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A systematic review of current literature

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REVIEW

Transcatheter aortic valve implantation: evidence on safety and efficacy compared with medical therapy. A systematic review of current literature

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Abstract
Objectives Transcatheter aortic valve implantation (TAVI) promises effective treatment for high-risk elderly patients with symptomatic severe aortic stenosis (AS). However, the adoption of TAVI must be justified and guarantee long-term performance. Systematic reviews are a core methodology in evidence-based health economics for judging medical effectiveness. In this work, the methodology was applied to provide objective evidence on the efficacy and safety of TAVI at 1-year follow-up and to assess whether TAVI confers a survival benefit compared with medical therapy.
Methods In accordance with the toolkit of the "German Scientific Working Group Technology Assessment for Health Care" (GSWG), a systematic literature review on the safety and efficacy of TAVI procedures was conducted in major bibliographic databases to identify all relevant publications. Preestablished inclusion criteria were defined. An initial screening of identified articles regarding titles and abstracts was followed by a full-text screening. Data from eligible articles were extracted and evaluated according to GSWG checklists followed by a qualitative synthesis of information.
Results The systematic literature search identified 12 primary publications (derived from 1,849 citations) for TAVI [number of patients (n) = 1,049] and 11 publications (derived from 189 citations) for medical therapy of AS (n = 946) that fulfilled the inclusion criteria.
Mean overall procedural success rate for included TAVI interventions was 93.3%. Mean combined procedural, postprocedural, and cumulative in-hospital/30-day mortality was 11.4% (n = 116; range 5.3–23%).
1 year after TAVI, the mean overall survival rate was 75.9% (range 64.1–87%) compared with 62.4% (range 40–84.8%) for medically treated patients (p value < 0.01). 1-year survival after TAVI for patients treated with transvascular (TV) procedures was higher than after transapical (TA) procedures (79.2 vs. 73.6%) (p value = 0.04). At 1-year follow-up, the improved valvular function remained stable, and there was a trend towards an improved ventricular function.
Conclusion Based on the best available data, in patients with symptomatic severe AS, TAVI demonstrates an improved 1-year survival compared with medical treatment. The survival benefit of TV-TAVI over medical therapy elucidated from this systematic literature review is +16.8% and therefore, in good congruence with the recently published results from the randomized PARTNER US trial (+20%).

Keywords Aortic stenosis · Transcatheter aortic valve implantation · Medical treatment · Systematic review

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1 Introduction

1.1 Rationale and objectives of this work

Degenerative aortic stenosis (AS) is the most common severe valvular heart disease in the elderly with an estimated prevalence of 2.8-5% in individuals above an age of 75 years (Nkomo, V. T. et al. 2006, Lindroos, M. et al. 1993). Thus, the prevalence of degenerative AS is strongly linked to the phenomenon of population ageing. According to the United Nations 2008 Population Database (United Nations Population Division 2008), by 2050, the number of people older than 80 years in developed countries will have increased by +227% from 53 million today to 120 million. As the age of the Western population increases, AS will become more frequent and is expected to represent an increasingly important public health burden (Vahanian, A. et al. 2007). Currently, each year more than 21,000 aortic heart valve operations are performed in Germany (Table 3), thereof over 40% in patients older than 70 years (Gummert, J. F. et al. 2008). The total number of these interventions has grown steadily in recent years and is expected to further increase, particularly in elderly patients (Gummert, J. F. et al. 2008).

The natural course of symptomatic severe AS is dismal with high mortality rates. The 3-year survival in the untreated course of patients with AS is only 25% in comparison to a matched population with 77% (O'Keefe, J. H., JR et al. 1987). After the onset of heart failure, median survival is only 11 months, after onset of syncope and angina 27 months and 45 months, respectively (Horstkotte, D. and Loogen, F. 1988). Because of the high risk of restenosis, balloon aortic valvuloplasty (BAV) can only be considered as a palliative treatment method for patients with a good quality of life (QoL) who are not eligible for surgical aortic valve replacement (AVR) (Figulla, H. R. et al. 2009, Carabello, B. A. and Paulus, W. J. 2009). Currently, surgical AVR is regarded to be the mainstay for improved survival and symptom relief, even in elderly patients (Varadarajan, P. et al. 2006b, Bouma, B. J. et al. 1999).

However, the European Heart Survey of patients with valvular heart disease suggests that up to 33% of patients over the age of 75 years are not considered for surgical AVR because of age and comorbidities (Iung, B. et al. 2005). An emerging less invasive treatment – transcatheter aortic valve implantation (TAVI) – promises effective treatment for high-risk patients not suitable for surgical AVR. As of today, TAVI is intended as a treatment alternative to “no intervention” for inoperable patients. The initial successful report of a TAVI intervention for AS in a patient with a cardiogenic shock was reported by Cribier and colleagues in 2002 (Cribier, A. et al. 2002). Since then, various devices were introduced and evaluated with promising clinical results. Recently, larger studies have demonstrated that TAVI can be performed in these patients with reasonably low mortality rates (Rodés-Cabau, J. et al. 2010). As of today, approximately 20,000 TAVI procedures

have been performed worldwide – and this number experiences exponential growth (communication with TAVI devices manufacturers in June 2010). However, the adoption of TAVI must be justified and guarantee long-term performance. If TAVI outcomes can fulfill these expectations, the technology will have a strong impact not only on the number of treatable patients, but also on the division of work between clinical departments. In the past, effective therapy of AS had been exclusively performed by cardiac surgeons. With the development of TAVI, cardiologists have gained ground in the effective treatment of AS because TAVI requires hybrid procedures and joint patient selection. Regardless the narrow definition of the eligible TAVI patient population, the statistics from Table 3 are well suited to trigger speculations to which extent TAVI will replace traditional heart surgery in the future.

Systematic reviews are core to formal decision making processes in evidence-based health economics (Drummond, M. F. et al. 2007). They apply a series of methodological principles which aim at systematically identifying, evaluating and summarizing all available data to provide objective evidence for judging medical effectiveness. To date, few systematic reviews on the safety and efficacy of TAVI procedures have been conducted, but none of them have focused on 1-year follow-up data nor have earlier reviews conducted a comparison with recent evidence on medical therapy. Therefore, the objectives of this work are firstly, to objectively assess the safety and efficacy of TAVI at 30-day and 1-year follow-up, and secondly, to assess whether TAVI confers a survival benefit in patients with symptomatic severe AS when compared with patients potentially eligible for TAVI who did not receive an intervention – either they refused or were turned down – and continue with medical therapy.

1.2 Brief overview aortic stenosis (AS)

1.2.1 Clinical background, incidence and natural history

The aortic valve acts as a gateway for the flow of blood between the left ventricle and the aorta. During systole (the period of left ventricular contraction), the aortic valve opens and allows blood to flow from the left ventricle to the aorta towards the body. During diastole (the period of left ventricular filling) the aortic valve closes, preventing the backflow of blood to the heart, and the left ventricle is filled with blood arriving from the lungs through the left atrium across the mitral valve. In patients with AS, a narrowing of the aortic valve opening creates increased resistance to the flow of blood from the left ventricle to the aorta, thus increasing the afterload of the left ventricle. This may lead to symptoms, such as angina pectoris, syncope, dyspnoea, or heart failure, and in symptomatic patients with a severe stenosis, to sudden death. In case of aortic regurgitation (AR), the aortic valve leaks every time the left ventricle relaxes, allowing blood to flow backwards from the

aorta into the left ventricle. The amount of regurgitation can be estimated by echocardiography. The backflow of blood causes overloading and dilatation of the left ventricle and may lead to symptoms and to irreversible damage to the left ventricle and heart failure (Carabello, B. A. and Paulus, W. J. 2009). AS can mostly be suspected clinically and diagnosis is confirmed by echocardiographic examination and Doppler which enables to assess the severity of the stenosis and its consequences on the left ventricle. An aortic valve opening <1.0 cm² and a mean transaortic gradient >40 mmHg indicate severe AS (Bonow, R. O. et al. 2006, Iung, B. et al. 2003).

AS is the most common severe valvular heart disease in Western countries. In the Euro Heart Survey, AS constituted 46.5% of all valvular heart disease identified in a population of 5,001 (Iung, B. et al. 2003). Of 1,197 cases of AS screened in several academic and non-academic centers from 25 countries, 81.9% were degenerative, 11.2% rheumatic, 5.4% congenital, and 0.8% due to endocarditis (Iung, B. et al. 2003). In a population-based study, hemodynamically significant AS affected 2.8% of the general population ≥ 75 years of age (Nkomo, V. T. et al. 2006).

Development of severe symptoms of AS remains the major demarcation point in the natural history of AS (Bonow, R. O. et al. 2006, Ross, J., JR. and Braunwald, E. 1968). The asymptomatic patient has a good outlook even with severe obstruction, but once symptoms occur, there is a sudden increase in mortality rate in the ensuing years (Carabello, B. A. and Paulus, W. J. 2009). According to some authors, average survival after onset of symptoms is 2 to 3 years (Ross, J., JR. and Braunwald, E. 1968). These claims originate from work published in the late 1960s, but controlled trials comparing conservative medical therapy with surgical aortic AVR have never been performed. Over time, the primary etiology of AS in Western countries has changed from rheumatic to senile degeneration resulting from a progressive age-dependent build-up of calcium. Today's patient population is older and has more associated comorbidities, such as coronary artery disease. Thus, it seems questionable whether the results of earlier studies on the natural history of AS can be generalized in respect to today's patient population. The natural history of AS nowadays and the impact of valvular correction, especially in the elderly, is not well known and may be different from the often cited historic data from Ross and Braunwald, obtained from clinical and postmortem studies in an era when the age at the time of clinical presentation averaged 48 years and echocardiography had not yet been introduced into clinical practice (Ross, J., JR. and Braunwald, E. 1968). However, even in a more recent study, the median survival in elderly patients with severe AS and symptomatic heart failure was only 13 months (Aronow, W. S. et al. 1993).

1.2.2 Treatment options and their limitations

1.2.2.1 Medical therapy

Recent studies have indicated that AS is caused by an active inflammatory process similar to that of atherosclerosis (Carabello, B. A. and Paulus, W. J. 2009). Thus, treatments for slowing down progression of coronary disease, most notably statins, have been investigated for similar effects in patients with AS. Findings of several retrospective studies showed that patients receiving statins had a slower progression of AS than patients not receiving them (Rajamannan, N. M. 2004). However, an important randomized controlled trial (RCT) of patients with moderate AS, could not report survival benefits from statin use (Cowell, S. J. et al. 2005). Contrary, Moura and colleagues (Moura, L. M. et al. 2007) reported significantly slower progression of AS for patients with mild disease. Other medical treatment is exclusively directed towards symptoms such as diuretics in fluid retentions. From these results one can conclude, that presently available medical therapy can only result in a temporary alleviation of symptoms but curing AS requires replacement of the stenosed valve.

1.2.2.2 Surgical aortic valve replacement (AVR)

The surgical therapy with prosthetic replacement of the aortic valve is considered the gold standard for treatment of symptomatic AS (Bonow, R. O. et al. 2006). Surgical AVR allows access to the stenosed aortic valve through a median sternotomy or minimal-invasive opening of the chest and the aorta. This surgical procedure always requires the use of a heart-lung machine with the associated risks. Current guidelines on the management of valvular heart disease (Bonow, R. O. et al. 2006, Vahanian, A. et al. 2007) recommend surgical AVR for symptomatic patients even in the very elderly as increased perioperative mortality rates appear to be acceptable compared to the natural history of valvular heart disease. In particular, these risks are accepted because previous studies have not only reported significant survival benefits but also improvement of NYHA functional class (Varadarajan, P. et al. 2006b) and QoL (Sundt, T. M. et al. 2000, Olsson, M. et al. 1996) even for octogenarians. However, this recommendation from guidelines applies only as long as the patients have no severe comorbidities, which increase the risk of the procedure disproportionately. For this reason, a high proportion (33%-41%) of patients who might benefit from surgical AVR is rejected by surgeons or rejects the procedure (Iung, B. et al. 2005, Bouma, B. J. et al. 1999).

1.2.2.3 Balloon aortic valvuloplasty (BAV)

BAV has been introduced in the 1980s as a non-surgical treatment alternative for inoperable patients with symptomatic severe AS. BAV consists in stretching and cracking the stenosed aortic valve by means of an inflating balloon in an attempt to reduce the degree of stenosis. The technique

has shown to provide temporary improvement of valvular function and relief of symptoms in inoperable patients (Letac, B. et al. 1989, Eltchaninoff, H. et al. 1995). However, its use was diminished by an unacceptably high early restenosis rate and lacking mortality benefits (Lieberman, E. B. et al. 1995, Letac, B. et al. 1991). Therefore, BAV is only considered as a palliative treatment option today (Figulla, H. R. et al. 2009, Eltchaninoff, H. et al. 2000). However, with the advent of TAVI, there has been a resurgence of interest in BAV procedures in bridging patients to TAVI (Kapadia, S. R. et al. 2009, Sack, S. et al. 2008).

1.2.2.4 Transcatheter aortic valve implantation (TAVI)

The above described traditional treatment options are challenged by an emerging non-surgical method of AVR which has revived interest in the management of severely ill patients. The concept of transcatheter insertion of an aortic valve was first performed by Cribier, A. et al. 2002. Initially, TAVI insertion was completed via an antegrade approach, indicating that the catheter was advanced along the direction of the blood flow. Because of potential complications at the level of the mitral valve, this approach has been replaced by the retrograde (transvascular (TV)) approach. This technique, however, can be impeded due to difficulties to advance large catheter through frail femoral or iliac arteries encountered in elderly patients. These difficulties led to the development of the transapical (TA) approach requiring a mini-thoracotomy for delivery of the device via the cardiac apex of the left ventricle. Due to the patient selection process illustrated in Figure 1, patients treated by the TA route mostly have a higher risk profile than patients treated by the TV approach. However, the feasibility of TAVI does not only depend on the vascular accessibility, but also on the anatomy of the ascending aorta and the aortic annulus. Therefore, correct sizing of the valve is critical to minimize potential for post-procedural prosthesis migration and paravalvular leakage (Vahanian, A. et al. 2007).

Several types of TAVI systems are currently tested at various stages of development. For the time being, two systems have received CE-marking required for clinical use and are in scope of this work: firstly, the Edwards SAPIEN® system (Edwards Life Sciences, Inc.), a balloon-expandable transcatheter aortic valve which consists of 3 pericardial bovine leaflets mounted within a tubular, slotted, stainless steel balloon-expandable stent. Both insertion techniques (TV and TA access) are commonly used for the Edwards system. The second system - the self-expandable Medtronic CoreValve® system (Medtronic CoreValve, LLC) - consists of 3 pericardial tissue porcine leaflets, mounted and sutured in a self-expandable nitinol stent. The current CoreValve device was further redesigned in the fixing of the valve tissue onto the stent, decreasing the profile to 18F sheaths; the CoreValve system is delivered via the TV route.

Until a convincing evidence base from long-term and randomized studies becomes available, TAVI should only be considered in inoperable or very high risk patients such as patients with a very high estimated surgical risk or of old age and with a degenerated bioprosthesis or porcelain aorta. According to existing evidence, only patients with an expected operative mortality of >10% (which corresponds to a logistic EuroSCORE >20% or to a STS score >10%) should be eligible for TAVI (Figulla, H. R. et al. 2009).

European (Vahanian, A. et al. 2008, Figulla, H. R. et al. 2009) and American (Bonow, R. O. et al. 2006) guidelines recommend that a careful TAVI patient evaluation involving a joint decision by multidisciplinary teams of interventional cardiologists, cardiothoracic surgeons, and cardiac anesthesiologists is needed to avoid the risk of uncontrolled diffusion of the TAVI technique. The experts also warn against extending the technique to lower-risk patients, given the low mortality rates achieved by surgical AVR.

2 Methods

2.1 Systematic review of TAVI

2.1.1 Inclusion and exclusion criteria

This systematic review was based on published clinical case series and cohort studies as well as published secondary literature, such as systematic reviews and health technology assessments (HTAs) either published in peer-reviewed scientific journals or published by known HTA institutes. Only primary publications that met the criteria listed in Table 4 were eligible for consideration. Unpublished study results presented at international conferences were excluded because of the difficulty in appraising methodology. Characteristics of included patient populations were defined in accordance with the most recent German positioning statement on TAVI patient selection (Figulla, H. R. et al. 2009).

For secondary publications, inclusion requirements were a matching thematic focus along with a detailed documentation of the included primary literature, the period during which the literature search was conducted, the applied search strategy, and the databases used.

2.1.2 Data sources, selection, extraction and evaluation of information

2.1.2.1 Data sources for peer-reviewed publications

Peer-reviewed literature searches were conducted for the clinical review on March 4, 2010. The bibliographic databases MEDLINE, EMBASE Ovid, Centre for Reviews and Dissemination (CRD), and Cochrane Library were searched. The search strategy consisted of controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings) terms, and free text keywords. The main search concepts were "aortic valve" OR "aortic valve stenosis" AND "percutaneous" OR "transcatheter" OR "transvascular" OR "transapical". The detailed search strategy is provided in the Appendix 7.6. The search was not restricted to any publication period, but to English and German language and an adult patient population. EMBASE and MEDLINE AutoAlerts were set-up to send monthly updates with new literature until April 30, 2010. An internet search using Google Advanced Search was also conducted. These searches were supplemented by hand searching the reference lists of key papers for further identification of potentially relevant studies and through contacts with appropriate experts. No limitation was included on the study type, and therefore, identification of systematic reviews and cost-effectiveness data was combined within the above search strategy.

2.1.2.2 Data sources for publications from health technology institutes

In order to find HTAs and systematic reviews on TAVI previously published by health technology institutes, the Centre for Reviews and Dissemination (CRD), Cochrane Database of Systematic Reviews (CDSR), and International Network of Agencies for Health Technology Assessment (INAHTA) electronic databases were searched on March 4, 2010. The MeSH terms “aortic stenosis” AND “heart valve prosthesis” were used to identify potentially relevant publications. In addition, the databases of major HTA institutes (Deutsche Agentur für Health Technology Assessment (DAHTA), Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG), and National Institute for Health and Clinical Excellence (NICE)) were consulted for further references on the above keywords. The reference lists of all retrieved secondary reports were reviewed for further identification of potentially relevant publications.

2.1.2.3 Data selection and extraction

The references resulting from the literature search were exported into a literature database (Citavi 2.5.2.0). Literature selection was conducted in three stages: an initial screening of titles and abstracts against the inclusion criteria defined in Table 4 to identify potentially relevant reports followed by screening of the full text publications identified as possibly relevant. The data from the remaining reports was extracted and evaluated again against selection criteria to identify the relevant reports to be included into the literature review. For all reports that were excluded based on extracted data, the rationale for exclusion was recorded (Table 1).

A structured Microsoft Excel data extraction form was used to extract the following data from each study:

- Study characteristics: number of patients, enrollment period, study center, study design, valve type, TAVI approach, duration of follow-up
- Patient characteristics: age, gender, estimated operative risk, New York Heart Association (NYHA) functional class, baseline echocardiographic data (transaortic mean/ peak gradient, aortic valve area (AVA), left ventricular ejection fraction (LVEF))
- Primary outcome measures (safety): procedural success rate, complications, mortality, survival
- Secondary outcome measures (efficacy): post-procedural echocardiographic data, NYHA functional class, length of hospital stay, QoL, cost-effectiveness

In the Appendix 7.5/ Table 17, the extracted data from all included primary publications on TAVI is provided.

2.1.2.4 Evaluation and synthesis

The methodological quality of identified primary publications was evaluated using the checklist #2a for primary studies published by the German Scientific Working Group Technology Assessment for Health Care (GSWG) (German Scientific Working Group for Health Care 2000c).

Secondary publications were assessed along the checklists #1b for systematic reviews/ meta-analyses and #1a for context documents/ HTAs which were also developed by the GSWG (German Scientific Working Group for Health Care 2000b, 2000a).

For the qualitative information synthesis of primary publications, a structured Microsoft Excel reporting template was developed that summarized the study design, methodological approach, patient characteristics, and primary and secondary outcome measures for each included study (Appendix 7.5/ Table 17).

The information synthesis of included secondary publications, describing the institutional background, objectives, methodological approach, results, and conclusions, was conducted for each of the recent secondary publications[1] in chapter 3.1.3.

2.1.3 Statistical methods

Categorical or binary variables are expressed as percentages (absolute number of patients (n); range). Metric variables are expressed as (mean (range))$_{\text{all included studies}}$/ (mean±standard deviation (SD))$_{\text{subset studies reporting SD}}$.

Except for the number of patients, only aggregated statistics (study means and SD) were available from primary publications. Means were calculated based on all included studies and, to ensure consistent analysis of study characteristics, based on the subset of those studies reporting the SD. With few exceptions, deviations between means based on all included studies and means of the subset of studies reporting SD were small, and no significant mean difference was found. In conclusion, it is reasonable to regard those SD as representative for all studies. Where SD were reported, the overall SD was calculated as the square root of the mean of variances plus the variance of means. With the exception of number of patients, specified ranges refer to extreme values of reported study means, not to extreme values of raw data which were not available.

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[1] For earlier secondary publications which are already captured in the systematic review of the Belgian Health Care Knowledge Center (KCE) (van Brabandt, H. and Neyt, M. 2008), only a tabularized overview and a summary of conclusion is provided in chapter 3.1.3.

The estimation of 95%-confidence intervals (CI) for survival rates relied on the normal approximation to the binomial distribution.

Significance tests were conducted to compare baseline data, and, if data for both subgroups was available, procedural and outcome results of TV-TAVI versus TA-TAVI[2]. All significance tests were two-sided. For metric variables, which were assumed normal, homogeneity of variance was first tested with the F-test. Mean difference was tested with the t-test for independent groups if the p-value was greater than the significance level $\alpha=0.05$. Otherwise the Welch-test was chosen as the appropriate test. Binary and categorical variables were compared assuming the null hypothesis of equal distribution within the two groups, i.e. observed and expected counts were calculated, and the Chi-square (χ^2)-test was performed on the contingency tables. The null hypothesis of equal means or equal distributions respectively, was rejected if the p-value was smaller than or equal the significance level $\alpha=0.05$.

Data collection and statistical analysis were performed using Microsoft Excel.

2.2 Systematic review on medical therapy of AS

2.2.1 Inclusion and exclusion criteria

Only published peer-reviewed clinical cohort studies that met the inclusion criteria listed in Table 5 were considered for the information synthesis on medical therapy of AS. The characteristics of included patient populations were defined in accordance with the preceding review on TAVI in chapter 2.

2.2.2 Data sources, selection, extraction and evaluation of information

2.2.2.1 Data sources

For the review on medical therapy of AS, a peer-reviewed literature search analogous to the search described in detail in chapter 2.1.2.1 was conducted on March 4, 2010. Findings in EMBASE and MEDLINE were updated until April 30, 2010. The search strategy consisted of controlled vocabulary, including The National Library of Medicine's MeSH terms, and free text keywords, such as

[2] These comparisons should only be assessed in conjunction with the described baseline differences between the respective patient groups.

“aortic valve stenosis” AND “natural history” OR “medical therapy” OR “conservative treatment”. The detailed search strategy is provided in the Appendix 7.6.

2.2.2.2 Data selection and extraction

The references resulting from the literature search were exported into a literature database (Citavi 2.5.2.0). Data selection was conducted in two stages: an initial screening of titles and abstracts against the selection criteria in Table 5 to identify potentially relevant reports followed by a detailed screening of the full-text publications identified as possibly relevant in the initial screening. For all reports that were excluded based on the full-text screening, the rationale for exclusion was recorded (Table 2).

A structured Microsoft Excel data extraction form was used to extract the following data from each included study:

- Study characteristics: number of patients, enrollment period, study center, study design, intervention of treatment cohorts, duration of follow-up
- Patient characteristics: age, gender, estimated operative risk, NYHA functional class, baseline echocardiographic data (transaortic mean/ peak gradient, AVA, LVEF)
- Primary outcome measures (safety): complications, mortality, survival

In the Appendix 7.5/ Table 18, the extracted data from all included primary publications on medical therapy of AS is provided.

2.2.2.3 Evaluation and Synthesis

The methodological quality of identified studies was evaluated using the checklist #2a for primary studies of the GSWG (German Scientific Working Group for Health Care 2000c).

For the qualitative information synthesis of primary publications, a structured Microsoft Excel reporting template was developed that summarized the study design, methodological approach, patient characteristics, and primary and secondary outcome measures for each included study. The template and extracted data are provided in the Appendix 7.5/ Table 18.

2.2.3 Statistical methods

The statistical methods applied for the evaluation of extracted data for this review were identical to those described in chapter 2.1.3.

Significance tests were conducted to compare baseline characteristics and survival of TAVI patients versus medically treated patients.[3]

[3] These comparisons should only be assessed in conjunction with the described baseline differences between the respective patient groups.

3 Results

3.1 Systematic review on TAVI

3.1.1 Results of literature search

As illustrated in Figure 2, the original literature searches identified a total of 1,849 citations of which 1,590 citations were excluded based on a systematic screening of titles and abstracts (mostly laboratory and animal studies, case reports, editorials, commentaries, and non-English and non-German publications). 259 potentially relevant publications were retrieved for full text screening. Based on the full text screening, another 212 publications were excluded. Together with 10 potentially relevant publications identified through supplementary EMBASE and MEDLINE database alerts and cross-referencing, 57 reports were selected for data extraction. These reports underwent a third screening based on a detailed evaluation of extracted data - leaving 12 [4] primary publications and 7 systematic reviews/ publications from HTA institutes for inclusion in the information synthesis.[5] No distinct health economic evaluation of TAVI was identified through the literature search.

3.1.2 Description and information synthesis of primary publications

3.1.2.1 Study quality

The quality of all included primary publications on TAVI was assessed along the criteria of the checklist #2a of the GSWG (German Scientific Working Group for Health Care 2000c). Each of the 12 primary publications included in the information synthesis was evaluated (Appendix 7.7.1). The quality assessment below was structured according to the sections of the checklist: patient selection, assignment and participation, intervention/exposure, study administration, outcome measurement, drop-outs, statistical analysis, and discussion.

Except for three retrospective studies, the inclusion and exclusion criteria were defined and established before the intervention. The diagnostic criteria for symptomatic severe AS were described and a reliable and valid assessment of disease status was ensured by echocardiographic and Doppler hemodynamic assessment. All included patients met the current eligibility criteria defined for

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[4] Results from the two largest industry-sponsored US and European registries (SOURCE and PARTNER EU) could not be considered because full-text publications of results were missing.

[5] The complete lists of relevant primary and secondary publications included in the review on TAVI are provided in the bibliography sections 6.2.1 and 6.2.2.

TAVI, and could thus be considered as “standard users” of the intervention. The recruitment period was specified in all studies whereas the mean follow-up was only provided in seven studies.

The included studies were neither randomized nor blinded. Seven studies were designed as observational clinical case series without control groups, and five as small comparative cohort studies. For latter, the interventional cohorts and control groups were recruited from a patient population of patients referred for TAVI intervention or compared to patients undergoing surgical AVR. The control cohorts were comparable in respect to demographic and clinical characteristics.

A comparable and valid assessment of the intervention was generally provided in all studies. Outcome measurement was usually conducted centrally. In the only multi-center study, a systematic workup protocol ensured consistent measurement. Details on co-therapies were not provided.

In all studies, procedural success, post-procedural mortality and complications were a priori defined as primary endpoints. In addition, echocardiographic and clinical parameters were collected which are of particular interest from the patients’ perspective. However, none of the studies assessed the impact on patients’ QoL. Only few case series assessed the distribution of prognostic factors.

Most included studies reported complete follow-up data. The remaining studies provided little or no details on the completeness of follow-up.

Primary and secondary endpoints were reported for all patients undergoing the intervention. For control groups, only primary endpoints were reported. Testing methods to compare metric and categorical variables and p-values of the corresponding hypothesis tests were described. Several studies provided CI or standard errors to assess the precision of effect estimates.

