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REPORT

A SINGLE-TECHNOLOGY ASSESSMENT

Sutureless aortic valve replacement for treatment of severe aortic stenosis: A single technology assessment of Perceval sutureless aortic valve

Norwegian Institute of Public Health

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Executive summary

Background

Aortic stenosis is the most common valvular heart disease in Western countries. A Norwegian study estimates that the prevalence of aortic stenosis is 0.2% in adults aged 50 to 59, 1.3% in adults aged 60 to 69, and up to 9.8% in patients 80 to 89. Aortic stenosis is generally caused by calcification of the aortic valve that ultimately can lead to heart failure. The three most important symptoms are chest pains, shortness of breath on exertion, and fainting. The disease may be asymptomatic for long periods of time, but once symptoms appear (severe aortic stenosis), an untreated individual has an average life expectancy of 2 to 3 years. The only effective treatment is aortic valve replacement (AVR) surgery.

Objective

The National System for Managed Introduction of New Health Technologies within the Specialist Health Care Service in Norway commissioned us to perform single technology assessment(s) on the use of sutureless aortic valve replacement in treatment of aortic stenosis (Nye metoder ID2015 042). One company, Livanova, Sorin group, provided a submission file. Based on the commission and the submission file, our assessment has been restricted to effectiveness, safety and cost effectiveness of Perceval sutureless aortic valve replacement (Perceval) compared to traditional aortic valve replacement (traditional AVR) for treating adult operable patients with severe aortic stenosis. We have evaluated the submitted documentation in relation to the best available published evidence.

Methods

Clinical effectiveness and safety

The clinical documentation submitted by the firm consisted of 25 studies included after a systematic search. We excluded six studies with transcathether aortic valve implantion (TAVI) as comparator, but included comparisons to other types of sutureless valves.We identified one additional study based on an independent systematic search, leaving 20 studies to be assessed. We aimed to identify the best available evidence for the outcomes long and short-term mortality, morbidity, quality of life,

resource use and adverse events. We evaluated internal validity of the studies based on the submitted information and a simplified risk of bias analysis. Data from all assessed studies, are presented in an appendix to this report, but only studies considered to represent best available evidence, were in depth assessed based on full text inspection. RevMan 5 was used to pool data from comparative studies. We assessed the quality (confidence in estimates) of the best available evidence based on the guidelines provided by The Grading of Recommendations Assessment, Development and Evaluation (GRADE).

The firm submitted an economic model consisting of three elements: (1) a hierarchical, random-effects Bayesian meta-analysis of clinical data from studies used to estimate pooled clinical parameters; (2) a probabilistic, patient-level simulation model that used clinical outcomes from the meta-analysis to determine the life-time effectiveness (30-day mortality, life-years gained, QALYs) and costs of Perceval compared to traditional valves based on 10,000 simulated patients; and (3) a five-year budget impact model to translate the cost-effectiveness results into a budget impact statement. The model examined six treatment groups consisting of four isolated AVR groups (full-sternotomy with traditional vs. Perceval valve; minimally invasive surgery with traditional vs. Perceval valve) and two groups undergoing concomitant surgical procedures via full-sternotomy (traditional vs. Perceval valve).

The model relied heavily on a published study (not included in the clinical effect documentation) relating outcomes of aortic valve replacement surgery to cross-clamp time (CCT). To capture the independent effects of surgical procedure and valve type on CCT, the submission included data from seven published studies, only one of which was part of the submitted clinical evidence on effect. The data were pooled using Bayesian meta-analyses in order to estimate relative effects of valve type and surgical procedure on cross-clamp time (CCT), and the baseline mean values and associated distributions for adverse events for the model reference group (CCT < 60 min). Cost data were retrieved, when possible, from Norwegian sources. A healthcare-payer perspective was used for the analysis.

Results

Clinical effectiveness and safety

Among the 20 assessed studies there were no randomized controlled trials (RCTs). Except for two studies from Canada, the assessed studies were based on European case series. The only study for which we identified an entry in a trial registry was the single-arm CAVALIER study (NCT01368666). As some studies are overlapping, we can not give an estimate on the total number of patients in the assessed studies. Ten studies were non-comparative and ten were comparative. Eight studies compared Perceval with traditional AVR and two studies compared Perceval with other types of sutureless valves.

Based on a simplified risk of bias assessment we considered four propensity score matched cohort studies comparing Perceval with traditional AVR (1033 patients in total) and the single arm CAVALIER study (658 patients receiving Perceval) to represent the best available evidence for the predefined indication and outcomes. We considered the remaining studies to represent very low quality evidence and did not assess them further.

Based on pooled data from the four propensity score matched studies, it is uncertain whether Perceval reduces, increases or has a similar 30-day mortality compared with traditional AVR. There were 19 deaths in the Perceval group (N=484)and 22 in the traditional AVR group (N= 549). A random effects meta-analysis provided a risk ratio of 1.09; 95% CI 0.58 to 2.06 (GRADE quality of evidence: low).

There may be small or no differences in hemodynamic measures at 30 days between Perceval and traditional AVR (mean gradient (mm Hg) -0.73; 95% CI -1.75, 0.30; GRADE quality of evidence: low). We also found that Perceval may provide lower cross-clamp time and cardiopulmonary bypass time (mean difference, respectively = -22.53; 95% CI -34.28 to -10.78 and -26.83; 95% CI -32.10 to -21.55; GRADE quality of evidence: low). Postoperative differences in functional status (NYHA class) was not reported in any of the comparative studies. None of the studies reported quality of life data. No conclusions could be made with regard to the influence of Perceval on intensive care unit or hospital length of stay due to very low quality of evidence.

No published comparative studies were available to allow for subgroup analyses based on surgical procedure (minimally invasive versus full sternotomy). The same type of adverse events, if reported, were present in both groups of the comparative studies. No adverse events occurred at a rate higher than 10% in the Perceval arm of the propensity matched comparative studies. The need for pacemaker implantation was higher in the Perceval group compared to traditional AVR (risk ratio = 1.62; 95% CI 0.98 to 2.67; GRADE quality of evidence: low). No conclusions could be made regarding Perceval versus other sutureless valves because there were no propensity score matched studies. No conclusions could be made with regard to differences in long-term outcomes.

Short-term (30-day) adverse events, including death (3.7%), stroke (2.2%), major bleeding (4.5%), and the need for permanent pacemaker implantation (11.8%) were common in the single-arm CAVALIER study (N=614). Freedom from valve or procedure related death among patients available to follow up decreased from 97.2% (95% CI 95.9 to 98.5) after one year (N=554) to 89.5% (95% CI 85.1 to 93.8) at four years (N=83).

Health economic results

The results of the submitted cost-effectiveness simulations are mainly based on data not included in the submitter's effect evidence. Based on the model, Perceval can be cost-effective (less costly and slightly more effective) relative to traditional surtured valves for the three types of surgical procedures considered: isolated full sternotomy (FS), isolated minimally invasive surgery (MiS), and concomitant surgery with full sternotomy (CONC).

For isolated FS procedures the estimated effect gains for Perceval relative to traditional valves are a 2.1% reduction in mortality, a 0.13 increase in life-years gained, and a 0.11 increase in QALYs gained. The estimated gains associated with Perceval are slightly lower for isolated MiS and slightly higher for CONC procedures. The largest estimated gains come with a switch from FS with a traditional valve to MiS with Perceval, with a 2.9% reduction in 30-day mortality, a 0.19 increase in life-years gained and a 0.15 increase in QALYs gained. This supports the idea that there are independent gains from a MiS rather than FS procedure and from using Perceval rather than traditional sutured valves.

Estimated costs are lower using Perceval valves compared to sutured valves across all surgical procedures. Estimated savings for Perceval compared to trational valves are approximately NOK 133,300 with a full sternotomy and NOK 114,350 for minimally invasive surgery. The estimated savings for concomitant procedures using Perceval is NOK 206,900. As with effects, the largest estimated cost savings occur with a switch from FS with a traditional valve to MiS with Perceval, a saving of approximately NOK 181,600.

The five-year budget impact compares total costs for annual aortic replacement surgery for 698 patients in two scenarios: (1) no use of sutureless valves and (2) a gradual, linear market penetration by Perceval of 15% over five years. The budget impact analysis also shows cost savings with Perceval of 1.33%, 2.01%, 2.72%, 3.43% and 4.15% in years 1 to 5, respectively. The total five-year saving with the specified gradual introduction of Perceval is approximately NOK 44,660,000. The analysis is based on the assumption that 50% AVR procedures are minimally invasive.

Sensitivity analysis of both the cost-effectiveness results and the budget impact analysis showed that the base case results were robust for analyses reflecting uncertainty in the simulated outcomes in the model and for a variation in the assumed base case Perceval price (NOK 32,500) within a price range from NOK 25,000 to 40,000.

Discussion

Effectiveness and safety

Our major objection to the submitted material is the low quality level of currently available evidence. There is one ongoing highly relevant RCT (PERSIST-AVR trial, NCT02673697) with planned enrollement of 1234 patients. Primary data from this trial is anticipated to be available in 2019. We considered the most appropriate argument for including non-randomized studies, at this time, is that it is early in the life cycle of the technology, and that there may be a need for a temporary decision on whether to offer this technology based on best available evidence and/or evaluate the need for additional trials. Thus, we have focused on identifying the best available evidence. More definitive conclusions can be made when results of the ongoing RCT are available.

There are several new methods available for treatment of operable patients with severe aortic stenosis, including other types of sutureless procedures. In addition, both sutureless and transcathether based procedures (TAVI) have been suggested for patients with severe aortic stenosis and an intermediate to high operative risk as well as patients with anatomical characteristics not suited for traditional AVR. This may provide new options for patients with unmet needs, but it also increases the need for additional clinical trials, i.e trials comparing sutureless AVR to TAVI.

Health economics

The economic analysis relies on a model that relates clinical outcomes for aortic valve replacement surgery to cross-clamp time (a surrogate endpoint) and surgical technique. The model itself is well-constructed, relevant for the Norwegian context, and exhibits, as far as we can tell, internal validity. The data used in the model, however, were mostly from studies that were not part of the clinical evidence submitted by the firm and were therefore not graded for quality. The one study that was included in the submitted evidence was considered to be of very low quality.

Two competing effects could influence model-estimated savings when using Perceval instead of traditional valves. Savings across all procedure types may be lower than suggested in the cost-effectiveness analysis if the reduction in time needed for surgery cannot be fully translated into additional operations. On the other hand, savings estimated in the five-year budget impact analysis are based on the assumption that approximately half of valve replacement procedures are minimally invasive surgeries. Because aortic valve replacement in Norway is usually performed as a full-sternotomy, and savings using Perceval are higher compared to traditional valves for FS than MiS, the actual savings may tend to be higher than reported.

Conclusion

Effectiveness and safety

The quality of the available evidence comparing Perceval sutureless AVR to traditional AVR is low to very low. More robust conclusions will be available upon publications of primary data from an ongoing RCT expected in 2019. Based on best available evidence, it is uncertain whether Perceval AVR reduces, increases or has a similar 30-day mortality compared with traditional AVR. Perceval AVR may reduce perioperative cardiac bypass time and cross-clamp time, and may provide little or no difference in hemodynamic function at 30 days compared to traditional AVR. However, no firm conclusions can be made with regard to superiority of either method.

Health economics

Based on the cost-effectiveness and budget impact analyses performed by the firm Perceval can be cost-saving compared to traditional sutured valves for isolated full sternotomy or minimally invasive valve replacement surgery, and for concomitant surgeries with full sternotomy. Model estimates of clinical effect indicate that there may be small gains connected with Perceval. Estimates from the five-year budget impact analysis show cost savings with expanded use of Perceval. Because the data used in the model were not based on the assessed comparative studies, there remains uncertainty about the likelihood and validity of the results. More robust conclusions will be possible on publication of the ongoing RCT.

Sammendrag (norsk)

Bakgrunn

Aortastenose er den vanligste hjerteklaffsykdommen i vestlige land. I en norsk studie ble forekomsten av aortastenose anslått å være 0,2 % hos voksne i alderen 50 til 59 år, 1,3 % hos de i alderen 60 til 69 år, og 9,8 % hos de i alderen 80 til 89 år. Aortastenose er vanligvis forårsaket av forkalkning av aortaklaffen som med tiden kan føre til hjertesvikt. De tre vanligste symptomene på hjertesvikt er smerter i brystet, kortpustethet ved anstrengelse og besvimelse. Sykdommen kan over lengre tid være asymptomatisk, men når symptomene først vises (alvorlig aortastenose) er gjennomsnittlig levetid hos ubehandlede 2 til 3 år. Den eneste effektive behandlingen er kirurgisk erstatning av aortaklaffen.

Problemstilling

Oppdraget for denne hurtig metodevurderingen ble gitt av Nasjonalt system for innføring av nye metoder i spesialisthelsetjenesten (Nye metoder ID2015 042). Ett firma (Livanova, Sorin group) sendte inn dokumentasjonspakke på Perceval suturløse aortaklaffer i behandling av voksne pasienter med alvorlig aortastenose. Vår metodevurdering er avgrenset til effekt, sikkerhet og kostnadseffetivitet av Perceval suturløse aortaklaffer i behandling av operable voksne pasienter med alvorlig aortastenose sammenliknet med tradisjonelle aortaklaffer. Vi har vurdert den innsendte dokumentasjonen mot det best tilgjengelige publiserte kunnskapsgrunnlaget.

Metode for vurdering av dokumentasjonen

Effekt og sikkerhet

Den kliniske dokumentasjonen levert av firmaet besto av 25 studier (publikasjoner) som var identifisert ved et systematisk søk. For vår metodevurdering ekskluderte vi seks studier som sammenlignet suturløse hjerteklaffer med transkateter aortaklaff implantasjon (TAVI), men inkluderte studier som hadde to andre typer suturløse aortaklaffer for sammenligning. Vi vurderte totalt 19 av de 25 innsendte studiene. I tillegg inkluderte vi en studie basert på et uavhengig systematisk søk.

Vårt formål var å identifisere den beste tilgjengelige kliniske dokumentasjonen for utfallene dødelighet, sykelighet, livskvalitet, ressursbruk og uønskede hendelser. Vi vurderte studienes interne validitet basert på den innsendte dokumentasjonen og utførte en forenklet risiko for skjevhet-analyse. Resultater fra alle studiene er presentert i et vedlegg til metodevurderingen, men bare studier ansett som best tilgjengelig kunnskap ble vurdert i mer dybde ved fulltekts gjennomgang av publikasjoner. Vi brukte RevMan 5 til å slå sammen resultater på tvers av komparative studier. Vi vurderte kvaliteten på dokumentasjonen (vår tillit til resultatene) ved hjelp av The Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Helseøkonomisk dokumentasjon

Den økonomiske modellen innsendt av firmaet besto av tre elementer: (1) en hierarkisk, «random-effects" Bayesian meta-analyse med kliniske data fra studier for å estimere kliniske parametere; (2) en probabilistisk simuleringsmodell basert på 10 000 simulerte pasienter som brukte kliniske utfall fra meta-analysen til å bestemme levetid (30-dagers dødelighet, antall vunnet leveår og kvalitetsjusterte leveår) og kostnader ved Perceval sammenlignet med tradisjonelle hjerteklaffer; (3) en modell for budsjettkonsekvenser over 5 år for å «oversette» kostnadseffektivitet til budsjettkonsekvenser. Modellen undersøkte seks behandlingsgrupper bestående av fire isolerte AVR-prosedyrer (åpen kirurgi hvor tradisjonell AVR ble sammenlignet med Perceval; minimalt invasiv kirurgi hvor tradisjonell AVR ble sammenlignet med Perceval) og to åpne prosedyrer som består av AVR samtidig med en annen type hjerteprosedyre (hvor tradisjonell AVR ble sammenlignet med Perceval).

De innsendte økonomiske analysene brukte data fra syv publiserte studier, hvorav kun en var en del av den innsendt kliniske dokumentasjonen. Det ble utført Bayesianske meta-analyser for å beregne både den relative effekten av type hjerteklaff og type kirurgisk prosedyre for cross-clamp-time (CCT). Det ble også beregnet baseline gjennomsnittsverdier og tilhørende fordelinger for uønskede hendelser for referansegruppen (CCT <60 min). Kostnadsdata ble, der det var mulig, hentet fra norske kilder. Analysene ble utført i et helsetjenesteperspektiv.

Resultat

Effekt og sikkerhet

Blant de 20 vurderte studiene var det ingen randomiserte kontrollerte studier (RCTer). Med unntak av to studier fra Canada, var studiene basert på europeiske pasientserier. Den eneste studien hvor vi identifiserte en oppføring i et studieregister var CAVALIER studien (NCT01368666). Siden flere av studiene var overlappende, kan vi ikke oppgi det eksakte antallet pasienter som er inkludert i de vurderte studi-

ene. Ti av studiene er ikke-komparative og ti er komparative. Syv studier sammenlignet Perceval med tradisjonell AVR og to studier sammenlignet Perceval med andre typer suturløse aortaklaffer.

Basert på en forenklet risiko for skjevhet analyse vurderer vi fire matchede kohorte studier (med totalt 1033 pasienter) og CAVALIER studien (815 konsekutivt innrullerte pasienter hvorav 658 fikk implantert Perceval) til å representere den beste tilgjengelige kliniske dokumentasjonen for «våre» forhåndsdefinerte utfallsmål. Etter vår vurdering gir de øvrige studiene klinisk dokumentasjon av svært lav kvalitet.

Basert på sammenlagte tall fra de fire matchede kohorte studiene, vurderer vi at kortidsdødelighet kan være redusert, lik eller økt i Perceval gruppen sammenliknet med gruppen som fikk tradisjonell AVR. Det var 19 døde etter 30 dager i Perceval gruppen (N=484) og 22 døde i gruppen som fikk tradisjonell AVR (N= 549). En random effects meta-analyse ga en risk ratio på 1,09; 95% KI 0,58 til 2,06 (GRADE kvalitet: lav).

Det er muligens liten eller ingen forskjell i hemodynamiske mål 30 dager etter operasjon (gjennomsnittlig forskjell i gradient (mm Hg) -0.73; 95% CI -1.75, 0.30; GRADE kvalitet: lav), men postoperative forskjeller i funksjonell status (NYHA klasse) ble ikke rapportert i noen sammenlignende studie. Ingen studier rapportertet livskvalitet. Vi fant også at Perceval kan redusere tid på hjertelungemaskin og «cross-clamp» tid med en gjennomsnittlig forskjell på henholdsvis -22,53 minutter (95 % KI -34,28 til -10,78) og - 26.83 minutter (95 % CK -32.10 til -21.55) (GRADE kvalitet: lav). Vi kunne ikke konkludere med hensyn til om Perceval påvirker liggetid i intensivavdelingen eller på sykehus (GRADE kvalitet: svært lav).

Ingen publiserte sammenlignende studier var tilgjengelige for å tillate sub-gruppeanalyser basert på kirurgisk tilgang (minimalt invasiv versus full sternotomi). De samme type bivirkninger, dersom rapportert, ble funnet i begge gruppene i de komparative studiene.

Ingen av bivirkningene opptrådde hos flere enn 10 % av pasientene i Perceval-gruppen i de matchede sammenlignende studiene. Behovet for pacemakerimplantasjon var muligens noe høyere i Perceval gruppen sammenliknet med tradisjonell AVR (risk ratio = 1.62; 95 % CI 0.98 to 2.67; GRADE kvalitet: lav). Vi kan ikke konkludere med hensyn til Perceval sammenlignet med andre typer suturløse hjerteklaffer eller med hensyn til langtidseffekter.

Korttidsbivirkninger (30 dager), inkludert død (3,7 %), slag (2,2 %), alvorlig blødning (4,5 %), og behov for permanent pacemakerimplantasjon (11,8 %) var vanlig i den en-armede CAVALIER studien. Fravær av implantat- eller prosedyrerelaterte dødsfall hos pasienter som var tilgjengelig for oppfølging ble redusert fra 97,2%

(95% KI 95,9 til 98,5) etter ett år (N = 554) til 89,5 % (95 % KI 85,1 til 93,8) og etter fire år (N = 83).

Helseøkonomiske resultat

Resultatene av den innsendte simuleringen av kostnadseffektivitet er hovedsaklig basert på kliniske data som ikke direkte stammer fra innsendt dokumentasjon av effekt, og som er forskjellige fra våre kliniske effektdata. Basert på modellen kan Perceval være kostnadseffektiv (færre kostnader og noe mer effektiv) sammenliknet med bruk av tradisjonelle aortaklaffer ved de tre hovedtypene av kirurgiske prosedyrer vurdert: åpen kirurgi (full sternotomi (FS)), minimal invasiv kirurgi (MiS), og åpen krirgi sammen med en annen hjertekirurgisk prosedyre.

Ved åpen kirurgi er den estimerte effekten av Perceval sammenlignet med tradisjonell AVR en forskjell i dødelighet på 2,1 prosentpoeng, 0,13 vunne leveår og 0,11 økning i kvalitetsjusterte leveår. Den estimerte gevinsten knyttet til bruk av Perceval er noe lavere ved minimalt invasiv kirurgi og litt høyere for åpen AVR samtidig med en annen hjerteprosedyre. Den største beregnede effekten kommer ved et bytte fra åpen kirurgi med tradisjonell AVR til minimalt invasiv kirurgi med Perceval med en gevinst på 2,9 prosentpoeng i 30-dagers dødelighet, 0,19 økning i antall vunnet leveår og 0,15 økning i kvalitetsjusterte leveår. Dette støtter tanken/hypotesen om fortrinnene ved minimalt invasiv kirurgi versus åpen kirurgi og Perceval versus tradisjonell AVR.

De estimerte kostnadene er lavere ved bruk av Perceval sammenlignet med tradisjonelle hjerteklaffer med alle typer kirurgiske prosedyrer. Beregnede besparelser ved bruk av Perceval sammenlignet med tradisjonelle hjerteklaffer er omtrent 133 300 kroner ved åpen kirurgi og 114 350 kroner ved minimalt invasiv kirurgi. Beregnet besparelse for begge prosedyrene og ved bruk av Perceval er 206 900 kroner. De største estimerte kostnadsbesparelsene ser man ved et bytte fra åpen kirurgi med tradisjonell AVR til minimalt invasiv kirurgi med Perceval med en besparelse på ca. 181 600 kroner.

Budsjettkonsekvensene over fem år sammenligner de årlige kostnadene for 698 pasienter i to scenarier: (1) uten bruk av suturløse hjerteklaffer og (2) en gradvis introduksjon av Perveval i markedet på 15 % over fem år. Budsjettkonsekvensanalysene viser også kostnadsbesparelser ved bruk av Perceval på henholdsvis 1,33%; 2,01%; 2,72%; 3,43% og 4,15% fra ett til fem år. Den samlede besparelsen i løpet av fem år med den gradvise introduksjonen av Perceval er ca. 44 660 000 kroner. Denne analysen er basert på antagelsen om at 50% av aortaklaff-prosedyrene er minimalt invasive.

Sensitivitetsanalyser på resultatene for både kostnadseffektivitet og budsjettkonsekvenser viste at basecase resultatene var robuste med hensyn til usikkerhet i de kliniske dataene og en variasjon i den antatte Perceval-prisen (NOK 32 500) innenfor et prisspenn fra 25 000 til 40 000 kroner.

Diskusjon

Effekt og sikkerhet

Vår viktigste innvending mot den kliniske dokumentasjonen innsendt av firmaet er relatert til den lave kvaliteten av studiene. Det finnes en pågående svært relevant RCT (PERSIST-AVR, NCT02673697) med planlagt innrullering av 1234 pasienter. Tidlige data fra denne studien er forventet å være tilgjengelig i 2019. Argumentet for å inkludere ikke-randomiserte studier på dette tidspunktet er at det ennå er tidlig i livssyklusen av teknologien og at det kan være behov for en midlertidig beslutning om å tilby denne teknologien, eller for å vurdere behovet for ytterligere studier. Vi har derfor fokusert på å identifisere den beste tilgjengelige dokumentasjonen. Mer definitive konklusjoner kan trekkes når resultatene av den pågående RCTen er tilgjengelig.

Det finnes flere nye metoder for behandling av opererbare pasienter med alvorlig aortastenose, deriblant andre typer suturløse prosedyrer. I tillegg har både suturløse prosedyrer og transkateterbaserte prosedyrer (TAVI) blitt foreslått for pasienter med alvorlig aortastenose og en intermediær til høy operativ risiko, og for pasienter med anatomiske egenskaper der tradisjonell AVR ikke er mulig. Dette kan gi nye muligheter for pasienter som per i dag ikke har noe behandlingsalternativ, men øker også behovet for kliniske studier, f.eks suturløs AVR sammenliknet med TAVI.

Helseøkonomi

Den økonomiske modellen baserer seg på endepunktet cross-clamp time (et surrogat endepunkt) og på kirurgisk prosedyre. Modellen er velfundert og viser, så vidt vi vet, intern og er relevant for norske forhold. En stor svakhet er at dataene som ble brukt i modellen, med unntak av en studie, ikke er en del av det innsendte kliniske dokumentasjonsgrunnlaget og følgelig ikke er kvalitetsvurderte. Den ene studien som ble brukt var av svært lav kvalitet. Retningen på resultatene antyder imidlertid at bruk av Perveval kan være kostnadsbesparende uavhenig av kirurgisk prosedyre.

To konkurrerende effekter kan påvirke omfanget av besparelsene ved bruk av Perceval i stedet for tradisjonelle aortaklaffer. Besparelsene kan være lavere enn antydet i den økonomiske analysen for alle prosedyrene dersom reduksjonen i operasjonstid ikke kan omsettes i flere operasjoner. På den annen side antok man i analysene for femårs budsjettkonsekvenser at omtrent halvparten av aortaklaff operasjonene ble utført med minimalt invasiv prosedyrer. De fleste aortaklaff operasjonene i Norge

blir utført med åpen kirurgisk prosedyre. Da besparelsene ved bruk av Perceval sammenlignet med tradisjonelle aortaklaffer er høyere ved åpen kirurgi enn ved minimalt invasiv prosedyre kan de faktiske besparelsene muligens være høyere enn rapportert.

Konklusjon

Effekt og sikkerhet

Kvaliteten av tilgjengelig dokumentasjon for effekt av Perceval sammenliknet med tradisjonell AVR er lav til svært lav. Resultater av en pågående RCT er forventet å foreligge i 2019 og vil kunne gi sikrere konklusjoner. Det er ikke mulig å trekke sikre konklusjoner med hensyn til om den ene metoden er bedre enn den andre.

Helseøkonomi

Analysene for kostnadseffektivitet og budsjettkonsekvenser som firmaet utførte, antyder at bruk av Perceval kan være kostnadsbesparende sammenlignet med tradisjonelle hjerteklaffer både ved åpen kirurgi og ved minimalt invasiv prosedyrer, samt for åpen kirurgi som består av klaffebytte samtidig med en annen type hjerteprosedyre. Estimerte resultater fra modellen for vunne leveår og kvalitetsjusterte leveår antyder at det kan være små gevinster knyttet til bruk av Perceval. En budsjettkonsekvensanalyse for 5 år anslår at det kan være kostnadsbesparende å øke bruken av Perceval. Fordi dataene som ble brukt i modellen ikke var basert på de sammenlignende studiene som vi har vurdert, er det usikkerhet omkring sannsynligheten og validiteten av resultatene. Mer robuste konklusjoner vil kunne trekkes når det foreligger resultater fra den pågående RCTen.

