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HEALTH TECHNOLOGY ASSESSMENT:
Transcatheter aortic valve implantation (TAVI) versus surgical aortic valve replacement (SAVR) for patients with severe aortic stenosis and low surgical risk and across surgical risk groups

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Table of contents

Key messages

In August 2019 the Ordering Forum Regional Health Authority commissioned the Norwegian Institute of Public Health (NIPH) to perform a health technology assessment of transcatheter aortic valve implantation/ replacement (TAVI/TAVR) compared with surgical aortic valve replacement (SAVR) in patients with severe aortic stenosis across surgical risk groups.

We conducted an overview of systematic reviews that included the two newest randomised trials on TAVI in low risk group published in May 2019. We included 15 systematic reviews (2 covering all risk groups, 11 the low risk group, and 2 the intermediate and low risk groups). Based on evidence from eight randomised trials, we conclude that TAVI compared with SAVR in patients with severe aortic stenosis across all surgical risk groups:

- probably improves all-cause mortality or disabling stroke up to two years
- may slightly reduce major bleeding, new-onset fibrillation and acute kidney injury
- probably increases transient ischemic attacks, major vascular complications, permanent pacemaker implantation, re-intervention and paravalvular leak
- may make little or no difference for all-cause and cardiovascular mortality, myocardial infarction and stroke at long-term follow-up.

Health economic analysis was limited to the low surgical risk group, as the intermediate risk group was evaluated in a 2019 NIPH report. The cost-utility analysis in a lifetime perspective indicated that TAVI was more effective (gain of 0.05 QALYs) and less costly (saving of NOK 35 000) than SAVR for patients with severe aortic stenosis at low surgical risk. The analysis is based on 1-year follow-up data from the PARTNER 3 study and long-term mortality and adverse events for TAVI and SAVR beyond this period remain unclear. The results are sensitive to variations in procedure costs.

The budget impact analysis indicates that the introduction of TAVI for low risk patients is likely to be cost-neutral in the short run. We have not accounted for the costs of the capacity expanding.

Title:
Transcatheter aortic valve implantation (TAVI) versus surgical aortic valve replacement (SAVR) for patients with severe aortic stenosis and low surgical risk and across surgical risk groups: a health technology assessment

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Type of publication:

Health Technology Assessment
A health technology assessment provides an evidence-base for decision makers, which systematically evaluates research on the effect and safety of measures in the health service. HTAs may include economic, ethical, social, organizational or legal consequences.

Doesn't answer everything:

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

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Executive summary (English)

Background

Heart failure due to aortic stenosis is an increasing health problem with increasing age, and hence in an aging society. In general, medical therapy does not treat severe aortic stenosis, but may be used to optimise blood flow and to alleviate symptoms in patients with symptomatic severe aortic stenosis. Therefore, until a few years ago, surgical treatment was the treatment of choice for patients with severe aortic stenosis. This changed with the introduction of transcatheter aortic valve implantation (TAVI), deploying a bioprosthesis in the aortic valve using a catheter. In contrast to traditional open-heart surgery or surgical aortic valve replacement, the procedure is less invasive and can be performed with light sedation and without cardiopulmonary bypass. With increasing clinical use and established effect and safety for TAVI in patients with severe aortic stenosis at high/intermediate surgical risk, the focus of TAVI producers shifted to patients at low surgical risk. In August 2019, in light of two newly completed RCTs including patients with severe aortic stenosis at low surgical risk, the Ordering Forum RHA commissioned the Norwegian Institute of Public Health to perform an assessment across all risk groups.

Objective

The objective of this health technology assessment is to update and summarise current knowledge on effectiveness and safety with transcatheter aortic valve implantation/ replacement (TAVI/TAVR) compared with surgical aortic valve replacement (SAVR) in the treatment of patients with severe aortic stenosis across surgical risk groups, including patients with severe aortic stenosis and high surgical risk.

The aim of the health economic evaluation is to assess the cost-effectiveness and budget impact of TAVI for patients with severe aortic stenosis and low surgical risk compared with open surgery and to evaluate the intervention against the priority setting criteria applicable in Norway. This information will supplement the 2019 report on the intermediate risk group.

Method

We conducted an overview of systematic reviews guided by the methodology handbook used at the Division for Health Services at the Norwegian Institute of Public Health. We excluded reviews published before April 2019, before the publication of the newest studies on patients with low surgical risk. We assessed the quality of identified systematic reviews with a 9-point checklist from our methodology handbook. We reported on the most updated reviews of acceptable quality, and communicated their findings, including GRADE assessment of the confidence in the effect estimates; both across all risk groups and for the low risk group specifically.

We narratively summarised the findings of our earlier reports and supplemented our former findings with the newly identified literature where possible and relevant.

In the economic evaluation, we performed a cost-utility analysis (CUA) comparing TAVI with open surgery for patients at low surgical risk, where we accounted for all relevant cost and health outcomes related to both procedures. The costs were expressed in 2020 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 ® 2020. 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), and its recommendations related to quantification of the severity criterion, we estimated absolute shortfall for patients with severe aortic stenosis and low 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 extending TAVI as a routine treatment onto patients with severe aortic stenosis and lower risk groups.

Results

Of the 78 identified references, we assessed all titles and abstracts against the inclusion criteria and considered 15 as possibly relevant. We assessed the quality of all 15 reviews. The reviews cover a total of eight randomised trials, including the two most recent trials on patients with low surgical risk published in 2019.

Based on evidence from eight randomised trials captured in several systematic reviews, we conclude that TAVI compared with SAVR in patients with severe aortic stenosis across all surgical risk groups

- probably improves all-cause mortality or disabling stroke up to two years
- may slightly reduce major bleeding, new-onset fibrillation and acute kidney injury
- probably increases transient ischemic attacks, major vascular complications, permanent pacemaker implantation, re-intervention and paravalvular leak
- may make little or no difference for all-cause and cardiovascular mortality, myocardial infarction and stroke at long-term follow-up.

The results of the cost-utility analysis in the base-case scenario show that TAVI for patients at low risk is associated with a higher QALY-gain (incremental QALY 0.05) and lower cost (incremental costs – NOK 35 000) when compared to surgical aortic valve replacement (SAVR). These results are most sensitive to changes in estimates of the procedure costs.

The expansion of use of TAVI onto patients with lower surgical risk is likely to be cost-neutral in the short run. This expansion would imply a doubling in the numbers of TAVI procedures performed within the next five years. The costs of the capacity expanding were not included in the analyses.

The calculated absolute shortfall for patients with severe aortic stenosis and low surgical risk is equal to 2 QALYs.

Conclusion

Based on available evidence from eight RCTs, captured in several systematic reviews, we conclude that for patients with severe aortic stenosis across all surgical risk groups TAVI compared with SAVR probably improves all-cause mortality or disabling stroke up until 2 years. TAVI may slightly reduce incidences of major bleeding, new-onset fibrillation, and acute kidney injury. On the other hand, TAVI probably increases the incidence of transient ischemic attacks, major vascular complications, permanent pacemaker implantation, reintervention, and paravalvular leak. Moderate-quality evidence suggests that TAVI may make little or no difference for the incidences of all-cause and cardiovascular mortality, myocardial infarction, and stroke after two years; based on the limited long-term data. The clinical decision for either option may benefit from a broader evaluation of the patient's medical state and their life expectancy due to uncertainty regarding long term effects.

The results of our cost-utility analysis based on 1-year follow-up data from the PARTNER 3 study indicate, that TAVI for patients at low surgical risk is slightly more effective (0.05 QALYs gained) and less costly (saving of NOK 35 000) than SAVR. The results are sensitive to variations in procedure costs. The budget impact analysis indicated that the extension of use of TAVI to patients at low surgical risk is likely to be cost-neutral in the short run.

The calculated absolute shortfall for patients with severe aortic stenosis and low surgical risk relative to their age cohort in the general population is equal to 2 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.

Hovedbudskap

Bestillerforum RHF ga i august 2019 Folkehelseinstituttet (FHI) i oppdrag å metodevurdere kateterbasert implantasjon av aortaklaffer (TAVI) sammenlignet med kirurgisk utskifting av aortaklaff (SAVR) for pasienter med alvorlig aortastenose på tvers av risikogrupper.

Vi utarbeidet en oversikt over systematiske oversikter som inkluderte de to nyeste randomiserte studiene om pasienter med lav kirurgisk risiko publisert i mai 2019. Vi identifiserte 15 systematiske oversikter (to på tvers av risikogrupper, 11 om lav risiko og to om intermediær og lav risiko; åtte randomiserte studier). På tvers av kirurgiske risikogrupper konkluderer vi at TAVI sammenlignet med SAVR hos pasienter med alvorlig aortastenose:

- sannsynligvis reduserer totaldødelighet og risiko for alvorlig hjerneslag inntil to år
- muligens reduserer forekomst av større blødninger, nyoppstått atrieflimmer og akutt nyreskade
- sannsynligvis øker risiko for transitorisk iskemisk anfall, vaskulære komplikasjoner, permanent pacemakerimplantasjon, reintervensjon og klaffelekkasje
- muligens gir liten eller ingen forskjell i kardiovaskulær dødelighet, hjerteinfarkt og hjerneslag ved langvarig oppfølging.

Kostnadseffektivitetsanalysen ble begrenset til gruppen med lav kirurgisk risiko ettersom andre risikogrupper er vurdert i tidligere rapporter. Kostnadseffektivitetsanalysen indikerte at TAVI var marginalt mer effektiv (en gevinst på 0,05 kvalitetsjusterte leveår, QALYs) og mindre kostbar (besparelse på 35 000 NOK) enn SAVR for pasienter med alvorlig aortastenose og lav kirurgisk risiko. Analysen er basert på ett års oppfølgingsdata fra PARTNER 3-studien. Langtidsdødelighet og bivirkninger for TAVI og SAVR utover denne perioden er fortsatt uklare. Resultatene er følsomme for variasjoner i prosedyrekostnader.

Analysen av budsjettsmessige konsekvenser indikerte at innføring av TAVI for pasienter med lav risiko sannsynligvis vil være kostnadsnøytral på kort sikt. Vi har ikke beregnet kostnadene ved å utvide behandlingskapasiteten.

Tittel:

Kateterbasert implantasjon av aortaklaffer (TAVI) versus kirurgisk utskifting av aortaklaffer for pasienter med alvorlig aortastenose med lav risiko og på tvers av risikogrupper

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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. En metotodevurdering kan også inneholde helseøkonomisk evaluering, vurdering av konsekvenser for etikk, jus, organisasjon eller sosiale forhold

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Svarer ikke på alt:

- Ekskluderer studier som faller utenfor inklusjonsskriteriene
- Ingen anbefalinger

Utgiver:

Folkehelseinstituttet

Når ble litteratursøket utført?

Søk etter studier ble avsluttet i juli 2020.

Eksterne fagfeller:

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Sammendrag

Innledning

Hjertesvikt på grunn av aortastenose er et økende helseproblem med økende alder, og dermed i et aldrende samfunn. Medisinsk behandling kan ikke helbrede pasienter med alvorlig aortastenose, men kan brukes til å forbedre blodstrømmen for å lindre symptomene. Åpen klaffekirurgi var inntil nylig den eneste behandlingen, men dette endret seg med introduksjonen av transkateter aortaklaffimplantasjon (TAVI) der man plasserer en bioprotese i aortaklaffen ved hjelp av et kateter. I motsetning til tradisjonell åpen hjertekirurgi med kirurgisk utskifting av aortaklaffen, er fremgangsmåten mindre invasiv og kan utføres med lett sedering og uten hjerte-lungemaskin. Med økende klinisk bruk og etablert effekt og sikkerhet for TAVI hos pasienter med alvorlig aortastenose og høy/ intermediær kirurgisk risiko, rettet TAVI-produsentene oppmerksomheten mot pasienter med lav kirurgisk risiko. I august 2019, i lys av to nylig publiserte randomiserte studier, som kun inkluderte pasienter med alvorlig aortastenose og lav kirurgisk risiko, ga Bestillerforum RHF FHI i oppdrag å metodevurdere TAVI for pasienter med alvorlig aortastenose på tvers av alle risikogrupper.

Mål

Målet med denne metodevurderingen er å oppdatere og oppsummere eksisterende kunnskap om effekt og sikkerhet ved kateterbasert implantasjon av aortaklaffer (TAVI/ TAVR) sammenliknet med åpen klaffekirurgi (SAVR) i behandlingen av pasienter med alvorlig aortastenose på tvers av risikogrupper.

Målet med den helseøkonomiske evalueringen er å vurdere kostnadseffektiviteten og budsjettvirkningen av TAVI sammenlignet med åpen kirurgi for pasienter med alvorlig aortastenose og lav kirurgisk risiko, og å vurdere TAVI opp mot prioriteringskriteriene som gjelder i Norge. Denne informasjonen vil supplere vår helseøkonomiske vurdering fra 2019 om TAVI versus SAVR for pasienter med intermediær kirurgisk risiko.

Metode

Vi utarbeidet en oversikt over systematiske oversikter basert på vår metodebok. Vi ekskluderte oversikter publisert før april 2019, før publiseringen av de nyeste studiene som kun inkluderte pasienter med lav kirurgisk risiko. Vi vurderte kvaliteten for systematiske oversiktene med en 9-punkts sjekkliste fra vår metodebok. Vi rapporterte de mest oppdaterte oversiktene av pålitelig kvalitet, og formidlet deres funn, inkludert GRADE-vurdering av tilliten til effektestimatene.

I den økonomiske evalueringen utførte vi en kostnadseffektivitetsanalyse (cost-utility

analysis, CUA), der vi sammenlignet TAVI med åpen kirurgi for pasienter med alvorlig aortastenose og lav kirurgisk risiko. Vi inkluderte alle relevante kostnads- og helseresultater knyttet til begge prosedyrene. Kostnadene ble uttrykt i 2020 norske kroner (NOK), og effekter i kvalitetsjusterte leveår (QALY). Resultatene ble uttrykt som gjennomsnittlig inkrementell kostnadseffektivitets ratio (ICER). Markov-modellen ble utviklet og analysert i TreeAge Pro ® 2020. Usikkerheten i modellparametere ble håndtert ved å utføre probabilistiske sensitivitetsanalyser (PSA). Analysene ble utført fra helsevesenets perspektiv. Både kostnader og effekter ble neddiskontert med en årlig diskonteringsrente på 4 %.

I samsvar med Stortingsmeldingen om prioritering, (Meld. St. 34 2015–2016), og dens anbefalinger knyttet til kvantifisering av alvorlighetsgraden, estimerte vi absolutt prognosetap for pasienter med alvorlig aortastenose og lav kirurgisk risiko. Med utgangspunkt i registerdata om utvikling av TAVI bruk i Norge og kostnadsdata hentet fra Markov-modellen, beregnet vi sannsynlige budsjettmessige konsekvenser av å utvide tilbudet om TAVI til rutinebehandling for pasienter med alvorlig aortastenose og lav kirurgisk risiko.

Resultat

Av de 78 identifiserte referansene vurderte vi alle titler og sammendrag opp mot inklusjonskriteriene og anså 15 som relevante. Vi kvalitetsvurderte alle 15 oversiktene. Oversiktene omfattet til sammen åtte randomiserte.

Basert på tilgjengelig dokumentasjon fra åtte randomiserte studier konkluderer vi at på tvers av alle kirurgiske risikogrupper så vil TAVI sammenlignet med SAVR hos pasienter med alvorlig aortastenose:

- sannsynligvis reduserer totaldødelighet og risiko for alvorlig hjerneslag inntil to år
- muligens reduserer risiko for større blødninger, nyoppstått atrieflimmer og akutt nyreskade
- sannsynligvis øker risiko for transitorisk iskemisk anfall, store vaskulære komplikasjoner, permanent pacemakerimplantasjon, reintervensjon og klaffelekkasje
- muligens gir liten eller ingen forskjell i kardiovaskulær dødelighet, hjerteinfarkt og hjerneslag ved langvarig oppfølging

Kostnadseffektivitetsanalysen viser at TAVI for pasienter med lav risiko gir høyere QALY-gevinst (gevinst på 0,05 kvalitetsjusterte leveår) og lavere kostnad (inkrementelle kostnader - 35 000 NOK) sammenlignet med kirurgisk utskifting av aortaklaffen (SAVR). Sensitivitetsanalyser viste at prosedyrekostnadsestimater hadde størst innvirkning på resultatene.

Utvidelse av tilbud om TAVI til pasienter med lav kirurgisk risiko vil sannsynligvis være kostnadsnøytral på kort sikt, og vil innebære dobling i antall TAVI-prosedyrer i løpet av de neste fem årene. Vi inkluderte ikke kostnadene ved kapasitetsutvidelsen i analysene.

Beregnet absolutt prognosetap for pasienter med alvorlig aortastenose og lav kirurgisk risiko er to kvalitetsjusterte leveår.

Konklusjon

Åtte randomiserte studier viser at for pasienter med alvorlig aortastenose vil TAVI sammenlignet med SAVR sannsynligvis redusere totaldødelighet og risiko for alvorlig hjerneslag i inntil to år – dette gjelder uavhengig av kirurgisk risiko. TAVI kan muligens redusere forekomst av større blødninger, nyoppstått atrieflimmer og akutt nyreskade. På den annen side øker TAVI sannsynligvis risiko for transitoriske iskemiske anfall, store vaskulære komplikasjoner, permanent pacemakerimplantasjon, reintervensjon og klaffelekkasje. Dokumentasjon av moderat kvalitet antyder at TAVI muligens gir liten eller ingen forskjell i kardiovaskulær dødelighet, hjerteinfarkt og hjerneslag etter to år. Bred vurdering av pasientens medisinske tilstand og forventet levealder er viktig i den kliniske beslutningen om TAVI versus SAVR for pasienter med lav kirurgisk risiko på grunn av usikkerheten om langtidseffektene.

Kostnadseffektivitetsanalyser basert på 1-års resultatene fra PARTNER 3 - studien viser at TAVI for pasienter med aortastenose og lav kirurgisk risiko gir noe høyere helsegevinst (gevinst på 0,05 kvalitetsjusterte leveår, QALYs) til noe lavere kostnad (besparelser på 35 000 norske kroner) sammenlignet med SAVR. Variasjon i kostnadsestimatene til prosedyrer har størst påvirkning på robustheten i resultatene.

Absolutt prognosetap for pasienter med alvorlig aortastenose og lav risiko som mottar standard behandling ble beregnet til 2.0 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

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. $ICER = \frac{Cost_{\text{intervention}} - Cost_{\text{comparator}}}{Effect_{\text{intervention}} - Effect_{\text{comparator}}} = \frac{\Delta C}{\Delta E}$
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.
HRQoL	**Health-related quality of life**
NHB	**Net Health Benefit.** In a decision-making process, a positive NHB suggests that the intervention represents good value for money $NHB = \Delta E - \frac{\Delta C}{\lambda}$, λ – cost-effectiveness threshold
NMB	**Net Monetary Benefit.** In a decision-making process, a positive NMB suggests that the intervention represents good value for money. $NMB = \lambda \cdot \Delta E - \Delta C$
NIPH	Norwegian Institute of Public Health
Odds	The odds of an event happening is defined as a measure of the likelihood that an event will occur, expressed as the ratio of the number of people incurring an event to the number of people who don't have the event.
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 assuming that the null hypothesis is true (no difference between groups).
SAVR	Surgical aortic valve replacement
TAVI / TAVR	Transcatheter aortic valve implantation / transcatheter aortic valve replacement
TIA	Transient ischemic attack
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).

Preface

The Ordering Forum RHF commissioned in August 2019, through the National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway, the Norwegian Institute of Public Health (NIPH) to perform a health technology assessment of transcatheter aortic valve implantation/replacement (TAVI/TAVR) compared with surgical aortic valve replacement (SAVR) in the treatment of patients with severe aortic stenosis across risk groups.