All study results were analyzed in the context of previous evidence from other relevant studies, and references to the study hypothesis were made. A generalization of the statements on the effectiveness of TAVI in patient populations was raised in some publications. Most publications commented on possible sources of distortion and limitations of the study design, e.g. observational or retrospective nature, uncertainties in respect to patient selection and the impact of learning curve. In general, statistical limitations, e.g. small sample size, were discussed.

3.1.2.2 Study characteristics

As a result of the systematic literature search, 12 studies were identified for the information synthesis. The general study characteristics to describe the study design, the TAVI approach and valve type for each case series are provided in Table 6. All included studies were conducted in either Western European or North American/Canadian specialized tertiary referral centers and reported results of observational studies including patients who underwent TAVI via the TV or TA approach.

The studies' patient enrollment period ranged from January 2005 until June 2009, and they were published between 2008 and 2010. Except for the Canadian multi-center study by Rodés-Cabau, J. et al. 2010, the authors reported results collected in a single center. None of the studies was randomized or blinded, but three publications (Rajani, R. et al. 2010, Kapadia, S. R. et al. 2009, Otten, A. M. et al. 2008) conducted small comparative cohort studies to compare TAVI patients to control groups of patients referred for TAVI, but undergoing either alternative aortic valve interventions (surgical AVR or palliative BAV) or medical therapy. Walther, T. et al. 2010 conducted a propensity-matched comparison between TAVI and surgical AVR. Zierer, A. et al. 2009 evaluated outcomes of two matched groups of patients undergoing either TAVI or minimally invasive surgical AVR.

Five series had ≥ 75 patients (range 75-339) (Rodés-Cabau, J. et al. 2010, Walther, T. et al. 2010, Himbert, D. et al. 2009, Webb, J. G. et al. 2009, Grube, E. et al. 2008), and the remaining seven series had <75 patients (range 18-50) (Rajani, R. et al. 2010, Al-Attar, N. et al. 2009, Kapadia, S. R. et al. 2009, Thielmann, M. et al. 2009, Ye, J. et al. 2009, Zierer, A. et al. 2009, Otten, A. M. et al. 2008). The number of patients captured by this review totaled 1,049 of which almost half (48.3% (n=507)) stemmed from the two largest studies from Canada (Rodés-Cabau, J. et al. 2010, Webb, J. G. et al. 2009). There were three studies exclusively on the TV-TAVI approach with the CoreValve device (20.3% (n=213)) (Rajani, R. et al. 2010, Grube, E. et al. 2008, Otten, A. M. et al. 2008). The other studies implanted valve prostheses manufactured by Edwards (Cribier Edwards/ Edwards Sapien) (79.7% (n=836)). Of these, three series report exclusively on the TA-TAVI approach (14% (n=147)) (Walther, T. et al. 2010, Ye, J. et al. 2010, Zierer, A. et al. 2009) and five of patients who underwent either approach (TV 35.8% (n=376), TA 28.1% (n=295)). In the study of Kapadia, S. R. et al. 2009, the TAVI approach was not specified (1.7% (n=18)). All studies clearly defined the techniques of the standard TAVI intervention, and there was reasonable consistency in their description of the techniques used for each access route. Three studies were based on retrospective data reviews (Rajani, R. et al. 2010, Walther, T. et al. 2010, Zierer, A. et al. 2009), the remaining nine were prospective studies. The mean clinical follow-up duration was 9.6 months (range 8-13 months)/ 10.4±6 months. One-year follow-up data was reported by all included studies.

3.1.2.3 Patient characteristics

Details on **demographic baseline characteristics** are provided in Table 7. Most case series required a minimum patient age of 75 years for enrollment, thus, the mean age of included series was consistently high with a mean of 82 years (range 80.1-85 years)/ 81.6±7.4 years. The difference of mean age between patients undergoing the TV and TA approach (82.7 years (range 79.6-85 years)/ 81.6±7.4 years versus 81.6 years (range 80-85 years)/ 81.4±7.6 years) was not significant (p-value=0.154). Mean 45% (range 23%-67%) of the patients were male, with a significantly higher

share of male patients of 51% (range 38%-58%) among those treated via the TV access route versus 36% (range 23%-67%) in the TA subgroup (p-value<0.0001).

All included patients presented with pre-procedural outcome measures that indicated severe AS according to the 2006 position statement of the American College of Cardiology (ACC)/ American Heart Association (AHA) (Bonow, R. O. et al. 2006). The patients were symptomatic, and considered "inoperable" or at "very high risk" for surgery, however, no consistent definition for these terms was applied; five studies referred only to the estimated operative risk score and age (Rodés-Cabau, J. et al. 2010, Rajani, R. et al. 2010, Walther, T. et al. 2010, Al-Attar, N. et al. 2009, Thielmann, M. et al. 2009). Details on the baseline measures are summarized in Table 7.

All but one (Rodés-Cabau, J. et al. 2010) included studies calculated the logistic EuroSCORE to determine the **estimated operative risk** which was mean 27.8% (range 15%-44.2%)/ 27.5%±15.6% for all patients. Due to the patient selection process illustrated by Figure 1, patients treated by the TV route generally have a lower risk profile than those treated by the TA approach. This different risk profile was reflected in a significant difference of mean logistic EuroSCORE results between TV and TA subgroups (23.9% (range 15%-38.1%)/ 23.6%±14.2% versus 34% (range 28%-52%)/ 33.7%±15.5%) (p-value<0.0001). Nine studies conducted an operative risk estimation via the score of the Society of Thoracic Surgeons (STS) (Rodés-Cabau, J. et al. 2010, Walther, T. et al. 2010, Al-Attar, N. et al. 2009, Himbert, D. et al. 2009, Kapadia, S. R. et al. 2009, Webb, J. G. et al. 2009, Thielmann, M. et al. 2009, Ye, J. et al. 2009, Grube, E. et al. 2008). The mean STS score was 11.3% (range 8.9%-17.9%)/ 11.8%±7.4% for all patients and 10.1% (range 8.7%-15.1%)/ 10.5%±6.7% and 12.9% (range 10.3%-19.9%)/ 13.3%±8.2% for TV and TA subgroups, respectively (p-value<0.0001).

The clinical status of TAVI patients was usually assessed by means of the **NYHA functional classification** scale which represents a measure to assess the functional impact of the valvular dysfunction. NYHA classification ranges from class I in which the patient has no limitation in daily physical activity, to class IV, in which the patient is breathless at rest. Except for two studies (Rodés-Cabau, J. et al. 2010, Otten, A. M. et al. 2008), all included studies reported the mean NYHA functional class at baseline which was mean 3.2 (range 2.6-3.7)/ 3.3±0.6.[6] Eight studies (n=490) provided the distribution of patients per NYHA class at baseline (Rajani, R. et al. 2010, Walther, T. et al. 2010, Al-Attar, N. et al. 2009, Himbert, D. et al. 2009, Kapadia, S. R. et al. 2009, Thielmann, M.

[6] It is recognized that NYHA classes are discrete variables, and therefore, the calculation of a mean might distort the evidence. However, two studies considered in this review only provided a mean NYHA class, and would not have been considered otherwise.

et al. 2009, Webb, J. G. et al. 2009, Ye, J. et al. 2009): 1% (n=5), 8.6% (n=42), 60.8% (n=298), and 29.6% (n=145) were in NYHA class I, II, III, and IV, respectively.

3.1.2.4 Primary outcome measures (safety)

Mean overall **procedural success rate**, defined by most authors as implantation of a functioning prosthetic valve in the correct position and without intra-procedural mortality, was 93.3% (n=948; range 86%-100%) for all included TAVI interventions. Success rates extracted from each included study are provided in Table 8. Due to the high technical demand of the TV access route, the mean procedural success rate of 89.6% (n=382; range 85.7%-100%) in these procedures was significantly lower as compared to the TA access route with a mean success rate of 97.3% (n=353; range 96.1%-100%) (p-value=0.0002). In TV series, the mean procedural success rate ranged from 85.7% in an older series of 136 patients published in 2008 (Grube, E. et al. 2008) to 100% in a recently published, smaller series of 39 patients at very high surgical risk (Thielmann, M. et al. 2009). For TA series, four smaller series including in total 47 patients reported 100% success rates (Al-Attar, N. et al. 2009, Himbert, D. et al. 2009, Zierer, A. et al. 2009, Ye, J. et al. 2009). The success rates of the two most recent and largest TA series were 96.1% (Rodés-Cabau, J. et al. 2010) and 97% (Walther, T. et al. 2010). One publication (Otten, A. M. et al. 2008) did not report the procedural success rate.

Only three studies with a total patient population of n=428, provided detailed reasons for technical failure of TV procedures (Rodés-Cabau, J. et al. 2010, Al-Attar, N. et al. 2009, Thielmann, M. et al. 2009). The procedures failed due to the inability to pass the iliac artery in 2.6% (n=11) of patients, to cross the native valve with the prosthesis in 1.6% (n=7), prosthesis embolization in 1.4% (n=6), major vascular injuries in 0.5% (n=2), cardiac perforation 0.5% (n=2), or procedural death in 1.4% (n=6). For TA procedures, only one study (Walther, T. et al. 2010) (n=100) reported the following reasons for technical failure: dissection of aortic root in 1% (n=1) of patients, valve dislocation in 1% (n=1), and left main stem occlusion in 1% (n=1). Survivors of failed TAVI procedures were either converted to surgical AVR including full sternotomy (Walther, T. et al. 2010) or treated medically (Al-Attar, N. et al. 2009).

Except for two studies (Zierer, A. et al. 2009, Otten, A. M. et al. 2008), all included studies reported **major procedural and post-procedural complications**[7] (n=989; thereof TV n=550/ TA n=421). As illustrated in Table 9, the mean incidence of the adverse events in total and per subgroup was the following: major vascular complication 3.1% (n=31; range 0%-12.8%), for TV 4.5% (n=25; range 0%-33.3%), and for TA 2.4% (n=6; range 0%-13.3%) (p-value=0.0061); cerebrovascular

[7] If a publication reported any adverse events, it was assumed that if a type of major complication was not mentioned, it would not have occurred.

accident/ stroke 2.9% (n=29; range 0%-4.2%), for TV 4.4% (n=24; range 0%-4.4%), and for TA 1.2% (n=5; range 0%-6.7%) (p-value=0.004); myocardial infarction (MI) 0.8% (n=8; range 0%-3.8%), for TV 0.7% (n=4; range 0%-2.2%), and for TA 1% (n=4; range 0%-3.8%) (p-value=0.703); cardiac tamponade 1.4% (n=14; range 0%-6%), for TV 1.5% (n=8; range 0%-6.7%), and for TA 1.4% (n=6; range 0%-13.3%) (p-value=0.97); atrioventricular heart block requiring permanent pacemaker (PPM) insertion 9.7% (n=96; range 0%-6%), for TV 12% (n=66; range 5%-34.2%), and for TA 6.9% (n=29; range 0%-11.5%) (p-value=0.008); "valve in valve" 1.8% (n=18; range 0%-4%), for TV 1.6% (n=9; range 0%-2.9%), and for TA 2.1% (n=9; range 0%-8.3%) (p-value=0.566). Other less frequently observed complications included renal failure (Rajani, R. et al. 2010, Webb, J. G. et al. 2009), major access site complication/ infection (Rodés-Cabau, J. et al. 2010, Kapadia, S. R. et al. 2009, Webb, J. G. et al. 2009), major bleeding (Ye, J. et al. 2009, Kapadia, S. R. et al. 2009), prolonged ventilation (Kapadia, S. R. et al. 2009, Ye, J. et al. 2009, Webb, J. G. et al. 2009), and valve embolization (Thielmann, M. et al. 2009).

The mean combined procedural, post-procedural and cumulative **inhospital/30-day mortality** was 11.4% (n=116; range 5.3%-23%) (95%-CI: 9.4%-13.3%) as reported by all but one (Otten, A. M. et al. 2008) included studies. For TV procedures, the mean inhospital/30-day mortality was 9.5% (n=53; range 5.3%-13.3%) (95%-CI: 7.1%-12%), which was significantly lower than for TA procedures with a mean of 14% (n=62; range 10%-27%) (95%-CI: 10.8%-17.2%) (p-value=0.03). Detailed 30-day mortality rates from each included study are provided in Table 8. In addition, Figure 3 visualizes the 30-day mortality rates differentiated by the chosen interventional access route.

The **mean 1-year survival rate** after TAVI derived from all included studies was 75.9% (range 64.1%-87%)/ 74.4%±6.2% (95%-CI: 73.3%-78.4%), with significant difference between TV and TA subgroups (79.2% (range 68.1%-87%)/ 76.1%±6.5% (95%-CI: 75.5%-82.8%) versus 73.6% (range 60%-78%)/ 74.9%±6.7% (95%-CI: 69.2%-77.9%)) (p-value=0.041) (Table 8, Figure 4). Three authors reported that the incidence of late mortality was mostly non-cardiac and due to comorbidities (Rodés-Cabau, J. et al. 2010, Webb, J. G. et al. 2009, Grube, E. et al. 2008).

None of the studies observed any evidence on structural valve deterioration or other prosthetic valve dysfunction during follow-up.

3.1.2.5 Secondary outcome measures (efficacy)

The efficacy of TAVI seemed to be good with significant post-TAVI effects. Patients in whom a TAVI had been successfully performed were reported to experience an improved valvular function and a trend towards an improved ventricular function, in accordance with an improvement in their NHYA functional class. The results from included studies were statistically significant and reported

efficacy outcomes were consistent. Table 10 provides an overview of the evidence on TAVI efficacy.

3.1.2.5.1 Echocardiographic assessment

A summary of the reported echocardiographic and clinical baseline measures and post-TAVI outcomes at 30-day and 1-year follow-up is provided in Table 11. Irrespective of the TAVI approach, the mean calculated **aortic valve area (AVA)** improved significantly after the procedure. Based on the observation of a subset of studies which reported data for both 30-day and 1-year follow-up (Himbert, D. et al. 2009, Thielmann, M. et al. 2009, Webb, J. G. et al. 2009), the AVA increased by over 170% from the pre-procedural baseline of mean 0.61cm² (range 0.6-0.64cm²)/ 0.61±0.19cm² for all patients, and 0.61cm² (range 0.6-0.63cm²)/ 0.63±0.16cm² for TV and 0.62cm² (range 0.6-0.65cm²)/ 0.65±0.17cm² for TA subgroups (p-value=0.374), to mean 1.65cm² (range 1.6-1.73cm²)/ 1.65±0.44cm² at 30-day follow-up for all patients. Beyond 30-day follow-up, the AVA decreased somewhat towards a mean of 1.49cm² (range 1.45-1.7cm²)/ 1.54±0.34cm² observed at 1-year follow-up (Figure 5).

The assessment of the post-TAVI effect on the **transaortic mean gradient** was also based on the subset of three studies (Himbert, D. et al. 2009, Thielmann, M. et al. 2009, Webb, J. G. et al. 2009). At baseline, the mean gradient was 47.6±12.2mmHg[8] (range 45.5–52mmHg) for all patients. Immediately after the TAVI intervention and regardless the chosen approach, the mean gradient was reported to fall significantly, and to remain stable until 30-day follow-up at a mean of 10.3±4.2mmHg (range 10-12mmHg). In patients surviving until 1-year follow-up, the mean gradient remained stable with minor further improvement towards a mean of 10.1mmHg (range 8–11.2mmHg)/ 10.9±4.9mmHg (Figure 5).

Four case series reported the pre-procedural baseline and the effect of TAVI on the ventricular function at 30-day and 1-year follow-up (Walther, T. et al. 2010, Himbert, D. et al. 2009, Thielmann, M. et al. 2009, Ye, J. et al. 2009). The pre-procedural **left ventricular ejection fraction (LVEF)** at baseline was mean 53.1%±15.3% (range 46%–56%) for all patients, with no significant difference between TV and TA subgroups (52.7%±16% versus 54.2%±14.3%) (p-value=0.164). Post-TAVI, the LVEF continued to increase from a mean 56.2% (range 51.1%–59%)/ 55.3%±13.5% at 30-day follow-up towards a mean of 60.2% (range 58%–63%)/ 59%±11.4% at 1-year follow-up.

Aortic regurgitation (AR) was present after TAVI in most patients to some degree as reported by seven studies (n=678) (Rodés-Cabau, J. et al. 2010, Al-Attar, N. et al. 2009, Himbert, D. et al. 2009, Thielmann, M. et al. 2009, Webb, J. G. et al. 2009, Ye, J. et al. 2009, Grube, E. et al. 2008).

[8] Mean±SD was reported by all studies.

Postoperatively, 80.5% (n=564) of survivors had none to mild (grade 0/I) AR and 16.7% (n=113) had moderate (grade II) AR. Severe (grade III) AR occurred in 2.8% (n=19) of patients. Four studies monitored AR during follow-up and consistently reported that the postoperative degree of AR remained unchanged until 1-year follow-up (Walther, T. et al. 2010, Thielmann, M. et al. 2009, Webb, J. G. et al. 2009, Ye, J. et al. 2010).

3.1.2.5.2 Functional improvement

Eight studies reported the distribution of patients per NYHA class at baseline (Rajani, R. et al. 2010, Walther, T. et al. 2010, Al-Attar, N. et al. 2009, Himbert, D. et al. 2009, Kapadia, S. R. et al. 2009, Thielmann, M. et al. 2009, Webb, J. G. et al. 2009, Ye, J. et al. 2009): 1% (n=5), 8.6% (n=42), 60.8% (n=298), and 29.6% (n=145) were in NYHA class I, II, III, and IV respectively. The mean NYHA class was 3.2 (range 2.6-3.7)/ 3.3 ±0.6 without significant difference between TV (3.3 (range 2.6-3.5)/ 3.3±0.7) and TA (3.2 (range 2.8-3.4)/ 3.3±0.4) subgroups[9] (p-value=0.271) and was calculated including two studies without detailed assessment per NYHA class (Grube, E. et al. 2008, Zierer, A. et al. 2009).

Three studies provided the pre-procedural NYHA class and the post-TAVI effect at 30-day and 1-year follow-up in detail per functional classification (Figure 6) (Walther, T. et al. 2010, Thielmann, M. et al. 2009, Ye, J. et al. 2009). At 30-day follow-up, 22% (n=31), 51% (n=71), and 26% (n=36) of survivors were in classes I, II, and III. At 1-year follow-up, the improvement of functional status was sustained with 26% (n=26) of patients in class I, 40% (n=39) in class II, and 34% (n=34) in class III. None of the survivors remained in functional class IV at any follow-up interval. The corresponding mean NYHA class including one additional study (Grube, E. et al. 2008) was 1.9±0.3 (range 1.6–2.3) at 30-day and 1.8 ±0.4 (range 1.3–2.4) at 1-year follow-up.

In addition, two authors described a reduction of at least one functional class in most patients – in particular, patients were more likely to be in class I/II compared to III/IV which is the poorest preoperative functional status (Webb, J. G. et al. 2009, Al-Attar, N. et al. 2009).

3.1.2.5.3 Length of hospital stay

Seven studies reported a mean length of hospital and intensive care unit (ICU) stay associated with TAVI: mean stay in hospital was 9.5 days (range 5–19 days), and thereof, mean stay of 2.7 days in ICU. Hospital stay for TV patients was not significantly shorter than for TA patients (9 days (range 5–15 days) versus 10.6 days (range 7–19 days)) (p-value=0.658) (Al-Attar, N. et al. 2009, Himbert,

[9] Only partially reported per TA/ TV subgroup.

D. et al. 2009, Kapadia, S. R. et al. 2009, Webb, J. G. et al. 2009, Thielmann, M. et al. 2009, Ye, J. et al. 2009, Zierer, A. et al. 2009).

3.1.2.5.4 Quality of life and cost-effectiveness

None of the included primary publications[10] provided data on patients' QoL before or after TAVI procedures or an economic analysis to assess the cost-effectiveness of TAVI. Apart from the length of hospital stay[11], which is summarized in chapter 3.1.2.5.3, major health cost drivers were not reported.

3.1.3 Description and information synthesis of secondary publications

3.1.3.1 Study quality

The quality of all included secondary publications was assessed along the criteria of the checklist #1b for systematic reviews/ meta-analyses published by the GSWG. Each of the seven secondary publications included in the information synthesis was evaluated, and the results are provided in the Appendix 7.7.3. In addition, one so-called "rapid HTA" (van Brabandt, H. and Neyt, M. 2008) was also assessed along the criteria of the GSWG checklist #1a for context documents (German Scientific Working Group for Health Care 2000a). The quality assessment below was structured according to the sections of the checklists: research question, information retrieval and evaluation, information synthesis, conclusions, and transferability of results.

All included systematic reviews aimed to assess the safety and efficacy of TAVI interventions. Details of the literature search (sources, search strategy, and inclusion and exclusion criteria) were always documented. Whether the evaluation and extraction of information was conducted by several independent reviewers remained unclear in most publications. The data extraction was usually structured along study and patient characteristics, and key safety and efficacy outcome measures. All information syntheses were of qualitative nature, and only three publications evaluated the ex-

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[10] In the course of literature selection, three studies without 1-year follow-up were excluded from the information synthesis (Bleiziffer, S. et al. 2009, Ussia, G. P. et al. 2009, Svensson, L. G. 2008). These studies reported significant improvement of pre-procedural physical and mental QoL scores from pre- to postoperatively at 6 months. Results on QoL improvements beyond 6-months follow-up have not been published yet.

[11] In Germany, from the statutory payers' perspective, charges from hospitals are based on diagnosis-related groups (DRG) which are independent from the actual length of hospital stay. However, DRGs reflect only charges, not actual costs imposed on the public health system.

isting evidence systematically. In the conclusions, methodological limitations of the existing evidence were critically discussed by all publications. Specific recommendations, e.g. to health care providers or clinicians, were provided in three publications. The remaining four publications postponed specific recommendations due to lack of convincing evidence.

3.1.3.2 Reconciliation of included studies from this work with those included in earlier reviews

The literature search for secondary publications on TAVI revealed two systematic reviews published in peer-reviewed journals (Yan, T. D. et al. 2010, van Brabandt, H. and Neyt, M. 2008), four systematic reviews issued by health technology institutes (Wild, C. and Geiger-Gritsch, S. 2009, National Institute for Health and Clinical Excellence (NICE) 2008, Blanchard, S. 2008, Wild, C. et al. 2008), as well as one "rapid" HTA (van Brabandt, H. and Neyt, M. 2008) which already provided a summary of results from the three reviews published earlier in 2008.

As illustrated in Table 12, the update (Wild, C. and Geiger-Gritsch, S. 2009) of the systematic review of the Austrian Ludwig-Boltzmann-Institut (LBI) from 2008 (Wild, C. et al. 2008) and the recent Australian systematic review (Yan, T. D. et al. 2010) concur by two and one publications respectively with the references selected for this review. The other secondary publications published in 2008 (van Brabandt, H. and Neyt, M. 2008, National Institute for Health and Clinical Excellence (NICE) 2008, Blanchard, S. 2008)) and recent published systematic review published in 2009 by the same authors as the HTA of the Belgian Health Care Knowledge Center (KCE) (van Brabandt, H. and Neyt, M. 2009), did not consider the primary publications included for discussion in this work. However, earlier publications from the same teams and study centers as the publications this work was based upon were incorporated in these previous secondary publications. Thus, the reviews might bear potential for overlapping patient populations. The overview in Table 12 compares this work's references and according related previous publications[12] with those of earlier systematic reviews/ HTAs to point out potential overlaps with earlier reviews.

3.1.3.3 Information synthesis

The following brief descriptions of systematic reviews/ HTAs included in the information synthesis of this work summarize the institutional background, objectives, methods, results, and conclusions of the authors.

[12] Related publications were defined as duplicate publications from the same centers with overlapping enrollment period and accumulating number of patients, or increased length of follow-up.

Systematic reviews published in peer-reviewed journals

Yan, T. D. et al. 2010, Australia

Objectives

The systematic review assessed the safety and clinical effectiveness of TAVI for patients at high surgical risk with severe AS.

Methods

Electronic searches were performed in MEDLINE, EMBASE, PubMed, Cochrane Central Register of Controlled Trials, CDSR, and Database of Abstracts of Review of Effectiveness from January 2000 to March 2009. The end points included feasibility, safety, efficacy, and durability. Literature selection was conducted by two reviewers. Clinical effectiveness was synthesized through a narrative review with full tabulation of results of all included studies.

Results

The review captured the results of 1173 patients from 17 short-term observational studies. The safety assessment included overall procedural success rates in a range from 74%-100% and the following ranges of 30-day major adverse events: mortality (0%–25%), major ventricular tachyarrhythmia (0%–4%), myocardial infarction (0%–15%), cardiac tamponade (2%–10%), stroke (0%–10%), conversion to surgery (0%–8%), conversion to valvuloplasty (0%–4%), vascular complication (8%–17%), moderate to major paravalvular leak (4%–35%), "valve-in-valve" (2%–12%), and aortic dissection/rupture (0%–4%). With regard to the efficacy of TAVI, the mean AVA improved from a preoperative range from 0.5-0.8 cm^2 to a range from 1.3–2 cm^2 after TAVI. The mean pressure gradient ranged from 34–54 mmHg before TAVI and from 3–12 mmHg after the procedure. The mean length of hospital stay ranged from 7-17 days. Postoperative 6-months mortality ranged from 18%-48%. QoL data retrieved from one study incorporating 40 patients indicated improvement from preoperatively until 6-months postoperatively (Svensson, L. G. et al. 2008).

Conclusions

In their discussion, the authors stressed the potential for serious complications, lacking evidence of long-term outcomes including QoL, and inappropriate operative risk estimation methods. Therefore, the authors recommend that TAVI procedures should be considered only within the boundaries of clinical trials and at highly specialized centers with appropriate experience and infrastructure.

van Brabandt, H. and Neyt, M. 2009, Belgium

Institutional background

This systematic review published in September 2009 was conducted by employees of the Belgian KCE (van Brabandt, H. and Neyt, M. 2009).[13]

Objectives

The systematic review aimed at assessing the safety of TAVI and to compare it with published primary data reporting the risk of surgical AVR in high-risk patients with severe, symptomatic aortic AS.

Methods

Relevant published and presented primary studies were identified from a search in major databases (MEDLINE, EMBASE, CDSR, and CRD), dedicated websites, and through contacts with manufacturers which was conducted on December 15, 2008. Structured data extraction included patient characteristics, procedural success rate, operative risk status, early and late all-cause mortality. To minimize the impact of learning curve and device improvements, only series starting recruitment in April 2007 or later (n=1975) were included in the safety assessment.

Results

Due to the limited publication period, all peer-reviewed publications were excluded, leaving only three industry-sponsored series presented at international meetings for information synthesis: 1. "PARTNER EU" (Edwards Sapien) with 130 patients (TV=60/ TA=70); 2. "SOURCE" (Edwards Sapien) including 602 patients (TV=293/ TA=309); and 3. "CoreValve 18F EE" with 1,243 patients undergoing TV-TAVI. The procedural success rate was high with 97.7%-98.2% in TV and 91% in TA series. 30-day mortality rates ranged from 6.4%-7.4% for the TV and 11.6%-18.6% for the TA access route. The 6-months mortality rates were reported to range from 10%-25% in TV and 26.1%-42.8% in TA series. None of the included series starting recruitment after April 2007 reported long-term outcomes, but – inconsistent with inclusion criteria – 1-year survival from previous much smaller presented series were reported which ranged between 65%-80% in TV and from 54.7%-66% in TA series. Secondary outcomes on the efficacy of TAVI were not assessed.

[13] The same authors wrote the rapid HTA published by the KCE in 2008 (van Brabandt, H. and Neyt, M. 2008).

Conclusions

The authors concluded that TAVI procedures, especially via the TA access route, are risky in respect to safety and short-term survival, and thus, should not be performed in clinical routine as long as results from a randomized trial become available.

Systematic reviews/ HTAs published by HTA institutes

Wild, C. and Geiger-Gritsch, S. 2009, LBI Austria

Institutional background

The Austrian LBI published this systematic review in 2009 as the first update of its previously published systematic review on TV-TAVI (Wild, C. et al. 2008).