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Preface

The 'New Health Technologies' system

The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway ('New Methods', ID2015 042) was established in 2013 to promote the systematic use of health technology assessments (HTA) to inform rational decisions about introducing and prioritizing new health technologies and drugs in the specialist health services at the local and national level. The system is meant to ensure a predictable process through which patients can gain access to new technologies that are documented to be effective and meet safety and cost-effectiveness standards, while obsolete health technologies are retired.

Within New Methods, a commissioning forum ("Bestillerforum RHF'") evaluates submitted suggestions for new assessment, and decides which new technologies should be evaluated and the type of evaluation to be performed. For introduction of new technologies at the national level two types of analyses are relevant: single technology assessments (STA) and full health technology assessments (HTA). STAs evalute a single new method (device, procedure or drug) relative to a comparator based on documentation submitted by the company owning the method or their representatives. A template is available to aid the submission of necessary information and documentation https://nyemetoder.no/Documents/Administrativt%20(brukes%20kun%20av%20sekretariatet!)/Template%20medical%20device%20etc%20v3.pdf. A full health technology assessment (HTA) is a broader assessment that is appropriate when several similar technologies are available for the same indication.

The Norwegian Institute of Public Health performs all requested HTAs and those STAs related to medical devices and procedures. Completed analyses are available on the Institute's website. The Norwegian Medicines Agency performs STAs for new pharmaceuticals. "Beslutningsforum RHF", consisting of the directors of the four Health regions in Norway, decides whether or not to introduce the new methods at the national level after receiving the final STA or HTA report.

Commission

To perform a single technology assessment (STA) of the clinical effectiveness, safety, and cost-effectiveness of sutureless, implantable aortic valves compared to traditional valves in the treatment of aortic stenosis, based on submitted documentation.

Log

"Bestillerforum RHF" reviewed an early awareness alert regarding use of sutureless, implantable, aortic valves, ID2015_042, on October 19, 2015, and on August 24, 2015 commissioned The Norwegian Institute of Public Health to conduct a single technology assessment of sutureless, implantable, aortic valves in patients with aortic stenosis (https://nyemetoder.no/metoder/suturlose-implanterbare-hjerteklaffer-i-behandling-av-aortasenose).

We identified three firms with relevant devices and informed them of the possibility of submitting documentation for evalutation: LivaNova, PLC (Perceval); Edwards Lifesciences Corporation (Edwards INTUITY); Medtronic (3f Aortic Bioprosthesis). Only LivaNova chose to submit a documentation package.

25.06.2015: Suggestion submitted
24.08.2015: "Bestillerforum RHF" comissioned a single technology assessment
September 2015-February 2016: dialogue and meeting with concerned company
30.09.1.2016: Valid submission

Project group

The project group consisted of:
Project coordinator: Researcher Arna Desser
Researchers: Vigdis Lauvrak and Helene Arentz-Hansen
Health economists: Arna Desser and Beate Charlotte Fagerlund
Research librarian: Ingrid Harboe
Research director: Ingvil Sæterdal

We gratefully acknowledge help and feedback from the following indivduals:
Co-workers: Geir Smedslund and Espen Movik
Clinical expert: Reidar Bjørnerheim, Senior consultant, Ekkolaboratoriet, Oslo University Hospital
Peer review: Gry Dahle, Senior consultant, Thoracic surgery section, Oslo University Hospital

Signe Agnes Flottorp	Ingvil Sæterdal	Arna Desser
Department director	*Research director*	*Project coordinator*

Background

Name of device and manufacturer who prepared the submission

Name of device: Perceval sutureless heart valve.
Documentation submitted by: LivaNova PLC, London, United Kingdom.

Description of the technology

The Perceval sutureless heart valve (Perceval) is a bioprosthetic valve designed to replace a diseased native or malfunctioning prosthetic aortic valve via open heart surgery using full sternotomy, hemi-sternotomy, or right thoracotomy. The valve, a development of traditional tissue valves, comprises a bovine pericardium tissue component and a self-expandable stent. A dedicated delivery system, which includes a Perceval collapser, holder, and dialator, allows surgeons to position and anchor the valve suturelessly. Perceval valves are available in four sizes: small, medium, large, and extra large. Contraindications for Perceval are aneurysmal dilation or dissection of the ascending aortic wall; known hypersensitivity to nickel or cobalt alloys; or anatomical characteristics incompatible with size specifications. Figure 1 illustrates the valve and its delivery system (1).

According to the submission, Perceval valves are intended to improve performance relative to traditional stented or stentless valves. Perceval's smaller pre-expansion size and sutureless insertion method reduce cross-clamp time (CCT)[1] during valve replacement surgery. In addition, the submitter suggests that Perceval can also reduce CCT during minimally invasive surgical procedures (MiS), and as such may be considered a "platform enabler" for MiS. Research indicates that surgical duration is a factor for successful surgical outcomes (2;3).

[1] Cross-clamp time is the period during which blood does not circulate through the heart.

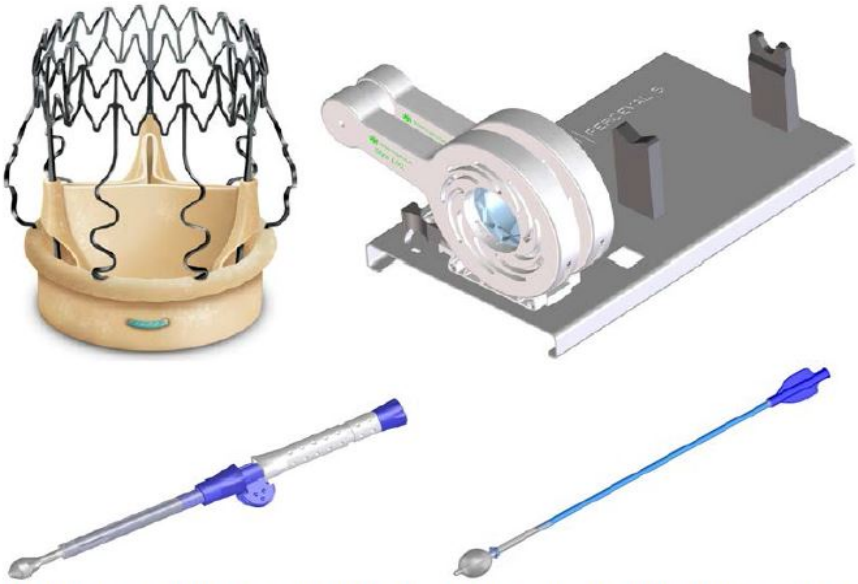


Figure 1. Top Left: Perceval Sutureless Heart Valve, Top Right: Perceval Dual Collapser, Bottom Left: Perceval Dual Holder, Bottom Right: Perceval Post-dilation Catheter.

Current certification status and approvals

The Perceval Sutureless Heart Valve first gained CE marking in 2011 for the small (PVS21) and medium (PVS23) sized valves for patients aged 75 and above. Based on results from subsequent interim analyses, it was granted CE marking for the large valve (PVS25) in 2011 and the extra large valve (PVS27) in 2013. Extension of the certifications to include patients aged 65 and older occurred in 2012. As of 2014 CE marking certification was extended to all adult patients. Perceval received approval from the Australian Therapeutic Goods Administration (4) and Health Canada-Therapeutic Products Directorate, Medical Device (5) in 2015, and the United States Food and Drug Administration (FDA) in January 2016 (1).

The FDA approved the pre-market approval (PMA) application for Percival based on an indication of replacement of diseased, damaged, or malfunctioning native or prosthetic aortic valves. PMA approval indicates "that the application contains sufficient valid scientific evidence to provide reasonable assurance that the device is safe and effective for its intended use(s) (1)."

Approval in Canada for patients aged ≥ 65 was contingent on providing annual marketing history in Canada and worldwide with unit sales, a summary and estimated rates of occurrence of adverse events and complaints; progress reports and final study reports for the Percival Investigational Device Exemption (IDE) and the (non-randomized) CAVALIER clinical trial; and a summary of additional clinical data

from a literature study that provides significant insight into Perceval's safety and effectiveness in clinical use (5). Australian approval also included a standard requirement for three years of annual reports that include all complaints and adverse events associated with the device. In addition, distribution records for the device must be retained for a minimum of ten years (4).

Aortic stenosis

Aortic stenosis is the most common valvular heart disease in Europe and North America. It most frequently occurs (80% of cases (6)) when calcification causes a narrowing of a normal trileaflet aortic valve, reducing blood flow from the left ventricle of the heart to the aorta. The result is a chronic progressive disease in which the heart must work increasingly hard to maintain normal circulation (7). Over time this leads to a thickening of the heart muscle (hypertrophy), which reduces the size of the heart chamber, and ultimately results in heart failure. Damage to the valve can also lead to leakage into the left ventricle (aortic insufficiency) if the valve does not close properly. Most of the remaining cases of aortic stenosis occur in individuals with congentially malformed (unicuspid or bicuspid) valves (8).

The three most important symptoms of severe aortic stenosis are chest pains (angina pectoris), shortness of breath (dyspnea) on exertion, and fainting (syncope). Aortic stenosis can be a possible diagnosis when there is evidence of heart failure or bouts of dizziness. The disease can be asymptomatic for long periods of time, but once symptoms appear expected survival without valve replacement is short, on average from 2 to 3 years (8).

Aortic stenosis is largely related to advanced age and typically presents after age 70 or 80. Estimates from 1997 indicate that the disease affects 2.6% of individuals older than 75 years (9). A Norwegian study (10) estimates that the prevalence of aortic stenosis is 0.2% in adults aged 50 to 59, 1.3% in adults aged 60 to 69, and up to 9.8% in patients 80 to 89. The number of patients is expected to increase because of larger cohorts of elderly indivdiuals.

Current treatment of patients with aortic stenosis

The current standard treatment for severe, symptomatic aortic stenosis is open heart surgery to replace the aortic valve. Surgery is typically peformed as a cardiopulmonary bypass procedure under general anesthesia. Open heart surgery is contraindacted in patients with high operative risk based on medical and/or anatomical causes. Heightened surgical risk occurs with advanced age and comorbidities. Frequently, anesthesia and intensive treatments following surgery are critical factors for patients with high operative risk. Operative risk is determined

using risk algorithms, such as EuroSCORE, and discretionary evaluations of individual patients. Mortality with open surgical aortic valve replacement (AVR) is approximately 3% (7;11) and risk for stroke, approximately 1.5% (11). With increased operative risk, mortality increases significantly. Based on data from the Annual Report on Cardiac Surgery in Norway for 2015 (12), there were 1,502 patients who had surgery to implant or replace an aortic valve. Of these, 1,178 were perfomed as open surgery while connected to a cardiopulmonary pump, and the remaining 324 involved transcathether aortic valve implantion (TAVI). The majority of these patients were under age 80.

It is currently assumed that 30% to 40% of patients with severe aortic stenosis are not eligible for surgery because of advanced age or comorbities (13-15). Until recently, the alternative treatment for patients who are either ineligible for or wish to avoid surgery has been nonsurgical, palliative treatment that has limited clinical effect. Standard palliative treatment in Norway generally relies on medications. Although balloon valvoplasty (11) is also a possible treatment, it is rarely used in Norway or Europe because the risk for complications and rapid relapse is high (7;16).

Current treatment options in Norway for patients with severe aortic stenosis are

- traditional sutured aortic valve replacement (AVR)
- AVR with sutureless valves (in very limited use)
- transcathether aortic valve implantation (TAVI) (an option for those with high operative risk or anatomical restrictions with regard to AVR)
- optimal pharmaceutical treatment (the option for those with high operative risk or anatomical restrictions to both AVR and TAVI)

Research questions and inclusion criteria for the clinical evidence

Based on the commission from “Bestillerforum RHF”, the main research question addressed in this single technology assessment can be formulated as:

- For patients with severe aortic stenosis, what is the clinical effectiveness, safety and cost-effectiveness of Perceval sutureless aortic valve replacement compared to traditional aortic valve replacement?

The main research questions, organized according to the relevant PICO-S (P= Population, I= Intervention, C= Comparator, O=Outcomes (Endpoints) and S=study design) and how these are covered by the submission file and our assessment, is shown in Table 1 and discussed below.

Table 1. *Inclusion criteria*

	Submission file	**Our assessment**
Patient group:	Adult patients with severe aortic stenosis	Adult patients with severe aortic stenosis. Subgroup analysis based on patient characteristics is relevant.
Intervention:	Perceval AVR	Perceval AVR. Subgroup analysis based on type of surgery (FS or MiS) is relevant.
Comparator:	Traditional AVR; Another type of sutureless valve; TAVI;	Traditional AVR and another type of sutureless valve.
Outcomes:	Data on survival were considered as primary outcomes. Complications and other outcomes were considered secondary.	Short- and long-term mortality/survival, morbidity, quality of life, adverse events, resource usage*, the effect of a learning curve*, patient volume and patient preferences*.
Study design	Comparative studies; Single-arm studies with 100 or more patients	Best available evidence for each outcome agreeing on a restriction for not including single-arm studies with less than 100 patients
Exclusion criteria	Studies where Perceval is not the only sutureless valve included in the study; Case report studies	Studies where data from Perceval AVR could not be distinguished from other sutureless AVR (as studies comparing Perceval with other types of surtureless valves were included)

*Additional relevant outcomes not directly defined by the research question, AVR= Aortic valve replacement, TAVI = Trans catheter aortic valve implantation, RCT= randomized controlled trial, FS= full sternotomy, MiS= Minimally invasive (cardiac) Surgery

Comments on the PICO-S

Both Perceval AVR and traditional AVR may be performed by full sternotomy or minimally invasive cardiac surgery, making subgroup analysis based on type of surgery relevant. Our assessment is restricted to studies where traditional AVR or another type of sutureless AVR is the comparator. In our opinion, TAVI should be considered as a comparator in a separate assessment where the population is more clearly defined and the economic analysis includes this comparator. In the submission file, any comparative study, as well as studies with at least 100 patients were included. To evaluate the appropriateness of including non-randomized studies, we created a table specifying arguments for and against (see Appendix 1). We believe the most appropriate argument for including non-RCTs in this particular case is that

it is early in the life cycle of the technology, and that there may be a need for a temporary decision based on best available evidence on whether to offer this technology, and/or to initiate trials for additional evidence generation. Thus, for each relevant outcome we have aimed to identify and assess the best available evidence.

Assessing cost-effectiveness

The submitter was required to include a cost-effectiveness analysis of the intervention as part of the documentation submission. The suggested form for a cost-effectiveness analysis, based on the Norwegian Directorate of Health's guideline for economic analyses (17) is a cost utility analysis in which parameters for clinical outcomes are taken from the systematic literature review, and model effects are measured in quality-adjusted life years (QALYs). A QALY is defined as taking on a value of 1 for an individual in perfect health and a value of 0 at death, and can therefore capture changes in both life-expectancy and quality of life for a given intervention. Measuring QALYs requires applying a health-related quality of life (HRQoL) utility weight, often called a "utility", to the various health outcomes and potential adverse events included in the economic model. These weights capture changes in the quality of life, either in terms of HRQoL improvements resulting from treatment or HRQoL declines associated with adverse events.

Although many clinical studies report changes in quality of life as measured by disease-specific intruments, the recommendations for cost-effectiveness analysis specify using a generic multi-attribute instrument capable of measuring changes in HRQoL across both different types of diseases and a variety of treatment outcomes. The preferred instrument for measuring generic health-related quality of life is EQ-5D, primarily because it is the most widely used. Other generic instruments can be acceptable if no EQ-5D utility weights are available. Including utility weights measured using a variety of generic instruments in a single analysis is problematic.

In addition to the cost-effectiveness analysis, the submitter was required to provide a five-year budget impact statement, based on the results of the cost-effectiveness analysis. A description of the methods used to evaluate the submitted economic analysis is provided in the section "Presentation and evaluation of the submitted economic evidence".

Evaluation of the clinical documentation

Clinical documentation provided in the submission

The submitter was asked to answer the following question:

"What clinical documentation is available to demonstrate that the health technology is effective and safe?

- *In cases where the actual health technology has been through clinical studies, a certification and/or an approval process in Norway or abroad, the information should be included.*

- *Additionally, systematic searches for studies involving the new technology and comparison alternatives must be performed in relevant databases detailing relevant outcome objectives.…"*

The submission provided information on CE marking, and approval in the United States of America, Canada and Australia. The CAVALIER trial, as well as interim analyses of other studies are mentioned as grounds for CE marking and approval. However, except for the CAVALIER study no other study is cited in the submission. The firm did perform a systematic search (see Appendix 2 and below) and reported descriptive information and results from the included studies.

Characteristics of the submitted systematic search

The submitter performed a systematic search for published clinical documentation the 26th of May 2016 (see Appendix 2 for details).

- Inclusion and exclusion criteria defining the research question as well as the search strategy are reported. The search was restricted to PubMed, which we consider to be sufficiently comprehensive for this purpose.
- The quality of each included study was evaluated, in accordance with our guidelines (18) using either the Newcastle-Otawa checklist for cohort studies or the NIPH checklist for case series.

- Each included publication was described by several tables providing information on population, intervention, patient flow/withdrawals and outcomes.
- The extent to which the publications involved overlapping cohorts of patients was not described.
- Results were mainly presented as provided by the included studies, but the authors present their conclusions about what the study reveals.
- With one exception, data from the included studies are not used in the economic model.
- Selected results from six included comparative studies identified in the systematic search were chosen as data sources for five meta-analyses of in-hospital outcomes found in the appendix of the submission file. These data were not used in the economic model, but are used to validate the model's simulated clinical results by comparing them with actual effectiveness data from the clinical evidence before using model results in the budget impact analysis. No statements on confidence in results or ranking of the evidence in relation to quality is made.
- An additional literature search for relevant studies of late outcomes (survival, explantation or re-intervention, thromboembolism and/or stroke rate, pacemaker implantation) is mentioned in a second appendix in the submission file. Of 966 retrieved citations, 142 papers were examined and appraised using the MEDDEV.2.7.1 Rev.3 Guidelines on Medical Devices. The actual appraisal was not included in the submission. Data from 31 articles were deemed suitable and were used to calculate cumulative survival (freedom from event) for the cost-effectiveness model.
- The authors present an overall conclusion based on the included evidence: *"..Evidence proves safety for Perceval and more precisely: a low level of hospital mortality, low rate for paravalvular leakage, endocarditis, stroke/TIA, bleeding, respiratory insufficiency or explants and re-operation, especially (but not limited to) for intermediate and high risk patients. The Perceval sutureless valve presents positive clinical outcome also in comparison with traditional AVR and TAVI. More precisely there is a positive trend of lower mortality when Perceval is compared with traditional AVR or TAVI, although mortality values are not statistically significantly lower in both the comparisons…"*

Our main objections to this conclusion are not related to the systematic search, but rather reflect the low quality of the clinical evidence, the lack of discussion of uncertainty, and the lack of a clear ranking of the evidence in terms of quality.

Quantity and quality of the included documentation

The submitted systematic search identified a total of 185 publications, of which 25 were included as documentation. No randomized controlled trials (RCTs) were identified. Of the included publications, 15 are studies with comparative data while ten have no comparative data. Six of the studies compared Perceval to TAVI. These studies are excluded from our assessment, leaving nine comparative studies and ten non-comparative studies. Based on an independent systematic search (see below), we identified and included one additional propensity score matched comparative study (19). Except for two studies from Canada, the studies are from Europe. We cannot preclude that some of the publications may report data from the same patients and outcomes. Therefore, we are not able to give an estimate of the total number of patients receiving Perceval in the 20 assessed studies.

To evaluate the internal validity of the studies, we performed a simplified risk of bias evaluation based on the information provided by the firm. In the evaluation we considered selection bias, performance bias, detection bias and attrition bias. We ignored potential reporting bias.

We considered reports from comparative studies that made no attempt to avoid selection bias and retrospective single-arm case series as very low quality evidence. We considered prospectively planned single-arm studies and propensity score matched comparative studies to represenent the best available evidence, and our assessment below focuses on these studies. However, characteristics of all studies and our overall quality rating are presented in Appendix 3 and results reported by all studies as presented in the submission file are provided in Appendix 4.

Calcualtions of pooled estimates from comparative studies were performed using RevMan 5.3 based on full text inspection of the publications. Confidence in individual endpoint estimates provided by best available evidence from comparative studies was assessed based on guidelines provided by The Grading of Recommendations Assessment, Development and Evaluation (GRADE) (20). In accordance with the GRADE guidelines we considered risk of bias, inconsistency, imprecision and indirectness (relative to our predefined PICO-S). However, as all non-RCTs have a starting level of low quality according to GRADE, we did not further downgrade due to imprecision (few events) alone. All quality evaluation, data extraction and calculations were performed by one researcher (VL) and checked by another (HAH). Results are commented on below and details on all anlysis and grading of evidence is provided in Appendix 7.

Best available evidence from comparative studies

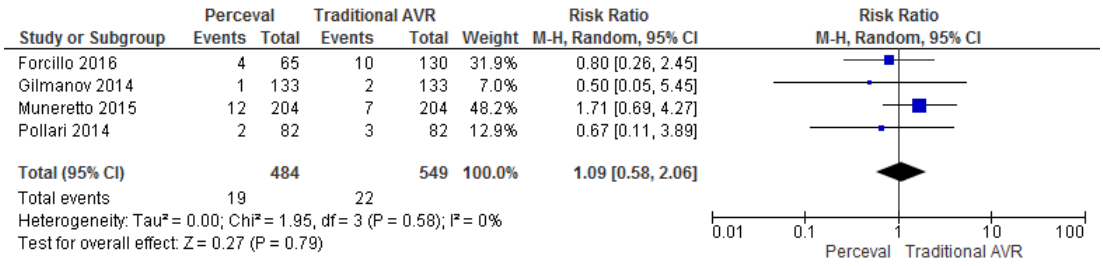
Ten comparative studies reported data from patients undergoing Perceval AVR compared to traditional AVR (see Appendix 3 and 4). We were unable to find an entry in a trial registry for any of these studies, which were all retrospective comparative analysis of data from independent single-arm case series. Five of these studies (19;21-24), used propensity score matching (PSM) to ensure comparable groups. For one PSM study (21), both the valve and the surgical procedure varied between the groups (MiS in the Perceval group and FS in the traditional AVR group). As a result, we downgraded this study for all outcomes from low to very low quality due to high risk of performance bias and indirectness in addition to selection and detection bias.

The total number of patients in the four included PSM studies (19;21-24) was 1033 after matching, with 484 receiving Perceval and 549 receiving a traditional aortic valve.

Mortality and survival: Perceval AVR compared to traditional AVR

All four included PSM studies reported short term mortality (30-day or in-hospital mortality). There were a total of 19 deaths per 484 patients (3.9%) in the Perceval groups and 22 deaths per 549 patients (4.0%) in the traditional AVR groups. Based on a random effects meta-analysis this provided a risk ratio of 1.09 (95% CI 0.58 to 2.06). There was no critical heterogeneity (I^2 =0%) in the analysis (see Figure 1, and Table 2).

Figure 1 *In-hospital mortality rate based on best available evidence (4 non-randomized PSM studies)*



Anticipating a 30-day mortality event rate of 4% with traditional AVR, this risk ratio would provide 4 more deaths per 1000 patients treated with Perceval (95% CI from 17 fewer to 42 more) compared with traditional AVR. Mortality may be similar, but due to wide confidence intervals and risk of bias we cannot preclude that Perceval may reduce or increase mortality compared with traditional AVR (GRADE quality of evidence: low).

One PSM study (22) reported outcomes on survival up to 54 months and one PSM study (23), reported outcomes up to 24 months after surgery based on Kaplan-Meier analysis (see Appendix 4). In both studies long-term survival was reported to be better in the Perceval group. No risk ratios were calculated as patients in each group were followed for different time periods. We consider this to represent very low quality evidence, and have not calculated any estimates of differences in survival based on these two studies.

Morbidity: Perceval AVR versus traditional AVR

Postoperative differences in functional status (NYHA class) were not reported by any comparative study. Two PSM studies reported mean transaortic gradient at discharge in mm Hg. The pooled mean difference (MD) was -0.73 mm Hg (95% CI -1.75 to 0,64), suggesting that there may be little or no difference in short-term hemodynamic function after Perceval AVR compared to traditional AVR (GRADE quality of evidence: low). Details of the analysis are provided in Appendix 7.

Quality of life: Perceval AVR versus traditional AVR

None of the comparative studies reported quality of life data.

Resource use: Perceval AVR versus traditional AVR

Cross-clamp time (CCT) and cardiopulmonary bypass time (CBP) may influence the overall time for each procedure, and may also be surrogate indicators for outcome of surgery. All four PSM studies reported CCT and CBP. In addition, all four PSM studies reported intensive care unit length of stay (ICU-LOS) and three PSM studies reported hospital length of stay (Hospital-LOS).

The pooled mean difference in CCT was -22.53 minutes (95% CI -34.28 to -10.78) and the pooled mean difference in CBP was -26.83 minutes (95% CI -32.10 to -21.55). Pooled mean difference was in ICU-LOS was -0.31 hours (95% CI -1.12 to 0.49) and pooled mean difference in in Hospital-LOS was -0.40 days (95% CI -1.88 to 1.08). In conclusion, CCT and CBP may be reduced during surgery with Perceval compared to traditional AVR (GRADE quality of evidence: low). Due to heterogeneity in the analysis no conclusion can be made with regard to the effect of Perceval on ICU or hospital length of stay.

Adverse effects

Pooled risk ratios based on meta-analysis of the included PSM studies are shown in Table 2 (see Appendix 7 for details). No conclusions can be made with regard to inferiority or superiority of either method (GRADE quality of evidence: low to very low).

Table 2. Risk ratios for adverse effects *of Perceval AVR versus traditional AVR based on random effects meta-analysis (see Appendix 7 for details).*

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI) *	Quality
In hospital mortality № of participants: 1033 (4 observational studies)	RR 1.09 (0.58 to 2.06)	4 more per 1000 (17 fewer to 42 more)	⊕⊕◯◯ LOW
Need for pacemaker implantation № of participants: 1033 (4 observational studies)	RR 1.62 (0.98 to 2.67)	35 more per 1000 (1 fewer to 94 more)	⊕⊕◯◯ LOW
Reexploration for bleeding № of participants: 838 (3 observational studies)	RR 1.29 (0.59 to 2.82)	11 more per 1000 (16 fewer to 69 more)	⊕⊕◯◯ LOW
Stroke № of participants: 838 (3 observational studies)	RR 0.70 (0.29 to 1.68)	9 fewer per 1000 (20 fewer to 19 more)	⊕⊕◯◯ LOW
Infective complications № of participants: 266 (1 observational study)	RR 1.00 (0.30 to 3.37)	0 fewer per 1000 (26 fewer to 89 more)	⊕◯◯◯ VERY LOW
Pulmonary or respiratory complications № of participants: 430 (2 observational studies)	RR 0.53 (0.10 to 2.75)	52 fewer per 1000 (100 fewer to 195 more)	⊕◯◯◯ VERY LOW
Nephrotic complications № of participants: 869 (3 observational studies)	RR 0.90 (0.24 to 3.35)	9 fewer per 1000 (67 fewer to 206 more)	⊕⊕◯◯ LOW

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio; MD: Mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

In conclusion, based on best available comparative evidence, short-term mortality may be reduced, similar or increased in Perceval compared with traditional AVR. There may be little or no difference in hemodynamic function after 30 days, and Perceval may reduce perioperative cardiac bypass time and cross-clamp time. There is

no available evidence to conclude with regard to functionality (NYHA class), quality of life or resource consumption. At present, no firm conclusions can be made with regard to superiority of either method.

