistiske sensitivitetsanalyser (PSA). Analysene ble utført ut fra helsetjenesteperspektivet. Både kostnader og effekter ble diskontert med en årlig diskonteringsrente på 4 prosent.

I samsvar med Meldingen om prioritering (Meld. St. 34 (2015-2016)) (2), og dens anbefalinger om kvantifisering av alvorlighetsgradkriteriet, beregnet vi et absolutt prognosetapp for pasienter med alvorlig aortastenose og intermediær operativ risiko.

Basert på antakelser om ulike opptaksrater for TAVI, samt kostnadsdata fra Markovmodellen, beregnet vi budsjettmessige konsekvenser av innføring av TAVI som rutinebehandling for pasienter med alvorlig aortastensose og intermediær kirurgisk risiko.

Resultat

Kostnadsanalysen viste at TAVI var noe mer effektiv (inkrementell effekt: 0,07 QALY) og dyrere (inkrementelle kostnader: omtrent 71 000 norske kroner) enn åpen kirurgi.
Den inkrementelle kostnadseffektivitets ratioen (ICER) var rundt 1,04 millioner norske kroner per QALY i analyse med to års perspektiv, og sank til omtrent 800 000 kroner per QALY i livstidsperspektivet. Resultatene av sensitivitetsanalyse viste at kostnadsparametere relatert til TAVI-prosedyren hadde størst innvirkning på resultatene.
Beregnet absolutt prognosetap for pasienter med alvorlig aortastensose og intermediære kirurgisk risiko er lik 3,6 QALY.
Analyse av budsjettmessige konsekvenser basert på kostnadsresultatene fra modellen og noen konservative antagelser om utvidelsen i bruk av TAVI, indikerer at den inkrementelle årlige totalkostnaden for denne utvidelsen vil utgjøre 32,5 millioner norske kroner i løpet av fem år.

Diskusjon

Kostnadseffektivitetsanalysen er basert på de kliniske dataene fra en enkelt randomisert kontrollert studie (PARTNER 2A). For en rekke utfall var det ikke mulig å bruke sammenlagte data fra begge studiene som inngår i EUnetHTAs metodevurderingen om relativ effekt og sikkerhet på grunn av betydelig heterogenitet. Teknologien som brukes i studien er i tråd med teknologien som brukes oftest i norsk klinisk praksis.

Vi brukte et toårsperspektiv i basecase scenarioet, i samsvar med tidsperspektivet for effektdataene som informerte modellen. Dødelighetsratene samt ventilfunksjon ved to års oppfølging var ikke signifikant forskjellige mellom de to behandlingsalternativene. I tillegg oppsto de aller fleste komplikasjonene i den akutte fasen etter aortaklaffeprosedyren, og frekvensratioen falt med tiden. Vi vurderte dette perspektivet tilstrekkelig til å gjenspeile alle relevante forskjeller. En separat scenarioanalyse, med livtidsperspektivet, viste lignende resultater med ICER på om lag 800 000 kroner per QALY.

Konklusjon

Resultatene av vår kostnadseffektivitetsanalyse indikerer at TAVI for pasienter med aortastenose og intermediær kirurgisk risiko sammenlignet med åpen kirurgi, gir relativt små helsegevinster (inkrementell effektivitet: 0,07 QALYs) til høyere kostnader (inkrementelle kostnader: 71 000 norske kroner). Den inkrementelle kostnadseffektivitetsratioen (ICER) er beregnet til omtrent 1,04 millioner norske kroner per vunnet kvalitetsjusterte leveår i standardanalysen.
Beregnet absolutt prognosetap for pasienter med alvorlig aortastenose og intermediær risiko som mottar standard behandling er lik 3,6 QALYs. Dette setter den aktuelle pasientpopulasjonen i alvorlighetsklasse 1 som er laveste alvorlighetsgrad ifølge Magnussen-gruppen.
Disse funnene kan hjelpe beslutningstakerne med å vurdere intervensjonen mot de offisielle prioriteringskriteriene i norsk helsetjeneste.

Glossary and abbreviations	
ICER	**Incremental cost-effectiveness ratio**. The ratio of the difference in costs between two alternative health technologies to the difference in effectiveness between these two technologies. $ICER = \frac{Cost_{intervention} - Cost_{comparator}}{Effect_{intervention} - Effect_{comparator}} = \frac{\Delta C}{\Delta E}$
CI	**Confidence interval.** A measure of uncertainty around the results of a statistical analysis that describes the range of values within which we can be reasonably sure that the true mean effect lies. Wider intervals indicate lower precision; narrow intervals, greater precision.
CUA	**Cost-utility analysis.** An economic evaluation where health consequences are measured in **QALY**s.
NHB	**Net Health Benefit.** In a decision-making process, a positive NHB suggests that the intervention represents good value for money $NHB = \Delta E - \frac{\Delta C}{\lambda}$
NMB	**Net Monetary Benefit.** In a decision-making process, a positive NMB suggests that the intervention represents good value for money. $NMB = \lambda \cdot \Delta E - \Delta C$
Odds	The odds of an event happening is defined as the probability that an event will occur, expressed as a proportion of the probability that the event will not occur.
OR	**Odds ratio.** The ratio of the odds of an outcome in one treatment group divided by the odds of the same outcome in a different treatment group.
PSA	**Probabilistic sensitivity analysis.** An analysis of the uncertainty related to all parameters in a decision analytic model. Typically performed by Monte Carlo simulation, hence by drawing values from probability distributions for all parameters simultaneously
QALY	**Quality-adjusted life-year.** A measure of health outcomes that combines quantity and quality of life by assigning to each year of life a weight from 1 (perfect health) to 0 (state judged equivalent to death) dependent on the individual's health related quality of life during that year
RCT	**Randomised controlled trial.** An experiment in which investigators use randomisation to allocate participants into the groups that are being compared. Usually allocation is made at the level of individuals, but sometimes it is done at group level e.g. by schools or clinics. This design allows assessment of the relative effects of interventions.

RR	**Relative risk / risk ratio.** The relative risk is the absolute risk (AR) in the intervention group divided by the AR in the control group. It is to be distinguished from odds ratio (OR), which is the ratio of events over non-events in the intervention group over the ratio of events over non-events in the control group.
SR	**Systematic review.** A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.
Statistically significant	Means that the findings of a study are unlikely to have arisen because of chance. Significance at the commonly cited 5% level ($P < 0.05$) means that the observed difference or greater difference would occur by chance in only 1/20 similar cases. Where the word "significant" or "significance" is used without qualification in the text, it is being used in this statistical sense.
Absolute shortfall	Is used as a proxy for the severity of the disease or condition. Absolute shortfall (AS) is the number of future health loss in terms of quality-adjusted life-years (QALYs) that an average patient in the patient group will lose because of his/her disease, compared to the average in the population of the same age.
Severity class	Diseases or conditions can be divided into six severity classes according to absolute shortfall (AS), as suggested by the Magnussen group. These classes range from: AS < 4 QALYs lost (severity class 1), 4-7,9; 8-11,9; 12-15,9; 16-19,9, and AS ≥ 20 QALYs (severity class 6).
WTP (λ)	**Willingness to pay**. A pre-specified limit of what society is willing to pay for a given unit of health (e.g. QALY or life year). In Norway, there is no official threshold, but it is established that the threshold used should be based on considerations of opportunity cost (St.meld 34/2015-2016). The Magnussen group on severity suggested a possible set of thresholds, ranging from NOK 275 000 for the lowest severity level (AS < 4 QALYs lost) to NOK 825 000 for the highest severity level (AS ≥ 20 QALYs lost).

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Preface

The Division of Health Services in the Norwegian Institute of Public Health was commissioned by the the National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway to conduct a health technology assessment on Transcatheter Aorta Valve Implantation (TAVI) for patients with severe aortic stenosis and intermediate surgical risk compared with open surgery.
The effect and safety aspects of the intervention are addressed by the rapid assessment published by EUnetHTA in December 2018 (1), co-authored by NIPH.
The aim of this report on health economic evaluation was to assess the cost-effectiveness of TAVI for patients with severe aortic stenosis and intermediate surgical risk compared with open surgery against the priority criteria applicable in Norway.

The project group consisted of:

- Beate Charlotte Fagerlund, Health economist, Norwegian Institute of Public Health (BCF)
- Anna Stoinska-Schneider, Health economist, Norwegian Institute of Public Health (AS-S)
- Vigdis Lauvrak, Senior researcher, Norwegian Institute of Public Health (VL)
- Lene Kristine Juvet, Department director, Norwegian Institute of Public Health (LKJ)
- Bjarne Robberstad, Health economist, Norwegian Institute of Public Health (BR)

We wish to thank dr. Gry Dahle, prof. Svein Færestrand, and dr. Reidar Bjørnerheim for their expertise in this project as well as prof. Eline Aas for peer-reviewing our health economic model. We also would like to thank Kjetil Gudmundson Rogne with colleagues from Oslo Univeristy Hospital for providing the cost estimates related to aorta valve procedures. Norwegian Institute of Public Health assumes final responsibility for the content of this report.
The aim of this report is to support well-informed decisions in health care that lead to improved quality of services. The evidence should be considered together with other relevant issues, such as clinical experience and patient preference.

Objective

Overall objective

- To examine the cost-effectiveness of Transcatheter aorta valve implantation (TAVI) for patients with severe aortic stenosis and intermediate surgical risk compared with open surgery against the priority criteria applicable in Norway.

Specific objectives

- To carry out a health economic evaluation ascertaining cost-effectiveness of TAVI compared with open surgery aorta valve replacement in patients at intearmediate surgical risk in Norwegian settings in a health care perspetive
- To assess the impact of introduction of TAVI as rutine treatment for patients with severe aorta stenosis and intermediate surgical risk on the Norwegian health care budget
- To evaluate the intervention in relation to the priority criteria that apply in the Norwegian health care: the benefit, the resource use and the severity criterion.

Background

Introduction to Economic Evaluation of Health Care Programmes

The basic aim of any economic evaluation is to identify, measure and compare costs and consequences of the alternatives under consideration in an incremental analysis—one in which the differences in costs are compared with differences in consequences (xx). Results of economic evaluations can be expressed as an incremental cost-effectiveness ratio (ICER), which is defined by the following equation:

$$ICER = \frac{Cost_{\text{intervention}} - Cost_{\text{comparator}}}{Effect_{\text{intervention}} - Effect_{\text{comparator}}} = \frac{\Delta C}{\Delta E}$$

The health care sector, similarly to society in general, is restricted by scarce resources and budget constraints. Therefore, economic evaluations are important tools for decision makers facing questions of how to prioritize treatments and maximize health benefits using scarce resources. For an economic evaluation to be meaningful in a decision making process, the ICER must be judged with regard to a ceiling ratio that reflects the decision maker's maximum willingness to pay (WTP) for a health gain. The decision rule for an economic evaluation can therefore be expressed as:

$$\frac{\Delta C}{\Delta E} < \lambda ,$$

where λ equals WTP, and means that if the ICER of an intervention is below the ceiling ratio, introducing the intervention represents good value for money. Because the ICER has poor statistical properties, ICERs are often re-arranged to express either incremental net monetary benefit (INMB) or incremental net health benefit (INHB), which yields the following decision rules related to INMB or INHB.

INMB: $\lambda \cdot \Delta E - \Delta C > 0$

INHB: $\Delta E - (\Delta C/\lambda) > 0$

In other words, an intervention can be considered cost-effective if it yields a positive INHB or INMB.

Economic evaluations are often based on decision models (such as decision trees, Markov models, etc.) that calculate results based on various input parameters in the model. Because there are always uncertainties related to the values of these parameters, sensitivity analysis is an important feature of any economic evaluation based on a decision model framework. In short, sensitivity analysis illustrates how much the results vary when model parameters are changed.

Probabilistic sensitivity analysis (PSA) is a kind of sensitivity analysis. The advantage of PSA is that it makes it possible to take the uncertainties of all of the model-parameters into account simultaneously. The basic approach in PSA is to assign appropriate probability distributions to the model-parameters, which makes it possible to replace the "fixed" values of the parameters with values generated by random draws from the distributions. Doing this repeatedly, with a specified number of iterations, makes it possible to estimate the probabilities that alternative interventions are cost-effective subject to different ceiling values of WTP. The calculation is based on the alternative that renders the highest values of NMB or NHB. Results from PSAs are often presented as scatter plots, which show point estimates of the ICER for all iterations in the cost-effectiveness plane, and also as cost-effectiveness acceptability curves (CEACs), which show the probability of the alternatives being cost-effective subject to changing values of WTP.

Another result from PSA is the expected value of perfect information (EVPI). This is a number that indicates the value to society of having more accurate information about the decision, given a WTP. If EVPI for a given population seems large, it might be of interest to determine for which parameters it would be most useful to obtain additional data. Expected value of perfect information for parameters is a more time-consuming analysis that can help determine for which single parameters or groups of parameters it is most cost-effective to conduct new research.

In short, making a model probabilistic means that it is possible to estimate the uncertainty associated with a decision to implement alternative interventions, and also provides a possibility of estimating the value of collecting additional information from new research.

Priority setting criteria

There are three primary criteria for setting priorities in the Norwegian health care sector: the benefit criterion, the resource criterion, and the severity criterion.

Benefits

According to the benefit criterion, priority increases with the size of the expected health benefit of the intervention.

The benefit criterion primarily refers to a technology's expected health gains: increased longevity and/or improved health-related quality of life. By combining these two types of health gains into a single outcome measure, the quality-adjusted life-year (QALY), it is possible to compare treatment outcomes across different diseases, patient groups and types of treatments.

Resources

According to the resource criterion, priority increases, as fewer resources are needed for the intervention.

The resource criterion focuses attention on how the health sector uses its limited resources. Introducing a new technology creates demands for personnel, equipment, facilities, etc. that could be used to provide treatments for other patients – a reality that is referred to as the "opportunity cost" of the new technology. The larger the quantity of resources allocated to a technology for one patient group, the fewer the resources available for treating others. In addition to resource use within the health sector, a technology may also engender costs for other parties.

In practice, the resource criterion can also be taken into account by weighing costs against benefits in a cost-effectiveness analysis of the technology of interest. Resource use, measured as monetary costs, enters into the numerator of the cost-effectiveness ratio (see "Cost-effectiveness" below).

In addition to the cost-effectiveness analysis, a budget impact analysis may help inform decisions.

Severity

According to the severity criterion, priority increases with expected future health loss resulting from the disease.

Severity is measured as "absolute shortfall", defined as the expected loss of future health (QALYs) associated with a specified diagnosis. For treatment of a diagnosed disease, severity is the average expected absolute shortfall for the relevant patient group given the current standard treatment.

Generally, the greater the absolute shortfall associated with a disease, the more resources per QALY-gained the authorities may be willing to allocate.

Cost-effectiveness

Cost-effectiveness is an expression of the amount of health gains (in QALYs) created by a given amount of resources, or seen from an opportunity cost perspective, the cost per additional QALY gained. A health economic analysis evaluates a new technology relative to a comparator. The ratio between the incremental (additional) cost of the new technology and its incremental effect is referred to as the incremental cost-effectiveness ratio (ICER). The Norwegian White paper on priority setting (2) indictates that weighting of resource use against utility should be based on the opportunity cost principle, and that priority should be further increased according to severity (absolute shortfall).

Economic evaluation-Methods

General

Transcatheter aortic valve implantation (TAVI), is the replacement of the aortic valve with a bioprosthesis delivered with use of a catheter in patients with severe aortic stenosis. TAVI has been in use in Norwegian hospitals for nearly a decade. Until recently the use of TAVI was restricted to treatment of patients with severe symptomatic aortic valve stenosis that were inoperable or at high surgical risk of mortality or of complications from open surgery. In 2016 the indication for use covered by CE marking was extended to treatment of patients with intermediate risk for open-heart surgery as determined by the heart team (1). The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway (Nye Metoder) commissioned the National Institute of Public Health (NIPH) to perform a health technology assessment evaluating TAVI as treatment for patients with severe aortic stenosis and intermediate surgical risk. The effect and safety aspects of the intervention were appraised in the rapid assessment published by EUnetHTA in December 2018 (1), which NIPH co-authored. The present report addresses health economics and organisational aspects of the intervention in the Norwegian settings.