The report is intended to help decision-makers in the specialist health service to make well-informed decisions. The National Institute of Public Health follows a standard procedure in the work with systematic reviews, described in the handbook «Slik oppsummerer vi forskning». This means, among other things, that we can use standard formulations when describing methods, results and the discussion of the findings.

The authors certify that they have no affiliations with or involvement in any organisation or entity with any financial or non-financial interest in the subject matter or materials discussed in this review. In addition, consulted experts have declared no conflict of interest.

The Norwegian Institute of Public Health thanks Gry Dahle, Øyvind Bleie, and Reidar Bjørnerheim who have supported this project with peer reviews, as well as Eline Aas for peer-reviewing our health economic model. The authors thank Olav Asserson for reviewing the draft from a patient's perspective as well as sharing his personal experience. The authors also thank their colleagues Martin Lerner and Per Vandvik who have supported this project with their constructive feedback. The Norwegian Institute of Public Health assumes final responsibility for the content of this report.

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1- Introduction

Heart failure due to aortic stenosis is an increasing health problem with increasing age, and hence in an aging society (1, 2). In general, medical therapy does not cure severe aortic stenosis, but may be used to optimise blood flow and to alleviate symptoms in patients with symptomatic severe aortic stenosis. Therefore, until only a few years ago, surgical treatment was the treatment of choice. This changed with the introduction of the transcatheter aortic valve implantation (TAVI) method, also referred to as transcatheter aortic valve replacement (TAVR), a bioprosthesis deployed in the aortic valve using a catheter. In contrast to traditional open-heart surgery or surgical aortic valve replacement (SAVR), the procedure is less invasive and can be performed with light sedation and without cardiopulmonary bypass. Exhaustive background information can be found in the EUnetHTA report (3).

The effect and safety of TAVI in comparison to SAVR was initially established in patients at high surgical risk (based on the Society of Thoracic Surgeons Predicted Risk of Mortality (STS) score > 8 -15%) (4). For many years, TAVI has been the endorsed form of treatment for patients at high surgical risk. Evidence supporting this came from two large industry funded clinical trials in high-risk patients (5, 6). The Norwegian Institute of Public Health (NIPH) published a summary of these findings in 2012 (7). The report concluded that TAVI can increase quality of life and survival in selected non-operative patients with severe aortic stenosis, based on limited documentation.

With progressive clinical use and established effect and safety for TAVI in high-risk patients, the TAVI producers shifted their focus to patients with intermediate surgical risk (STS score 4–8%). The two dominant manufacturers, Edwards Lifesciences and Medtronic, conducted clinical trials to assess the effect and safety for this patient group (8, 9).

The Ordering Forum RHA (Bestillerforum RHF) on 14.11.2016 commissioned the Norwegian Institute of Public Health (NIPH) to conduct a single technology assessment, based on a horizon scan from NIPH, and then changed this to a full HTA 24.04.2017. In 2018, the NIPH, in cooperation with EUnetHTA, published a report describing the non-inferiority of TAVI in the intermediate risk population compared to SAVR (3). NIPH also published a supplementary health economic assessment (10).

Use of TAVI is on the rise in Norway; from 2017 onwards, there have been more TAVI procedures than open-heart surgeries for aortic stenosis (Figure 1 and 2). Data from the Norwegian register for cardiac surgery shows that this increase is associated with an absolute increase of aortic valve interventions since 2015 (11).

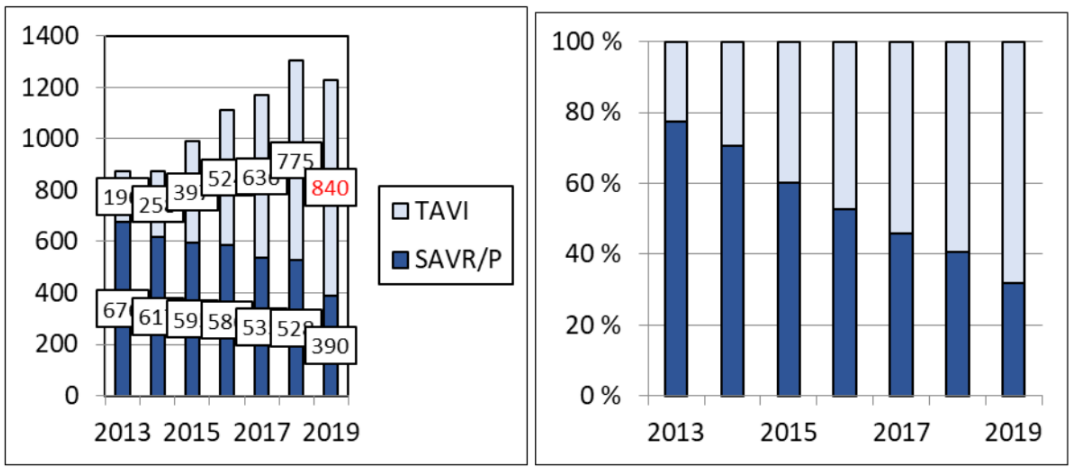


Figure 1 TAVI/SAVR performed in Norway expressed in absolute- (left) and relative numbers (right graph), Norwegian registry for cardiac surgery

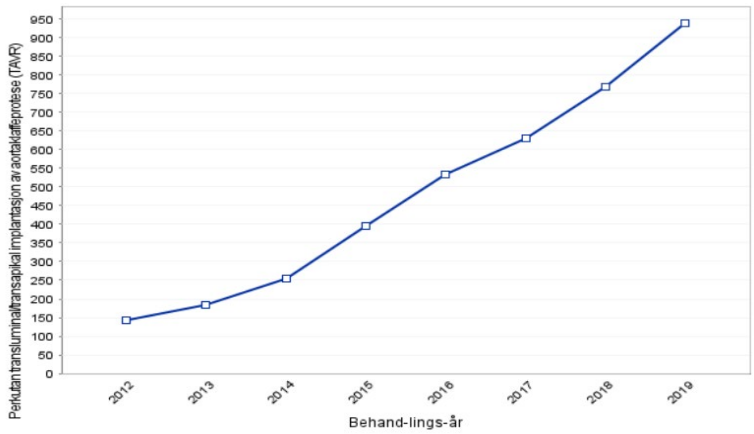


Figure 2 TAVI performed in Norway, Norwegian registry for cardiac surgery, http://statistikkbank.fhi.no/hkr/

In August 2019, in light of two newly completed randomized trials (12, 13) that included patients with low surgical risk (STS score <4%), Ordering Forum RHA decided to await a review across all risk groups before concluding. Ordering Forum RHA commissioned the NIPH to perform an assessment across all risk groups (ID2019_089, (14)).

2 - Method of review

With a multitude of systematic reviews available right after the publication of the results from the most recent randomised trials, we conducted an overview of systematic reviews guided by the methods Handbook used at the Division for Health Services at the Norwegian Institute of Public Health (15).

2.1 Inclusion criteria

Population	Patients with severe aortic stenosis at high / intermediate / low surgical risk of death, as described by New York Heart Association Functional class (NYHA class), or by The Society of Thoracic Surgeons' risk model score (STS score), or European System for Cardiac Operative Risk Evaluation (EuroScore) or EuroSCORE II, with emphasis on studies reporting on low risk.
Intervention	Catheter based implantation of aortic valves (Transcatheter aortic valve implantation (TAVI)). Evaluation will be based on devices with market approval.
Comparison	Open surgery aortic valve replacement (Surgical aortic valve replacement (SAVR)). No exclusion by chosen method.
Outcomes	• Mortality at 30 days or longest available (all-cause mortality, cardiovascular mortality, non-cardiovascular mortality) • Improvement of symptoms (reduction in New York Heart Association (NYHA) class) • Improvement of indicators for health-related life quality (e.g. EQ-5D score, SF-12 score, KCCQ score) • Procedural success (successful implantation) • Hemodynamic function of aortic valve • Days in ICU (ICU stay) • Days in hospital • Readmission to the hospital due to heart attack • Need for permanent pacemaker implantation • All undesired outcomes (e.g. vascular complications, stroke, transient ischemic attack (TIA), major bleeding, re-intervention, heart attack ≤72 hours after procedure, new or worsened atrial fibrillation-flutter, moderate or severe valve leakage (regurgitation), acute kidney damage. radiation damage patient or staff.)
Study design	Systematic reviews and meta-analyses

Inclusion criteria were adapted from the 2019 EUnetHTA report (3), and reviewed by three clinical experts. We excluded reviews published before April 2019 (before the publication of randomised trials on patients with low surgical risk (12, 13)).

2.2 Literature search

JH conducted a literature search in PubMed/Medline last updated 03.07.2020, searching for published peer reviewed systematic reviews including the two newest randomised trials in low-risk patients published on web May 2nd 2019 in the New England Journal of Medicine (12, 13). No limitation in publication language was defined. The search strategy is in Appendix 1. We also checked "similar articles" on PubMed and the reference lists of included studies, and other relevant literature. We did not search for primary studies. We checked the electronic search for duplicates in EndNote (16).

2.3 Article selection

Due to time constraints, and in deviation from the protocol (Appendix 4), only one researcher instead of two selected studies using the above-defined inclusion criteria based on title and abstract. We placed emphasis on studies evaluating the low surgical risk group. One researcher performed full text screening for all potentially eligible studies. Article selection was reviewed by second reviewer, consensus-based discussion resolved disagreements.

2.3 Quality and risk of bias assessments

Two researchers independently assessed the quality for each of the included systematic reviews with a 9-point checklist from NIPH methodology handbook (15). Based on information in the included reviews, we assessed risk of bias in the included studies.

2.4 Data extraction

One researcher extracted information from the included studies; another researcher independently checked the extraction for accuracy and relevance. We extracted data on the following: full reference, location and date of study. We extracted effect estimates for relevant outcomes.

We narratively summarised the findings of earlier NIPH reports providing an overview across all risk groups. Former NIPH findings were updated with new data from recently identified literature where possible and relevant.

We narratively summarised identified reviews and summarised estimates based on existing meta-analyses from the included reviews, supplemented by tables where possible. We checked for potential discrepancies between the systematic reviews and meta-

analyses and searched for explanations for such discrepancies. We used the most updated review of highest quality, and communicated the findings from this review, including GRADE assessment of the confidence in the effect estimates.

2.5 Certainty of evidence

Our assessment of the certainty of evidence using GRADE was based on the information provided in the included reviews.

2.6 Ethics

We have not assessed ethics in this report. According to the EUnetHTA report, patient autonomy might be an issue (3). In general, patients with indication for SAVR may demand TAVI regardless of risk. Denying TAVI to low-risk patients might challenge patient autonomy.

2.7 User involvement

We contacted The National Association for Heart and Lung Disease (LHL) with a request to provide a user's perspective. LHL was at the time unable to contribute to this HTA. We therefore requested the centres that conduct TAVI to assist us with relevant user representatives. Our clinical experts reached out to the affected patient population. We asked the selected users to provide input to the draft of the report.

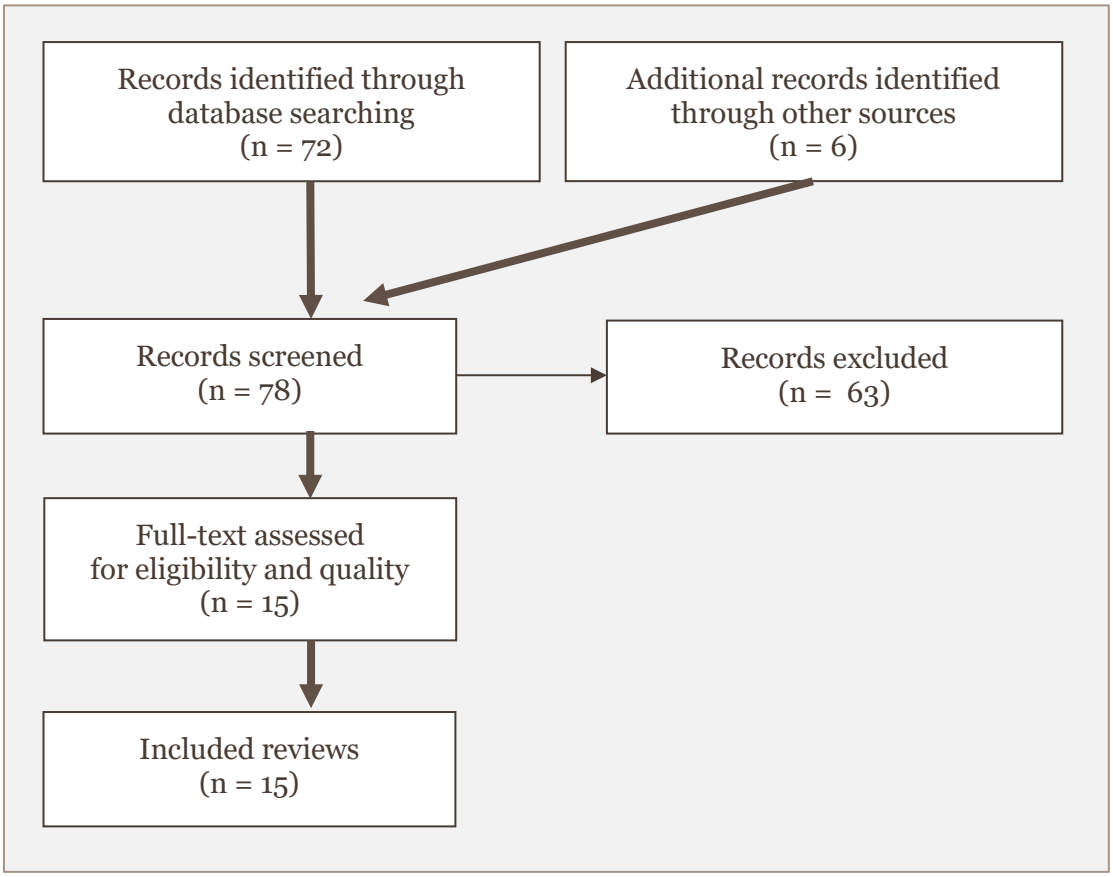
3 - Results

3.1 Description of studies

Results of the literature search

We identified 72 references through the systematic literature searches in PubMed, and one additional record through "Similar articles" in PubMed. We identified five further systematic reviews through reference lists and other searches. We considered 15 possibly relevant. We read these 15 in full text.

Figure 3 Flow diagram of study inclusion



Included studies

We included 15 systematic reviews evaluating the effect of TAVI/TAVR versus SAVR in patients with severe aortic stenosis published since April 2019 in our analysis. Two of the reviews considered patients with severe aortic stenosis across all surgical risk groups (17, 18), two reviews assessed patients at low to intermediate surgical risk (19, 20), and 11 reviews summarised studies on low risk patients (21-31).

The included systematic reviews performed their searches from March to July 2019, and all have included the two most recently published RCTs on low risk patients (12, 13).

Table 1 – Included reviews (* reviews reviewed in detail)

First author, year of publication	Date of last search	Surgical risk group	Quality assessment
Zhang 2020 * (17)	**April 6 2019**	**All**	**Moderate**
Siontis 2019 (18)	March 19 2019	All	High
Ando 2019 (19)	March 20 2019	Low/ interm.	Low
Fang 2019 (20)	April 15 2019	Low/ interm.	High
Al-Abdouh 2020 (22)	March 19 2019	Low	Moderate
Anantha-Narayanan 2020 (23)	March 2019	Low	Low
Kheiri 2020 (24)	Not stated	Low	Low
Kolkailah 2019 (25)	**April 29 2019**	**Low**	**High**
Kolte 2019 (26)	March 20 2019	Low	High
Kundu 2020 (27)	May 15 2020	Low	Moderate
Levett 2020 (28)	May 28 2020	Low	Low
Rawasia 2020 (21)	March 23 2020	Low	High
Saleem 2019 (29)	2019	Low	Low
Vipparthy 2020 (30)	2020	Low	Moderate
Witberg 2019 (31)	June 15 2019	Low	High

3.2 Quality of included reviews

All included systematic reviews reported the search strategy and the databases searched, and they had acceptable search strategies. All but one review stated that at least two reviewers assessed references and full texts for inclusion of studies in the review (24). All reviews reported the methods for analysing the results and conducting meta-analyses. Most of the reviews did not report assessment of risk of bias in included primary studies, and some of the reviews that claimed having assessed risk of bias did not report the assessments, some reviews reported risk of bias assessment of included studies in attached supplementary files, without commenting on risk of bias in the text of the review (17, 18, 22-24, 26-31). Only three of the systematic reviews used the assessment of risk of bias to assess the certainty of the effect estimates by using GRADE (17, 20, 25). The reason for downgrading the quality of some of the systematic reviews was because of the lack of assessment of risk of bias of the primary studies, or the lack of reporting of risk of bias assessment (Table 1).

3.3 Risk of bias in the primary studies in the included reviews

All systematic reviews included data in some variation from eight RCTs, three reviews also included findings from observational studies (21, 29, 31). The eight included RCTs were generally considered to have a low risk of bias overall. The risk of selection bias (sequence generation) was considered low, although regarding allocation concealment two studies were rated as unclear in Kolkailah et al. (25), and all studies except NOTION were rated as unclear in Siontis (18). Lack of blinding was not considered a risk of performance bias, since it is unlikely that operative or interventional outcomes are influenced by lack of blinding of participants and personnel. Risk of detection bias because of lack of blinding of outcome assessor was considered low for objective outcomes such as mortality, but high for potentially subjective outcomes such as rehospitalisation and length of stay. All studies were assessed at low risk of attrition bias (incomplete outcome data) for short-term outcomes (within 30 days), but Evolut was considered at high risk of attrition bias for longer term outcomes (25).

3.3.1 Across all surgical risk groups

We identified two systematic reviews on TAVI versus SAVR for patients with severe aortic stenosis across all risk groups combined (17, 18). We chose to report the results of the newest systematic review and meta-analysis with GRADE assessment by Zhang et al. (17), and briefly report the findings of the systematic review by Siontis et al (18).

Zhang et al. identified relevant literature up to 06.04.2019 through a systematic search of three databases and relevant websites. The authors' results are based on eight randomised trials and seven additional secondary reports with eligible data of these eight randomised trials. A total of 7,841 patients were randomly assigned to TAVI (n = 4,013) or SAVR (n = 3,828) treatments. The mean age of patients were 80.6 years (range 67.5 – 90.4), and 59.4% were men.

The covered population came from all surgical risk groups, four trials included mainly low-risk patients, three trials mainly intermediate-risk patients and one trial high-risk patients. The median Society for Thoracic Surgeon risk score was 3.8 (ranging from 1.9 to 11.8). Both the balloon expandable TAVI system, and a self-expanding system were used in four trials. Due to continuous progress in valve development, the two most recent trials were performed with new-generation TAVI valves, whereas the other trials included early-generation valves. About 90% of the TAVI procedures were performed with the transfemoral approach, which was associated with reduction in all-cause mortality or disabling stroke compared with comparators. Overview of the trial characteristics are listed in table 2.

All included trials reported 30-day data, seven reported 1-year data and six trials reported 2-year data. For analysis of long-term follow-up data, the median follow-up duration was 3.5 years; 5-year follow-up data was available in three trials.

Zhang et al also conducted a GRADE assessment for the effect at long term follow up (≥ 2years), their assessment is presented in table 3.

Zhang et al (17) concluded that TAVI was associated with reduced all-cause mortality or disabling stroke within two years, but not at long-term follow-up. The authors found that TAVI may slightly reduce major bleeding, new-onset fibrillation and acute kidney injury at 30-day, 1-year, 2-year, but not at long-term follow-up; that TAVI probably increases major vascular complications, permanent pacemaker implantation, re-intervention and paravalvular leak at 30-day, 1-year, 2-year, and long-term follow-up. Major vascular complications (RR 2.36, 95% CI: 1.39-4.01), re-intervention (RR 3.41, 95% CI: 1.88-6.17) and paravalvular leak (RR 7.32, 95% CI: 2.30-23.28) stand out with a RR greater than two for TAVI.