Perceval versus other sutureless valves

Two studies (see Appendix 3 and 4 for details) reported data from patients treated with Perceval AVR compared to patients treated with other sutureless valves. These studies were not PSM and we have not assessed them further.

Results from studies with no comparator

Ten studies reported data from single-arm case series (see Appendix 3 and 4 for details). Nine of these involved patients from various clinical centers in Europe while one was from Canada. Several of the European studies are probably overlapping. For one of the European studies (CAVALIER) (25) we identified an entry in a clinical trial registry (NCT01368666). This study is the basis for the CE marking and United States FDA approval of Perceval AVR (see above).

We consider this study to present the best available data from case series. We do not consider it appropriate to perform meta-analyses involving results from this study and other single-arm studies as this, in our opinion, will increase uncertainty with regard to the confidence in any estimates of outcomes, thus reducing the quality of the data. Reported results from all studies are available in Appendix 4. We have inspected the full-text publication of the CAVALIER study (25) and the FDA Summary of Safety and Effectiveness Data (1) to assess outcomes of the CAVALIER study. Only follow-up at discharge (30 days) is reported in the currently available publication (25). The study was prospective, with follow-up at 30 days and 12 months. Preliminary results from the follow-up period are available in the USA FDA Summary of Safety and Effectiveness Data (1).

A total of 815 consecutive patients, aged 65 years or older, were enrolled in the CAVALIER study. A total of 157 patients were excluded before implant. Implant was attempted in 658 patients and 599 patients were followed for longer than 31 days post-procedure. According to the USA FDA file, 30 patients classified as implant failures, received a non-study valve (1).

After inspecting the data in the FDA file we decided, with two exceptions (mortality and freedom from valve-related and procedure related mortality), to only extract safety data for early (≤ 30 days) adverse events (Table 3). We consider these results to represent evidence of low quality. We consider the preliminary data on long-term outcomes as very low quality of evidence. Notably, both the patients and detailed

procedures in the CAVALIER study may differ significantly from the comparative studies. Thus, for other outcomes we have only commented on the results.

Table 3. *Early Adverse events in the CAVALIER study (based on data in the USA FDA file)*

Adverse events	Early events[1] (≤ 30 days)	
	N=614 (1 missed)	%
All mortality	23	3.7
Valve-related and valve- and procedure-related death	8	1.3
Valve reintervention	5	0.8
Explant	5	0.8
All bleeding	28	4.5
Major bleeding	22	3.5
Major anticoagulation-related bleeding	11	1.8
Thromboembolism	27	4.3
Stroke	14	2.2
Endocarditis	1	0.2
Valve thrombosis	0	0
Structural valve deterioration	0	0
All paravalvular leak	4	0.6
Major paravalvular leak	2	0.3
All hemolysis	4	0.6
Adverse events leading to pulse generator implant*	46 (+27)	7.3 (11.8)
Nonstructural valve dysfunction	7	1.1

*There were 27 additional perioperative adverse events leading to pulse generator (pacemaker) implantation.

For each outcome in Table 3, the FDA file provided preliminary annual follow-up data for four years. Survival (based on all-cause mortality) at 1 year (N=537) was 91.7% (95% CI 88.6 to 93.9), at 2 years (N=435) 88.7% (95% CI 86.1 to 91.3), at 3 years (N=308) 83.2% (95% CI 79.9 to 86.5), and at 4 years (N=83) 77.4% (95% CI 72.5 to 82.4). Freedom from valve related and procedure related death at 1 year was 97.2% (95% CI 95.9 – 98.5), at 2 years 96.2% (94.6 – 97.8), at 3 years 94.4% (92.4– 96.5) and at 4 years 89.5% (85.1– 93.8). Due to incompleteness in follow-up we consider these results to be very low quality evidence.

The FDA file provides the following conclusions with regard to long-term safety: *"The results of the CAVALIER trial demonstrate that the linearized late adverse event rates for valvular thrombosis, valve-related thromboembolism, all and major perivalvular leak, and endocarditis are significantly lower than the established PMA standard of twice the FDA Objective Performance Criterion (OPC)….."*

For permanent pacemaker implantation the following comments were made: "The rate for all-cause pulse generator implant following aortic valve replacement (AVR) with the Perceval valve in the CAVALIER study is higher than the 3.1-11.8% rate range for all-cause permanent cardiac pacemaker implant after surgical AVR noted in the published literature."

Based on available results from the CAVALIER study, we find it fair to conclude that the level of adverse events, with the potential exception of the need for permanent pacemaker implantation, may not be inferior to those observed with traditional AVR. The need for pacemaker implantation, however, is higher in the CAVALIER trial compared to the comparative PSM studies. We cannot preclude that this could be related to a difference in populations, and that the need for pacemaker implantation might not be directly linked to the implant.

Differences between NYHA class at 12 months and at baseline, as reported in the FDA file, revealed that 77.5% of patients (362 of 467) displayed a decrease in NYHA of at least one class, while 19.7% of patients remained stable over the period. Only 2.8% of patients displayed a worsened clinical status.

Additional evidence provided by the firm

In the economic model, data from one comparative study was included. This study (26) was not included in the submitted search results. It involves a sub-group (n=50) of patients from the single-arm CAVALIER study (see below) compared without matching to a group of patients undergoing traditional AVR (n=50). We consider this study, like the other non-randomized, non-matched studies to provide evidence of very low quality and have not further commented on this study.

Probably the most important data used in the economic model is “cross-clamp time” (CCT), a measure of the time the patient’s blood does not circulate through the heart. CCT is considered to be an important independent predictor of outcomes following cardiovascular surgery. This assumption is based on a study (2) of cardiac surgery that does not specifically involve Perceval sutureless AVR.

The CCT used in the model is derived from one case series (27) rather than from the CAVALIER study (see Appendix 3 and 4 for details). This was done as this is the only study providing CCT separately for full sternotomy and minimally invasive surgery. The submitter deemed this information necessary for isolating the separate effects of valve type and surgical procedure on clinical outcomes of AVR. We consider data derived from this study to be of very low quality.

In an appendix to the submission file the firm present results of five meta-analyses with data from six of the included comparative studies (see Appendix 4). These meta-analyses were used only to permit validation of simulated outcomes from the model by comparing them to observed study outcomes. We do not consider results of these analyses to provide the best available evidence.

The firm also described two published systematic reviews with meta-analyses (28;29). In the first of these systematic reviews (28), pooled single-arm outcomes

were reported based on weighted pooled estimates involving all types of sutureless valves. No subgroup analyses for Perceval were conducted. We have not assessed the quality of this systematic review. No additional studies were included based on this systematic review. Notably, no information from the systematic review was used in the economic model. In the second of these systematic reviews (29), sutureless AVR (any type) was compared to TAVI. In our assessment, we have excluded TAVI as comparator.

In an additional unpublished, and only partly described, systematic review presented in the appendix of the submission file, a total of 31 studies were included, six of these were studies reporting long-term outcomes (until five years) after Perceval AVR and the rest were studies reporting long-term outcomes after traditional AVR. The Perceval AVR studies represent a sub- fraction of studies identified by the principal systematic search. Data from these studies were used to provide cumulative models (Weibull distributions) on long-term outcomes over a 15-year time horizon. Outcomes analyzed were: survival, freedom from late explant or re-intervention, late thromboembolism, and late pacemaker implantation. We have not reported estimates of outcomes or assessed these results further as we consider these results to represent evidence of very low quality.

Results of an independent systematic search

To rule out selective reporting and identify possible new important evidence, we performed an independent systematic literature search. This literature search is focused on all types of sutureless AVR and a sorted list of findings will be published separately from this assessment (work in progress).

For this assessment we included relevant systematic reviews, HTA reports, as well as potentially relevant comparative studies, according to the predefined research question published in 2015 and later. The quality of included systematic reviews was evaluated using the NIPH checklist for systematic reviews (Appendix 5). We have not assessed any new data in details, but rather pointed out if the data may have a substantial influence on the conclusions provided by the submission file and our overall conclusion. Results are discussed below.

Systematic reviews

We identified five relevant systematic reviews published in 2015 or later (Appendix 6). Only one of these, a rapid review from a Canadian HTA agency from 2015 (30), was solely focused on Perceval AVR. A total of 14 publications were included. The newest review (31) only examined mortality, comparing sutureless AVR with both

traditional AVR and TAVI. One additional propensity matched study from 2016 (32) was included in our meta-analysis.

Entries in trial registries and ongoing studies

We performed a search in the ICTRP database of clinical trials (18.02.2017) with the search string "Sutureless OR Perceval". Among 40 records for 40 trials we found seven relevant and unique entries (see Table 4). Except for the the CAVALIER trial (25) we have not identified any corresponding publications. The most important of the identified trials is a randomized controlled trial, registered at clinicaltrials.gov (NCT02673697), that compares Perceval AVR with traditional biological stented valves. This trial, PERSIST-AVR (Perceval Sutureless Implant versus Standard Aortic Valve Replacement), is a prospective, randomized, stratified non-blinded, multicenter, international, post-market trial. A minimum of 1,234 subjects will be enrolled at approximately 60 worldwide investigational sites where the device is commercially available. The primary objective of this post-market trial is to test the noninferiority of the safety and efficacy of Perceval versus standard sutured stented bioprosthetic aortic valves among the intended trial population. The first patient was enrolled on March 22, 2016 and the planned enrollment period is two years. The primary endpoint is freedom from MACCE (a composite endpoint of all-cause death, myocardial infarction, stroke, and valve re-intervention) at one-year. The endpoint is planned to be reached in the first quarter of 2019.

Table 4. *Identified trials in clinical trial registries*

Population (Number of partisipants)	Intervention	Comparator	Outcomes	Study number/ Name (Country)	Study type (Sponsor)	Status/ completion
Patients with aortic valve disease suitable for implantation of Perceval AVR (1234)	Perceval AVR	T-AVR	- Freedom from MACCE -Surgical times - Hospital Discharge -Normalized Consumption Index - Quality of life EQ5D - Rate of PMI -Echocardiographic and hemodynamic endpoints	NCT02673697 Perceval Sutureless Implant Versus Standard-Aortic Valve Replacement (Europe, Canada and Australia: 44 Centers)	RCT (LivaNova)	Recruiting/ Primary data 2019/Final 2023
Patients aged 50-80 with (operation worthy) AS eligible for both sutureless AVR and T-AVR and concomitant coronary heart disease (requires installation of at	Perceval AVR (N=10)	Balloon expendable AVR with suture: Intuity (N=10); T-AVR: Perimount (N=5) or Crown (N=5)	- hemodynamics - operation times - postoperative course - hospital stay - duration of ventilation - ICU stay - complications - re-hospitalization	DRKS00011049 Medical and economic implications of free bioprosthesis in aortic valve position (Germany, Single Centre)	RCT (NA)	Recruiting since july 2016/ NA

least one IMA graft and a vein graft) (N=30 planned)			- quality of life (3 and 12 months) - Costs			
Population (Number of partisipants)	Intervention	Comparator	Outcomes	Study number/ Name (Country)	Study type (Sponsor)	Status/ completion
Calcific/degenerative Aortic Valve Isolated Elective Aortic Valve Replacement recipient NYHA class III, IV or V (N=150)	Perceval AVR	No comparator	Safety, effectiveness and QoL related endpoints	ACTRN12613000306718 Is less more? A sutureless valve study. Assessing the safety and efficacy of the Perceval S Sutureless Valve implantation (Australia)	Single-arm	Not yet recruiting (terminated?)/NA
Adults (>18) with AS or AIS (N=355)	Perceval AVR	No comparator	Safety and effectiveness related endpoints	NCT01810679 Perceval S Aortic Heart Valve Study- North America (USA 22 locations)	Single-arm (Sorin group)	Terminated (due to FDA approval based on NCT01368666?)
Patients (>65) with AS or AIS (N=658)	Perceval AVR	No comparator	Safety and effectiveness data peri and postoperative and at 12 months after implant	NCT01368666 Safety and Effectiveness Study of Perceval S Valve for Extended CE Mark (Europe Multi Centre (CAVALIER)	Single-arm (LivaNova)	Ongoing –not recruiting/ Primary 2014/ Final 2018 Laborde 2016: Publications of primary data
Patients (>75) with AS or AIS (N=150)	Perceval AVR	No comparator	Safety; mortality and morbidity rates at discharge until 12 months after implant.	NCT00860730 PERCEVAL Pivotal Trial	Single-arm (LivaNova)	Probably completed (status not updated in registry)/Shresta 2014: some data published together with other data
Patients with AS implanted with Perceval since 2012 (N=47)	Diagnostic follow with 4-dimensional volume-rendered computed tomography up from 30 days until 10 years	No comparator	Reduced aortic valve leaflet motion	NCT02671474 Valve Leaflet Motion in Sutureless Bioprosthetic Aortic Valves (Sweden Single Centre)	Single-arm (NA)	Recruiting/ NA

Presentation and evaluation of the submitted economic evidence

Methods for evaluating submitted cost-effectiveness models

Cost-effectiveness analysis

The primary objectives of health economic modeling are to provide a mechanism to determine the relative cost-effectiveness of the specified health intervention(s) compared to standard treatment, using the best available evidence, and to assess the most important sources of uncertainty surrounding the results. In order to make comparisons across different types of treatments and multiple potential health outcomes, economic models typically measure health outcomes in terms of quality-adjusted life years (QALYs), a variable designed to capture both life extension and health improvement. QALYs, by definition, take on a value of 1 for perfect health and 0 at death (33). The output of a cost-effectiveness model is expressed as an incremental cost-effectiveness ratio (ICER), which can be thought of as the extra cost of obtaining an extra life-year in perfect health. The ICER is defined as

$$Cost_{Intervention} - Cost_{Comparator} \Big/ QALY_{Intervention} - QALY_{Comparator}$$

Evaluating cost-effectiveness models

There is no single correct way to build an economic model to estimate the cost-effectiveness of a specific health initiative. Modeling requires consulting with clinical experts to gain an understanding of normal disease progression, and to determine, based on the research question, the relevant treatment population, relevant comparator; and important health outcomes and adverse events connected to treatment. This information informs the basic model structure, and also determines which clinical effect data is most important to retrieve in the systematic literature search. Once the model structure is in place, the modeler relies on colleagues who perform the systematic search and evidence grading to provide the most reliable risk information for the model, but must also collect all of the relevant cost and quality of life data that is needed for cost-effectiveness calculations.

A model is rarely meant to capture every potential detail of the treatment landscape; rather the goal is to include enough detail to provide a realistic view of the most significant pathways in disease progression, given the research question(s) one is trying to answer. Evaluating any given model is primarily about determining whether the choices made by the submitter regarding model structure and treatment comparator are reasonable given the research question; whether baseline epidemiological data reflect the population in which the analysis is being performed; whether the clinical effect data used in the model are of adequate quality; whether resource use and costs reflect the conditions of the healthcare system in question; whether there has been sufficient sensitivity and scenario analysis to determine the degree and source of uncertainty in the model results; and whether the model displays external and internal validity. Checklists are available to help researchers systematically examine these issues.

We proceed by first describing the health economic model used in the submission and the results generated by the model. We then provide our evaluation of the model, focusing on the following issues: model structure, choice of model parameters, use of appropriate sensitivity and/or scenario analysis to examine the extent of uncertainty in model results, and relevance of the model for the Norwegian context (33).

Earlier economic analyses of Perceval identified in the submission

The submission identifies four, previously published economic analyses of Perceval (Table 5), all based on versions of the simulation model used in this submission. The baseline population for the simulation is medium-to-high risk candidates for AVR with life expectancy after 30 days based on published data for 80-year-old AVR survivors.

The first analysis (34) is a cost-minimization study based on the probabilistic, patient-level simulation model coded in WinBUGS. The model uses published correlations to predict costs and outcomes of AVR with Perceval compared to traditional valves for full sternotomy (FS) and minimally invasive surgical (MiS) procedures for Italy, France, Germany and the United Kingdom (UK). Device costs are not included in the analysis. The model also predicts outcomes based on whether the surgery involved isolated AVR or comcomitant procedures. For isolated AVR under full sternotomy the model predicts cost savings with Perceval ranging from approximately €3,600 (Italy) to £3,900 (UK) [NOK 26,900 to 36,950][2] and of approximately €6,000 (Italy) to £6,700 (UK) [NOK 44,850 to 61,800] for minimally invasive

[2] Average annual exchange rates for 2012: €1 = NOK 7.4744 and £1 = NOK 9.2199 (Norges Bank).

Table 5. *Results of previously published cost-effectiveness analyses (copied from submission document)*

Study	Year	Country in which the study was conducted	What type of model analysis?	Patient population (age, gender, state of health, etc.)	Incremental QALY benefit	Incremental costs	ICER	Comparison
Pradelli L, Zaniolo O. [47]	2012	Italy, France Germany and UK	Cost-minimization	medium-to-high risk patients for AVR, whose life expectancies after 30 days is based on published data for octogenarian AVR survivors	**NA**	• **Italy: MiS P**: -5,970 €, **FS P**: -3,602 € • **France: MiS P:** -6,663 €, **FS P**: -4,164 € • **Germany: MiS P**: -6,257 €, **FS P**: -3,641 € • **UK: MiS P**: -6,711 £, **FS P**: -3.915 £	**NA**	FS T
http://www.ispor.org/research_pdfs/45/pdffiles/PCV106.pdf http://www.ispor.org/research_pdfs/45/pdffiles/PCV113.pdf http://www.ispor.org/research_pdfs/45/pdffiles/PCV110.pdf	2013	France, Germany and UK	CEA	medium-to-high risk patients for AVR, whose life expectancies after 30 days is based on published data for octogenarian AVR survivors	*Isolated* • **MiS P:** 0.20 • **FS P**: 0.13 *Concomitant* • **FS P**: 0.16	*Isolated* • **France: MiS P**: -3,054 €, **FS P**: -1,995 € • **Germany: MiS P**: -2,810 € • **UK: MiS P**: -3,241 £, **FS P**: -1,424 £ *Concomitant* • **France: FS P**: -4,914 € • **Germany: FS P**: -3,778 € • **UK: FS P**: -4,199 £	For every surgical approach and every country, Perceval is **Dominant**	FS T

QALY: Quality-adjusted life year, **CEA**: cost effectiveness analysis, **ICER**: Incremental cost effectiveness ratio, **P**: Perceval valve, **MiS**: Minimally-invasive surgery, **FS:** Full sternotomy

procedures. For comcomitant FS surgery, estimated savings using Perceval ranged from €6,000 (Italy) to £6,750 (UK) [NOK 44,850 to 62,200]. The submitter attributes savings to the effect of reduced cross-clamp time (CCT) with Perceval on surgery costs and ICU/hospital bed stays estimated in the model. The study suggests that estimated cost savings with Perceval outweigh the higher price of acquiring the device.

The three other references (35;36) are published abstracts that present the life-time results of cost-utility analyses implemented in Excel based on clinical effect inputs from the Pradelli simulation model (34). Together the abstracts examine use of Perceval in Germany, France and the UK. Results predict an incremental QALY gain with Perceval compared to traditional valves of 0.02 with minimally invasive surgery, 0.13 with full sternotomy, and 0.16 for concomitant surgery with full sternotomy. Estimated total costs, which include the valves, are lower for Perceval in all three countries for MiS isolated procedures and for both isolated and concomitant FS procedures. Perceval is estimated to be the dominant strategy in all cases because of improved clinical outcomes and lower costs. In the UK, results are robust for Perceval valve prices that are up to 3.8 (FS, concomitant) to 4.9 times (MiS, isolated) higher than traditional valves. Similar results for France show Perceval as dominant for prices that are up to 4.1 (FS, concomitant) to 5.6 (MiS, isolated) times higher than traditional valves.

Because health care costs and organization of care vary from country to country, none of the identified analyses can directly answer the question of whether the Perceval sutureless aortic valve would be cost-effective in the Norwegian context. The submitted model is therefore an extension of the Pradelli cost-minimization model (34) using Norwegian cost data where possible.

Description of the submitted model

General

The firm submitted an economic analysis of valve replacement surgery with the Perceval sutureless aortic valve (Perceval) compared to traditional aortic valve replacement surgery (AVR) for treatment of aortic stenosis in patients with medium–to-high operative risk. The choice to limit the comparator to traditional AVR patients is based on the most recent European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) guidelines on management of valvular heart disease.

The submission includes a probabilistic, patient-level cost-effectiveness model implemented in Excel with clinical effect data derived from a Bayesian hierarchical meta-analysis coded in WinBUGS. The meta-analysis does not rely on the evidence

from the submitter's systematic search (see previous chapter), but instead includes clinical results from studies that isolate the effects of valve choice and surgical technique on cross-clamp time (CCT). Al-Sarraf (2) has shown CCT to be an independent predictor of morbidity and in-hospital mortality among cardiac patients. The submitter suggests that this approach provides the best mechanism for determining the cost-effectiveness of the Perceval valve. A five-year budget impact statement, based on the results of the cost-effectiveness model, is also included as part of the economic analysis.

All analysis is conducted from a healthcare-payer perspective, which includes direct treatment costs. The cost-effectiveness model assumes a lifelong time horizon, with costs measured in Norwegian kroner and effects measured in quality-adjusted life years (QALYs). Future costs and QALYs are discounted at a 4% rate, as recommended by Norwegian Directorate of Health guidelines (17).

Model basics

The submitted Perceval model is an updated version of the Pradelli (34) cost-minimization model and allows for a full cost-effectiveness analysis. The model relies on the important assumption that AVR clinical outcomes depend on cross-clamp time (CCT) (2) and the type of surgical technique employed, i.e. full sternotomy or minimally invasive surgery. In addition, the model differentiates between patients undergoing isolated AVR (only valve replacement) and those undergoing AVR concomitant to other procedures.

The submitted Perceval model comprises three parts: (1) a hierarchical, random-effects meta-analysis of clinical data from seven studies, coded in WinBUGS, an open-source software package for Bayesian statistical analysis; (2) a probabilistic, patient-level simulation model, developed in Excel, that uses clinical outcomes from the meta-analysis to determine the life-time effectiveness (30-day mortality, life-years gained, QALYs) and costs of Perceval compared to traditional valves based on 10,000 simulated patients; and (3) a five-year budget impact model, also developed in Excel, to translate the cost-effectiveness results into a budget impact statement. Figure 2 provides a schematic representation of the model structure related to the first two parts.

Figure 2. *Graphical representation of the model structure*

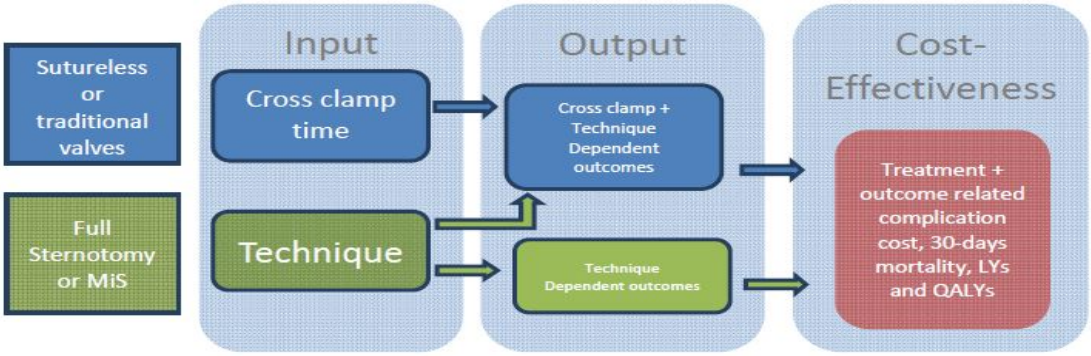


Figure copied from submission file.

In total, six treatment strategies were evaluated. Four strategies involved isolated AVR: traditional valve with full sternotomy (FS), traditional valve with minimally invasive surgery (MiS), Perceval with FS and Perceval with MiS. Two strategies involved concomitant procedures: traditional valve with FS and Perceval with FS.

Effect data

With the exception of data from one study (26) none of the effect data used in the model is from studies presented in the submitter's literature search. Instead all effect data used in the cost-effectiveness analysis are based on values taken from published articles (2;26;27;37-42) and used in the Bayesian meta-analysis as described below to determine pooled values. Table 6 indicates which studies contributed data for estimation of each variable in the meta-analysis. All final effect data used in the cost-effectiveness analysis are presented in Appendix 8.

Underlying relationships in effect data

Cross-clamp time (CCT) is the key variable used to simulate clinical outcomes for the six different treatment strategies that are evaluated in the cost-effectiveness model. The baseline values are for patients with low CCT (< 60 minutes). All other effect data is determined in WinBUGS using Bayesian analysis to estimate relative risks relating CCT to valve type (RRV) and surgical technique (RRT) and to perform meta-analyses to determine baseline risks for all adverse events in the model.

CCTs for the alternative treatment strategies are defined as follows:

- FS T = **FS P** * RRV, where RRV is the relative risk associated with the valve
- MiS P = **FS P** * RRT, where RRT is the RR associated with surgical procedure
- MiS T = MiS P + DELTA_V
- CONC T = **CONC P** + DELTA_V, where DELTA_V = FS T – FS P

For MiS and concomitant procedures, an absolute reduction is evaluated (delta=35.71±51.42), when comparing cross-clamp times in FS surgery in order to exploit the effect of sutureless valve only on the time dedicated to AVR.

