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RAPID REVIEW:
Treatment options for inoperable patients with severe aortic stenosis: rapid review for a patient decision aid

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Content

Key messages

Patients who suffer from severe aortic stenosis may require replacement of the aortic valve, either by open-heart surgery or transcatheter aortic valve implantation (TAVI). Conservative treatment, such as medical therapy or active surveillance of the patient, are therapeutic alternatives.

We were commissioned to summarize the evidence for inoperable patients with severe aortic stenosis, i.e. patients who are ineligible for surgical aortic valve replacement.

We found evidence that TAVI compared with medical therapy:

- Probably reduces all cause mortality at one and five years follow-up
- Probably improves quality of life
- Probably reduces moderate to severe cardiac symptoms up to three years follow-up
- Probably reduces hospital admissions five years follow-up
- Probably makes little or no difference in deaths at 30 days follow-up
- Probably makes little or no difference in major bleeding events at three years follow-up
- Probably makes little or no difference for the risk of myocardial infarction at three years follow-up
- Probably makes little or no difference for the need of a permanent pacemaker at three years follow-up
- Probably increases the risk of stroke at one year

We did not find any evidence comparing TAVI with active surveillance, or active surveillance compared with conservative treatment.

Title
Treatment options for inoperable patients with severe aortic stenosis: rapid review for patient decision aid

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Publication type
Rapid review
A rapid review is a review that makes use of less comprehensive methods than a systematic review due to limited timeframe, e.g. less comprehensive search strategy, search in fewer databases, no grading of the quality of selected studies, no external peer review, and simpler quality check of both project plan and final manuscript.

We cannot answer everything:
No recommendations
No economic evaluation

Publisher
The Norwegian Institute of Public Health was commissioned by the University Hospital of North Norway

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Updated
Search for literature was conducted in January 2020

Hovedbudskap

Pasienter med alvorlig aortastenose kan behandles ved å erstatte hjerteklaffen. Dette kan gjøres ved åpen hjertekirurgi eller ved å føre en kunstig hjerteklaff gjennom et kateter fra lysken til hjertet (*transcatheter aortic valve implantation*, TAVI). Konservativ (ikke-invasiv, dvs. medikamentell eller palliativ) behandling og aktiv overvåkning av pasienten er andre alternativer.

Vårt oppdrag er å oppsummere kunnskapsgrunnlaget for inoperable pasienter med alvorlig aortastenose, dvs. pasienter som ikke kan få åpen hjertekirurgi.

Vi fant oppsummert forskning som viste at TAVI sammenliknet med medikamentell behandling:

- trolig reduserer dødelighet ett og fem år etter behandling
- trolig forbedrer pasientens livskvalitet
- trolig reduserer moderate og alvorlige hjerte- og karsymptomer de første tre år etter behandling
- trolig reduserer reinnleggelse på sykehus fem år etter behandling
- trolig har ingen eller liten effekt på dødelighet 30 dager etter behandling
- trolig har ingen eller liten effekt på alvorlig blødning tre år etter behandling
- trolig har ingen eller liten effekt på hjerteinfarkt tre år etter behandling
- trolig har ingen eller liten effekt på behov for pacemaker tre år etter behandling
- trolig øker risikoen for hjerneslag et år etter behandling

Vi fant ingen forskning som sammenlikner TAVI med aktiv overvåkning, eller som sammenlikner aktiv overvåkning med konservativ behandling.

Tittel
Behandlingsalternativer for inoperable pasienter med alvorlig aortastenose: hurtig oversikt for samvalgsverktøy

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Publikasjonstype
Hurtigoversikt
En hurtigoversikt er resultatet av å sammenfatte forskningsbasert kunnskap:
- med kort tidsfrist og
- med mindre omfattende metode enn ved systematisk kunnskapsoppsummering.