The other review on TAVI versus SAVR in patients across risk groups by Siontis et al (18) included seven of the studies also included in the review by Zhang et al (17), but did not include the STACCATO trial (with only 70 participants). The primary outcome was all-cause mortality up to two years. The authors concluded that TAVI compared with SAVR for patients with severe aortic stenosis was associated with a reduction in all-cause mortality and stroke. The mortality benefit of TAVI up to two years was observed consistently in patients at low, intermediate and high surgical risk.

Table 2 Overview of included studies in Zhang et al.

Trial	PARTNER (5)	STACCATO (32)	US CoreValve (6)	NOTION (33)	PARTNER 2A (34)	SURTAVI (9)	PARTNER 3 (13)	Evolut Low Risk Trial (12)
Author	Smith et al.	Nielsen et al.	Thyregod et al.	Thyregod et al.	Baron et al.	Reardon et al.	Mack et al.	Popma et al.
Year of publication	2011	2012	2014	2015	2016	2017	2019	2019
Recruitment period	2007-09		2011-12	2009-13	2011-13	2012-16	2016-17	2016-18
No. of patients	699	70	795	280	2032	1746	1000	1468
Funding source	Edwards Lifesciences	Edwards Lifesciences	Medtronic	Danish Heart-Foundation	Edwards Lifesciences	Medtronic	Edwards Lifesciences	Medtronic
Design	Non-inferiority		Non-inferiority	Superiority	Non-inferior-ity	Non-inferi-ority	Non-inferi-ority	Non-inferiority
Available follow-up (months)	1, 12, 24, 60	1, 3	1, 12, 24, 36, 60	1, 12, 24, 60	1, 12, 24	1, 12, 24	12	1, 12, 24
Mean age/Standard deviation (years)	83.6 +/-6.8	80 +/- 3.6	83,2 +/- 7.1	79,2 +/- 4.9	81.5 +/- 6.7	79.6 +/- 6.2	73.3 +/- 5.8	74 +/- 5.9
Men	57.1%	30%	43.2%	53.2%	54.5%	56.8%	69.2%	65.1%
Low-risk (<4%)	0	100%	9.4%	81.8%	6.7%	15.5% (<3%)	100%	100%
Intermediate-risk (4-10%)	0	0	75%	17.5%	81.3% (4-8%)	81.3% (3-8%)	0	0
High-risk (>10%)	100%	0	15.6%	0.7%	12% (>8%)	3.2% (>8%)	0	0

Table 3. Effects at long term follow up (≥ 2years) by Zhang et al. across risk groups

Outcome	Risk with SAVR	Rate ratio (95% CI)	Risk difference with TAVI (per 1000) [1]	Certainty of evidence[2]
All-cause mortality	214 per 1000[6]	1.04 (0.94, 1.16)	7 more events (-10 to 26)	Moderate[3] ⨁⨁⨁◯
All-cause mortality or disabling stroke	240 per 1000[6]	1.02 (0.92, 1.13)	4 more (-15 to 23)	High ⨁⨁⨁⨁
Cardiovascular mortality	-	1.05 (0.92, 1.20)	7 more (-11 to 27)	Moderate[3] ⨁⨁⨁◯
Myocardial infarction	-	0.94 (0.69, 1.28)	2 fewer (-10 to 9)	Moderate[4] ⨁⨁⨁◯
Cerebrovascular event	-	1.04 (0.86, 1.26)	4 more (-15 to 26)	Moderate[3] ⨁⨁⨁◯
Stroke	-	0.93 (0.78, 1.11)	6 fewer (-19 to 9)	Moderate[3] ⨁⨁⨁◯
Transient ischemic attack	-	1.44 (1.06, 1.94)	11 more (2 to 24)	Moderate[4] ⨁⨁⨁◯
Major bleeding	-	0.56 (0.28, 1.12)	131 fewer (-249 to 28)	Low[3,4, 5] ⨁⨁◯◯
Acute kidney injury	-	0.62 (0.38, 1.02)	28 fewer (-47 to 1)	Low[4, 5] ⨁⨁◯◯
Major vascular complications	-	2.36 (1.39, 4.01)	54 more (16 to 112)	Low[3, 5] ⨁⨁◯◯
Valve endocarditis	-	1.26 (0.73, 2.18)	3 more (-3 to 14)	Moderate[4] ⨁⨁⨁◯
Permanent pace-maker implantation	-	1.93 (1.11, 3.33)	74 more (9 to 165)	Moderate[5] ⨁⨁⨁◯
New-onset atrial fibrillation	288 per 1000[6]	0.45 (0.35, 0.58)	134 fewer (-164 to -98)	Moderate[5] ⨁⨁⨁◯
Rehospitalisation	157 per 1000[6]	1.30 (1.14, 1.49)	38 more (18 to 60)	Moderate[5] ⨁⨁⨁◯
Reintervention	-	3.41 (1.88, 6.17)	14 more (5 to 30)	Moderate[4] ⨁⨁⨁◯
Moderate-severe paravalvular leak	-	7.32 (2.30, 23.28)	74 more (16 to 219)	Low[3, 5] ⨁⨁◯◯

[1] per 1000 patients (95% CI).
[2] Indicates the extent to which one can be confident that an estimate of effect is correct.
[3] Publication bias
[4] Precision: serious limitation
[5] Consistency: serious limitation
[6] Calculated based on absolute numbers reported in original study

3.3.2 High surgical risk

The Norwegian Institute of Public Health published an early horizon scanning report in 2012 regarding TAVI in high-risk patients (35). The report concluded in favour of TAVI. Eight years later, the method is firmly established in high risk patients, clinical experts judge that the advancements in the procedure and valves have further contributed to better results. Siontis et al. found in a subgroup analysis for two year, all-cause mortality in high risk surgical patients based on PARTNER 1A and US CoreValve high risk (US CoreValve high risk was not included in the 2012 NIPH report) a hazard ratio 0.85 (95% CI: 0.71-1.01) in favour of TAVI. Two-year all-cause mortality was in the high risk group was comparable to the overall (across risk groups) hazard ratio of 0.88 (95% CI: 0.78-0.99).

3.3.3 Intermediate surgical risk

The Norwegian Institute of Public Health published a health technology assessment in collaboration with EUnetHTA in 2018 (36). The Norwegian Institute of Public Health published a supplementary health economic evaluation for the Norwegian setting (37). The assessments concluded:

"Based on available evidence from two RCTs, we conclude that the effectiveness of TAVI for patients with severe aortic stenosis at intermediate surgical risk is probably non-inferior to SAVR in terms of all-cause mortality and cardiac mortality at 30-day follow-up. Moreover, TAVI probably reduces the length of hospital stay compared with SAVR. However, important uncertainties remain regarding whether TAVI is better or worse than SAVR in terms of symptom improvement." (36)

"Moderate-quality evidence suggests that, compared with SAVR, TAVI probably reduces new-onset atrial fibrillation and enhances the risk of para-valvular regurgitation. However, important uncertainties remain regarding the evidence on the following outcomes: stroke, acute kidney injury, new permanent pacemaker, major vascular complications, aortic valve re-intervention, and life-threatening and/or disabling bleeding,"(36)

"The cost-utility analysis indicated that TAVI was slightly more effective (incremental effectiveness: 0.07 QALYs) and more costly (incremental costs: 71000 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." (10, 37)

The Ordering Forum RHA postponed a decision on this matter on 26.08.2019, requesting NIPH to provide a broader assessment across all risk groups, including evidence from newer studies on patients with low surgical risk.

3.3.4 Low surgical risk

We chose to report the results of a high quality Cochrane systematic review with GRADE assessment on patients with low surgical risk by Kolkailah et al. updated in April 2019 (25).

The results are based on four randomised trials. A total of 2,818 patients were randomly assigned to TAVI (n = 1,416) or SAVR (n = 1,402). The two most recent trials were also the biggest: EVOLUT 2019 (funded by Medtronic, 1468 participants) and PARTNER 3 2019 (funded by Edwards Lifesciences, 1000 participants) (12, 13). The two other included studies were NOTION 2015 (280 participants) and STACCATO 2012 (70 participants) (32, 38). All included studies had predominantly elderly participants (i.e. aged 70 or older). The two most recent trials on only low risk patients (12, 13), included patients with a mean age of more than 5 years younger than in the two smaller and older RCTs also looking at the other risk groups.

Most included participants in all the four studies were at a low surgical risk as per their baseline STS/EuroSCORE II and/or as deemed by the study investigators. Two trials used the balloon-expandable TAVI system, and two trials used a self-expanding system. Most TAVI procedures were performed via transfemoral access. The review authors conducted GRADE assessments for the effect estimates of TAVI compared to SAVR at short term follow up (i.e. assessed during hospitalisation and up to 30 days of follow-up), their assessment is presented in table 4.

Table 4. GRADE assessment of results from Kolkailah et al. for patients at low surgical risk at 30 days of follow-up

Outcome	Risk with SAVR	Relative effect (95% CI)	Risk difference with TAVI[1] (95% CI)	Certainty of evidence (GRADE)[2]
All-cause mortality	11 per 1000	RR 0.69 (0.33 to 1.44)	3 fewer per 1000 (-7 to 5)	Moderate [3] ⨁⨁⨁◯
Stroke	21 per 1000	RR 0.73 (0.42 to 1.25)	5 fewer per 1000 (-12 to 6)	Moderate[3] ⨁⨁⨁◯
Rehospitalisation	30 per 1000	RR 0.64 (0.39 to 1.06)	11 fewer per 1000 (-18 to 2)	Low[3,4] ⨁⨁◯◯
Myocardial infarction	14 per 1000	RR 0.82 (0.42 to 1.58)	3 fewer per 1000 (-8 to 7)	Moderate[3] ⨁⨁⨁◯
Cardiac death	10 per 1000	RR 0.71 (0.32 to 1.56)	3 fewer per 1000 (-7 to 6)	Moderate[3] ⨁⨁⨁◯
Permanent pacemaker implantation	47 per 1000	RR 3.65 (1.50 to 8.87)	123 more per 1000 (23 to 366)	Moderate[5] ⨁⨁⨁◯

[1] per 1000 patients: risk is based on the assumed risk in the SAVR group and the relative effect of the intervention
[2] Indicates the extent to which one can be confident that an estimate of effect is correct.
[3] Confidence interval includes the null effect and appreciable benefit. Downgraded 1 level for imprecision
[4] High risk of detection bias due to lack of masking. Downgraded 1 level for study limitations (risk of bias)
[5] Considerable unexplained heterogeneity. Downgraded 1 level for inconsistency

The results showed that TAVI compared with SAVR for patients with low surgical risk:

- probably leads to little or no difference for the following short-term outcomes: all-cause mortality; stroke; myocardial infarction and cardiac death
- may reduce the risk of short-term rehospitalisation, although the confidence interval also includes the possibility of no difference in risk between groups
- probably increases the risk of permanent pacemaker implantation
- reduces the risk of atrial fibrillation, acute kidney injury, and bleeding
- We are uncertain whether TAVI, compared with SAVR, affects the length of hospital stay in days, although it appears to be associated with shorter length of hospital stay.

The authors concluded that we need more data to further assess and validate these outcomes, and we need long-term follow-up to assess durability in the low surgical risk population.

The other included systematic reviews on patients with low surgical risk consistently found either non-inferiority or superiority for TAVI compared with SAVR regarding short term all-cause mortality and incidence of stroke. We have not explored why some of the meta-analyses found a statistically significant difference in mortality in favour of

TAVI, whereas other based on similar studies did not. For the other outcomes most reviews reported that TAVI reduces the risk of atrial fibrillation, acute kidney injury and bleeding, but probably increases the risk of permanent pacemaker implantation and vascular complications.

User involvement

One user contributed with feedback to the draft of this report, in addition to sharing his personal experience (appendix 5).

4 - Economic evaluation – Introduction

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 in which the differences in costs between an intervention and its comparator are compared with differences in consequences. 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 budget constraints. Therefore, economic evaluations are important tools for decision makers facing questions of how to prioritize treatments and maximize health benefits using limited 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 due to its ratio nature, 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: $\lambda \bullet \Delta E - \Delta C > 0$

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 analyses are important in economic evaluations based on decision models. In short, sensitivity analyses illustrate how much the results vary when model parameters are changed.

Probabilistic sensitivity analysis (PSA) has the advantage making it possible to take the uncertainties of many 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. For each iteration, the alternative that renders the highest values of NMB or NHB is considered cost-effective. 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 as cost-effectiveness acceptability curves (CEACs), which show the probability of the alternatives being cost-effective subject to a range of values of WTP.

In short, making a model probabilistic means that it is possible to estimate the uncertainty associated with a decision to implement alternative interventions, and it also provides a possibility of estimating the value of collecting additional in-formation 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. In practice, the benefits criterion is taken into account by weighing costs against benefits in a cost-effectiveness analysis of the technology of interest.

Resources

According to the resource criterion, priority increase when 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 person-

nel, 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 resources are available for treating others. In addition to resource use within the health sector, a technology may also impose costs for other parties. While potentially important for society, these resources are not considered for HTAs submitted within the system of New Methods.

In practice, the resource criterion is 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 (39) indicates 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).

5 - Economic evaluation - Methods

5.1 General

In summer 2019 NIPH submitted the health economic evaluation of TAVI for patients with intermediate risk (10). The Ordering Forum RHF asked NIPH to perform an assessment across all risk groups. The present economic evaluation addresses cost-effectiveness and budget impact of TAVI for patients with severe aortic stenosis at low surgical risk in the Norwegian settings.

In order to assess the cost-effectiveness of transcatheter aortic valve implantation compared with conventional surgical replacement (SAVR), for patients with severe aortic stenosis and low surgical risk, we performed a cost-utility analysis (CUA). We expressed relevant costs in 2020 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 incremental cost-effectiveness ratio (ICER).

In accordance with the Government White Paper about priority setting, (Meld. St. 34 2015–2016) (39), 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. We also performed one-way sensitivity analyses to explore potential impact of uncertainty in single parameters. The ranges of parameter values explored were based on an assumption of a +- 30% variation from the point estimate. We present the results of the one-way sensitivity analyses in a tornado diagram.

The model was developed and analysed in TreeAge Pro ® 2020. 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 and low surgical risk using costs results from the cost-effectiveness model.

In conformity with the recommendations from the White Paper and the severity criterion, we estimated absolute shortfall for patients with severe aortic stenosis and low surgical risk and assessed cost-effectiveness in the light of the suggested cost-effectiveness thresholds.

5.2 Population, interventions and model structure

In order to assess the cost-utility of transcatheter aortic valve replacement compared with open surgery in patients with low risk, we developed a decision analytic model in TreeAge pro® 2020. This Markov model follows a cohort of patients over a specified period for both treatment alternatives.

We assumed a typical patient with severe symptomatic aortic valve stenosis and low surgical risk to be 73 years old, in accordance with the mean age of participants of the randomized control multicentre trial PARTNER 3 (Placement of Aortic Transcatheter Valves) (13).

The two treatment options for these patients that are compared: aortic valve replacement with conventional surgery (Surgical Aortic Valve Replacement, SAVR) and transcatheter aortic valve implantation (TAVI), have some differences in terms of costs and outcomes that are captured in the model.

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 (entering through the femoral artery in the groin). TAVI can be carried out under local anaesthesia with sedation. 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 costs, costs of treating procedure-related complications, health utility related to the condition and disutility related to complications.

The model we used to assess TAVI for patients with aortic stenosis at intermediate risk as a commission from The Ordering forum RHF (10) was adapted for patients at low risk. We made several adjustments both regarding model-structure and input data. We were also inspired by several assumptions and solutions applied from the recently published model developed as part of an HTA by Health Information and Quality Authority in Ireland (40).

The present Markov model has three health states: (i) alive and well, (ii) post major complications, and (iii) dead. 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 able 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 180 cycles, i.e. 15 years in the base case scenario.

The model captures both short and long-term effects. First, short term consequences of the aorta valve replacement alternatives were captured by the probabilities of each procedure being successful (alive and well) or resulting in death or a procedure-related complication (post major complication). The outcomes defined by these starting probabilities had a duration of one cycle before transition to different health states were considered. After the first cycle, the patients entered the long term phase, where transitions and health events were modelled for a duration of 180 cycles, or 15 years. Each health state is associated with specific health outcomes and costs, so called "health state rewards".

In addition to the three health states, the model encompasses two types of procedure-related events (health state transitions), affecting both cost and health outcomes: "major complications" and "other complications".

Among the "Major complications", we have included the following:

- stroke,
- acute kidney injury,
- myocardial infarction.

Among the "Other complications", we have included the following:

- major vascular complications
- new pacemaker implantation,
- life threatening bleeding
- paravalvular regurgitation
- new-onset atrial fibrillation.

Major complications were considered chronic, implying that patients who experience them cannot recover and return to the "alive and well" state, but instead move to the "post major complications" state.
"Other complications" on the other hand, were assumed to be immediate, and patients would recover after one cycle and move to the "alive and well" state.

All complications were 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 (patients move on to either "alive and well" or "post major complications" states). We assumed that patients not experiencing complications had a successful valve replacement and a functioning valve.

Death is an absorbing state. Once an individual makes a transition into the absorbing state, no further costs or health attainments are included in the analysis. An overview of the model is presented in Figure 4.

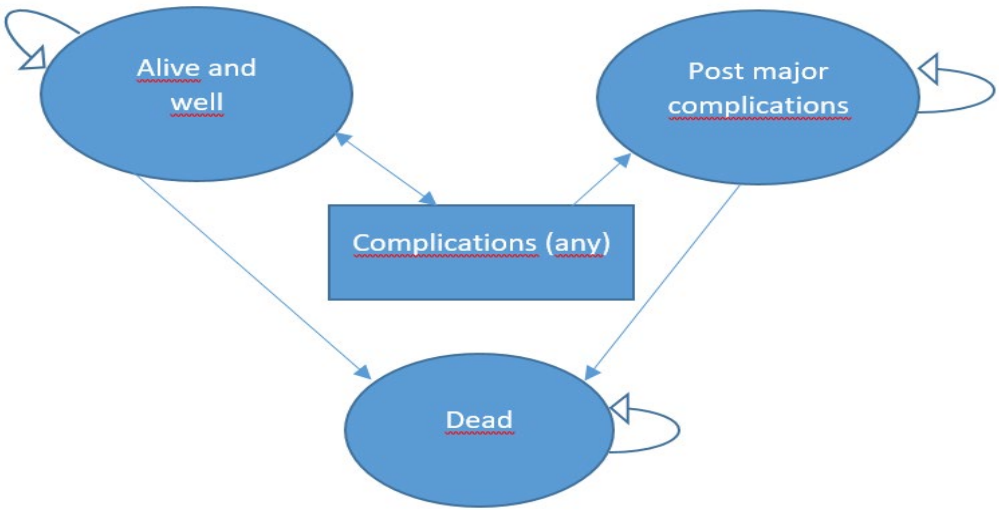


Figure 4. Structure of the model, with health states (round figure), complications (rectangular figure) and possible transitions (arrows).

The complete structure of the model is presented in Appendix 2.

In the base case scenario, we have followed a hypothetical cohort of patients over a period of 15 years.

5.3 Model Parameters

Transition probabilities

All transition probabilities that inform the model were derived from data for clinical outcomes at 30-days and 1-year from the randomised controlled multicentre trial PARTNER 3 (Placement of Aortic Transcatheter Valves 3) (13) (Appendix 3). A total of 1 000 patients with severe calcific aortic stenosis classified as being at low surgical risk were randomly assigned to receive either TAVI or SAVR. All TAVI procedures used transfemoral access route. Primary analysis was performed in as-treated population of 950 patients (496 TAVI versus 454 SAVR). Data for mortality in the acute phase at 30-days were applied directly in the model (see Table 5), whereas we converted the probabilities at 1-year 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. Trial data beyond 1 year were not available at the time of the analysis. For this period, we therefore extrapolated by assuming that all patients with aortic stenosis following the aortic valve replacement have an increased risk of death compared with the general population. For patients who were alive and well, we extrapolated using age-adjusted mortality data for the general Norwegian population, recalculated to monthly probabilities, multiplied by hazard ratio equal to 1.2 (41). For patients who had experienced major complications we applied a hazard ratio of 1.65, which is a weighted average of risks for patients with history of stroke, myocardial infraction and acute kidney injury (42-44). Table 6 presents all relative risks of mortality applied in the model. Relative risks were defined as log-normal distributions.