In order to assess the health economic effectiveness of transcatheter aortic valve implantation (TAVI) compared with conventional surgical replacement (SAVR), for patients with severe aorta stenosis and intermediate surgical risk, we performed a cost-utility analysis (CUA). We expressed relevant costs in 2018 Norwegian kroner (NOK), and effects in quality-adjusted life-years (QALYs). We present the results from the baseline scenario, as well as from scenario analyses, as mean incremental cost-effectiveness ratio (ICER).

In accordance with the Government White Paper about priority setting, (Meld. St. 34 2015–2016) (2), we carried out the analysis from a healthcare perspective. The health care perspective is relevant for prioritisation of interventions within a fixed budget (no expansion of the budget is assumed).

We handled uncertainties in model parameters by assigning probability distributions to the parameters and performing probabilistic sensitivity analyses, designed as a Monte Carlo simulation, with 10 000 iterations. By assigning probability distributions to all model parameters – performing a probabilistic sensitivity analysis (PSA), we simultaneously explore the consequence of underlying uncertainty in all parameters. With this approach, we re-estimate the probabilities that alternative interventions are

cost-effective subject to different ceiling values of willingness to pay (WTP). Results from PSAs are presented as scatter plots, which show point estimates of the ICER for all iterations in the cost-effectiveness plane, and as cost-effectiveness acceptability curves, which show the probability of the alternatives being cost-effective subject to changing values of WTP. We also performed one-way sensitivity analyses to explore potential impact of uncertainty in single parameters. We present the results of the one-way sensitivity analyses in a tornado diagram.
The model was developed and analysed in TreeAge Pro ® 2018. Both costs and effects were discounted using an annual discount rate of 4%. In addition, we estimated the budget impact of introducing TAVI as a routine treatment option for patients with intermediate operative risk using costs results from the cost-effectiveness model.
In conformity with the recommendations from the White Paper and the severity criterion, we have estimated absolute shortfall for patients with severe aorta stenosis and intermediate surgical risk and assessed cost-effectiveness in the light of the suggested cost-effectiveness thresholds.

Population, interventions and model structure

In order to assess the cost-utility of transcatheter aortic valve replacement compared with open surgery in patients with intermediate risk, we developed a decision analytic model in TreeAge pro® 2018. The model is of the Markov type, in which a cohort of patients is followed over a specified period.
We assumed a typical patient with severe symptomatic aortic valve stenosis and intermediate surgical risk to be 80 years old, in accordance with the mean age of participants of the randomized control multicentre trial PARTNER 2A (Placement of Aortic Transcatheter Valves 2A) (3).
Two treatment options are available to these patients: aorta valve replacement with conventional surgery (Surgical Aorta Valve Replacement, SAVR) or transcatheter aortic valve implantation (TAVI).
SAVR is the replacement of the aortic valve of the heart through a surgical procedure, performed under general anaesthesia with the use of cardiopulmonary bypass. During SAVR, a cardiac surgeon removes the native aortic valve and replaces it with a prosthetic valve. In contrast, TAVI is the replacement of the aortic valve with a prosthesis delivered through a blood vessel using a catheter or via a small incision through the heart wall, depending on the shape of the arteries and the anatomy of the patient. The most common and preferred route is transfemoral (through the upper leg). TAVI can be carried out under local anaesthesia with sedation (1). Compared with SAVR, TAVI is a minimally invasive procedure. However, both procedures carry mortality risk as well as risk of complications. Both options are associated with procedure and rehabilitation costs, costs of treating complications, health utility related to the condition and procedure-related disutility.
An existing model developed by the Health Economics Appraisal Team at Glasgow University as a pilot project for the Scottish Technology Group (4) partly inspired

the structure in our model although we made several adaptations both regarding model-structure and input data.
The model captures two time periods. In the course of the first cycle, reflecting the acute aorta valve treatment phase, the patients with aorta stenosis and intermediate surgical risk receive one of the available treatment options available to them: TAVI or SAVR. Each of the procedures carries a mortality risk, a certain risk of complications and the risk that the treatment will not be successful. Beyond the first cycle the patients enter the long term phase, which is modelled with the help of the Markov model, which has three health states: (i) living with functioning aorta valve, (ii) failed valve and (iii) death. A health state is a defined clinical condition that characterises the patient during a given unit of time (cycle). The health states are mutually exclusive, meaning that patients can be in only one of them at any time. In the model, patients are allowed to move between health states between each cycle, depending on transition probabilities. The cycle length was defined as one month, and we ran the model for 24 cycles, i.e. two years in the base case scenario. Each health state is associated with specific health outcomes and costs.
I addition to the three health states, the model encompasses two possible types of procedure-related complications (health state transitions), affecting both cost and health outcomes: valve-related complications potentially leading to loss of functioning valve and other complications, with no impact on valve functioning.
Among the “Valve-related complications”, we have included the following:

- major vascular complications,
- life thretening bleeding,
- valve endocarditis,
- moderate or severe paravalvular leakage and
- myocardial infarction.

Among the “Other complications”, we have included the following:

- pacemaker implantation,
- stroke,
- acute kidney injury and
- new-onset fibrillation.

All complications are associated with costs and disutilities. Since all-cause mortality is being accounted for between each monthly cycle, all non-fatal complications are assumed to be resolved with successful treatment. We assume that patients experiencing no complications have had a successful valve replacement and a functioning valve.
Death is modelled as an absorbing state. Once an individual makes a transition into the absorbing state, no further incurred costs or health outcome are included in the analysis. An overview of the model is presented in Figure 2.

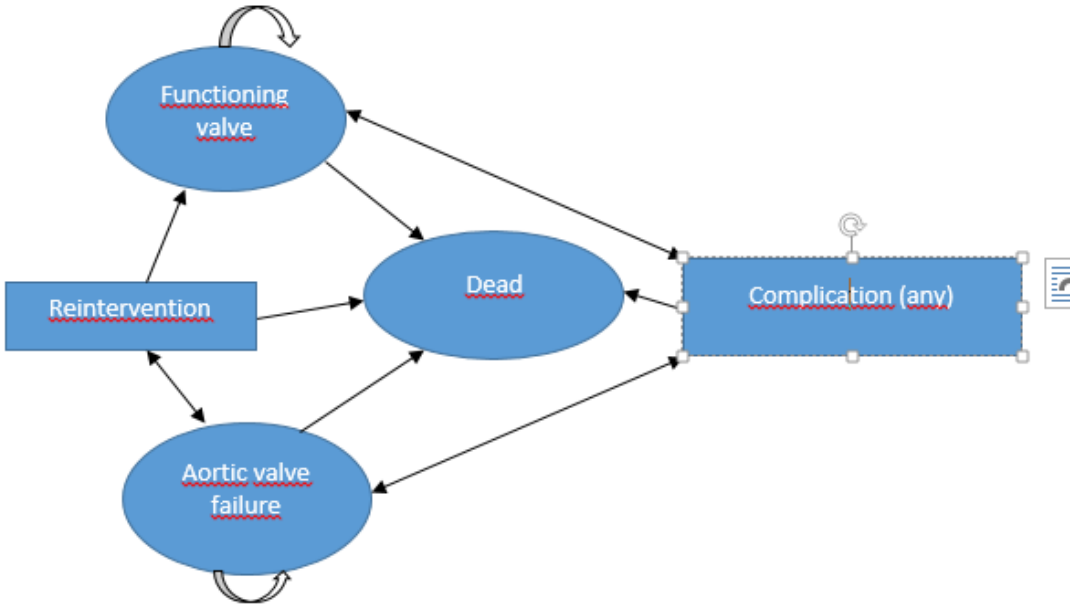


Figure 2. Structure of the model, with health states (round figure), complications (rectangular figure) and transitions (arrows).

The complete structure of the model is presented in Appendix 1.

In the base case scenario, we have followed a hypothetical cohort of patients over a period of two years.

Model Parameters

Transition probabilities

All transition probabilities that inform the model were derived from data for clinical outcomes at 30-days, 1-year and 2-years from the randomized controlled multicentre trial PARTNER 2A (Placement of Aortic Transcatheter Valves 2A) (3) (Appendix 2). A total of 2 032 patients (Intention-to-Treat) with severe aortic stenosis classified as being at intermediate surgical risk (1011 TAVI versus 1021 SAVR) were included in the study. Data for mortality in the acute phase and initial treatment failure at 30-days were applied directly in the model, whereas we recalculated the rates at 1- and 2-years follow-up into monthly probabilities to inform the model beyond 30-days. The 30-days data were used to inform transitions after the first modelling cycle, the 1 year data for cycles 2-12, while we used 2 year data to inform transitions during cycles 13-24. For subsequent cycles, we used age-adjusted mortality data for the general Norwegian population, recalculated to monthly probabilities, multiplied by hazard ratio equal to 1.5 (4) for patients with non-functioning valve, to reflect increased mortality in these patients. The complete tables of transition probabilities used in the model are presented in Appendix 3.

As mentioned, we grouped possible complications into two categories: valve-related complications and other complications. We estimated the transition probabilities for complications by averaging the absolute probabilities obtained from the study.
Table 1 presents the transition probabilities from PARTNER 2A study, that in-formed the Markov model in the base case scenario.

Table 1. Transition probabilities derived from the PARTNER2A study at 30 days, 1 year and 2 years used as input in the model (3).

Outcome	At 30 Days		At 1 year		At 2 years	
	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR
All –cause mortality	0,039	0,041	0,123	0,129	0,167	0,18
Major vascular complication	0,079	0,05	0,084	0,053	0,086	0,055
Life threatening bleeding	0,104	0,434	0,152	0,455	0,173	0,47
Valve endocarditis	0	0	0,008	0,007	0,012	0,007
Moderate or severe paravalvular leak	0,038	0,005	-	-	0,08	0,006
Myocardial infraction	0,012	0,019	0,025	0,03	0,036	0,041
Pacemaker implantation	0,085	0,069	0,099	0,089	0,118	0,103
Stroke (any)	0,055	0,061	0,08	0,081	0,095	0,089
Acute kidney injury	0,013	0,031	0,034	0,05	0,038	0,062
New onset atrial fibrillation	0,091	0,264	0,101	0,272	0,113	0,273
Aortic-valve reintervention	0,004	0	0,012	0,005	0,014	0,006

We defined initial treatment failure (at 30-days) as patients who initiated the procedure but did not receive a valve implant, as patients who initiated TAVI but was converted into surgery, and as patients who received the second valve (with TAVI) due to valve embolization (3). 20 TAVI and 8 SAVR patients did not get a new valve, four had a new TAVI valve, two aborted procedure and three converted to surgery. Seven out of 29 received re-intervention in the TAVI-arm. 22 patients (2,2 %) got a second valve placed within the first one because of aortic regurgitation (2).

Table 2. Cumulative probabilities of experiencing complications following aorta valve implantation.

Transition probability	TAVI	SAVR

Cycle	Cycle 0 (30 days)	Beyond 30 days	Cycle 0 (30 days)	Beyond 30 days
Probability of experiencing any complication	0,4768	0,0108	0,9333	0,0081
Probability of experiencing valve-related complications (absolute)	0,2328	0,0092	0,5083	0,0034
Probability of experiencing valve-related complications (conditional, used in Markov)	0,4883	0,8581	0,5446	0,4231
Probability of experiencing other complications	0,244	0,002	0,425	0,005

In order to express increased mortality for patients, for whom the aorta valve replacement has failed, we have applied an assumed a relative risk of death equal to 1,5 (4). To enable a fully probabilistic analysis we have assigned beta distributions to all transition probabilities and a log normal distribution to the relative mortality risk ratio of living with aortic valve failure. In our TreeAge model, the all-cause mortality tables are made probabilistic by multiplication with a distribution (Beta-distribution for binominal data) of a specially created parameter: dist_sensvar_pMort. Alpha and beta parameters of this distribution were informed by patient data from PARTNER 2A study (3).

Costs

We included all direct cost associated with the procedures, rehabilitation and complications associated with the alternative treatments. We obtained information about procedure costs associated with aorta valve replacement both with open surgery and with TAVI from Oslo University Hospital (Oslo Universitetetssykehus, OUS). The estimates were based on average costs per patient for the entire hospital stay including surgery, medicines, materials, stay at the intensive care-unit and regular ward. The cost did not include the value added tax and overheads.
We calculated costs of rehabilitation after TAVI and surgical aortic valve replacement as the average of the DRG-estimates (5) and per-diem costs obtained from Unicare Hokksund (6). The need for rehabilitation in acute rehabilitation units following valve replacement differs between patients receiving SAVR and TAVI. The total rehabilitation cost estimates were based on the Delphi-assumption from the panel of clinical experts that patients need 7 days of institutionalised rehabilitation following TAVI and 20 days following SAVR.
Long-term medical management following the aortic valve replacement is standardised in Norway regardless of type of replacement procedure the patient underwent,

and was therefore not included in the model. This includes that all patients are carefully examined before discharge. Later controls and follow-ups are performed at local hospital (7).

We estimated the costs for treatment of complications as the weighted average of unit cost estimates for individual complications, and by using the relative incidence rates as weights. We derived most of the unit costs related to acute treatment of adverse events (complications) following valve replacement from the updated DRG weights (5).
The calculation of cost related to treatment of moderate or severe paravalvular leak were based on the following assumptions: 33 of 1011 (3.3%) patients in the PARTNER2A study TAVI group had moderate or severe paravalvular leak. Furthermore, 22 of these 33 patients (66%), got a second TAVI placed within the first valve. Direct costs related to the implantation procedure constitute about a half of the total costs for TAVI (Based on the cost information received from OUS (8)) . We assumed that implantation of a new valve during the same procedure raises costs with about 30%, due to cost of the new prosthesis and personnel cost. That makes additional cost of 110 930 kroner (30% of NOK 369 765 in TAVI procedure costs). Therefore, we assume a sum of 73 214 kroner to be representative for estimating of treatment cost for moderate or severe paravalvular leak.

All costs were measured in 2018 Norwegian kroner (NOK). The uncertainty surrounding cost parameters were assessed by using gamma distribution. Table 3 provides a complete overview of unit costs used as input in the model. Confidence ranges (value interval) for sensitivity analyses were calculated as base case value +/- 30%, while the standard errors for estimation of gamma distributions were based on the formula: (Value interval/2) * 1,96.