Svarer ikke på alt
Gir ingen anbefaling
Gir ingen økonomisk vurdering

Hvem står bak denne publikasjonen?
Folkehelseinstituttet har gjennomført oppdraget etter forespørsel fra Universitetssykehuset Nord-Norge

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Når ble litteratursøket utført?
Søk etter studier ble utført i januar 2020

Preface

The Centre for Shared Decision Making at the University Hospital of North Norway and the Division for Health Services, Norwegian Institute of Public Health, have started a co-operation in 2017 to develop evidence-based shared decision making tools.

Patient decision aid are continuously published at www.helsenorge.no/samvalg/.

Our aim is to:
- be resource effective
- be trustworthy
- work in line with national quality criteria for patient decisison making tools
- present updated and evidence-based information in a format that is easily understood by laypeople, including patients and their caretakers

The authors report no conflict of interest.

For this rapid review, we aimed to summarise findings about the effectiveness of alternative treatment strategies for aortic stenosis in patients who are not suited for surgery.

We wish to thank Tove Skjelbakken (Centre for Shared Decision Making, the University Hospital of North Norway), Andreas Kristensen (the University Hospital of North Norway) and Christian Eek (Oslo Universitetssykehus) for peer review.

Hege Kornør, PhD
Department director

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Senior adviser

Background

Aortic stenosis is a pathological narrowing of the passage of blood across the aortic valve. The aortic valve is a one-way valve between the left ventricle of the heart and the aorta. The disease usually progresses for a long time (years) before symptoms develop.

Average survival of patients after diagnosis of severe aortic stenosis is only 2 to 3 years if the aortic valve is not replaced. Aortic valve replacement can be performed either by open-heart surgery (surgical aortic valve replacement, SAVR) or by virtue of a transcatheter implant, also called transcatheter aortic valve implantation or replacement (TAVI or TAVR).

For patients with severe aortic stenosis who are ineligible for open-heart surgery (due to frailty or comorbidities), TAVI is an option for valve replacement. Conservative approaches, including medical therapy, palliative care, monitoring and watchful waiting, are other, non-invasive treatment alternatives for inoperable patients.

Method

Our aim was to provide evidence for non-surgical treatment alternatives for patients with severe aortic stenosis who cannot undergo surgical replacement of the aortic valve.

Inclusion criteria

Population	People with severe, inoperable aortic stenosis
Interventions	TAVI
Comparators	No replacement (conservative treatment, medical therapy) Active surveillance (watchful waiting, monitoring)
Outcomes	Mortality Stroke Myocardial infarction Re-hospitalization Symptoms, i.e. shortness of breath, angina, exhaustion Quality of life Mobility Permanent need for a pacemaker Major bleeding
Study designs	Patient decision aids Guidelines Systematic reviews Randomized controlled trials (RCTs)

Literature search

We searched for decision aids and guidelines online, and for systematic reviews in the Epistemonikos database (Supplement 1). These literature searches were conducted in January 2020. We also checked reference lists in relevant publications.

Selection of studies

We screened the titles and abstracts of systematic reviews retrieved from Epistemonikos. Selected guideline literature and review articles were presented and discussed for eligibility within the project group.

Presenting the results and assessing our confidence in the evidence

We used the GRADE (Grading of Recommendations Assessment, Development and Evaluation, Table 1) tool to express our confidence in the results for each predefined outcome with a summarized effect estimate. We present the results in a Summary of Findings table (Supplement 2).

Table 1. GRADE Working Group grades of evidence

High certainty ⊕⊕⊕⊕	*We are very confident that the true effect lies close to that of the estimate of the effect.*
Moderate certainty ⊕⊕⊕⊖	*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 certainty ⊕⊕⊖⊖	*Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.*
Very low certainty ⊕⊖⊖⊖	*We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect.*

We also present the results by using standardized statements about effects developed by Cochrane (Figure 1).