As mentioned, we grouped possible complications into two categories: major complications and other complications. We estimated the transition probabilities for complications by averaging the absolute probabilities obtained from the study.
Table 5 presents the transition probabilities from PARTNER 3 study that informed the Markov model in the base case scenario.

Table 5. Transition probabilities derived from the PARTNER3 study at 30 days, and 1 year used as input in the model (13)

Outcome	**At 30 Days**		**At 1 year***	
	TAVI	SAVR	TAVI	SAVR
All –cause mortality	0,0043	0,01	0,011	0,026
Stroke	0,006	0,024	0,012	0,031
Acute Kidney Injury	0,004	0,018	0,038	0,062
Myocardial Infraction	0,01	0,013	0,012	0,022
Major vascular complications	0,022	0,015	0,028	0,015
Life threatening bleeding	0,036	0,245	0,077	0,259
New pacemaker implantation	0,065	0,04	0,073	0,054
Paravalvular regurgitation (severe or moderate)	0,008	0,002	0,006	0,005
New onset atrial fibrillation	0,05	0,395	0,07	0,409

*Cumulative probabilities as per Mack et al. 2019 (13). In the model, subtractive, monthly probabilities were used

Table 6. Relative risk of mortality following major complications applied in the model

Complication	**RR estimate**	**Lower CI- Upper CI**	**Source**
Stroke	2,2	(1,95 – 2,5)	Mathisen et al. 2016 (43)
Myocardial infarction (men)	1,47	(1,39 – 1,55)	Norgaard et al. (42)
Myocardial infarction (women)	2,02	(1,91 – 2,15)	Norgaard et al. (42)
Acute kidney injury	1,44	(1,31 – 1,58)	Sawhney et al. 2017 (44)
Aortic stenosis (patients in general)	1,2	(1,11 – 1,3)	Chacos et al. 2017 (41)

Table 7. Cumulative monthly probabilities of experiencing complications following aortic 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	0,2010	0,0302	0,7501	0,1215
Probability of experiencing other complications (absolute)	0,1810	0,0263	0,6951	0,1159
Probability of experiencing other complications (conditional, used in Markov)	0,9005	0,8710	0,9267	0,9538
Probability of experiencing major complications	0,02	0,004	0,055	0,006

*Beyond 30 days until 12 months. After 1 year we assume no differences in the rates of complications between the interventions

To enable probabilistic analysis we assigned beta distributions to all transition probabilities and a log normal distribution to the relative mortality risk parameters. 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 3 study (13).

Costs

We included all direct cost related to the procedures and complications associated with the alternative treatments. We obtained information about procedure costs associated with aortic valve replacement both with open surgery and with TAVI from the Norwegian activity-based payment system (DRG tariffs) (45). There is a separate DRG code representing TAVI procedure: 104D: catheter-based implantation of the heart valve. SAVR is represented by two DRGs: 104A: heart valve surgery and 104B: surgery on multiple heart valves or heart valve surgery with complications. In base case scenario we have used an average of the two procedure codes to represent the direct SAVR costs. In separate scenario analyses, we explore results with either 104A or 104B as input.

Long-term medical management following the aortic valve replacement is standardised in Norway regardless of type of replacement procedure the patient received 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 (46).

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 (45).

All costs were measured in 2020 Norwegian kroner (NOK). The uncertainty surrounding cost parameters were assessed by using gamma distribution. Table 8 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: SE=(Value interval/2) * 1,96.

Table 8. 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	294 500 (45 076)	(206 150 – 382 850)	Gamma	ISF 2020 (45)
TAVI-procedure costs	325 741 (49 858)	(228 018 – 423 463)	Gamma	ISF 2020 (45)
Pacemaker implantation during within 30 days of valve replacement	31 882 (4 880)	(22 318 – 41 447)	Gamma	ISF 2020 (45)
Isolated pacemaker implantation	76 728 (11 744)	(53 710 – 99 747)	Gamma	ISF 2020 (45)
Major vascular complications	13 193 (2 019)	(9 235 – 17 151)	Gamma	ISF 2020 (45)
Treatment Life threatening bleeding	5 634 (862)	(3 944– 7 325)	Gamma	ISF 2020 (45)
Moderate or severe paravalvular leak	73 214 (11 206)	(51 250 – 95 179)	Gamma	Assumption
Treatment of acute myocardial infarction	53 206 (8 603)	(39344 – 73068)	Gamma	ISF 2020 (45)
Acute stroke treatment	86 073 (13 174)	(60251 – 111895)	Gamma	ISF 2020 (45)
Treatment of acute kidney injury	67 979 (10 405)	(47585 – 88373)	Gamma	ISF 2020 (45)
Treatment of new onset atrial fibrillation	22 996 (3 520)	(16097– 29894)	Gamma	ISF 2020 (45)

Monthly incremental costs post major complications	6 561 (1 004)	(4 593 – 8 529)	Gamma	Assumption based on (TLV report 2015) (47)

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 9.

Table 9. Weighted unit costs of treating complications per cycle

	Cost at 30-days		**Cost beyond 30-days**	
	TAVI	SAVR	TAVI	SAVR
Major complications	67 521	73 092	69 203	70 604
Other complication	23 762	17 183	33 281	20 986

**Weighted costs were obtained by multiplying the calculated weights by the unit costs listed in Table 7.*

Health-related Quality of Life

We used utilities reported by intermediate risk patients from PARTNER 2 (34) as estimates of effect in the model. In this study, the 3-level EQ-5D questionnaire was obtained at baseline, 30 days, 6 months and one year following the procedure, as listed in Table 10. We used the state utilities at one year to inform the model for the cycles beyond 1 year assuming a steady state after this point. Beta distributions were used for the state utility values (QALYs) in the model.

Table 10: State utilities based on EQ-5D used in the model

	QALY estimate	*(Lower CI – Upper CI)*	*Distribution*	*Source*
TAVI				
Baseline	0,75	(0,738-0,762)	Beta	Baron et al. 2017 (34)
30 days	0,808	(0,794-0,822)	Beta	Baron et al. 2017 (34)
6 months	0,794	(0,778-0,809)	Beta	Baron et al. 2017 (34)
1 year	0,794	(0,778-0,809)	Beta	Baron et al. 2017 (34)
SAVR				
Baseline	0,73	(0,716-0,744)	Beta	Baron et al. 2017 (34)
30 days	0,728	(0,712-0,744)	Beta	Baron et al. 2017 (34)
6 months	0,796	(0,778-0,813)	Beta	Baron et al. 2017 (34)
1 year	0,796	(0,778-0,813)	Beta	Baron et al. 2017 (34)

We applied disutilities (negative utility values) for each of the complications to capture worsened health state due to complications and accounting for average duration of ill effects for the patient.

Disutility values related to major complications and other complications were taken from published studies: Kaier et al. 2016 (48), Sullivan et al. 2014 (49) and Davies et al. 2015 (50), that also reported EQ-5D values (see table 11). 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 11. We used gamma distributions for disutility values in the model.

Table 11: Disutility values for valve-related complications

Valve-related complications	Disutility (monthly)	Duration of monthly disutility	Disutility x duration	Disutility (monthly) source	Duration source
Stroke (any)	-0.1610	3	-0.483	Kaier et al. 2016 (48)	Assumption
Acute kidney injury	-0.1580	2	-0.316	Kaier et al. 2016 (48)	Federspiel et al. 2018 (51)
Myocardial infarction	-0.005	4	-0.02	Davies et al. 2015 (50)	The Norwegian Electronic Health Librarian (52)
Major vascular complications	-0.007	1	-0.007	Kaier et al. 2016 (48)	Assumption
Life threatening bleeding	-0.046	1	-0.046	Kaier et al. 2016(48)	Assumption
New pacemaker implantation	-0.1577	1	-0.1577	Assumption	Assumption based on Lopez-Jimenez (53)
Moderate or severe paravalvular leak	-0.049	1	-0.049	Sullivan et al. 2014 (49)	Panaich et a. 2017 (54)
New-onset atrial fibrillation	-0.0377	1	-0.0377	Kaier et al. 2016 (48)	Filardo et al. 2018 (55)

HRQoL: Health-Related Quality of Life

Severity considerations – absolute shortfall (AS)

We calculated absolute shortfall (AS) based on projections from the health economic model. Calculation of AS has been described in more detail in the submission guideline for pharmaceutical reimbursements of the Norwegian Medicines Agency, which is based on the white paper on priority setting, and a Norwegian life table and age adjusted health related quality of life information from a general Swedish population (56). Absolute shortfall is defined as the difference in quality adjusted life expectancies at age (A) without the disease (QALYsA), and prognosis with the disease (PA):

$$AS = QALYsA - PA$$

5.4 Sensitivity analysis

In addition to performing probabilistic sensitivity analysis, we carried out a series of one-way sensitivity analyses to investigate how uncertainty around single parameters affects cost-effectiveness results.

In Table 12 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 12. List of parameters for series of one-way sensitivity analyses

Parameter	Name of parameter in the model	Root definition	Minimum inference	Maximum inference
Procedure costs TAVI	cost_Intervention_TAVI	325 741	228 018	423 463
Procedure costs SAVR	cost_Intervention_SAVR	235 682	164 978	306 387
Cost of treatment of other complications	Cost_Other_event	23 803	16 662	30 944
Disutility for other complications following SAVR	Start_disU_Other_compl_SAVR	-0,047	-0,0328	-0,061
Monthly cost after major complications	Cost_post_major_complications_monthly	6 561	4 593	8 529
Disutility for other complications following TAVI	Start_disU_Other_compl_TAVI	-0,0793	-0,0555	-0,103

5.5 Scenario analyses

While there is a separate DRG code representing costs of TAVI procedure, SAVR is represented by two DRGs: 104A: heart valve surgery and 104B: surgery on multiple heart valves or heart valve surgery with complications. There is a substantial difference between these two costs (nearly 119 000 Norwegian kroner). In the base case scenario, we have used an average of the two procedure codes of 294 500 Norwegian kroner to represent the direct SAVR costs. In scenario analyses we explore results with either 104A or 104B as input, all other parameters remaining unchanged.

We based our model on results of the PARTNER 3 study (13). At the time of the analysis, only 1-year follow up data on key effectiveness parameters are available. In the scenario analysis, we explore the output of the model run in a one-year perspective.

5.6 Budget impact

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

Although our cost-effectiveness analyses regard patients with aortic stenosis and at low surgical risk, we assume that a potential expansion of TAVI on to these patients cannot happen with omission of the patients who are at intermediate risk.
To estimate the total incremental cost of introduction of TAVI for patients with severe aortic stenosis at intermediate and low surgical risk we extracted expected annual costs from cohort analyses carried out separately for both treatment arms within the Markov model. We used undiscounted costs, in line with recommendations from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) for budget impact analyses. Just as in the cost-effectiveness analysis, we used a health care perspective.

6 - Economic evaluation – Results

6.1 Incremental cost–effectiveness estimates in the base case scenario

The results of the probabilistic sensitivity analysis in the base case scenario with a 15-year time perspective are illustrated in figure 6. These are results based on all 10 000 iterations of the probabilistic Monte Carlo simulation in the base-case analysis. The blue dots in the scatter plot represent results for patients following SAVR and the red ones TAVI – patients. The graph illustrates that uncertainty ranges are wide for both alternatives, with "clouds" of cost-effectiveness pairs that are largely overlapping.

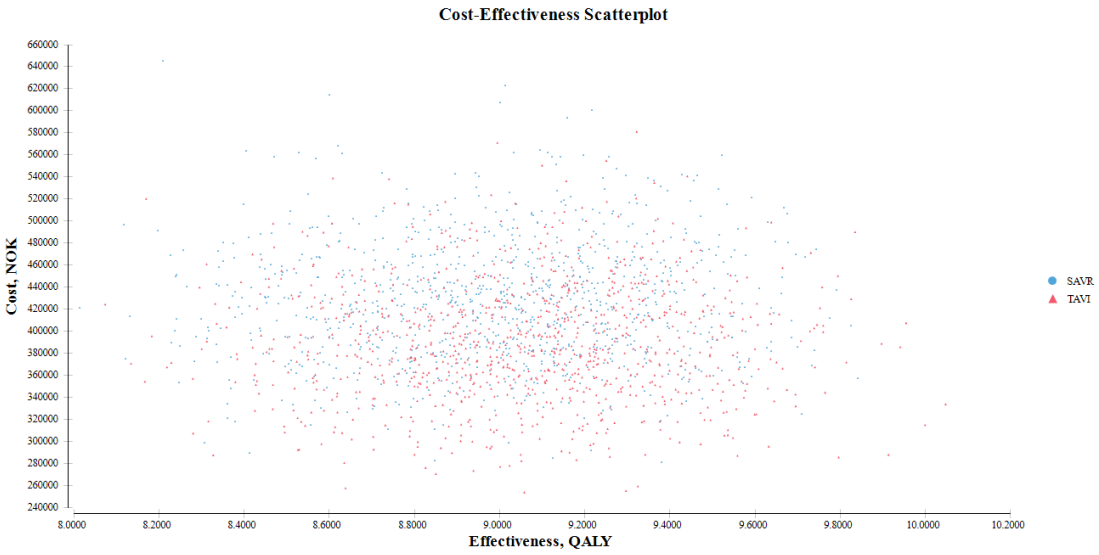


Figure 6. Cost-effectiveness scatterplot for base case analysis (15-year time horizon)

The average results were also computed based on the 10 000 iterations of the analysis as presented in Table 13.

Table 13. Results of the base case cost-effectiveness analysis

Procedure type	Total costs (NOK)	Effects (QALYs)	Incremental cost (NOK)	Incremental effect (QALYs)	ICER (NOK/QALY)
SAVR	428 070	9.0079			
TAVI	392 788	9.0617	-35 283	0.054	Dominant

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 7 below.

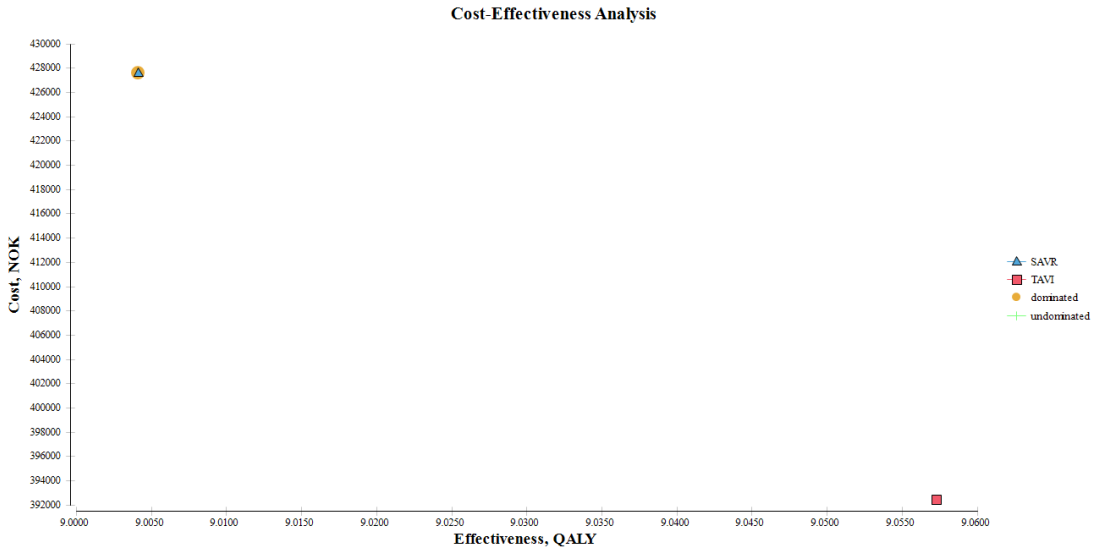


Figure 7. Cost-effectiveness graph TAVI versus SAVR, base case analysis

The results in the base-case scenario show that, on average, the total expected intervention-related costs per patient in a 15-years perspective are about 428 thousand kroner for patients who undergo SAVR and about 393 thousand kroner for patients who receive TAVI. These include the costs of the procedures, and treatment of complications. The TAVI procedure is associated with a cost saving of about 35 thousand Norwegian kroner of compared to SAVR.

During the same years, TAVI patients accumulate also slightly more QALYs, with a difference of about 0.054 QALYs. Average results show that TAVI is both better in terms of effect, i.e. QALYs, and also less expensive, which makes it a dominant strategy over SAVR for this group of patients.

However, it is worth mentioning that in the first year cumulative costs for both procedures are very close, with TAVI being more costly only by approximately 1 700 kroner, a difference of less than 1 %. This difference is also relatively low in the years following valve procedure, this time in favour of TAVI, as shown in Table 14. The first year the

main cost drivers are the procedure costs and, to the much lesser extent, the acute procedure-related complications. In the following years, they are major complications that are the main cost factors.

Table 14. Results of the base case cost-effectiveness analysis

Incremental annual costs in NOK	TAVI	SAVR	Net difference
First year	*344 818*	*343 128*	*1 690*
Year 2 after procedure	*4 949*	*8 789*	*-3 840*
Year 3 after procedure	*4 761*	*8 456*	*-3 695*
Year 4 after procedure	*4 561*	*8 100*	*-3 539*
Year 5 after procedure	*4 350*	*7 727*	*-3 377*

Below, we present cost-effectiveness acceptability curves at willingness-to-pay (WTP) for one additional QALY between zero and 825 000 NOK (see figure 8). The figure demonstrates that TAVI has a higher probability of being cost-effective than SAVR, when simultaneously taking into account all parameter uncertainties. Because of dominance in favour of TAVI, the WTP does not matter for which interventions is likely to be cost-effective.

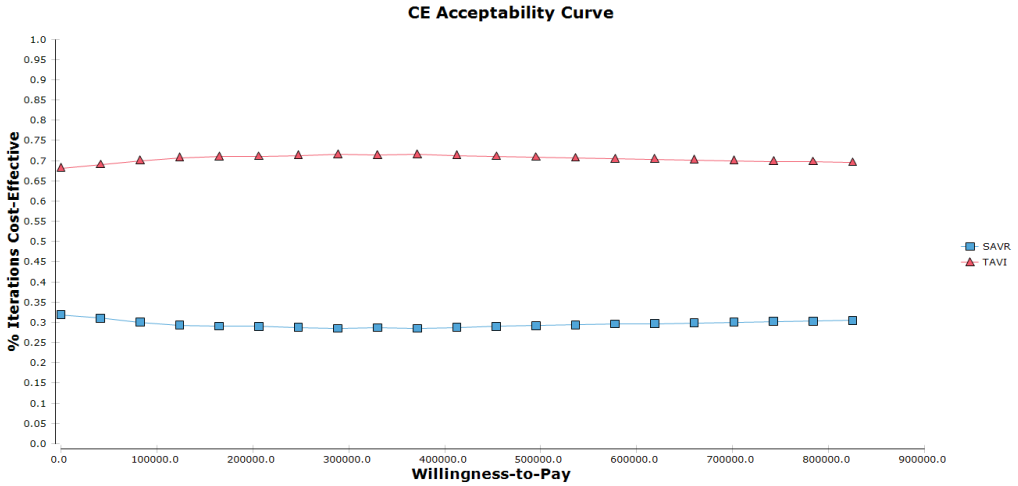


Figure 8. Cost-effectiveness acceptability curves indicating the probability that either intervention is cost-effective for a WTP range from zero to 825 000 NOK per QALY.