Table 3. *Cost estimates used in the analyses (Gamma distribution)*

Cost	Base case unit value (standard error)	Value interval for the sensitivity analysis (based on CI)	Distribution	Source/Comment
SAVR-procedure costs	259 802 (39 766)	(181 861 – 337 743)	Gamma	OUS 2018 (8)
TAVI-procedure costs	369 765 (56 597)	(258 836 – 480 695)	Gamma	OUS 2018 (8)
Rehabilitation following SAVR (assumed 20 days)	67 960 (10 402)	(47 572 – 88 347)	Gamma	Unicare Hokksund (6); ISF 2018; DRG 462B (5)
Rehabilitation following TAVI (assumed 7 days)	29 138 (4 460)	(20 397 – 37 880)	Gamma	Unicare Hokksund (6); ISF 2018; DRG 462B (5)

Pacemaker implantation during within 30 days of valve replacement	25 840 (3 955)	(18 088 – 33 592)	Gamma	ISF 2018; DRG 116O (5)
Islolated pacemaker implantation	69 181 (10 589)	(48 427 – 89 935)	Gamma	ISF 2018; DRG 115B (5)
Major vascular complications	12 551 (1 921)	(8 796 – 16 316)	Gamma	ISF 2018; DRG 110O (5)
Treatment Life threatening bleeding	4 169 (638)	(2 918 – 5 420)	Gamma	ISF 2018; DRG 816 R (5)
Valve endocarditis	201 723 (30 876)	(141 206 – 262 240)	Gamma	ISF 2018; DRG 126 (5)
Moderate or severe paravalvular leak	73 214 (11 206)	(51 250 – 95 179)	Gamma	Assumption
Treatment of acute myocardial infarction	53 286 (8 156)	(37 300 – 69 272)	Gamma	ISF 2018; DRG 121 (5)
Acute stroke treatment	59 236 (9 067)	(41 465 – 77 007)	Gamma	ISF 2018; DRG 14B (5)
Treatment of acute kidney injury	61 885 (9 472)	(43 320 – 80 451)	Gamma	ISF 2018; DRG 316 (5)
Treatment of new onset atrial fibrillation	21 149 (3 237)	(14 804 – 27 494)	Gamma	ISF 2018; DRG 139 (5)
Re-intervention	259 802 (39 766)	(181 861 – 337 743)	Gamma	Assumption: equal to cost of SAVR

The costs of treating complications applied in the model were obtained by calculating weighted average costs, according to frequency at which the complications occurred. The complications occur with varying frequency between the two treatment alternatives and varying in time following procedure. In addition, some complications occur immediately or very shortly following the primary valve implantation, and can be treated within the same hospitalisation episode as the procedure. We have therefore calculated costs separately for TAVI and SAVR and for short (up to 30-days) and longer term (beyond 30-days) time perspective. The calculations are presented in Table 4.

Table 4. Weighted costs of treating complications applied in the model per patient

Valve-related complication	**Probability at 30-days**		**Weight**		**Weighted cost***	
	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR
Major vascular complications	0,079	0,05	0,34	0,10	4 258	1 235
Life threatening bleeding	0,104	0,434	0,45	0,85	1 862	3 560
Valve endocarditis	0	0	0	0	0	0
Moderate or severe paravalvular leak	0,038	0,005	0,16	0,04	11 899	761
Myocardial infarction	0,012	0,019	0,05	0,04	2 746	1 992
TOTAL at 30-days	**0,233**	**0,508**	**1,00**	**1,00**	**20 766**	**7 547**

Valve-related complication	Probability at 2-years		Weight		Weighted cost	
	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR
Major vascular complications	0,007	0,005	0,04	0,07	458	828
Life threatening bleeding	0,069	0,036	0,36	0,47	1 498	1 979
Valve endocarditis	0,012	0,007	0,06	0,09	6 052	18 620
Moderate or severe paravalvular leak	0,08	0,006	0,42	0,08	30 506	5 635
Myocardial infraction	0,024	0,022	0,13	0,29	6 661	15 458
TOTAL – beyond 30 days	**0,192**	**0,076**	**1,00**	**1,00**	**51 730**	**42 519**

**Weighted costs has been obtained by multiplying the calculated weight by the unit cost listed in Table 3.*

Health-related Quality of Life

In order to obtain QALY weights we searched for published articles with health-related quality of life (HRQoL) values. The randomized control multicentre trial, Placement of Aortic Transcatheter Valves 1 (PARTNER 1), returned one article (9) reporting quality of life outcomes measured with the preference-based, health-related quality of life instrument, EQ-5D, considered appropriate for cost-utility analyses. We used these utilities on the health states: Functioning valve and valve failure in the base-case model (see table 5). Beta distributions were used for the state utility values (QALYs) in the model.

Table 5: State utilities based on EQ-5D

	TAVI (interval for sensitivity analysis)		SAVR (interval for sensitivity analysis)		Source/ comment
	Base case value (standard error)	Value interval for the sensitivity analysis	Base case value (standard error)	Value interval for the sensitivity analysis	
Valve failure	0.055 (0.0085)	(0.0383 – 0.0717)	0.055 (0.0085)	(0.0383 – 0.0717)	Reynolds et al. 2012(9)
Functioning valve	0.062 (0.0015)	(0.0583 – 0.0642)	0.057 (0.0017)	(0.0533 – 0.0600)	Reynolds et al. 2012(9)

The state utilities presented in this table are derived from EQ-5D utilities in Reynolds et al. 2012 (9), measured one month after the procedure.

We applied disutilities for each intervention to capture ill-health of undergoing the procedures themselves. The disutility for receiving TAVI was considered to be 0.005

(0.004-0.007), while we assumed a disutility for receiving SAVR of 0.027 (0.019-0.035). We adopted these values from a Scottish study (4).

Disutility values related to valve-related complications and other complications were taken from published studies: Kaier et al. 2016 (10), Sullivan et al. 2014 (11) and Davies et al. 2015 (12) that reported EQ-5D values (see table 6 and table 7). We multiplied the duration of time spent in the given health state by the HRQoL weight to calculate the specific reduction in QALYs for each complication. The monthly disutilities are presented in table 6 and table 7.

Table 6: Disutility values for valve-related complications

Valve-related complications	Disutility (monthly)	Duration of monthly disutility	Disutility x duration	Disutility (monthly) source	Duration source
Major vascular complications	-0.007	1	-0.007	Kaier et al. 2016 (10)	Assumption
Life threatening bleeding	-0.046	1	-0.046	Kaier et al. 2016 (10)	Assumption
Valve endocarditis	-0.006	3	-0.018	Sullivan et al. 2014 (11)	Issa et al. 2003 (13)
Moderate or severe paravalvular leak	-0.049	1	-0.049	Sullivan et al. 2014 (11)	Panaich et a. 2017 (14)
Myocardial infarction	-0.060	4	-0.240	Alternative disutility value Davies et al. 2015 (12)	The Norwegian Electronic Health Librarian (15)

HRQoL: Health Related Quality of Life

Table 7: Disutility values for other complications

Other complications	HRQoL weight (Monthly disutility)	Duration of monthly disutility	Disutility x duration	Disutility (monthly) source	Duration source
Pacemaker implantation	0.1577	1	-0.1577	Assumption	Assumption based on Lopez-Jimenez (16)
Stroke (any)	0.1610	3	-0.483	Kaier et al. 2016 (10)	Assumption

Acute kidney injury	0.1580	2	-0.316	Kaier et al. 2016 (10)	Federspiel et al. 2018 (17)
New-onset atrial fibrilia-tion	0.0377	1	-0.0377	Kaier et al. 2016 (10)	Filardo et al. 2018 (18)

HRQoL: Health-Related Quality of Life

For the complications, we used 30 days disutility weight as baseline and the 2 years disutility weight for the following months. For the valve-related complications, we calculated 30 days and 2 years disutility weights by dividing the probability of the specific complication on the total probability for valve-related complications (major vascular complications, life threatening bleeding, endocarditis, moderate or severe paravalvular leak and myocardial infarction). We repeated the process for disutility weights related to other complications. We used gamma distributions for disutility values in the model.

The total mean values and standard errors of the disutility weights for 30 days and 2 years used in our model are presented in Table 8 and Table 9.

Table 8: Weighted disutility for valve-related complications

	Weights 30 days		**Weighted disutility 30 days**		**Weights year 2**		**Weighted disuti-lity year 2**	
	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR
Major vascu-lar complica-tions	0.34	0.10	-0.002	-0.001	0.04	0.07	0.000	0.000
Life threaten-ing bleeding	0.45	0.85	-0.021	-0.040	0.36	0.47	-0.017	-0.022
Valve endocarditis	0.00	0.00	-0.000	-0.000	0.06	0.09	-0.001	-0.002
Moderate or severe para-valvular leak	0.16	0.01	-0.008	-0.001	0.42	0.08	-0.021	-0.004
Myocardial infarction	0.05	0.04	-0.012	-0.009	0.13	0.29	-0.030	-0.070
Total	1.00	1.00	-0.043 (0.007)	-0.050 (0.008)	1.00	1.00	-0.069	-0.098

The total probability for valve-related complications in 30 days was 0.23 for TAVI and 0.51 for SAVR. In year 2, the total probability for valve-related complications was 0.29 for TAVI and 0.08 for SAVR (see table 1).

Table 9: Weighted disutility for other complications

	Weights 30 days		Weighted disutility 30 days		Weights year 2		Weighted disutility year 2	
	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR
Pacemaker implantation	0.35	0.16	-0.055	-0.026	0.42	0.20	-0.067	-0.031
Stroke (any)	0.23	0.14	-0.109	-0.069	0.03	0.17	-0.016	-0.082
Acute kidney injury	0.05	0.07	-0.017	-0.023	0.14	0.12	-0.043	-0.037
New-onset atrial fibriation	0.37	0.62	-0.014	-0.023	0.41	0.52	-0.015	-0.020
Total	**1.00**	**1.00**	**-0.195 (0.030)**	**-0.141 (0.022)**	**1.00**	**1.00**	**-0.142**	**-0.169**

The total probability for other complications in 30 days was 0.24 for TAVI and 0.43 for SAVR. In year 2, the total probability for other complications was 0.28 for TAVI and 0.53 for SAVR (see Table 1).

Sensitivity analysis

In addition to performing probabilistic sensitivity analysis, we carried out a series of one-way sensitivity analyses in order to investigate how uncertainty around single parameters affects cost-effectiveness results.
In Table 10 we present list of parameters for the series of one-way sensitivity analyses. We present results of this analysis as a tornado diagram in the results chapter.

Table 10. List of parameters for series of one-way sensitivity analyses

Parameter	Name of parameter in the model	Root definition	Minimum inference	Maximum inference
Probability of treatment failure TAVI	prob_Failure_TAVI	0.0287	0.0196	0.0415
Probability of treatment failure SAVR	prob_Failure_SAVR	0.0078	0.0037	0.0160
Probability of an adverse event following TAVI	prob_Event_TAVI	0.477	0.4460	0.5075
Probability of an adverse event following SAVR	prob_Event_SAVR	0.933	0.9181	0.9487

Probability of having a valve-related complication TAVI	prob_Compl_Valve_TAVI	0.488	0.3418	0.6348
Probability of having a valve-related complication SAVR	prob_Compl_Valve_SAVR	0.545	0.3812	0.7080
Probability of having a new intervention following TAVI	p_Reintervention_TAVI	0.01142	0.00800	0.01485
Probability of having a new intervention following SAVR	p_Reintervention_SAVR	0.0001	0.00007	0.00013
Mortality hazard ration for patients living with valve failure	rrDeath_Failure	1.5	1.05	1.95
Monthly utility of functioning valve following TAVI	u_Functioning_TAVI	0.062	0.0583	0.0642
Monthly utility of functioning valve following SAVR	u_Functioning_SAVR	0.057	0.0533	0.0600
Monthly utility when living with valve failure	u_Failure	0.055	0.0383	0.0717
Disutility of having TAVI procedure	disU_Intervention_TAVI	0.00525	0.0037	0.0068
Disutility of having SAVR procedure	disU_Intervention_SAVR	0.027	0.0189	0.0351
Disutility of having a valve complication following TAVI	disU_Valveevent_TAVI	0.0434	0.03038	0.05642
Disutility of having a valve complication following SAVR	disU_Valveevent_SAVR	0.0496	0.03479	0.06461
Disutility of having other complication following TAVI	disU_Otherevent_TAVI	0.1947	0.13629	0.25312
Disutility of having other complication following SAVR	disU_Otherevent_SAVR	0.1413	0.09898	0.18381
Procedure costs TAVI	cost_Intervention_TAVI	369 765	258 836	480 695
Procedure costs SAVR	cost_Intervention_SAVR	259 802	181 861	337 743
Rehabilitation costs TAVI	cost_Rehab_TAVI	29 138	20 397	37 880

Rehabilitation costs TAVI	cost_Rehab_SAVR	67 960	47 572	88 347

Scenario analyses

While the base case scenario had a horizon of 24 months, we also performed a scenario analysis, with a lifetime time horizon (15 years). All transition probabilities for the first two years were kept identical with the base case scenario. In absence of mortality data for patients with intermediate operative risk beyond the first two years, we assumed that the mortality rates beyond 2 years corresponded to those for general population of the same age. We collected age and gender specific Norwegian all-cause mortality data from Statistics Norway (19) and used them in the model beyond the 24th month.

In the base-case analysis, we considered patients at the age of 80 years when entering the model. In order to explore how a possible extension of the TAVI procedure on to younger patients, we performed a second scenario analysis, where the start age for entering the model was reduced to 70 years and the time perspective extended to 25 years.

Budget impact

Budget impact analysis can be defined as an assessment of the financial consequences of adopting a new intervention at an aggregate population level. In other words, budget impact is the total incremental cost of introduction of an intervention versus non-introduction.

To estimate the total incremental cost of introduction of TAVI for patients with severe aorta stenosis at intermediate surgical risk we have extracted total costs calculated by the Markov model. We used undiscounted costs, in line with recommendations from the International Society for Pharmacoeconomics and Outcomes Reasearch (ISPOR) for budget impact analyses (11).

Economic evaluation – Results

Incremental cost–effectiveness estimates in the base case scenario

The results of the probabilistic sensitivity analysis in the base case scenario with a two-year time perspective are illustrated in figure 3. The blue dots in the scatter plot represent results for patients following SAVR and the red ones TAVI – patients. The red "cloud" is, on average, situated to the right and somewhat higher than the blue "cloud", indicating that TAVI is likely to be both more effective and more costly than SAVR.

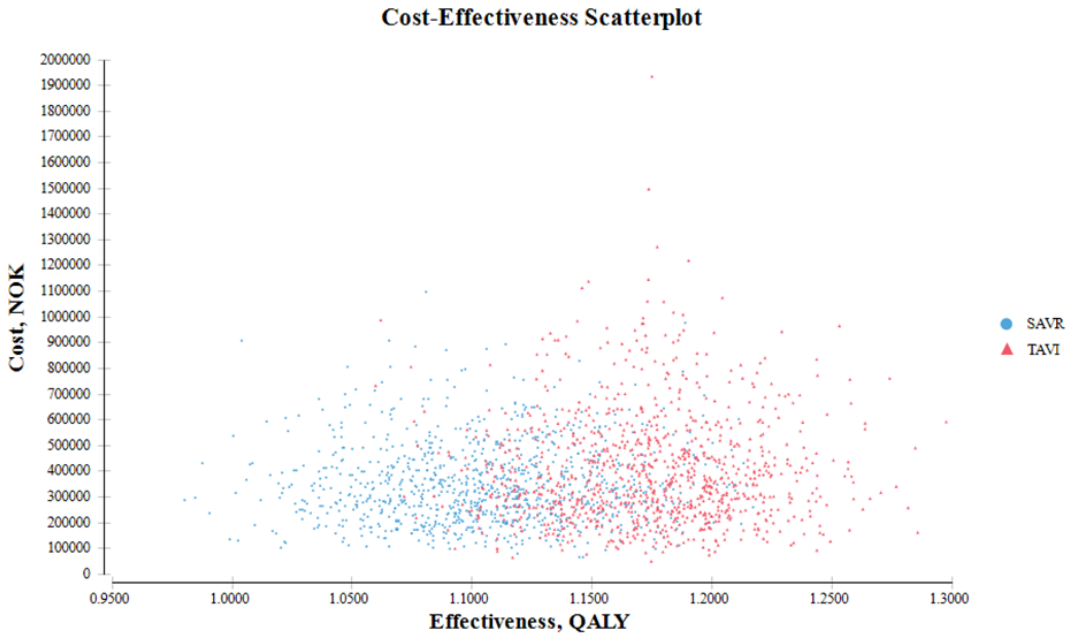


Figure 3. Cost-effectiveness scatterplot for base case analysis (2-year time horizon)

The average results of the Monte Carlo simulation in base-case analysis are presented in Table 11.