Table 6. *Data sources used for meta-analyses of each variable used in the cost-effectiveness model*

	Tech.	Valve	Sharony 2003	Bakir 2006	Bonacchi 2002	DeSmet 2004	Doll 2002	Glauber 2012	Folliguet 2012	Santarpino 2013
XCT (min) mean (SD)	FS	P							30.1 (12.2)	
		T	74.8 (19.5)	69.5 (16.0)	52.4 (9.8)	79.0 (16.0)	55.0 (23.0)	72.8 (27.0)		
	MiS	P							33.6 (9.5)	40.0 (13.8)
		T	76.8 (18.0)	61.8 (16.6)	51.7 (12.2)	79.0 (16.0)	60.0 (22.0)	83.8 (27.2)		66.0 (20.4)
In-hospital mortality dead/pts (%)	FS			12/274 (4.4%)	2/40 (5.0%)					
	MiS			6/232 (2.6%)	1/40 (2.5%)					P: 2/50 (4%) T: 3/50 (6%)
Renal failure cases/pts (%)	FS		3/189 (1.6%)	14/274 (5.1%)						
	MiS		5/189 (2.6%)	8/232 (3.4%)						
Re-op bleeding cases/pts (%)	FS		9/189 (4.8%)	17/274 (6.2%)	3/40 (7.5%)		24/258 (9.3%)			
	MiS		6/189 (3.2%)	18/232 (7.8%)	0/40 (0.0%)		12/176 (6.8%)			
Hospital stay mean days (SD)	FS		14 (18.56)	12.8 (10.6)	8.2 (2.3)	14 (5.9)	12 (7)			
	MiS		10.9 (14.71)	10.8 (7.1)	7.2 (1.6)	14.7 (7.5)	10 (6)			
ICU stay mean days (SD)	FS			2.5 (5.3)	1.4 (0.8)	2.3 (3.3)	4.5 (5.6)			
	MiS			2.1 (2.5)	1.1 (0.4)	1.8 (2.4)	3.7 (5.4)			
Ventilation time mean hours (SD)	FS			1.64 (4.1)	5.3 (1.8)					
	MiS			1.17 (1.0)	4.4 (0.9)					
Blood loss surgery mean ml (SD)	FS					291 (172)				
	MiS					292 (344)				
Blood loss in ICU mean ml (SD)	FS					380 (400)	927 (1046)			
	MiS					295 (350)	736 (843)			
Sepsis rate cases/pts (%)	FS		6/189 (3.2%)							
	MiS		3/189 (1.6%)							
Rehab rate cases/pts (%)	FS		142/189 (75.1%)							
	MiS		84/189 (44.4%)							

The bold variables in the above relationships indicate that the model is developed by first determining the distributions of cross-clamp times for the Perceval valve under full-sternotomy procedures (either for isolated or concomitant) using data from Folliguet (27), the only published clinical study that examines CCT with respect to FS isolated, FS concomitant and MiS procedures using sutureless valves. Our GRADE evaluation of Folliguet (see previous chapter) indicated that the results were of very low quality.

Once the baseline distribution of CCTs for Perceval (FS and CONC) were established, Bayesian methods were used to generate pooled RRV and RRT from the relevant studies, thus establishing baseline CCTs for all six treatment strategies.

Identifying clinical outcomes dependent on both CCT and surgical procedure and those dependent only on surgical procedure

The submitter distinguished between clinical outcomes that were determined by surgical technique alone and those determined by both CCT and surgical technique. To do so they relied on results for the subgroup of high-risk surgical patients in Al-Sarraf et al. (2) to identify clinical outcomes for which there was a statistically significant association between the outcome and at least one of the CCT categories (<60 min, 60 – 90 min, and > 90 min). Table 7 provides relative risks (versus the reference group with CCT < 60 min), adjusted for age and sex, for those outcomes that were significantly related to at least one of the cross-clamp time groups.

Table 7. *Modeled relationship between CCT strata and clinical outcomes for high-risk cardiac patients (EuroSCORE ≥6)* [Based on 1108 patients]*

RR vs. CCT < 60 minutes	CCT 60-90 minutes	CCT > 90 minutes
Outcome	mean (95% CI)	mean (95% CI)
Ward stay	2.03 (1.30 – 5.36)	3.23 (1.20 – 7.66)
ICU stay	1.30 (0.99 – 1.61)	3.00 (1.40 – 4.62)
Renal complications	1.54 (0.93 – 2.15)	2.05 (1.07 – 3.03)
Blood transfusion	1.05 (0.93 – 1.17)	1.60 (1.35 – 1.85)
Ventilation time	1.47 (0.71 – 2.23)	3.41 (1.70 – 5.12)

* Copied from LivaNova submission. Outcomes were converted from ORs reported in Al-Sarraf to RRs.
CCT: cross-clamp time, RR: relative risks, OR: odds ratio.

Outcomes determined by surgical technique alone were those identified in Sharony (42), which occurred at rates that were significantly different for patients undergoing full sternotomy versus minimally invasive surgery, but were not found to be connected to CCT in Al-Sarraf. The submission identified sepsis and discharge to rehabilitation as outcomes that were related only to surgical technique. Table 8 provides the risk of these outcomes based on surgical procedure. These results are used directly in the cost-effectiveness model, with no further estimations required.

***Table 8**. Values of CCT-unrelated parameters, by surgical technique: mean (SD)*

Outcome	Full Sternotomy	Minnimally Invasive Surgery
Sepsis (%)	3.2 (0.0128)	1.6% (0.0092)
Discharge to Rehabilitation (%)	75.1% (0.03)	44.5% (0.04)

Table copied from LivaNova submission.

Outcomes dependent on both cross-clamp time and surgical technique were established using two meta-analyses (43;44) of studies that compared clinical outcomes for FS and MiS procedures. Outcomes were deemed related to both CCT and surgical technique if they were shown to be CCT-dependent in Al-Sarraf and had better results with the MiS technique despite higher CCTs in the meta-analyses. The outcomes included in this group are: in-hospital mortality, incident dialysis, re-operation for bleeding, ward stay, ICU stay, ventilator days, blood loss in OP, and blood loss in ICU.

Estimating baseline values and distributions for outcomes dependent on both CCT and surgical technique

Mortality

To decompose the independent contributions of CCT and surgical technique on mortality, the submission used a relationship established in Ranucci (3) showing that the logit of mortality depends linearly on CCT as described in the formula

$$\text{logit}(\text{mortality}) = \text{logit}(\text{morality}_{CCTind}) + \beta \times CCT$$

Mortality rates from three published papers (26;37;38) were aggregated in WinBUGS and used to calculate morality_{CCTind}, where morality_{CCTind} is the mortality independent of CCT and β, which represents the impact of an extra minute of on mortality risk, is equal to 1.o8%. From this the baseline mortality, risks for full sternotomy and minimally invasive surgery were estimated to be 2.59% ± 0.0043 and 2.04% ± 0.0038, respectively.

Other clinical outcomes

For all remaining clinical outcomes, the model estimated technique-specific rates (R_{lowCCT}) for the baseline CCT (< 60 min) by decomposing the overall observed rate (R_{OBS}) using the relative risks from Al-Serraf (Table 7) and the trial reported distribution of CCTs for that rate according to the general formula:

$$R_{OBS} = R_{lowCCT} \times \%_{lowCCT} + R_{medCCT} \times \%_{medCCT} + R_{highCCT} \times \%_{highCCT}$$

where $\%_{XCCT}$ is the proportion of the CCT in the X category among the patient population contribution to the R_{OBS} as estimated by WinBUGS on the basis of the reported mean ± standard deviation, assuming a gamma distribution. When several studies report on the same outcome, this procedure was repeated for each study and then the results were aggregated using WinBUGS. Table 9 provides the estimated risks for the low CCT groups according to surgical approach of clinical outcomes dependent on both surgical technique and CCT.

Table 9. *Estimated values (mean ± SD) for low CCT groups, by surgical approach*

Outcome	FS	MiS	Sources
In-hospital mortality (%)	2.59 ± 0.43	2.04 ± 0.0038	Bakir, Bonacchi, Santarpino
Incident dialysis (%)	3.07 ± 0.92	2.70 ± 0.91	Sharony, Bakir
Re-op for bleeding (%)	6.60 ± 1.05	5.51 ± 0.97	Sharony, Bakir, Bonacchi, Doll
Ward LOS (days)	9.53 ± 8.03	8.29 ± 6.62	Sharony, Bakir, Bonacchi, Doll, DeSmet
ICU LOS (days)	2.12 ± 3.11	1.83 ± 2.33	Bakir, Bonacchi, Doll, DeSmet
Ventilator (days)	3.13 ± 2.64	2.57 ± 0.99	Bakir, Bonacchi
Blood loss in OP (mL)	248.01 ± 146.60	284.23 ± 292.50	DeSmet
Blood loss in ICU (mL)	692.59 ± 605.35	580.97 ± 542.23	DeSmet, Doll

Costs

The submitter identified resource use and cost data by searching in published Norwegian cost studies and administrative databases. When data were not available, they used the cost found in Pradelli's cost-minimization model (34).

The cost of the Perceval sutureless aortic valve procedure used in the model only included direct health care costs accrued for valve replacement and for managing complications. All cost were updated to reflect 2015 prices using official Norwegian inflation indices and the most recent tariffs, where applicable. Figure 3 shows the simplified cost structure used in the model. Table 10 provides the total unit cost for each major procedure or event included in the model. Costs cited in the text are rounded to the nearest whole number. Detailed cost calculations for the total cost of hospital stay and of each potential complication are provided in Appendix 9.

Figure 3. *Cost structure*

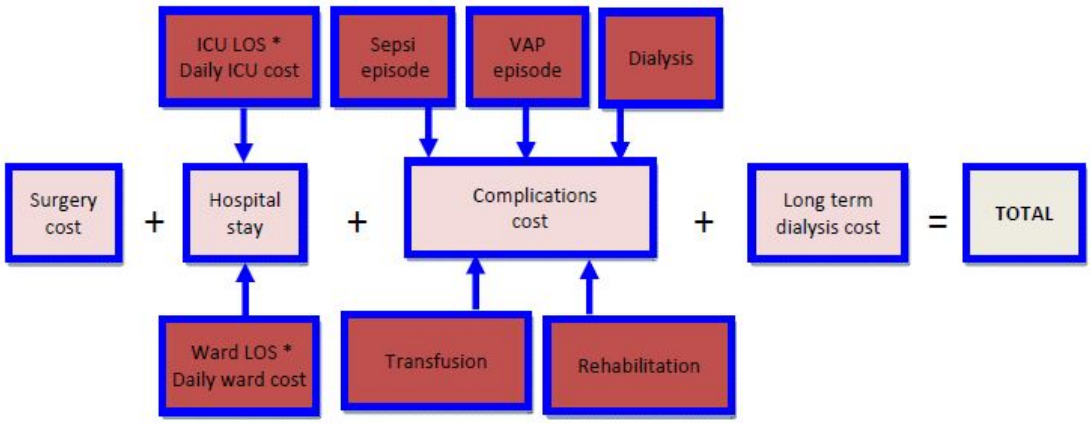


Figure taken from LivaNova submission
VAP: ventilator-associated pneumonia

Surgery cost

The submitted cost of the operating room was based on the cost related to the mean procedure time, common to all the procedure types. The average procedure time was estimated to be 130 minutes in addition to the CCT specific to each procedure. In case of reoperation for bleeding, 130 minutes plus half an hour for asepsis was assumed.

The operation room cost of NOK 230 per minute was taken from a Norwegian study (45) and was estimated as the weighted mean cost of two different cardiac procedures. Operating room cost includes mean cost per staff-hour, other direct resources, e.g. blood, and indirect administrative and capital costs.

Because a specific cost for asepsis could not be identified for the Norwegian health system, the cost of asepsis was calculated by applying the proportion of asepsis cost to total surgery cost found in the original Italian cost-minimization model (34) to the total cost of surgery in Norway. The cost of asepsis was assumed to be NOK 168.

Surgical costs related to the acquisition cost of the valves were derived from an internal analysis. Acquisition costs were assumed to be NOK 11,500 and NOK 32,500 for traditional sutured bioprostheses and Perceval valves, respectively.

Hospital stay costs

The total cost of hospital stay was determined by the number of days spent in the intensive care unit (ICU) immediately following the surgical procedure and number of days in the standard ward, once the critical post-operative phase is completed. The average daily cost of the intensive care unit was NOK 31,043. The average daily cost of the standard ward was NOK 6,096 (46).

Complication costs

Complication costs were based on the following surgical procedure-related events: sepsis, renal failure and ventilator-associated pneumonia. Also included as part of complication costs were any costs associated with rehabilitation and any bleeding requiring red blood cell unit transfusion in the ICU. Because extensions to length of hospital stay resulting from complications are already included in average length of stay costs, only diagnostic tests/procedures, medications, and extra materials needed for managing complications are included in complication costs.

Cost per sepsis episode was calculated to be NOK 12,926 (47). The cost of renal failure was based on hospital dialysis. The cost per day was estimated to be NOK 347. Cost of hospital dialysis was based on the mean of three different procedures according to a Norwegian dialysis report (48). The mean cost per ventilator-associated pneumonia episode was calculated to be

NOK 63,139 (49). The cost of rehabilitation NOK 68,171 was estimated according to Norwegian diagnosis-related groups (DRGs) (50) based on an assumption of 20 days of ordinary rehabilitation. Total cost per blood transfusion was based on the personnel cost per transfusion, NOK 513, and the cost per unit of blood, NOK 1,537 (51). Further, patients that develop renal failure were assumed to receive dialysis until the end of the simulation. The annual cost of hemodialysis was calculated to be NOK 934,368 (48).

Table 10. *Costs used in cost-effectiveness model*

Cost item	Cost (NOK)	References
Operating room (cost per minute)	230.03	Mishra et al. 2008
Asepsis operating room (cost per minute)	167.92	N/A – calculated
Hospital dialysis (cost per day)	347.42	HTA Norway, 2013
Length of stay, intensive unit care (cost per day)	31,040.92	Mishra et al. 2016
Length of stay, ward (cost per day)	6,096.44	Mishra et al. 2016
Personnel cost per transfusion	513.36	Norum et al. 2008
Red blood cells (cost per unit)	1,537.29	Norum et al. 2008
Sepsis (cost per episode)	12,926.31	Flaatten et al. 2003
Ventilator-associated pneumonia (cost per episode)	63,130.28	Elaborated from Kollef et al. 2012
Rehabilitation (cost of 20 days rehab)	68,171.22	ISF (DRG)
Long-term dialysis (cost per year)	943,367.94	HTA Norway, 2013

Table copied from LivaNova submission

Health related quality of life

The submitter reported locating two published quality of life utility weights that could be used in the model. These were average utility weights, measured using the EQ-5D instrument, for AVR surviors with (52) and without (53) the need for renal dialysis (0.46 and 0.68, respectively). The weights were applied to discounted life expectancy for the relevant groups.

Cost-effectiveness results and sensitivity analysis

The base-case cost-effectiveness simulation results were presented in separate tables for effectiveness and costs. The results are all based on simulations of 10,000 patients. The results were not presented as ICERs because the model predictions of slightly larger effect and lower costs using the Perceval valve means that Perceval is the dominant strategy in all cases.

Effectiveness results

Table 11 provides mean effectiveness results (30-day mortality, life-years gained, and QALYs gained), simulated in the cost-effectiveness model, for isolated and concomitant surgeries based on valve type and surgical procedure. The base case results indicate that the Perceval sutureless valve provides gains relative to traditional valves for full sternotomy procedures (isolated and concomitant) and minimally invasive surgery (isolated).

For isolated full sternotomy procedures the estimated effect gains for Perceval relative to traditional valves are 2.1% reduction in mortality, 0.13 increase in life-years gained, and 0.11 increase in QALYs gained. The estimated gains associated with Perceval are slightly lower for isolated MiS, with 1.6% reduction in mortality, 0.11 increase in life-years gained, and 0.09 increase in QALYs gained; and slightly higher for CONC procedures, with 2.9% reduction in mortality, 0.14 increase in life-years gained, and 0.12 increase in QALYs gained.

The largest gains come with a switch from FS with a traditional valve to MiS with Perceval, with a 2.9% reduction in 30-day mortality, a 0.19 increase in life-years gained and a 0.15 increase in QALYs gained. This supports the idea that there are independent gains from a MiS compared to an FS procedure and from Perceval compared to a traditional valve.

Table 11. *Effectiveness results for isolated and concomitant procedures*

	Procedures	30-day mortaility	LY	QALY
Isolated	Traditional (FS)	5.5%	6.08	4.07
	Perceval (FS)	3.4%	6.21	4.18
	FS P vs. FS T	- 2.1%	0.13	0.11
	Traditional (MiS)	4.2%	6.16	4.13
	Perceval (MiS)	2.6%	6.26	4.22
	MiS P vs. MiS T	-1.6%	0.11	0.09
	MiS P vs FS T	-2.9%	0.19	0.15
Concomitant	Traditional	6.4%	6.02	4.03
	Perceval	4.2%	6.16	4.15
	P vs. T	-2.2%	0.14	0.12

LY: life-years, QALY: quality-adjusted life years, FS: Full sternotomy, MiS: minimally invasive surgery, P: Perceval, T: Traditional.
Table copied from submission

Cost results

Mean cost results by type of isolated surgical procedure are detailed in Table 12. Results for concomitant procedures are presented in Table 13. The base case results of the cost-effectiveness model simulations show lower costs using Perceval across surgical procedures and isolated versus concomitant surgeries. In isolated procedures the largest estimated cost savings, NOK 181,605, are associated with using an MiS procedure with Perceval instead of

an FS procedure and a traditional sutured valve. Savings for Perceval compared to trational valves are NOK 133,266 with a full sternotomy and NOK 114,350 for minimally invasive surgery. The estimated savings for concomitant procedures using Perceval is NOK 206,902.

Table 12. *Cost results for isolated procedures*

	FS Traditional	FS Perceval	MiS Traditional	MiS Perceval	MiS P vs FS T	FS P vs FS T	MiS P vs MiS T
Total cost	558,411	425,145	491,156	376,806	-181,605	-133,266	-114,350
Valve	11,500	32,500	11,500	32,500	21,000	21,000	21,000
Surgery	47,464	39,057	47,362	38,972	-8,492	-8,407	-8,390
ICU	91,803	63,612	81,265	56,206	-35,597	-28,191	-25,059
Ward	103,576	60,812	89,646	52,034	-51,542	-42,764	-37,612
Rehabilitation	48,170	49,288	29,034	29,443	-18,727	1,118	409
Complications	4,623	3,901	3,994	3,298	-1,325	-722	-696
Long-term dialysis	251,276	175,976	228,355	164,353	-86,922	-75,300	-64,002

FS: Full sternotomy, MiS: minimally invasive surgery, P: Perceval, T: Traditional.
Table copied from submission

Table 13. *Cost results for concomitant procedures*

	Traditional	Perceval	Perceval vs Traditional
Total cost (NOK)	637,912	431,010	-206,902
Valve	11,500	32,500	21,000
Surgery	50,968	42,375	-8,593
ICU	110,351	58,053	-52,298
Ward	130,701	67,400	-63,301
Rehabilitation	47,761	48,879	1,118
Complications	5,051	3,961	-1,091
Long-term dialysis	281,581	177,843	-103,738

Table copied from submission.

Sensitivity analysis

The submitter notes that two types of uncertainty are addressed in the probabilistic version of the model: inter-individual variability among patients and uncertainty regarding parameter estimates. In addition the cost of Perceval is varied in the probabilistic run of the model by selecting a value from a random distribution with a standard deviation of 20% around the mean value of NOK 32,500. Outcomes by AVR procedure are presented in Table 14. Comparisons between procedures are presented in Table 15.

The submitter interprets the results of the sensitivity analysis as confirming the base case results.

Table 14. *Probabilisitc Sensitivity Analysis results for isolated and concomitant AVR procedures (means and 95% CI)*

Outcomes	FS T	FS P	MiS T	MiS P	Conc T	Conc P
30-day mortality	5.4% (2.3% - 8.6%)	3.6% (2.1% - 5.0%)	4.4% (1.7% -7.1%)	2.9% (1.6% - 4.1%)	6.2% (2.2% - 10.2%)	4.2% (2.3% - 6.0%)

LY	6.06 (5.73 – 6.40)	6.18 (5.90 – 6.46)	6.13 (5.81 – 6.45)	6.23 (5.95 – 6.50)	6.01 (5.65 – 6.39)	6.14 (5.85 6.43)
Outcomes	FS T	FS P	MiS T	MiS P	Conc T	Conc P
QALY	4.07 (3.84 – 4.29)	4.16 (3.97 – 4.35)	4.12 (3.90 – 4.33)	4.20 (4.01 – 4.38)	4.02 (3.77 – 4.28)	4.13 (3.94 – 4.33)
Total Cost	563,872 (368,030 - 759,715)	443,567 (312,759 - 574,376)	498,025 295,197 - 700,853)	387,631 (252,136 - 523,126)	650,529 (401,821 – 899,238)	453,869 (313,597 – 594,141)

T: Traditional, P: Perceval, FS: full-sternotomy, MiS: minimally invasive surgery

Table 15. *Comparison between techniques and valves simulated in Probabilistic Sensitivity Analysis*

Outcomes	MiS P vs FS T	FS P vs FS T	MiS P vs MiS T	Conc P vs Conc T
30-day mortality	-2.6%	-1.9%	-1.5%	-2.0%
LY	0.16	0.12	0.10	0.13
QALY	0.13	0.09	0.08	0.11
Total Cost	-176,241	-120,305	-110,394	-196,661

Mean differences for isolated and concomitant AVR procedures
T: Traditional, P: Perceval, FS: full-sternotomy, MiS: minimally invasive surgery

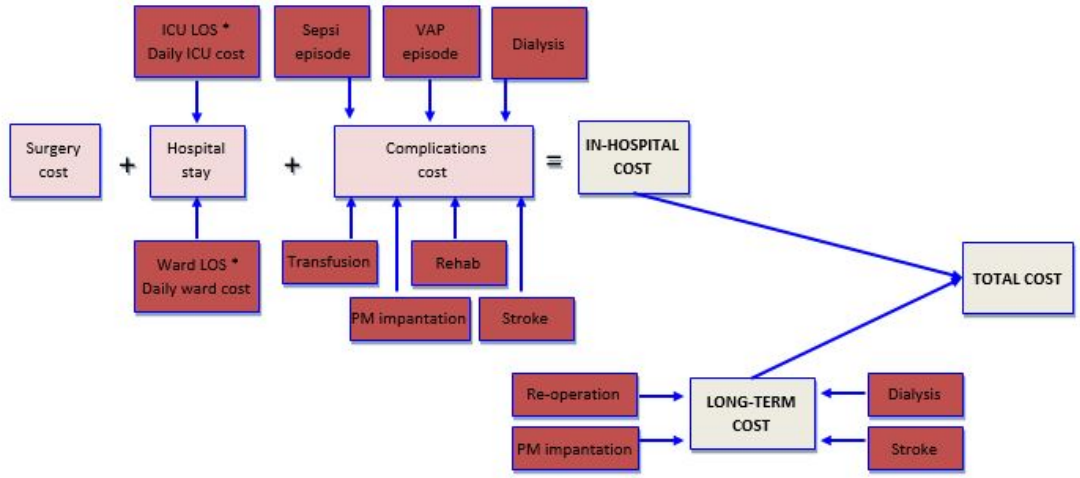
Budget impact analysis

The submitter performed a five-year budget impact assessment to evaluate the potential economic consequences of a gradual adoption in Norway of the Perceval valve in place of traditional sutured valves. The analysis includes a "current scenario" (without Perceval) and an "alternative scenario" with the following assumptions:

- Market size: 698 AVR surgeries annually (based on HINAS 2015)
- Average price of traditional valve: 11,500 NOK (internal LivaNova analysis)
- Average price of Perceval: 32,500 NOK (with sensitivity analysis)
- Progression of Perceval market share in Aortic Tissue Market: 16.5% at five years, with linear progression from market entry, consistent with a specific mid-size EU country five years after full market launch
- Approximately 50% of AVR procedures are full sternotomy and 50% are minimally invasive surgery

Figure 4 diagrams the structure of the budget impact model.

Figure 4. *Structure of the Perceval budget impact model*



Clinical inputs for budget impact model

Clinical inputs for the budget impact model are divided into *in-hospital parameters* and *late outcomes*. The short-term in-hospital data are taken from the results of the cost-effectiveness model (Appendix 10). The in-hospital calculations also include costs of pacemaker implantation and stroke, variables that were not included in the cost-effectiveness model. The risks for these two outcomes for Perceval valves versus traditional valves, were determined by a separate literature search (see "Additional evidence presented by the firm"). Event rates for late outcomes (re-operation, pacemaker implantation, stroke, and dialysis) and long-term mortality were also determined by a separate literature search. Cumulative survival and annual probability of freedom from re-operation, pacemaker implantation and stroke were elaborated in WinBUGS.

To check the internal validity of the results, the submitter compared the results for some outcomes in the cost-effectiveness model with results of meta-analyses performed by the submitter on studies revealed by their systematic literature search (details in Appendix 4A). The submitter contends that the results (Table 16) are similar enough to validate the use of the cost-effectiveness model results. Appendix 11 provides the details of this comparison. As we consider these results to be of very low quality we have included the results from our meta-analyses, while noting that we cannot preclude that no meaningful differences exist among these results.

Table 16. Comparisons of RR or MD for Perceval vs Traditional valves between CEA andMA

Clinical Outcome		P vs Trad from CEA (mean)	P vs. Trad from MA performed by the firm (mean, 95% CI)	P vs Trad from our MA
Early mortality <30 days	RR	0.63	0.58 (0.25, 1.33)*	1.09 [0.58, 2.06]**
ICU stay (days)	MD	- 1.14	-0.16 (-0.75, 0.43)*	-0.31 [-1.12, 0.49]*
Stroke rate	RR	1.15	1.12 (0.45, 2.78)*	0.70 [0.29, 1.68]**
PM implantation rate	RR	1.79	1.76 (1.03, 2.99)*	1.62 [0.98, 2.67]**

RR: relative risk, MD: mean difference, CEA: cost-effectiveness analysis, MA: meta-analysis, *Considered by us as very low quality of evidence, **Considered by us as low quality of evidence

Budget impact model results

The results of the five-year budget impact analysis, based on 698 AVR patients annually, indicate that compared to the current scenario (no Perceval), a gradual increase in the use of the Perceval valve, from 42 surgeries in year 1 to 115 in year 5, would result in cost savings of 1.33%, 2.01%, 2.72%, 3.43% and 4.15% in years 1 to 5, respectively. The results assume that approximately half of patients undergo minimally invasive surgery. The total five-year savings with the specified gradual introduction of Perceval are NOK 44,659,834. Detailed changes in costs and overall results are presented in Appendix 12 and Appendix 13.

The submitter also performed sensitivity analyses around the budget impact results by examining the different prices for the Perceval valve. The estimated five-year savings would be NOK 47,630,974 at a price of NOK 25,000, and NOK 41,688,694 at a price of NOK 40,000.

Discussion and Conclusions

Discussion

We have performed a single technology assessment on the use of Perceval Sutureless aortic valve replacement (Perceval AVR) for adult operable patients with severe aortic stenosis compared to traditional sutured aortic valve replacement. The submission came from Livanova, Sorin group. We have reviewed the submission file and assessed the clinical documentation using a predefined PICO-S (Population, Intervention, Comparator and Outcomes/endpoints and Study design), quality assessment of data provided by the submission file, data extraction, and a simplified GRADE assessment of the quality of clinical effectiveness and safety. We have also performed an assessment of the health economic evaluation.