6.2 Sensitivity analysis

A tornado diagram is a graphical method for presenting a series of one-way sensitivity analyses. It shows how cost-effectiveness results are influenced by variation in individual model parameters. Figure 9 presents parameters with greatest impact on results.

The blue bar represents low parameter estimate and the red one represents high values of the parameter. Only two of these parameters may influence cost-effectiveness to the degree that willingness to pay for health potentially could matter for the decision, namely if TAVI is 30% more costly than assumed, and if SAVR is 30% less costly than assumed.

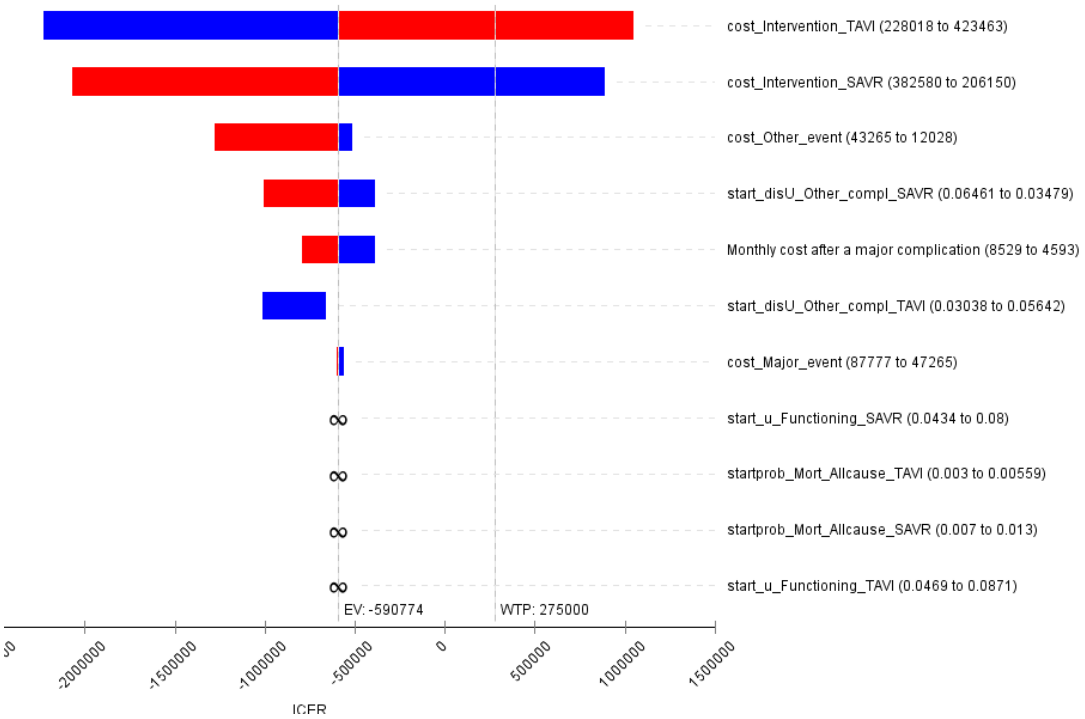


Figure 9. Tornado diagram revealing possible impact of reasonable variation in main parameters on the ICER of TAVI compared to SAVR.

6.3 Scenario analyses

In the base-case analysis, we used a composite of two DRGs that are being used to code the SAVR procedures in the Norwegian cardiac surgery centres, i.e. 294 500 kroner per procedure. Below, we consider DRG codes 104A and 104B in separate scenario analyses.

Minimal SAVR estimate

In the first scenario analyses we used a minimal cost of SAVR procedure represented by DRG 104A: Heart valve surgery and equal to 235 682 Norwegian kroner. All other parameters remain unchanged. The results of this analysis are presented in Table 15, results on the cost-effectiveness plane and acceptability curve are presented in Figures 10 and 11.

Table 15. Results of the scenario analysis of cost-effectiveness (min. SAVR procedure costs)

	Total costs (NOK)	Effects (QALYs)	Incremental cost (NOK)	Incremental effect (QALYs)	ICER (NOK/QALY)
SAVR	369 900	9.0026			
TAVI	393 900	9.0574	24 000	0.0548	436 363

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

With DRG 104A the TAVI procedure has an incremental cost of 24 000 NOK compared with SAVR. TAVI has a slight QALY gain, which unchanged from the base case scenario, which yields and incremental cost-effectiveness ratio (ICER) of 436 400 Norwegian kroner per QALY, making TAVI a cost-effective strategy when willingness-to-pay is over 436 400 kroner. For WTP lower that 436 400 kroner SAVR is more likely to be cost-effective (Figure 11).

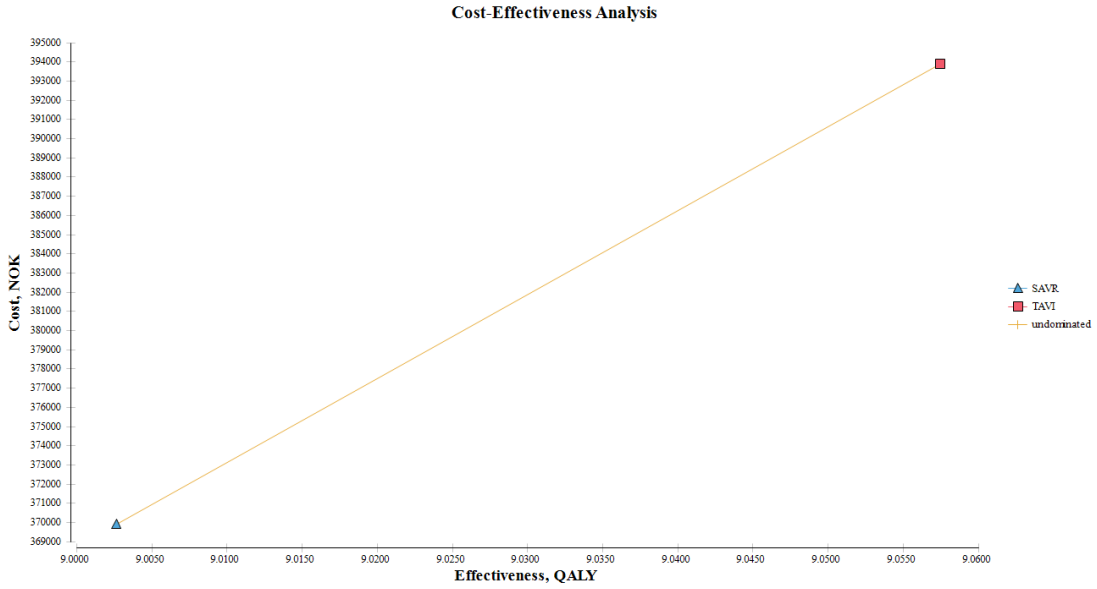


Figure 10. Cost-effectiveness graph TAVI versus SAVR, scenario analysis with minimal SAVR costs

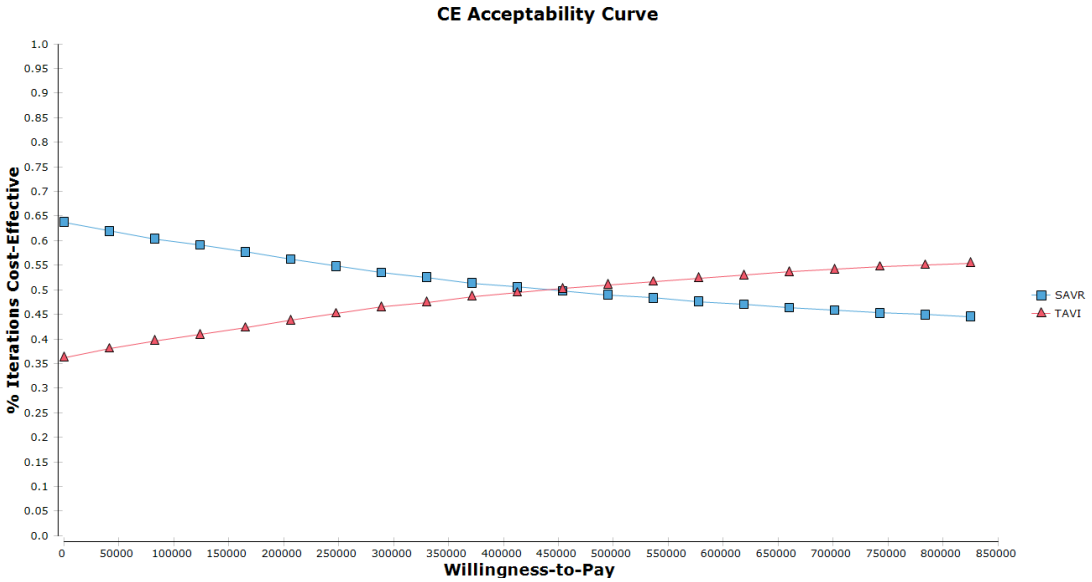


Figure 11. Cost-effectiveness acceptability curves for scenario analysis with minimal SAVR costs indicating the probability that either intervention is cost-effective for a WTP range from zero to 825 000 NOK per QALY.

Maximal SAVR estimate

In the second scenario analysis we assume that SAVR procedure costs are represented by the DRG 104B: surgery on multiple heart valves or heart valve surgery with complications, equal to 354 371 Norwegian kroner, all remaining parameters unchanged.
The average results of this analysis are presented in Table 16, results on the cost-effectiveness place and acceptability curve are presented in Figures 11 and 12.

Table 16. Results of the scenario analysis of cost-effectiveness (max SAVR procedure costs)

Procedure type	Total costs (NOK)	Effects (QALYs)	Incremental cost (NOK)	Incremental effect (QALYs)	ICER (NOK/QALY)
SAVR	488657	9.0073			
TAVI	394 084	9.0629	-94 573	0.0556	dominant

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

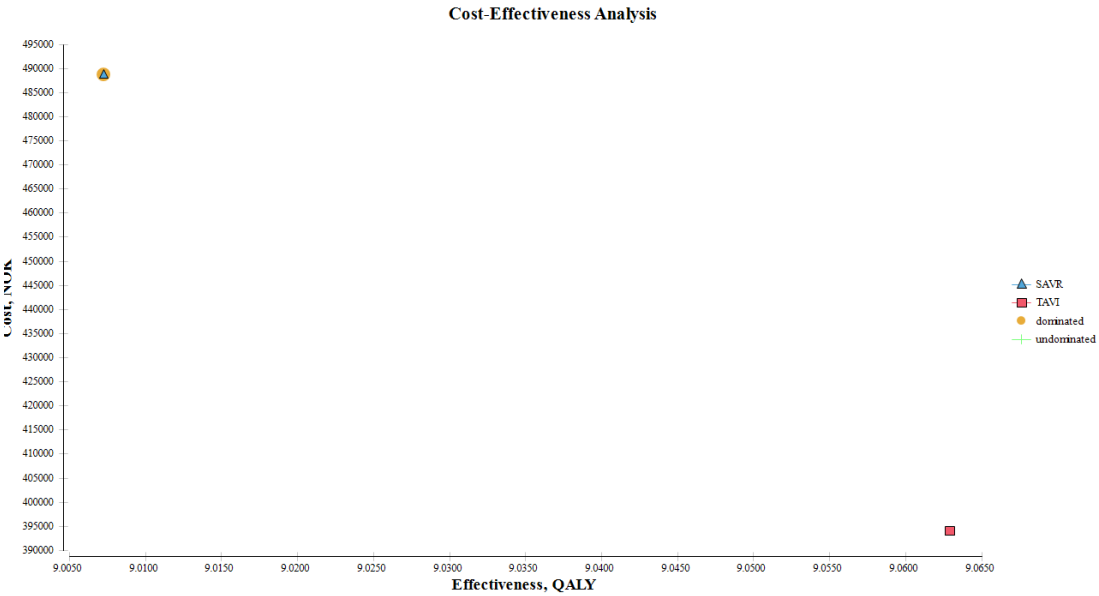


Figure 12. Cost-effectiveness graph TAVI versus SAVR, scenario analysis with maximal SAVR cost estimates

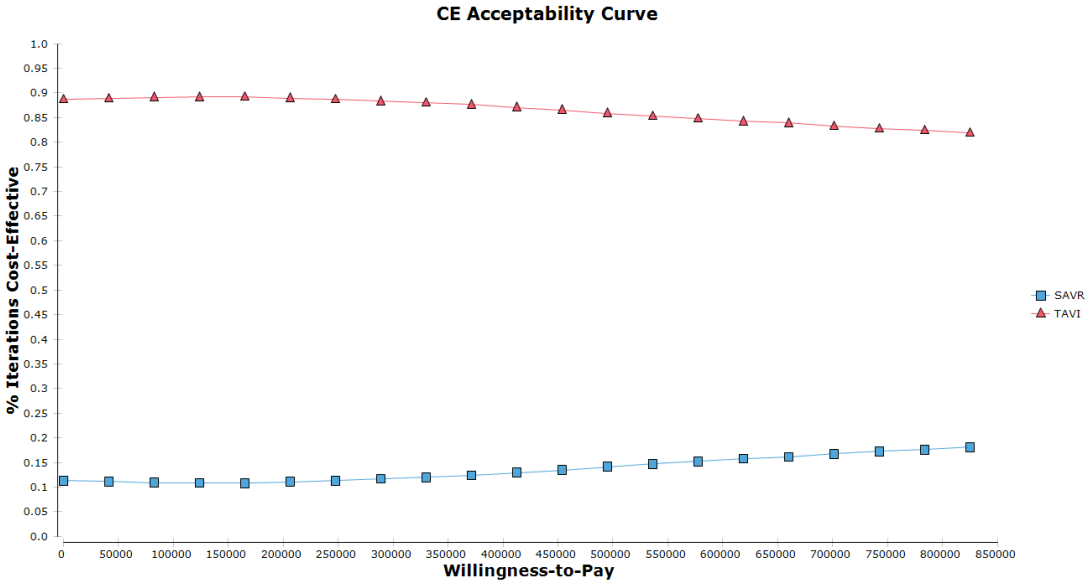


Figure 13. Cost-effectiveness acceptability curve (maximal SAVR cost estimates).

The results of the analysis when a maximum SAVR cost was used, show that TAVI is both less costly (95 000 kroner) and better in terms of effectiveness than SAVR. TAVI is a dominant strategy over SAVR and consistently has at least 80% probability of being cost-effective (Figure 13).

<u>One-year perspective</u>

In another scenario, we modified the base care scenario by shortening the time perspective of the model from 15 years to one year, but the conclusion that TAVI is cost-effective remained robust (Table 17, Figure 14 and Figure 15).

Table 17. Results of the scenario analysis of cost-effectiveness (one-year perspective)

	Total costs (NOK)	Effects (QALYs)	Incremental cost (NOK)	Incremental effect (QALYs)	ICER (NOK/QALY)
SAVR	340 789	0.6625			
TAVI	344 118	0.7610	3 329	0.0985	33 800

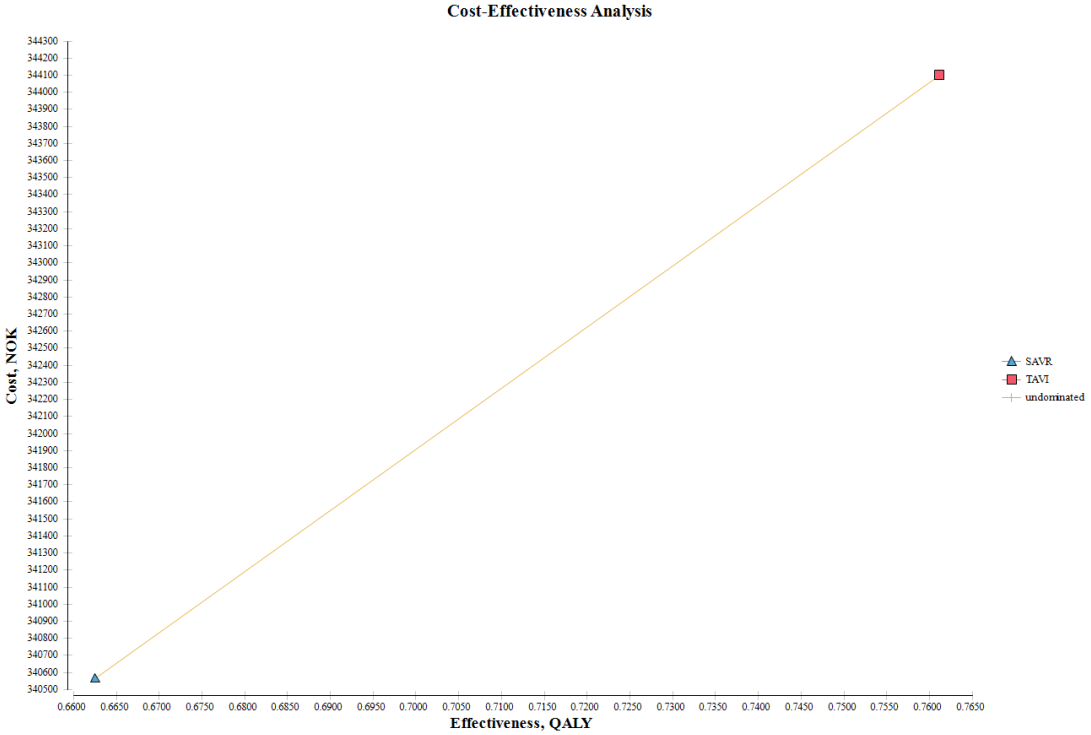


Figure 14. Cost-effectiveness graph TAVI versus SAVR, scenario analysis with one-year time perspective

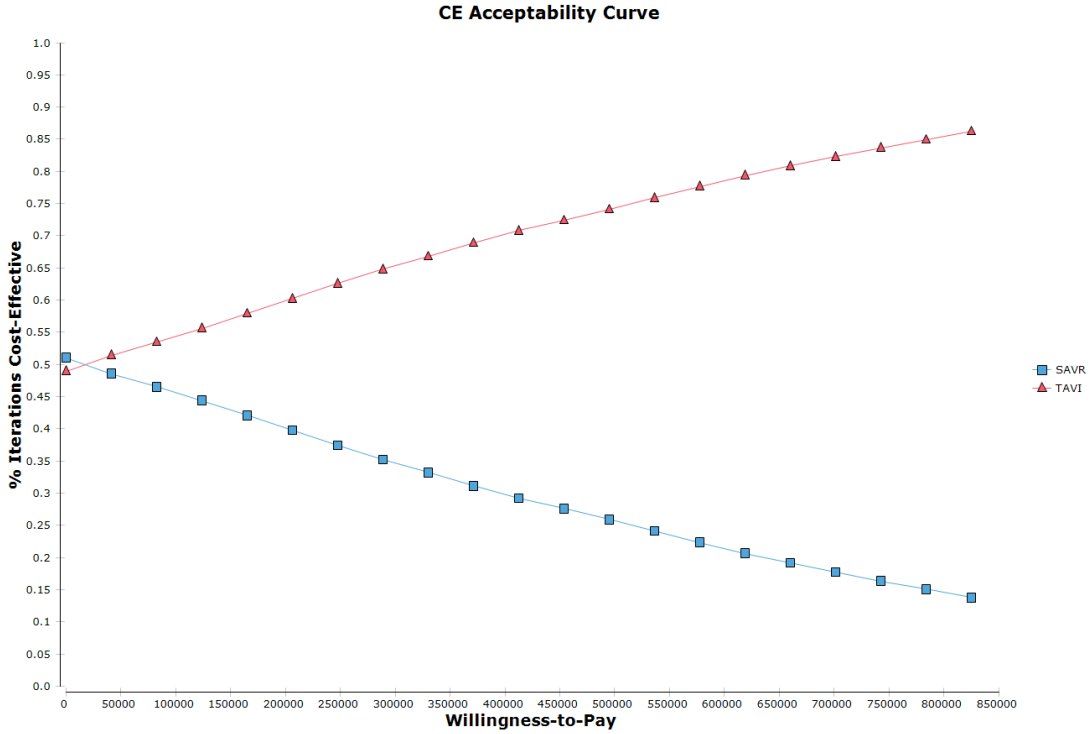


Figure 15. Cost-effectiveness acceptability curve (one-year time perspective)

6.4 Severity considerations - Absolute shortfall

In accordance with the economic model, we assume that patients are 73 years of age when entering the model. At this age, the expected quality-adjusted life expectancy in the absence of disease is equal to 11.0 (57). The prognosis with disease expected to be 8.98 QALYs for standard treatment i.e. SAVR, based on simulations from the health economic model with lifetime (15 years) time horizon (see Table 13). The absolute shortfall with these assumptions is:

AS = 11.0 – 8.98 = 2.02 QALYs

This puts patients with severe aortic stenosis and low surgical risk in severity class 1 (see glossary: severity class).