Objectives

This review aimed to bring the preceding publication (Wild, C. et al. 2008) up to date and to revise the resulting recommendation in respect to the safety and efficacy assessment of TAVI compared to conservative treatment of patients with severe AS.

Methods

The literature search was conducted in 7 major databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trial, CDSR, Cochrane Database of Review of Effects, CRD database, and INAHTA database) and limited to German and English language, and publication date between 2008 and 2009. Handsearching and industry contacts complemented the electronic search.

Results

Compared to the previous review, four additional clinical studies published between 2008 and 2009 were included which captured the results from 833 TAVI interventions. The outcome parameter of these four studies largely complied with the results of the preceding publication, and ranged between 70%-97% for the procedural success rate, and 8%-40% for 30-day mortality. Further outcomes were only partially reported. The authors questioned the independence of two industry-sponsored studies (Piazza, N. et al. 2008, Grube, E. et al. 2008) and therefore, focused their review on only two small series (Otten, A. M. et al. 2008, Descoutures, F. et al. 2008). The two studies illustrated that a high share of the very old and sick patient population - especially those with a high EuroSCORE (>25%) – was prone to refuse the treatment. In one study (Otten, A. M. et al. 2008), in 100 patients assigned to TAVI, only 39% (n=39) TAVI procedures were performed. Descoutures, F. et al. 2008 reported similar observations: of 39 inoperable patients assigned to TAVI, only 31%

(n=12) underwent the intervention. The majority of 69% (27) were referred to either medical therapy 41% (16), BAV 18% (7), or redirected to surgical AVR 10% (4). On average, the included patients in NYHA classes III and IV improved their functional status by one class to class III and II, respectively.

Conclusions

The authors retained their recommendation provided in their previous publication insofar as current evidence was low and did not allow a reliable assessment of the safety and the clinical efficacy of the TAVI technology.

van Brabandt, H. and Neyt, M. 2008, KCE Belgium

Institutional background

This so-called "rapid HTA" was published by the Belgian KCE health technology institute. The KCE is in charge of conducting studies that support the political decision making on health care and health insurance in Belgium.

Objectives

The rapid HTA report summarized current evidence supporting the use of TAVI heart valves in degenerative aortic valve disease.

Methods

All searches were performed in June 2008. For primary publications and systematic reviews, MEDLINE, EMBASE, CRD and Cochrane databases were searched. In addition, a search in CRD HTA and INAHTA databases was conducted to identify published HTA reports. Data presented at meetings was not included. Data extraction was conducted for all included publications. The search on economic evaluations was performed in CRD, CDSR, MEDLINE, and EMBASE databases. The search was complemented by handsearching websites of HTA institutes, and reference lists of selected studies. Only full economic evaluations, i.e. studies comparing alternative treatments in terms of costs and outcomes were eligible for inclusion. The literature search and selection process was replicated by a second reviewer.

Results

Observational data from series published in peer-reviewed journals and data presented at international cardiology conferences were included. Procedural success rates of 68%-93% in published series, and up to 100% in unpublished data, indicated that TAVI procedures are feasible in the

hands of experienced teams. However, TAVI was associated with a high risk: 30-day mortality rates ranged from 6.4%-13.2% in TV, and 8%-22.5% in TA patients. Vascular complications occurred – especially when the TV access route was chose – in 10%-15% of patients. Stroke was also observed more frequently in TV patients, and was reported in 3%-10% of cases. Efficacy of TAVI was reported to be good: improvement of NYHA functional class, and improved valvular function were observed in the majority of included patients. Reported 6-months survival rates were based on unpublished data, and mortality ranged from 10%-21.7% in TV and 26.1%-45% in TA series. Long-term data (≥ 1-year follow-up), and data on QoL were not reported. None of the included HTA reports provided a full economic analysis. A market price of TAVI devices of 2000€ and an annual number of eligible Belgian patients of 135-290 were estimated.

Conclusions

A reimbursement was not recommended because of patient safety concerns, and a poorly defined target population. If RCT data provided evidence on clinical safety and efficacy, the supplemental cost-effectiveness and budget impact analyses deferred in this report would need to be conducted. Until then, an uncontrolled diffusion of the TAVI technique patients should only be subjected to TAVI within the boundaries of an RCT.

Summary of earlier systematic reviews/ HTAs captured in the review of the Belgian KCE HTA

In addition to the "rapid HTA" of the Belgian KCE (van Brabandt, H. and Neyt, M. 2008), three further systematic reviews/ HTAs on TAVI have been published in 2008 by health technology institutes from UK, France and Austria (National Institute for Health and Clinical Excellence (NICE) 2008, Blanchard, S. 2008, Wild, C. et al. 2008). As illustrated in Table 13, the case series included for information synthesis in these reviews are highly consistent with those from the rapid HTA of the Belgian KCE. Latter provides an extensive overview of methods, outcomes, and ensuing guidance of the NICE, HAS, and LBI systematic reviews. Therefore, this work only summarized the key results in Table 14 and resulting recommendations for each of these earlier reviews below in the text.

In summary, all systematic reviews/ HTAs published in 2008 which were captured in the work of van Brabandt, H. and Neyt, M. 2008 concluded from observational series of high-risk elderly patients that short-term efficacy of TAVI procedures was promising. However, limitations of published series, such as small patient populations, missing long-term follow-up or QoL effects, impeded reliable full-scale HTA reports, including economic evaluations. All authors emphasized the requirement for re-assessments as soon as evidence from the PARTNER U.S. RCT (Placement of

AoRTic traNscathetER Valve trial in the U.S. [PARTNER U.S.]; ClinicalTrials.gov identifier NCT00530894) would be available. In the light of the first published results from the PARTNER U.S. RCT in September 2010 (Leon, M. B. et al. 2010), the recommendations summarized below will now require a re-assessment and can thus, only be regarded as provisional.

National Institute for Health and Clinical Excellence (NICE) 2008, NICE UK

The "Interventional procedure overview of transcatheter aortic valve implantation for aortic stenosis" published by the NICE was based on a rapid literature review and specialist opinion and, explicitly, should not be regarded as a definitive HTA of the procedure. The authors remarked that current evidence on TAVI for AS was limited to small numbers of patients who were considered to be at high risk for conventional surgery. It showed good short-term efficacy, but there was little evidence on long-term outcomes. There was a potential for serious complications, but the patients on whom this procedure had been used had a poor prognosis without treatment and were at high risk if treated by open heart surgery. The authors encouraged clinicians to ensure that patients understand the uncertainties about the procedure. They recommended that TAVI should be performed only by clinicians and interventional cardiology teams with special training. Units undertaking this procedure should have both cardiac and vascular surgical support for emergency treatment of complications. Details about all patients undergoing TAVI should be entered into a central database.

Blanchard, S. 2008, HAS France

The French review recommended a conditional reimbursement of TAVI for patients that are considered at high risk of conventional surgery or deemed inoperable. They estimated that without an expansion of the indication, in minimum 600 patients per year in France would be eligible for TAVI. The following prerequisites were formulated: reimbursement limited in time and limited to specialized cardiac centers, and all patients to be included in a mandatory registry. A re-assessment of reimbursement is intended when more data on clinical effectiveness will become available.

Wild, C. et al. 2008, LBI Austria

This systematic review concluded that current evidence from small patient series with short follow-up is low and would not allow a reliable assessment of the safety and the clinical effectiveness of TAVI. The number of annual eligible patients in Upper Austria, and the costs for a TAVI intervention were estimated in a range of 30 patients and 2400€ per intervention, respectively. The authors

objected the reimbursement of TAVI procedures, and recommended to use TAVI only as a palliative procedure until reliable clinical data is available.

3.2 Systematic review on medical therapy of AS

3.2.1 Results of literature search

As illustrated in Figure 7, the original literature search identified 189 citations of which 169 citations were excluded based on a systematic screening of titles and abstracts (mostly editorials, commentaries, and non-English and non-German publications). Together with 11 potentially relevant publications identified through supplementary EMBASE and MEDLINE database alerts, and handsearching the reference lists of key papers, 31 reports underwent a detailed full-text screening - leaving 11 reports to be included in the literature synthesis [14, 15].

3.2.2 Description and information synthesis

3.2.2.1 Study quality

The quality of all included primary publications was assessed along the criteria of the checklist #2a of the GSWG. Each of the 11 primary publications included in the information synthesis was evaluated. The evaluation results for each publication are provided in the Appendix 7.7.2. The quality assessment below was structured according to the sections of the checklist: patient selection, assignment and participation, intervention/exposure, study administration, outcome measurement, drop-outs, statistical analysis, and discussion.

Due to the retrospective nature of most included studies, the inclusion and exclusion criteria could not be defined and established before the intervention. The diagnostic criteria for symptomatic severe AS were described and a reliable and valid assessment of disease status was ensured by echocardiographic and Doppler hemodynamic assessment extracted from clinical records. The recruitment period and mean follow-up were provided in most studies.

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[14] Three comparative cohort studies were also included for the review on TAVI (chapter 3.1.1) (Rajani, R. et al. 2010, Kapadia, S. R. et al. 2009, Otten, A. M. et al. 2008).

[15] The complete list of relevant publications included in the review on medical therapy is provided in the bibliography section 6.2.3.

None of the studies was randomized or blinded, but most attempted to match exposed patients to control groups with comparable demographic and clinical characteristics. A comparable and valid assessment of the intervention of the treatment cohorts was generally provided in all studies. Details on co-therapies of control groups were not provided. In all studies, outcome measurement was usually conducted centrally and based on retrospective reviews of clinical records. Little or no details on the completeness of follow-up were provided. All studies reported primary and secondary endpoints. Testing methods to compare metric and categorical variables between groups and p-values of the corresponding hypothesis tests were described. Several studies provided CI or standard errors to assess the precision of effect estimates.

The study results were analyzed in the context of previous evidence, and they usually addressed the study hypothesis. Most publications commented on the methodological limitations of the non-randomized study design and the external validity of their results. Discussion of statistical uncertainties was mostly missing.

3.2.2.2 Study characteristics

For the following information synthesis, 11 relevant primary publications on medical therapy of AS were identified (bibliography section 6.2.3). The key characteristics of each study are summarized in Table 15. All included publications were observational comparative cohort studies with control groups of medically treated patients that did not receive an intervention – either they refused or were not offered aortic valve implantation. The treatment groups of the studies consisted of patients that underwent either TAVI (Rajani, R. et al. 2010, Kapadia, S. R. et al. 2009, Otten, A. M. et al. 2008), surgical AVR (Bakaeen, F. G. et al. 2010, Kapadia, S. R. et al. 2009, Bach, D. S. et al. 2009, van Geldorp, M. W. A. et al. 2009, Kojodjojo, P. et al. 2008, Otten, A. M. et al. 2008, Charlson, E. et al. 2006, Varadarajan, P. et al. 2006b, Iung, B. et al. 2005), or palliative BAV (Kapadia, S. R. et al. 2009, O'Keefe, J. H., JR et al. 1987, Otten, A. M. et al. 2008). Eight studies were based on retrospective data reviews (Bakaeen, F. G. et al. 2010, Rajani, R. et al. 2010, Bach, D. S. et al. 2009, van Geldorp, M. W. A. et al. 2009, Kojodjojo, P. et al. 2008, Charlson, E. et al. 2006, Varadarajan, P. et al. 2006b, O'Keefe, J. H., JR et al. 1987) and three collected data prospectively (Kapadia, S. R. et al. 2009, Otten, A. M. et al. 2008, Iung, B. et al. 2005). The studies' data collection periods ranged from January 1978 until June 2009, and, except for one (O'Keefe, J. H., JR et al. 1987), they were published between 2005 and 2010. The studies were conducted in centers from Western Europe (UK: Rajani, R. et al. 2010, Kojodjojo, P. et al. 2008, Netherlands: Kapadia, S. R. et al. 2009, Otten, A. M. et al. 2008, and France: Iung, B. et al. 2005), and North American centers (Bakaeen, F. G. et al. 2010, Bach, D. S. et al. 2009, Kapadia, S. R. et al. 2009, Charlson, E. et al. 2006, Varadarajan, P. et al. 2006b, O'Keefe, J. H., JR et al. 1987). Three studies included < 50 patients (range 16-47) (Rajani, R. et al. 2010, Kapadia, S. R. et al. 2009, Otten, A. M. et al. 2008), and

eight studies >50 patients (range 50-277) (Bakaeen, F. G. et al. 2010, Bach, D. S. et al. 2009, van Geldorp, M. W. A. et al. 2009, Kojodjojo, P. et al. 2008, Charlson, E. et al. 2006, Varadarajan, P. et al. 2006b, Iung, B. et al. 2005, O'Keefe, J. H., JR et al. 1987). The total number of medically treated patients captured by this review was n=946.

In 7 studies (n=797), the control group consisted exclusively of patients treated by surgical AVR (Bakaeen, F. G. et al. 2010, Bach, D. S. et al. 2009, van Geldorp, M. W. A. et al. 2009, Kojodjojo, P. et al. 2008, Charlson, E. et al. 2006, Varadarajan, P. et al. 2006b, Iung, B. et al. 2005). Two studies (n=52) analyzed the treatment assignment for high-risk, elderly patients, and compared the outcomes in medically treated patients with those of all available interventional treatment forms for AS, i.e. TAVI, surgical AVR, and BAV (Kapadia, S. R. et al. 2009, Otten, A. M. et al. 2008). One recent study (n=47) investigated the survival benefit of TAVI patients against those managed medically – either with or without concomitant BAV (Rajani, R. et al. 2010). In one case series, outcomes of medical therapy for 50 BAV candidates that refused the intervention were described (O'Keefe, J. H., JR et al. 1987). In 1987, when this series was published, BAV was the only treatment option for inoperable patients with severe AS that would nowadays be eligible for TAVI. The clinical follow-up period was specified in eight studies and was mean 19.6 months (range 6–30 months)/ 15.5±13.7 months[16] (Rajani, R. et al. 2010, Bach, D. S. et al. 2009, Kapadia, S. R. et al. 2009, van Geldorp, M. W. A. et al. 2009, Kojodjojo, P. et al. 2008, Otten, A. M. et al. 2008, Varadarajan, P. et al. 2006b, O'Keefe, J. H., JR et al. 1987). In minimum, the included studies reported 1-year follow-up data.

3.2.2.3 Patient characteristics

Details on pre-procedural demographic, clinical and echocardiographic patient characteristics are provided in Table 16. The age of included patients was mean 79.9 years (range 73.3-86.2 years)/ 79.4±10.1 years (p-value<0.0001).[17] On average, 47% (range 29.3%-72%) of the included patients were males (p-value=0.385). Where a baseline was provided, the patients consistently presented with characteristics of severe AS as assessed by echocardiographic measurement of the degree of AS.

Three studies (Kapadia, S. R. et al. 2009, Rajani, R. et al. 2010, van Geldorp, M. W. A. et al. 2009) reported the functional status assessed by NYHA class. The mean NYHA class at baseline was 2.7

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[16] The difference between means for all included studies compared to studies reporting the SD was significant for the follow-up duration (p-value<0.0001).

[17] In this part of the review, levels of significance (p-values) indicate the comparison between medically managed patients and TAVI patients.

(range 2.4–3.5). The detailed distribution of patients per class was only provided for 83 patients from two studies (Rajani, R. et al. 2010, Kapadia, S. R. et al. 2009): 10% (n=8) of these patients were in class I, 17% (n=14) in class II, 51% (n=42) in class III, and 23% (n=19) in class IV (p-value<0.0001).

The pre-procedural estimation of operative risk resulted in a mean logistic EuroSCORE of 13.5% (range 9%-25.4%)/ 13.6%±11.3% (p-value<0.0001) as reported by six studies (Bakaeen, F. G. et al. 2010, Rajani, R. et al. 2010, Kapadia, S. R. et al. 2009, van Geldorp, M. W. A. et al. 2009, Kodjodjojo, P. et al. 2008, Otten, A. M. et al. 2008). In addition, Kapadia, S. R. et al. 2009 reported a mean STS score of 12.6%±9.2% and Bach, D. S. et al. 2009 a median STS score of 3.8% (interquartile range 2.1%–7.3%).

3.2.2.4 Primary outcome measures (safety)

None of the included studies reported data on the incidence of complications. The mean 1-year survival rate of medically treated patients was 62.4% (range 40%-84.8%)/ 69.8%±10.35% (95%-CI: 59.3%-65.5%) (p-value<0.0001). As illustrated in Figure 8, the reported survival rates were consistent with two exceptions: a survival rate of 40% was reported in a small cohort of 16 high-risk patients who refused TAVI (Otten, A. M. et al. 2008), and a favorable 84.8% survival rate occurred in a cohort of 72 patients that were denied surgical AVR (Iung, B. et al. 2005). The authors of latter argued that the inclusion of non-hospitalized potentially “healthier” patients from outpatient clinics might have accounted for this exceptional outcome. None of the studies provided details on causes of deaths to assess whether they were caused by cardiac or other causes.

3.2.2.5 Secondary outcome measures (efficacy)

None of the included studies provided any follow-up data on secondary outcome measures for medically treated patients.

4 Discussion

4.1 Research context

With the population aging, AS is becoming a more prevalent public health issue. As soon as symptoms develop, medical therapy is unlikely to modify the dismal course of the disease. Median survival after the onset of heart failure, syncope, and angina is 11 months, 27 months, and 45 months, respectively (Horstkotte, D. and Loogen, F. 1988). Valve replacement is therefore indicated once patients develop symptoms (Bonow, R. O. et al. 2006, Vahanian, A. et al. 2007). Surgical AVR remains the therapeutic gold standard, but open heart surgery involves significant risks, in particular for elderly and frail patients. For this reason, many elderly patients are denied surgery. In the past, these patients could only be managed conservatively with medical therapy or palliative BAV. With TAVI, an additional, less invasive option has emerged for these "inoperable" patients. Since the first TAVI was performed by Cribier, A. et al. in 2002, many thousands of TAVI devices have been implanted in high-risk patients worldwide.

Until the data freeze for this work on April 30, 2010, no randomized trials have compared TAVI with conservative medical treatment yet, and the clinical experience with TAVI is deducted mainly by short-term results. However, the finalization of this work in September 2010 coincided with the publication of the results from the first PARTNER U.S. RCT study which compared TV-TAVI versus surgical AVR in patients at high surgical risk and TV-TAVI versus medical therapy or BAV in patients who are denied surgery due to extreme surgical risk (Leon M. B. et al. 2010). Therefore, the RCT data could not be considered as part of the formal information synthesis. Nonetheless, for informational purposes, the results reported by Leon and his colleagues are discussed below against the background of our findings.

Few systematic reviews on the safety and efficacy of TAVI procedures have been conducted, but none of them have focused on 1-year follow-up data nor have earlier reviews performed a comparison with recent evidence on medical therapy. To complement previously published reviews on TAVI, the present work followed the formal methodology recommended by the toolkit of the GSWG (German Scientific Working Group for Health Care 2000) to address the following objectives: firstly, in view of available observational series, to objectively assess safety and efficacy of TAVI up to 1-year follow-up, and secondly, to substantiate 1-year survival benefits after TAVI versus 1-year survival of medically treated patients with a comparable clinical profile.

4.2 Safety of TAVI and comparison with medical therapy of AS

Concerning the safety of TAVI, the main finding resulting from the two systematic reviews is that high-risk, elderly patients undergoing TAVI have a better outcome in terms of absolute **1-year survival** compared with their medically treated counterparts. This finding is important as it provides an indication of the potential survival benefit of TAVI of up to +16.8% for a group of patients in whom there was previously no effective treatment option. The magnitude of this result corresponds well to the 20% survival benefit reported by the PARTNER U.S. trial for TV-TAVI procedures (Leon M. B. et al. 2010). Yet it remains unclear, whether patients actually gain prolonged survival, taking into account the risk of procedure-related mortality as well as from underlying comorbidities. As illustrated by Figure 9, the mean 1-year survival rate after TAVI is 75.9% (95%-CI: 73.3%-78.4%) versus 62.4% (95%-CI: 59.3%-65.5%) with medical therapy. Nonetheless, the lower boundary of the CI for the TA subgroup survival rate comes close to the upper boundary of the CI of medically treated patients. This can at least partly be explained by a high procedural mortality and the very poor general condition of these patients with inherent mortality risk, questioning the appropriateness of AS intervention in this population.

Consistent with previous secondary publications (Yan, T. D. et al. 2010, van Brabandt, H. and Neyt, M. 2009), the collated data on short-term safety presented in this review demonstrates that TAVI is feasible with procedural success rates ranging from 86%–100% (TV-TAVI 85.7%-100% versus TA-TAVI 95.8%-100%), yet it remains a high-risk procedure. In recent series included in this review, 30-day mortality rates, which most likely reflect procedure-related mortality, ranged from 5.3%-23%. Apart from mortality related to the procedure, safety issues of TAVI also include **major non-fatal complications**. Major vascular complications occurred on average in 3.1% of all patients included in this review, however, when the TV access route was chosen, the incidence was up to 33.3% (Table 9). Mean incidence of stroke was 4.4% in TV-TAVI and 1.2% in TA-TAVI patients. Atrioventricular block requiring PPM implantation occurred in 9.7% of all TAVI patients, with a higher incidence of 12% (range 5%-34.2%) in TV-TAVI patients compared to 6.9% in TA-TAVI patients.

Previous systematic reviews concluded that safety outcomes were likely to improve with accumulating numbers of patients, increasing technical experience, better patient selection and technology (Yan, T. D. et al. 2010, van Brabandt, H. and Neyt, M. 2008). Himbert, D. et al. 2009 demonstrated procedural success from 84% in the first 25 patients to 98% in the subsequent 50 patients and an associated decrease in 30-day mortality from 24% to 4%. Nevertheless, in most recent series published in 2010, where improving technical skills and technology performance might have attained the flat end on the **learning curve**, procedure-related 30-day mortality rates remain in the range of 10% even at very experienced centers (Rodés-Cabau, J. et al. 2010, Walther, T. et al. 2010).

These procedure-related mortality rates should be compared with the operative risk patients are facing in conventional **surgical AVR**. However, reliable surgical AVR mortality data is not available for presumed target TAVI patients. In a study on patients over ≥75 years with severe AS, 5% died during the post-operative period (Iung, B. et al. 2005). In a literature review on results of AVR in octogenarians, operative mortality of isolated AVR varied between 4.3% and 10.3% (Iung, B. 2008). In the series of Kapadia, S. R. et al. 2009, of 92 patients referred for TAVI, approximately 20% were found to be surgical candidates and underwent surgical AVR without operative deaths (only one death at 2 months). However, compared to TAVI patients, surgical AVR patients were younger (78±7 versus 81±6 years) and had a lower logistic EuroSCORE (18.3%±8.4% versus 27.8%±18.8%). Other observations indicated that patients with AS believed inoperable by one group of surgeons were considered operable by another (Svensson, L. G. et al. 2008). About half of the patients that were referred as potential TAVI candidates were further treated medically, 20% were treated with a TAVI with a mortality of 9%, 18% were treated surgically with no mortality at all and 11% were treated by means of BAV. In the series of Descoutures, F. et al. 2008, of 66 elderly patients referred for treatment of severe AS, 39 had a calculated operative risk of >20%. Twelve patients were treated with TAVI while from the remaining 27 patients, four were redirected towards AVR. All of them recovered without adverse events.

Due to patient safety concerns described above, TAVI is restricted to elderly patients who are considered at very high risk for surgical AVR (Figulla, H. R. et al. 2009). Accordingly, all included studies recruited patients at **"high surgical risk" or "nonsurgical candidates**". However, the surgical risk and operability status are not uniformly defined concepts, but are mostly based on a combination of clinical assessment and information from operative risk estimation scores. Most included studies, estimated the operative mortality according to the logistic EuroSCORE which has been criticized to overestimate the risk, particularly in high-risk patients (Kalavrouziotis, D. et al. 2009, Osswald, B. R. et al. 2009, Dewey, T. M. et al. 2008, Brown, M. L. et al. 2008). Rajani, R. et al. 2010 observed that patients in the medically treated group who had been rejected for TAVI had a lower logistic EuroSCORE than those patients who underwent TAVI. This could be interpreted as a sign that different criteria are used to identify eligible TAVI patients (e.g. aortic annulus size or iliac anatomy). If this assumption proves true, criteria for patient selection should be adapted accordingly.

As illustrated by Figure 10, the estimated mortality rates from literature are sharply contrasted by the observed mortality rates which are significantly lower, irrespective of the chosen interventional approach. In clinical practice, the logistic EuroSCORE is divided by two to approximate the operative risk in high-risk patients more accurately (Figulla, H. R. et al. 2009) (dotted line in Figure 10). It should be noted that a range of significant comorbidities that are often encountered in patients

eligible for TAVI are not included in the EuroSCORE scoring method (Rodés-Cabau, J. et al. 2010, Al-Attar, N. et al. 2009). From the online calculation tool for the logistic EuroSCORE it can inferred which conditions are not taken into account: heart failure, diabetes mellitus, presence and degree of mitral regurgitation, arrhythmias, previous stroke, and renal failure.[18]

In a study of 1,177 patients that underwent surgical AVR, the estimated 30-day mortality for the highest risk patients was mean 23.6% based on the logistic EuroSCORE. This was sharply contrasted by an actual mortality of 5.7% (Brown, M. L. et al. 2008). Whereas the mean logistic EuroSCORE of patients undergoing surgical AVR from the study of Brown and colleagues differed only slightly from the mean logistic EuroSCORE calculated in this review for TAVI patients (23.6% versus 27.8%), 30-day mortality was substantially lower among surgical AVR patients than for TAVI patients (5.7% versus 11.4%). This result might suggest that procedure-related mortality in high-risk patients could be lower when they are treated by surgical AVR than if treated by TAVI. Only data from an RCT would clarify this.

The STS score which has been applied in eight included studies, seems to predict the operative risk of TAVI patients more precisely (Figure 11). However, particularly for TA patient populations with a high actual 30-day mortality, it seems to underestimate the operative risk. Several included studies (Rodés-Cabau, J. et al. 2010, Webb, J. G. et al. 2009, Himbert, D. et al. 2009) consistently observed that the STS score was unable to identify those patients who would die within 30 days after TAVI.

From the above observations it is clear that one should be cautious to predict operative mortality in elderly high-risk patients based on risk scores obtained from historic observational data. Overestimation of risk can lead to denying surgery in patients that may be suitable candidates. In fact, the vast majority of patients who underwent TAVI would not have been operated on in the past, and therefore, new predictive risk score models including specific variables for this particular subset of patients are required in the future.

4.3 Efficacy of TAVI

In respect to short- to mid-term efficacy, post-TAVI improvements of echocardiographic measurements (AVA, transaortic mean gradient, and LVEF) and NYHA functional class seem encouraging, irrespective of the chosen access route. However, long- term outcomes, particularly in respect to device durability, are not available yet. At present this might be a less critical issue, given the lim-

[18] http://www.euroscore.org/calc.html (accessed August 14, 2010).

ited life expectancy of eligible TAVI patients, but it might become important in the future, if the indication was expanded to broader patient populations.

Based on the currently available study results described in chapter 3.1.2.5, the improvements of echocardiographic measurements after TAVI are stable at 30-day follow-up and sustained until 1-year follow-up without significant functional deterioration. It is however not clear how this improvement can be translated into an improved overall QoL of an elderly and generally frail patient population with severe co-morbidities. As of today, no QoL data at 1-year follow-up after TAVI has been published.

A comparison of the evidence on efficacy of TAVI and medical therapy was impeded because none of the included studies on medical therapy reported follow-up results on the efficacy of medical therapy.

Neither preceding primary nor secondary publications included in this review provided an economic evaluation to assess the cost-effectiveness of TAVI.