Clinical effectiveness and safety

In line with the submitted economic model, Perceval AVR is in this assessment considered to be an option for operable patients who currently would be treated with traditional-AVR. The submitted clinical evidence consisted of a total of 25 studies. None of these studies were randomized controlled trials. We considered 19 studies to be relevant for the question defined by the applied PICO-S. Ten of the 19 studies were single-arm studies. Due to overlap between the studies, no conclusions could be made on the total number of patients receiving Perceval AVR in these studies. In addition we included one study from an independent systematic search.

Randomized controlled trials (RCTs) are considered to provide the most robust evidence on relative efficacy or effectiveness of medical interventions. However, other types of studies may provide additional information. No general recommendation can be made as to which alternative is preferable because the decision depends on topic-specific circumstances, regulatory context, resources available, and time expenditure. (54) In this case, we consider the most appropriate argument for including non-RCTs is that it is early in the life cycle of the technology, and that there may be a need for a temporary decision on whether to offer this technology and/or to initiate additional studies based on best available evidence. Thus our assessment was restricted to identifying the best available evidence. Ten relevant studies were retrospective comparative analysis of data from patient series and ten were studies of data from single-arm caseseries. Only one study (the CAVALIER single-arm study) had an

entry in a trial registry. Studies vary in both external validity and internal validity. A simplified risk of bias evaluation and GRADE evaluation was used to identify what we consider to be the best available evidence based on the submitted material. We can not preclude that a more detailed inspection of each individual publications could have changed our grading of evidence slightly, but we do not think that it would have changed our overall conclusions. We considered four propensity score matched cohort (PSM) studies with a total of 1033 patients and the single-arm CAVALIER study (NCT NCT01368666) with 815 consecutively enrolled patients to represent the best available evidence. All other studies were considered to represent evidence of very low quality and were not further assessed. More definitive conclusions on effectivenss and safety of Perceval AVR compared to traditional AVR can be made based on data from the ongoing RCT (NCT02673697) anticipated to be available in 2019.

Based on a random effects meta-analysis of best available evidence, we did not provide any firm conclusions. For short-term mortality, the risk ratio of the meta-analyis involving all PSM studies was slightly in favor of traditional AVR (risk ratio= 1.09; 95% CI 0.58 to 2.06), but due to a wide confidence interval and risk of bias we cannot preclude that 30-day mortality may be reduced or increased compared with traditional AVR. Notably, one of these studies (23) compared Perceval to both traditional AVR and TAVI. This study may have included a population with higher operative risk compared to the other propensity matched studies. The study is weighted by 48% in our meta-analysis. Excluding this study from the analysis would change the risk ratio to be in favor of Perceval (risk ratio = 0.72 (95% CI 0.30 to 1.73)). As this study most likely represents patients that might have received traditional AVR we did not exclude the data. However, we do not preclude that differences in mortality rates between the studies may, at least in part, reflect differences in sub-populations or other factors of the studies.

There may be little or no difference in hemodynamic function between treatment groups (GRADE quality of evidence: low). Perceval AVR may reduce cardiovascular bypass time and cross-clamp time during operation (GRADE quality of evidence: low). Postoperative differences in functional status (NYHA class) was not reported by any comparative study. No studies reported quality of life data. No firm conclusions could be made with regard to long-term outcomes. Adverse events including death, stroke, reexploration due to bleeding, infection, the need for atrioventricular block and the need for permanent pacemaker implantation and pulmonary complications were common (more than 1%) in both groups. No firm conclusions could be made on relative outcomes of safety.

Early adverse events observed in at least 1%, but no more than 5% of the patients included in the CAVALIER study were death, reexploration due to bleeding, and stroke. Early adverse events observed in at least 0,1% but no more than 0,9% of patients included explant for intra- and/or paravalvular leakages, myocardial infarction, endocarditis, and tamponade. The incidence rate of permanent pacemaker (PM) implantation in the CAVALIER study was overall

11.6%. In the PSM studies, the rate of pacemaker implantation was 8,5% in the Perceval group and 5,6% in the traditional AVR group. Whether the high rate of pacemaker implantation with Perceval is attributable to the nature of the intervention, the functional status of the patients or other factors needs to be further explored.

To rule out selective reporting and to identify possible new important evidence, we performed an independent systematic literature search. This literature search was focused on all types of sutureless AVR and a sorted list of findings will be published separately from this assessment (in progress). Based on the sorted list we included five systematic reviews and identified one new PSM study. We found no additional information that influenced our conclusions.

Cost-effectiveness

We have evaluated the economic model submitted by the firm in support of the Purceval sutureless valve with consideration given to the following issues: model structure, choice of model parameters, use of appropriate sensitivity and/or scenario analysis to examine the extent of uncertainty in model results, and relevance of the model for the Norwegian context.

The submitted model is somewhat unconventional in that it does not rely directly on the hard clinical endpoints reported in the literature from the submitter's systematic search. Instead, the model examines the cost-effectiveness of aortic valve replacement with the Purceval sutureless valve compared to traditional sutured valves by relying on evidence (2) that establishes cross-clamp time (CCT) as the primary determinant of several important clinical outcomes for patients undergoing valve replacement surgery.

The submission employs data from seven published studies (not part of the clinical evidence record) to perform Bayesian analyses that allow estimation of both the relative effects of valve type and surgical procedure on CCT, and baseline mean values and associated distributions for 30-day mortality and adverse events for the Perceval reference group (CCT < 60 min). Along with estimates of mean values and distributions for events that are only related to surgical technique or that are determined by a combination of surgical technique and CCT, these estimates can be used along with costs to determine the cost-effectiveness of Perceval for the six treatment groups examined in the model.

The submitters have justified the choice of model and the use of clinical evidence not included in their supporting literature by noting that the major benefits of the Perceval valve are gains in terms of cost savings and improved clinical outcomes that result from reduced cross-clamp time. They claim that being able to isolate the independent effects of valve choice and surgical technique is necessary to accurately capture the effect of using Perceval. The seven studies used to estimate model parameters had the advantage of providing data for comparisons that permitted calculation of the isolated effects. Only one of these studies (26)

was evaluated in the clinical effect and safety section of this report; the others were not graded. However, in our opinion, the model's structure can provide a reasonable context for a cost-effectiveness analysis.

Costs data used in the model are, for the most part, from Norwegian sources. When Norwegian cost data were unavailable the included data seemed appropriate. It also involved sums that were not large enough to have a meaningful influence on model results.

The submitters chose to present results separately for clinical effects (30-day mortality, life-years gained and QALYs) and costs rather than using an incremental cost-effectiveness ratio (ICER), which is the standard outcome reported in cost-effectiveness analyses. Because the results of the model unambiguously favored Perceval, showing that Perceval was always less expansive and somewhat more effective than the traditional valve regardless of surgical procedure or isolated vs. concomitant surgery, an ICER was not needed to evaluate whether the valve represented good value for money.

The submitters performed appropriate sensitivity analysis for both the cost-effectiveness model and the budget impact analysis, but two factors could affect the estimated cost-savings with Perceval. The first factor is whether the reduction in cross-clamp time when using Perceval AVR translates into savings equal to the full cost of the time 'saved'. If, as is likely to be the case, not all of that extra time can be used for additional surgeries, then cost savings will be somewhat reduced. The second factor is the assumption that approximately half of valve replacement procedures are minimally invasive surgeries could also affect the five-year budget impact analysis. Because aortic valve replacement in Norway is usually performed as a full-sternotomy, and estimated savings using Perceval were higher compared to traditional valves for FS than MiS, the actual savings may tend to be higher than reported.

The submitter chose not to include the outcomes *possibility of stroke* and *pacemaker implantation* in the cost-effectiveness model although these were included as part of costs in the budget impact analysis. Without an ability to run our own simulations using the sumitted model, we could not evaluate whether this would have had a large impact on cost-effectiveness outcomes. The fact that these two variables were included in the budget impact analysis, without changing the cost saving results, may be an indication that there would not have been a significant impact on the cost-effectiveness results. As noted in the clinical effect discussion, it is uncertain whether observed differences in rates of pacemaker implantation between Perceval and traditional AVR indicates differences between the valves or is a reflection of differences in study populations.

Our most important concern about the economic model is the impact of using data taken from studies that were not part of what we judged to be the best available evidence on clinical effectiveness.. While we accept that the model structure necessitated using data from studies

in which it was possible to distinguish between the effects of valve type and surgical procedure on clinical outcomes, we also acknowledge that the choice of data used in the model introduces additional uncertainty about the results. The issue is likely to become clearer when results of an RCT involving Perceval is completed.

General

Selection of the right treatment for patients with severe aortic stenosis is a complex multidisciplinary task that depends on each patient's functional status, operative risk and anatomical details. Currently, there is an unmet need for effective treatment for several groups of inoperable patients with severe aorta stenosis. Neither, the assessed documentation nor the ongoing RCT will provide answers to questions about the use of Perceval AVR for patients with very high operative risks or who are ineligible for surgery with traditional AVR based on anatomicic factors.

Effectiveness and safety of other types of sutureless AVR is beyond the scope of this assessment. However, at least one other type of sutureless valve is currently available and has been used in Norwegian hospitals (personal communication). In addition there has been a steady increase in the use of TAVI (12), which has recently been suggested as an option for intermediate risk patients (55). Unlike sutureless AVR and traditional AVR, TAVI needs to be performed under radiological guidance, putting other demands on resource use under surgery. So far, we have not identified any trial registry entries for trials comparing Perceval AVR to other types of sutureless AVR or TAVI. (55)(55)

Conclusions

Clinical effectiveness and safety

The quality of available evidence in support of Perceval sutureless AVR compared to traditional AVR is low to very low.

Based on best available comparative evidence short-term mortality may be reduced, similar or increased, and there may be little or no difference in hemodynamic function for Perceval AVR compared to traditional AVR. Perceval AVR may reduce perioperative cardiac bypass time and cross-clamp time. At present, no firm conclusions can be made with regard to superiority of either method. More robust evidence will be available upon publication of primary data from an ongoing RCT, expected in 2019.

Cost-effectiveness

Based on the cost-effectiveness and budget impact analyses performed by the firm Perceval can be cost-saving compared to traditional sutured valves for isolated full sternotomy or minimally invasive valve replacement surgery, and for concomitant surgeries with full sternotomy. Model estimates of clinical effect indicate that there may be small gains connected with Perceval. Estimates from the five-year budget impact analysis show cost savings with expanded use of Perceval. However, data used in the model were not based on the assessed comparative studies and there is uncertainty about the likelihood of these outcomes. More robust conclusions should be possible on publication of the ongoing RCT.

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Appendices

Appendix 1. Appropriateness of including non-randomized studies (NRS)

Vigdis Lauvrak 02.03.2017. A pro and contra table based on EUnetHTA guideline on assessing risk of bias in non-randomized controlled studies. The arguments were used to evaluate the appropriateness of including non-randomized studies (NRS) for assessing effectiveness and safety of Perceval AVR compared to Traditional AVR (EUnetHTA guideline): http://www.eunethta.eu/outputs/publication-ja2-methodological-guideline-internal-validity-non-randomized-studies-nrs-interv)

Possible reasons favoring the inclusion of non-randomized studies (NRS) include:	How does this apply to the technology and individual outcomes assessed in this report?
1. The research question cannot (or only with the greatest difficulty) be answered in RCTs. This may be the case because of organizational reasons (e.g. in public health interventions), epidemiologic circumstances (e.g. very rare diseases), *or long term effects and rare outcomes (safety issues)*.	In this case, for outcomes related to effectiveness this only applies to rare long-term outcomes. Since safety has been evaluated acceptable in a larger single arm study (CAVALIER), we do consider RCTs can and should be performed to provide firm evidence on the effectiveness of the intervention in different populations. For some patients with severe aortic stenosis and rare anatomical conditions, this would have been the case. Effectiveness assessment of the intervention for these patients is not the scope of this assessment.
2. The research question can probably be answered with NRS evidence, because very large effects are likely (or at least possible), *or because the outcomes are very unlikely in the comparator (often safety issues).*	For many relevant outcomes (mortality and morbidity), non-inferiority and not superiority is aimed at and expected. For certain outcomes related to the surgical procedure (particular adverse events and hospital resource consumption) superiority and large effects are not unlikely and could potentially be detected by well conducted comparative NRS.
3. There is an external need to offer a 'best guess' rather than no answer at all. Such a situation may be present early in the life cycle of a new intervention or when HTA is used to make only a temporary decision which is followed by an early reassessment (e.g. in a coverage with evidence development [CED] model).	It is early in the life cycle of the technology, and there may be a need for a temporary decision on whether to offer this technology based on best available evidence. However, there is not a large unmet-need for this indication (operable patients)
Possible reasons against inclusion of non-randomized studies (NRS) include:	**How does this apply to the technology and individual outcomes assessed in this report?**
1. The HTA report aims at providing a highly reliable result. The inclusion of NRS as the sole information source will very often prevent the results from being 'definitive'.	Only NRS are included in the submission file: We consider that any assessment of these data will not provide definitive results. To avoid reporting very uncertain results of low value for the decision makers, we have restricted the assessment to be focused on only the best available evidence.
2. There is an external need to complete the HTA report within a short time period. As indexing of studies in electronic databases and reporting of study details is less complete for NRS than for RCTs, HTA-associated workload increases when NRS are included.	To avoid excess workload, we have restricted the assessment to be focused on only the best available evidence.

	Possible reasons favoring the inclusion of non-randomized studies (NRS) include:	How does this apply to the technology and individual outcomes assessed in this report?
3.	The inclusion of NRS evidence might mislead researchers into the false belief that RCTs are not worthwhile to perform. Thus, HTA might act as a barrier in finding out the 'true' effect of an intervention.	there is an ongoing RCT (see below)
4.	The reasons favoring the inclusion of NRS have considerably less weight, if it is clear that RCTs (of adequate quality and sample size) exist *or will be available in short time*. Thus, HTAs should rather include NRS as the sole (when RCTs do not exists) rather than an additional source of information on effectiveness and safety.	Results from an ongoing relevant RCT (NCT02673697) with 1234 patients is scheduled to be available in 2019.
5.	The inclusion of NRS leads to specific challenges in terms of internal validity assessment. *Time and resource use spent for Risk of Bias (RoB) evaluation should be weighed against the value of the information provided by inclusion of NRS*	We have limited our RoB analysis to a simplified version relying on information provided by the company in the submission file.

Appendix 2. Characteristics of the systematic search

Submission of documentation for Single Technology Assessment: LivaNova Perceval sutureless aortic valve (This table mainly relates to the clinical evidence included after a systematic search performed May 26 2016)		
Project details	Reviewed by	Vigdis Lauvrak (VL) and Helene Arentz Hansen (HAH)
	Date of review	18.01.2017
	Project name	Sutureless aortic valves in the treatment of aortic stenosis
	Project ID	Nye metoder D2015_042
Study type	Type of information	Company (LivaNova) submission file for single technology assessment
	Country (area)Year	Norway 2017
	Last updated search	26.05.2016
Research question	From the submission file: "What clinical evidence is available to demonstrate that the health technology is effective and safe?" Reformulated by NIPH based on the commission: For patients with severe aortic stenosis, what is the clinical effectiveness and safety of Perceval sutureless aortic valve replacement (SU-AVR) compared to traditional AVR	
Sources of information	Systematic search: Clinical studies to answer the research question were identified with a literature search performed 26.05.2016 using the following search string limited to the database PubMed: "(((((perceval[Title/Abstract]) OR sutureless valve[Title/Abstract]) OR sutureless aortic bioprosthesis[Title/Abstract]) OR sutureless aortic valve[Title/Abstract]) OR sutureless bioprosthesis[Title/Abstract]) OR ("sutureless"[Title/Abstract] AND "TAVI"[Title/Abstract])) OR ("sutureless"[Title/Abstract] AND "transcatheter aortic valve"[Title/Abstract])" Additional sources of information: 1. The submission file provides information on the CAVALIER single armed study to provide the grounds for the CE mark and FDA approval 2. The submission file provides data from two systematic reviews (both published in 2015) with meta-analysis of results from studies comparing SU-AVR (not limited to Perceval) with AVR and TAVI respectively. There was no information on how these reviews were selected. In addition the authors state that there is a systematic review published in 2014 summarizing non-comparative studies. No quality assessment or grading of evidence was reported. 2. The submission file also includes an appendix were some data on another systematic search and analysis for studies reporting on late outcomes (1 year or more) is described, but not revealed in detail. The search was conducted April 21.2016 in PubMed. Interventions were both Perceval SU-AVR and AVR. There were no restrictions with regard to comparator (only data from one arm used). The submission file states that the data appraisal was performed in accordance to the MEDDEV 2.7.1.Rev 3 Guidelines on Medical Devices. A total of 31 publications were included, six of these with Perceval SU-AVR and 25 with AVR. All Perceval studies were also identified by the main systematic search (see below). Data were used to provide cumulative models (Weibull distributions) over a time frame of 15 years on the following outcomes: Survival, Freedom from late explant or re-intervention, Late thromboembolism, Late pacemaker implantation.	
Studies included	Total number of articles identified by the systematic literature search: 185 Total number of publications included: 25 - No RCTs were identified - 15 publications from non-randomized comparative studies.The total number of patients is uncertain as some studies may be overlapping - 10 publications of data from 100 or more patients receiving Perceval SU-AVR. The number of patients in each publication was from 134 to 731 patients in each. Total number of patients is uncertain as some studies are overlapping.	
Validity	The internal and external validity of the included comparative studies were assessed by The Newcastle Ottawa scale for cohort studies and the NIPH (former Norwegian Knowledge Centre) checklist was used for patient series.	

Inclusion criteria and reported data: Given by the PICO below. Patient series with less than 100 patients and studies were Perceval SU-AVR was not the only SU-AVR were excluded	
Population	Adults with severe aortic stenosis
Intervention	LivaNova Perceval sutureless aortic valve (Perceval SU-AVR).
Comparison	Predefined comparators were - Tradiotional aortic valve replacement (AVR). - Another type of sutureless valve - Transcathether aortic valve implantation (TAVI).
Outcomes / Endpoints	- Predefined primary outcome: Survival/mortality - Predefined secondary outcome: Complications and other outcomes
Analysis	Outcomes are reported as presented by the studies. Five meta-analysis presented in an appendix to the submission file.
Main Conclusions	Main conclusions of the authors: "..Evidence proves safety for Perceval and more precisely: a low level of hospital mortality, low rate for para-valvular leakage, endocarditis, stroke/TIA, bleeding, respiratory insufficiency or explants and re-operation, especially (but not limited to) for intermediate and high risk patients. The Perceval sutureless valve presents positive clinical outcome also in comparison with traditional AVR and TAVI. More precisely there is a positive trend of lower mortality when Perceval is compared with traditional AVR or TAVI, although mortality values are not statistically significantly lower in both the comparisons…"
Comments from NIPH:	
The submission file provides a comprehensive selection of studies based on a systematic search. However, we cannot exclude bias in the process of study inclusion. No analyses are performed and no clear statements are presented to indicate which studies or outcome estimates represent the best available evidence. There is very limited connection between the submitted clinical evidence and the economic model. However, our main objection to the main conclusion is the very low quality level of evidence.	

Appendix 3. Characteristics of studies

Comparator = Traditional-AVR

Title	Study ID (in sub file)	Type of study/ comparator	Baseline characteristics Perceval SU-AVR (number of patients)	Baseline characteristics Traditional AVR (number of patients)	Patient accountability/ withdrawals	Follow up time	Outcomes	Newcastle-Ottawa Scale (submitted)	Quality by NIPH*
Forcillo J, Bouchard D, Nguyen A, Perrault L, Cartier R, Pellerin M, et al. Perioperative outcomes with sutureless versus stented biological aortic valves in elderly persons. J Thorac Cardiovasc Surg 2016;151(6):1629-36.	Forcillo 2016 (Not part of submission file)	PSM/ Trad AVR	(65) Age 83±3; Female 48; Log EuroSCORE: 4.4% (2.8-8.4); NYHA III or IV: 30 (46.2%)	(130) Age 83±3; Female 39; Log EuroSCORE: 5.3% (3.1-9.0); NYHA II or IV: 67 (51.9%)	76 patients Perceval; 319Traditional (Biological) AVR; 1:2 matching based on baseline data	Within 30 days	After PSM: CCT; CBP; 30 day Mortality; Prolonged ventilation; ICU LOS; Hospital LOS; Readmission; Any 30-d morbidity; Selected AE	NA	Low
Gilmanov, D., Miceli, A., Ferrarini, M., Farneti, P., Murzi, M., Solinas, M., & Glauber, M. (2014). Aortic valve replacement through right anterior minithoracotomy: can sutureless technology improve clinical outcomes? *The Annals of thoracic surgery, 98*(5), 1585-1592.	Gilmanov 2014 (11)	PSM/ Trad AVR	(133) Female: 59 (44.4%); Mean age 75.3 (70.1–79.6); Median EuroSCORE: 5.83 (3.74–8.77); NYHA III or IV: 39 (29.3%);	(133) Female: 57 (42.9%); Mean age:73.6 (68.1–78.7); Median EuroSCORE: 5.46 (3.53–8.17); NYHA III or IV 40 (30.1%)	515 valves: 269sutured/246sutureless: 156 pts (30%) excluded after 1:1matching)	Follow-up time 53.6±29 months	In hospital mortality; Survival; Hemodynamic measures; CBP and CCT; AE; ICU stay; In hospital stay	S: 4/4; C:2/2 (Propensity Score Matched); O: 3/3	Low
Konig, K. C., Wahlers, T., Scherner, M., & Wippermann, J. (2014). Sutureless Perceval aortic valve in comparison with the stented Carpentier-Edwards Perimount aortic valve. *The Journal of heart valve disease, 23*(2), 253-258.	Konig 2014 (12)	Single center (no matching)/ Trad AVR	(14) Female:12; Mean age:74 ±4.4; Additive EuroSCORE: 7.4 ± 1.1	(14) Female: 5 Mean age:74 ±4.4; Additive EuroSCORE:5.9±2.2	NA	Follow-up to discharge	30 days hospital mortality; AE; Isolated AVR CBP and CCT; Concomitant AVR CBP and CCT	S: 4/4; C:0;2 O: 2/3	Very low
Pollari, F., Santarpino, G., Dell'Aquila, A. M., Gazdag, L., Alnahas, H., Vogt, F., . . . Fischlein, T. (2014). Better short-term outcome by using sutureless valves: A propensity-matched score analysis. *Annals of Thoracic Surgery, 98*(2), 611-617.	Pollari 2014 (13)	PSM -Single center experience/ Trad AVR	(82) Female: 50; Mean age: 75.5 ± 5; Mean EuroSCORE:12.1 ±4.9; Mean NYHA: 2.9 ±0.8	(82) Female: 43; Mean age:74.5 ± 8.1; Mean EuroSCORE:10.9 ± 4.2; Mean NYHA: 3.1 ± 0.6	566 patients: 400 sutured/166 sutureless 402 excluded after 1:1 matching	30 days	Hospital mortality; AE; CBP and CCT; ICU stay	S: 4/4; C: 2/2 (Propensity Score Matched); O: 2/3	Low

Title	Study ID (in sub file)	Type of study/ comparator	Baseline characteristics Perceval SU-AVR (number of patients)	Baseline characteristics Traditional AVR (number of patients)	Patient accountability/ withdrawals	Follow up time	Outcomes	Newcastle-Ottawa Scale (submitted)	Quality by NIPH*
Santarpino, G., Pfeiffer, S., Concistre, G., Grossmann, I., Hinzmann, M., & Fischlein, T. (2013). The perceval S aortic valve has the potential of shortening surgical time: Does it also result in improved outcome? *Annals of Thoracic Surgery, 96*(1), 77-82.	Santapino 2013 (14)	Single center (no matching)/ Trad AVR	(49) Female: 30; Mean age: 77.5 ± 5.3; Mean EuroSCORE: 9.9 ± 6.5;	(50) Female: 20; Mean age: 71.7 ± 10; Mean EuroSCORE:4.3 ± 1;	83 patients with sutureless AVR: 50 with isolated AVR included / 50 sutured AVR 1 withdrawal	30 days	30 days mortality; Hemodynamic measures; PM and selected AE; CBP/CTT	S: 4/4; C: 0/2; O:2/3	Very low
Dalen, M., Biancari, F., Rubino, A. S., Santarpino, G., Glaser, N., De Praetere, H., . . . Sartipy, U. (2016). Aortic valve replacement through full sternotomy with a stented bioprosthesis versus minimally invasive sternotomy with a sutureless bioprosthesis. *European Journal of Cardio-Thoracic Surgery, 49*(1), 220-227.	Dalen 2016 (15)	PSM; Perceval registry/ Trad AVR	MiS (171); Female: 102; Mean age:77.3 ± 5.1; EuroSCORE (mean):9.8 ± 5.5;	FS (171); Female: 108; Mean age:77.4 ± 6.1; EuroSCORE (mean):9.6 ± 6.9;	189 sutureless (7 excluded due to concordant cardiac procedure)/ 787 sutured of these 383 sutured FS used in propensity matched (182 isolated AVR with MiS excluded)	Up to 2 years	30 days mortality: Kaplan-Meier: 2 years cumulative survival; CBP and CCT; Selected AE; ICU stay:	S3/4; C:2/4 (Propensity Score Matched); O: 3/3	Very low
Shrestha, M., Maeding, I., Hoffler, K., Koigeldiyev, N., Marsch, G., Siemeni, T., . . . Haverich, A. (2013). Aortic valve replacement in geriatric patients with small aortic roots: Are sutureless valves the future? Interactive Cardiovascular and Thoracic Surgery, 17(5), 778-782.	Shresta 2013 (16)	Single center retrospective observational (no matching)/ Trad AVR	(50) Female:47; Age:79.8 ± 4.5 ; NYHA III: 44 (89.8%); NYHA IV: 2 (4.1%)); (120 patients selected: 50 patients from the Cavalier feasibility study/ 70 patients sutured)	(70) Female:86; Age:77.4 ± 5.5; NYHA III:53 (76.8%); NYHA IV:5 (7.2%)	50 patients from the Cavalier feasibility study/ 70 patients sutured	Up to 5 years mean follow up 22.7± 17.5/32.7± 15.5 months	30 day mortality: 1 year mortality***: 3 years mortality*** 5 Years mortality***: Hemodynamic measures; Re-operation Endocarditis	S:4/4; C:0; O:3/3	Very low
Muneretto, C., Alfieri, O., Cesana, B. M., Bisleri, G., De Bonis, M., Di Bartolomeo, R., . . . Folliguet, T. (2015). A comparison of conventional surgery, transcatheter aortic valve replacement, and sutureless valves in "real-world" patients with aortic stenosis and intermediate- to high-risk profile Read at the 95th Annual Meeting of the American Association for Thoracic Surgery, Seattle, Washington, April 25-29, 2015. *Journal of Thoracic and Cardiovascular Surgery, 150*(6), 1570-1579.	Muneretto 2015 (24)* *In the submission file some places there is a mix up were this study is also labelled 23	Multi centre retrospective PSM / Trad AVR and TAVI	(204) Female: 105 (51.4) Age (mean ± SD) y 79±4; EuroSCORE (mean) 18.9 ± 5.9; NYHA III-IV: 130 (64)	Trad AVR (204) Female: 98(48); Age 80±3 EuroSCORE (mean)19.2 ±7.4; NYHA III-IV: 125 (61.2) TAVI (204) Female: 91 (44.6) Age 80 ± 2 EuroSCORE (mean)19.5 ± 6.7 NYHA III-IV: 137 (67.1)	336 patients Traditional AVR; 288 Perceval; 367 TAVI: After matching 204 in each group. No mention of further withdrawal	Until 24 months	30 day mortality; CBP and CCT 24-months follow up; survival free from composite endpoints (MACCE);	S: 3/4; C: 2/2 (Propensity Score Matched); O: 2/3	Low
Muneretto, C., Bisleri, G., Moggi, A., Di Bacco, L., Tespili, M., Repossini, A., & Rambaldini, M. Treating the patients in the 'grey-zone' with aor-	Muneretto 2014 (25)	Multi centre; retrospective (no matching)/	(55) Mean age: 79 ± 4; NYHA III or IV: 47 (88.7%)	Trad AVR (53); Mean age: 79 ± 5;	NA	24 months	Hospital mortality; Survival at 24-month follow-up;	S:4/4; C:0/2; O:2/3	Very low