6.5 Budget impact

The budgetary impact of expanding use of TAVI to patients with low (and intermediate) surgical risk in the coming years depends on several factors, including changes in clinical 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 and the Norwegian Register for Invasive Cardiology (NORIC), the absolute number of TAVI procedures as

well as their share in all aortic valve replacement procedures are rising. In 2019 TAVI made for more than 60% of all aortic valve implantations (Figure 16).
In 2019 there were 939 TAVI procedures performed in Norway, compared with 796 procedures in 2018 and 632 in 2017, see Table 18.

Table 18. Number of TAVI procedures performed in Norway, years 2015-2019

Year	2015	2016	2017	2018	2019
Number of TAVI procedures	396	534	632	796	939
Increase from previous year		35%	18%	26%	18%

Data from the Norwegian Register for Invasive Cardiology (58).

According to the Norwegian Register for Cardiac Surgery, the number of all aortic valve replacements is also steadily increasing, whereas the number of open surgery procedures has been relatively stable, falling in the recent years (see figure 16).

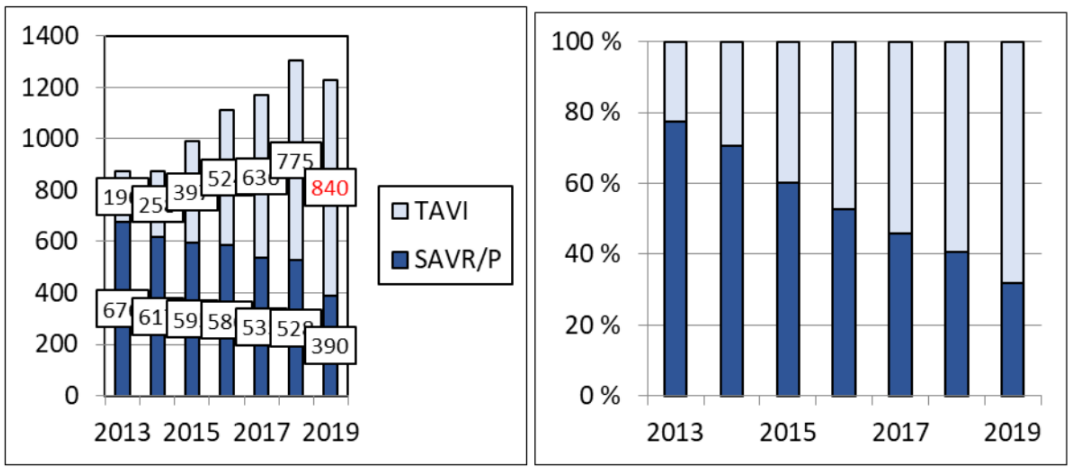


Figure 16. Use of TAVI and SAVR in Norway in absolute numbers (left) and increase in TAVI-share among all isolated aortic procedures (right). Source: Norwegian Register for Cardiac Surgery (2019-report)(11)

Based on the above figures, the annual increase in total number of isolated aortic valve replacement procedures has been between 5 and 15%. The use of TAVI has been growing faster: 18-35% annually, which indicates that, in clinical practice, the indication expansion is already happening. It is therefore difficult to estimate the impact of the formal inclusion of patients with intermediate and low risk in the indication for TAVI on the health care budget. It seems reasonable to assume that the use of TAVI will continue to increase in the nearest future. At the same time, a certain group of patients will continue to benefit from and qualify for the open surgery option due to anatomy, endocarditis, triple vessel disease or other factors (46).

For our present calculation, we made a conservative assumption that the uptake of TAVI will continue to rise at the rate of between 10 and 20% annually. We also assumed that about a half of this increase is due to ageing population, patient preferences and improvements in diagnostics.

Based on the above assumptions we calculated the number of patients eligible for TAVI as prognosis for the next four years as well as incremental number of patients due to indication expansion, see table 19.

The budget impact was calculated based on the same cost inputs (procedure and cost of treating procedure-related complications) used in the cost-effectiveness model (see table 3). The results of the cost analysis show that in the first year of the procedure TAVI patients incur on average 344 818 Norwegian kroner compared with 343 128 incurred by the SAVR patients (1 690 NOK in incremental cost), as shown in Table 14. In the years following the procedure these differences also remain low. Considering the differences in cost of the two procedures in the first year being so minor (less than 1%), uncertainty of the true procedure costs and lack of data beyond one year, we conclude that transfer of patients from SAVR onto TAVI is likely to be cost-neutral in the short run.

Table 19. 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	2020*	2021*	2022*	2023*	2024*
Number of TAVI procedures*	1 080	1 242	1 428	1 642	1 877
Incremental annual increase in number of TAVI patients	141	162	184	214	235

**Prognosis, based on the assumptions listed above*

7 - Discussion

7.1 Key findings

Through a total of eight randomised trials, including the two most recent and biggest trials on patients with low surgical risk published in 2019, evidence on TAVI for patients with severe aortic stenosis has accumulated. The systematic review by Zhang et al. evaluated the effect of TAVI across all risk groups, and showed that TAVI compared with SAVR

- probably improves all-cause mortality or disabling stroke at 30-day, 1-year, and 2-year, but not at long-term follow-up
- probably reduces incidence of new-onset atrial fibrillation at all follow-ups, although increases with time
- may slightly reduce incidences of major bleeding, new-onset fibrillation, and acute kidney injury
- probably increases the incidence of transient ischemic attacks, major vascular complications, permanent pacemaker implantation, reintervention, and paravalvular leak
- probably makes little or no differences for all-cause mortality and cardiovascular mortality and myocardial infarction after 2 years

As identified for the individual risk groups in our earlier reports, we need more data to determine longer-term performance of TAVI across all risk groups. This is especially relevant to patients at low surgical risk where follow up data is more limited. Long term data is also vital for patients with severe aortic stenosis of younger age, independent of surgical risk. Better documentation on structural valve degeneration over time is increasingly relevant with longer post procedural life expectancy.

7.2 Strengths and weaknesses of this systematic review

We performed an exhaustive search to identify all eligible systematic reviews that addressed our review questions published after April 2019. We did not apply language restrictions to the publications searched. Our systematic review identified two systematic reviews, one moderate and one high quality, on patients across all surgical risk groups.

We identified eleven systematic reviews on the low surgical risk group and two systematic reviews on patients at low to intermediate risk. All systematic reviews included the two large RCTs on patients with low risk published in May 2019 (12, 13). We did not perform a search for primary studies, but the risk that other relevant primary studies have been published is low. The Cochrane review (25) searched for ongoing studies and identified one ongoing trial: Comparison of Transcatheter Versus Surgical Aortic Valve Replacement in Younger Low Surgical Risk Patients With Severe Aortic Stenosis (NOTION-2) (59).

Due to the many available systematic reviews, we focused our review on one systematic review spanning all risk groups and one systematic review analysing the lowest risk group (25). They were chosen due to their robust reporting manner and the GRADE assessments of their results. We compared the findings of all included reviews. As we chose to report the authors' findings without further analysis beyond quality assessment, the weaknesses acknowledged in both original systematic reviews remain as reported in their original form. The breadth of information available provides a thorough overview of effects associated with TAVI and SAVR and mirrors the complexity of the intervention and the heterogeneity of persons with severe aortic stenosis. The absence of long-term data across all risk groups makes it difficult to identify persons who may benefit most from TAVI. In addition, the outcomes may change with increasing age, this was not separately analysed by either systematic reviews across risk groups. Based on the found increased risk for re-intervention after TAVI, age may play an important role in identifying patients which benefit the most. To further address the clinical decision making for individual patient groups, a more stratified analysis of outcomes may be more practical. The ongoing update of the 2016 rapid recommendation published by the BMJ will address this (60).

A point of relevance is that the majority of the RCTs covered in all reviews are industry sponsored.

7.3 Consistency with other reviews

The findings of the 2018 EUnetHTA report on TAVI in patients with intermediate surgical risk, and the 2012 NIPH report concerning high risk patients are relevant, although longer follow up data has reduced earlier uncertainties (3, 7). Echoing this, for patients at high surgical risk, TAVI is evaluated as non-inferior to SAVR and considered the recommended treatment by the American Heart Association, Class I (strength of recommendation) (61). The recent US Food and Drug Administration approval of certain TAVI devices in low-risk individuals indicates an ever-broader acceptance for this approach (FDA 2019). For the Norwegian setting the Norwegian registry for invasive cardiology collects yearly data across all risk groups. The annual report shows increased use and outcomes in line with the favourable findings of the included systematic reviews (58).

7.4 Need for further research

With short term outcomes well studied for all risk groups, RCTs with longer follow-up data are needed to further assess the durability of TAVI for patients with severe aortic stenosis. It may also be beneficial to extend investigation into further outcomes such as pain scores, quality of life measures, and recovery time, etc. Additionally, investigators should aim to include younger participants. The ongoing NOTION-2 trial for the low surgical risk population (NCT02825134) is including younger participants and has planned a minimum of five-year follow-up (59). However, even longer follow up with ten years and beyond is needed to be more certain about how TAVI performs for patients with greater life expectancy. Most participants in all RCTs were 70 years or older, so these findings might not be transferable to much younger patients. Furthermore, with younger patients targeted, better documentation on structural valve degeneration is needed to inform treatment choice for patients with longer post procedural life expectancy.

7.5 Economic evaluation

In the economic evaluation, we assessed cost-effectiveness of TAVI compared with SAVR for patients with severe aortic stenosis at low risk. We chose to use clinical data from the randomised multicentre trial PARTNER 3 (Placement of Aortic Transcatheter Valves 3) to inform the analyses. The results of the base-case scenario in our cost-effectiveness analysis show that the total expected average intervention-related costs per patient in a 15-year perspective are about 428 000 NOK for patients who undergo SAVR and 393 00 NOK for patients who get TAVI. These include costs of the procedures, and treatment of complications. That makes TAVI about 35 000 less costly per patient in the 15- years perspective, despite higher procedure costs (the difference of about 31 000 NOK) used in the model. At 1 year both procedures come out nearly equal when it comes to the total cost (Table 14).

When it comes to the effectiveness, TAVI patients accumulated also slightly more QALYs, with a difference of about 0.055 QALYs. That makes TAVI a dominant alternative (both better and less costly) over SAVR in the base case analysis. However, these results should be interpreted with caution.

The sensitivity analyses show that results are most influenced by the procedure cost parameters. The aortic valve procedure costs used in the model were based on the DRG-estimates. In Norway, patients in higher risk categories are most often treated with TAVI. It is therefore likely that the DRG representing TAVI is estimated on basis of older and higher risk patients. It is possible that treating patients with lower risks will also impact total procedure costs.

While there is a separate DRG code representing average costs of TAVI procedure, two DRGs: 104A (heart valve surgery) and 104B (surgery on multiple heart valves or heart valve surgery with complications) are used to register SAVR for reimbursement within

the activity-based financing system. There is some variation in coding practices between different hospitals, but a large proportion of isolated, one-valve SAVR procedures are being registered as complicated surgeries (using the 104B code). While in the base-case scenario we assumed the average cost of SAVR being equal to the average of the two DRGs, we note a substantial difference between these two costs (nearly 119 000 Norwegian kroner). In the base case scenario, we have used an average of the two codes to represent the direct SAVR costs. In the scenario analyses we explored results with either 104A or 104B as input, all other parameters remaining unchanged. When the higher value of SAVR estimate was used, TAVI was a dominant strategy by an even higher margin (total difference in costs was 95 000 kroner, with SAVR being the more costly option). However, SAVR was a less costly option (by 24 000 kroner), with the lower SAVR estimate, with ICER of 436 000 kroner per QALY.

In general, the results of both base-case and scenario analyses indicate that relatively modest differences in both effect and total costs between the two procedures. The model is based on data at only one-year follow up and long-term studies on survival, procedure-related complications, prostheses' longevity (used both in TAVI and SAVR) and need for future re-intervention remain to be established and documented. We have only accounted for complications until one year following aorta procedure, assuming no procedure-related complications beyond this point.

There are some considerable variations in clinical practice in Norway regarding the length of stay among the hospitals performing TAVI procedures, with average lengths of stay between 1 and 4 days in 2019 (58). Hospitals with shortest lengths of stay represent also highest proportion of discharge to local hospitals and rehabilitation centres, while centres with longer average stays tend to have higher proportion of discharging the patient directly home. That has an impact on accuracy of procedure cost estimates. The costs of post-discharge institutionalised follow-up and rehabilitation are not included in the analysis.

In the PARTNER 3 study, 95.8% of patients were discharged to home or self-care following the aortic valve procedure in the TAVR group compared with 73.1% in the surgery group (13). In our analysis, we could only account for costs and QALYs related to the post-procedure complications and not cost related to formal or informal care after discharge. However, these costs are indirectly included if a patient experienced any of the major complication (MI, stroke or acute kidney injury).

We used DRG cost weights as estimates of costs of treatment of procedure-related complications. Complications that have long term impact on health status as well as health care costs were gathered in a separate group with major complications and patients who experienced those complications have long time costs in our model. However, the long-term costs of remaining complications, including for example costs of monitoring and replacing pacemakers are not included in the analysis.

Both technologies 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 (46). For TAVI, several different systems

are available. Newer generation devices involve modifications of valve prostheses as well as delivery systems and delivery techniques, having impact on rates of complications. Valve replacement is a complex procedure with the operator learning curve playing an important role for both efficacy and costs of the procedure.

The lifetime of bioprosthetic valves and subsequent need for a new replacement procedure are another key aspect for long-term cost-effectiveness of valve replacement. This is problematic particularly in younger patients, for whom SAVR with insertion of a mechanic valve is a strong option.

We based our health-related quality of life estimates on the results from a single study performed on patients with intermediate risk (PARTNER 2) (34). More evidence on health-related quality of life following the procedures might warrant a revision of these analyses.

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 the choice between the two alternative procedures. 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 degree of invasiveness and convalescence time. The white paper on priority setting 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.

According to the model's assumptions, all complications are treated independently. Our model hasn't got the "memory" of the past adverse events. In line with the recommendations included in the White Paper (39) about use of a health care perspective for health economic analyses, we have not included potential production losses due to differential length of recovery time with TAVI and SAVR and subsequent sick leave. Along with expansion of TAVI, the average age of the patients decreases. At the same time the average age for retirement has a growing trend. An average patient with aortic stenosis and with low risk is 71 years old in our model and retirement age in Norway is 67. However, it is reasonable to assume that in practice, at least some of these patients are still professionally active and the shorter recovery time following TAVI compared with SAVR would have an economic impact in the broader societal perspective.

In the budget impact analysis, we tried to stipulate how the potential expansion of TAVI on to lower risk patients would influence the total number of TAVI performed in the next five years, as well as its budgetary consequences. We have assumed that a steady growth in TAVI uptake of about 15% annually continues following expansion of the indication. It can be argued that the expansion we have observed in the recent years on

the level of 18-35% annually might slow down considerably. This is due to the fact that the informal inclusion of patients with low risk happens already and, on the other hand, very frail patients with extreme surgical risks are also already treated with TAVI (46).

The Norwegian TAVI centers use either hybrid operating rooms, hybrid light rooms or angiography laboratories during TAVI procedures. Further expansion of TAVI implies that the capacity in the form of hybrid operating rooms or catheterization angiography laboratories, postoperative posts and trained medical teams will have to expand. We concluded that the transfer of patients from SAVR to TAVI is likely to be cost-neutral in the short run. We did not include the potential costs of increasing capacity for TAVI expansion, and potentially freed resources at the cardiac surgical ward, neither in the TAVI cost estimates nor in the budget impact analysis.

Finally, in absence of an officially defined willingness to pay (WTP) threshold for a QALY gained in Norway, we abstained from performing a net benefits analysis. Such calculations require assuming a fixed value of WTP as they combine both costs, effectiveness and WTP into a single measurement.

7.6 Consistency of the economic evaluation with other studies

We identified two relevant published cost-effectiveness evaluations of TAVI versus SAVR for patients with severe aortic stenosis at low surgical risk surgical risk: one Danish study (62) and an economic evaluation as part of an HTA from Ireland (40). In Table 20 we present the main results of both cost-effectiveness analyses.

Geisler with colleagues constructed a decision-analytic model, a combination of a decision tree and Markov model with 30-day cycles, to estimate the difference in cost and QALYs of TAVI versus SAVR for lower risk patients over a lifetime time horizon from a societal perspective in the Danish setting (63). Their model is based on calibrated 5-years follow up date from the NOTION trial (33). These are currently the longest follow-up available data comparing TAVI and SAVR in lower risk patients. Results of the trial showed no statistical difference for major clinical outcomes (mortality, myocardial infraction and stroke after TAVI compared to SAVR. Higher rates of prosthetic regurgitation and pacemaker implantation following TAVI were observed.

The authors evaluated cost-effectiveness in relation to the willingness-to-pay (WTP) threshold of 1.13 million Danish kroner (DKK). The base-case results showed that TAVI was associated with an incremental cost of DKK 65 000 and a QALY gain of 0.09 compared with SAVR, resulting an ICER of DKK 696 264 per QALY. They also performed various scenario analyses to assess the effect of uncertainty on their results, which ranged from DKK 334 200 to DKK 904 100 per QALY, all below the WPT accepted for reimbursement in the Danish health care system. The conclusion was that TAVI is likely to be a cost-effective strategy for low risk patients. The higher TAVI device prices were partly compensated for by the lower procedural and hospitalization costs (63).

Table 20: TAVI vs. SAVR cost-effectiveness evaluations for patients at low surgical risk

Study	**Geisler et al. 2019 (62)**	**Health Information and Quality Authority 2019 (40)**
Model Analysis	CUA	CUA
Population	Study population reflects the Nordic Aortic Valve Intervention (NOTION) (patients with lower surgical risk). The average patient age is 79.1 years, 46.8% are female, the average STS score is 2-3%. 60-month data	Study population reflects PARTNER 3 (patients with low surgical risk). The average patient age is 71 years, 67.5% are male, the average STS score < 4% 12-month data
Intervention	Core Valve (Medtronic)	2nd gereration Sapien 3 (Edwards)
Setting	Denmark	Ireland
Comparison	SAVR	SAVR
Incremetal QALY (TAVI-SAVR)	0.09	0.021
Incremental costs (TAVI-SAVR)	DKK 65 000	€- 387
ICER/QALY	DKK 696 264 / QALY	Dominant

The authors of the Irish HTA from Health Information and Quality Authority evaluated TAVI against SAVR both in patient with intermediate and low risk. In this summary we are only referring to the analyses that apply to the low risk patients. The 30-days and 12-months data from the PARTNER 3 trial were used as effectiveness and safety input in the analysis. A Markov model was constructed where the overall costs and QALYs associated with TAVI and SAVR were calculated by averaging the results of the Monte Carlo simulations. The base-case scenario assessed the cost-utility of TAVI compared with SAVR over a 15-year time horizon. Resulting cost-effectiveness measures included an incremental cost-effectiveness ratio (ICER) and incremental net monetary benefit (INMB). The intervention was considered cost-effective if the ICER fell below 20 000 Euro (€) per QALY gained, which is the most conservative WTP threshold assumed in Ireland. The results of the base-case scenario demonstrated a QALY gain of 0.021 (95% CI: -0.129 to 0.172) in favor of TAVI. TAVI was also associated with a €387 (95% CI: €-8,355 to €7,702) saving in a 15-year perspective. Initially higher procedure costs for TAVI were compensated for with somewhat lower rates of adverse event rates for TAVI than for SAVR. Sensitivity analyses showed that TAVI was no longer cost-effective at the €20,000 per QALY gained threshold when the higher procedural cost estimate for TAVI (and lower procedural cost estimate for SAVR) was applied in the economic model (40).