Table 11.Results of the base case cost-effectiveness analysis (2-year time horizon, discounted)

Procedure type	Total costs (NOK)	Effects (QALYs)	Incremental cost (NOK)	Incremental effect (QALYs)	ICER (NOK/QALY)
SAVR	343 607	1.11			
TAVI	414 526	1.17	70 920	0.07	1 037 083

QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; NOK: Norwegian kroner

The same results can also be presented as a cost-effectiveness graph, as in Figure 4. below.

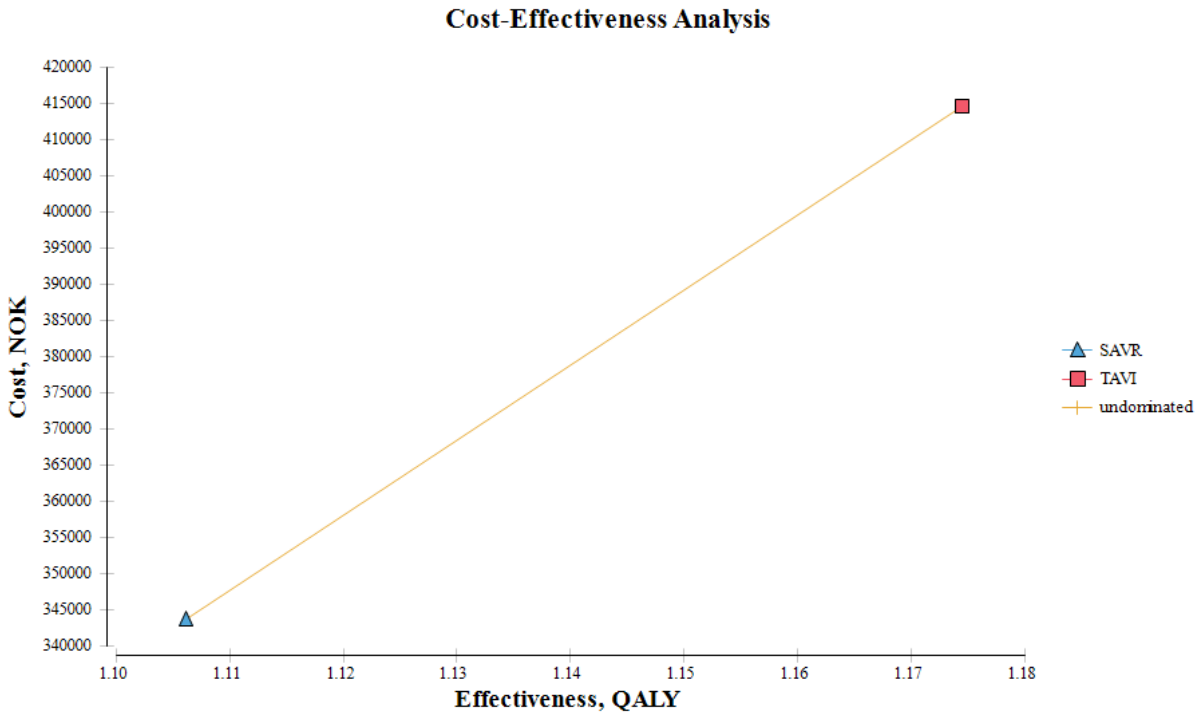


Figure 4. Cost-effectiveness graph TAVI versus SAVR, base case analysis

The results show that the total expected intervention-related costs per patient in a two-year perspective are about 340 000 NOK for patients who undergo SAVR and 410 000 NOK for patients who get TAVI. These include the costs of the procedures, rehabilitation and treatment of complications. The incremental cost for TAVI patients is thus about 70 000 Norwegian kroner. During the same two years, TAVI patients accumulate also slightly more QALYs, with a difference of about 0.07 QALYs. The modest difference in health effect is the main driver for the result that TAVI costs 1,0 million Norwegian kroner per QALY (ICER).

Below, we present cost-effectiveness acceptability curves at willingness-to-pay (WTP) for one additional QALY between zero and 825 000 NOK (see figure 5). The figure demonstrates that SAVR has a higher probability of being cost-effective than TAVI for this range of WTP, when simultaneously taking into account all parameter uncertainties.

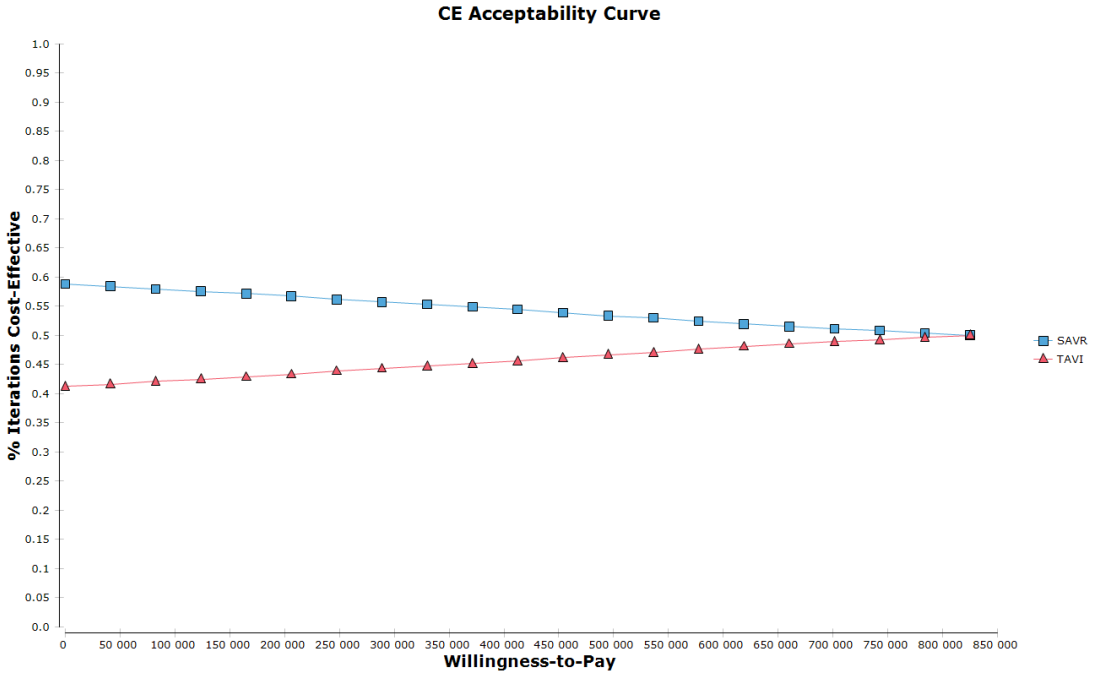


Figure 5. Cost-effectiveness acceptability curves indicating the probability that either intervention is cost-effective for a WTP range from zero to 825 000 NOK per QALY.

Sensitivity analysis

A tornado diagram is a graphical method for presenting a series of one-way sensitivity analyses. It shows how cost-effectiveness results (ICER) are influenced by variation in individual model parameters. Figure 6 presents parameters with greatest impact on results.

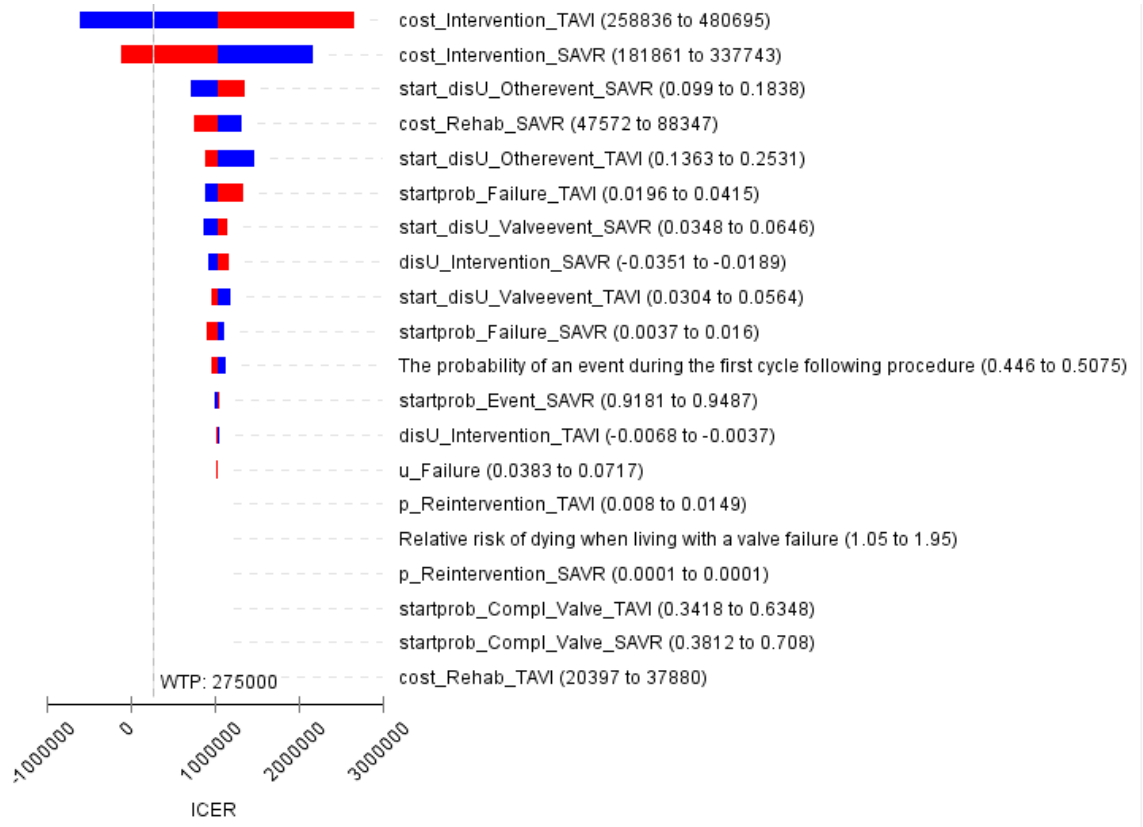


Figure 6. Tornado diagram revealing possible impact of reasonable variation in main parameters on the ICER of TAVI compared to SAVR.

We can observe that the results are most affected by variation in procedure related cost data. In fact, intervention costs are the only two assumptions for which the result of SAVR being cost-effective is sensitive, if WTP is defined at NOK 275 000 per QALY. Parameters such as disutility values related to complications and to procedures, rehabilitation costs following open surgery and treatment failure rates also impact the results, but to a much lesser degree, and the main result is not sensitive to reasonable variation in their values.

Below, we explore how the cost of TAVI procedure would have to be reduced to achieve cost-effectiveness at a given a WTP threshold value of NOK 275 000:

$$ICER = \frac{Cost_{\text{intervention}} - Cost_{\text{comparator}}}{Effect_{\text{intervention}} - Effect_{\text{comparator}}} = \frac{\Delta C}{\Delta E}$$

Both costs of intervention and comparator include procedure costs, rehabilitation costs and costs of treating complications

$\Delta C/\Delta E$ = WTP; where ΔE = 0.0681 and $C_{comparator}$ = NOK 343 607 and WTP = NOK 275 000
Today's Cost of TAVI procedure = C_{TAVI} =NOK 369 765

Cost intervention = 414 526 = C_{TAVI} + Cost rehabilitation + Cost complications

Cost rehabilitation + Cost complications = 44 761

$C_{TAVI} = \Delta E * WTP + C_{comparator} - (\text{Cost rehabilitation} + \text{Cost complications})$

$C_{TAVI} = \text{NOK } 317\,573$

Necessary reduction in TAVI procedure costs = 52 192 NOK, which translates into about 14% of the total TAVI procedure costs. Procedure costs include both TAVI system (aorta valve prostheses together with stent), as well as personal costs and other hospital costs.

With an assumption about cost of a TAVI system being within the interval from 130 000 to 170 000 Norwegian kroner and all other costs constant, the cost of a TAVI system would have to reduce with 30-40 % to achieve a 275 000 kroner per QALY threshold of cost-effectiveness.

Scenario analyses

Extending from two years to life-time perspective

In the base-case analysis, a time horizon of two years was considered. We assumed that all relevant differences between the alternative treatment options manifest themselves in the immediate aftermath of intervention and then within the course of 2 years following procedure. In order to investigate the validity of this assumption, a scenario analysis was conducted where the time perspective was extended into life-time (15 years following procedure).

The time horizon extension to 15 years resulted in somewhat lower ICER – 800 275 kroner per QALY versus 1 037 083 kroner per QALY in the base case. However, the conclusion remained the same as in the base-case analysis (Table 12).

Table 12 .Results of the scenario analysis of cost-effectiveness (15-year time horizon, discounted)

	Total costs (NOK)	Effects (QALYs)	Incremental cost (NOK)	Incremental effect (QALYs)	ICER (NOK/QALY)
SAVR	354 166	5.4020			
TAVI	430 252	5.4971	76 087	0.0951	800 275

QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; NOK: Norwegian kroner

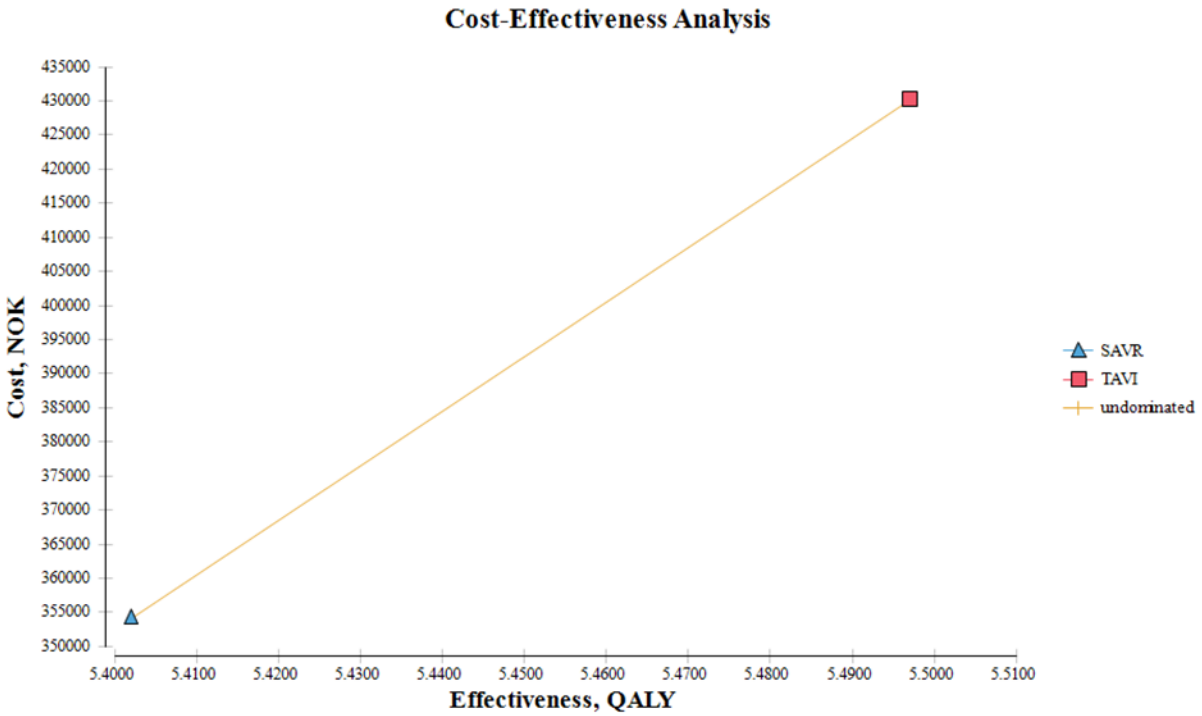


Figure 7. Cost-effectiveness graph TAVI versus SAVR, scenario analysis

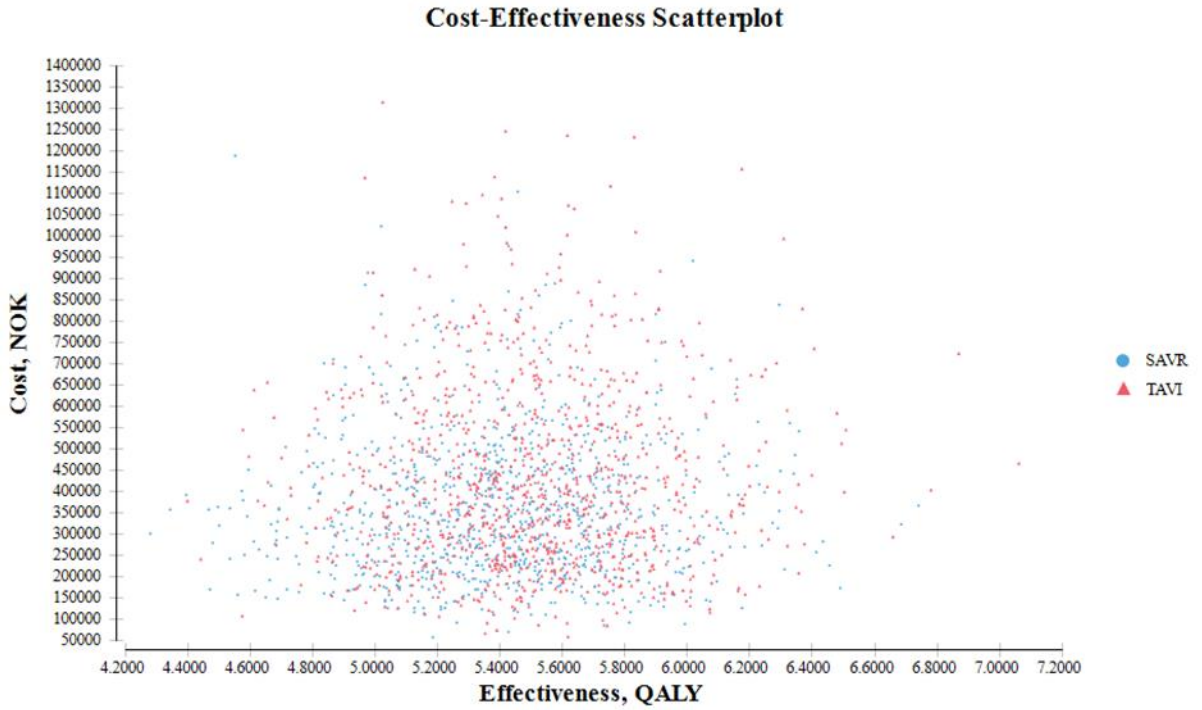


Figure 8. Cost-effectiveness scatterplot for base case analysis (15-year time horizon)

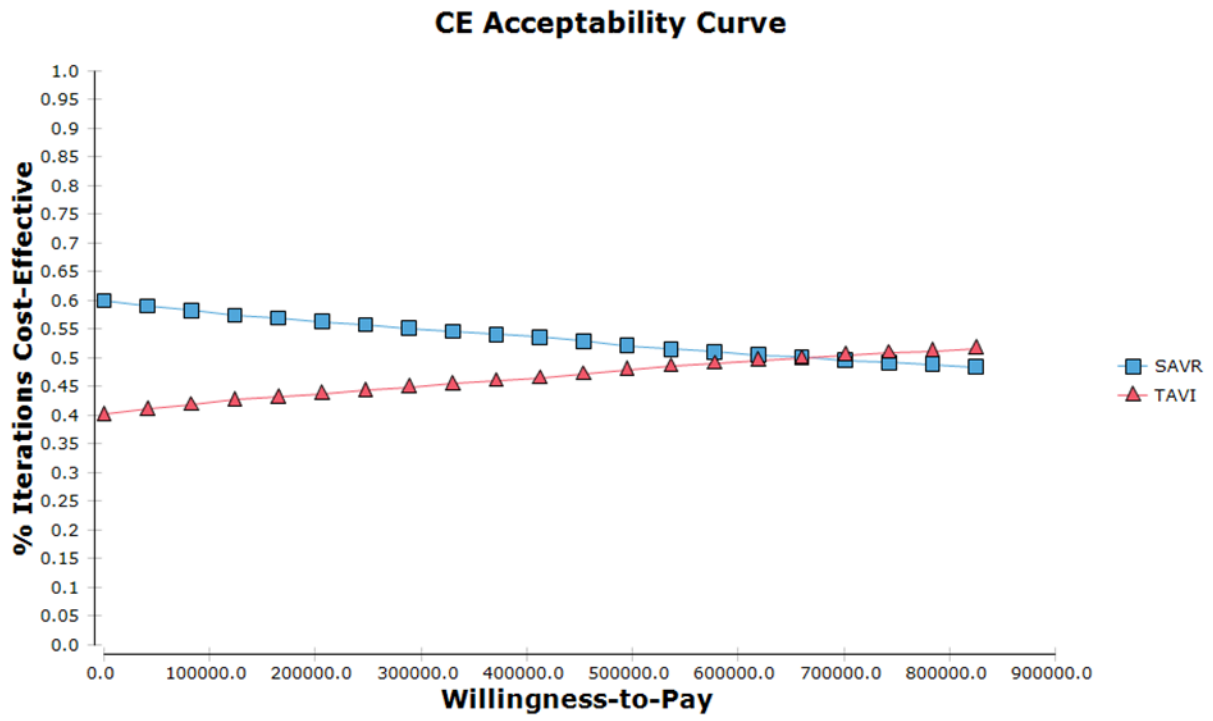


Figure 9. Cost-effectiveness acceptability curves indicating the probability that either intervention is cost-effective for a WTP range from zero to 825 000 NOK per QALY.

Reducing age from 80 to 70 years and extend time perspective from 2 to 25 years

In the second scenario analysis the start age of patients entering the model was lowered to 70 years and time perspective extended to 25 years. These adjustments resulted in a lower ICER – 643 758 kroner per QALY versus 1 037 083 kroner per QALY in the base case (Table 13), with no substantial consequence for conclusions

Table 13. Results of the scenario analysis of cost-effectiveness (start age is 70 years, 25 years time horizon, discounted)

Procedure type	Total costs (NOK)	Effects (QALYs)	Incremental cost (NOK)	Incremental effect (QALYs)	ICER (NOK/QALY)
SAVR	364 808	8.89			
TAVI	446 658	9.02	81 850	0.13	643 758

QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; NOK: Norwegian kroner

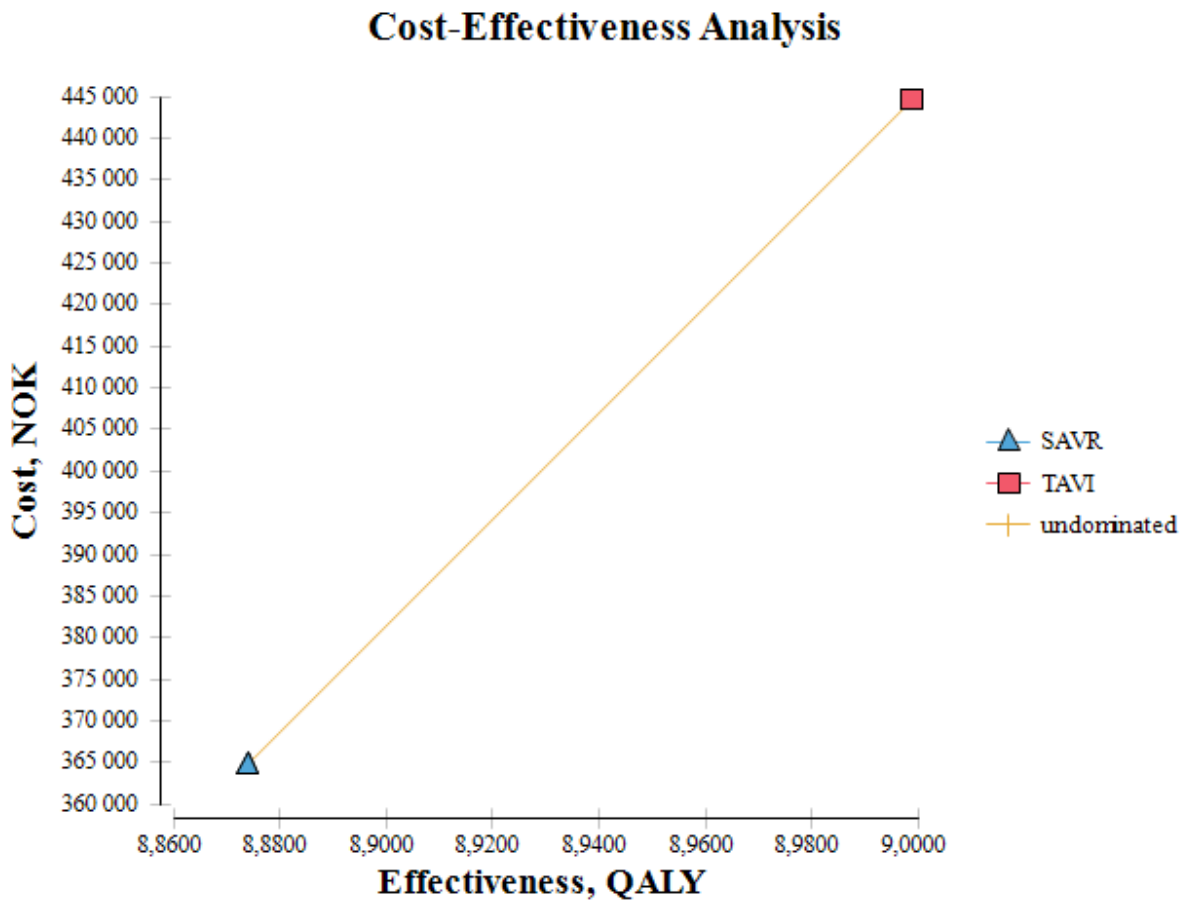


Figure 10. Cost-effectiveness graph TAVI versus SAVR, scenario analysis

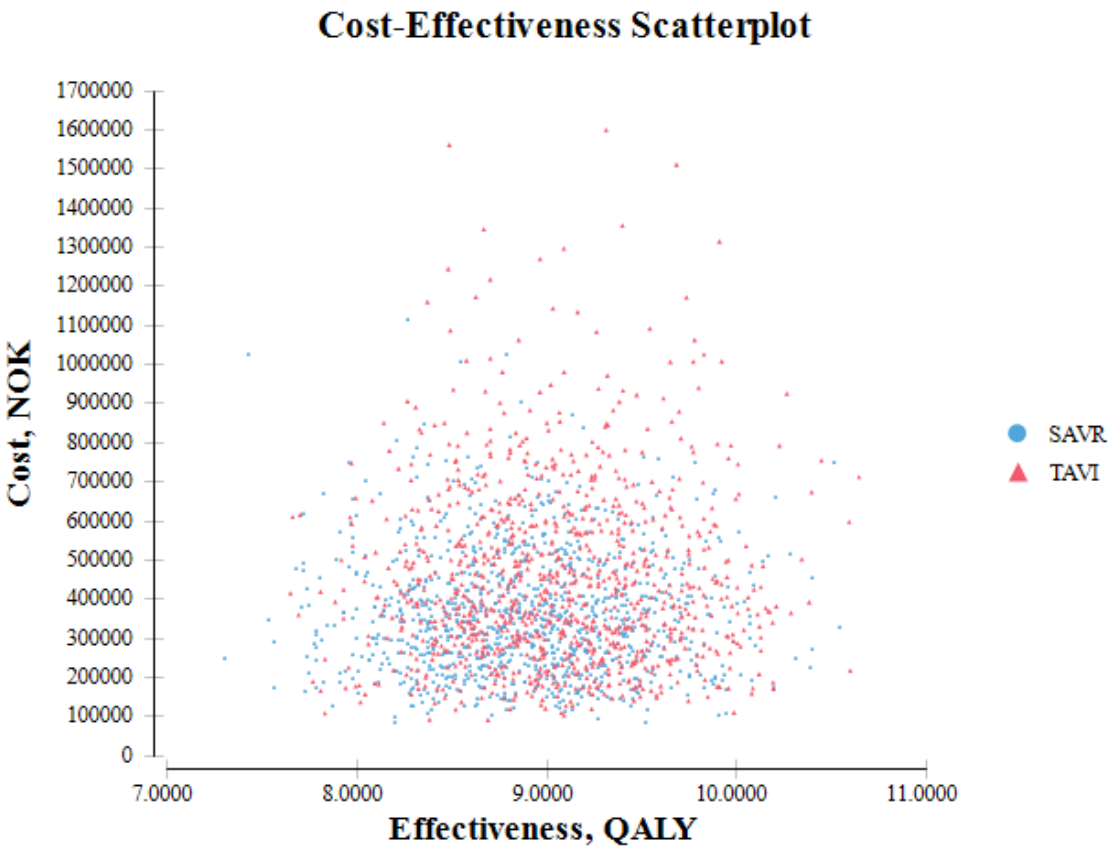


Figure 11. Cost-effectiveness scatterplot for base case analysis (start age is 70 years of age, 25-year time horizon)

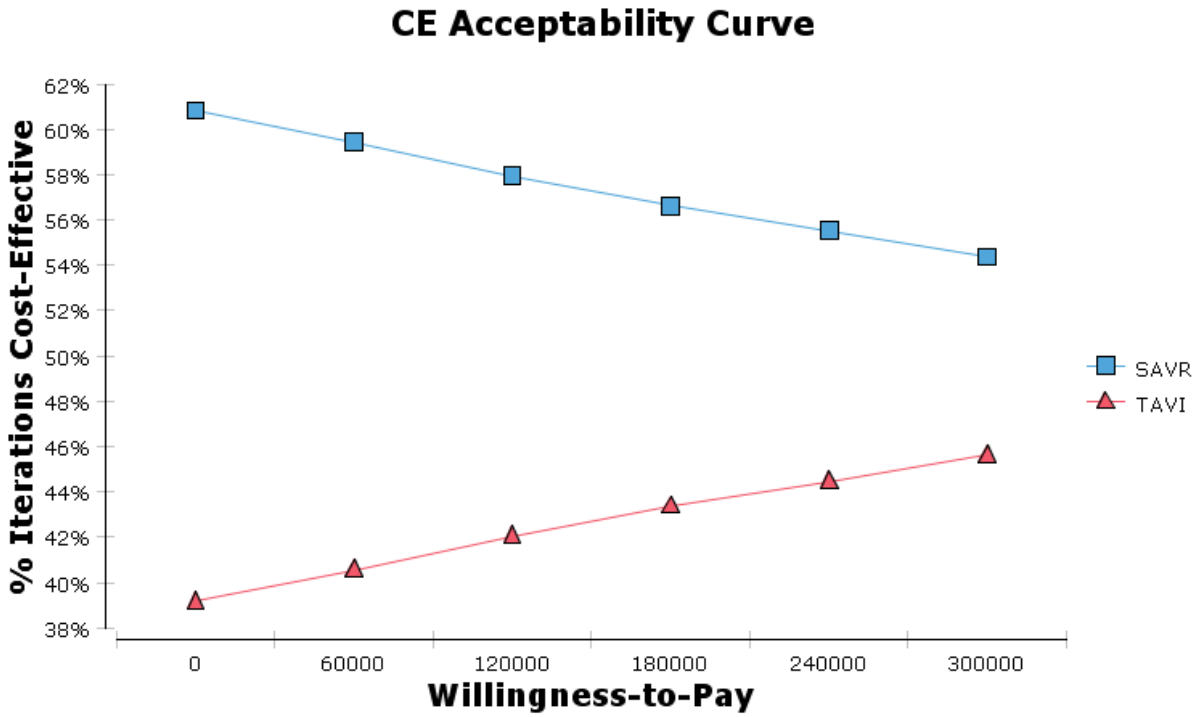


Figure 12. Cost-effectiveness acceptability curve (start age is 70 years of age, 25-year time horizon).