Figure 1. Standardised statements about effect

Table of standardised statements about effect

	Important benefit/harm	Less important benefit/harm	No important benefit/harm
High quality / certainty[1] evidence	[*Intervention*] improves/reduces [*outcome*] (high quality / certainty evidence)	[*Intervention*] slightly improves/reduces [*outcome*] (high quality / certainty evidence)	[*Intervention*] makes little or no difference to [*outcome*] (high quality / certainty evidence)
Moderate quality / certainty[1] evidence	[*Intervention*] probably improves/reduces [*outcome*] (moderate quality / certainty evidence)	[*Intervention*] probably slightly improves/reduces / probably leads to slightly better/worse [*outcome*] (moderate quality / certainty evidence)	[*Intervention*] probably makes little or no difference to [*outcome*] (moderate quality / certainty evidence)
Low quality / certainty[1] evidence	[*Intervention*] may improve/reduce [*outcome*] (low quality / certainty evidence)	[*Intervention*] may slightly improve/reduce [*outcome*] (low quality / certainty evidence)	[*Intervention*] may make little or no difference to [*outcome*] (low quality / certainty evidence
Very low quality / certainty[1] evidence	We / The review authors are uncertain whether [*intervention*] improves/reduces [*outcome*] as the quality / certainty of the evidence has been assessed as very low		
No studies	No studies were found that looked at [*outcome*]		

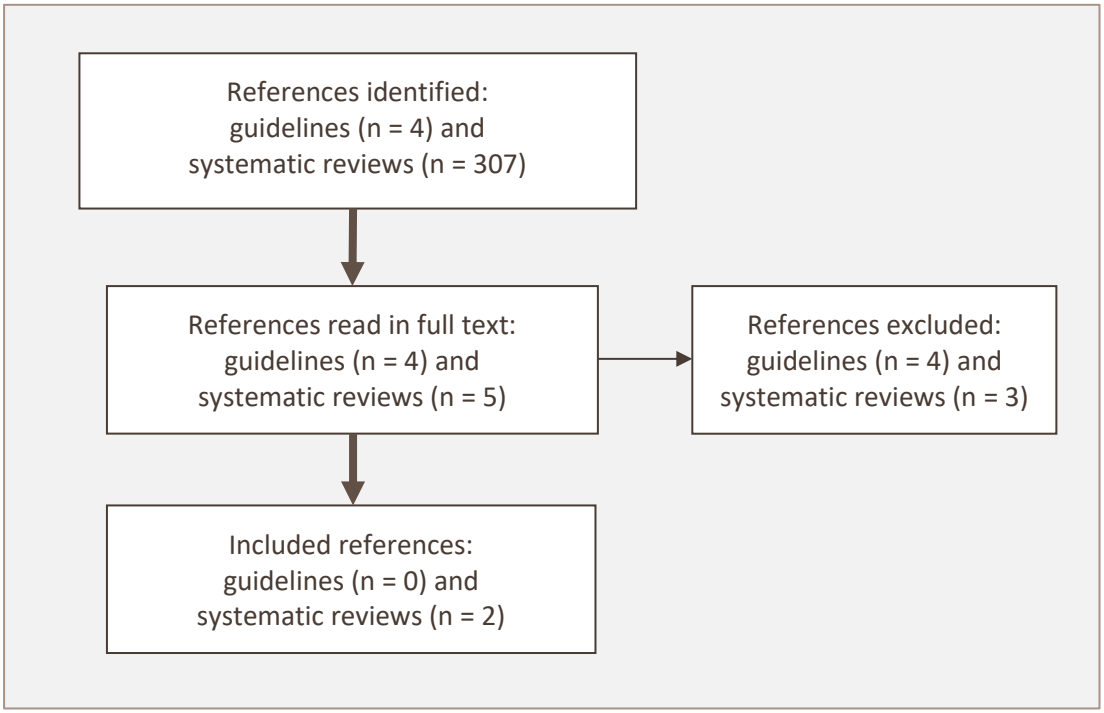
[1]Within GRADE, the phrase "quality of the evidence" is increasingly referred to as "certainty of" the evidence. Use the same term that has been used elsewhere in the review.