4.4 Limitations of this work

The limitations of the results are obvious and should be addressed in future work. Firstly, the findings are based on merely observational studies. Until the data freeze for this work on April 30, 2010, no RCTs have compared TAVI with surgical AVR, medical treatment or BAV. The publication of first results from the randomized PARTNER U.S. trial did not occur before September 22, 2010 (Leon M. B. et al. 2010) and thus, could not be considered as part of the formal information synthesis. Apart from the lack of randomization, major shortcomings of the published studies which are summarized in this review, are the lack of long-term data, selected and small patient groups, and in some cases the involvement of manufacturers. The above discussed inconsistent patient selection criteria complicate the interpretation of outcomes from included studies. In addition, the following significant differences in baseline characteristics – on the one hand, TV-TAVI versus TA-TAVI patients and, on the other hand, TAVI versus medically treated patients – should be pointed out which might distort the reported results. Comparing TV-TAVI and TA-TAVI patients, the pre-procedural transaortic mean gradient reported by all included studies was mean 46.6±15.6 mmHg with significant difference between TV and TA patients (47.9±17.7 mmHg versus 44.7±16.2 mmHg) (p-value=0.02). In addition, 51% of TV patients were male compared with only 36% in the TA subgroup (p-value<0.0001). For the comparison of TAVI and medically treated patients, included studies reported a significantly higher estimated operative risk score as assessed by the logistic EuroSCORE for TAVI patients compared to medically treated patients (27.8% versus 13.5%) (p-

value<0.0001). In addition, the pre-procedural mean AVA of TAVI patients was significantly smaller than the AVA of medically treated patients (0.63±0.39cm² versus 0.68±0.21cm²) (p-value<0.0001). Reported differences in other baseline measures were not significant.

As we were unable to verify to which extent authors had potentially published duplicate trials with accumulating numbers of patients or increased lengths of follow-up, all publications meeting our inclusion criteria were considered for critical appraisal.[19]

4.5 Outlook and Conclusion

Applying a formal methodology used in evidence-based health economics, this review aimed to objectively evaluate the safety and efficacy of TAVI, although data from RCT and on long-term outcomes were still missing. Based on available data, in patients with inoperable AS, TAVI promises improved 1-year survival when compared with medical treatment. To date, no medical therapy is effective for patients with symptomatic severe AS. However, due to patient selection bias, the results should be interpreted with caution.

Before the publication of the first RCT data in September 2010 which coincided with the finalization of this work, our results represented the best available data set. As the TAVI survival benefit elucidated from the systematic literature review is in good congruence with the RCT data, we conclude that this methodology represents a powerful tool to confirm - or even anticipate - RCT outcomes.

Going forward, future research should address whether the current evidence on safety and efficacy of TAVI can be translated into an improved long-term QoL for patients and whether TAVI interventions are effective from an economic point of view.

[19] Namely three publications from Canada (Rodés-Cabau, J. et al. 2010, Webb, J. G. et al. 2009, Ye, J. et al. 2009) and two publications from Paris, France (Al-Attar, N. et al. 2009, Himbert, D. et al. 2009) with overlapping patient enrollment periods bear potential for redundant patient populations.

5 Abstract

Objectives: Transcatheter aortic valve implantation (TAVI) promises effective treatment for high-risk elderly patients with symptomatic severe aortic stenosis (AS). However, the adoption of TAVI must be justified and guarantee long-term performance. Systematic reviews are a core methodology in evidence-based health economics for judging medical effectiveness. In this work, the methodology was applied to provide objective evidence on the efficacy and safety of TAVI at 1-year follow-up and to assess whether TAVI confers a survival benefit compared to medical therapy.

Methods: In accordance with the toolkit of the "German Scientific Working Group Technology Assessment for Health Care" (GSWG), two independent systematic literature reviews on the safety and efficacy of TAVI procedures and medical therapy of AS were conducted in major bibliographic databases. Preestablished inclusion criteria were defined that were consistent for both reviews. For each review, an initial screening of identified articles regarding titles and abstracts was followed by a full-text screening. Data from eligible articles was extracted and evaluated according to GSWG checklists followed by a qualitative synthesis of information.

Results: The systematic literature search identified 12 primary publications (derived from 1,849 citations) for TAVI (number of patients [n]=1,049) and 11 publications (derived from 189 citations) for medical therapy of AS (n=946) that fulfilled the inclusion criteria.

The mean overall procedural success rate for included TAVI interventions was 93.3%. The mean combined procedural, post-procedural, and cumulative in-hospital/30-day mortality was 11.4% (n=116; range 5.3%–23%). For transvascular (TV) TAVI procedures, the mean inhospital/30-day mortality was significantly lower than for transapical (TA) TAVI procedures (9.5% versus 14%) (p-value=0.03). Major vascular complications occurred on average in 3.1% of all patients included in this review, particularly when the TV access route was chosen the incidence was up to 33.3%. Mean incidence of stroke was 4.4%. One year after TAVI, the mean overall survival rate was 75.9% (range 64.1%–87%) compared with 62.4% (range 40%–84.8%) for medically treated patients (p-value<0.0001). One-year survival after TAVI for patients treated with TV procedures was significantly higher than after TA procedures (79.2% versus 73.6%) (p-value=0.041). At 1-year follow-up, the improved valvular function remained stable, and there was a trend towards an improved ventricular function.

Conclusion: Based on the best available data, in patients with symptomatic severe AS, TAVI demonstrates an improved 1-year survival compared with medical treatment. The survival benefit of TV-TAVI over medical therapy elucidated from this systematic literature review is +16.8% and therefore, in good congruence with the recently published results from the randomized PARTNER U.S. trial (+20%).

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66. van Brabandt, H., Neyt, M. (2009): Safety of percutaneous aortic valve insertion. A systematic review. BMC Cardiovasc Disord. 9, 45–51.

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68. Varadarajan, P., Kapoor, N., Bansal, R. C., Pai, R. G. (2006b): Survival in elderly patients with severe aortic stenosis is dramatically improved by aortic valve replacement: Results from a cohort of 277 patients aged > or = 80 years. Eur J Cardiothorac Surg. 30, 722–727.

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73. Webb, J. G., Altwegg, L., Boone, R. H., Cheung, A., Ye, J., Lichtenstein, S. V., Lee, M., Masson, J.-B., Thompson, C. R., Moss, R. R., Carere, R. G., Munt, B., Nietlispach, F., Humphries, K. (2009): Transcatheter aortic valve implantation: impact on clinical and valve-related outcomes. Circulation. 119, 3009–3016.

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76. Wild, C. et al. (2008): Minimal-invasiver perkutaner Aortenklappenersatz. Systematischer Review. Decision Support Document 18. Online publication; http://eprints.hta.lbg.ac.at/766/1/DSD_18.pdf.

77. Yan, T. D., Cao, C., Martens-Nielsen, J., Padang, R., Ng, M., Vallely, M. P., Bannon, P. G. (2010): Transcatheter aortic valve implantation for high-risk patients with severe aortic stenosis: a systematic review. J Thorac Cardiovasc Surg. 139, 1519–1528.

78. Ye, J., Cheung, A., Lichtenstein, S. V., Pasupati, S., Carere, R. G., Thompson, C. R., Sinhal, A., Webb, J. G. (2007): Six-month outcome of transapical transcatheter aortic valve implantation in the initial seven patients. Eur J Cardiothorac Surg. 31, 16–21.

79. Ye, J., Cheung, A., Lichtenstein, S. V., Altwegg, L. A., Wong, D. R., Carere, R. G., Thompson, C. R., Moss, R. R., Munt, B., Pasupati, S., Boone, R. H., Masson, J.-B., Ali, A., Webb, J. G. (2009): Transapical transcatheter aortic valve implantation: 1-year outcome in 26 patients. J Thorac Cardiovasc Surg. 137, 167–173.

80. Ye, J., Cheung, A., Lichtenstein, S. V., Nietlispach, F., Albugami, S., Masson, J.-B., Thompson, C. R., Munt, B., Moss, R. R., Carere, R. G., Jamieson, W. R., Webb, J. G. (2010): Transapical transcatheter aortic valve implantation: follow-up to 3 years. J Thorac Cardiovasc Surg. 139, 1107-1113. really less invasive than minimally invasive aortic valve replacement? J Thorac Cardiovasc Surg. 138, 1067–1072.e1.

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82. Zierer, A., Wimmer-Greinecker, G., Martens, S., Moritz, A., Doss, M. (2009): Is transapical aortic valve implantation really less invasive than minimally invasive aortic valve replacement? J Thorac Cardiovasc Surg. 138, 1067–1072.

6.2 Publications included for information synthesis

6.2.1 Primary publications for TAVI review

1. Rodés-Cabau, J., Webb, J. G., Cheung, A., Ye, J., Dumont, E., Feindel, C. M., Osten, M., Natarajan, M. K., Velianou, J. L., Martucci, G., DeVarennes, B., Chisholm, R., Peterson, M. D., Lichtenstein, S. V., Nietlispach, F., Doyle, D., De Larochellière, R., Teoh, K. H., Chu, V., Dancea, A., Lachapelle, K., Cheema, A., Latter, D., Horlick, E. (2010): Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. J Am Coll Cardiol. 55, 1080–1090.

2. Rajani, R., Buxton, W., Haworth, P., Khawaja, M. Z., Sohal, M., Brum, R. L., Hutchinson, N., Belder de, A., Trivedi, U., Hildick-Smith, D. (2010): Prognostic benefit of transcatheter aortic valve implantation compared with medical therapy in patients with inoperable aortic stenosis. Catheter Cardiovasc Interv. 75, 1121–1126.

3. Walther, T., Schuler, G., Borger, M. A., Kempfert, J., Seeburger, J., Rückert, Y., Ender, J., Linke, A., Scholz, M., Falk, V., Mohr, F. W. (2010): Transapical aortic valve implantation in 100 consecutive patients: comparison to propensity-matched conventional aortic valve replacement. Eur Heart J. 31, 1398–1403.

4. Al-Attar, N., Himbert, D., Descoutures, F., Iung, B., Raffoul, R., Messika-Zeitoun, D., Brochet, E., Francis, F., Ibrahim, H., Vahanian, A., Nataf, P. (2009): Transcatheter aortic valve implantation: selection strategy is crucial for outcome. Ann Thorac Surg. 87, 1757-62; discussion 1762-3.

5. Himbert, D., Descoutures, F., Al-Attar, N., Iung, B., Ducrocq, G., Detaint, D., Brochet, E., Messika-Zeitoun, D., Francis, F., Ibrahim, H., Nataf, P., Vahanian, A. (2009): Results of transfemoral or transapical aortic valve implantation following a uniform assessment in high-risk patients with aortic stenosis. J Am Coll Cardiol. 54, 303–311.

6. Kapadia, S. R., Goel, S. S., Svensson, L. G., Roselli, E. E., Savage, R. M., Wallace, L., Sola, S., Schoenhagen, P., Shishehbor, M. H., Christofferson, R., Halley, C., Rodriguez, L. L., Stewart, W. J., Kalahasti, V., Tuzcu, E. M. (2009): Characterization and outcome of patients with severe symptomatic aortic stenosis referred for percutaneous aortic valve replacement. J Thorac Cardiovasc Surg. 137, 1430–1435.

7. Thielmann, M., Wendt, D., Eggebrecht, H., Kahlert, P., Massoudy, P., Kamler, M., Erbel, R., Jakob, H., Sack, S. (2009): Transcatheter aortic valve implantation in patients with very high risk for conventional aortic valve replacement. Ann Thorac Surg. 88, 1468–1474.

8. Webb, J. G., Altwegg, L., Boone, R. H., Cheung, A., Ye, J., Lichtenstein, S. V., Lee, M., Masson, J.-B., Thompson, C. R., Moss, R. R., Carere, R. G., Munt, B., Nietlispach, F.,

Humphries, K. (2009): Transcatheter aortic valve implantation: impact on clinical and valve-related outcomes. Circulation. 119, 3009–3016.

9. Ye, J., Cheung, A., Lichtenstein, S. V., Altwegg, L. A., Wong, D. R., Carere, R. G., Thompson, C. R., Moss, R. R., Munt, B., Pasupati, S., Boone, R. H., Masson, J.-B., Ali, A., Webb, J. G. (2009): Transapical transcatheter aortic valve implantation: 1-year outcome in 26 patients. J Thorac Cardiovasc Surg. 137, 167–173.

10. Zierer, A., Wimmer-Greinecker, G., Martens, S., Moritz, A., Doss, M. (2009): Is transapical aortic valve implantation really less invasive than minimally invasive aortic valve replacement? J Thorac Cardiovasc Surg. 138, 1067–1072.

11. Grube, E., Buellesfeld, L., Mueller, R., Sauren, B., Zickmann, B., Nair, D., Beucher, H., Felderhoff, T., Iversen, S., Gerckens, U. (2008): Progress and current status of percutaneous aortic valve replacement: results of three device generations of the CoreValve Revalving System. Circ Cardiovasc Interv. 1, 167–175.

12. Otten, A. M., van Domburg, R. T., van Gameren, M., Kappetein, A. P., Takkenberg, J. J., Bogers, A. J., Serruys, P. W., De Jaegere, P. (2008): Population characteristics, treatment assignment and survival of patients with aortic stenosis referred for percutaneous valve replacement. EuroIntervention. 4, 250–255.

6.2.2 Secondary publications for TAVI review

1. Yan, T. D., Cao, C., Martens-Nielsen, J., Padang, R., Ng, M., Vallely, M. P., Bannon, P. G. (2010): Transcatheter aortic valve implantation for high-risk patients with severe aortic stenosis: a systematic review. J Thorac Cardiovasc Surg. 139, 1519–1528.

2. van Brabandt, H., Neyt, M. (2009): Safety of percutaneous aortic valve insertion. A systematic review. BMC Cardiovasc Disord. 9, 45–51.

3. Wild, C. and Geiger-Gritsch, S. (2009): Minimal-invasiver perkutaner Aortenklappenersatz. Systematischer Review - 1. Update 2009. Online publication; http://eprints.hta.lbg.ac.at/766/2/DSD_18_Update2009.pdf

4. Blanchard, S. (2008): Pose de bioprothèses valvulaires aortiques par voie artérielle fémorale et par abord transapical. Online publication; http://www.has-sante.fr/portail/upload/docs/application/pdf/document_avis_valves_2008.pdf

5. National Institute for Health and Clinical Excellence (NICE) (2008): Interventional Procedure Overview: transcatheter aortic valve implantation for aortic stenosis. Online publication; http://www.nice.org.uk/nicemedia/live/11914/39663/39663.pdf

6. van Brabandt, H. and Neyt, M. (2008): Percutaneous heart valve implantation in congenital and degenerative valve disease. A rapid health technology assessment. KCE reports 95C. Online publication; http://www.kce.fgov.be/index_en.aspx?SGREF=5212&CREF=12220

7. Wild, C. et al. (2008): Minimal-invasiver perkutaner Aortenklappenersatz. Systematischer Review. Decision Support Document 18. Online publication; http://eprints.hta.lbg.ac.at/766/1/DSD_18.pdf

6.2.3 Primary publications for review on medical therapy of AS

1. Bakaeen, F. G., Chu, D., Ratcliffe, M., Gopaldas, R. R., Blaustein, A. S., Venkat, R., Huh, J., LeMaire, S. A., Coselli, J. S., Carabello, B. A. (2010): Severe aortic stenosis in a veteran population: treatment considerations and survival. Ann Thorac Surg. 89, 453–458.

2. Rajani, R., Buxton, W., Haworth, P., Khawaja, M. Z., Sohal, M., Brum, R. L., Hutchinson, N., Belder de, A., Trivedi, U., Hildick-Smith, D. (2010): Prognostic benefit of transcatheter aortic valve implantation compared with medical therapy in patients with inoperable aortic stenosis. Catheter Cardiovasc Interv. 75, 1121–1126.

3. Bach, D. S., Siao, D., Girard, S. E., Duvernoy, C., McCallister, B. D., Gualano, S. K. (2009): Evaluation of patients with severe symptomatic aortic stenosis who do not undergo aortic valve replacement: The potential role of subjectively overestimated operative risk. Circ Cardiovasc Qual Outcomes. 2, 533–539.

4. Kapadia, S. R., Goel, S. S., Svensson, L. G., Roselli, E. E., Savage, R. M., Wallace, L., Sola, S., Schoenhagen, P., Shishehbor, M. H., Christofferson, R., Halley, C., Rodriguez, L. L., Stewart, W. J., Kalahasti, V., Tuzcu, E. M. (2009): Characterization and outcome of patients with severe symptomatic aortic stenosis referred for percutaneous aortic valve replacement. J Thorac Cardiovasc Surg. 137, 1430–1435.

5. van Geldorp, M. W., van Gameren, M., Kappetein, A. P., Arabkhani, B., De Groot-de Laat, L. E., Takkenberg, J. J., Bogers, A. J. (2009): Therapeutic decisions for patients with symptomatic severe aortic stenosis: room for improvement? Eur J Cardiothorac Surg. 35, 953–957.

6. Kojodjojo, P., Gohil, N., Barker, D., Youssefi, P., Salukhe, T. V., Choong, A., Koa-Wing, M., Bayliss, J., Hackett, D. R., Khan, M. A. (2008): Outcomes of elderly patients aged 80 and over with symptomatic, severe aortic stenosis: impact of patient's choice of refusing aortic valve replacement on survival. QJM. 101, 567–573.

7. Otten, A. M., van Domburg, R. T., van Gameren, M., Kappetein, A. P., Takkenberg, J. J., Bogers, A. J., Serruys, P. W., De Jaegere, P. (2008): Population characteristics, treatment assignment and survival of patients with aortic stenosis referred for percutaneous valve replacement. EuroIntervention. 4, 250–255.

8. Charlson, E., Legedza, A. T., Hamel, M. B. (2006): Decision-making and outcomes in severe symptomatic aortic stenosis. J Heart Valve Dis. 15, 312–321.

9. Varadarajan, P., Kapoor, N., Bansal, R. C., Pai, R. G. (2006b): Survival in elderly patients with severe aortic stenosis is dramatically improved by aortic valve replacement: Results from a cohort of 277 patients aged > or = 80 years. Eur J Cardiothorac Surg. 30, 722–727.

10. Iung, B., Cachier, A., Baron, G., Messika-Zeitoun, D., Delahaye, F., Tornos, P., Gohlke-Bärwolf, C., Boersma, E., Ravaud, P., Vahanian, A. (2005): Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? Eur Heart J. 26, 2714–2720.

11. O'Keefe, J. H., JR, Vlietstra, R. E., Bailey, K. R., Holmes, D. R. (1987): Natural history of candidates for balloon aortic valvuloplasty. Mayo Clin Proc. 62, 986–991.

6.3 Publications excluded from information synthesis after detailed evaluation

6.3.1 Publications excluded from TAVI review[21]

Table 1 Study characteristics and rationale for exclusion from TAVI review

#	Publication	Study characteristics					Rationale for exclusion
		N			Enrollment period	Study center	
		Total	TV	TA			
1	Ye, J., Cheung, A., Lichtenstein, S. V., Nietlispach, F., Albugami, S., Masson, J.-B., Thompson, C. R., Munt, B., Moss, R. R., Carere, R. G., Jamieson, W. R., Webb, J. G. (2010): Transapical transcatheter aortic valve implantation: follow-up to 3years. J Thorac Cardiovasc Surg. 139, 1107-1113.e1.	71		71	10/2005-02/2009	Vancouver, Canada	Published 05/2010 (after data freeze)
2	Aregger, F., Wenaweser, P., Hellige, G. J., Kadner, A., Carrel, T., Windecker, S., Frey, F. J. (2009): Risk of acute kidney injury in patients with severe aortic valve stenosis undergoing transcatheter valve replacement. Nephrol Dial Transplant. 24, 2175–2179.	58	46	12	08/2007-09/2008	Bern, Switzerland	Missing 1-year follow-up.
3	Ben-Dor, I., Goldstein, S. A., Waksman, R., Satler, L. F., Li, Y., Syed, A. I., Maluenda, G., Collins, S. D., Suddath, W. O., Torguson, R., Xue, Z., Kaneshige, K., Okubagzi, P., Wang, Z., Kent, K. M., Pichard, A. D. (2009): Effects of percutaneous aortic valve replacement on coronary blood flow assessed with transesophageal Doppler echocardiography in patients with severe aortic stenosis. Am J Cardiol. 104, 850–855.	17			NA	Washington DC, USA	Missing 1-year follow-up; Mortality not a relevant outcome measure.

[21] Publications excluded from information synthesis which are not cited in the main document are not included in the reference list (bibliography section 6.1).

4	Bleiziffer, S., Ruge, H., Mazzitelli, D., Schreiber, C., Hutter, A., Laborde, J. C., Bauernschmitt, R., Lange, R. (2009): Results of percutaneous and transapical transcatheter aortic valve implantation performed by a surgical team. Eur J Cardiothorac Surg. 35, 615–621.	137			06/2007-08/2008	Munich, Germany	Missing 1-year follow-up.
5	Bleiziffer, S., Ruge, H., Mazzitelli, D., Hutter, A., Opitz, A., Bauernschmitt, R., Lange, R. (2009b): Survival after transapical and transfemoral aortic valve implantation: talking about two different patient populations. J Thorac Cardiovasc Surg. 138, 1073–1080.	203	153	50	06/2007-02/2009	Munich, Germany	Missing 1-year follow-up.
6	Bleiziffer, S., Bauernschmitt, R., Ruge, H., Mazzitelli, D., Schreiber, C., Hutter, A., Opitz, A., Lange, R. (2009a): Transcatheter aortic valve implantation: surgeon's view. Herz. 34, 374–380.	234	175	56	06/2007-04/2009	Munich, Germany	Missing 1-year follow-up.
7	Clavel, M. A., Webb, J. G., Pibarot, P., Altwegg, L., Dumont, E., Thompson, C. R., De Larochellière, R., Doyle, D., Masson, J.-B., Bergeron, S., Bertrand, O. F., Rodés-Cabau, J. (2009): Comparison of the hemodynamic performance of percutaneous and surgical bioprostheses for the treatment of severe aortic stenosis. J Am Coll Cardiol. 53, 1883–1891.	50			NA	Québéc, Canada	Missing 1-year follow-up; Mortality not a relevant outcome measure.
8	Covello, R. D., Maj, G., Landoni, G., Maisano, F., Michev, I., Guarracino, F., Alfieri, O., Colombo, A., Zangrillo, A. (2009): Anesthetic management of percutaneous aortic valve implantation: focus on challenges encountered and proposed solutions. J Cardiothorac Vasc Anesth. 23, 280–285.	18	18		11/2007-05/2008	Milan, Italy	Missing 1-year follow-up.
9	De Robertis, F., Asgar, A., Davies, S., Delahunty, N., Kelleher, A., Trimlett, R., Mullen, M., Moat, N. (2009): The left axillary artery - a new approach for transcatheter aortic valve implantation. Eur J Cardiothorac Surg. 36, 807–812.	8	8		04/2007-08/2008	London, UK	Missing 1-year follow-up. n<10
10	Fassl, J., Walther, T., Groesdonk, H. V., Kempfert, J., Borger, M. A., Scholz, M., Mukherjee, C., Linke, A., Schuler, G., Mohr, F. W., Ender, J. (2009): Anesthesia management for transapical transcatheter aortic valve implantation: a case series. J Cardiothorac Vasc Anesth. 23, 286–291.	100		100	02/2006-01/2008	Leipzig, Germany	Missing 1-year follow-up; Mortality not a relevant outcome measure.

11	Gutierrez, M., Rodés-Cabau, J., Bagur, R., Doyle, D., De Larochellière, R., Bergeron, S., Lemieux, J., Villeneuve, J., Cote, M., Bertrand, O. F., Poirier, P., Clavel, M. A., Pibarot, P., Dumont, E. (2009): Electrocardiographic changes and clinical outcomes after transapical aortic valve implantation. Am Heart J. 158, 302–308.	33		33	04/2007-10/2008	Montreal, Canada	Missing 1-year follow-up.
12	Jilaihawi, H., Jeilan, M., Spyt, T., Chin, D., Logtens, E., Kovac, J. (2009b): Early regression of left ventricular wall thickness following percutaneous aortic valve replacement with the CoreValve bioprosthesis. J Invasive Cardiol. 21, 151–155.	15	15		01/2007-07/2007	Leicester, UK	Missing 1-year follow-up.
13	Jilaihawi, H., Chin, D., Vasa-Nicotera, M., Jeilan, M., Spyt, T., Ng, G. A., Bence, J., Logtens, E., Kovac, J. (2009a): Predictors for permanent pacemaker requirement after transcatheter aortic valve implantation with the CoreValve bioprosthesis. Am Heart J. 157, 860–866.	34	34		01/2007-03/2008	Leicester, UK	Missing 1-year follow-up.
14	Kahlert, P., Al-Rashid, F., Weber, M., Wendt, D., Heine, T., Kottenberg, E., Thielmann, M., Kuhl, H., Peters, J., Jakob, H. G., Sack, S., Erbel, R., Eggebrecht, H. (2009): Vascular access site complications after percutaneous transfemoral aortic valve implantation. Herz. 34, 398–408.	60	60		01/2006-NA	Essen, Germany	Missing 1-year follow-up.
15	Piazza, N., van Gameren, M., Jüni, P., Wenaweser, P., Carrel, T., Onuma, Y., Gahl, B., Hellige, G. J., Otten, A. M., Kappetein, A. P., Takkenberg, J. J., van Domburg, R. T., De Jaegere, P., Serruys, P. W., Windecker, S. (2009): A comparison of patient characteristics and 30-day mortality outcomes after transcatheter aortic valve implantation and surgical aortic valve replacement for the treatment of aortic stensis: a two-center study. EuroIntervention. 5, 580–588.	114	114		01/2006-12/2008	Rotterdam, Netherlands/ Bern, Switzerland	Missing 1-year follow-up.
16	Tamburino, C., Capodanno, D., Mule, M., Scarabelli, M., Cammalleri, V., Barbanti, M., Calafiore, A., Ussia, G. P. (2009): Procedural success and 30-day clinical outcomes after percutaneous aortic valve replacement using current third-generation self-expanding CoreValve prosthesis. J Invasive Cardiol. 21, 93–98.	30	30		01/2007-07/2008	Catania, Italy	Missing 1-year follow-up.

17	Ussia, G. P., Mule, M., Barbanti, M., Cammalleri, V., Scarabelli, M., Imme, S., Capodanno, D., Ciriminna, S., Tamburino, C. (2009): Quality of life assessment after percutaneous aortic valve implantation. Eur Heart J. 30, 1790–1796.	39	39		04/2007-08/2008	Catania, Italy	Missing 1-year follow-up.
18	Walther, T., Falk, V., Borger, M. A., Kempfert, J., Ender, J., Linke, A., Schuler, G., Mohr, F. W. (2009): Transapical aortic valve implantation in patients requiring redo surgery. Eur J Cardiothorac Surg. 36, 231-4; discussion 234-5.	25		25	02/2006-03/2008	Leipzig, Germany	Population inappropriate (redo patients with earlier surgical intervention)
19	Wendt, D., Eggebrecht, H., Kahlert, P., Heine, T., Kottenberg, E., Massoudy, P., Kamler, M., Peters, J., Erbel, R., Jakob, H., Thielmann, M. (2009): Experience and learning curve with transapical aortic valve implantation. Herz. 34, 388–397.	40		40	10/2007-05/2009	Essen, Germany	Missing 1-year follow-up.
20	Descoutures, F., Himbert, D., Lepage, L., Iung, B., Detaint, D., Tchetche, D., Brochet, E., Castier, Y., Depoix, J. P., Nataf, P., Vahanian, A. (2008): Contemporary surgical or percutaneous management of severe aortic stenosis in the elderly. Eur Heart J. 29, 1410–1417.	12	12		10/2006-04/2007	Paris, France	Missing 1-year follow-up.
21	Dewey, T. M., Brown, D. L., Das, T. S., Ryan, W. H., Fowler, J. E., Hoffman, S. D., Prince, S. L., Herbert, M. A., Culica, D., Mack, M. J. (2008): High-risk patients referred for transcatheter aortic valve implantation: management and outcomes. Ann Thorac Surg. 86, 1450-6; discussion 1456-7.	21			12/2005-12/2007	Dallas, TX, USA	Missing 1-year follow-up.
22	Piazza, N., Grube, E., Gerckens, U., den Heijer, P., Linke, A., Luha, O., Ramondo, A., Ussia, G. P., Wenaweser, P., Windecker, S., Laborde, J. C., De Jaegere, P., Serruys, P. W. (2008): Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 Fr) CoreValve Revalving System: results from the multicentre, expanded evaluation registry 1-year following CE mark approval. EuroIntervention. 4, 242–249.	646	646		04/2007-04/2008	Rotterdam, Netherlands	Missing 1-year follow-up.