Severity considerations - Absolute shortfall

The calculation of absolute shortfall (AS) is based on the submission guideline of the Norwegian Medicines Agency (20) which is based on the white paper on priority setting (2), a Norwegian life table (19) and health related quality of life information from a Swedish population (21). Absolute shortfall is defined as the difference in quality adjusted life expectancies at age (A) without the disease ($QALY_{sA}$) and prognosis with the disease (P_A):

$AS = QALY_{sA} - P_A$

In accordance with the economic model, we first assume that patients are 80 years of age when entering the model. At this age, the expected quality adjusted life expectancy is 7.0. The prognosis with disease expected to be 5,5102 QALYs for standard treatment i.e. SAVR, based on simulations from the health economic model with lifetime (15 years) time horizon. (see Table 12). The absolute shortfall with these assumptions is:

AS = 7.0 – 5.4 = 1.6 QALYs

We also considered the AS with respect to an extension of the TAVI procedure for younger patients. In this AS scenario, we assumed that patients are 70 years of age when entering the health economic model. Because of the 10 years lower age, we run the model for 25 years instead of 15 years as we did for the model with lifetime time horizon. At 70 years of age, the expected quality adjusted life expectancy is 12.5 QALYs. The prognosis with disease expected to be 8.9 QALYs for standard treatment (Table 13). Therefore, the absolute shortfall with these assumptions is:

AS = 12.5 – 8.9 = 3.6 QALYs

This puts patients with severe aortic stenosis and intermediate surgical risk in severity class 1 (see glossary) irrespective of age scenario.

Budget impact

The budgetary impact of expanding TAVI indication on to patients with intermediate surgical risk for the next years is difficult to predict. The prediction depends on several factors, including any change in clinical practice from current practice, the relative changes in procedure costs and the number of patients eligible for different treatment alternatives.
According to data from the Norwegian Register for Cardiac Surgery, the absolute number of TAVI procedures as well as their share in all aortic valve replacement procedures are rising. In 2017 there were 632 TAVI procedures performed in Norway (compared with 395 procedures in 2015 and 524 in 2016), which made about a half of all isolated aorta valve procedures, see figure 13 in the chapter about organisational aspects and Table 14. below (22).

Table 14. Number of TAVI procedures performed in Norway, years 2015-2017

Year	**2015**	**2016**	**2017**
Number of TAVI procedures	396	534	632

Data from the Norwegian Register for Cardiac Surgery

Based on the above figures, the annual increase in total number of isolated aorta replacement procedures has been between 5 and 15%. The use of TAVI has been growing faster: 18-34% annually, which suggests that, in clinical practice, the indication

expansion is already happening. It is therefore difficult to estimate the impact of including patients with intermediate risk in the indication for TAVI on health care budget. It seems reasonable to assume that the use of TAVI will continue to increase in the nearest future.

For the present calculation, we make a conservative assumption that this growth continues at the rate of 20% annually. We also assume that about a half of this increase (10%) is due to other factors than widening of the indication, such as growing elderly population, patient preference and improvements in diagnostics.

Based on the above assumptions we calculated the numbers of patients eligible for TAVI as prognosis for the next four years as well as incremental number of patients due to indication expansion in reference to today's 632 patients, presented in Table 16.

The budget impact was calculated based on the same cost inputs (procedure and rehabilitation costs, as well as cost of treating procedure-related complications) used in the cost-effectiveness model (see table 11 and 12). The results of the cost analysis show that in the first year following procedure of aorta valve implantation TAVI patients gather on average 69 317 Norwegian kroner in incremental costs. All estimations are based on 2018-price. The results of the budget impact analysis are shown in Table 15.

Table 15 Predicted impact of expansion of indication for TAVI on the number of patients and results of the budget impact; estimated costs based on future practice compared to estimated costs based on current practice

Year	**2018**	**2019**	**2020**	**2021**	**2022**
Number of TAVI procedures*	758	910	1 092	1 311	1 573
Incremental increase as result of indication expansion	63	139	230	339	470
Incremental costs in million NOK	4.4	9.6	15.9	23.5	32.6

**Prognosis*

Organisational aspects

Background

Cardiac surgery and aorta valve implantation in Norway is centralised at regional level, in the four state-run regional hospitals (Oslo University Hospital, Haukeland University Hospital, St. Olav's University Hospital and University Hospital of North Norway). In addition to the four regional hospitals, until autumn 2018 the private Feiring Clinic was performing aortic valve replacement procedures along with other types of cardiac operations. Presently, this type of intervention is only available at the four regional university hospitals.

Method

We used the Norwegian Register for Cardiac Surgery to illuminate the organisational conditions of TAVI in Norway. In order to evaluate the organizational consequences related to a potential increase in volume of TAVI procedures performed in Norwegian hospitals, we also asked clinical experts from the five respective centers that performing cardiac surgery in Norway, to answer a questionnaire regarding their present capacity: patient selection, procedures and ongoing trials. We received answers from all of the five hospitals. The questions used in the questionnaire are listed up in Appendix 4 (in Norwegian).

Organisational conditions in Norway

According to the Norwegian Register for Cardiac Surgery, the number of all aorta valve replacements is increasing, whereas the number of open surgery procedures has been stable, falling slightly recently (see figure 13). The absolute number of TAVI procedures is rising, so is their share in all aortic valve replacement procedures. In 2017 there were 636 TAVI procedures performed in Norway (compared with 395 procedures in 2015 and 2016 there were 524), which made about a half of all isolated aorta valve procedures, see figure 13 (23;24). The proportion of procedures performed via femoral access is rising (22). In 2017, about 92% of all TAVI procedures were performed transfemorally (24). A possible explanation of the trend can be expansion in the use of TAVI on to younger patients with fewer comorbidities.

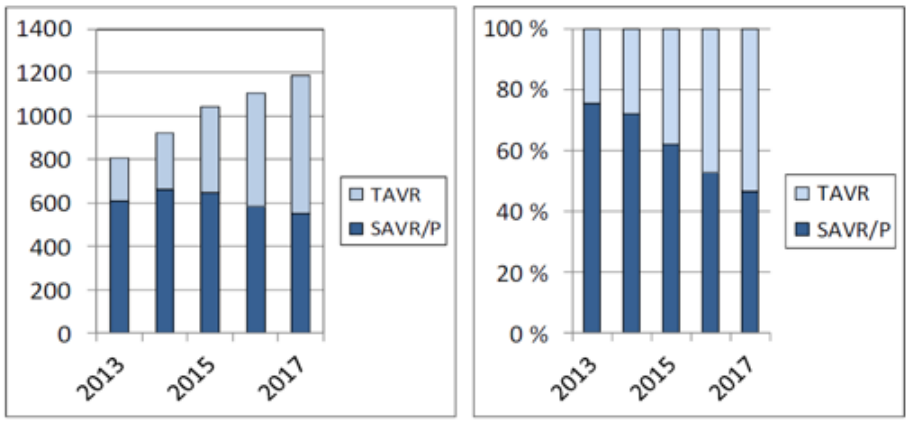


Figure 13. Use of TAVI and SAVR in Norway in absolute numbers (left) and increase in TAVI-share among all isolated aorta procedures (right). Source: Norwegian Register for Cardiac Surgery (2017-report)(23)

Capacity in the Norwegian cardiac surgery centres

Table 16 presents the number of patients treated with TAVI procedure by hospital in years 2015 to 2017.

Table 16: Number of patients treated with TAVI procedure

Year	Feiring hospital	Haukeland University Hospital	Oslo University Hospital		St.Olavs hospital	University Hopsital of North Norway
			Ullevål hospital	Rikshospitalet		
2015	50	65	2	101	53	70
2016	62	120	47	146	62	61
2017	79	118	68	208	65	87

Numbers reported from clinical experts in each hospital

Patient selection

In all of the five hospitals, patients with indication for aortic valve replacement are first assessed by a heart team at so called “heart meeting”. Heart teams consist of a cardiologist and a cardiac surgeon or anesthesiologist. Patients are preselected to either TAVI procedure or SAVR procedure, based on assessment of their risk profile. The following criteria favor TAVI procedure: high age (> 80 age, lower limit 75 age), comorbidity (kidney failure, chronic obstructive pulmonary disease, earlier coronary surgery, porcelain aorta etc.), and frailty (short physical performance battery (SPPB), mini-mental state exam (MMSE)). SAVR is recommended for patients under 75 years with low operational risk, but there may exist modifying conditions that must be taken into account and it is the “heart meeting” that is the determining or “advisory” body of the patient.

The patients relevant for TAVI are furtherly examined, and discussed for suitability in a separate TAVI meeting (weekly) after CT scan. For patients who do not qualify for TAVI for technical reasons SAVR is reconsidered.

The use of radiology and echocardiography

In all of the five hospitals, the patients evaluated for aortic stenosis undergo transthoracic echocardiographic examination and coronary angiography, preoperatively. In addition, transesophageal echocardiography may be a part of the procedure (progress). All patients eligible for TAVI must also undergo a CT of a total aorta and pelvis. All of the TAVI-patients undergo preoperative x-ray or/and echography before leaving the hospital.

Type of valve used in the aortic valve implantation procedures

Sapien 3 and *Evolut R* were the most used valves in TAVI procedures. The most used in surgical aortic valve replacement procedures was the biological valve *Perimount*. In table xx the different valves used in Norwegian hospitals are presented.

Table 17: Type of valve used in the aortic valve implantation procedure in the respective centers.

Hospital	**TAVI valve**	**SAVR valve**	
		Biological	**Mechanical**
Haukeland University Hospital	*Portico* (Abbot) *CoreValve, EvolutR and EvolutPro* (Medtronic), *Sapien 3* (Edwards), *Lotus* (Boston Scientific) (temporarily out of market)	*Hankock Ultra* (Medtronic), *Perimount, Perimount Magna ease* (Edwards) *Trifecta* (St. Jude/Abbot), *Freestyle* (Medtronic), Exceptionally: *Intuity, Inspiris Resilia* (Edwards)	*OnX* (CryoLife – distributed by Mediplast) *Regent* (St Jude/Abbott)
Oslo University Hospital	*Sapien 3* (Edwards), *Evolut R, Evolut Pro* (Medtronic) *Symetis Acurate Neo* (Boston Scientific) *Lotus* (Boston Scientific) (temporarily out of market)	*Perimount* (Edwards) *Trifecta* (St Jude/Abbott), *Hancock* (Medtronic), Under consideration: *Inspiris* (Edwards) *Avalus* (Medtronic)	*ATS* (Medtronic) *OnX* (CryoLife – distributed by Mediplast) *Regent* (St Jude/Abbott)
St. Olavs hospital	*Sapien 3* (Edwards), *CoreValve* (Medtronic)	(no answer)	(no answer)
University Hospital of North Norway	*Sapien 3* (Edwards), *Evolute* (Medtronic), *Portico* (Abbot)	*Perimount* (Edwards)	-

Feiring Hospital	*CoreValve, Evolute XT, Evolute R, Evolute Pro* (Medtronic) *Symetis Acurate Neo* (Boston Scientific)	*Hancock 11* (Medtronic), *Mitroflow, Perceval (sutureless)* (Sorins)	*ATS* (Medtronic)

Use of hybrid operating rooms and catheterization angiography laboratory
Most of the hospitals use hybrid operating rooms during TAVI procedures or hybrid light room. The clinical experts stated that there may be some limitations when the operating room is used to non-cardiac and other thoracic procedures. There are also high equipment costs related to the TAVI procedure. Further, some of the clinicians mentioned that there are no postoperative capacity.

An extension of the indication for TAVI and organizational consequences
The clinical experts suggest that there is need for more or/and improved access to hybrid operating rooms in Haukeland hospital, Oslo University Hospital and in St. Olavs hospital. Further, the clinical experts stated that an extension of TAVI to younger patients will lead to a reduction of SAVR. A change from surgical to catheter-based valve replacement may lead to either increased resources for invasive activity (laboratories, beds and CTes) or increased training of thoracic surgeons, cardiologists and surgical nurses. An increased capacity for TAVI along with an extension of the population group causes more patients having valve procedures. The patients must be monitored more closely by hospitals or by cardiologists in private practice. Treatments of patients with complex issues requires increased bed capacity.

Most likely, TAVI procedures will continue to be performed only in the hospitals that carry out cardiac surgery. It is currently recommended internationally that this procedure should only be done in hospitals with cardiovascular surgery, but the future may change.

Discussion

In this economic evaluation, we assessed cost-effectiveness of TAVI compared with SAVR for patients with severe aorta stenosis at intermediate operative risk.
We chose to use clinical data from the randomized control multicentre trial PARTNER 2A (Placement of Aortic Transcatheter Valves 2A) to inform the analyses. This is because on a number of endpoints, due to heterogeneity, it was not possible to pool data from both studies included in EUnetHTA's relative effectiveness assessment (PARTNER 2A and SURTAVI). We considered methodological consistency in sourcing effect data important. Moreover, type of technology used in the trial is in accordance with technology used most often in Norwegian clinical practice.
The results show that the total expected average intervention-related costs per patient in a two-year perspective are about 340 000 NOK for patients who undergo SAVR and 410 000 NOK for patients who get TAVI. These include the costs of the procedures, rehabilitation and treatment of complications. The incremental cost for TAVI patients are thus about 71 000 Norwegian kroner. At the same time, TAVI patients accumulated also slightly more QALYs, with a difference of about 0.07 QALYs. The modest gain of health effect in favour of TAVI causes the incremental cost-effectiveness ratio (ICER) to amount to about 1.0 million Norwegian kroner.
We used a two-year perspective in the base case scenario which was also the time perspective for the efficacy data that informed the model. Mortality rates at two years follow-up were not significantly different between treatment options, also when considering pooled data from both trials (1). The main differences in efficacy therefore manifested themselves in the rates of procedure-related complications, for some complications in favour of TAVI, for others in favour of SAVR. Most of the complications occurred in the acute phase following aortic valve implantation and their rates were falling with time. We considered the two-year perspective sufficient to capture all relevant differences in outcomes. However, in order to investigate validity of this assumption, we conducted a separate analysis (scenario analysis), where the time perspective considered was extended into lifetime (15 years following procedure). The impact of the extended time perspective was not sufficiently substantial to be likely to change any decisions regarding cost-effectiveness.
The above scenario results should be interpreted with some caution as long-term effects on survival, complications, prostheses' longevity and need for future re-intervention remain to be established and documented.

When considering costs related to both procedures, we only included direct cost of intervention, rehabilitation and treatment of complications. We did not include potential differences in follow-up costs following TAVI and SAVR, assuming (based on experts' opinion) that the way patients with new valves are receiving similar follow-up regardless of type of procedure.
Both technologies (TAVI and SAVR) are in constant development. There are many different prostheses and generations of prostheses available for SAVR: mechanical and bioprosthetic valves, which are the most common choice nowadays. Traditionally, prostheses for SAVR are anchored using surgical sutures. More recent approaches include sutureless valves and rapid deployment valves (1). For TAVI, several different systems are available, with evolving valve prostheses as well as delivery systems and techniques. It is reasonable to assume that the costs of these technologies will also evolve. In addition, as presently TAVI procedure costs are estimated on basis of older and higher risk patients, it is possible that including patients with lower risks will also impact total procedure costs. The sensitivity analyses show that results are most influenced by the procedure cost parameters. Reductions in the cost of the TAVI procedure will influence estimates of cost-effectiveness.
In accordance with a health care perspective, we did not include any costs related to productivity losses or cost incurred outside of the health care system.
The mortality rates for general population that we used in the scenario analysis to reflect mortality rates beyond 24 months following valve procedure, turned out to be slightly higher than the rate at 24 months in the trial. We assumed that since we applied the same rates to both intervention and comparator, and since there was no significant difference in mortality rates up to 24 months, this should not affect the analysis's results considerably.
Since we accounted for all cause-mortality in the course of each cycle (monthly), we assumed all complications to resolve within a defined period, accounting for disutility with duration varying according to the nature of a complication.