Title	Study ID (in sub file)	Type of study/ comparator	Baseline characteristics Perceval SU-AVR (number of patients)	Baseline characteristics Traditional AVR (number of patients)	Patient accountability/ withdrawals	Follow up time	Outcomes	Newcastle-Ottawa Scale (submitted)	Quality by NIPH*
tic valve disease: A comparison among conventional surgery, sutureless valves and transcatheter aortic valve replacement. *Interactive Cardiovascular and Thoracic Surgery, 2014* (141), 90-95.		Trad AVR and TAVI		NYHA III or IV: 39 (71%) TAVI (55) Mean age: 81 ± 6; NYHA III or IV: 31 (56.4%)			Overall survival free from MACCE; Prosthetic regurgitation; PM Peripheral vascular complications		

SU-AVR= sutureless aortic valve replacement; T-AVR= Traditional (sutured) aortic valve replacement; TAVI= Transcatheter aortic valve implantation; FS = full sternotomy; MS = mini-sternotomy; AE= adverse events; CBP = Cardiovascular Bypass; CCT= Cross Clamp Time; Newcastle Ottawa scale ratings in stars: S= Selection (max score 4 stars), Comparability (max score 2 stars), Outcome assessment (max score 3 stars). *Overall quality based on a simplified risk of bias evaluation and Criteria provided by GRADE as described in methods

Comparator= alternative sutureless AVR

Title	Study ID (ID sub file)	Baseline Characteristics Perceval SU AVR (number of patients)	Baseline Charactersistics Comparator (number of patients)	Follow up	Outcomes Results: Mortality/survival	Newcastle-Ottawa Scale	Quality by NIPH*
Concistre, G., Santarpino, G., Pfeiffer, S., Farneti, P., Miceli, A., Chiaramonti, F., . . . Fischlein, T. (2013). Two alternative sutureless strategies for aortic valve replacement: A two-center experience. *Innovations: Technology and Techniques in Cardiothoracic and Vascular Surgery, 8*(4), 253-257.	Concistre 2015 (17)	Perceval valve (n=45) Female:29 (64%); Mean age: 77.1 (5.3); Mean EuroSCORE:11.4 (8.1);	3f Enable (n=19): Female: 12 (63); Mean age: 77.1 (5.1); Mean EuroSCORE: 15.4 (11.8);	6 months	In Hopsital deaths; 6-month survival; Functional score (NYHA); Hemodynamic measures:	S:3/4; C:0; O:2/3	Very low
Concistre G, Miceli A, Chiaramonti F, Farneti P, Bevilacqua S, Varone E, et al. Sutureless aortic valve implantation through an upper v-type ministernotomy: An innovative approach in high-risk patients. Innovations: Technology and Techniques in Cardiothoracic and Vascular Surgery 2013;8(1):23-8.	Concistre 2013 (18)	Perceval valve (n=97): Female:64 (66%); Mean age:76.9 ± 5.3 ; Mean EuroSCORE: 11.4 ± 8.1;	3f Enable (n=32): Female: 20 (62%); Mean age:76.8 ± 5.1; Mean EuroSCORE:13.8 ± 10.3	30 days	30 day mortality; Functional score (NYHA): Hemodynamic measures: Lung insufficiency: Stroke; Renal insufficiency: Permanent PM: Moderate paravalvular leakage: CCT and CBP isolated AVR and concomitant	S:3/4; C:0; O:2/3	Very low

SU-AVR= sutureless aortic valve replacement; Trad-AVR= Traditional (sutured) aortic valve replacement; TAVI= Transcatheter aortic valve implantation; FS = full sternotomy; MS = mini-sternotomy; AE= adverse events; CBP = Cardiovascular Bypass; CCT= Cross Clamp Time; Newcastle Ottawa scale ratings in stars: S= Selection (max score 4 stars), Comparability (max score 2 stars), Outcome assessment (max score 3 stars). *Overall quality based on a simplified risk of bias evaluation and Criteria provided by GRADE as described in methods

No comparator

Title	Study ID (ID sub file)	Type of study	Population	Outcomes reported	Quality by NIPH*
Folliguet, T. A., Laborde, F., Zannis, K., Ghorayeb, G., Haverich, A., & Shrestha, M. (2012). Sutureless perceval aortic valve replacement: Results of two European centers. *Annals of Thoracic Surgery, 93*(5), 1483-1488.	Folliguet 2012 (1)	Single arm; Multicenter (N=208)	AS or SI; Age ≥65; NYHA III or IV requiring AVR; High risk = EuroSCORE > 5; Isolated AVR (n=163)	In hospital mortality; Cumulative survival (freedom from valve related mortality); Cumulative freedom from valve-related mortality; Functional score (NYHA); Hemodynamic measures; Adverse events; CBP and CCT	Very low
Gilmanov, D., Miceli, A., Bevilacqua, S., Farneti, P., Solinas, M., Ferrarini, M., & Glauber, M. (2013). Sutureless implantation of the perceval s aortic valve prosthesis through right anterior minithoracotomy. *Annals of Thoracic Surgery, 96*(6), 2101-2108.	Gilmanov 2013 (2)	Single arm; Retrospective on prospective collected data (N=137)	Patients eligible for isolated AVR	In hospital mortality; Functional score (NYHA); Hemodynamic measures; Adverse events; CBP and CCT; Assisted ventilation; ICU length of stay; Postoperative length of stay	Very low l
Miceli, A., Santarpino, G., Pfeiffer, S., Murzi, M., Gilmanov, D., Concistre, G., . . . Glauber, M. (2014). Minimally invasive aortic valve replacement with Perceval S sutureless valve: Early outcomes and one-year survival from two European centers. *Journal of Thoracic and Cardiovascular Surgery, 148*(6), 2838-2843.	Miceli 2014 (3)	Single arm; Retrospective; two centers (N=281)	Calcified AVS or SI; Small calcified Aortic root or annulus; Age ≥65; EuroSCORE > 5	In hospital mortality; Functional score (NYHA); Hemodynamic measures; Adverse events; CBP and CCT; ICU length of stay; Postoperative length of stay	Very low
Shrestha, M., Folliguet, T. A., Pfeiffer, S., Meuris, B., Carrel, T., Bechtel, M., . . . Haverich, A. (2014). Aortic valve replacement and concomitant procedures with the perceval valve: Results of european trials. *Annals of Thoracic Surgery, 98*(4), 1294-1300.	Shresta 2014 (4)	Single arm; Retrospective on prospective collected data; (N=243)	Subgroup of patients from three trials undergoing SU-AVR and concomitant procedures	In hospital mortality; 2 years mortality; Functional score (NYHA); Hemodynamic measures; Adverse events;	Very low
Rubino, A. S., Santarpino, G., De Praetere, H., Kasama, K., Dalen, M., Sartipy, U., . . . Biancari, F. (2014). Early and intermediate outcome after aortic valve replacement with a sutureless bioprosthesis: Results of a multicenter study. *Journal of Thoracic and Cardiovascular Surgery, 148*(3), 865-871; discussion 871.	Rubino 2014 (5)	Single arm retrospective; Multicenter (N=314)	Patients undergoing Isolated SU-AVR;	In hospital mortality; 1 year and 2 year mortality; Adverse events; CBP and CCT; ICU stay; Hospital stay	Very low l
Mazine, A., Teoh, K., Bouhout, I., Bhatnagar, G., Pelletier, M., Voisine, P., . . . Bouchard, D. (2015). Sutureless aortic valve replacement: A Canadian multicentre study. *Canadian Journal of Cardiology, 31*(1), 63-68.	Mazine 2015 (6)	Single arm retrospective; Multicenter (N=215)	Patients undergoing SU-AVR	In hospital mortality; Hemodynamic measures; Adverse events; CBP and CCT; ICU stay ;Hospital stay	Very low
Shrestha, M., Fischlein, T., Meuris, B., Flameng, W., Carrel, T., Madonna, F., . . . Laborde, F. (2016). European multicentre experience with the sutureless Perceval valve: Clinical and haemodynamic outcomes up to 5 years in over 700 patients. *European Journal of Cardio-Thoracic Surgery, 49*(1), 234-241.	Shresta 2016 (7)	Single arm retrospective analysis of prospective collected data; Multicenter (25 centers 2007-20129) (n=731) (765 of which 34 cases (4,4%) conversion to commercial valves)	Patients undergoing Perceval SU-AVR; Age ≥65	Mortality; 5 years survival; Causes of early and late death are reported; Functional score (NYHA); Hemodynamic measures; Adverse events; CBP and CCT; Conversion to other AVR	Very low
Zannis, K., Joffre, J., Czitrom, D., Folliguet, T., Noghin, M., Lansac, M. N., . . . Laborde, F. (2014). Aortic valve replacement with the perceval S bioprosthesis: single-center experience in 143 patients. *The Journal of heart valve disease, 23*(6), 795-802.	Zannis 2014 (8)	Single arm retrospective analysis of consecutive patients (Single center 2007-2011)	Patients with AS or SI undergoing Perceval SU-AVR (n= 143)	Mortality; 5 years survival; Functional score (NYHA); Hemodynamic measures; CBP and CCT; Adverse events;	Very low l

Title	Study ID (ID sub file)	Type of study	Population	Outcomes reported	Quality by NIPH*
Fischlein, T., Pfeiffer, S., Pollari, F., Sirch, J., Vogt, F., & Santarpino, G. (2015). Sutureless Valve Implantation via Mini J-Sternotomy: A Single Center Experience with 2 Years Mean Follow-up. *Thoracic and Cardiovascular Surgeon, 63*(6), 467-471.	Fischlein 2015 (9)	Single arm (Single center) (n=145) (262 Perceval/117 FS excluded) Part of the CAVALIER study	Patients with symptomatic severe calcified AS undergoing Perceval SU-AVR	See the CAVALIER study	Very low
Laborde, F., Fischlein, T., Hakim-Meibodi, K., Misfeld, M., Carrel, T., Zembala, M., . . . Wendt, D. (2016). Clinical and haemodynamic outcomes in 658 patients receiving the Perceval sutureless aortic valve: Early results from a prospective European multicentre study (the Cavalier Trial). *European Journal of Cardio-Thoracic Surgery, 49*(3), 978-986.	Laborde 2016 (10)	Single arm prospective Multicenter (815 consecutive patients/157 excluded due to intra-operative exclusion criteria) CAVALIER study NCT01368666	Patients with AS or SI and a need for a prosthetic valve; ≥65 years (n=658)	Incidence of mortality and morbidity. (time frame 12 months) Effectiveness: NYHA functional class and hemodynamic performance. Mortality and morbidity, adverse event categories: valvular thrombosis, thromboembolism, hemorrhage, paravalvular leak, endocarditis, hemolysis, SVD, nonstructural dysfunction, reoperation, explant, death, device dislodgement and device migration Hemodynamic performance : mean gradient and peak gradient, EOA, EOAI, PI, cardiac output, cardiac index and degree of regurgitation Safety and effectiveness [Time Frame: 3-6 months] The secondary endpoints of the clinical investigation are: Assessment of mortality and morbidity rates at discharge and at 3-6 months	Low level (prospective study)

SU-AVR= sutureless aortic valve replacement; Trad-AVR= Traditional (sutured) aortic valve replacement; TAVI= Transcatheter aortic valve implantation; FS = full sternotomy; MS = mini-sternotomy; AE= adverse events; CBP = Cardiovascular Bypass; CCT= Cross Clamp Time; Newcastle Ottawa scale ratings in stars: S= Selection (max score 4 stars), Comparability (max score 2 stars), Outcome assessment (max score 3 stars). *Overall quality based on check list for patient series provided in the submission file as well as a simplified risk of bias analysis. According to GRADE all non-randomized studies start at low level, all retrospective single arm studies were further downgraded.

B) Studies excluded from submitted search and not further assessed (due to comparator being transcatheter aortic valve replacement (TAVI))

Reference	Study ID (ID submission file)	Type of study/Comparator
D'Onofrio, A., Messina, A., Lorusso, R., Alfieri, O. R., Fusari, M., Rubino, P., . . . Gerosa, G. (2012). Sutureless aortic valve replacement as an alternative treatment for patients belonging to the "gray zone" between transcatheter aortic valve implantation and conventional surgery: a propensity-matched, multicenter analysis. *The Journal of thoracic and cardiovascular surgery, 144*(5), 1010-1016.	D'Onofrio 2012 (19)	PSM/ TAVI
Santarpino, G., Pfeiffer, S., Jessl, J., Dell'Aquila, A. M., Pollari, F., Pauschinger, M., & Fischlein, T. (2014). Sutureless replacement versus transcatheter valve implantation in aortic valve stenosis: A propensity-matched analysis of 2 strategies in high-risk patients. *Journal of Thoracic and Cardiovascular Surgery, 147*(2), 561-567.	Santarpino 2014 (20)	PSM/ TAVI
Biancari, F., Barbanti, M., Santarpino, G., Deste, W., Tamburino, C., Gulino, S., . . . Rubino, A. S. (2016). Immediate outcome after sutureless versus transcatheter aortic valve replacement. *Heart and Vessels, 31*(3), 427-433.	Biancari 2016 (21)	PSM/ TAVI
Miceli, A., Gilmanov, D., Murzi, M., Marchi, F., Ferrarini, M., Cerillo, A. G., . . . Glauber, M. (2016). Minimally invasive aortic valve replacement with a sutureless valve through a right anterior mini-thoracotomy versus transcatheter aortic valve implantation in high-risk patients. *European Journal of Cardio-Thoracic Surgery, 49*(3), 960-965.	Miceli 2016 (22)	PSM/ TAVI
Santarpino, G., Pfeiffer, S., Jessl, J., Dell'Aquila, A., Vogt, F., Von Wardenburg, C., . . . Fischlein, T. (2015). Clinical Outcome and Cost Analysis of Sutureless Versus Transcatheter Aortic Valve Implantation with Propensity Score Matching Analysis. *American Journal of Cardiology, 116*(11), 1737-1743.	Santarpino 2015 (23)	PSM/ TAVI

PSM = propensity matched, TAVI = transcatheter aortic valve implantation

Appendix 4. Outcomes reported by the included studies

Comparative studies

Study ID	Mortality/survival	Morbidity (functionality (NYHA class); Hemodynamic measures; other	Quality of life	Complications (other than death)	CCT and CBP (minutes)	Resource consumption	Costs	Other
Forcillo 2016 Perceval N= 65; Trad AVR: N= 130	30-d Mortality Perceval/Trad AVR 4 (6.2 %)/10 (7.7%)	Not reported	Not reported	Perceval/Trad AVR Prolonged ventilation (>24 h): 4 (6.2%)/ 5 (4.1%); Reintubation: 5 (7.8%)/6 (4.7%); Readmission to ICU: 3 (4.6%)/8(6.2%); Transfusion 46 (70.8%)/ 93(71.5%); Cardiac reoperation 7 (10.8%)/10 (7.7%); Renal failure 9 (13.8%)/ 11 (8.5%); Acute kidney injury (delta creatinine >100 mmol/L or>50%) 30 (46.2%)/ 46 (35.4%); Cerebrovascular accident 2 (3.1%)/7(5.4%); Myocardial infarction 0 (0)/ 1 (0.8%); Atrial fibrillation 27 (41.5%)/ 63 (48.5%); PM 10 (15.4%)/ 13 (10.0%); Multiple organ failure 0 (0)/ 2 (1.5%); Any 30-d morbidity 55 (84.6%)/ 99 (76.2%)	Perceval/Trad AVR CCT: min 43 (37-53)/ 64 (51-89); CBP: min 59 (48-79)/85 (64-107)	Perceval/Trad AVR ICU LOS (first stay): d 2.0 (1.0-6)/ 2.0 (1.0-4) Hospital LOS: (d) 10 (6-15)/ 8 (7-13); Prolonged LOS (>14 d) 18 (27.7%)/ 26 (20.0%);	NA	
Gilmanov 2014 (N= 466)	In hospital mortality: Perceval 2/133 (0.8%) versus Traditional AVR 1/133(1.5%); Overall survival rate for matched cohort (K-M curve): 87.2% sutured valves versus 97.0% for Perceval valve (p=0.33). In elderly patients, a sub-group analyses from matched cohort, the survival for patients treated with traditional sutured valves is 50% versus 100% for patients implanted with Perceval valve (p =0.02) although with unequal duration of follow-up. Selecting patients with a follow-up restricted to 40 months or less, the survival for traditional valves is, 78.6% versus 97.0% for Perceval valves.	Haemodynamic measures: Transaortic gradients are 12 ± 8 mm Hg for traditional sutured valves and 11± 7 mm Hg for Perceval, they present similar values (p=0.78).		Perceval / Trad AVR: Re-exploration for bleeding: 9 (6.8%)/5(3.8%); New onset of AF: 29(21.8%)/23(17.3%); Stroke: 2 (1.5%)/0; Transient CVA: 2(1.5%)/1(0.8%); Infective complications: 5 (3.8%)/5(3.8%); Perioperative MI: 2 (1.5%)/0; Third degree AV-block: 6(4.5%)/3 (2.3%); Pulmonary complications: 15 (11.3%)/14 (10.6%); Pleural effusion requested drainage: 6 (4.5%)/3 (2.3%); Hemodialysis: 1 (0.8%)/0; PM: 6/133 (4.5%)/3/133 (2.25%)	Perceval CCT and CBP: 56 (48-72.5) and 90 (78-108.5) minutes, Trad AVR CCT and CBP: 88 (77-110) and 120 (105-155) minutes.	Perceval/ Trad AVR: ICU stay median: 1 (1-2)/1 (1-1) days; In hospital stay median: 6 (6-7.5)/6 (6-7); In hospital stay more than 6 days: 57 (42.9%)/60(45.1%); In hospital stay more than 9 days: 14 (10.5%)/13(9.8%);		

Study ID	Mortality/survival	Morbidity (functionality (NYHA class); Hemodynamic measures; other	Quality of life	Complications (other than death)	CCT and CBP (minutes)	Resource consumption	Costs	Other
Konig 2014	No 30 days hospital mortality in either group	Not reported	Not reported	Perveal/Trad AVR: PM: 4/1 (p=0.326). Stroke 1/0; Paravalvular leakage: 1/0; Re-operations due to structural valve: 0/0	Isolated AVR CCT and CBP time: Perceval/Trad AVR: 37.3 ± 6.8 / 49.1 ±11.2 (p = 0.006) and 58.4±11.0/71.8±11.3 (p = 0.015); Concomitant AVR CCT and CBP: Perceval/Trad AVR: 51.6±5.6/ND and 74.8±7.1/ND	Not reported	Not reported	
Pollari 2014 (N=174)	Hospital mortality: Perceval vs Trad AVR 2/82 (2.4%) vs 3/82 (3.65%)	Not reported	Not reported	Perceval /Trad AVR: Re-exploration due to bleeding: 2 (2.4%)/7 (8.5%); PM: 5 (6.1%)/ 7(8.5%); Paroxymal AF: 3/74 (4.1%)/ 12/76 (15.8%); Stroke or TIA: 3(3.7%)/6(7.3%); Respiratory insufficiency: 2 (2.4%)/10(12.25%)	Perceval/ Trad AVR: CCT: 47±16/59±23; (Isolated AVR: 35±12 (n=57)/49±62(n=62); CBP: 71±11/92±33	Perceval/Trad AVR: Intensive care unit stay: 2.0 ± 1.2/ 2.8 ± 1.3 days, p < 0.001; Hospital stay: 10.9 ±2.7/ 12.4 ± 4.4 days, p =0.001; Blood transfusion: 1.2 ± 1.3/ 2.5 ± 3.7 units, p =0.005	Euro 2,153 vs Euro 1,387), operating room (Euro 5,879 vs Euro 5,527), and hospital stay (Euro 9,873 vs Euro 6,584), with a total cost saving of approximately 25% (Euro 17,905 vs Euro13,498).	
Santapino 2013	Perceval/Trad-AVR:Short term (< 1 year): 30 days mortality: 2/49 (4%)/3/50(6%)	The Perceval valve presents comparable hemodynamic performance to that of non-Perceval valves (mean gradient 8.4 ± 6 mm Hg versus 10 ± 4.9 mm Hg, p=0.24).	Not reported	No significant differences are observed between groups in postoperative arrhythmias and need for pacemaker implantation (p=0.3 and p=0.5, respectively). Despite the higher surgical risk, patients treated with Perceval less frequently require blood transfusion (1.1 ± 1.1 units versus 2.3 ± 2.8 units, p=0.007), and have a shorter intensive care unit stay (1.9 ± 0.7 versus 2.8 ± 1.9 days, p=0.002) and a shorter intubation time (9.2 ± 3.6 hours versus 15 ± 13.8 hours, p=0.01).	Aortic cross-clamp and cardiopulmonary bypass times are 39.4% and 34% shorter among patients treated with Perceval (both p < 0.001).	Not reported	Not reported	
Dalen 2016	Perceval MiS/T-AVR FS (only propensity matched cohort): Short term (< 1 year):30	Not reported	Not reported	Perceval MiS/Trad-AVR FS: Reoperation for bleeding: 7 (41.%)/11(6.4%); PM 17 (9.9%)/5 (2.9%);	Perceval MiS vs Trad-AVR FS:	Perceval MiS/Trad-AVR FS: ICU stay: 2.5±2.3/1.9±2.9 days;		

Study ID	Mortality/survival	Morbidity (functionality (NYHA class); Hemodynamic measures; other	Quality of life	Complications (other than death)	CCT and CBP (minutes)	Resource consumption	Costs	Other
	days mortality: 3 (1.8%)/4(2.3%) Long term (>1 year): Kaplan-Meier: 2 years cumulative survival: no significant difference at 2 years			De novo dialysis: 2 (1.2%)/3(1.8%9; Stroke 4(2.3%)/2(1.2%); No paravalvular regurgiation: 167 (98%)/165 (95%)	CCT (40 vs. 65 min, P < 0.001) and CBP(69 vs. 87 min, P < 0.001)			
Shresta 2013	Perceval/T-AVR:Short term (< 1 year): 30 day mortality: 0/50(0)/3/70 (4.3%) Long term (>1 year): 1 year mortality*: 5 (13.2%)/10(16.4%) Long term (>2 year): 3 years mortality* 9(39.1%)/12 (34.3%)/ Long term (>5 year): 5 Years mortality: 7(14%)/12(17.4%) *based on eligible patients at time of measurement (not all are follwed for the same length of time)	Difference in mean gradient (Perceval 1.5±0.25/Trad AVR 1.3±02)	Not reported	Perceval/Trad-AVR: Re-operation: 2(4%)/1(1.4%); Endocarditis: 3 (6%)/1(1.4%)	Perceval/Trad AVR CCT: 30.1 ± 9/50.3±14.2; CBP: 58.7±20.9/75.3±23	Not reported		
Concistre 2015	Short term (< 1 year): No in hospital deaths At 6-month follow-up, survival is 96.9%. Two deaths in P group versus 0 in the 3f Enable (P = 0.49).	Functional score (NYHA): 6 months: All patients are in good functional status [mean (SD) New York Heart Association (NYHA) class, 1.1 (0.5) in the Perceval group vs 1.7 (0.9) in the 3f Enable group] (P = 0.68). Hemodynamic measures: Mean pressure gradient is 10.4 (4.3) mm Hg in the Perceval group and 12.2 (5.3) mm Hg in the 3f Enable group (P = 0.184) without significant differences between the two groups (P = 0.184).						
Concistre 2013	Short term (< 1 year): 30 day mortality Perceval/Enable: 2(2%)/1(3%)	Functional score (NYHA): 30 day: Perceval/Enable: 1.1±0.54/1.24±0.43; Hemodynamic measures: Mean transvalvular gradient: 9.1±3.3/11.2±5.2;		Perceval/Enable: Lung insufficiency: 3(3%)/2(6%9; Stroke 2(2%)/1(3%); Renal insufficiency: 3(3%)/1(3%); Permanent PM: 6(6%)/2(6%); Moderate paravalvular leakage: 1(1%)/4(12%)	CCT and CBP Perceval/3f Enable: Isolated AVR 36±12.7 and 66±21/66±18 and 103±32; Concomitant 55±29 and 82.7±34/86.8±38 and 123.7±44			

Study ID	Mortality/survival	Morbidity (functionality (NYHA class); Hemodynamic measures; other	Quality of life	Complications (other than death)	CCT and CBP (minutes)	Resource consumption	Costs	Other
Muneretto 2015b	Hospital mortality: Perceval = 0% / traditional AVR = 0% / TAVI = 1.8%, P = NS). Survival at 24-month follow-up, overall survival free from major adverse cardiac and cerebrovascular events and prosthetic regurgitation: Perceval = 91.6 ± 3.8%/ traditional AVR = 95.2 ± 3.3% /TAVI = 70.5 ± 7.6%; P = 0.015).			Post-procedural pacemaker implantation (Perceval= 2% vs traditional AVR = 1.8% vs TAVI = 25.5%, P <0.001); Peripheral vascular complications (Perceval = 0% vs traditional AVR = 0% vs TAVI = 14.5%, P <0.001)				

A) Results of meta-analysis presented in appendix to submission file based on the six comparative studies (unpublished data)

Table 20 – Effect estimate for each analyzed outcome (Perceval vs Traditional).

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Mortality	6	1019	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.25, 1.33]
1.2 ICU LOS	6	1019	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.75, 0.43]
1.3 Hospital LOS	4	649	Mean Difference (IV, Random, 95% CI)	-0.51 [-1.34, 0.32]
1.4 Pacemaker implantation	5	899	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [1.03, 2.99]
1.5 Stroke	3	772	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.45, 2.78]

Table 21 – Forest plot for hospital mortality.