23	Rodés-Cabau, J., Dumont, E., De Larochellière, R., Doyle, D., Lemieux, J., Bergeron, S., Clavel, M. A., Villeneuve, J., Raby, K., Bertrand, O. F., Pibarot, P. (2008): Feasibility and initial results of percutaneous aortic valve implantation including selection of the transfemoral or transapical approach in patients with severe aortic stenosis. Am J Cardiol. 102, 1240–1246.	22	11	11	04/2007-01/2008	Montreal, Canada	Missing 1-year follow-up.
24	Spargias, K., Manginas, A., Pavlides, G., Khoury, M., Stavridis, G., Rellia, P., Smirli, A., Thanopoulos, A., Balanika, M., Polymeros, S., Thomopoulou, S., Athanassopoulos, G., Karatasakis, G., Mastorakou, R., Lacoumenta, S., Michalis, A., Alivizatos, P., Cokkinos, D. (2008): Transcatheter aortic valve implantation: first Greek experience. Hellenic J Cardiol. 49, 397–407.	12		12	11/2007-02/2008	Athens, Greece	Missing 1-year follow-up.
25	Svensson, L. G., Dewey, T. M., Kapadia, S. R., Roselli, E. E., Stewart, A., Williams, M., Anderson, W. N., Brown, D. L., Leon, M. B., Lytle, B. W., Moses, J., Mack, M. J., Tuzcu, M. E., Smith, C. R. (2008): United States feasibility study of transcatheter insertion of a stented aortic valve by the left ventricular apex. Ann Thorac Surg. 86, 46-54; discussion 54-5.	40		40	12/2006-02/2008	Cleveland, OH, USA	Missing 1-year follow-up.
26	Walther, T., Falk, V., Kempfert, J., Borger, M. A., Fassl, J., Chu, M. W., Schuler, G., Mohr, F. W. (2008): Transapical minimally invasive aortic valve implantation; the initial 50 patients. Eur J Cardiothorac Surg. 33, 983–988.	50		50	02/2006-03/2007	Leipzig, Germany	Missing 1-year follow-up.
27	Zierer, A., Wimmer-Greinecker, G., Martens, S., Moritz, A., Doss, M. (2008): The transapical approach for aortic valve implantation. J Thorac Cardiovasc Surg. 136, 948–953.	26		26	02/2006-02/2008	Frankfurt, Germany	Missing 1-year follow-up.
28	Berry, C., Asgar, A., Lamarche, Y., Marcheix, B., Couture, P., Basmadjian, A., Ducharme, A., Laborde, J. C., Cartier, R., Bonan, R. (2007): Novel therapeutic aspects of percutaneous aortic valve replacement with the 21F CoreValve Revalving system. Catheter Cardiovasc Interv. 70, 610–616.	13	13		03/2005-08/2006	Montreal, Canada	Missing 1-year follow-up.

29	Grube, E., Schuler, G., Buellesfeld, L., Gerckens, U., Linke, A., Wenaweser, P., Sauren, B., Mohr, F. W., Walther, T., Zickmann, B., Iversen, S., Felderhoff, T., Cartier, R., Bonan, R. (2007): Percutaneous aortic valve replacement for severe aortic stenosis in high-risk patients using the second-and current third-generation self-expanding CoreValve prosthesis: device success and 30-day clinical outcome. J Am Coll Cardiol. 50, 69–76.	86	86		08/2005-02/2007	Siegburg, Germany	Missing 1-year follow-up.
30	Kempfert, J., Walther, T., Borger, M. A., Falk, V., Blumenstein, J., Fassl, J., Lehmann, S., Holzhey, D., Schuler, G., Mohr, F. W. (2007): Minimally transapical aortic valve implantation. Z Herz Thorax Gefasschir. 21, 170–178.	30		30	02/2006-09/2006	Leipzig, Germany	Missing 1-year follow-up.
31	Marcheix, B., Lamarche, Y., Berry, C., Asgar, A., Laborde, J. C., Basmadjian, A., Ducharme, A., Denault, A., Bonan, R., Cartier, R. (2007): Surgical aspects of endovascular retrograde implantation of the aortic CoreValve bioprosthesis in high-risk older patients with severe symptomatic aortic stenosis. J Thorac Cardiovasc Surg. 134, 1150–1156.	10	10		12/2005-08/2006	Québéc, Canada	Missing 1-year follow-up.
32	Walther, T., Falk, V., Borger, M. A., Dewey, T. M., Wimmer-Greinecker, G., Schuler, G., Mack, M. J., Mohr, F. W. (2007a): Minimally invasive transapical beating heart aortic valve implantation--proof of concept. Eur J Cardiothorac Surg. 31, 9–15.	30		30	02/2006-09/2006	Leipzig, Germany	Missing 1-year follow-up.
33	Walther, T., Simon, P., Dewey, T. M., Wimmer-Greinecker, G., Falk, V., Kasimir, M. T., Doss, M., Borger, M. A., Schuler, G., Glogar, D., Fehske, W., Wolner, E., Mohr, F. W., Mack, M. J. (2007b): Transapical minimally invasive aortic valve implantation: multicenter experience. Circulation. 116, I240-5.	59		59	02/2006-10/2006	Leipzig, Germany/ Vienna, Austria/ Frankfurt, Germany/ Dallas, TX, USA	Missing 1-year follow-up.
34	Webb, J. G., Pasupati, S., Humphries, K., Thompson, C. R., Altwegg, L., Moss, R. R., Sinhal, A., Carere, R. G., Munt, B., Ricci, D., Ye, J., Cheung, A., Lichtenstein, S. V. (2007): Percutaneous transarterial aortic valve replacement in selected high-risk patients with aortic stenosis. Circulation. 116, 755–763.	50	50		01/2005-NA	Vancouver, Canada	Missing 1-year follow-up.

35	Cribier, A., Eltchaninoff, H., Tron, C., Bauer, F., Agatiello, C., Nercolini, D., Tapiero, S., Litzler, P.-Y., Bessou, J. P., Babaliaros, V. (2006): Treatment of calcific aortic stenosis with the percutaneous heart valve: mid-term follow-up from the initial feasibility studies: the French experience. J Am Coll Cardiol. 47, 1214–1223.	36	36		08/2003-NA	Rouen, France	Missing 1-year follow-up.
36	Grube, E., Laborde, J. C., Gerckens, U., Felderhoff, T., Sauren, B., Buellesfeld, L., Mueller, R., Menichelli, M., Schmidt, T., Zickmann, B., Iversen, S., Stone, G. W. (2006): Percutaneous implantation of the CoreValve self-expanding valve prosthesis in high-risk patients with aortic valve disease: the Siegburg first-in-man study. Circulation. 114, 1616–1624.	25	25		02/2005-11/2005	Siegburg, Germany	Missing 1-year follow-up.
37	Lichtenstein, S. V., Cheung, A., Ye, J., Thompson, C. R., Carere, R. G., Pasupati, S., Webb, J. G. (2006): Transapical transcatheter aortic valve implantation in humans: initial clinical experience. Circulation. 114, 591–596.	7		7	12/2005-NA	Vancouver, Canada	Missing 1-year follow-up. n<10
38	Cribier, A., Eltchaninoff, H., Tron, C., Bauer, F., Leon, M. B. (2005): Percutaneous valve insertion for the treatment of calcific aortic valve stenosis. In: Herrmann, H. C. (Ed.): Interventional cardiology. Percutaneous Noncoronary Intervention. Totowa, NJ: Humana Press Inc.	8	8		04/2002-NA	Rouen, France	Missing 1-year follow-up. n<10

6.3.2 Publications excluded from review on medical therapy of AS[22]

Table 2 Study characteristics and rationale for exclusion from review on medical therapy of AS

#	Publication	Study characteristics				Rationale for exclusion
		N		Enrollment period	Study center	
		Total	Symptomatic severe AS			
1	Ben-Dor, I., Pichard, A. D., Satler, L. F., Okubagzi, P., Torguson, R., Xue, Z., Kaneshige, K., Goldstein, S. A., Syed, A. I., Li, Y., Lemesle, G., Maluenda, G., Collins, S. D., Wang, Z., Suddath, W. O., Kent, K. M., Lindsay, J., Waksman, R. (2010): Clinical profile, treatment assignment and clinical outcome of patients with severe aortic stenosis not eligible to participate in a clinical trial of percutaneous aortic valve replacement. Am J Cardiol. 105, 857–861.	69	69	04/2007-07/2009	Washington, DC, USA	Missing 1-year follow-up
2	Rosenhek, R. M., Zilberszac, R., Schemper, M., Czerny, M. M., Mundigler, G. M., Graf, S. M., Bergler-Klein, J. M., Grimm, M. M., Gabriel, H. M., Maurer, G. M. (2010): Natural history of very severe aortic stenosis. Circulation. 5, 151–156.	116		01/1995-12/2008	Vienna, Austria	Focus on asymptomatic AS; mean age ≤ 75
3	Descoutures, F., Himbert, D., Lepage, L., Iung, B., Detaint, D., Tchetche, D., Brochet, E., Castier, Y., Depoix, J. P., Nataf, P., Vahanian, A. (2008): Contemporary surgical or percutaneous management of severe aortic stenosis in the elderly. Eur Heart J. 29, 1410–1417.	16	16	10/2006-04/2007	Paris, France	Missing 1-year follow-up
4	Dewey, T. M., Brown, D. L., Das, T. S., Ryan, W. H., Fowler, J. E., Hoffman, S. D., Prince, S. L., Herbert, M. A., Culica, D., Mack, M. J. (2008): High-risk patients referred for transcatheter aortic valve implantation: management and outcomes. Ann Thorac Surg. 86, 1450-6; discussion 1456-7.	52	52	12/2005-12/2007	Dallas, TX, USA	Missing 1-year follow-up

[22] Publications excluded from information synthesis which are not cited in the main document are not included in the reference list (bibliography section 6.1).

5	Bach, D. S., Cimino, N., Deeb, G. M. (2007): Unoperated patients with severe aortic stenosis. J Am Coll Cardiol. 50, 2018–2019.	75	53	01/2005-12/2005	Ann Arbour, MI, USA	Mean age ≤ 75; mostly asymptomatic patients
6	Schumm, J., Pethig, K., Rademacher, W., Figulla, H.-R. (2006): Valvular aortic stenosis and adverse events under therapy with angiotensin-converting enzyme inhibitors. Original Investigation: Jena	128		01/2003-12/2004	Jena, Germany	Missing 1-year follow-up
7	Varadarajan, P., Kapoor, N., Bansal, R. C., Pai, R. G. (2006a): Clinical profile and natural history of 453 nonsurgically managed patients with severe aortic stenosis. Ann Thorac Surg. 82, 2111–2115.	453	240	01/1993-12/2003	Los Angeles, CA, USA	47% of patients asymptomatic
8	Cowell, S. J., Newby, D. E., Prescott, R. J., Bloomfield, P., Reid, J., Northridge, D. B., Borger, M. A. (2005): A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. N Engl J Med. 352, 2389–2397.	155	36		Edinburgh, UK	Mean age ≤ 75
9	Bouma, B. J., van den Brink, R. B., van der Meulen, J. H., Verheul, H. A., Cheriex, E. C., Hamer, H. P., Dekker, E., Lie, K. I., Tijssen, J. G. (1999): To operate or not on elderly patients with aortic stenosis: the decision and its consequences. Heart. 82, 143–148.	111			Rotterdam, Netherlands	Missing 1-year follow-up
10	Iivanainen, A. M., Lindroos, M., Tilvis, R., Heikkilä J, Kupari, M. (1996): Natural history of aortic valve stenosis of varying severity in the elderly. Am J Cardiol. 78, 97–101.	64	13		Helsinki, Finland	Missing 1-year follow-up
11	Horstkotte, D., Loogen, F. (1988): The natural history of aortic valve stenosis. Eur Heart J. 9 Suppl E, 57–64.	55	55		Düsseldorf, Germany	Mean age ≤ 75; Missing 1-year follow-up
12	Turina, J., Hess, O. M., Sepulcri, F., Krayenbühl, H. P. (1987): Spontaneous course of aortic valve disease. Eur Heart J. 8, 471–483.	110	50	01/1963-12/1983	Zürich, Switzerland	Mean age ≤ 75
13	Schwarz, F., Ehrmann, J., Olschewski, M., Scheurlen, H., Manthey, J., Storch, H. H., Saggau, W., Kubler, W. (1985): Long-term prognosis of drug and surgery treated patients with acquired aortic valve diseases: survival statistics and multivariate Cox regression analysis. Z Kardiol. 74, 598–603.	68		1975-1982	Heidelberg, Germany	Mean age ≤ 75

14	Turina, J., Hess, O. M., Turina, M., Krayenbühl, H. P. (1985): Severe symptomatic valve defects in elderly patients. Spontaneous prognosis and surgical results. Schweiz Med Wochenschr. 115, 698–702.	18		1970-1982	Zürich, Switzerland	Mean age ≤ 75
15	Chizner, M. A., Pearle, D. L., deLeon, A. C., JR (1980): The natural history of aortic stenosis in adults. Am Heart J. 99, 419–424.	42	32		Washington, DC, USA	Mean age ≤ 75; Missing 1-year follow-up
16	Haerten, K., Dohn, G., Dohn, V., Seipel, L., Loogen, F. (1980): Natural history of patients with severe aortic valve disease under medical therapy. Z Kardiol. 69, 757–762.	35		1967-1976	Düsseldorf, Germany	Mean age ≤ 75
17	Rapaport, E. (1975): Natural history of aortic and mitral valve disease. Symposium on the Effects of Surgical Treatment on the Natural History of Acquired Heart Disease Part II: Aortic and Mitral Valve Disease. Am J Cardiol. 35, 221–227.	42			San Francisco, CA, USA	Missing 1-year follow-up
18	Frank, S., Johnson, A., Ross, J., JR. (1973): Natural history of valvular aortic stenosis. Br Heart J. 35, 41–46.	15	15		Bethesda, MD, USA	Mean age ≤ 75
19	Ross, J., JR., Braunwald, E. (1968): Aortic stenosis. Circulation. 38, V-61-V-67.	12	12		Bethesda, MD, USA	Mean age ≤ 75
20	Takeda, J., Warren, R., Holzman, D. (1963): Prognosis of aortic stenosis. Arch Surg. 87, 931–936.	60		1948-1959	Boston, MA, USA	Mean age ≤ 75; Missing 1-year follow-up

7 Appendix

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Table 3: Annual statistics 2008/2009 for aortic valve replacement in Germany (adapted from the German Society for Thoracic and Cardiovascular Surgery 2010)

	2008	2009	Δ
Surgical AVR	12,262	11,457	-6.6%
TAVI	921	2,154	+133.9%
Surgical AVR + Coronary Artery Bypass Grafting (CABG)	8,514	8,005	-6%
Total	21,697	21,616	-0.4%

Table 4: Inclusion and exclusion criteria for publications on TAVI

Characteristic	Criteria
Publication Type	Peer-reviewed full-text publications that report clinical outcomes, systematic reviews, and publications from health technology institutes. Editorials, laboratory or animal studies excluded
	Published (either print or online) by 04/ 2010
Language	English or German
Intervention	Transcatheter aortic valve implantation (TAVI)
Patient characteristics	Patients at risk for surgical AVR with severe AS, excluding asymptomatic patients
	Mean age of study population ≥ 75 years
Study characteristics	Clinical studies, excluding case reports
	Patient population larger than n ≥ 10
	Follow-up duration of ≥ 12 postoperative months
Clinical outcome	Safety, efficacy, and/ or cost-effectiveness of TAVI

Table 5: Inclusion and exclusion criteria for publications on medical therapy of AS

Characteristic	Criteria
Publication Type	Peer-reviewed full-text publications that report clinical outcomes, systematic reviews, and publications from health technology institutes. Editorials, laboratory or animal studies excluded
	Published (either print or online) by 04/ 2010
Language	English or German
Intervention	None
Patient characteristics	Patients with severe AS who either refused or were denied surgical AVR, excluding asymptomatic patients
	Mean age of study population ≥ 75 years
Study characteristics	Clinical studies, excluding case reports
	Patient population larger than n ≥ 10
	Follow-up duration of ≥ 12 postoperative months
Clinical outcome	Safety, efficacy, and/ or cost-effectiveness of medical treatment of AS

Table 6: Study characteristics of included primary publications on TAVI

Publication	Study center	Study design	Enrollment period	N	Valve type implanted	Duration follow-up (mean; months)
Rodés-Cabau, J. et al. 2010	6 centers, Canada	Prospective, multi-center study	01/2005-06/2009	339[23] (TV 162 / TA 177)	Cribier-Edwards/ Edwards Sapien	8.0*
Rajani, R. et al. 2010	Brighton, UK	Retrospective, single-center, matched cohort study	12/2007 – 06/2009	38 (TV)	CoreValve	8.8*
Walther, T. et al. 2010	Leipzig, Germany	Retrospective, single-center, matched cohort study	10/2006 – 11/2008	100 (TA)	Edwards Sapien	12.0
Al-Attar, N. et al. 2009	Paris, France	Prospective, single-center case series	09/2006-05/2008	50 (TV 35 / TA 15)	Edwards Sapien	8.6
Himbert, D. et al. 2009	Paris, France	Prospective, single-center case series	02/2006-01/2008	75 (TV 51 / TA 24)	Edwards Sapien	10.0
Kapadia, S. R. et al. 2009	Cleveland, OH, USA	Prospective, single-center, cohort study	02/2006 – 03/2007	18 (NA[24])	Cribier-Edwards	9.3
Thielmann, M. et al. 2009	Essen, Germany	Prospective, single-center case series	05/2007 – 11/2008	39 (TV 15 / TA 24)	Cribier-Edwards/ Edwards Sapien	12.0
Webb, J. G. et al. 2009	Vancouver, Canada	Prospective, single-center case series	01/2005 - 04/2008	168 (TV 113 / TA 55)	Cribier-Edwards/ Edwards Sapien	7.4

[23] The number of patients was 339, but a total of 345 (TV 168 / TA 177) procedures was performed in these patients.

[24] Approach not specified

Ye, J. et al. 2009	Vancouver, Canada	Prospective, single-center case series	10/2005 - 01/2007	26 (TA)	Edwards Sapien	12.0
Zierer, A. et al. 2009	Frankfurt, Germany	Retrospective, single-center, matched cohort study	01/2006 – 04/2007	21 (TA)	Cribier-Edwards	12.0
Grube, E. et al. 2008	Siegburg, Germany	Prospective, single-center case series	02/2005 – 03/2008	136 (TV)	CoreValve	12.0
Otten, A. M. et al. 2008	Rotterdam, Netherlands	Prospective, single-center, cohort study	09/2005-09/2007	39 (TA)	CoreValve	13.0

*—median; NA—not available

Table 7: Demographic and pre-procedural clinical patient characteristics (mean±SD)

Publication	**Age (years)**	**Gender (% males)**	**Estimated operative risk (%)**		**NYHA classification [%(n)]**
			Log EuroSCORE	STS score	
Rodés-Cabau, J. et al. 2010	81.0±8.0 (TV 83.0±8.0/TA 80.0±8.0)	45 (TV 56/ TA 35)	NA	9.8±6.4(TV 9±5.8/TA 10.5±6.9)	NA
Rajani, R. et al. 2010	83.0*	55	24.0±15.0	NA	I. 8% (3) II. 29% (11) III. 55% (21) IV. 8% (3)
Walther, T. et al. 2010	82.7±5.0	23	29.4±13	15.2±8.3	I. 0% (0) II. 0% (0) III. 76% (76) IV. 24% (24)
Al-Attar, N. et al. 2009	83.0±8.0 (TV 83.0±6.0/TA 83.0±10.0)	54 (TV 51/ TA 60)	28.0 ±14.0 (TV 26.0 ±14.0/ TA 30.0 ±12.0)	16.0 ±7.0 (TV 15.0 ±6.0/ TA 19.0 ±9.0)	I. 0% (0) II. 6% (3) III. 52% (26) IV. 42% (21)

Himbert, D. et al. 2009	82.0±8.0 (TV 82.0±7.0/TA 82.0±10.0)	55 (TV 49/ TA 67)	26.0 ±13.0 (TV 25.0 ±13.0/ TA 28.0 ±13.0)	16.0 ±7.0 (TV 15.0 ±7.0/ TA 18.0 ±9.0)	I. 0% (0) II. 5% (4) III. 53% (40) IV. 41% (31)
Kapadia, S. R. et al. 2009	81.0±6.0	67	27.8±18.8	11.4±7.5	I. 0% (0) II. 0% (0) III. 33% (6) IV. 67% (12)
Thielmann, M. et al. 2009	81.4±5 (TV 79.6 ±4.5/TA 82.7±5.1)	38 (TV 47/ TA 33)	44.2 ±12.6 (TV 38.1 ±8.1/ TA 52.5 ±13.4)	17.9 ±6.1 (TV 15.1±4.1/ TA 19.9 ±7.5)	I. 0% (0) II. 5% (2) III. 62% (24) IV. 33% (13)
Webb, J. G. et al. 2009	84.0* (TV 85.0*/ TA 83.0*)	52 (TV 58/ TA 40)	28.6* (TV 25.0*/ TA 35.0*)	9.1* (TV 8.7*/ TA 10.3*)	I. 1% (2) II. 12% (17) III. 61% (88) IV. 26% (37)
Ye, J. et al. 2009	80.1±9.1	50	37.0±20.0	11.0±6.0	I. 0% (0) II. 19% (5) III. 65% (17) IV. 16% (4)
Zierer, A. et al. 2009	85.0±6.0	29	38.0 ±14.0	NA	3.4±0.4
Grube, E. et al. 2008	81.5 ±6.9	42	23.1±15	8.9±6.5	3.3±0.5
Otten, A. M. et al. 2008	81±7	46	15.0±6.0	NA	NA

*—median; NA—not available

Table 8: Procedural, 30-day, and 1-year primary outcomes after TAVI

Publication	Procedural success rate [% (n)]			30-day mortality rate [% (n)]			1-year survival rate (%)		
	Overall	TV	TA	Overall	TV	TA	Overall	TV	TA
Rodés-Cabau, J. et al. 2010	93.3 (322)	90.5 (152)	96.1 (170)	10.4 (36)	9.5 (16)	11.3 (20)	76	75	78
Rajani, R. et al. 2010	97.3 (37)	97.3 (37)	NA	5.3 (2)	5.3 (2)	NA	87	87	NA
Walther, T. et al. 2010	97 (97)	NA	97 (97)	10 (10)	NA	10 (10)	72	NA	72
Al-Attar, N. et al. 2009	90 (45)	85.7 (30)	100 (15)	14 (7)	8 (3)	27 (4)	67	74	60
Himbert, D. et al. 2009	93 (70)	90 (46)	100 (24)	10 (8)	8 (4)	16 (4)	78	81	74
Kapadia, S. R. et al. 2009	94 (17)	NA	NA	5.6 (1)	NA	NA	78	NA	NA
Thielmann, M. et al. 2009	97.4 (38)	NA	NA	17.9 (7)	13.3 (2)	20.8 (5)	64.1	68.1	61.9
Webb, J. G. et al. 2009	94.1 (158)	NA	NA	11.3 (19)	8 (9)	18.2 (10)	73.8	NA	NA
Ye, J. et al. 2009	100 (26)	NA	100 (26)	23 (6)	NA	23 (6)	65.4	NA	65.4
Zierer, A. et al. 2009	100 (21)	NA	100 (21)	14 (3)	NA	14 (3)	76	NA	76
Grube, E. et al. 2008	86 (117)	86 (117)	NA	12.5 (17)	12.5 (17)	NA	81.6	81.6	NA
Otten, A. M. et al. 2008	NA	NA	NA	NA	NA	NA	87	87	NA

NA—not available

Table 9: Procedural and post-procedural complications [% (n)] [25]

Publication	Major vascular complication			Cerebrovascular accident/ strokes			Myocardial infarction			Cardiac tamponade			Heart block/ PPM requirement			"Valve in valve"		
	Overall	TV	TA	Overall	TV	TA	Overall	TV	TA	Overall	TV	TA	Overall	TV	TA	Overall	TV	TA
Rodés-Cabau, J. et al. 2010	0.6 (2)	1.2 (2)	0 (0)	2.3 (8)	3.1 (5)	1.7 (3)	1.2 (4)	0.6 (1)	1.7 (3)	0 (0)	0 (0)	0 (0)	4.9 (17)	3.7 (6)	6.2 (11)	2.6 (9)	2.5 (4)	2.8 (5)
Rajani, R. et al. 2010	2.6 (1)	2.6 (1)		2.6 (1)	2.6 (1)		0 (0)	0 (0)		2.6 (1)	2.6 (1)		34.2 (13)	34.2 (13)		0 (0)	0 (0)	
Walther, T. et al. 2010	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	9 (9)*		9 (9)*	0 (0)		0 (0)
Al-Attar, N. et al. 2009	12 (6)	11.4 (4)	13.3 (2)	4 (2)	5.7 (2)	0 (0)	0 (0)	0 (0)	0 (0)	6 (3)	2.9 (1)	13.3 (2)	4 (2)	2.9 (1)	6.7 (1)	4 (2)	2.9 (1)	6.7 (1)
Himbert, D. et al. 2009	10.7 (8)	11.8 (6)	8.3 (2)	4 (3)	5.9 (3)	0 (0)	0 (0)	0 (0)	0 (0)	5.3 (4)	3.9 (2)	8.3 (2)	5.3 (4)	5.9 (3)	4.2 (1)	4 (3)	2 (1)	8.3 (2)
Kapadia, S. R. et al. 2009	0 (0)			0 (0)			0 (0)			0 (0)			5.6 (1)			0 (0)		
Thielmann, M. et al. 2009	12.8 (5)	33.3 (5)	0 (0)	2.6 (1)	6.7 (1)	0 (0)	0 (0)	0 (0)	0 (0)	2.6 (1)	6.7 (1)	0 (0)	10.3 (4)	26.7 (4)	0 (0)	2.6 (1)	0 (0)	4.2 (1)
Webb, J. G. et al. 2009	6.5 (11)	8 (9)	3.6 (2)	4.2 (7)	5.3 (6)	1.8 (1)	0 (0)	0 (0)	0 (0)	2.4 (4)	1.8 (2)	3.6 (2)	5.4 (9)	4.4 (5)	7.3 (4)	0 (0)	0 (0)	0 (0)
Ye, J. et al. 2009	0 (0)		0 (0)	3.8 (1)		3.8 (1)	3.8 (1)		3.8 (1)	0 (0)		0 (0)	11.5 (3)		11.5 (3)	0 (0)		0 (0)
Zierer, A. et al. 2009	NA		NA	NA		NA	NA		NA	NA		NA	NA		NA	NA		NA
Grube, E. et al. 2008	0 (0)	0 (0)		4.4 (6)	4.4 (6)		2.2 (3)	2.2 (3)		1.5 (2)	1.5 (2)		25 (34)	25 (34)		2.2 (3)	2.2 (3)	
Otten, A. M. et al. 2008	NA	NA		NA	NA		NA	NA		NA	NA		NA	NA		NA	NA	

NA—not available; *11 of 100 patients already carried a PPM before the TAVI procedure

[25] If a publication reported any adverse events, it was assumed that if a type of major complication was not mentioned, it would not have occurred.