Information about utility values for TAVI or SAVI procedures is scarce in the literature. Since we were not able to identify any systematic reviews, we had to base our estimates on the results from a single study (PARTNER 1). More evidence on health related quality of life following the procedures might warrant a revision of these analyses.

Primary, the disutility values related to both "valve-related complications" and "other complications": major vascular complications, life threatening bleeding, stroke, acute kidney injury and new-onset atrial-fibrillation, derived from the article by Kaier et al. 2016 (10). This article included 169 elderly patients above 75 years of age wither with transcatheter aortic valve replacement (TAVR; n = 92), surgical aortic-valve replacement (n = 70), or drug-based therapy (n = 7), was evaluated using the standardized EQ-5D questionnaire. The disutility for valve endocarditis and moderate or severe paravalvular leak were sourced from an article by Sullivan et al. 2014 (11) that listed up preference-based EQ-5D index scores for chronic conditions

in the United States. The disutility value for myocardial infarction was given an alternative disutility value based on the article by Davies et al. 2015 (12). As we did not identify in the literature any relevant disutility value related to pacemaker implantation, we assigned a disutility value based on an assumption to this complication.

The HRQoL-instrument, EQ-5D, was used in all the included sources to obtain the QALY weights. There is some degree of uncertainty about how well the instrument's dimensions (mobility, self-care, usual activities, pain /discomfort and anxiety /depression) and levels reflect patients' preferences regarding choice between the two alternative procedures.

We presented data from the Norwegian Register for Cardiac Surgery and information given by clinical experts from five respective Norwegian hospitals performing TAVI procedures, to inform organizational consequences following a possible extension of this procedure. Some possible weaknesses to our survey (see Appendix 4) are that some of the clinicians answered more completely than others, and there might also have been some different in the understanding of the respective questions that we asked.

Finally, all patients in Norway have the right to shared decision-making. It is the multidisciplinary heart team that individually evaluates patients to the most appropriate treatment using the predefined clinical criteria. However, the patients are more and more aware of different treatment alternatives and might have preferences when it comes to – for example - the convalescence time. The white paper on priority setting (2) does not indicate that such patient preferences should be accounted for when making priority setting decisions at group level, and consequently they are not incorporated into the present analysis. At the same time, the white paper suggests that the decision maker can take other considerations into account when making priorities, if they consider them relevant.

Consistency of the economic evaluation with other studies

Through an ad-hoc search in autumn 2018, we identified two relevant published cost-effectiveness evaluations of TAVI for patients with severe aortic stenosis at intermediate surgical risk. Both studies compared TAVI with SAVR. Economic analysis performed by Tam and colleagues (25) evaluated cost-effectiveness of TAVI versus SAVR from the Canadian third-party payer's perspective, while the study by Kodera and colleagues (26)assessed the intervention in Japanese settings. Both of the economic evaluations used clinical trial data from PARTNER 2 (3) to inform the efficacy inputs.

In the Table 18 below, the main results of both cost-effectiveness analyses are presented.

Table 18: TAVI vs. SAVR cost-effectiveness evaluations for patients with intermediate surgical risk

Study	**Tam et al. 2018 (25)**	**Kodera et al. 2018 (26)**
Model Analysis	CEA	CEA
Population	Study population reflects PARTNER 2 cohort A (patients with intermediate surgical risk). The average patient age is 82 years, 55% are male, the average STS score is 6 and 77% are New York Heart Association class III or IV.	Study population reflects PARTNER 2 cohort A (patients with intermediate surgical risk). The average patient age is 82 years, 55% are male, the average STS score is 6 and 77% are New York Heart Association class III or IV.
Intervention	Sapien XT valve implantation	Sapien XT valve implantation
Comparison	SAVR	SAVR
Incremetal QALY (TAVI-SAVR)	0.23	0.22
Incremental costs (TAVI-SAVR)	$10,547	Yen 1,723,516
ICER/QALY	$46,083/QALY (297,073 NOK/QALY)*	Yen 5,715,471/QALY (446,746 NOK/QALY)*

CEA: Cost-effectiveness analysis, $: Canadian dollar, ICER: incremental cost effectiveness ratio, QALY: quality adjusted life year, PARTNER 2: Placement of Aortic Transcatheter Valves trial 2 (3)* Converted into Norwegian kroner with XE Currency Converter in January 2019

Tam with colleagues (25) constructed a probabilistic Markov model with 30-day cycles, to estimate the difference in cost and QALYs of TAVI versus SAVR for intermediate risk patients over a lifetime time horizon. Costs were obtained from the Canadian Institute of Health Information and the Ontario Schedule of Benefits. The authors evaluated cost-effectiveness in relation to two thresholds: $50,000 and $100,000 per QALY (322 335 and 644 670 Norwegian kroner respectively). They also performed a sensitivity analysis to assess the effect of uncertainty on their results. The analysis resulted in ICER of $46,083/QALYs gained. There was moderate-to-high parameter uncertainty. TAVI was the preferred option in only 52.7% and 55.4% of the simulations at a $50,000 and $100,000 per QALYs willingness-to-pay thresholds, respectively. The authors concluded that TAVI may be cost-effective for the treatment of severe aortic stenosis in patients with intermediate surgical risk. There remains moderate-to-high uncertainty surrounding the ICER.

The Japanese study by Kodera et al. 2018 (26) also estimated the cost-effectiveness of transfemoral TAVI compared to SAVR through a Markov model with Monte Carlo simulations. The authors evaluated the QALYs and costs of TAVI and SAVR over a 10-year time horizon from the perspective of Japanese public healthcare payers. The authors assumed a cost-effectiveness threshold of 5,000,000 (about 391 000 Norwegian kroner) yen per QALY, and assessed the cost-effectiveness probability with 100,000 simulations. They also performed a sensitivity analysis to assess the effect of uncertainty on their results. The ICER for TAVI compared with SAVR turned out to be 7,523,821 yen per QALYs gained (about 446 746 Norwegian kroner per QALY). The cost-effectiveness probability of TAVI was calculated to be 46% for these patients. The cost-effectiveness threshold of TAVI was <5,427,439 yen. The study concluded that TAVI is not cost-effective compared to SAVR in operable patients. A main difference between this study and the Canadian and Japanese ones, is that the latter ones find incremental effects between SAVR and TAVI that are about three times higher.

Conclusion

The cost-utility analysis indicated that TAVI was marginally more effective (incremental effectiveness: 0.07 QALYs) and more costly (incremental costs: 71 000 Norwegian kroner) than the open surgery. The incremental cost-effectiveness ratio (ICER) was about 1.04 million Norwegian kroner per QALY in analysis with two-years perspective, falling to about 800 000 kroner per QALY in life time perspective.
The calculated absolute shortfall for patients with severe aorta stenosis and intermediate surgical risk is equal to 3.6 QALYs for patients aged 70 years when receiving the intervention, and lower when patients are 80 years.
The results of the sensitivity analysis showed that cost parameters related to both procedures, but particularly to TAVI, had the greatest impact on the results.

Appendices

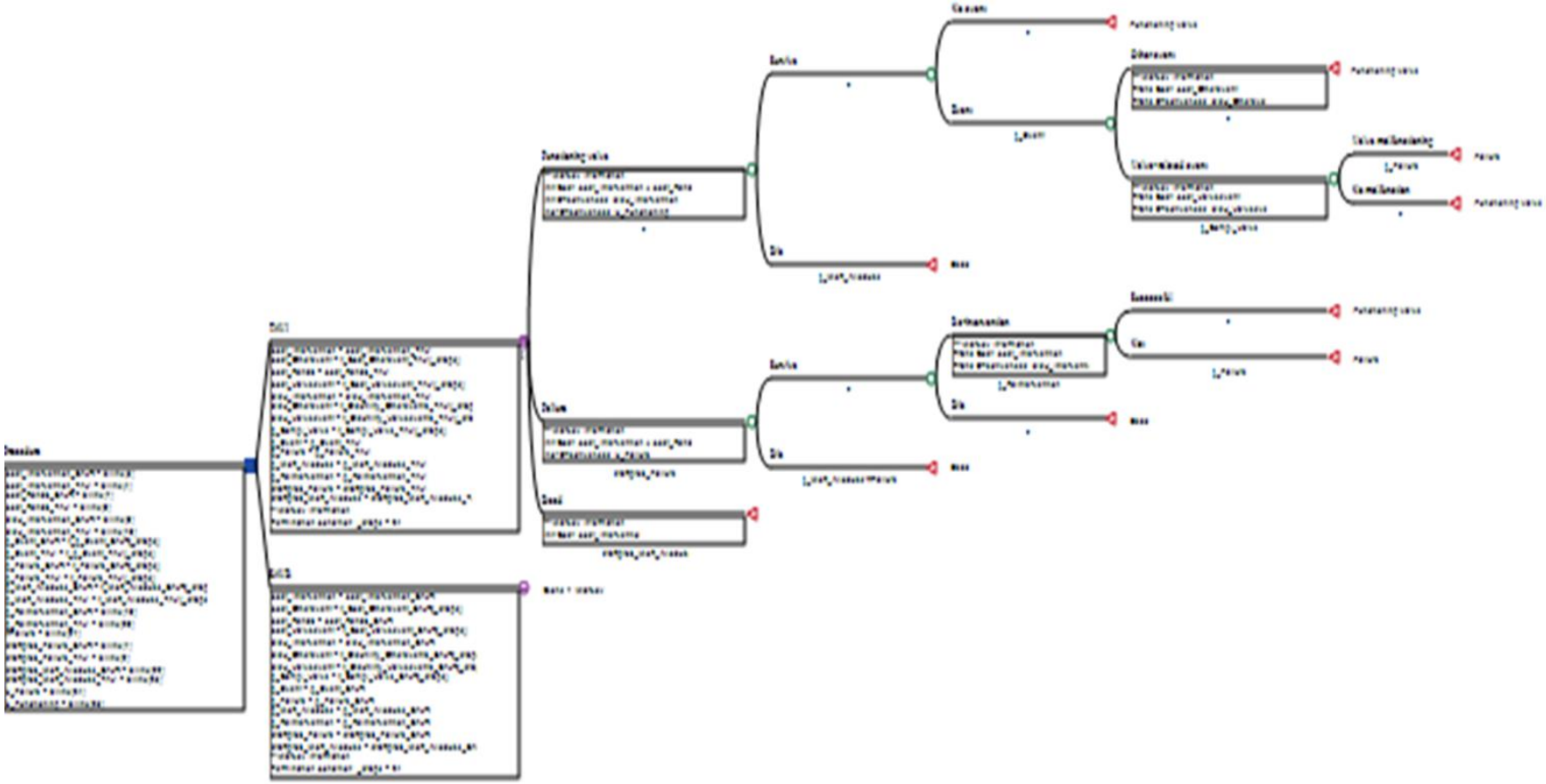
Order of appendices

Name appendices as they appear in the text:

- Model structure
- Clinical outcomes from PARTNER 2A study
- Complete tables used in the model (transition probabilities, utilities, costs)
- Survey about organisational requirements

Appendix 1. Model structure

Appendix 1. Model structure: TAVI vs. SAVR in patients with severe aorta stenosis and intermediate surgical risk



Appendix 2. Clinical outcomes from PARTNER 2A

Appendix 2. Clinical outcomes from PARTNER2A study. Source: Copy of Table from Leon et al. 2016 (3)

Table 2. Clinical End Points at 30 Days, 1 Year, and 2 Years.[a]

End Point	At 30 Days			At 1 Year			At 2 Years		
	TAVR (N=1011)	Surgery (N=1021)	P Value	TAVR (N=1011)	Surgery (N=1021)	P Value	TAVR (N=1011)	Surgery (N=1021)	P Value
	no. of patients (%)			*no. of patients (%)*			*no. of patients (%)*		
Death from any cause or disabling stroke	62 (6.1)	80 (8.0)	0.11	145 (14.5)	160 (16.4)	0.24	192 (19.3)	202 (21.1)	0.33
Death									
From any cause	39 (3.9)	41 (4.1)	0.78	123 (12.3)	124 (12.9)	0.69	166 (16.7)	170 (18.0)	0.45
From cardiac causes	33 (3.3)	32 (3.2)	0.92	70 (7.1)	77 (8.1)	0.40	97 (10.1)	104 (11.3)	0.38
Not from cardiac causes	6 (0.6)	9 (0.9)	0.41	53 (5.6)	47 (5.2)	0.71	69 (7.4)	65 (7.4)	0.98
Neurologic event									
Any event	64 (6.4)	65 (6.5)	0.94	99 (10.1)	93 (9.7)	0.76	121 (12.7)	103 (11.0)	0.25
Transient ischemic attack	9 (0.9)	4 (0.4)	0.17	23 (2.4)	16 (1.8)	0.38	34 (3.7)	20 (2.3)	0.09
Any stroke	55 (5.5)	61 (6.1)	0.57	78 (8.0)	79 (8.1)	0.88	91 (9.5)	85 (8.9)	0.67
Disabling stroke	32 (3.2)	43 (4.3)	0.20	49 (5.0)	56 (5.8)	0.46	59 (6.2)	61 (6.4)	0.83
Nondisabling stroke	23 (2.3)	18 (1.8)	0.43	30 (3.0)	24 (2.5)	0.44	33 (3.4)	27 (2.9)	0.51
Rehospitalization	64 (6.5)	62 (6.5)	0.99	142 (14.8)	135 (14.7)	0.92	183 (19.6)	156 (17.3)	0.22
Death from any cause or rehospitalization	99 (9.8)	101 (10.2)	0.78	234 (23.4)	225 (23.3)	0.97	303 (30.5)	281 (29.6)	0.67
Death from any cause, any stroke, or rehospitalization	140 (13.9)	153 (15.3)	0.37	274 (27.4)	276 (28.3)	0.64	344 (34.6)	326 (33.9)	0.75
Myocardial infarction	12 (1.2)	19 (1.9)	0.22	24 (2.5)	29 (3.0)	0.47	33 (3.6)	37 (4.1)	0.56
Major vascular complication	80 (7.9)	51 (5.0)	0.008	84 (8.4)	54 (5.3)	0.007	86 (8.6)	55 (5.5)	0.006
Life-threatening or disabling bleeding	105 (10.4)	442 (43.4)	<0.001	151 (15.2)	460 (45.5)	<0.001	169 (17.3)	471 (47.0)	<0.001
Acute kidney injury	13 (1.3)	31 (3.1)	0.006	32 (3.4)	48 (5.0)	0.07	36 (3.8)	57 (6.2)	0.02
New atrial fibrillation	91 (9.1)	265 (26.4)	<0.001	100 (10.1)	272 (27.2)	<0.001	110 (11.3)	273 (27.3)	<0.001
New permanent pacemaker	85 (8.5)	68 (6.9)	0.17	98 (9.9)	85 (8.9)	0.43	114 (11.8)	96 (10.3)	0.29
Endocarditis	0	0	—	7 (0.8)	6 (0.7)	0.84	11 (1.2)	6 (0.7)	0.22
Aortic-valve reintervention	4 (0.4)	0	0.05	11 (1.2)	4 (0.5)	0.10	13 (1.4)	5 (0.6)	0.09
Coronary obstruction	4 (0.4)	6 (0.6)	0.53	4 (0.4)	6 (0.6)	0.53	4 (0.4)	6 (0.6)	0.53

[a] All percentages are Kaplan–Meier estimates at the specific time point and thus do not equal the number of patients divided by the total number of patients in the treatment group. P values are for point-in-time comparisons.