The structure of our model was partly inspired by the Irish model from HIQA, we used the same efficacy data, included the same types of complications and carried our analyses in similar time perspective.

We consider the results of our cost-effectiveness analysis of TAVI for low risk patients to be consistent with the two above studies. The evaluations found TAVI to be slightly more effective (incremental QALY-gains of between 0.021 and 0.09), while results from our base-case analysis showed 0.05 QALY. The studies also indicate that TAVI is likely to be either cost-effective under defined WTP thresholds or cost-saving when compared to SAVR.

8 - Conclusion

We conclude that TAVI compared with SAVR probably reduces all-cause mortality and disabling stroke until two years, and that this result is valid across all surgical risk groups. TAVI may slightly reduce the risk of major bleeding, new-onset fibrillation, and acute kidney injury whereas SAVR probably reduces the risk of transient ischemic attacks, major vascular complications, permanent pacemaker implantation, re-intervention, and paravalvular leak. Across all risk groups, TAVI probably makes little or no difference for all-cause and cardiovascular mortality, myocardial infarction, and stroke at long-term follow-up. The clinical decision for either option may benefit from a broader evaluation of the patient's medical state and life expectancy due to uncertainty regarding long term effects.

The cost-utility analysis indicated that TAVI for patients at low surgical risk was marginally more effective (incremental effectiveness: 0.05 QALYs) and less costly (saving of NOK 35 000) than SAVR. The analysis is based on 1-year follow-up data from the PARTNER 3 study and long-term mortality and adverse events for TAVI and SAVR beyond this period remain unclear. The results are sensitive to variations in procedure costs.

The budget impact analysis indicates that the introduction of TAVI for low risk patients is likely to be cost-neutral in the short run. However, we have not accounted for the costs of the capacity expanding.

The calculated absolute shortfall for patients with severe aortic stenosis and low surgical risk relative to individuals in the general population is calculated to two QALYs.

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Appendices

Order of appendices

Name appendices as they appear in the text:

- Search strategy
- Model structure
- Clinical outcomes from PARTNER 3 study used as input in the model
- Project plan
- User involvement

Appendix 1. Search strategy

Database: PubMed/Medline: **<2019/4/1 - 2020/7/5>, Search date: 2020-07-05**

Search:
(Transcatheter aortic valve replacement) OR (Transcatheter aortic valve implantation) OR (Transcatheter aortic valve implantation) Filters: **Meta-Analysis, Systematic Review, from 2019/3/1 - 2020/7/5**

((("transcatheter aortic valve replacement"[MeSH Terms] OR ((("transcatheter"[All Fields] AND "aortic"[All Fields]) AND "valve"[All Fields]) AND "replacement"[All Fields])) OR "transcatheter aortic valve replacement"[All Fields]) OR ((((("transcatheter aortic valve replacement"[MeSH Terms] OR ((("transcatheter"[All Fields] AND "aortic"[All Fields]) AND "valve"[All Fields]) AND "replacement"[All Fields])) OR "transcatheter aortic valve replacement"[All Fields]) OR ((("transcatheter"[All Fields] AND "aortic"[All Fields]) AND "valve"[All Fields]) AND "implantation"[All Fields])) OR "transcatheter aortic valve implantation"[All Fields])) OR ((((("transcatheter aortic valve replacement"[MeSH Terms] OR ((("transcatheter"[All Fields] AND "aortic"[All Fields]) AND "valve"[All Fields]) AND "replacement"[All Fields])) OR "transcatheter aortic valve replacement"[All Fields]) OR ((("transcatheter"[All Fields] AND "aortic"[All Fields]) AND "valve"[All Fields]) AND "implantation"[All Fields])) OR "transcatheter aortic valve implantation"[All Fields])

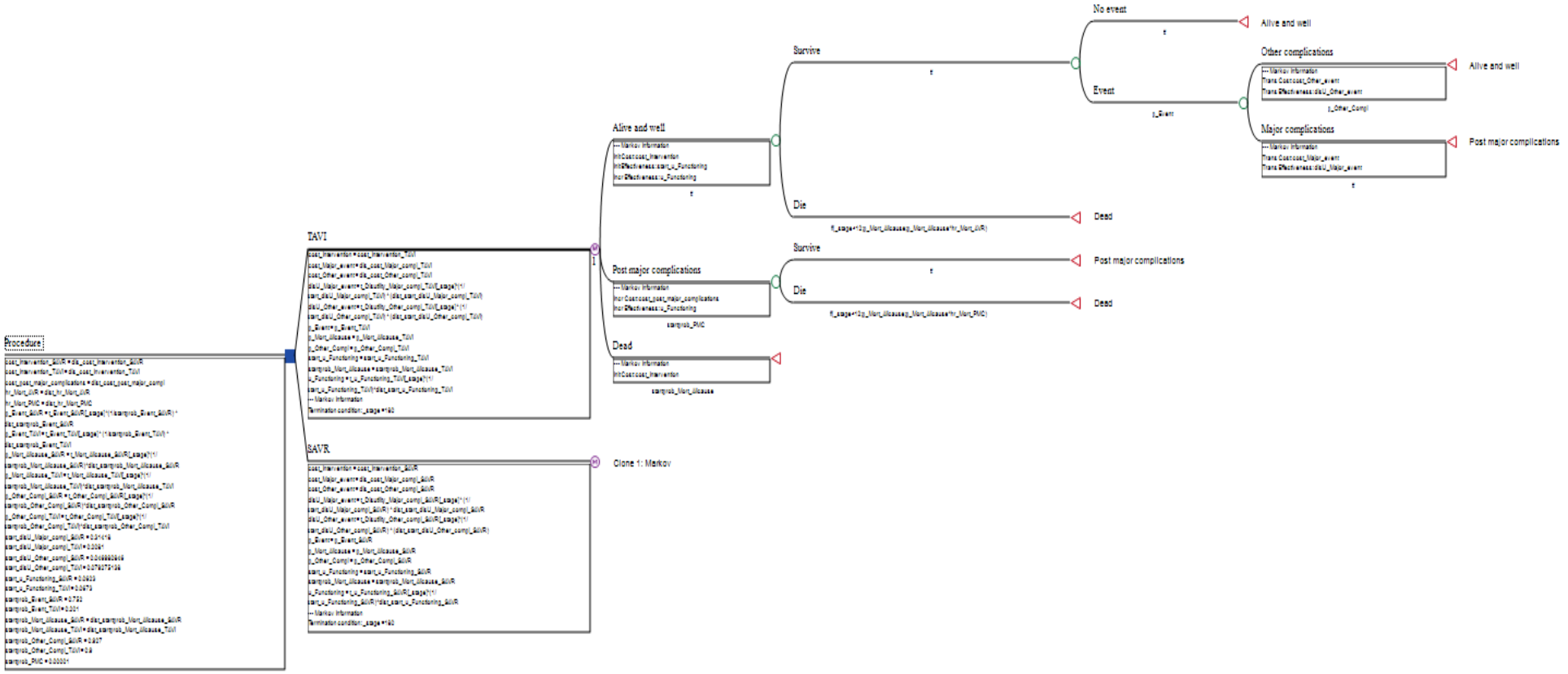
Translations

Transcatheter aortic valve replacement: "transcatheter aortic valve replacement"[MeSH Terms] OR ("transcatheter"[All Fields] AND "aortic"[All Fields] AND "valve"[All Fields] AND "replacement"[All Fields]) OR "transcatheter aortic valve replacement"[All Fields]

Transcatheter aortic valve implantation: "transcatheter aortic valve replacement"[MeSH Terms] OR ("transcatheter"[All Fields] AND "aortic"[All Fields] AND "valve"[All Fields] AND "replacement"[All Fields]) OR "transcatheter aortic valve replacement"[All Fields] OR ("transcatheter"[All Fields] AND "aortic"[All Fields] AND "valve"[All Fields] AND "implantation"[All Fields]) OR "transcatheter aortic valve implantation"[All Fields]

Appendix 2. Model structure

Appendix 2. Model structure: TAVI vs. SAVR in patients with severe aortic stenosis and low surgical risk



Appendix 3. Clinical outcomes from PARTNER 3

Appendix 3. Clinical outcomes from PARTNER3 study. Source: Supplement to: Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with balloon-expandable valve in low-risk patients (13)

	30 Days			1 Year		
	TAVR (N = 496)	Surgery (N = 454)	Treatment Effect [95% CI]	TAVR (N = 496)	Surgery (N = 454)	Treatment Effect [95% CI]
Death, Stroke, or Rehospitalization†	4.2% (21)	9.3% (42)	0.45 [0.27, 0.76]	8.5% (42)	15.1% (68)	0.54 [0.37, 0.79]
Death						
From any cause	0.4% (2)	1.1% (5)	0.37 [0.07, 1.88]	1.0% (5)	2.5% (11)	0.41 [0.14, 1.17]
Cardiac death	0.4% (2)	0.9% (4)	0.46 [0.08, 2.49]	0.8% (4)	2.0% (9)	0.40 [0.12, 1.30]
Non-cardiac death	0.0% (0)	0.2% (1)	0.00 [NA]	0.2% (1)	0.5% (2)	0.44 [0.04, 4.88]
Stroke						
Any stroke	0.6% (3)	2.4% (11)	0.25 [0.07, 0.88]	1.2% (6)	3.1% (14)	0.38 [0.15, 1.00]
Disabling stroke	0.0% (0)	0.4% (2)	0.00 [NA]	0.2% (1)	0.9% (4)	0.22 [0.03, 2.00]
Non-disabling stroke	0.6% (3)	2.0% (9)	0.30 [0.08, 1.12]	1.0% (5)	2.2% (10)	0.45 [0.15, 1.32]
TIA	0.0% (0)	0.7% (3)	0.00 [NA]	1.0% (5)	1.1% (5)	0.89 [0.26, 3.06]
Death or stroke	1.0% (5)	3.3% (15)	0.30 [0.11, 0.83]	1.8% (9)	4.9% (22)	0.36 [0.17, 0.79]
Death or disabling stroke	0.4% (2)	1.3% (6)	0.30 [0.06, 1.51]	1.0% (5)	2.9% (13)	0.34 [0.12, 0.97]
Rehospitalization†	3.4% (17)	6.5% (29)	0.53 [0.29, 0.97]	7.3% (36)	11.0% (49)	0.65 [0.42, 1.00]
Major vascular complications	2.2% (11)	1.5% (7)	1.44 [0.56, 3.73]	2.8% (14)	1.5% (7)	1.83 [0.74, 4.55]
Life-threatening / disabling, or major bleeding	3.6% (18)	24.5% (111)	0.12 [0.07, 0.21]	7.7% (38)	25.9% (117)	0.25 [0.17, 0.37]
Life-threatening / disabling bleeding	1.2% (6)	11.9% (54)	0.09 [0.04, 0.22]	2.8% (14)	12.8% (58)	0.20 [0.11, 0.36]
Myocardial infarction	1.0% (5)	1.3% (6)	0.76 [0.23, 2.50]	1.2% (6)	2.2% (10)	0.54 [0.20, 1.49]
Acute Kidney Injury Stage II or III‡	0.4% (2)	1.8% (8)	NA	NA	NA	NA
Requirement for renal replacement‡	0.2% (1)	0.7% (3)	0.30 [0.03, 2.93]	0.2% (1)	0.7% (3)	0.30 [0.03, 2.93]
New permanent pacemaker	6.5% (32)	4.0% (18)	1.66 [0.93, 2.96]	7.3% (36)	5.4% (24)	1.39 [0.83, 2.33]
New permanent pacemaker (Baseline pacemaker excluded)	6.6% (32)	4.1% (18)	1.65 [0.92, 2.95]	7.5% (36)	5.5% (24)	1.38 [0.82, 2.32]
New LBBB	22.0% (106)	8.0% (35)	3.17 [2.13, 4.72]	23.7% (114)	8.0% (35)	3.43 [2.32, 5.08]
New onset atrial fibrillation	5.0% (21)	39.5% (145)	0.10 [0.06, 0.16]	7.0% (29)	40.9% (150)	0.13 [0.09, 0.20]
Coronary obstruction requiring intervention	0.2% (1)	0.7% (3)	0.30 [0.03, 2.93]	0.2% (1)	0.7% (3)	0.30 [0.03, 2.93]
Aortic Valve Re-intervention	0.0% (0)	0.0% (0)	N/A	0.6% (3)	0.5% (2)	1.33 [0.22, 7.95]
Endocarditis	0.0% (0)	0.2% (1)	0.00 [N/A]	0.2% (1)	0.5% (2)	0.44 [0.04, 4.89]
Asymptomatic Valve thrombosis	0.2% (1)	0.0% (0)	N/A	1.0% (5)	0.2% (1)	4.47 [0.52, 38.24]
Discharged to home/self-care§	475/495 (96.0%)	331/453 (73.1%)	22.9% [18.45%, 27.33%]	N/A	N/A	N/A
NYHA Class II/III/IV§	97/493 (19.7%)	144/433 (33.3%)	-13.6% [-19.24%, -7.92%]	85/480 (17.7%)	68/407 (16.7%)	1.0% [-3.98%, 5.98%]
Six-minute walk test distance (m) change from baseline¶	17.2 ± 4.63	-15.2 ± 6.27	33.7 [19.9, 47.4]	15.4 ± 5.30	15.1 ± 5.85	-1.4 [-15.2, 12.5]
KCCQ-OS score change from baseline¶	18.5 ± 0.83	2.5 ± 1.05	16.1 [14.2, 18.0]	19.4 ± 0.87	17.4 ± 0.99	1.8 [0.2, 3.4]

Appendix 4. Project Plan

folkehelseinstituttet

Project plan for:
Transcatheter aortic valve implantation (TAVI) in severe aortic stenosis across all surgical risk groups

Project number:	Nye Metoder ID2019_089
Plan prepared	28.02.2020

Short title:
Review: Transcatheter aortic valve implantation (TAVI) in severe aortic stenosis across all surgical risk groups

Short summary:
Heart failure due to aortic stenosis represents an increasing health problem with increasing age, and hence in an aging society. Transcatheter aortic valve implantation (TAVI) is an alternative to the traditional open-heart surgery approach. For more than a decade, TAVI has been the endorsed form of treatment for patients at high surgical risk. In April 2017, Bestillerforum RHF commissioned the Norwegian Institute of Public Health to assess the effectiveness, safety and economic consequences of broadening the indication for TAVI to patients at intermediate operative risk. In meetings on 26.08.2019 and 23.09.2019, the Ordering forum (Bestillerforum RHF) commissioned an update on TAVI across all surgical risk groups, including the low surgical risk group.

Norsk:
Folkehelseinstituttet har fått oppdrag om å vurdere effekt, sikkerhet og helseøkonomiske konsekvenser av TAVI behandling i pasienter med alvorlig aortastenose på tvers av alle kirurgiske risikogrupper.

Hjertesvikt på grunn av aortastenose representerer et økende helseproblem med alderen, og i et aldrende samfunn. Transcatheter aortic valve implantation (TAVI) er et alternativ til tradisjonell åpen hjerteoperasjon. I nå over ti år har TAVI vært en godkjent behandlingsform for pasienter med høy kirurgisk risiko. I april 2017 fikk Folkehelseinstituttet i oppdrag av Bestillerforum RHF å vurdere effektiviteten, sikkerheten og økonomiske konsekvensene av å utvide indikasjonen for TAVI til pasienter med mellomliggende operativ risiko. På slutten av 2019 igangsatte Bestillerforum RHF en oppdatering om TAVI på tvers av alle kirurgiske risikogrupper, inkludert lav kirurgisk risiko gruppen.

Project category and commissioner	
Product:	Metodevurdering
Thematic area:	Specialist healthcare (Cardiology)
Commissioner:	Bestillerforum RHF, Nye Metoder
Project management and participants	
Project leader:	Jan Himmels
Responsible for the project:	Signe Flottorp
Internal project participants:	Beate Charlotte Fagerlund beate.charlotte.fagerlund@fhi.no ; Anna Stoinska-Schneider Anna.Stoinska-Schneider@fhi.no
External project participants:	Gry Dahle, overlege Thoraxkirurgisk avdeling OUS Rikshospitalet Øyvind Bleie, seksjonsoverlege, Hjerteavdelingen, Helse Bergen Reidar Bjørnerheim, seksjonsoverlege, dr. med. Ekkolaboratoriet, OUS Ullevål
Plan for replacement if project participants drop out:	Will be decided by the person responsible for the project

Mandate

The Ordering Forum representing the four Regional Health Authorities (Bestillerforum RHF) commissioned on the 23.09.2019 an updated assessment of the method across all risk groups: ID2019_089 Catheter-based implantation of aortic valves (TAVI / TAVR) in the treatment of patients with severe aortic stenosis (1).

The aim

The aim of this review is to collate existing systematic reviews about the effectiveness of TAVI in low risk patients and to extract and analyse their results across important outcomes. Additionally we will summarise findings for the high/intermediate surgical risk group, and supplement these with recently published evidence to provide a comprehensive overview of TAVI across risk groups, including an in-house health economic assessment for the lowest surgical risk group.

Introduction

Heart failure due to aortic stenosis is an increasing health problem with increasing age, and hence in an aging society (2;3). In general, medical therapy has relatively poor efficacy in treating severe aortic stenosis. Therefore, only until a few years ago, surgical treatment had been the treatment of choice. This has changed with the introduction of the transcatheter aortic valve implantation (TAVI) method, also referred to as transcatheter aortic valve replacement (TAVR), a bioprosthesis deployed in the aortic valve using a catheter. In contrast to traditional open-heart surgery or surgical aortic valve replacement (SAVR), the procedure is less invasive and can be performed with light sedation and without cardiopulmonary bypass (exhaustive background information can be found in the EUnetHTA report (4)).

The effect and safety of TAVI in comparison to SAVR was initially established in patients at high surgical risk (based on the Society of Thoracic Surgeons Predicted Risk of Mortality (STS) score > 8 -15%). For more than a decade, TAVI has been the endorsed form of treatment for patients at high surgical risk. Evidence supporting this came from two large industry funded clinical trials in high-risk patients (5;6). The Norwegian Institute of Public Health published a summary of these findings in 2012 (7).

With progressive clinical use and the established effect and safety for TAVI in high-risk patients, the focus for TAVI producers shifted to patients at intermediate surgical risk (STS score 4–8%). The two main producers, Edwards Lifesciences and Medtronic, conducted clinical trials to assess the effect and safety for the intermediate surgical risk group (8;9).

The Ordering Forum (Bestillerforum) on 14.11.2016 commissioned the Norwegian Institute of Public Health to conduct a single HTA, based on a horizon scan from NIPH (*Metodevarsel ID2016_076 Kateterbasert implantasjon av aortaklaffer (TAVI/TAVR) i behandling av pasienter med alvorlig aortastenose og intermediær operativ risiko*), and then changed this to a full HTA 24.04.2017. In 2018, the Norwegian Institute of Public Health published, in cooperation with EUnetHTA, a report describing the non-inferiority of TAVI in the intermediate risk population (4). In addition, NIPH published a supplementary health economic assessment (10).