Source: https://www.cochrane.no/sites/cochrane.no/files/public/uploads/how_to_write_a_cochrane_pls_15th_june_2018.pdf

Results

Our searches identified four guidelines and 307 systematic reviews (Figure 2). We found relevant guidelines from Up to Date, the British Medical Journal Best Practice, the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery, as well as the National Institute for Health and Care Excellence (NICE) (1-5). Among the systematic reviews, we included two, Liu 2018 (6) and Amato 2016 (7). Summarized results from Liu 2018 are included in the NICE guidelines (5).

Figure 2. Flow chart



In addition, we identified relevant ongoing trials (Supplement 3. Ongoing studies, page 20) from a recent publication (8).

Included evidence

The two systematic reviews we identified included one RCT, the Placement of Aortic Transcatheter Valves (PARTNER) trial (9-13), but there was not complete overlap in reporting of the results. Therefore, we included and extracted data from both reviews (Table 2).

Table 2. Included evidence

Study ID (reference)	No. of included studies	Intervention in addition to standard care	Comparator
Amato 2016 (7)	1 RCT (PARTNER) (9)	TAVI	Medical therapy
Liu 2018 (6)	1 RCT (PARTNER) (9-13)	TAVI	Medical therapy

Summary of Findings

What are the risks and benefits of TAVI compared to conservative management (medical therapy, palliative care) in patients with severe, inoperable aortic stenosis?

- TAVI probably reduces all-cause mortality at one and five years follow-up.
- TAVI probably makes little or no difference in deaths at 30 days follow-up.
- TAVI probably improves quality of life.
- TAVI probably increases the risk of stroke at one year.
- TAVI probably makes little or no difference in major bleeding at three years follow-up.
- TAVI probably reduces hospital admissions at five years follow-up.
- TAVI probably reduces moderate to severe cardiac symptoms up to three years follow-up.

See also Table 3, Supplement 2 (page 18).

Also, based on Kaplan-Meier estimates, TAVI probably makes little or no difference for the risk of myocardial infarction and the need of a permanent pacemaker up to three years follow-up (6).

Discussion

Main findings

We found evidence comparing TAVI with no treatment (including conservative treatment and medical therapy without surgical valve replacement).

Compared with medical therapy, TAVI:

- probably reduces all-cause mortality at one and five years follow-up, hospital admissions at five years follow-up, and moderate to severe cardiac symptoms up to three years follow-up;
- probably increases the risk of stroke at one year follow-up;
- probably makes little or no difference in deaths at 30 days, the risk of major bleeding events, the risk of myocardial infarction, and the need for a permanent pacemaker implant up to three years follow-up;
- probably improves quality of life;

We found no studies comparing TAVI with active surveillance (watchful waiting or monitoring). Several recent studies (14-16) have compared patient groups who received either SAVR or TAVI with those who did not, but no data was available on the comparison of active surveillance with TAVI alone.

We found no studies that compared non-invasive treatments with active surveillance.

Limitations

For the comparison of TAVI with active surveillance (watchful waiting), we found a systematic review (8), which summarized studies including both TAVI and SAVR patients, but could not provide separate analysis of these subgroups of patients.

Update and research gaps

There is a need for studies that compare TAVI with active surveillance. A recent meta-analysis by Sá and colleagues (8) identified ongoing (EARLY-TAVR, EVolVeD) or

planned (EVE-TAVI) randomized trials (see also Supplement 3, page 20) that aim to compare TAVI with conservative management in aortic stenosis.