Table 10: Summarized evidence on TAVI efficacy (based on subset of studies reporting baseline, 30-day, and 1-year follow-up outcomes)

Patients at baseline	Reported baseline	Survivors at 30-day follow up	Survivors at 1-year follow up	Reported outcome at 30-day follow-up	Reported outcome at 1-year follow-up	Consistency of results	Δ between baseline and 30-day follow-up	Δ between 30-day and 1-year follow-up
Mean AVA (cm^2)								
282	0.61	247	196	1.65	1.49	✔	+1.04 (+170.5%)	-0.16 (-9.7%)
Mean transaortic valve gradient (mmHg)								
282	47.6	247	196	10.3	10.1	✔	-37.3 (-78.4%)	-0.2 (-2%)
Mean LVEF (%)								
240	52.7	205	158	56.2	60.2	✔	+3.5 (+6.6%)	+4 (+7.1%)
Mean NYHA functional class								
301	3.3	257	210	2	1.8	✔	-1.3 (-39.4%)	-0.2 (-10%)
NYHA functional class distribution								
165	I. 0% (0) II. 4% (7) III.71%(117) IV. 25% (41)	138	99	I. 22% (31) II. 51% (71) III. 26% (36) IV. 0% (0)	I. 26% (26) II. 40% (39) III. 34% (34) IV. 0% (0)	✔	I. +22% II. +47% III. -45% IV. -25%	I. +4% II. -11% III. +8% IV. ±0%

Table 11: Baseline, 30-day, and 1-year secondary outcomes after TAVI (mean± SD)

Publication	Baseline				30-day follow-up				1-year follow-up		
	n	AVA (cm²)	Mean trans-aortic gradient (mmHg)	LVEF (%)	Survivors (n)	AVA (cm²)	Mean trans-aortic gradient (mmHg)	LVEF (%)	AVA (cm²)	Mean trans-aortic gradient (mmHg)	LVEF (%)
Rodés-Cabau, J. et al. 2010	339 (TV 162 / TA 177)	0.63±0.17 (TV 0.63±0.16/ TA 0.63±0.18)	46±17 (TV 48±18/ TA 44±17)	55±14 (TV 55±14/ TA 56±14)	303	1.55±0.41	10±4	NA	NA	NA	NA
Rajani, R. et al. 2010	38 (TV)	0.66±0.20	56±17	NA	36	NA	NA	NA	NA	NA	NA
Walther, T. et al. 2010	100 (TA)	NA	NA	54±15	90	NA	NA	NA	NA	NA	58±12
Al-Attar, N. et al. 2009	50 (TV 35 / TA 15)	0.61±0.16 (TV 0.60±0.16/ TA 0.63±0.17)	51±14 (TV 52±15/ TA 48±12)	49±15 (TV 50±16/ TA 45±13)	43	1.72±0.46	11±4	NA	NA	NA	NA
Himbert, D. et al. 2009	75 (TV 51 / TA 24)	0.64±0.16 (TV 0.63±0.16/ TA 0.65±0.17)	52±15 (TV 54±15/ TA 48±14)	51±15 (TV 52±16/ TA 48±13)	67	1.73±0.41	10±4	58**	1.45**	8**	62**
Kapadia, S. R. et al. 2009	18 (NA[26])	0.60±0.10	46±16	46±17	17	NA	NA	NA	NA	NA	NA
Thiel-mann, M. et al. 2009	39 (TV 15 / TA 24)	0.60 ±0.20	46±20	51±17 (TV 49±21/ TA 52±13)	32	1.70±0.60	12±5	51±17	1.70±0.60	10±4	59±9

[26] Approach not specified

Webb, J. G. et al. 2009	168 (TV 113 / TA 55)	0.60* (TV 0.60*/ TA 0.60*)	46* (TV 48*/ TA 41*)	NA	149	1.60±0.40	10±4	NA	1.50±0.30	11±5	NA
Ye, J. et al. 2009	26 (TA)	0.50±0.10	45±14	56 ±13	20	NA	NA	59±5	1.70±0.50	9±5	63±9
Zierer, A. et al. 2009	21 (TA)	NA	NA	NA	18	NA	NA	NA	1.50±0.80	10±4	NA
Grube, E. et al. 2008	136 (TV)	0.67 ±0.9	42±17	51±17	119	NA	NA	NA	NA	8±4	NA
Otten, A. M. et al. 2008	39 (TV)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

*—median; **—mean; NA—not available

Table 12: Potential overlaps of included references (or related previous publications[27]) and published systematic reviews/ HTA reports

Publication	Study center	Enrollment period	N	References in published systematic reviews/ HTA reports						
				van Brabandt, H. and Neyt, M. 2009 (KCE Belgium)	Yan, T. D. et al. 2010 2009 (Sydney, Australia)	van Brabandt, H. and Neyt, M. 2008 (KCE Belgium)	NICE 2008 (UK)	Blanchard, S. 2008 (Haute Autorité de Santé (HAS) France)	Wild, C. et al. 2008 (LBI Austria)	Wild, C. and Geiger-Gritsch, S. 2009 (LBI Austria)
Rodés-Cabau, J. et al. 2010	6 centers, Canada	01/2005-06/2009	339	Webb, J. G. et al. 2007 (n=50); enrollment 01/2005 – NA Lichtenstein, S. V. et al. 2006 (n=7); enrollment 10/2005 – NA Ye, J. et al. 2007 (n=7); enrollment 10/2005 – NA						
Rajani, R. et al. 2010	Brighton, UK	12/2007 – 06/2009	38							
Walther, T. et al. 2010	Leipzig, Germany	02/2006-01/2008	100	Walther, T. et al. 2008 (n=50); enrollment 02/2006-03/2007 Walther, T. et al. 2007b (n=59); enrollment 02/2006 - 10/2006 Walther, T. et al. 2007a (n=30); enrollment 02/2006 - 09/2006						
Al-Attar, N. et al. 2009	Paris, France	09/2006-05/2008	50	Descoutures, F. et al. 2008 (n=12); enrollment 10/2006 – 04/2007						
Himbert, D. et al. 2009	Paris, France	10/2006 – 11/2008	75							
Kapadia, S. R. et al. 2009	Cleveland, OH, USA	02/2006 – 03/2007	18							

[27] Related publications were defined as duplicate publications from the same centers with overlapping enrollment period and accumulating number of patients, or increased length of follow-up.

Thielmann, M. et al. 2009	Essen, Germany	05/2007 – 11/2008	39								
Webb, J. G. et al. 2009	Vancouver, Canada	01/2005 - 04/2008	168		Included						
Ye, J. et al. 2009	Vancouver, Canada	10/2005 - 01/2007	26	Webb, J. G. et al. 2007 (n=50); enrollment 01/2005 – NA Lichtenstein, S. V. et al. 2006 (n=7); enrollment 10/2005 – NA Ye, J. et al. 2007 (n=7); enrollment 10/2005 – NA							
Zierer, A. et al. 2009	Frankfurt, Germany	01/2006 – 04/2007	21	Zierer, A. et al. 2008 (n=26); enrollment 02/2006 – 02/2008							
Grube, E. et al. 2008	Siegburg, Germany	02/2005 – 03/2008	136	Grube, E. et al. 2006 (n=25); enrollment 02/2005 - 11/2005 Grube, E. et al. 2007 (n=86); enrollment 08/2005 - 02/2007							Included
Otten, A. M. et al. 2008	Rotterdam, Netherlands	09/2005- 09/2007	39								Included

NA—not available

Table 13: References of earlier systematic reviews/ HTAs which were already described by van Brabandt, H. and Neyt, M. 2008

Publication	Study center	Approach	N	References in 2008 systematic reviews/ HTAs			
				KCE Belgium	NICE UK	HAS France	LBI Aus-tria
Cribier, A. et al. 2004	Rouen, France	TV/ antegrade (Edwards)	6	X	X	X	X
Cribier, A. et al. 2006	Rouen, France	TV/ antegrade (Edwards)	36	X	X	X	X
Webb, J. G. et al. 2007	Vancouver, Canada	TV (Edwards)	50	X	X	X	X
Lichtenstein, S. V. et al. 2006	Vancouver, Canada	TA (Edwards)	7	X	X	X	X
Ye, J. et al. 2007	Vancouver, Canada	TA (Edwards)	7	X	X	X	
Walther, T. et al. 2007a	Leipzig, Germany	TA (Edwards)	30	X	X	X	
Walther, T. et al. 2007b	Multicenter, Germany	TA (Edwards)	59	X	X	X	
Svensson, L. G. et al. 2008	Multicenter, US	TA (Edwards)	40	X			
Grube, E. et al. 2006	Siegburg, Germany	TV (CoreValve)	35	X	X	X	X
Grube, E. et al. 2007	Multicenter, Germany/ Canada	TV (CoreValve)	86	X	X	X	X
Marcheix, B. et al. 2007	Montreal, Canada	TV (CoreValve)	10	X			X
Berry, C. et al. 2007	Montreal, Canada	TV (CoreValve)	11	X	X	X	X

X—reference included

Table 14: Key results of earlier systematic reviews/ HTAs

Outcome parameter	Access Route		2008 systematic reviews/ HTAs (n=included patients)			
			KCE Belgium (n=423)	NICE UK (n=336)	HAS France (n=470[28])	LBI Austria (n=257)
Procedural Success rate (%)	TV		68-93	75-88	NA	74-100
	TA		71-93	93-100	NA	NA
30-day mortality (%)	TV		6-13	12-22	NA	11-50
	TA		8-23	10-14	NA	NA
6-months survival (%)	TV		78-90	41-81	71-84	57
	TA		55-74	NA	68	NA
30-day procedural and post-procedural complications (%)	TV		Vascular complications 10-15, Stroke 3-10	Stroke 2-12, Bradyarrhythmia 36, Major bleeding 18, Cardiac tamponade 10, Vascular injuries 5, Access-site infection 5	NA	NA
	TA		NA	Pleural effusion 31-37, Stroke 3, Hemofiltration 14, Tracheotomy 14, Rethoracotomy 14	NA	NA
AVA (cm²)	TV	Pre-TAVI	0.5-0.7	0.6	0.6	0.5-0.7
		Post-TAVI	1.6-1.7	1.3-1.9	1.7	1-2
	TA	Pre-TAVI	0.6-0.7	0.7	0.6	NA
		Post-TAVI	1.6-1.8	1.8	1.4	NA

[28] Including approximately 135 patients from presented series

Transaortic mean gradient (mmHg)	TV	Pre-TAVI	37-46	37-51	45	31-51
		Post-TAVI	9-11	9-11	10	6-13
	TA	Pre-TAVI	NA	32-43	46	NA
		Post-TAVI	NA	8-11	9	NA
Economic evaluation	Cost assessment		NA	NA	NA	High-level cost estimate of 2,400 € per intervention excluding associated personnel, other operating expense, and hospital stay.
	Estimated number of eligible TAVI patients per year		135-290 in Belgium (population ~10.4 million)[29]	NA	Minimum 600 in France (population ~61.3 million)[30]	Approximately 30 in Upper Austria (population ~1.4 million)[31]
Recommendation on reimbursement			NA	NA	Conditional reimbursement for high-risk patients	NA

NA—not available

[29] Source: www.who.int/countries

[30] Source: www.who.int/countries

[31] Source: http://de.wikipedia.org/wiki/Oberösterreich#Bev.C3.B6lkerung

Table 15: Study characteristics of included studies on medical therapy

Publication	Study center	Study design	Enrollment period	N	Treatment groups for comparison	Mean fol-low-up (months)
Bakaeen, F. G. et al. 2010	Houston, TX, USA	Retrospective, single-center, cohort study	01/1997–04/2008	140 (M)	Surgical AVR (n=205)	NA
Rajani, R. et al. 2010	Brighton, UK	Retrospective, single-center cohort study	12/2007–06/2009	47 (M 33 / M+BAV 14)	TAVI (n=38), BAV (n=14)	7.2*
Bach, D. S. et al. 2009	Ann Arbor, MI, USA	Retrospective, multi-center cohort study	01/2005–12/2005	126 (M)	Asymptomatic AS (n=65), surgical AVR (n=205)	16.7
Kapadia, S. R. et al. 2009	Cleveland, OH, USA	Prospective, single-center cohort study	02/2006–03/2007	36 (M)	TAVI (n=18), surgical AVR (n=19), BAV, n=19)	6.0
van Geldorp, M. W. A. et al. 2009	Rotterdam, Netherlands	Retrospective, multi-center cohort study	10/2004–12/2007	101 (M)	Surgical AVR (n=76)	15.1
Kojodjojo, P. et al. 2008	Hertfordshire, UK	Retrospective, multi-center cohort study	01/2001–12/2006	86 (M)	Surgical AVR (n=15)	19.2
Otten, A. M. et al. 2008	Rotterdam, Netherlands	Prospective, single-center cohort study	09/2005–09/2007	16 (M)	TAVI (n=39), surgical AVR (n=14), BAV (n=3)	11.0
Charlson, E. et al. 2006	Boston, MA, USA	Retrospective, multi-center cohort study	01/1995–12/1997	75 (M)	Surgical AVR (n=49)	NA
Varadarajan, P. et al. 2006b	Los Angeles, CA, USA	Retrospective, single-center cohort study	01/1993–12/2003	197 (M)	Surgical AVR (n=80)	30.0
Iung, B. et al. 2005	Paris, France	Prospective, multi-center cohort study	04/2001–07/2001	72 (M)	Surgical AVR (n=144)	NA
O'Keefe, J. H., JR et al. 1987	Rochester, MN, USA	Retrospective, single-center case series	01/1978–12/1985	50 (M)	None	20.1

*—median; NA—not available; M—medical therapy

Table 16: Demographic and pre-procedural clinical and echocardiographic patient characteristics (mean±SD)

Publication	N	Age (years)	Gender (% males)	Estimated operative risk (%)		NYHA classification [%(n)]	Degree of AS		
				log EuroSCORE	STS score		AVA (cm²)	Transaortic mean gradient (mmHg)	LVEF (%)
Bakaeen, F. G. et al. 2010	140	75.7±8.6	NA	9.0±2.0	NA	NA	NA	NA	42±15
Rajani, R. et al. 2010	47	81.0*	48	13.0**	NA	I. 17% (8) II. 30% (14) III. 49% (23) IV. 4% (2)	0.71±0.23	45±20	NA
Bach, D. S. et al. 2009	126	75.0±12.5	62	NA	3.8*	NA	NA	NA	NA
Kapadia, S. R. et al. 2009	36	83.0±8.0	47	25.4±17.6	12.6±9.2	I. 0% (0) II. 0% (0) III. 53% (19) IV. 47% (17)	0.70±0.20	41±17	48±16
van Geldorp, M. W. A. et al. 2009	101	73.3±12.3	51	11.3±9.6	NA	2.5**	0.71±0.26	NA	NA
Kojodjojo, P. et al. 2008	86	86.2*	37	16.8±12.2	NA	NA	0.65±0.21	NA	61**
Otten, A. M. et al. 2008	16	82.0±14.0	38	25.0±14.0	NA	NA	NA	NA	NA
Charlson, E. et al. 2006	75	81.5±8.3	29	NA	NA	NA	NA	NA	NA
Varadarajan, P. et al. 2006b	197	85.3±4.1	42	NA	NA	NA	0.68±0.16	39±15	NA
Iung, B. et al. 2005	72	81.7±4.6	43	NA	NA	NA	0.73±0.23	52±20	52±18

O'Keefe, J. H., JR et al. 1987	50	77.0**	72	NA	NA	NA	0.57**	NA	NA

*—median; **—mean; NA—not available

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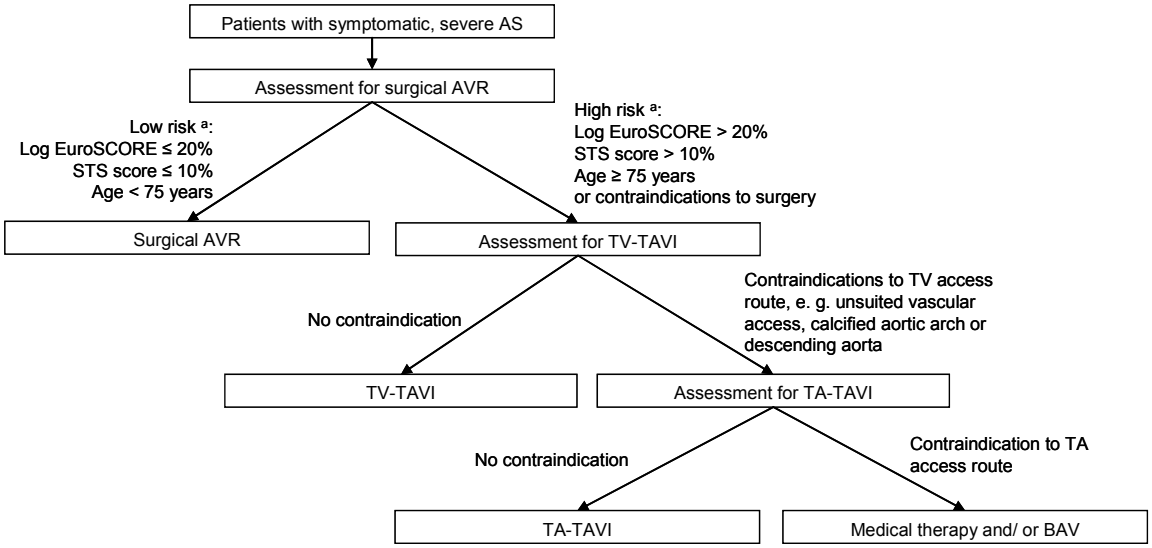
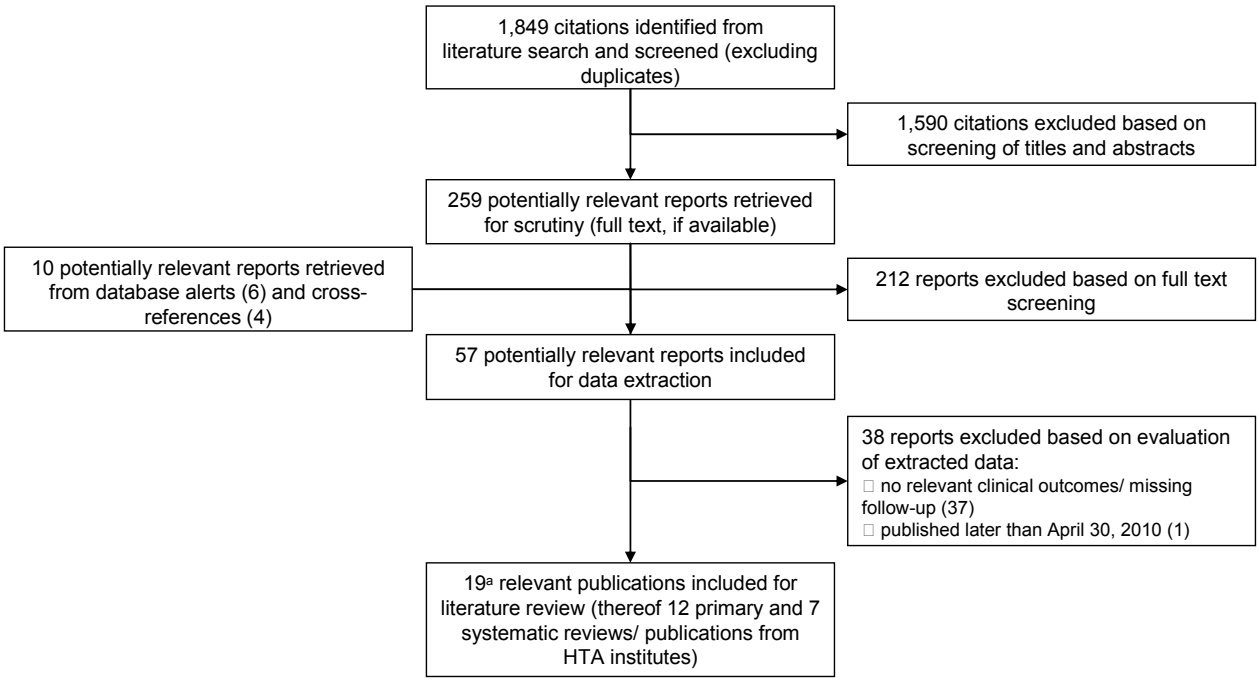
7.4 Figures

Figure 1: Schematic decision-making process for TAVI patient evaluation [a]



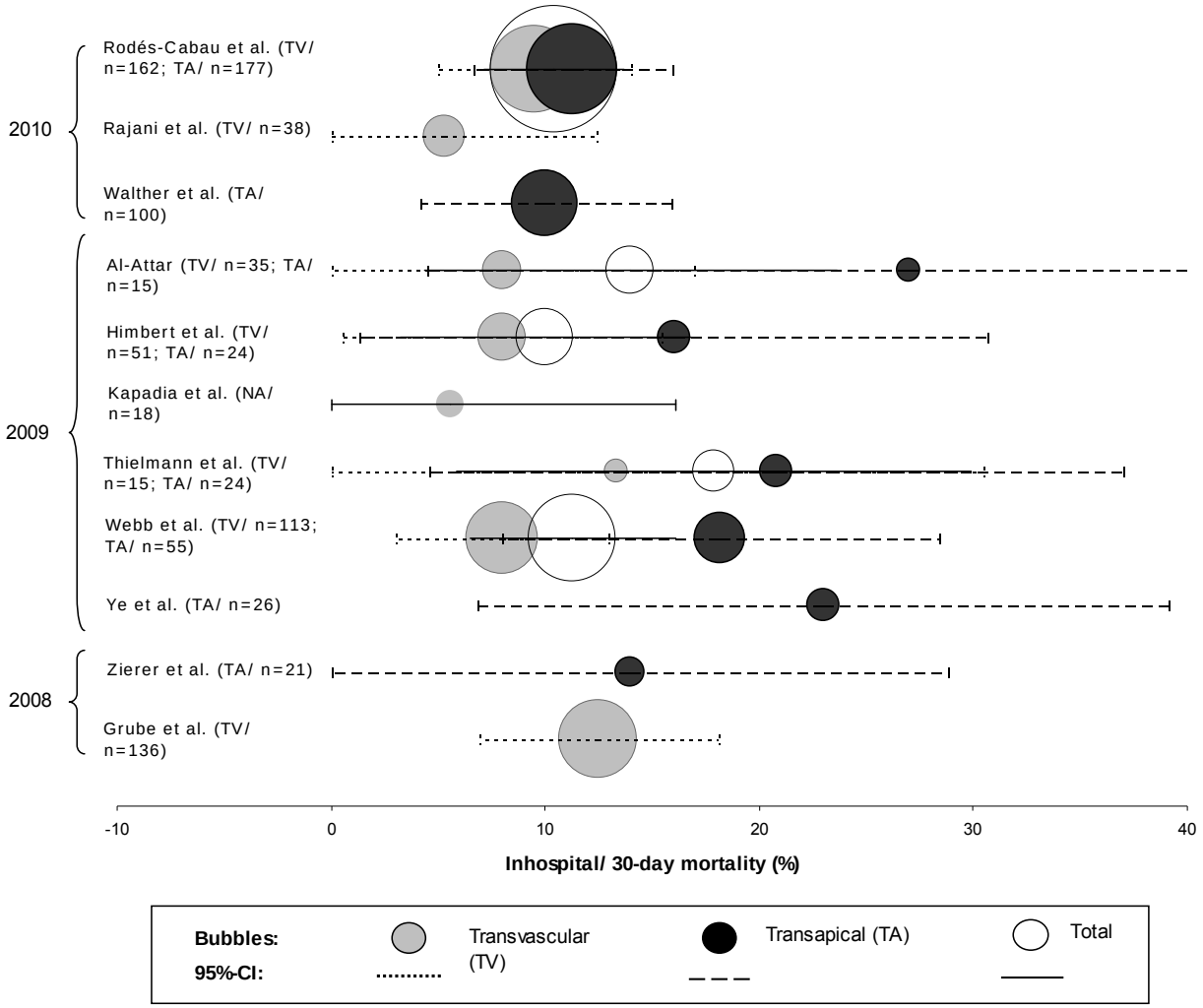
[a] Risk classification according to German Society of Cardiology (DGK) positioning statement (Figulla, H. R. et al. 2009)

Figure 2: Flow chart literature search results for review on TAVI [a]



[a] Three cohort studies (Rajani, R. et al. 2010, Kapadia, S. R. et al. 2009, Otten, A. M. et al. 2008) were also included for the information synthesis on medical therapy of AS.

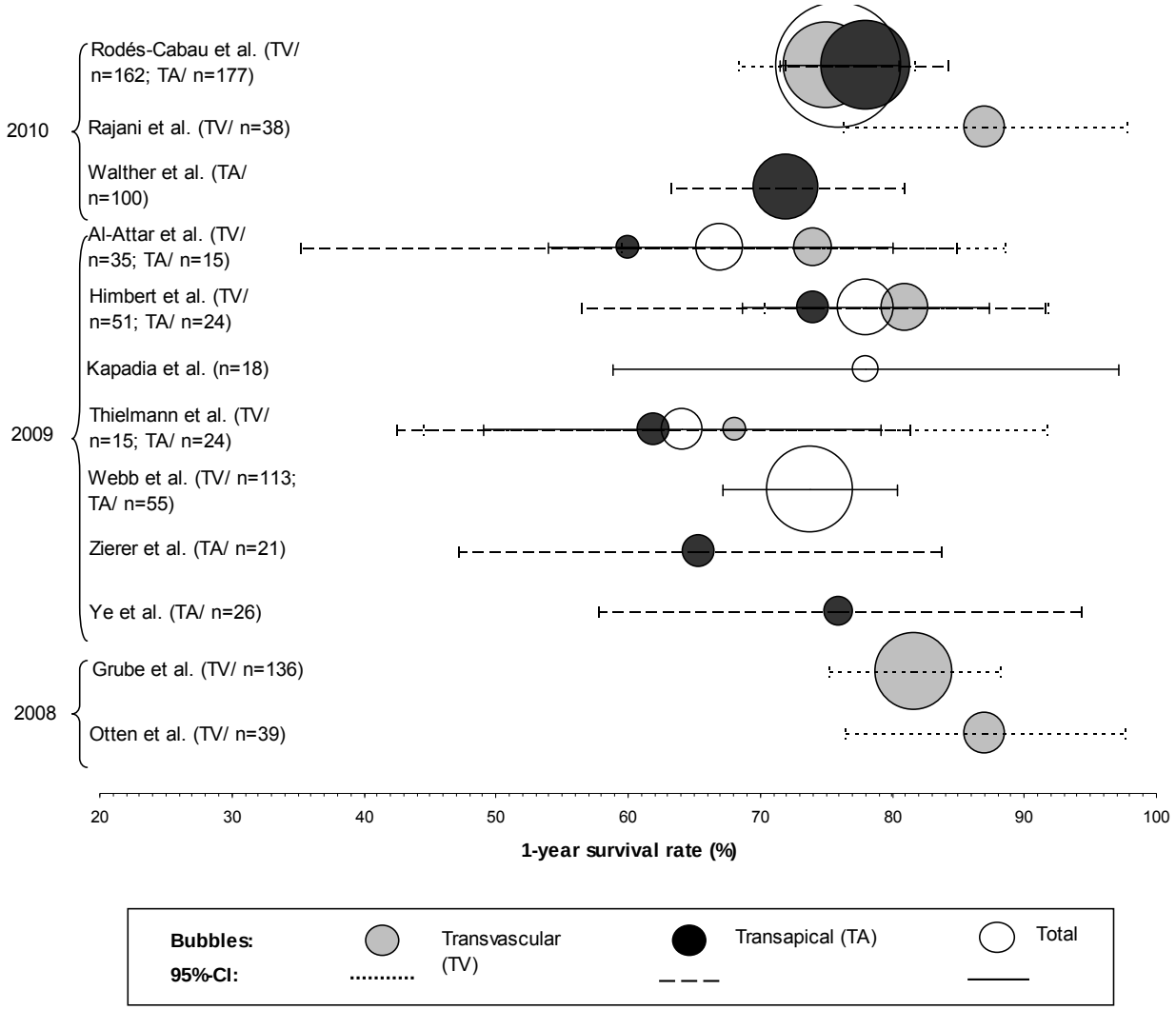
Figure 3: Mean inhospital/ 30-day mortality rates (from literature) and approximated 95%-CI [a, b]



[a] The area of bubbles represents the number of included patients (n).