Use of TAVI is on the rise in Norway; from 2017 onwards, there have been more TAVI procedures than open-heart surgeries for aortic stenosis (figure 1 and figure 2). Data from the Norwegian register for cardiac surgery shows that this increase is associated with an absolute increase of aortic valve interventions since 2015 (11).

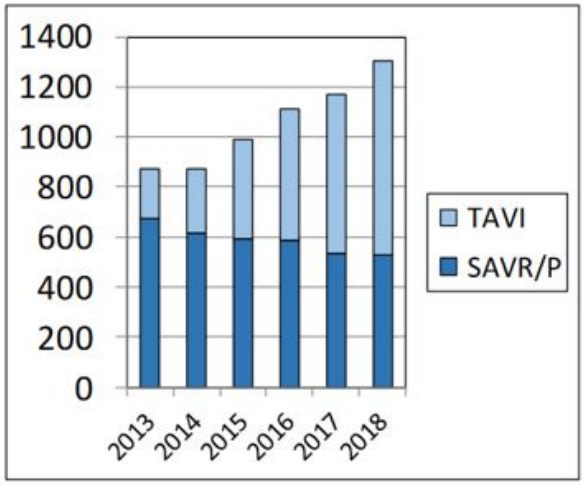


Figure 1 TAVI/SAVR performed in Norway, Norsk hjertekirurgiregister

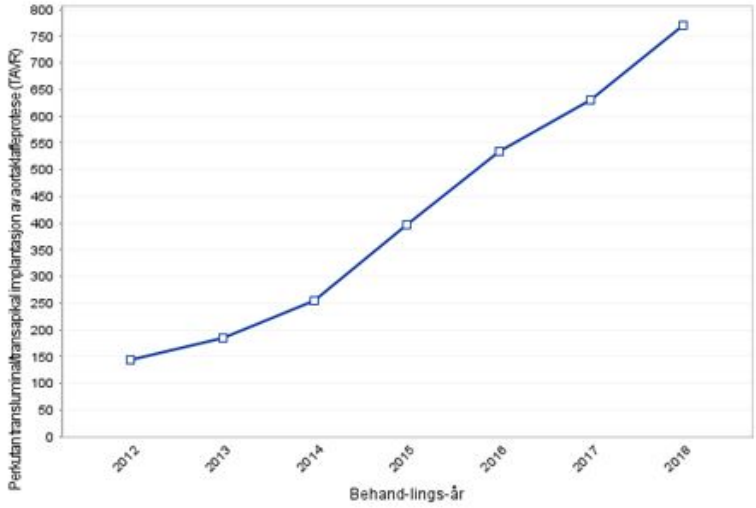


Figure 2 TAVI performed in Norway, Norsk hjertekirurgiregister, http://statistikkbank.fhi.no/hkr/

In August 2019, in light of two newly completed RCTs (12;13) including patients at low surgical risk (STS score <4%), Bestillerforum decided to await a review across all risk groups before concluding this matter (14;15). Bestillerforum RHF commissioned the Norwegian Institute of Public Health to perform an assessment across all risk groups (*ID2019_089_Catheter-based implantation of aortic flaps (TAVI / TAVR) in the treatment of patients with severe aortic stenosis. Assessment across risk groups* (16)).

Methods

We will conduct an overview of systematic reviews in guidance with the Handbook used at the Division for Health Services at the Norwegian Institute of Public Health (17).

Inclusion criteria

We will use the following inclusion criteria:

Population	Patients with severe aorta stenosis at high / intermediate / low risk surgical risk of death, as described by New York Heart Association Functional class (NYHA class), or by The Society of Thoracic Surgeons' risk model score (STS score), or European System for Cardiac Operative Risk Evaluation (EuroScore) or EuroSCORE II, with emphasis on studies reporting on low risk.
Intervention	Catheter based implantation of aortic valves (Transcatheter aortic valve implantation (TAVI)). Evaluation will be based on devices with market approval.
Comparison	Open surgery aortic valve replacement. No exclusion by chosen method.
Outcomes	*Effect:* • Mortality at 30 days or longest available (all-cause mortality, cardiovascular mortality, non-cardiovascular mortality) • Improvement of symptoms (reduction in NYHA class) • Improvement of indicators for health-related life quality (i.e. EQ-5D score, SF-12 score, KCCQ score) • Procedural success (successful implantation) • Hemodynamic function of aortic valve • Days in ICU (ICU stay); • Days in hospital; • Re-admission to the hospital due to heart attack (*>72 hours after TAVI*); • Need for permanent pacemaker implantation *Safety:* • All undesired outcomes (i.e. vascular complications, stroke, TIA, major bleeding, re-intervention, heart attack ≤72 hours after procedure, new or worsened atrial fibrillation-flutter, moderate or severe valve leakage(regurgitation), acute kidney damage. Radiation damage patient or staff.
Study design	Systematic reviews and meta-analyses

Literature search

We will conduct a literature search in PubMed/Medline, searching for published peer reviewed systematic reviews beginning May 2019. New England Journal of Medicine published the two newest randomised trials in low-risk patients on web May 2nd 2019 (12;13). Additionally, we plan to check "similar articles" on PubMed and the reference

lists of included studies and other relevant literature. We will not search for primary studies. We will check the electronic search for duplicates in EndNote (18).

Study selection
Two researchers will independently select studies using the above-defined inclusion criteria. We will place emphasis on studies evaluating the low surgical risk group. Two researchers will independently perform full text screening for all potentially eligible studies. A third reviewer or consensus-based discussion will resolve disagreements.

Quality assessment
Two researchers will independently assess the quality for each of the included systematic reviews with a 10-point checklist from our methodology handbook (based on the EPOC Checklist for Refereeing Protocols for Reviews. EPOC, Effective Practice and Organisation of Care group (17;19)).

Data extraction and analysis
One researcher will extract information from the included studies; another researcher will independently check the extraction for accuracy and relevance. We will extract data on the following: full reference, location and date of study. We will extract effect estimates for relevant outcomes.

We will narratively summarise the findings of our earlier reports and provide an overview across all risk groups. We will supplement our former findings with the newly identified literature where possible and relevant.

We will narratively summarise identified reviews and summarise estimates based on existing meta-analyses from the included reviews, supplemented by tables where possible. We will check for potential discrepancies between the systematic reviews and meta-analyses, and search for explanations for such discrepancies.

We will use the most updated review of highest quality, and communicate the findings from this review, including GRADE assessment of certainty of the findings.

Health economic evaluation

We will assess the cost-effectiveness and budget impact of TAVI for patients with severe aortic stenosis and low surgical risk compared with open surgery, and evaluate the intervention against the priority setting criteria applicable in Norway (20).

We will perform a model-based cost-utility analysis (CUA) comparing TAVI with open surgery, where we will account for all relevant costs and health outcomes related to both procedures. We will attempt to adapt and reuse the structure of an existing model, which we have built to assess cost-effectiveness of TAVI for patients with intermediate surgical risk (10). We will express all relevant costs in 2020 Norwegian Kroner (NOK), and effect in quality-adjusted life-years (QALYs), and we will present the results as incremental cost-effectiveness ratio (ICER). The uncertainty in model parameters will be handled by performing a probabilistic sensitivity analyses (PSA). We will perform the analyses from the health care perspective, and use annual discount rate of 4%.

We will also calculate likely budgetary consequences of introducing TAVI as a routine treatment option for patients with severe aortic stenosis and low surgical risk.
In addition, in accordance with the White Paper on Priority Setting (20), we will estimate absolute shortfall for patients with severe aorta stenosis and intermediate surgical risk.

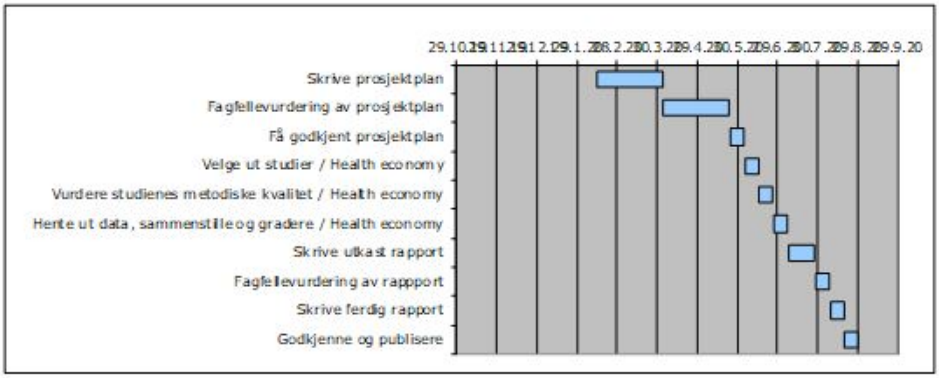
User involvement

We will contact The National Association for Heart and Lung Disease (LHL), and use the involved clinical experts to reach out to the affected patient population. We will ask the selected users to provide input to the draft of the report

Activities, milestones and timeplan

***Tabel 1** Timeplan*

Oppgave	Startdato	Kalender-tid i dager	Sluttdato
Skrive prosjektplan	13.02.2020	50	03.04.2020
Fagfellevurdering av prosjektplan	04.04.2020	50	24.05.2020
Få godkjent prosjektplan	25.05.2020	10	04.06.2020
Velge ut studier / Health economy	05.06.2020	10	15.06.2020
Vurdere studienes metodiske kvalitet / Health economy	16.06.2020	10	26.06.2020
Hente ut data, sammenstille og gradere / Health economy	27.06.2020	10	07.07.2020
Skrive utkast rapport	08.07.2020	20	28.07.2020
Fagfellevurdering av rappport	29.07.2020	10	08.08.2020
Skrive ferdig rapport	09.08.2020	10	19.08.2020
Godkjenne og publisere	20.08.2020	10	30.08.2020



Starting date (for FHI.no): 30/10/2019
Delivery Bestillerforum RHF: 01.09.2020
End date: 01/09/2020

Publication
– A health technology assessment with an evidence update
– Recipient is Bestillerforum RHF Nye metoder.
– The document will be published on the website of Norwegian Institute of Public Health and on the website of Nye metoder.

Indexing for the homepage
Aortic Valve Stenosis; Transcatheter aortic valve implantation (TAVI); Transcatheter aortic valve replacement (TAVR);

Related projects or publications

http://www.helsebiblioteket.no/mednytt/hjerte-og-kar/kateterbasert-implantasjon-av-aortaklaffer-tavi-tavr-i-behandling-av-pasienter-med-alvorlig-aortastenose-og-intermediaer-operativ-risiko

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https://eunethta.eu/wp-content/uploads/2018/12/OTCA06-TAVI-FOR-THE-TREATMENT-OFPATIENTS-AT-INTERMEDIATE-SURGICAL-RISK-FINAL-1.pdf

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Appendix 5. User involvement

Brukermedvirkning
Olav Asserson, 09.10.2020

Jeg er bedt om å være brukerrepresentant for Folkehelseinstituttet angående en rapport om TAVI. Rapportens tittel er "Transcatheter aortic valve implantation (TAVI) versus surgical aortic valve replacement (SAVR) for patients with severe aortic stenosis and low surgical risk and across surgical risk groups: a health technology assessment".

Årsaken til at jeg er utpekt, er at jeg selv fikk satt inn en ny aortaklaff ved hjelp av TAVI 6. september 2017.

Jeg vil presentere meg selv og beskrive hvordan jeg selv opplevde det å være pasient og få satt inn en ny aortaklaff hentet fra en kalv. Disse historiene vil kanskje kunne gi det tørre faglige et tillegg av det virkelige liv.

Om meg selv

Jeg er født i 1948. Medisinsk embetseksamen i 1972, fulgt av spesialisering i generell kirurgi og ortopedisk kirurgi. Leddprotesekirurgi har vært mitt arbeidsfelt. Jeg traff min ektefelle for 50 år siden i disse dager. Vi har barn og barnebarn sammen.

Om min far og arv

Min far fikk på sine eldre dager lungeødem, vann på lungene, og det ble påvist en alvorlig aortastenose. Avdelingsoverlege ved Kardiologisk avdeling, SUS, anbefalte å kun gi medikamentell behandling pga at min far ikke hadde fysikk og mentalitet til å takle en SAVR. Jeg opplever dette som et riktig råd og valg fra legen sin side. Det gikk bra med min far i flere år, men så fikk han lungeødem igjen, ble innlagt, utviklet sepsis og døde.

Min fars søster hadde også aortastenose. De alvorligste symptomene kom sent, og da hadde hun ikke fysikk til en SAVR. Hun ble utredet med tanke på TAVI, men forholdene lå ikke til rette. Med medikamenter fungerte det en stund, men så døde hun.

En ser her at dette kan være et uttrykk for arvelig disposisjon hos meg. Dersom TAVI hadde vært en «lavterskeltilbud» da de levde, så ville de antagelig ha blitt utredet tidligere pga at primærhelsetjenesten blir mer oppmerksom på og leter etter det som er lettere behandlingsbart. Da ville de antagelig ha blitt operert tidligere i sykdomsforløpet, og da ville de antagelig fått leve ytterligere noen år.

Om min TAVI

I en tid merket jeg en suselyd som hjerteslag i hodet når jeg lå på venstre side. Jeg er ikke så opptatt av å observere egne kroppssignaler, så jeg la ikke noen vekt på det, og jeg husker ikke hvor lang tid det sto på.

En gang jeg var til en årlig prat hos min pensjonerte almennpraktiserende lege, lyttet han samvittighetsfullt på hjertet mitt, og sa at han hørte en bilyd jeg burde få sjekket.

Jeg kontaktet en kardiolog på SUS, og han gjorde umiddelbart en ECHO-undersøkelse av meg. Han konstaterte en moderat aortastenose og planla en kontroll etter et år. I det følgende året ble jeg mer oppmerksom, og jeg merket at jeg lettere ble tungpusten enn jeg var vant med. Etter et år var det ny ECHO. Legen konstaterte en alvorlig aortastenose som burde opereres.

Så bar det videre til intervensjonskardiolog på SUS. Da ble det hjertekateterisering som viste fine koronarkar. Det tok bare sekunder fra han hadde lagt inn arterietilgangen til han var fremme og sprøytet kontrast i koronarkarene. Det eneste jeg merket var at det dunket i armhulen da han passerte den med spissen av sonden sin. Så var det CT aorta som var ok, osv. Jeg ble anbefalt å få en ny aortaklaff, og sa jatakk, men ba om at det ble brukt TAVI. Legen talte min sak i Bergen, og TAVI ble akseptert av teamet der oppe.

Inntil da var kardiologer kolleger som jeg diskuterte pasienter med, og som jeg drøftet våre antikoagulasjonsprosedyrer med for å få aksept for at de skal være så liberale som mulig for å unngå blødning og sivning ved proteseoperasjoner. Nå opplevde jeg som pasient meget stor profesjonalitet og empati fra dem alle, og jeg ble sterkt imponert over kardiologien på SUS.

Mottakelsen og forberedelsene i avdelingen i Bergen var strømlinjeformet, tillitsskapende og vennlig. Jeg havnet på 7-manns-rom – med vindusplass ut mot byen! Det var et svært hyggelig miljø blant oss pasienter.

Så var det selve TAVI-en. Forberedelsene inne på operasjonsstuen var svært rask og effektiv observert med mine kirurgøyne og ører. Jeg hadde ikke møtt behandlende lege på forhånd. Under operasjonen styrte han medarbeiderne med en meget hård og bestemt hånd. Jeg var nok litt pratsom pga premedikasjonen, og ble av ham bedt om å tie stille. Det var åpenbart en meget sterk konsentrasjon og nøyaktighet rundt innføringen av klaffen. Og han kom med et gledesutbrudd da han så at klaffen satt perfekt.

Jeg opplevde ikke smerte sterkere enn ubehag bortsett fra da anestesilegen absolutt ville legge inn en arterienål i venstre arteria radialis. Jeg advarte ham om at jeg der var operert med volar plate pga håndleddsbrudd, og at det ikke ville la seg gjøre. Jeg fikk rett, så det ble høyre håndledd til slutt etter en del mislykket stikking.

Etter operasjonen var det kvelden og natten på overvåkningsavdelingen. Det virket profesjonelt med hyggelige mennesker rundt meg. Jeg fikk også besøk av kone og yngstesønn som var i byen sammen med meg.

Tilbake på post neste morgen var det dusj, og så kledde jeg meg i egne klær og startet treningen. Posten lå midt i en meget lang korridor som gikk videre gjennom andre avdelinger i begge retninger. Jeg gikk korridoren til endes i begge retninger, gang etter gang, hele dagen. Det ble avbrudd for mat og visitt etc. Jeg merket at personalet først var litt forundret, og etter hvert litt bekymret for meg. Det var nok slik at de andre pasientene i stor grad tok det mer med ro.

Jeg har i hele min karriære arbeidet for å liberalisere prosedyrer og restriksjoner rundt leddprotesekirurgi for å effektivisere det hele. På arbeidsplassen min har vi nå kommet frem til et fast-track forløp hvor leddproteser for 90% sitt vedkommende reiser hjem etter <2 døgn og er svært fornøyd med det. Fast-track bygger på lynrask mobilisering og trygghet for at mye aktivitet er det sunneste og tryggeste. Da var jeg jo programforpliktet til å gjøre det samme selv! Jeg reiste hjem på andre postoperative dag etter at den elektroniske fjernovervåkningen var avsluttet. Da fikk jeg besøk av oversykepleier og assen hennes. De sa med et smil at de erkjente at de kom til å gå inn for å endre litt på rutinene for pasientene sine etter slike inngrep.

Intervensjonskardiologen traff jeg flere ganger i etterforløpet. Han var svært empatisk og hyggelig. Hans strenge måte å håndtere operasjonssalen under TAVI-inngrepet opplevde jeg som en bekreftelse på at det er han som står bak dette tilbudet i Bergen. Jeg oppfattet helheten som usedvanlig profesjonell. Jeg ser at en skal være svært forsiktig når TAVI skal alminneliggjøres, at en ikke opplever at det enkelte steder kan oppstå mindre stringente og mindre profesjonelle opplegg.

Jeg er svært takknemlig overfor intervensjonskardiologen og hans avdeling, Kardiologisk avdeling ved SUS, og faktisk det norske helsevesenet. Slik er det for meg å selv ha vært en pasient som fikk en ny aortaklaff gjennom TAVI. Jeg var tilbake på jobb etter seks dager og har aldri hatt problemer med klaffen min annet enn at jeg nok har tendens til litt arytmier. Kontroll ECHO etter noen måneder og etter et år var helt fin, og om en måned er det ny kontroll. Virker som at det blir kontroller hvert annet år fremover.

Min opplevelse at TAVI var meget positiv. Miljøene som hjalp meg gjennom det hele, er meget profesjonelle og empatiske. Det må, etter mitt syn, være svært mye som taler for at en heller velger SAVR før jeg ville ha valgt det i stedet.

Appendix 6. Log of activities

Aktivitet	Dato
Oppdrag om metodevurdering gitt av Bestillerforum RHF	26. august 2019
Oppdraget revidert av Bestillerforum RHF	23. september 2019
Forespørsel om eksterne fageksperter	09. januar 2020
Eksterne fageksperter oppnevnt; arbeid påbegynt	14. januar 2020
Oppstartsmøtet med fageksperter	12. mars 2020
Siste tilbakemelding fra eksterne fagfellevurdering (prosjektplan)	15. mai 2020
Økonomiske modellen kjøres for første gang	24. juni 2020
Forespørsel om ekstern fagfellevurdering (metodervurdering)	02. oktober 2020
Intern fagfellevurdering i FHI	02. oktober 2020
Skriftlig brukermedvirkning mottatt	16. oktober 2020
Forespørsel om fagfellevurdering helseøkonomi	22. oktober 2020
Siste tilbakemelding fra eksterne fagfellevurdering	05. november 2020
Rapport godkjent av fagdirektør i FHI	28. desember 2020
Rapport oversendt sekretariatet for Bestillerforum RHF	29. desember 2020

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