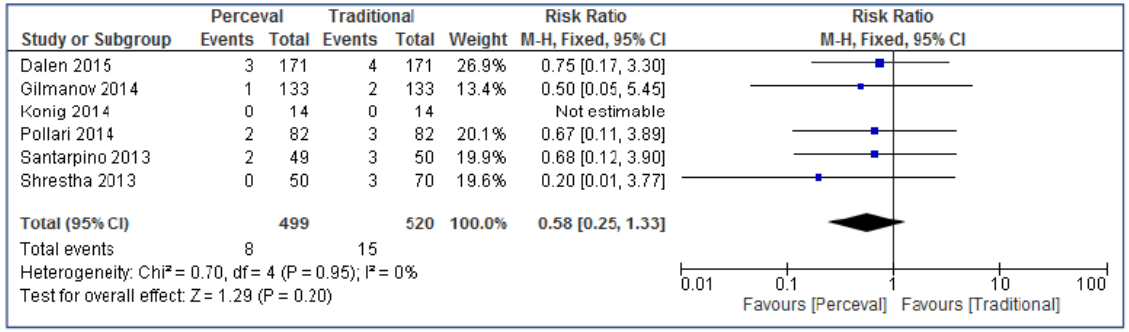


Table 22 – Forest plot for ICU LOS.

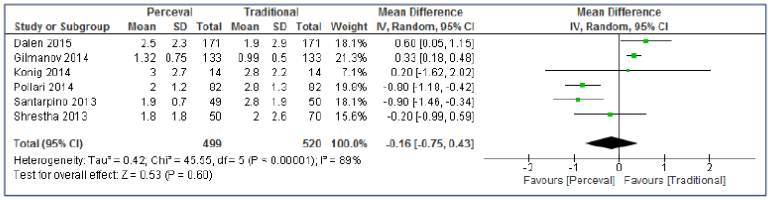


Table 23 – Forest plot for hospital LOS.

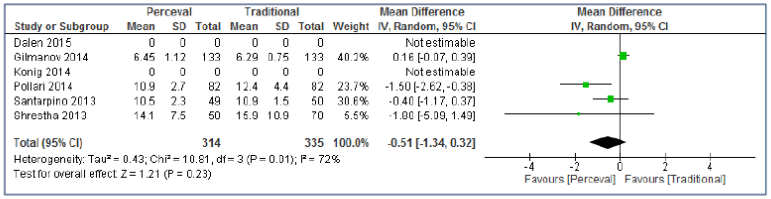


Table 24 – Forest plot for pacemaker implantation.

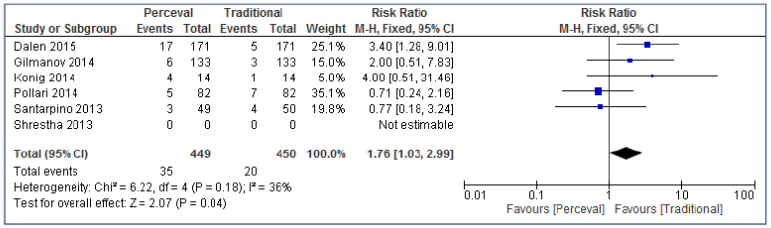
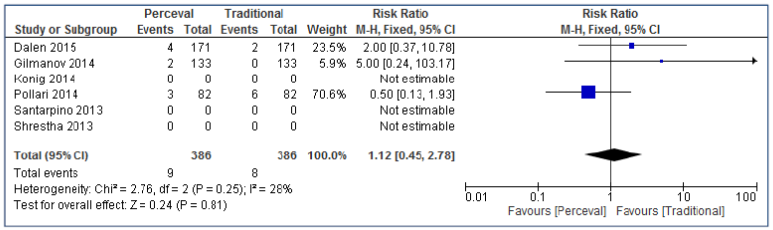


Table 25 – Forest plot for stroke rate.



Studies with no comparator

Study ID	Outcomes Results: Mortality/survival	Morbidity (functionality (NYHA class); Hemodynamic measures; other	Quality of life	Complications (other than death)	CCT and CBP (minutes)	Resource consumption	Costs	Other
Folliguet 2012	Short term (< 1 year): In hospital mortality: 2.4%; 20 patients died during folow up; Cumulative survival (freedom from valve related mortality) Long term (>1 year): 12 months 87.1 %; Long term (>2 year): 2 years 82.4%; 4years 69.7% Cumulative freedom from valve-related mortality: 87.1% at 1 year; 82.4% at 2 years, 82% at 3 years; 69.7% at 4 years	Functional score (NYHA): NYHA class I and II at 12 months: 82%; Hemodynamic effectiveness: Mean gradient (mm Hg): 10.4 ±4.3 (discharge) 8.9 ±3.2 (post-implantation 3-6 months) 8.7 ±3.7 (Post Implantation 1-4 years); Peak gradient (mm Hg): 21.3 ± 8.6 (at discharge) 19.6 ±6.7 (post implantation 3 to 6 months) 18.8 ± 7.6 (Post Implantation 1-4 years); Effective orifice area (cm2): 1.4 ±0.4 (discharge) 1.5 ±0.4 (post implantation 3-6 months) 1.5 ±0.3 (post implantation 1-4 years); Indexed effective orifice area (cm2/m2): 0.85 ± 0.23 (discharge) 0.89 ± 0.24 (post implantation 3-6 months) 0.91 ±0.22		Bleeding requiring transfusion:13 (9 early and 4 late); Thromboembolism: 10; (Stroke:2, TIA:1); Sepsis: 18; Heart failure requiring inotropic drugs: 5; Hemolysis due to PVL: 1; Endocarditis: 3; PVL leading to surgical reoperation: 9 (4%) ; PM for AV block: 16 (7%); Pericardial effusion requiring drainage: 4;	CCT time (minutes) Full cohort n=208 33.5 ± 13.8; Median Sternotomy n=163 33.5± 14.9; Mini Sternotomy n=45 33.6 ± 9.5; With Concomitant n=48 44.2 ± 13.4; Isolated AVR Patients n=163 30.1±12.2; CPB time (Minutes): Full cohort 208: 54.5 ± 24.2 Median Sternotomy n=163 51.1 ± 24; Mini Sternotomy n=45 65.7 ± 21.4; With Concomitant n=48 67.6 ± 23.9 Isolated AVR; Patients n=163 50.3 ± 22.8			Success of implantation: 95%

Study ID	Outcomes Results: Mortality/survival	Morbidity (functionality (NYHA class); Hemodynamic measures; other	Quality of life	Complications (other than death)	CCT and CBP (minutes)	Resource consumption	Costs	Other
Gilmanov 2013	No operative death reported Non cardiac death 1. S	Functional score (NYHA): NYHA I four weeks after discharge: 92 %; Hemodynamic measures:Mean pressure gradient/Mean peak pressure in mm Hg: Discharge (n=137): 11/20, 3 months (n=109): 12/21, 6 months (n=54): 11/21, 12 months (n=34): 10/19; Additional data reported: Paravalvular and intervalvular regurgitation		Bleeding: ND; Thromboembolism: ND; Perioperative stroke: 3 (2.2%); Perioperative TIA: 2 (1.5%); Perioperative myocardial infarction: 1 (0.7%) PM for AV block: 5 (3.6%); New onset atrial fibrillation or flutter: 37 (27.0%);	Sub-group analysis CPB/CTT min: High risk group (n=33): 94± 23/60 ± 18; Low risk group (n= 101) 92±29/59±20	Assisted ventilation time 10.10±26.7 h; ICU length of stay: 1.55 ± 1.8 days; Postoperative length of stay: 7.1		
Miceli 2014	Mortality short term (1 year): 2 (0.7%); At a median follow-up of 8 months (interquartile range, 4-14), the overall survival was 90.	Functional score (NYHA): Hemodynamic measures: Overall the 281 patients, no migration occurred, and the mean postoperative gradient was 13 ± 4 mm Hg		Stroke: 5 (1.8%); Re-exploration for bleeding: 8 (2.8%); Conversion to sternotomy: 4 (1.4%); AV block requiring PM 12 (4.2%); PVL 5 (1.8%);	CBP and CCT: MIAVR (n=281): 81 (68-98) and 48 (37-60); RT (n=117): 74 (87-107) and 55 (47-65); MS (n=117): 72 (58-89) and 37 (30-46)	ICU stay 1 day (1-2); Ward stay 8 (6-10)		
Shresta 2014	30 day mortality is 5 (2.1%); Overall patients survival at 2 years is 86%	Functional score (NYHA): 1 year after surgery (n=161): NYHA I: 80 (49.7%); NYHAII: 68 (42.2%); 2 years after surgery (n=61): approximately the same percentage. Hemodynamic measures: Mean gradient is equal to 40 mmHg before the intervention, while at discharge, decreases to 10 mmHg and this level is maintained up to 2 years after the intervention		Re-exploration for bleeding 9 (3.8%); Stroke 3 (1.3%); PM implantation: affects 14 (5.9%); Third-degree AV-block 8 (3.4%); Myocardial infarction: 2 (0.8%); Heart failure: 3 (1.3%); Explantation: 5 (2.1%); Endocarditis: 1(0.4%)				Freedom from re-operation 136 (99.3%)
Rubino 2014	Short term (< 1 year): In-hospital mortality/30 days mortality: 10 (3.2%), (1.4% isolated procedure and 7.4% concomitant coronary surgery); Prosthesis related mortality: 0; Survival (Kaplan Meyer) 1 year: 90.5% 2 year: 87%			Intraoperative PVL Mild: 38 (12.1%), Severe 2 (0.6%); Conversion to conventional AVR: 2 (0.6%); Prosthesis dislodgement 1 (0.3%); Stroke 6 (1.9%); De Novo dialysis 5 (1.6%); PM: 25 (8.0%); Reoperation for bleeding 8 (2.5%); Peripheral thromboembolism: 0	Mean aortic CCT 43± 20 minutes (isolated procedure, 39± 15 minutes; concomitant coronary surgery, 52± 26 minutes)	ICU stay: 3.2±3.4 days; In-hospital stay: 13.4±6.5 days;		At 1 and 2 years: freedom from valve-related mortality: was 99.0% and 98.0%; freedom from stroke was 98.1% and 98.1%; Freedom from endocarditis 99.2% and 99.2%;

Study ID	Outcomes Results: Mortality/survival	Morbidity (functionality (NYHA class); Hemodynamic measures; other	Quality of life	Complications (other than death)	CCT and CBP (minutes)	Resource consumption	Costs	Other
								Freedom from reoperation: 98.3% and 98.3% respectively.
Mazine 2015	Operative mortality: 9 (4%)	Functional score (NYHA): Not reported; Hemodynamic measures: Peak and mean transaortic gradients are significantly improved at discharge compared with baseline values, and the aortic effective orifice area is significantly increased.		Stroke: 7 (3%); Delirium: 46 (21%); Bleeding requiring re-operation: 10 (5%); MI: 1 (0%); Acute kidney injury: 42 (20%); Renal replacement therapy: 5 (2%); Atrial fibrillation 88 (41%); AV-block: 35 (16%); PM: 37 (17%) (variability between participating institutions, with one center (Montreal Heart Institute; n= 121) showing rates of 21%, compared with 12% for the rest (n = 94) of the cohort (P= 0.06));	Mean CCT and and CPB: isolated AVR were 40.5 ± 11.6 minutes and 56.6 ±16.6 minutes, respectively;	ICU length of stay: 3.7±3.9 days; Hospital stay: 11.4±7.6 days		
Shresta 2016	30 days moratlity: 25 (3.4%); Deaths total: 76 (10.4%); Overall survival (Kaplan Meier): 1 year: 92.1%, 5 years 74.7% (Causes of eaely and late death are reported)	Functional score (NYHA): Improvements are observed in clinical status (NYHA class) (details not revealed in submission file); Hemodynamic measures: Mean and peak gradients decrease from 42.9 and 74.0 mmHg preoperatively, to 7.8 and 16 mmHg at the 3-year follow-up; LV mass decreased from 254.5 to 177.4 g at 3 year Hemodynamic measures:		All patients,cumulative follow up 729 patient years: Explants 21 (2.9%); Thromboembolism 46 (6.3%); Stroke: 18 (2.5%); Non-structural valve dysfunction: 26 (3.6%); Endocarditis: 14 (1.9%); Hemolysis: 8 (1.1%); AV-block in patients without preoperative cardiac rhythm abnormalities: 54 (7.4%)	Mean CCT and CBP: 30.8 and 50.8 min			Conversion to other AVR 34 cases (4.4%)
Zannis 2014	In hospital mortality: 7 (4.9%); Survival (Kaplan Meier): 5 year 85.5%; Short term (< 1 year):	Functional score (NYHA): One year NYHA I: 37 (51.4), One year NYHAII: 31 (43.1%); Hemodynamic measures: mean pressure gradient and EOA are 9.0 ± 3.4	Not reported	PM 7 (4.9%); Early reoperations are due to paravalvular leak 3(2.0%) and intra-prosthetic regurgitation 3 (2.0%).; One late reoperation (at 29 months) due to fibrous pannus overgrowth.	mean CCT and CBP: 32.0 ± 14.9 and 44.7 ± 18.6 min, respectively			

Study ID	Outcomes Results: Mortality/survival	Morbidity (functionality (NYHA class); Hemodynamic measures; other	Quality of life	Complications (other than death)	CCT and CBP (minutes)	Resource consumption	Costs	Other
		mmHg and 1.60 ± 0.3 cm2, respectively.:		One late endocarditis (0.7%) at 26 months; No structural valve deterioration are reported during the follow up.				
Fischlein 2015	30-day mortality: 2.1% (all non-cardiac deaths). At follow-up (23.5 ±14.4 months), five patients were dead (three non-cardiac and two cardiac deaths).	Functional score (NYHA): Not reported; Hemodynamic measures: Mean transprosthetic gradients are as follows: 12.8 ±4.9, 12.5± 4.5, 11.8± 4.7 mm Hg, postoperatively at 6 months, 1 year, and 2 years, respectively		PM 11 (7.6%); No paravalvular leaks are reported, nor endocarditis. Five patients are re-hospitalized for heart failure.	CCT: concomitant procedures (38 ± 12 minutes) isolated surgery (35 ±11 minutes)	Mean hospital stay is 11.6± 4.9 days.		
Laborde 2016	30-day mortality rate: 23 (3.7%);	Functional score (NYHA): Hemodynamic measures: Preoperative mean and peak pressure gradients decreased from 44.8 and 73.24 mmHg to 10.24 and 19.27 mmHg at discharge, respectively. The mean effective orifice area improved from 0.72 to 1.46 cm2	Not reported	Perioperative explants: 1 (0.2%); 30 days explants (mean of 13.8 days post implant) 5 (0.8%); Reoperation for bleeding: 23 (3.7%); MI: 2 (0.3%); Stroke: 13 (2.1%); Endocarditis: 1 (0.2%); AV block without preoperative cardiac abnormalities: 42 (6.7%); Tamponade 3 (0.5%)	Isolated AVR CCT (n=424) and CBP (n=423) overall: 35.3 (12.1) and 58.4 (20.2) min, respectively; Combined AVR CCT (n=204) and CBP (n=203): 51.9 (22.8) and 78.2 (29.2); Overall CCT (n=627) and CBP (627): 40.7 (18.1) and 64.8 (25.2)	Not reported	Not reported	

Appendix 5. Check list for quality of systematic reviews

Check list for systematic reviews*

	Yes	Unclear	No
1. Is the specific purpose (question to be answered) stated?			
Comment:			
2. Are the sources and search methods used to find evidence (primary studies) on the questions to be answered stated?			
Comment:			
3. Is the search strategy for evidence reasonably comprehensive?			
Comment:			
4. Are explicit criteria used for deciding which studies to include in the review?			
Comment:			
5. Is bias in the selection of articles likely to be avoided?			
Comment:			
6. Are the criteria used for assessing the internal validity of the studies reported?			
Comment:			
7. Is the validity of all the studies to be reviewed assessed using appropriate criteria?			
Comment:			
8. Are the methods used to combine the findings of the relevant studies reported?			
Comment:			
9. Are the methods used to combine the findings of the relevant studies appropriate to the questions to be answered by the review?			
Comment:			
10. Were the conclusions made by the author(s) supported by the data and/or the analysis reported in the review?			
Comment:			
Overall quality:			
Assessed by/date:			

*Adapted from the Cochrane EPOC group appraisal list for systematic reviews. Grimshaw et.al 2003. (copied from: http://www.uio.no/studier/emner/medisin/med/MF9000E/h09/lectures/kornoer-metaanalysis/EPOC%20checklist.pdf)

High Quality: All or most criteria from the checklist are met. It is very unlikely that the study conclusions are affected.

Medium Quality: Some criteria from the checklist are not met. It is unlikely that the study conclusions are affected.

Inadequate Quality: Few or no criteria in the checklist are met. It is likely that the study conclusions may be affected.

Appendix 6. Systematic reviews published in 2015 and later

An independent systematic search was performed, details and a sorted list of results are available in a separate publication. Based on the sorted list the following systematic reviews published in 2015 and later were included and inspected in fulltext. Quality of the reviews was evaluated using the NIPH check list for systematic reviews (see appendix 6) details are revealed in a separate report on the systematic search

Included systematic reviews published in 2015 or later	Population	Intervention	Comparator	Outcome	Quality*
Cadth. (2015). Perceval S sutureless valve for aortic valve replacement: a review of the clinical effectiveness, safety, and cost-effectiveness. *Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH), Summary with critical appraisal*.	Patients currently receiving TAVI/ Patients at high risk for AVR	Perceval SU-AVR	Any comparator or none	Clinical benefit (reduced risk of stroke, ease of implantation, reduced pump time and cross-clamp time, reduced number of patients waiting for TAVI, improved hemodynamic performance) Clinical harm (complication rates, post-operative migration) Cost effectiveness	High
Davies, R. A., Bandara, T. D., Perera, N. K., & Orr, Y. (2016). Do rapid deployment aortic valves improve outcomes compared with surgical aortic valve replacement? *Interactive Cardiovascular & Thoracic Surgery, 1*, 1.	Patients requiring AVR	Rapid deployment valves (suture less valves any kind)	Conventional - AVR	Mortality; Morbidity; valve function	Inadequate quality
Hurley, E. T., O'Sullivan, K. E., Segurado, R., & Hurley, J. P. (2015). A meta-analysis examining differences in short-term outcomes between sutureless and conventional aortic valve prostheses. *Innovations: Technology and Techniques in Cardiothoracic and Vascular Surgery, 10*(6), 375-382.	Patients requiring AVR	Suture less valves any kind	Conventional-AVR	Short term outcomes: 30 day mortality; CCT; CBP; PVR; ICU stay; mean discharge Gradient; Permanent Pacemaker requirement (PPM)	Inadequate quality
Phan, K., Tsai, Y. C., Niranjan, N., Bouchard, D., Carrel, T. P., Dapunt, O. E., . . . Di Eusanio, M. (2015). Sutureless aortic	Patients undergoing sutureless AVR	Sutureless valves	No-limitation	Safety; Haemodynamic outcomes	Medium

Included systematic reviews published in 2015 or later	Population	Intervention	Comparator	Outcome	Quality*
valve replacement: a systematic review and meta-analysis. *Annals of Cardiothoracic Surgery, 4*(2), 100-111.					
Takagi, H., Ando, T., & Umemoto, T. (2017). Direct and adjusted indirect comparisons of perioperative mortality after sutureless or rapid-deployment aortic valve replacement versus transcatheter aortic valve implantation. *International Journal of Cardiology, 228*, 327-334. SR.	Patients with need for AVR due to aortic stenosis	Sutureless valves	TAVI or traditional AVR (Comments: Only propensity matched studies or RCTs claimed to be included, but the several included studies relevant for this STA where not PSM studies according to the submission file (not checked)). One additional study included based on this SR	Perioperative mortality	Inadequate

*Quality determined by the NIPH check-list for systematic reviews

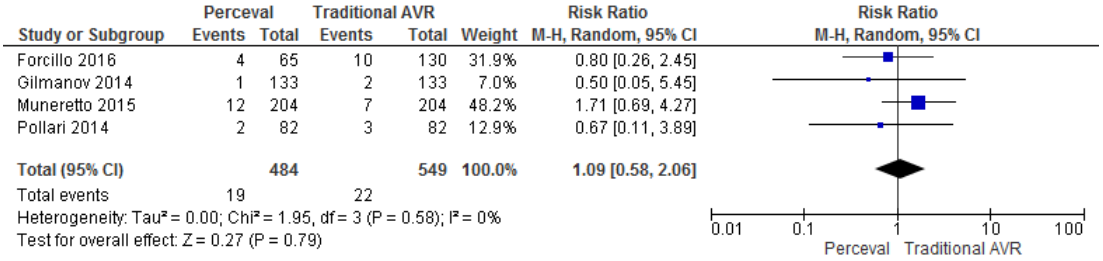
Excluded potential systematic reviews	**Reason for exclusion**
Chandola, R., Teoh, K., Elhenawy, A., & Christakis, G. (2015). Perceval Sutureless Valve - are Sutureless Valves Here? *Current cardiology reviews, 11*(3), 220-228.	Not an SR
Chung, J., Filatov, A., Ladoris, L., Farinas, A., Cruz Pico, C. X., Postoev, A., . . . Sanni, A. (2015). Postoperative outcomes of surgical sutureless aortic valve replacement vs transcatheter aortic valve implantation for severe symptomatic aortic stenosis. *Journal of the American College of Surgeons, 1)*, S26.	Only abstract
Gersak, B., Fischlein, T., Folliguet, T. A., Meuris, B., Teoh, K. H. T., Moten, S. C., . . . Glauber, M. (2016). Sutureless, rapid deployment valves and stented bioprosthesis in aortic valve replacement: Recommendations of an international expert consensus panel. *European Journal of Cardio-thoracic Surgery, 49*(3), 709-718.	A systematic search is performed, but no presentation or synthesis of data
O'Sullivan, K., Hurley, E. T., Segurado, R., & Hurley, J. P. (2015). A meta analysis examining the incidence of permanent pacemaker implantation following sutureless aortic valve implantation. *Heart, 101*, A33-A34.	Abstract
O'Sullivan, K. E., Hurley, E. T., Segurado, R., & Hurley, J. P. (2015). Sutureless aortic prostheses are associated with a higher incidence of permanent pacemaker insertion than conventional: A meta-analysis. *EuroIntervention. Conference: PCR London Valves,* (pagination).	Abstract
Santarpino, G., Kalisnik, J. M., Fischlein, T., & Pfeiffer, S. (2016). What's up on sutureless valves. *Minerva Cardioangiologica, 64*(5), 552-559.	Not an SR
Takagi, H., & Umemoto, T. (2015). A Meta-Analysis of Sutureless or Rapid-Deployment Aortic Valve Replacement. *The Thoracic and cardiovascular surgeon, 64*(5), 400-409.	Updated by Takagai 2017
Takagi, H., & Umemoto, T. (2016). Sutureless aortic valve replacement may improve early mortality compared with transcatheter aortic valve implantation: A meta-analysis of comparative studies. *Journal of Cardiology, 67*(6), 504-512.	Updated by Takagai 2017

Appendix 7. Meta-analysis and GRADE evaluations of best available evidence

Meta-analysis

1. **Mortality Perceval sutureless AVR compared to traditional AVR for treatment of operable patients with severe aortic stenosis**

a) In hospital (30-day) mortality



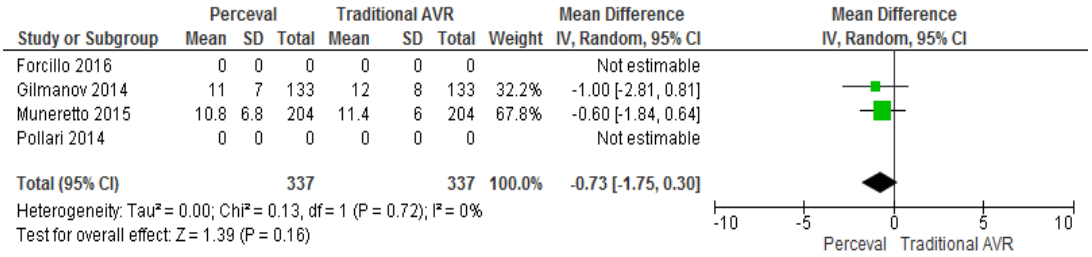
b) Long term mortality

Two studies reported Kaplan-Meier survival analysis of data up to 54 months. No risk ratios could be calculated

2. **Morbidity Perceval sutureless AVR compared to traditional AVR for treatment of operable patients with severe aortic stenosis**

a) NYHA class: No PSM study reported functionality

b) Hemodynamic parameters at discharge: Mean gradient (mm Hg)

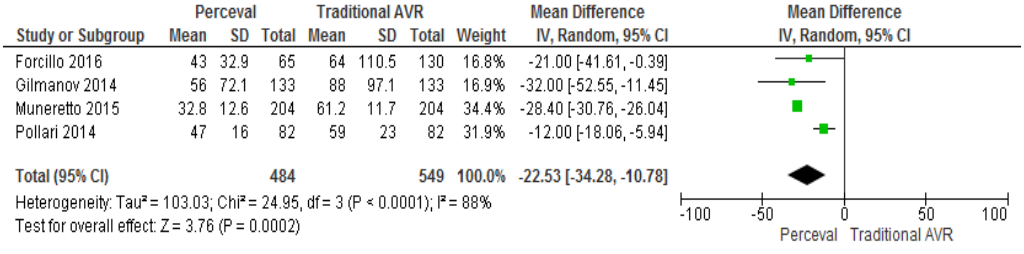


3. **Quality of life Perceval sutureless AVR compared to traditional AVR for treatment of operable patients with severe aortic stenosis**

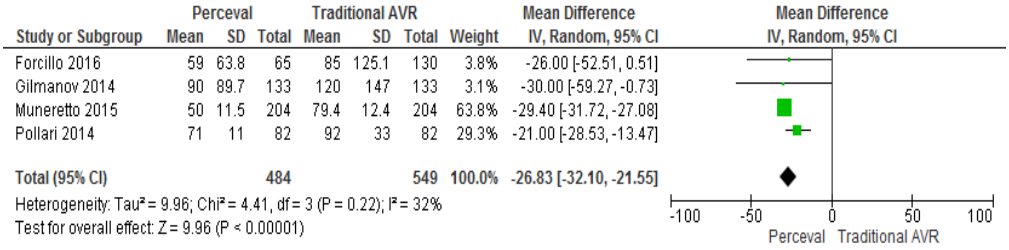
No study reported quality of life data

4. **Resource use Perceval sutureless AVR compared to traditional AVR for treatment of operable patients with severe aortic stenosis**

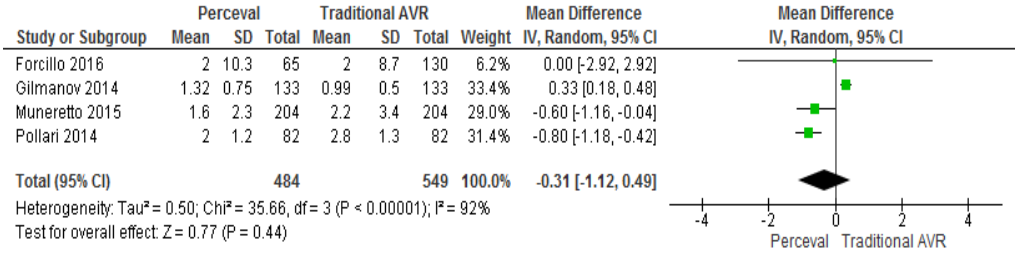
a) Cross-clamp time (CCT) during surgery