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Supplement 1. Search strategy

Database: Epistemonikos (Advanced search – Title/Abstract)
Search date: 08.01.2020
Search performed by: Tonje Lehne Refsdal, Research librarian, Norwegian Institute of Public Health

(("aortic stenosis" OR "aortic valve stenosis" OR "heart valve disease" OR "heart valve diseases"))

Number of hits: 307 (systematic review)

Supplement 2. Summary of Findings

Table 3. TAVI versus medical therapy for inoperable, severe aortic stenosis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence¥ (GRADE)	Comments
	Risk with medical therapy	Risk with TAVI				
Mortality (all causes) at 5 years	972 per 1 000	243 fewer per 1 000 (311 fewer to 175 fewer)	RR 0.75 (0.68 to 0.82)	358 (1 RCT)	⊕⊕⊕⊖ Moderate[1,2,3]	TAVI probably reduces all-cause mortality at five years follow-up
Mortality (all causes) at 1 year	497 per 1 000	189 fewer per 1 000 (264 fewer to 94 fewer)	**RR 0.62** (0.47 to 0.81)	358 (1 RCT)	⊕⊕⊕⊖ Moderate[1,2,3]	TAVI probably reduces all-cause mortality at one year follow-up
30-day Mortality	28 per 1 000	22 more per 1 000 (11 fewer to 119 more)	**RR 1.80** (0.62 to 5.27)	358 (1 RCT)	⊕⊕⊕⊖ Moderate[1,2,3,4]	TAVI probably makes little or no difference in deaths at 30 days follow-up
Quality of life at 1 year	KCCQ summary score 26 points higher, SF-12 physical score 5.7 points higher and SF-12 mental health score 6.4 points higher with TAVI		-	358 (1 RCT)	⊕⊕⊕⊖ Moderate[1,2,3]	TAVI probably improves quality of life
Stroke& at 1 year	45 per 1 000	**62 more per 1 000** (3 more to 191 more)	**RR 2.38** (1.07 to 5.28)	358 (1 RCT)	⊕⊕⊕⊖ Moderate[1,2,3,4]	TAVI probably gives a higher risk of stroke at one year
Major bleeding at 3 years			**HR 1.69** (1.06 to 2.70)	358 (1 RCT)	⊕⊕⊕⊖ Moderate[1,2,3]	TAVI probably makes little or no difference on major bleeding at three years follow-up
Repeat hospital admission at 5 years			**HR 0.40** (0.29 to 0.55)	358 (1 RCT)	⊕⊕⊕⊖ Moderate[1,2,3]	TAVI probably reduces hospital admissions after five years
Cardiac symptoms (NYHA class III/IV) at 1 year	268 per 1 000	113 fewer per 1 000 (166 fewer to 29 fewer)	**RR 0.58** (0.38 to 0.89)	358 (1 RCT)	⊕⊕⊕⊖ Moderate[1,2,3]	TAVI probably reduces moderate to severe cardiac symptoms at one year follow-up
Cardiac symptoms (NYHA class III/IV) at 2 years	128 per 1 000	39 fewer per 1 000 (80 fewer to 35 more)	**RR 0.70** (0.38 to 1.27)	358 (1 RCT)	⊕⊕⊕⊖ Moderate[1,2,3]	TAVI probably makes little or no difference in moderate to severe cardiac symptoms at two years follow-up

Cardiac symptoms (NYHA class III/IV) at 3 years	955 per 1 000	248 fewer per 1 000 (315 fewer to 182 fewer)	**RR 0.74** (0.67 to 0.81)	358 (1 RCT)	⨁⨁⨁⊖ Moderate[1,2,3]	TAVI probably reduces moderate to severe cardiac symptoms at three years follow-up

Data are from Amato 2016 (7) and Liu 2018 (6) based on the PARTNER 1B trial (9-13).
CI: confidence interval; **HR**: hazard ratio; **ITT**: intention to treat; **NYHA**: New York Heart Association, functional class; **RR:** risk ratio; **TAVI**: transcatheter aortic valve implantation;

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

¥**GRADE Working Group grades of evidence** (see also Table 1, page 9)
Moderate certainty: 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.

& A major stroke was defined as a focal or global neurologic deficit associated with a score of 2 or higher on the modified Rankin scale, which has a range of 0 to 6, with 0 indicating no symptoms and 6 indicating death.

[1] unblinded, [2] not free form industry funding, [3] allocation concealment process not specified, [4] wide CI

Supplement 3. Ongoing studies

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