Appendix 3. Tables for parameters used in the model

Appendix 3 Tables with monthly transition probabilities used in the model

Failure – monthly transition probability			
index	TAVI	index	SAVR
1	0,0011	1	0,0005
2	0,0011	2	0,0005
3	0,0011	3	0,0005
4	0,0011	4	0,0005
5	0,0011	5	0,0005
6	0,0011	6	0,0005
7	0,0011	7	0,0005
8	0,0011	8	0,0005
9	0,0011	9	0,0005
10	0,0011	10	0,0005
11	0,0011	11	0,0005
12	0,0002	12	0,0001
13	0,0002	13	0,0001
14	0,0002	14	0,0001
15	0,0002	15	0,0001
16	0,0002	16	0,0001
17	0,0002	17	0,0001
18	0,0002	18	0,0001
19	0,0002	19	0,0001
20	0,0002	20	0,0001
21	0,0002	21	0,0001
22	0,0002	22	0,0001
23	0,0002	23	0,0001

p_Reintervention-monthly probability			
index	TAVI	index	SAVR
1	0,0114	1	0,0001
2	0,0114	2	0,0001
3	0,0114	3	0,0001
4	0,0114	4	0,0001
5	0,0114	5	0,0001
6	0,0114	6	0,0001
7	0,0114	7	0,0001
8	0,0114	8	0,0001
9	0,0114	9	0,0001
10	0,0114	10	0,0001
11	0,0114	11	0,0001
12	0,0114	12	0,0001
13	0,0114	13	0,0001
14	0,0114	14	0,0001
15	0,0114	15	0,0001
16	0,0114	16	0,0001
17	0,0114	17	0,0001
18	0,0114	18	0,0001
19	0,0114	19	0,0001
20	0,0114	20	0,0001
21	0,0114	21	0,0001
22	0,0114	22	0,0001
23	0,0114	23	0,0001

Mortality				Mortality			
index	TAVI	index	SAVR	index	TAVI	index	SAVR
0	0,039	0	0,041	91	0,008862846	91	0,008863

1	0,008284657	1	0,00862713	92	0,008862846	92	0,008863
2	0,008284657	2	0,00862713	93	0,008862846	93	0,008863
3	0,008284657	3	0,00862713	94	0,008862846	94	0,008863
4	0,008284657	4	0,00862713	95	0,008862846	95	0,008863
5	0,008284657	5	0,00862713	96	0,008862846	96	0,008863
6	0,008284657	6	0,00862713	97	0,010248468	97	0,010248
7	0,008284657	7	0,00862713	98	0,010248468	98	0,010248
8	0,008284657	8	0,00862713	99	0,010248468	99	0,010248
9	0,008284657	9	0,00862713	100	0,010248468	100	0,010248
10	0,008284657	10	0,00862713	101	0,010248468	101	0,010248
11	0,008284657	11	0,00862713	102	0,010248468	102	0,010248
12	0,008284657	12	0,00862713	103	0,010248468	103	0,010248
13	0,004127717	13	0,00437737	104	0,010248468	104	0,010248
14	0,004127717	14	0,00437737	105	0,010248468	105	0,010248
15	0,004127717	15	0,00437737	106	0,010248468	106	0,010248
16	0,004127717	16	0,00437737	107	0,010248468	107	0,010248
17	0,004127717	17	0,00437737	108	0,010248468	108	0,010248
18	0,004127717	18	0,00437737	109	0,011826952	109	0,011827
19	0,004127717	19	0,00437737	110	0,011826952	110	0,011827
20	0,004127717	20	0,00437737	111	0,011826952	111	0,011827
21	0,004127717	21	0,00437737	112	0,011826952	112	0,011827
22	0,004127717	22	0,00437737	113	0,011826952	113	0,011827
23	0,004127717	23	0,00437737	114	0,011826952	114	0,011827
24	0,004127717	24	0,00437737	115	0,011826952	115	0,011827
25	0,004931412	25	0,004931	116	0,011826952	116	0,011827
26	0,004931412	26	0,004931	117	0,011826952	117	0,011827
27	0,004931412	27	0,004931	118	0,011826952	118	0,011827
28	0,004931412	28	0,004931	119	0,011826952	119	0,011827
29	0,004931412	29	0,004931	120	0,011826952	120	0,011827
30	0,004931412	30	0,004931	121	0,013771111	121	0,013771
31	0,004931412	31	0,004931	122	0,013771111	122	0,013771
32	0,004931412	32	0,004931	123	0,013771111	123	0,013771
33	0,004931412	33	0,004931	124	0,013771111	124	0,013771
34	0,004931412	34	0,004931	125	0,013771111	125	0,013771
35	0,004931412	35	0,004931	126	0,013771111	126	0,013771
36	0,004931412	36	0,004931	127	0,013771111	127	0,013771
37	0,005587999	37	0,005588	128	0,013771111	128	0,013771
38	0,005587999	38	0,005588	129	0,013771111	129	0,013771
39	0,005587999	39	0,005588	130	0,013771111	130	0,013771
40	0,005587999	40	0,005588	131	0,013771111	131	0,013771
41	0,005587999	41	0,005588	132	0,013771111	132	0,013771

42	0,005587999	42	0,005588	133	0,015298466	133	0,015298
43	0,005587999	43	0,005588	134	0,015298466	134	0,015298
44	0,005587999	44	0,005588	135	0,015298466	135	0,015298
45	0,005587999	45	0,005588	136	0,015298466	136	0,015298
46	0,005587999	46	0,005588	137	0,015298466	137	0,015298
47	0,005587999	47	0,005588	138	0,015298466	138	0,015298
48	0,005587999	48	0,005588	139	0,015298466	139	0,015298
49	0,005979267	49	0,005979	140	0,015298466	140	0,015298
50	0,005979267	50	0,005979	141	0,015298466	141	0,015298
51	0,005979267	51	0,005979	142	0,015298466	142	0,015298
52	0,005979267	52	0,005979	143	0,015298466	143	0,015298
53	0,005979267	53	0,005979	144	0,015298466	144	0,015298
54	0,005979267	54	0,005979	145	0,017178231	145	0,017178
55	0,005979267	55	0,005979	146	0,017178231	146	0,017178
56	0,005979267	56	0,005979	147	0,017178231	147	0,017178
57	0,005979267	57	0,005979	148	0,017178231	148	0,017178
58	0,005979267	58	0,005979	149	0,017178231	149	0,017178
59	0,005979267	59	0,005979	150	0,017178231	150	0,017178
60	0,005979267	60	0,005979	151	0,017178231	151	0,017178
61	0,007215578	61	0,007216	152	0,017178231	152	0,017178
62	0,007215578	62	0,007216	153	0,017178231	153	0,017178
63	0,007215578	63	0,007216	154	0,017178231	154	0,017178
64	0,007215578	64	0,007216	155	0,017178231	155	0,017178
65	0,007215578	65	0,007216	156	0,017178231	156	0,017178
66	0,007215578	66	0,007216	157	0,019559486	157	0,019559
67	0,007215578	67	0,007216	158	0,019559486	158	0,019559
68	0,007215578	68	0,007216	159	0,019559486	159	0,019559
69	0,007215578	69	0,007216	160	0,019559486	160	0,019559
70	0,007215578	70	0,007216	161	0,019559486	161	0,019559
71	0,007215578	71	0,007216	162	0,019559486	162	0,019559
72	0,007215578	72	0,007216	163	0,019559486	163	0,019559
73	0,007944157	73	0,007944	164	0,019559486	164	0,019559
74	0,007944157	74	0,007944	165	0,019559486	165	0,019559
75	0,007944157	75	0,007944	166	0,019559486	166	0,019559
76	0,007944157	76	0,007944	167	0,019559486	167	0,019559
77	0,007944157	77	0,007944	168	0,019559486	168	0,019559
78	0,007944157	78	0,007944	169	0,020200534	169	0,020201
79	0,007944157	79	0,007944	170	0,020200534	170	0,020201
80	0,007944157	80	0,007944	171	0,020200534	171	0,020201
81	0,007944157	81	0,007944	172	0,020200534	172	0,020201
82	0,007944157	82	0,007944	173	0,020200534	173	0,020201

83	0,007944157	83	0,007944	174	0,020200534	174	0,020201
84	0,007944157	84	0,007944	175	0,020200534	175	0,020201
85	0,008862846	85	0,008863	176	0,020200534	176	0,020201
86	0,008862846	86	0,008863	177	0,020200534	177	0,020201
87	0,008862846	87	0,008863	178	0,020200534	178	0,020201
88	0,008862846	88	0,008863	179	0,020200534	179	0,020201
89	0,008862846	89	0,008863	180	0,020200534	180	0,020201
90	0,008862846	90	0,008863				

	Probability of experiencing other complications	
Cycle	TAVI	SAVR
Cycle 0 (30 days)	0,244	0,425
Beyond 30 days	0,002	0,005

	Probability of experiencing valve-related complications (conditional, used in Markov)	
Cycle	TAVI	SAVR
Cycle 0 (30 days)	0,4883	0,5446
Beyond 30 days	0,8581	0,4231
	Probability of experiencing valve-related complications	
Cycle	TAVI	SAVR
Cycle 0 (30 days)	0,2328	0,5083
Beyond 30 days	0,0092	0,0034

	Probability of experiencing any complication	
Cycle	TAVI	SAVR
Cycle 0 (30 days)	0,4768	0,9333
Beyond 30 days	0,0108	0,0081

	TAVI	SAVR

Cycle / Transition probability	Cycle 0 (30 days)	Beyond 30 days	Cycle 0 (30 days)	Beyond 30 days
Probability of experiencing any complication	0,4768	0,0108	0,9333	0,0081

	Cost of experiencing valve-related complication in NOK	
Cycle	TAVI	SAVR
Cycle 0 (30 days)	20 766	7 547
Beyond 30 days	45 174	42 519

	Cost of experiencing other complication in NOK	
Cycle	TAVI	SAVR
Cycle 0 (30 days)	33 539	30 349
Beyond 30 days	48 358	41 761

	Disutility of experiencing other complication in QALYs	
Cycle	TAVI	SAVR
Cycle 0 (30 days)	-0,1947	-0,1414
Beyond 30 days	-0,1417	-0,1691

	Disutility of experiencing valve-related complication in QALYs	
Cycle	TAVI	SAVR
Cycle 0 (30 days)	-0,0434	-0,0497
Beyond 30 days	-0,0679	-0,0975

Valve-related complication	**Probability at 30-days**		**Weight**		**Weighted cost**	
	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR

Major vascular complications	0,079	0,05	0,34	0,10	4 258	1 235
Life threatening bleeding	0,104	0,434	0,45	0,85	1 862	3 560
Valve endocarditis	0	0	0	0	0	0
Moderate or severe paravalvular leak	0,038	0,005	0,16	0,04	11 899	761
Myocardial infraction	0,012	0,019	0,05	0,04	2 746	1 992
TOTAL at 30-days	**0,233**	**0,508**	**1,00**	**1,00**	**20 766**	**7 547**
Valve-related complication	**Probability at 2-years**		**Weight**		**Weighted cost**	
	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR
Major vascular complications	0,007	0,005	0,04	0,07	458	828
Life threatening bleeding	0,069	0,036	0,36	0,47	1 498	1 979
Valve endocarditis	0,012	0,007	0,06	0,09	6 052	18 620
Moderate or severe paravalvular leak	0,08	0,006	0,42	0,08	30 506	5 635
Myocardial infraction	0,024	0,022	0,13	0,29	6 661	15 458
TOTAL – beyond 30 days	**0,192**	**0,076**	**1,00**	**1,00**	**51 730**	**42 519**

Other complication	**Probability at 30-days**		**Weight**		**Weighted cost**	
	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR
Pacemaker implantation	0,085	0,069	0,35	0,16	9 002	4 195
Stroke	0,055	0,061	0,23	0,14	13 352	8 502
Acute kidney injury	0,013	0,031	0,05	0,07	3 297	4 514
New-onset atrial fibrillation	0,091	0,264	0,37	0,62	7 888	13 137
TOTAL at 30-days	**0,244**	**0,425**	**1,00**	**1,00**	**33 539**	**30 349**
	Probability at 2-years		**Weight**		**Weighted cost**	
	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR
Pacemaker implantation	0,118	0,103	0,42	0,20	29 312	13 521

Stroke	0,0095	0,089	0,03	0,17	2 021	10 004
Acute kidney injury	0,038	0,062	0,14	0,12	8 444	7 281
New-onset atrial fibrillation	0,113	0,273	0,41	0,52	8 581	10 956
TOTAL – beyond 30 days	**0,279**	**0,527**	**1,00**	**1,00**	**48 358**	**41 761**

Parameters in the sensitivity analysis

Parameter	**Name of parameter in the model**	**Root definition**	**Minimum inference**	**Maximum inference**
Probability of treatment failure TAVI	prob_Failure_TAVI	0,0287	0,0196	0,0415
Probability of treatment failure SAVR	prob_Failure_SAVR	0,0078	0,0037	0,0160
Probability of an adverse event following TAVI	prob_Event_TAVI	0,477	0,4460	0,5075
Probability of an adverse event following SAVR	prob_Event_SAVR	0,933	0,9181	0,9487
Probability of having a valve-related complication TAVI	prob_Compl_Valve_TAVI	0,488	0,3418	0,6348
Probability of having a valve-related complication SAVR	prob_Compl_Valve_SAVR	0,545	0,3812	0,7080
Probability of having a new intervention following TAVI	p_Reintervention_TAVI	0,01142	0,00800	0,01485
Probability of having a new intervention following SAVR	p_Reintervention_SAVR	0,0001	0,00007	0,00013
Mortality hazard ration for patients living with valve failure	rrDeath_Failure	1,5	1,05	1,95

Monthly utility of functioning valve following TAVI	u_Functioning_TAVI	0,062	0,0583	0,0642
Monthly utility of functioning valve following SAVR	u_Functioning_SAVR	0,057	0,0533	0,0600
Monthly utility when living with valve failure	u_Failure	0,055	0,0383	0,0717
Disutility of having TAVI procedure	disU_Intervention_TAVI	0,00525	0,0037	0,0068
Disutility of having SAVR procedure	disU_Intervention_SAVR	0,027	0,0189	0,0351
Disutility of having a valve complication following TAVI	disU_Valveevent_TAVI	0,0434	0,03038	0,05642
Disutility of having a valve complication following SAVR	disU_Valveevent_SAVR	0,0496	0,03479	0,06461
Disutility of having other complication following TAVI	disU_Otherevent_TAVI	0,1947	0,13629	0,25312
Disutility of having other complication following SAVR	disU_Otherevent_SAVR	0,1413	0,09898	0,18381
Procedure costs TAVI	cost_Intervention_TAVI	369 765	258 836	480 695
Procedure costs SAVR	cost_Intervention_SAVR	259 802	181 861	337 743
Rehabilitation costs TAVI	cost_Rehab_TAVI	29 138	20 397	37 880
Rehabilitation costs TAVI	cost_Rehab_SAVR	67 960	47 572	88 347

Appendix 4. Survey about organisational aspects

Appendix 4. Survey about organisational consequences

Organisatoriske konsekvenser (TAVI)

1. Hvor mange pasienter fikk TAVI ved sykehusene i regionen i 2015, 2016 og 2017?
2. Hvordan selekterer dere i dag pasientene som skal ha TAVI?
3. Beskriv hvor mye radiologi og ekkokardiografi blir brukt.
4. Hvilken type hjerteklaffer (både TAVI og SAVR) blir benyttet i regionen (ved de enkelte sykehusene) i dag?
5. Brukes hybrid operasjonsstue eller hjertelaboratorium ved å utføre TAVI per i dag?
6. Hvilken kapasitet har dere i dag med hensyn til operasjonsstuer?
7. Vil en utvidelse av indikasjonen for TAVI medføre organisatoriske konsekvenser for deres sykehus og eventuelt hvilke (investeringsbehov utstyr og bygninger (etablering av spesialrom), behov for personale med spesialkompetanse, opplæring, antall sykehus som utfører TAVI, endret behov for oppfølging i sykehus og primærhelsetjeneste)?
8. Foreligger det resultater fra, pågår det, eller er det planlagt relevante forskningsprosjekter i regionen/sykehuset?

(SAVR: Surgical aortic valve replacement)

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