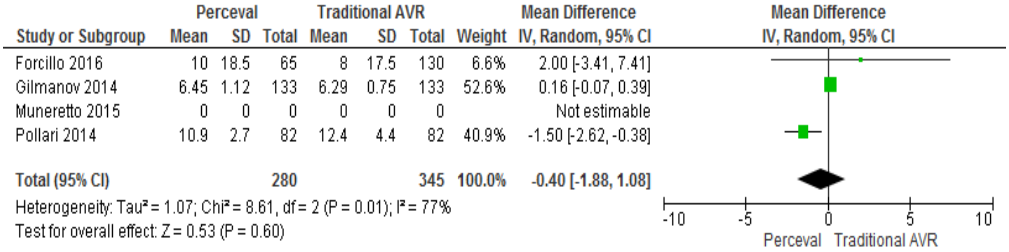
b) Cardiopulmonary bypass time



c) **Intensive care unit length of stay**



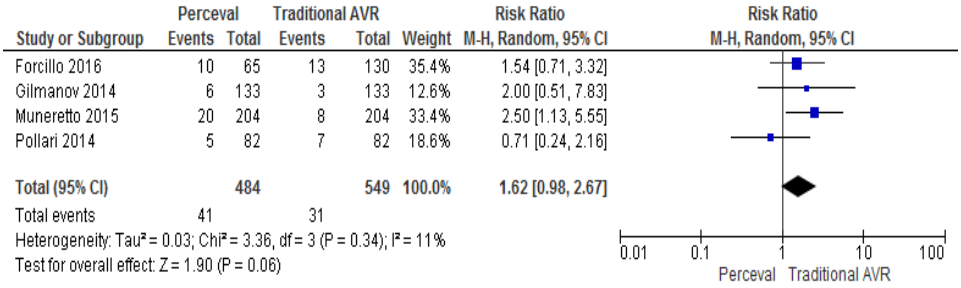
d) **Hospital length of stay**



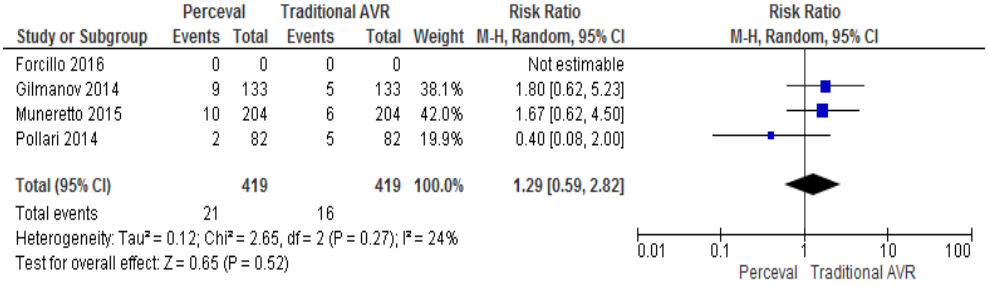
5. Adverse effects Perceval sutureless AVR compared to traditional AVR for treatment of operable patients with severe aortic stenosis

a) Mortality (see above)

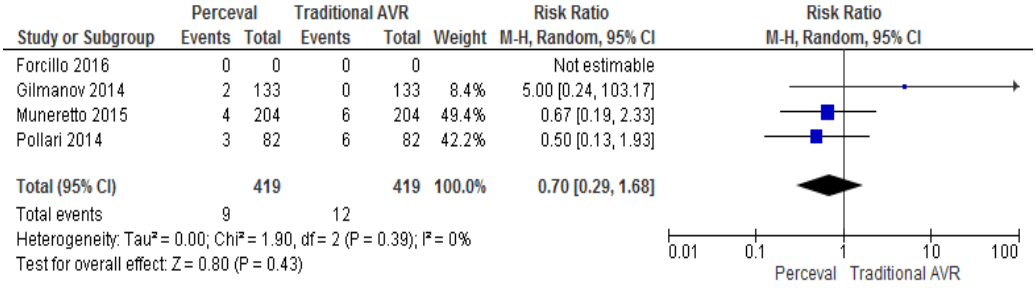
b) Need for Pacemaker implantation



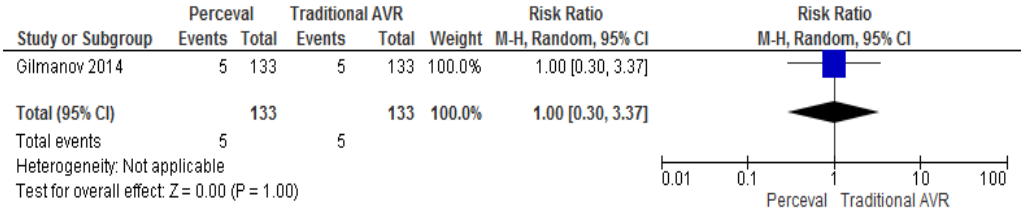
c) Re-exploration for bleeding



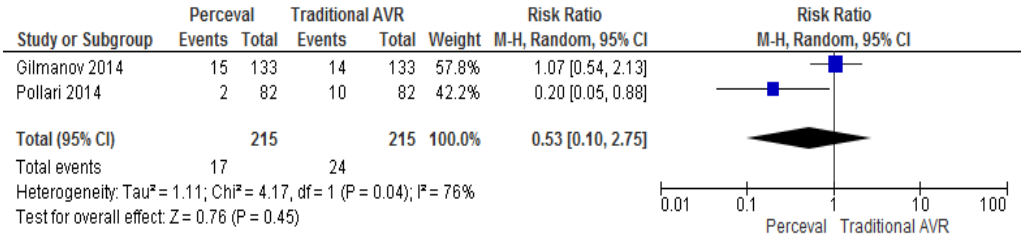
d) Stroke



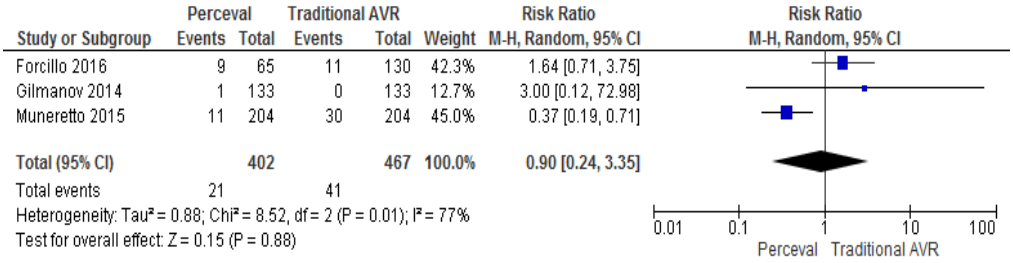
e) Infective complications



f) Pulmonary and respiratory complications



g) Nephrotic complications



GRADE evidence profile
Author(s): Vigdis Lauvrak and helene Arentz-Hansen
Date: 16.05.2017
Question: Perceval compared to Tradtional AVR for aortic stenosis[

Quality assessment							№ of patients		Effect		Quality	Importance
№ of stu-dies	Study design	Risk of bias	Inconsis-tency	In-directness	Impreci-sion	Other considera-tions	Perceval	Tradtional AVR	Relative (95% CI)	Absolute (95% CI)		
In hospital mortality												
4	observa-tional studies	not serious [a]	not serious	not serious	not serious [b]	none	19/484 (3.9%)	22/549 (4.0%)	RR 1.09 (0.58 to 2.06)	4 more per 1 000 (from 17 fewer to 42 more)	⊕⊕◯◯ LOW	High
Transaortic gradient (mean mmHG at discharge)												
2	observa-tional studies	not serious [a]	not serious	not serious	not serious	none	337	337	-	MD 0.73 lower (1.75 lower to 0.3 higher)	⊕⊕◯◯ LOW	Low
Cross Clamp Time minutes												
4	observa-tional studies	not serious [a]	not serious [c]	not serious	not serious	none	484	549	-	MD 22.53 lower (34.28 lower to 10.78 lower)	⊕⊕◯◯ LOW	Low
Cardiopulmonary bypass time (minutes)												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of stu-dies	Study design	Risk of bias	Inconsis-tency	In-directness	Impreci-sion	Other considera-tions	Perceval	Tradtional AVR	Relative (95% CI)	Absolute (95% CI)		
4	observa-tional studies	not serious [a]	not serious	not serious	not serious	none	484	549	-	MD 26.83 **lower** (32.1 lower to 21.55 lower)	⊕⊕◯◯ LOW	Low
ICU-LOS												
4	observa-tional studies	not serious [a]	serious [d]	not serious	not serious	none	484	549	-	MD 0.31 **lower** (1.12 lower to 0.49 higher)	⊕◯◯◯ VERY LOW	Low
Hospital LOS												
3	observa-tional studies	not serious [a]	serious [d]	not serious	not serious	none	280	345	-	MD 0.4 **lower** (1.88 lower to 1.08 higher)	⊕◯◯◯ VERY LOW	Low
Need for pacemaker implantation												
4	observa-tional studies	not serious [a]	not serious	not serious	not serious [e]	none	41/484 (8.5%)	31/549 (5.6%)	RR 1.62 (0.98 to 2.67)	**35 more per 1 000** (from 1 fewer to 94 more)	⊕⊕◯◯ LOW	High
Reexploration for bleeding												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of stu-dies	Study design	Risk of bias	Inconsis-tency	In-directness	Impreci-sion	Other considera-tions	Perceval	Tradtional AVR	Relative (95% CI)	Absolute (95% CI)		
3	observa-tional studies	not serious [a]	not serious	not serious	not serious [b]	none	21/419 (5.0%)	16/419 (3.8%)	RR 1.29 (0.59 to 2.82)	11 more per 1 000 (from 16 fewer to 69 more)	⊕⊕◯◯ LOW	High
Stroke												
3	observa-tional studies	not serious [a]	not serious	not serious	not serious [b]	none	9/419 (2.1%)	12/419 (2.9%)	RR 0.70 (0.29 to 1.68)	9 fewer per 1 000 (from 19 more to 20 fewer)	⊕⊕◯◯ LOW	High
Infective complications												
1	observa-tional studies	not serious [a]	not serious	not serious	serious	none	5/133 (3.8%)	5/133 (3.8%)	RR 1.00 (0.30 to 3.37)	0 fewer per 1 000 (from 26 fewer to 89 more)	⊕◯◯◯ VERY LOW	High
Pulmonary or respiratory complications												
2	observa-tional studies	not serious [a]	serious [d]	not serious	serious	none	17/215 (7.9%)	24/215 (11.2%)	RR 0.53 (0.10 to 2.75)	52 fewer per 1 000 (from 100 fewer to 195 more)	⊕◯◯◯ VERY LOW	High
Nephrotic complications												

Quality assessment							№ of patients		Effect		Quality	Importance
№ of stu-dies	Study design	Risk of bias	Inconsis-tency	In-directness	Impreci-sion	Other considera-tions	Perceval	Tradtional AVR	Relative (95% CI)	Absolute (95% CI)		
3	observa-tional studies	not serious [a]	not serious	not serious	not serious [b]	none	21/402 (5.2%)	41/467 (8.8%)	RR 0.90 (0.24 to 3.35)	9 fewer per 1 000 (from 67 fewer to 206 more)	⊕⊕◯◯ LOW	High

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations

a. Risk of bias is already accounted for under "study design" with observational studies starting at low quality
b. Imprecision, not further downgraded
c. CCT is expected to vary due to variations in procedures; Not further downgraded due to heterogeneity (I2=88%) as all studies reveal the same tendency towards lower CCT
d. Heterogeneity: I2>50%.
e. Adverse event with a tendency in favor of traditional AVR, not further downgraded
f. Adverse event, downgraded as only one study and large confidence interval
g. Only one study

Appendix 8. Clinical inputs to the cost-effectiveness analysis model.

Variable	Mean	SD	Distribution	Par 1	Par 2
Cross Clamp Circulation Time- CCTs (min)					
Full sternotomy with Perceval (FS P)	30.10	12.20	gamma	6.087	0.202
Concomitant with Perceval (CONC P)	44.19	13.40	gamma	10.88	0.246
Valve (RRV)	2.182	1.699			
Techniques (RRT)	1.038	0.09134			
Survival function					
Baseline survival time (years)	8.30	6.59	Weibull	0.062	1.267
Mortality					
Baseline mortality in FS	0.0259	0.0043	beta	35.59	1341
Baseline mortality in MiS	0.0204	0.0038	beta	28.09	1351
Beta Ranucci	0.0108	0.0038			
Renal failure					
Baseline renal failure rates (CCT≤60)					
FS	0.0307	0.0092			
MiS	0.0270	0.0091			
Relative risks for CCT>60					
CCT≤90 (rr2)	1.54	0.31			
CCT>90 (rr3)	2.05	0.50			
Re-operation for bleeding					
Baseline re-operation for bleeding risk (CCT≤60)					
FS	0.0660	0.0105			
MiS	0.0551	0.0097			
Relative risks for CCT>60					
CCT≤90 (rr2)	1.05	0.06			
CCT>90 (rr3)	1.60	0.13			
Hospital stay (days)					
Ward stay					
Baseline ward stay *(CCT≤60) in FS*	9.53	8.03	gamma	1.409	0.148
Baseline ward stay *(CCT≤60) in MiS*	8.29	6.62	gamma	1.568	0.189
Relative risks for CCT>60					
CCT≤90 (rr2)	2.03	1.70			
CCT>90 (rr3)	3.23	2.26			
ICU stay					
Baseline ICU stay *(CCT≤60) in FS*	2.12	3.11	gamma	0.463	0.219
Baseline ICU stay *(CCT≤60) in MiS*	1.83	2.33	gamma	0.613	0.336
Relative risks for CCT>60					
CCT≤90 (rr2)	1.30	0.16			
CCT>90 (rr3)	3.01	0.82			
Ventilation time (days)					
Baseline ventilation time *(CCT≤60) in FS*	3.13	2.64	gamma	1.411	0.45
Baseline ventilation time *(CCT≤60) in MiS*	2.57	0.99	gamma	6.698	2.602
Relative risks for CCT>60					

CCT≤90 (rr2)	1.47	0.39			
CCT>90 (rr3)	3.41	0.87			
Variable	Mean	SD	Distribution	Par 1	Par 2
Blood loss (ml)					
During operation					
Baseline blood loss *(CCT≤60) in FS*	248.01	146.60	gamma	2.862	0.012
Baseline blood loss *(CCT≤60) in MiS*	248.28	292.50	gamma	0.721	0.003
Relative risks for CCT>60					
CCT≤90 (rr2)	1.05	0.06			
CCT>90 (rr3)	1.60	0.13			
During ICU					
Baseline blood loss *(CCT≤60) in FS*	692.59	605.35	gamma	1.309	0.002
Baseline blood loss *(CCT≤60) in MiS*	580.97	542.23	gamma	1.148	0.002
Relative risks for CCT>60					
CCT≤90 (rr2)	1.05	0.06			
CCT>90 (rr3)	1.60	0.13			
Sepsis rate					
FS	0.0322	0.0123			
MiS	0.0164	0.0092			
Rehabilitation rate					
FS	0.75	0.03			
MiS	0.44	0.04			
Discount rate	0.04				
Utility post-AVR					
With renal failure	0.46				
Without renal failure	0.68				
Estimated cumulative incidence of VAP per 1000 invasive mechanical ventilation days					
Day 0	0.0053	0.0018			
Day 1	0.0083	0.0013			
Day 2	0.0118	0.0012			
Day 3	0.0155	0.0012			
Day 4	0.0188	0.0012			
Day 5	0.0211	0.0012			
Day 6	0.0225	0.0012			
Day 7	0.023	0.0013			
> Day 8	0.023	0.0011			

Table taken from submission.

Appendix 9. Detailed calculations for costs associated with hospital stay and complications (as presented in submission)

A. Surgery cost

Surgery	Ascending and arch	Descending aorta and thoraco-abdominal
N	10	14
OR time (min)	240	300
OR cost (USD)	4837	8464
OR cost/min (USD)	20.15	28.21
OR cost/min (NOK)*	151.16	211.60
OR cost/min (2007)	NOK 186.42	
Inflation rate (2007-2015)	1.2340	
OR cost/min (2015)	**NOK 230.03**	

* 1 USD=7.5 NOK (exchange rate used throughout)

B. Sepsis (extra cost per episode)

	Per stay	Per day	Mean LOS	Patients
Mean ICU cost	€ 14,223	€ 2,601	5.47 days	640
Mean ICU cost (with sepsis)	€35,906	€2,671	13.44 days	109
Mean ICU cost (w/o sepsis)	€ 9,772	€ 2,587	3.83 days	531
Extra cost due to sepsis		€ 84		
Cost per sepsis episode (EUR 2001)		€ 1,134		
Cost per sepsis episode (NOK 2001)		NOK 8,449.54		
Inflation rate (2001-2015)		1.5298		
Cost per sepsis episode (NOK 2015)		NOK 12,926.31		

* 1 EUR=7.45 NOK

C. Renal failure

Dialysis	%*	Cost/week
CAPD	7.90%	NOK 4,161.00
APD	7.90%	NOK 7,013.00
HD	84.20%	NOK 1650.00
Mean cost (NOK 2012 value)		NOK 2,272.05
Inflation rate (2012-2015)		1.0704
Mean cost (NOK 2015)		NOK 2,431.94
Cost per day		NOK 347.42

CAPD: continuous ambulatory peritoneal dialysis, APD: automated peritoneal dialysis, HD: hemodialysis

* From 2013 Kunnskapssenteret report (48).

D. Ventilation associated pneumonia (VAP)

	VAP	no VAP	Difference
Nursing time	$3,369	$2,980	$389
Pharmacy	$14,345	$8,547	$5,798
Ventilator	$4,710	$2,184	$2,526
Respiratory therapy	$2,650	$1,496	$1,154
Chest x-rays	$1,762	$1,009	$753

Total	$26,836	$16,216	$10,620
Extra cost for VAP (USD 2012)	$10,620		
Inflation rate (2012 -2015)	1.9027		
Mean cost (USD 2015)	$11,605		
Mean cost (NOK 2015)	NOK 63,130.28	1$ = 5.44 NOK	

Appendix 10. Short-term inputs for budget-impact model, from CEA model output

Clinical Outcomes	FS Traditional mean (95% CI)	FS Perceval mean (95% CI)	MiS Traditional mean (95% CI)	MiS Perceval mean (95% CI)	Conc Traditional mean (95% CI)	Conc Perceval mean (95% CI)
Surgery (min)	195.14 (194 – 197)	159.86 (159 – 161)	196.28 (195 – 199)	160.99 (160 – 162)	209.49 (209 – 211)	174.20 (173 – 175)
Early mortality	5.49% (2.3% - 8.7%)	3.39% (2.2% - 5.0%)	4.19% (1.7% - 7.1%)	2.64% (1.7% - 4.1%)	6.40% (2.3% - 10.3%)	4.17% (2.3% - 6.0%)
Re-operation bleeding	7.37% (4.5%- 10.3%)	6.54% (4.0% - 9.2%)	6.33% (3.6% - 8.9%)	5.55% (3.2% - 7.9%)	7.95% (4.8% - 11.0%)	6.59% (4.0% - 9.3%)
Need for RRT	4.34% (1.3% - 7.1%)	3.00% (0.9% - 5.3%)	3.90% (0.7% - 6.9%)	2.75% (0.6% - 4.9%)	5.02% (1.4% - 8.4%)	3.12% (1.0% - 5.6%)
LOS ICU (days)	2.96 (2.35 – 3.77)	2.05 (1.93 – 2.33)	2.62 (2.05 – 3.32)	1.81 (1.70 – 1.99)	3.56 (2.54 – 4.76)	1.87 (1.73 – 2.07)
LOS ward (days)	16.99 (2.88 – 29.79)	9.97 (8.90 – 10.55)	14.70 (2.53 – 26.32)	8.54 (7.67 - 9.34)	21.44 (-0.66 – 41.42)	11.06 (6.80 – 14.64)
Transfusion need	77.74% (77.5%-78.9%)	74.40% (74.1%-74.7%)	67.81% (67.5% - 68.1%)	64.11% (63.8% - 64.4%)	80.06% (79.8% - 80.4%)	74.66% (74.4% - 74.9%)
PRBC units*	2.04 (2.02 – 2.07)	1.83 (1.81 – 1.86)	2.02 (1.99 – 2.05)	1.82 (1.8 – 1.84)	2.16 (2.13 – 2.19)	1.85 (1.82 – 1.87)
Sepsis rate	3.44% (0.6% - 6.0%)	3.44% (0.6%-%)	1.83% (-0.3% - 3.6%)	1.83% (-0.3% - 3.6%)	3.44% (0.6% - 6.0%)	3.44% (0.6% - 6.0%)
VAP rate	1,54% (0.7% - 0.1%)	1.34% (0.6% - 1.9 %)	1.68% (0.7% - 2.1%)	1.35% (0.6% - 1.9%)	1.68% (0.7% - 2.2%)	1.36% (0.7% - 2.0%)
PO rehab needed	74.79% (68.4%-81.6%)	74.79% (68.4%-81.6%)	44.35% (36.6% - 52.2%)	44.35% (36.6% - 52.2%)	74.79% (68.4%-81.6%)	74.79% (68.4% - 81.6%)

FS: full sternotomy, **MiS:** minimally invasive surgery, **Conc:** concomitant, **RRT:** renal replacement therapy, **VAP:** ventilation associated pneumonia, **PO:** post-operative

* Mean packed red blood cell (PRBC) units transfused in patients needing transfusion

Appendix 11. Comparison between Relative Risk (RR) or mean difference (MD) from CEA Model and those calculated from the meta-analysis.

Clinical Outcomes	Sutured valves			Sutureless (Perceval)			Perceval vs. Traditional					Meta-analysis estimate
	FS	*MiS*	*Conc*	*FS*	*MiS*	*Conc*	*FS*	*MiS*	*Conc*	*mean*		Mean [95% CI]
Early mortality (<30 days)	5.5%	4.2%	6.4%	3.4%	2.6%	4.2%	0.62	0.63	0.65	0.63	RR	0.58 [0.25, 1.33]
LOS ICU (days)	2.96	2.62	3.56	2-05	1.81	1.87	-0.91	-0.81	-1.69	-1.14	MD	-0.16 [-0.75, 0.43]
Stroke rate	3.4%	3.4%	3.4%	3.9%	3.9%	3.9%	1.15	1.15	1.15	1.15	RR	1.12 [0.45, 2.78]
PM implantation rate	3.8%	3.8%	3.8%	6.8%	6.8%	6-8%	1.79	1.79	1.79	1.79	RR	1.76 [1.03, 2.99]

FS: full-sternotomy, **MiS:** minimally invasive surgery, **Conc:** concomitant

Table taken from submission file.

Appendix 12. Cost analysis in different budget scenarios

	Current scenario (no Perceval®)					Alternative scenario (Perceval®)				
Population	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Sutured	698	698	698	698	698	656	638	638	601	583
Sutureless	0	0	0	0	0	42	60	60	97	115
Costs (NOK)	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Sutured	261,082,261	289,301,635	315,886,426	340,856,246	364,096,858	245,372,440	265,051,612	282,455,012	297,643,908	310,553,261
In-hospital	*216,379,845*	*216,379,845*	*216,379,845*	*216,379,845*	*216,379,845*	*203,359,854*	*197,689,183*	*192,018,512*	*186,347,841*	*180,677,170*
Valve	*8,027,000*	*8,027,000*	*8,027,000*	*8,027,000*	*8,027,000*	*7,544,000*	*7,333,636*	*7,123,273*	*6,912,909*	*6,702,545*
Longterm dialysis	*26,165,894*	*52,955,462*	*78,163,996*	*101,671,146*	*123,401,141*	*24,591,442*	*49,083,300*	*71,387,183*	*91,431,418*	*109,189,379*
*Complication**	*10,509,522*	*11,939,328*	*13,315,585*	*14,778,255*	*16,288,872*	*9,877,144*	*10,945,492*	*11,926,044*	*12,951,740*	*13,984,166*
Sutureless	0	0	0	0	0	12,242,371	18,421,192	24,852,327	31,529,385	38,442,086
In-hospital	*0*	*0*	*0*	*0*	*0*	*9,378,425*	*13,246,844*	*16,984,063*	*20,590,081*	*24,064,899*
Valve	*0*	*0*	*0*	*0*	*0*	*1,365,000*	*1,959,506*	*2,554,013*	*3,148,519*	*3,743,025*
Longterm dialysis	*0*	*0*	*0*	*0*	*0*	*1,089,762*	*2,594,272*	*4,480,140*	*6,732,361*	*9,332,965*
*Complication**	*0*	*0*	*0*	*0*	*0*	*409,184*	*620,569*	*834,111*	*1,058,423*	*1,301,197*
Total cost	**261,082,261**	**289,301,635**	**315,886,426**	**340,856,246**	**364,096,858**	**257,614,810**	**283,472,803**	**307,307,338**	**329,173,293**	**348,995,347**
In-hospital	*216,379,845*	*216,379,845*	*216,379,845*	*216,379,845*	*216,379,845*	*212,738,279*	*210,936,027*	*209,002,575*	*206,937,922*	*204,742,069*
Valve	*8,027,000*	*8,027,000*	*8,027,000*	*8,027,000*	*8,027,000*	*8,909,000*	*9,293,143*	*9,677,285*	*10,061,428*	*10,445,570*
Longterm dialysis	*26,165,894*	*52,955,462*	*78,163,996*	*101,671,146*	*123,401,141*	*25,681,204*	*51,677,572*	*75,867,323*	*98,163,779*	*118,522,345*
*Complication**	*10,509,522*	*11,939,328*	*13,315,585*	*14,778,255*	*16,288,872*	*10,286,327*	*11,566,061*	*12,760,155*	*14,010,164*	*15,285,363*

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Appendix 13. Budget impact analysis results.

	Year 1	Year 2	Year 3	Year 4	Year 5
Budget Impact (alternative vs current)	**-3,467,450**	**-5,828,831**	**-8,579,088**	**-11,682,954**	**-15,101,511**
In-hospital	*-3,641,566*	*-5,443,817*	*-7,377,270*	*-9,441,922*	*-11,637,775*
Valve	*882,000*	*1,266,143*	*1,650,285*	*2,034,428*	*2,418,570*
Longterm dialysis	*-484,690*	*-1,277,890*	*-2,296,673*	*-3,507,367*	*-4,878,796*
*Complication**	*-223,194*	*-373,266*	*-555,430*	*-768,092*	*-1,003,509*
% savings (alternative vs current)	**1.33%**	**2.01%**	**2.72%**	**3.43%**	**4.15%**
In-hospital	*1.68%*	*2.52%*	*3.41%*	*4.36%*	*5.38%*
Valve	*-10.99%*	*-15.77%*	*-20.56%*	*-25.34%*	*-30.13%*
Longterm dialysis	*1.85%*	*2.41%*	*2.94%*	*3.45%*	*3.95%*
*Complication**	*2.12%*	*3.13%*	*4.17%*	*5.20%*	*6.16%*

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