[b] Particularly in small patient populations, the applied approximation method for 95%-CI can return negative lower boundaries. In these cases, the lower boundary of the 95%-CI was restricted to 0.

Figure 4: Mean 1-year survival rates (from literature) and approximated 95%-CI[a]



[a] The area of bubbles represents the number of included patients (n).

Figure 5: Improvement of AVA and transaortic mean gradient after TAVI (based on those studies reporting baseline, 30-day, and 1-year follow-up outcomes)

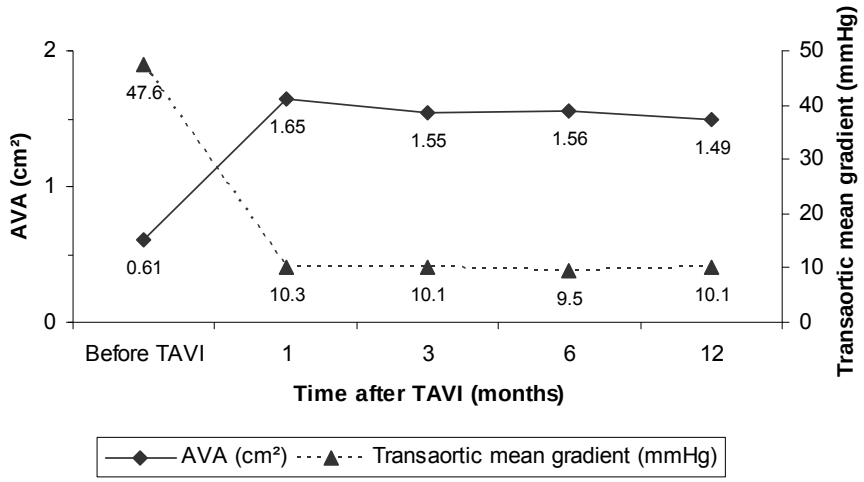
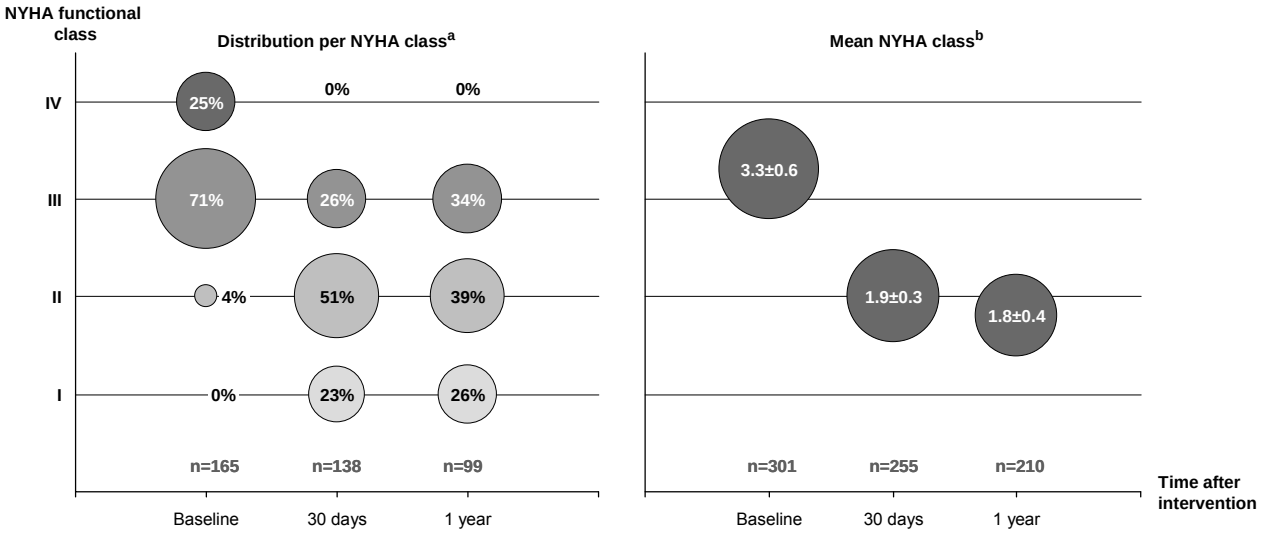


Figure 6: NYHA functional class improvement after TAVI (based on subset of studies reporting baseline, 30-day, and 1-year follow-up outcomes)



[a] Based on (Walther, T. et al. 2010, Thielmann, M. et al. 2009, Ye, J. et al. 2009)

[b] Based on (Walther, T. et al. 2010, Thielmann, M. et al. 2009, Ye, J. et al. 2009, Grube, E. et al. 2008)

Figure 7: Flow chart literature search results for review on medical therapy of AS

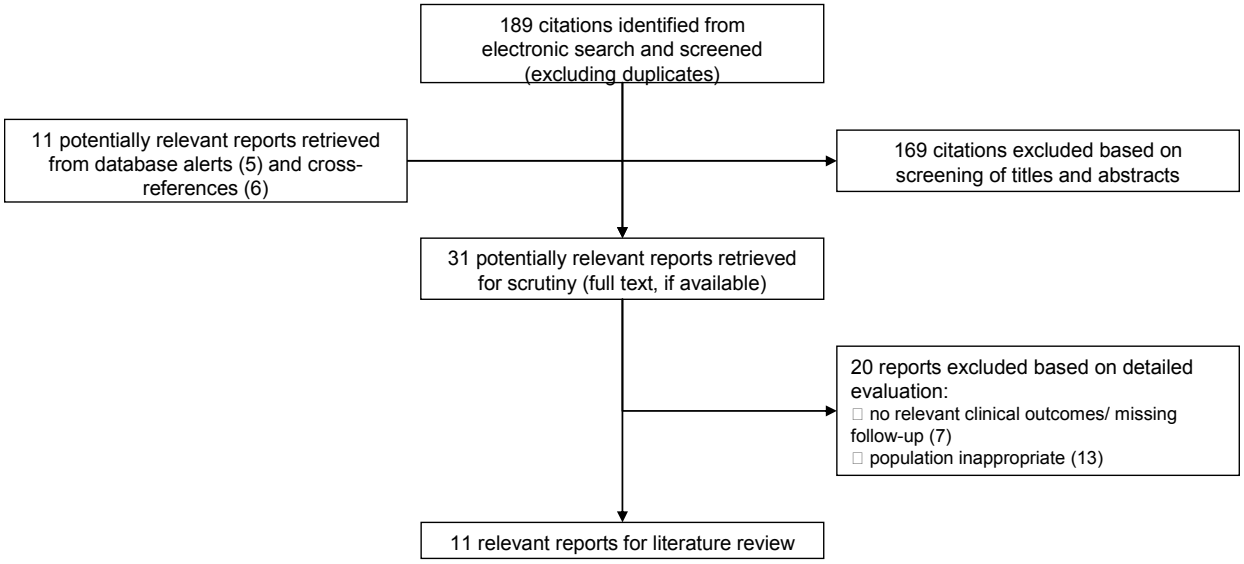
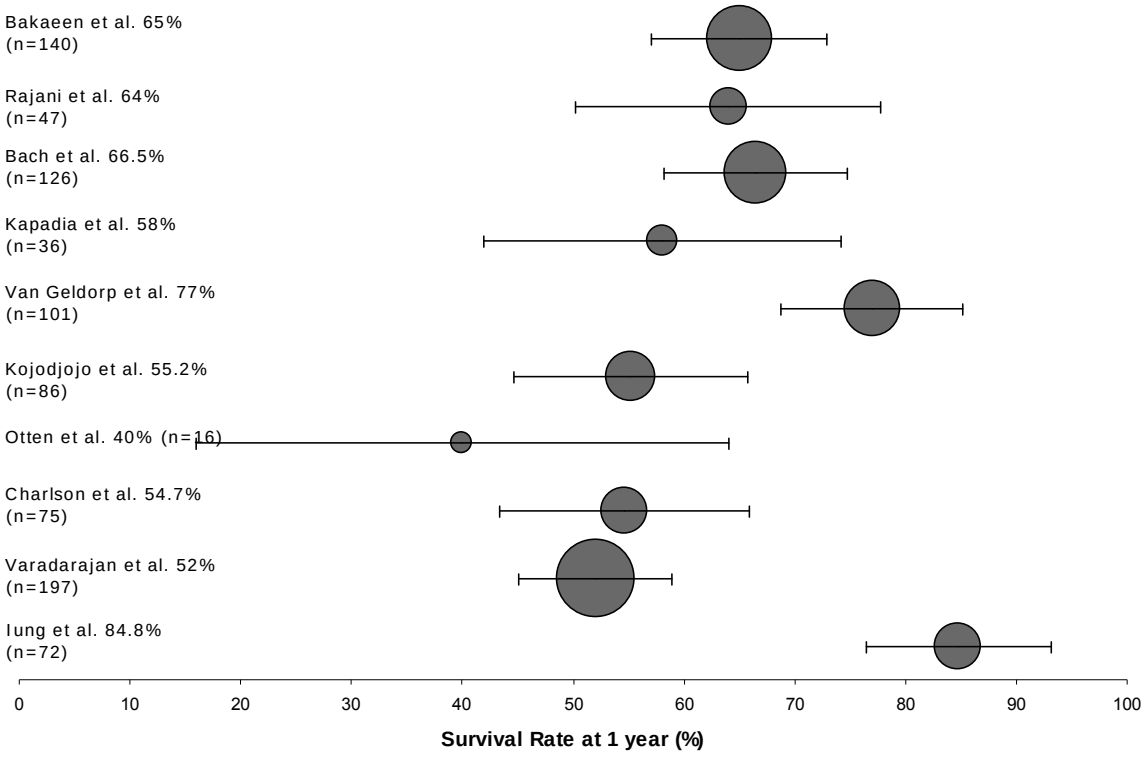
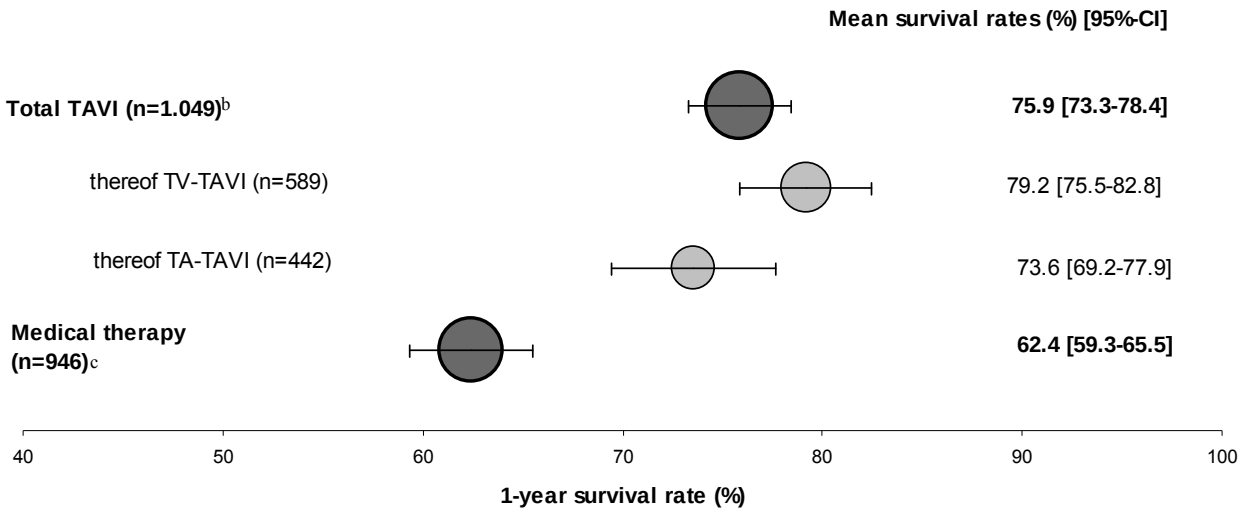


Figure 8: Mean 1-year survival rates (from literature) and approximated 95%-CI for medical treatment of AS [a]



[a] The area of bubbles represents the number of included patients (n).

Figure 9: 1-year survival rates resulting from information synthesis and approximated 95%-CI after TAVI or with medical treatment [a]

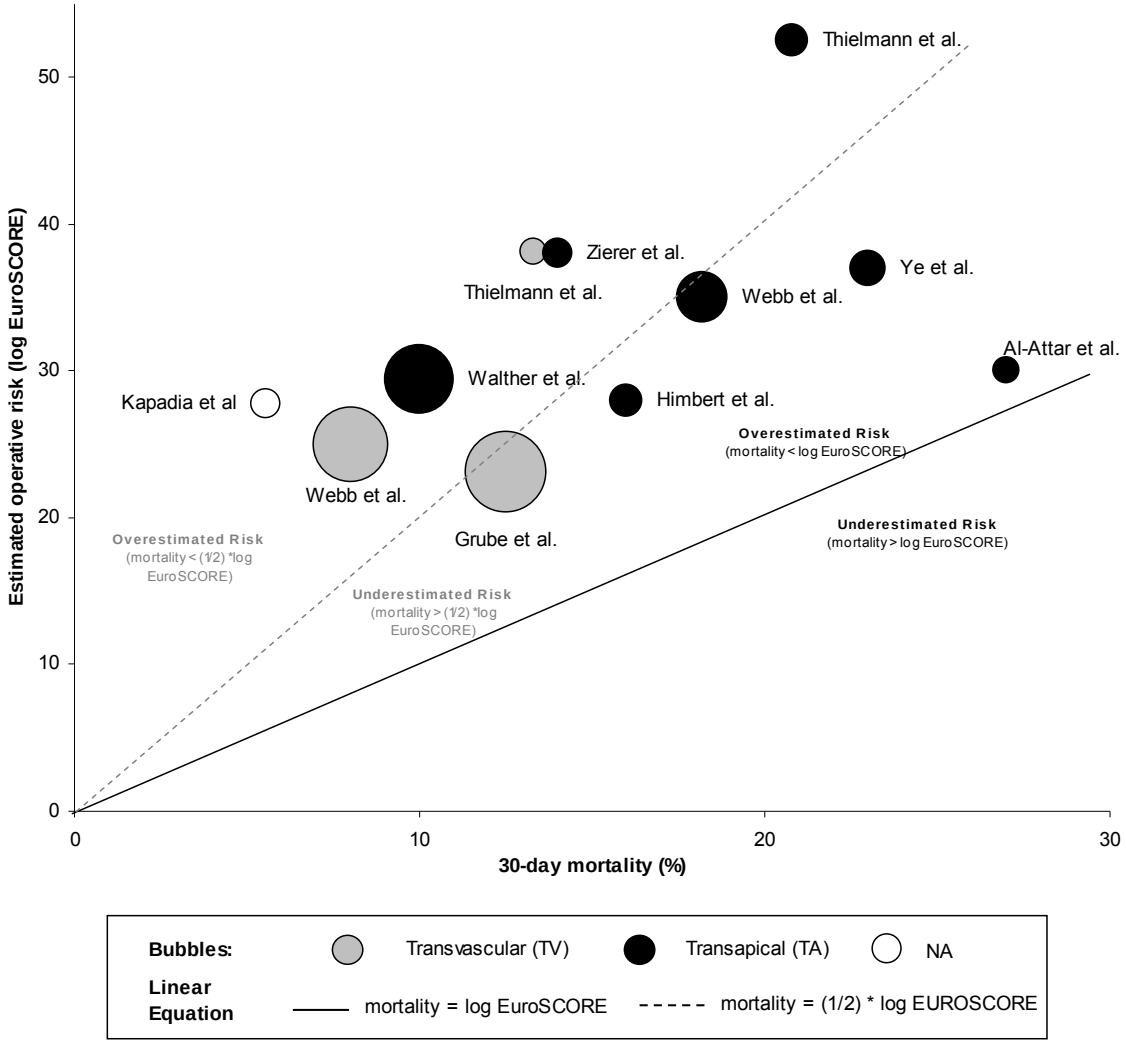


[a] The area of bubbles represents the number of included patients (n).

[b] An overview of included publications on TAVI is provided in the bibliograhy (6.2.1)

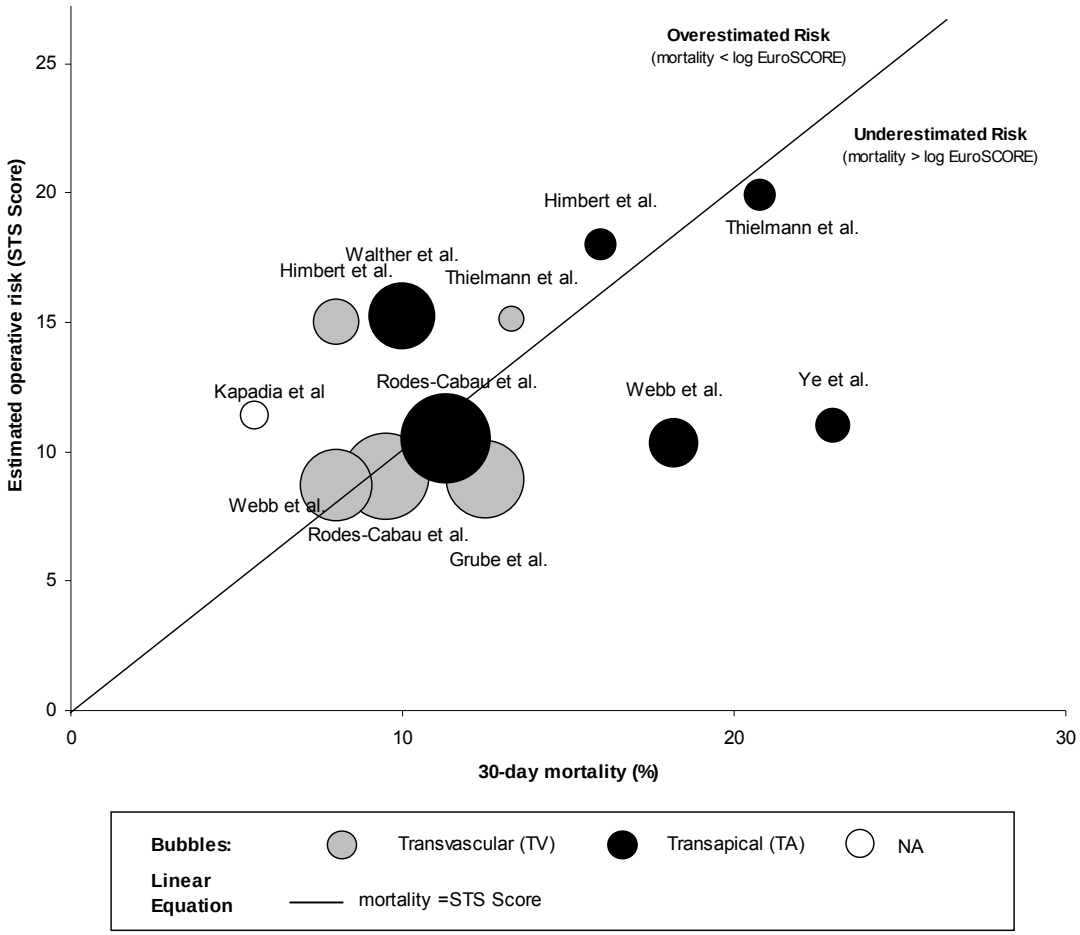
[c] An overview of included publications on medical therapy is provided in the bibliograhy (6.2.3)

Figure 10: Estimated operative risk (EuroSCORE) versus observed 30-day mortality rates [a]



[a] The area of bubbles represents the number of included patients (n).

Figure 11: Estimated operative risk (STS score) versus observed 30-day mortality rates[a]



[a] The area of bubbles represents the number of included patients (n).

7.5 Templates results section

7.5.1 Data extraction template TAVI

Table 17: Extracted data from included studies on TAVI

	Study characteristics								
	Number of patients			Enrollment period	Study center	Study design	Valve type	Mean duration follow-up (months)	
Publication	Total	TV	TV					Total	SD
Rodés-Cabau, J. et al. 2010	339	162	177	01/2005-06/2009	6 centers, Canada	prospective, multi-center study	Cribier-Edwards/ Edwards Sapien	8.0*	
Rajani, R. et al. 2010	38	38		12/2007-06/2009	Brighton, UK	retrospective, single-center, matched cohort study	CoreValve	8.8*	
Walther, T. et al. 2010	100		100	02/2006-01/2008	Leipzig, Germany	retrospective, single-center, matched cohort study	Edwards Sapien	12.0	
Al-Attar, N. et al. 2009	50	35	15	09/2006-05/2008	Paris, France	prospective, single-center cohort study	Edwards Sapien	8.6	5.6
Himbert, D. et al. 2009	75	51	24	10/2006-11/2008	Paris, France	prospective, single-center case series	Edwards Sapien	10.0	6.0
Kapadia, S. R. et al. 2009	18			02/2006-03/2007	Cleveland, USA	prospective, single-center cohort study	Cribier-Edwards	9.3	4.3
Thielmann, M. et al. 2009	39	15	24	05/2007-11/2008	Essen, Germany	prospective, single-center case series	Cribier-Edwards/ Edwards Sapien	12.0	
Webb, J. G. et al. 2009	168	113	55	01/2005-04/2008	Vancouver, Canada	prospective, single-center case series	Cribier-Edwards/ Edwards Sapien	7.4	
Ye, J. et al. 2009	26		26	10/2005-01/2007	Vancouver, Canada	prospective, single-center case series	Edwards Sapien	12.0	
Zierer, A. et al. 2009	21		21	01/2006-04/2007	Frankfurt, Germany	retrospective, single-center, matched cohort study	Cribier-Edwards	12.0	4.0
Grube, E. et al. 2008	136	136		02/2005-03/2008	Siegburg, Germany	prospective, single-center case series	CoreValve	12.0	
Otten, A. M. et al. 2008	39	39		09/2005-09/2007	Rotterdam, Netherlands	prospective, single-center cohort study	CoreValve	13.0	7.0

*—median

	Patient characteristics (at baseline, pre-operatively)																															
	Mean age (years)						Gender (% males)			Mean Operative Risk (log EuroSCORE) (%)						Mean Operative Risk (STS Score) (%)						Mean NYHA class						Distribution of NYHA class							
Publication	Total	SD	TV	SD TV	TA	SD TA	Total	TV	TA	Total	SD	TV	SD TV	TA	SD TA	Total	SD	TV	SD TV	TA	SD TA	Total	SD	TV	SD TV	TA	SD TA	NYHA class I		NYHA class II		NYHA class III		NYHA class IV	
																												abs.	%	abs.	%	abs.	%	abs.	%
Rodés-Cabau, J. et al. 2010	81.0	8.0	83.0	8.0	80.0	8.0	45	56	35							9.8	6.4	9.0	5.8	10.5	6.9													
Rajani, R. et al. 2010	83.0*		83.0*				55	55		24.0	15.0	24.0	15.0									2.6		2.6				3	8	11	29	21	55	3	8
Walther, T. et al. 2010	82.7	5.0			82.7	5.0	23		23	29.4	13.0			29.4	13.0	15.2	8.3			15.2	8.3	3.2	0.4			3.2	0.4	-	-	-	-	76	76	24	24
Al-Attar, N. et al. 2009	83.0	8.0	83.0	6.0	83.0	10.0	54	51	60	28.0	14.0	26.0	14.0	30.0	12.0	16.0	7.0	15.0	6.0	19.0	9.0	3.4		3.4		3.3		-	-	3	6	26	52	21	42
Himbert, D. et al. 2009	82.0	8.0	82.0	7.0	82.0	10.0	55	49	67	26.0	13.0	25.0	13.0	28.0	13.0	16.0	7.0	15.0	7.0	18.0	9.0	3.4		3.5		3.3				4	5	40	53	31	41
Kapadia, S. R. et al. 2009	81.0	6.0					67			27.8	18.8					11.4	7.5					3.7										6	33	12	67
Thielmann, M. et al. 2009	81.4	5.0	79.6	4.5	82.7	5.1	38	47	33	44.2	12.6	38.1	8.1	52.5	13.4	17.9	6.1	15.1	4.1	19.9	7.5	3.4	1.2	3.5	1.7	3.3	0.4	-	-	2	5	24	62	13	33
Webb, J. G. et al. 2009	84.0*		85.0*		83.0*		52	58	40	28.6*		25.0*		35.0*		9.1*		8.7*		10.3*		3.1						2	1	17	12	88	61	37	26
Ye, J. et al. 2009	80.1	9.1			80.1	9.1	50		50	37.0	20.0			37.0	20.0	11.0	6.0			11.0	6.0	3.0				2.8		-	-	5	19	17	65	4	16
Zierer, A. et al. 2009	85.0	6.0			85.0	6.0	29		29	38.0	14.0			38.0	14.0							3.4	0.4			3.4	0.4								
Grube, E. et al. 2008	81.5	6.9	81.5	6.9			42	42		23.1	15.0	23.1	15.0			8.9	6.5	8.9	6.5			3.3	0.5	3.3	0.5										
Otten, A. M. et al. 2008	81.0	7.0	81.0	7.0			46	46		15.0	6.0	15.0	6.0																						

*—median

	Degree of aortic stenosis at baseline																			
	Mean aortic valve area (cm²)						Mean transaortic mean gradient (mmHg)						Mean transaortic peak gradient (mmHg)		Mean LVEF (%)					
Publication	Total	SD	TV	SD TV	TA	SD TA	Total	SD	TV	SD TV	TA	SD TA	Total	SD	Total	SD	TV	SD TV	TA	SD TA
Rodés-Cabau, J. et al. 2010	0.63	0.17	0.63	0.16	0.63	0.18	46	17	48	18	44	17			55	14	55	14	56	14
Rajani, R. et al. 2010	0.66	0.20	0.66	0.20			56	17	56	17			99	26						
Walther, T. et al. 2010															54	15			54	15
Al-Attar, N. et al. 2009	0.61	0.16	0.60	0.16	0.63	0.17	51	14	52	15	48	12			49	15	50	16	45	13
Himbert, D. et al. 2009	0.64	0.16	0.63	0.16	0.65	0.17	52	15	54	15	48	14			51	15	52	16	48	13
Kapadia, S. R. et al. 2009	0.60	0.10					46	16					80	25	46	17				
Thielmann, M. et al. 2009	0.60	0.20					46	20							51	17	49	21	52	13
Webb, J. G. et al. 2009	0.60*		0.60*		0.60*		46*		48*		41*									
Ye, J. et al. 2009	0.50	0.10			0.50	0.10	45	14			45	14			56	13			56	13
Zierer, A. et al. 2009																				
Grube, E. et al. 2008	0.67	0.90	0.67	0.90			42	17	42	17			71	24	51	17	51	17		
Otten, A. M. et al. 2008																				

*—median

	Primary Outcome Measures (safety)																									
	Mean procedural success						Complications																			
Publication	Total		TV		TA		Major vascular complications/ injuries						Cerebral embolic events/ strokes						Infarction		Cardiac tamponade					
	abs.	%	abs.	%	abs.	%	abs.	%	TV abs.	TV %	TA abs.	TA %	abs.	%	TV abs.	TV %	TA abs.	TA %	abs.	%	abs.	%	TV abs.	TV %	TA abs.	TA %
Rodés-Cabau, J. et al. 2010	322	93.3	152	90.5	170	96.1	-	-	-	-	-	-	8	0.0	5	0.0	3	0.0	4	0.0	-	-	-	-	-	-
Rajani, R. et al. 2010	37	97.3	37	97.3			1	0.0	1	0.0			1	0.0	1	0.0			-	-	-	-	-	-		
Walther, T. et al. 2010	97	97.0			97	97.0	-	-			-	-	-	-			-	-	-	-	-	-			-	-
Al-Attar, N. et al. 2009	45	90.0	30	85.7	15	100.0	6	0.1	4	0.1	2	0.1	2	0.0	2	0.1	-	-	-	-	3	0.1	1	0.0	2	0.1
Himbert, D. et al. 2009	70	93.0	46	90.0	24	100.0	8	0.1	6	0.1	2	0.1	3	0.0	3	0.1	-	-	-	-	4	0.1	2	0.0	2	0.1
Kapadia, S. R. et al. 2009	17	94.0					-	-					-	-					-	-	-	-				
Thielmann, M. et al. 2009	38	97.4	15	100.0	23	95.8	5	0.1	5	0.3	-	-	1	0.0	1	0.1	-	-	-	-	1	0.0	1	0.1	-	-
Webb, J. G. et al. 2009	158	94.1					11	0.1	9	0.1	2	0.0	7	0.0	6	0.1	1	0.0	-	-	4	0.0	2	0.0	2	0.0
Ye, J. et al. 2009	26	100.0			26	100.0	-	-			-	-	1	0.0			1	0.0	1	0.0	-	-			-	-
Zierer, A. et al. 2009	21	100.0			21	100.0																				
Grube, E. et al. 2008	117	86.0	117	86.0			-	-	-	-			6	0.0	6	0.0			3	0.0	2	0.0	2	0.0		
Otten, A. M. et al. 2008																										

*—median

	Primary Outcome Measures (safety)																							
	Complications (continued)												Mean in-hospital/ 30d mortality (combined)						Mean 1-year survival (%)					
Publication	Heart block/ PPM						"Valve in Valve"						Total		TV		TA		Total		TV		TA	
	abs.	%	TV abs.	TV %	TA abs.	TA %	abs.	%	TV abs.	TV %	TA abs.	TA %	abs.	%	abs.	%	abs.	%	%	SD	%	SD	%	SD
Rodés-Cabau, J. et al. 2010	17	0.1	6	0.0	11	0.1	9	0.0	4	0.0	5	0.0	36	10.4	16	9.5	20	11.3	76.0	2.8	75.0	3.6	78.0	3.6
Rajani, R. et al. 2010	13	0.3	13	0.3			-	-	-	-			2	5.3	2	5.3			87.0		87.0			
Walther, T. et al. 2010	9	0.1			9	0.1	-	-			-	-	10	10.0			10	10.0	73.0	4.0			73.0	4.0
Al-Attar, N. et al. 2009	2	0.0	1	0.0	1	0.1	2	0.0	1	0.0	1	0.1	7	14.0	3	8.0	4	27.0	67.0	11.0	74.0	11.0	60.0	13.0
Himbert, D. et al. 2009	4	0.1	3	0.1	1	0.0	3	0.0	1	0.0	2	0.1	8	10.0	4	8.0	4	16.0	78.0	6.0	81.0	7.0	74.0	9.0
Kapadia, S. R. et al. 2009	1	0.1					-	-					1	5.6					78.0					
Thielmann, M. et al. 2009	4	0.1	4	0.3	-	-	1	0.0	-	-	1	0.0	7	17.9	2	13.3	5	20.8	64.1		68.1		61.9	
Webb, J. G. et al. 2009	9	0.1	5	0.0	4	0.1	-	-	-	-	-	-	19	11.3	9	8.0	10	18.2	73.8					
Ye, J. et al. 2009	3	0.1			3	0.1	-	-			-	-	6	23.0			6	23.0	65.4	9.5			65.4	
Zierer, A. et al. 2009													3	14.0			3	14.0	76.0				76.0	
Grube, E. et al. 2008	34	0.3	34	0.3			3	0.0	3	0.0			17	12.5	17	12.5			81.6		81.6			
Otten, A. M. et al. 2008																			87.0		87.0			

*—median

	Secondary outcomes (efficiency) - Improved valve function post-intervention																													
	Aortic regurgitation (in-hospital/ 30d)								Mean aortic valve area (cm²)								Mean transaortic mean gradient (mmHg)								Mean LVEF (%)							
Publication	Grade 0 (none/trace)		Grade 0 (trivial) - grade I (mild)		Grade II (moderate)		Grade III (severe)		in-hospital/ 30d FU		3m FU		6m FU		1y FU		in-hospital/ 30d FU		3m FU		6m FU		1y FU		in-hospital/ 30d FU		3m FU		6m FU		1y FU	
	abs.	%	abs.	%	abs.	%	abs.	%	Total	SD	Total	SD	Total	SD	Total	SD	Total	SD	Total	SD	Total	SD	Total	SD	%	SD	%	SD	%	SD	%	SD
Rodés-Cabau, J. et al. 2010			236	78	15	5	3	1	1.55	0.41							10	4														
Rajani, R. et al. 2010																																
Walther, T. et al. 2010																									56	13			59	12	58	12
Al-Attar, N. et al. 2009			35	78	7	15	3	7	1.72	0.46							11	4														
Himbert, D. et al. 2009			57	82	9	13	4	5	1.73	0.41	1.60		1.55		1.45		10	4	9		9		8		58		54		54		62	
Kapadia, S. R. et al. 2009																																
Thielmann, M. et al. 2009			23	75	8	25	0	0	1.70	0.60	1.40	0.30	1.60	0.50	1.70	0.60	12	5	13	5	13	5	10	4	51	17	53	12	56	12	59	9
Webb, J. G. et al. 2009			85	58	53	37	7	5	1.60	0.40					1.50	0.30	10	4					11	5								
Ye, J. et al. 2009			17	100							1.60	0.50	1.50	0.40	1.70	0.50			9	5	9	5	9	5	59	5			60	4	63	9
Zierer, A. et al. 2009															1.50	0.80							10	4								
Grube, E. et al. 2008			94	80	21	18	2	2															8	4								
Otten, A. M. et al. 2008																																

*—median

	Secondary Outcomes (efficacy)																							
Publication	Mean NYHA class (in-hospital/ 30d FU)	Distribution of NYHA class (in-hospital/ 30d FU)								Mean NYHA class (1-year FU)	Distribution of NYHA class (1-year FU)								Mean length of hospital stay (days)					
		NYHA class I		NYHA class II		NYHA class III		NYHA class IV			NYHA class I		NYHA class II		NYHA class III		NYHA class IV		Total	SD	TV	SD TV	TA	SD TA
		abs.	%	abs.	%	abs.	%	abs.	%		abs.	%	abs.	%	abs.	%	abs.	%						
Rodés-Cabau, J. et al. 2010																								
Rajani, R. et al. 2010																								
Walther, T. et al. 2010	2.3	7	7.8	51	56.3	32	35.9	-	-	2.4	6	8.8	34	47.1	32	44.1	-	-						
Al-Attar, N. et al. 2009																			15	8	15	6	19	10
Himbert, D. et al. 2009										1.8	20	33	35	57.0	6	10.0			13*		13*		12*	
Kapadia, S. R. et al. 2009																			12	6				
Thielmann, M. et al. 2009	1.6	15	48.0	14	45.0	2	7.0	-	-	1.3	8	80.0	1	10.0	1	10.0			13	10	11	9	12	10
Webb, J. G. et al. 2009																			6		5		7	
Ye, J. et al. 2009	1.6	9	53.0	6	35.0	2	12.0	-	-	1.4	12	71.0	4	23.0	1	6.0			9	5				
Zierer, A. et al. 2009																			5	0.9				
Grube, E. et al. 2008	1.7									1.5														
Otten, A. M. et al. 2008																								

*—median

7.5.2 Data extraction template medical therapy

Table 18: Extracted data from included studies on medical therapy of AS

	Study characteristics							
							Mean duration follow-up (months)	
Publication	Number of patients	Enrollment period	Study center	Study design	Intervention	Symptomatic status	Total	SD
Bakaeen, F. G. et al. 2010	140	01/1997-04/2008	Houston, TX, USA	retrospective, single-center, cohort study	medical therapy (n=140)/ surgical AVR (n=205)	71% symptomatic		
Rajani, R. et al. 2010	47	12/2007-06/2009	Brighton, UK	retrospective, single-center, matched cohort study	medical therapy (n=33)/ medical therapy + BAV (n=14)/ TAVi (n=38)	symptomatic	7.2*	
Bach, D. S. et al. 2009	126	01/2005-12/2005	Ann Arbour, MI, USA	retrospective, multi-center cohort study	medical therapy (n=126 symptomatic; n=65 asymptomatic)/ surgical AVR (n=205)	symptomatic	16.7	14.1
Kapadia, S. R. et al. 2009	36	02/2006-03/2007	Cleveland, OH, USA	prospective, single-center cohort study	medical therapy (n=36)/ TAVI (n=18)/ surgical AVR (n=19)/ BAV (n=19)	symptomatic	6.0	3.5
van Geldorp, M. W. A. et al. 2009	101	10/2004-12/2007	Netherlands	retrospective, multi-center cohort study	medical therapy (n=101)/ surgical AVR (n=76)	symptomatic	15.1	11.5
Kojodjojo, P. et al. 2008	86	01/2001-12/2006	Hertfordshire, UK	retrospective, multi-center cohort study	medical therapy (n=86)/ surgical AVR (n=15)	symptomatic	19.2	16.8
Otten, A. M. et al. 2008	16	09/2005-09/2007	Rotterdam, Netherlands	prospective, single-center cohort study	medical therapy (n=16)/ TAVI (n=39)/ surgical AVR (n=14)/ BAV (n=3)	81% symptomatic	11.0	7.0
Charlson, E. et al. 2006	75	01/1995-12/1997	Boston, MA, USA	retrospective, multi-center cohort study	medical therapy (n=75)/ AVR (n=49)	symptomatic		
Varadarajan, P. et al. 2006b	197	01/1993-12/2003	Los Angeles, CA, USA	retrospective, single-center cohort study	medical therapy (n=197)/ AVR (n=80)	symptomatic	30.0	
Iung, B. et al. 2005	72	04/2001-07/2001	Paris, France	prospective, multi-center cohort study	medical therapy (n=72)/ AVR (n=144)	symptomatic		
O'Keefe, J. H., JR et al. 1987	50	01/1978-12/1985	Rochester, MN, USA	retrospective, single-center case series	medical therapy (n=50)	symptomatic	20.1	

*—median

	Patient characteristics (at baseline, pre-operatively)																						*Primary Outcome (safety)*	
	Mean age (years)			Mean Operative Risk (log EuroSCORE) (%)		Mean Operative Risk (STS Score) (%)		Mean NYHA class	Distribution of NYHA class								Mean aortic valve area (cm²)		Mean transaortic mean gradient (mmHg)		Mean transaortic peak gradient (mmHg)		Mean LVEF (%)		Mean 1-year survival (%)	
Publication	Total	SD	Gender (% males)	Total	SD	Total	SD		NYHA class I		NYHA class II		NYHA class III		NYHA class IV		Total	SD	Total	SD	Total	SD	Total	SD	Total	SD
									abs.	%	abs.	%	abs.	%	abs.	%										
Bakaeen, F. G. et al. 2010	75.7	8.6		9.0	2.0																		42	15	65.0	8
Rajani, R. et al. 2010	81.0*		48	13.0				2.4	8	17	14	30	23	49	2	4	0.71	0.23	45	20	77	32			64.0	
Bach, D. S. et al. 2009	75.0	12.5	62			3.8*																			66.5	5
Kapadia, S. R. et al. 2009	83.0	8.0	47	25.4	17.6	12.6	9.2	3.5	-	-	-	-	19	53	17	47	0.70	0.20	41	17	72	29	48	16	58.0	
van Geldorp, M. W. A. et al. 2009	73.3	12.3	51	11.3	9.6			2.5									0.71	0.26			66	26			77.0	
Kojodjojo, P. et al. 2008	86.2		37	16.8	12.2												0.65	0.21					61		55.2	
Otten, A. M. et al. 2008	82.0	14.0	38	25.0	14.0																				40.0	
Charlson, E. et al. 2006	81.5	8.3	35																						54.7	
Varadarajan, P. et al. 2006b	85.3	4.1	42														0.68	0.16	39	15			50	21	52.0	
Iung, B. et al. 2005	81.7	4.8	43														0.73	0.23	52	20			52	18	84.8	5
O'Keefe, J. H., JR et al. 1987	77.0		72														0.57				81				57.0	

*—median

7.6 Literature search strategy

The following search strategies were used to identify papers on TAVI and medical therapy of AS in MEDLINE. A similar strategy was used to identify papers in other databases.

TAVI

#1 ("aortic stenosis"[MeSH Terms] OR "aortic valve stenosis") AND ("heart valve prosthesis"[MeSH Terms] OR "heart valve prosthesis implantation"[MeSH Terms] OR "valve replacement" OR "valve implantation" OR "aortic valve/surgery"[MeSH Terms] OR "aortic valve stenosis/surgery"[MeSH Terms])

#2 (#1) AND ("percutaneous" OR "transcatheter" OR "transvascular" OR "transapical" OR "transfemoral" OR "transluminal" OR "transaortic" OR "CoreValve" OR "Edwards Sapien" OR "Cribier")

#3 (#2) AND "humans"[MeSH Terms] AND (English[lang] OR German[lang]) AND ("adult"[MeSH Terms: noexp] OR "middle aged"[MeSH Terms] OR "aged"[MeSH Terms] OR "aged, 80 and over"[MeSH Terms])

Medical therapy of AS

#1 ("aortic stenosis"[MeSH Terms] OR "aortic valve stenosis") AND ("natural history" OR "natural course" OR (("medical" OR "conservative") AND ("therapy" OR "treatment" OR "management"))

#2 (#1) AND "humans"[MeSH Terms] AND (English[lang] OR German[lang]) AND ("adult"[MeSH Terms] OR "middle aged"[MeSH Terms] OR "aged"[MeSH Terms] OR "aged, 80 and over"[MeSH Terms])

7.7 Evaluation of study quality

7.7.1 Primary publications included for review on TAVI

Checklist 2a

Checklist 2a: Primary studies (RCTs / case-control studies / cohort studies / longitudinal studies / case series)					
Report No.: 9.5.1.1.1					
Title:	Transcatheter Aortic Valve Implantation for the Treatment of Severe Symptomatic Aortic Stenosis in Patients at Very High or Prohibitive Surgical Risk: Acute and Late Outcomes of the Multicenter Canadian Experience				
Authors:	Rodés-Cabau, J. et al. 2010				
Source:	J Am Coll Cardiol. 2010; 55: 1080–1090				
Document type	RCT: ☐ Cohort study: ☐ Case-control study: ☐ Longitudinal study: ☐ Case series: ☒ Other: ☐				
Clas	A	Selection of study participants	Yes	No	?
QA	1.	Are the inclusion and exclusion criteria for study participants sufficiently / clearly defined?	☒	☐	☐
QA	2.	Have the inclusion and exclusion criteria been defined before the intervention?	☒	☐	☐
QA	3.	Has the disease status been assessed in a valid and reliable manner?	☒	☐	☐
QBI	4.	Are the diagnostic criteria of the disease described?	☐	☒	☐
QB	5.	Is the study population / exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6.	For cohort studies: Were the study groups considered simultaneously?	☐	☐	☐
	7.	Has the determination of the sample size been specified?	☒	☐	☐
	8.	Are the period of recruitment and follow-up indicated?	☒	☐	☐
	B	Assignment and study participation	Yes	No	?
QA	1.	Do the exposed / cases and non-exposed/ controls come from a similar population?	☐	☐	☐
QA	2.	Are the intervention/ exposed group and the control/ non-exposed group comparable at baseline?			
		a) with respect to demographic characteristics	☐	☐	☐
		b) with respect to clinical characteristics	☐	☐	☐
QB	3.	Was the selection conducted randomized with a standard procedure?	☐	☒	☐
		a) was the allocation sequence generated by an accepted procedure?	☐	☐	☐
		b) was the allocation sequence concealed until the intervention?	☐	☐	☐
QC	4.	Was the randomization blinded?	☐	☐	☐
		a) for the patient	☐	☐	☐
		b) for the intervening physician	☐	☐	☐
QA	5.	Were known / possible confounders taken into account at the start of the study?	☐	☐	☒
	C	Intervention / Exposure	Yes	No	?
QA	1.	Were intervention or exposure recorded in a valid, reliable and similar manner?	☒	☐	☐
QB	2.	Were the intervention / control groups - with the exception of the intervention - treated alike?	☐	☐	☐
QB	3.	In case of different therapies, have they been recorded in a valid and reliable manner?	☐	☐	☐
QA	4.	For RCTs: Have placebos been used for the control groups?	☐	☐	☐
QA	5.	For RCTs: has the administration of placebos been documented?	☐	☐	☐
	D	Study Administration	Yes	No	?
QB	1.	Is there evidence of an "Overmatching"?	☐	☒	☐
QB	2.	In multicenter studies: were the diagnostic and therapeutic methods, and the outcome measurement identical in all participating centers?	☒	☐	☐
QA	3.	Was it ensured that study participants did not change between intervention and control groups?	☐	☐	☐
	E	Outcome measurement	Yes	No	?
I	1.	Were point-of-care outcome parameters used?	☐	☒	☐
QA	2.	Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
Q B	3.	Was the outcome measurement blinded?	☐	☒	☐
QC	4.	In case series: was the distribution of prognostic factors adequately covered?	☒	☐	☐
	F	Drop Outs	Yes	No	?
QA	1.	Was the response rate in intervention / control groups high enough or in cohort studies: could a sufficiently large part of the cohort be followed-up over the entire study period?	☒	☐	☐
QA	2.	Were the reasons for the drop-outs of study participants listed?	☐	☒	☐

QB	3.	Were the outcomes of the drop-outs described and considered in the evaluation?	☐	☒	☐
QB	4.	If differences were found - are they significant?	☐	☐	☐
QB	5.	If differences were found - are they relevant?	☐	☐	☐
	G	Statistical analysis	Yes	No	?
QA	1.	Are the described analytical procedures correct and is that information sufficient for a proper evaluation?	☒	☐	☐
	2.	For RCT: was an intention-to-treat analysis conducted?	☐	☐	☐
		a) Were all randomized individuals analyzed within the group to which they were assigned?	☐	☐	☐
		b) Were deviations of the non-randomized cases reported that were included in the analysis?	☐	☐	☐
		c) Has the effect of missing values been analyzed?	☐	☐	☐
QB	3.	Have the effect estimates and their precision (e.g. confidence intervals) been reported for all primary and secondary outcomes for each group?	☒	☐	☐
	4.	Has the distinction between a priori defined analysis and exploratory analysis been made and was the problem of multiple testing of hypotheses considered?	☐	☒	☐
I	5.	Are the results presented in a graphical form and are the underlying values for the graphics expressed?	☒	☐	☐
	H	Discussion	Yes	No	?
	1.	Are the following points in respect to the interpretation of results sufficiently covered?			
		a) the reference to the study hypothesis	☒	☐	☐
		b) the sources of distortion	☐	☒	☐
		c) statistical uncertainties	☐	☒	☐
		d) hazard multiple testing	☐	☒	☐
	2.	Was the external validity (generalizability) of the study results discussed?	☒	☐	☐
	3.	Were the study results discussed in the context of current evidence?	☒	☐	☐
Final assessment: This publication is included ☒ excluded ☐					

Checklist 2a

Checklist 2a: Primary studies (RCTs / case-control studies / cohort studies / longitudinal studies / case series)					
Report No.: 9.5.1.1.2					
Title:	Prognostic benefit of transcatheter aortic valve implantation compared with medical therapy in patients with inoperable aortic stenosis				
Authors:	Rajani, R. et al. 2010				
Source:	Catheter Cardiovasc Interv. 2010;75:1121–1126				
Document type	RCT: ☐ Cohort study: ☒ Case-control study: ☐ Longitudinal study: ☐ Case series: ☐ Other: ☐				
Clas	A	Selection of study participants	Yes	No	?
QA	1.	Are the inclusion and exclusion criteria for study participants sufficiently / clearly defined?	☒	☐	☐
QA	2.	Have the inclusion and exclusion criteria been defined before the intervention?	☒	☐	☐
QA	3.	Has the disease status been assessed in a valid and reliable manner?	☒	☐	☐
QBI	4.	Are the diagnostic criteria of the disease described?	☐	☒	☐
QB	5.	Is the study population / exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6.	For cohort studies: Were the study groups considered simultaneously?	☒	☐	☐
	7.	Has the determination of the sample size been specified?	☐	☒	☐
	8.	Are the period of recruitment and follow-up indicated?	☒	☐	☐
	B	Assignment and study participation	Yes	No	?
QA	1.	Do the exposed / cases and non-exposed/ controls come from a similar population?	☒	☐	☐
QA	2.	Are the intervention/ exposed group and the control/ non-exposed group comparable at baseline?			
		a) with respect to demographic characteristics	☒	☐	☐
		b) with respect to clinical characteristics	☒	☐	☐
QB	3.	Was the selection conducted randomized with a standard procedure?	☐	☒	☐
		a) was the allocation sequence generated by an accepted procedure?	☐	☐	☐
		b) was the allocation sequence concealed until the intervention?	☐	☐	☐
QC	4.	Was the randomization blinded?	☐	☐	☐
		a) for the patient	☐	☐	☐
		b) for the intervening physician	☐	☐	☐
QA	5.	Were known / possible confounders taken into account at the start of the study?	☐	☐	☒
	C	Intervention / Exposure	Yes	No	?
QA	1.	Were intervention or exposure recorded in a valid, reliable and similar manner?	☒	☐	☐
QB	2.	Were the intervention / control groups - with the exception of the intervention - treated alike?	☐	☐	☒
QB	3.	In case of different therapies, have they been recorded in a valid and reliable manner?	☐	☐	☒
QA	4.	For RCTs: Have placebos been used for the control groups?	☐	☐	☐
QA	5.	For RCTs: has the administration of placebos been documented?	☐	☐	☐
	D	Study Administration	Yes	No	?
QB	1.	Is there evidence of an "Overmatching"?	☐	☒	☐
QB	2.	In multicenter studies: were the diagnostic and therapeutic methods, and the outcome measurement identical in all participating centers?	☐	☐	☐
QA	3.	Was it ensured that study participants did not change between intervention and control groups?	☐	☐	☒
	E	Outcome measurement	Yes	No	?
I	1.	Were point-of-care outcome parameters used?	☐	☐	☒
QA	2.	Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
Q B	3.	Was the outcome measurement blinded?	☐	☒	☐
QC	4.	In case series: was the distribution of prognostic factors adequately covered?	☐	☐	☐
	F	Drop Outs	Yes	No	?
QA	1.	Was the response rate in intervention / control groups high enough or in cohort studies: could a sufficiently large part of the cohort be followed-up over the entire study period?	☒	☐	☐
QA	2.	Were the reasons for the drop-outs of study participants listed?	☐	☒	☐
QB	3.	Were the outcomes of the drop-outs described and considered in the evaluation?	☐	☒	☐
QB	4.	If differences were found - are they significant?	☐	☐	☐
QB	5.	If differences were found - are they relevant?	☐	☐	☐
	G	Statistical analysis	Yes	No	?
QA	1.	Are the described analytical procedures correct and is that information sufficient for a proper evaluation?	☒	☐	☐
	2.	For RCT: was an intention-to-treat analysis conducted?	☐	☐	☐
		a) Were all randomized individuals analyzed within the group to which they were assigned?	☐	☐	☐
		b) Were deviations of the non-randomized cases reported that were included in the analysis?	☐	☐	☐
		c) Has the effect of missing values been analyzed?	☐	☐	☐

QB	3.	Have the effect estimates and their precision (e.g. confidence intervals) been reported for all primary and secondary outcomes for each group?	☒	☐	☐
	4.	Has the distinction between a priori defined analysis and exploratory analysis been made and was the problem of multiple testing of hypotheses considered?	☐	☒	☐
I	5.	Are the results presented in a graphical form and are the underlying values for the graphics expressed?	☒	☐	☐
	H	Discussion	Yes	No	?
	1.	Are the following point in respect to the interpretation of results sufficiently covered?			
		a) the reference to the study hypothesis	☒	☐	☐
		b) the sources of distortion	☒	☐	☐
		c) statistical uncertainties	☐	☒	☐
		d) hazard multiple testing	☐	☒	☐
	2.	Was the external validity (generalizability) of the study results discussed?	☒	☐	☐
	3.	Were the study results discussed in the context of current evidence?	☒	☐	☐
Final assessment: This publication is included ☒ excluded ☐					

Checklist 2a

Checklist 2a: Primary studies (RCTs / case-control studies / cohort studies / longitudinal studies / case series)					
Report No.: 9.5.1.1.3					
Title:	Transapical aortic valve implantation in 100 consecutive patients: comparison to propensity-matched conventional aortic valve replacement				
Authors:	Walther, T. et al. 2010				
Source:	Eur H J 2010;31:1398-1403				
Document type	RCT: ☐ Cohort study: ☒ Case-control study: ☐ Longitudinal study: ☐ Case series: ☐ Other: ☐				
Clas	A	Selection of study participants	Yes	No	?
QA	1.	Are the inclusion and exclusion criteria for study participants sufficiently / clearly defined?	☒	☐	☐
QA	2.	Have the inclusion and exclusion criteria been defined before the intervention?	☐	☒	☐
QA	3.	Has the disease status been assessed in a valid and reliable manner?	☒	☐	☐
QBI	4.	Are the diagnostic criteria of the disease described?	☐	☒	☐
QB	5.	Is the study population / exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6.	For cohort studies: Were the study groups considered simultaneously?	☐	☒	☐
	7.	Has the determination of the sample size been specified?	☐	☒	☐
	8.	Are the period of recruitment and follow-up indicated?	☒	☐	☐
	B	Assignment and study participation	Yes	No	?
QA	1.	Do the exposed / cases and non-exposed/ controls come from a similar population?	☒	☐	☐
QA	2.	Are the intervention/ exposed group and the control/ non-exposed group comparable at baseline?			
		a) with respect to demographic characteristics	☒	☐	☐
		b) with respect to clinical characteristics	☒	☐	☐
QB	3.	Was the selection conducted randomized with a standard procedure?	☐	☒	☐
		a) was the allocation sequence generated by an accepted procedure?	☐	☐	☐
		b) was the allocation sequence concealed until the intervention?	☐	☐	☐
QC	4.	Was the randomization blinded?	☐	☐	☐
		a) for the patient	☐	☐	☐
		b) for the intervening physician	☐	☐	☐
QA	5.	Were known / possible confounders taken into account at the start of the study?	☐	☐	☒
	C	Intervention / Exposure	Yes	No	?
QA	1.	Were intervention or exposure recorded in a valid, reliable and similar manner?	☒	☐	☐
QB	2.	Were the intervention / control groups - with the exception of the intervention - treated alike?	☐	☒	☐
QB	3.	In case of different therapies, have they been recorded in a valid and reliable manner?	☐	☒	☐
QA	4.	For RCTs: Have placebos been used for the control groups?	☐	☐	☐
QA	5.	For RCTs: has the administration of placebos been documented?	☐	☐	☐
	D	Study Administration	Yes	No	?
QB	1.	Is there evidence of an "Overmatching"?	☐	☒	☐
QB	2.	In multicenter studies: were the diagnostic and therapeutic methods, and the outcome measurement identical in all participating centers?	☐	☐	☐
QA	3.	Was it ensured that study participants did not change between intervention and control groups?	☐	☐	☐
	E	Outcome measurement	Yes	No	?
I	1.	Were point-of-care outcome parameters used?	☐	☐	☒
QA	2.	Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
Q B	3.	Was the outcome measurement blinded?	☐	☒	☐
QC	4.	In case series: was the distribution of prognostic factors adequately covered?	☐	☐	☐
	F	Drop Outs	Yes	No	?
QA	1.	Was the response rate in intervention / control groups high enough or in cohort studies: could a sufficiently large part of the cohort be followed-up over the entire study period?	☒	☐	☐
QA	2.	Were the reasons for the drop-outs of study participants listed?	☐	☒	☐
QB	3.	Were the outcomes of the drop-outs described and considered in the evaluation?	☐	☒	☐
QB	4.	If differences were found - are they significant?	☐	☐	☐
QB	5.	If differences were found - are they relevant?	☐	☐	☐
	G	Statistical analysis	Yes	No	?
QA	1.	Are the described analytical procedures correct and is that information sufficient for a proper evaluation?	☒	☐	☐
	2.	For RCT: was an intention-to-treat analysis conducted?	☐	☐	☐
		a) Were all randomized individuals analyzed within the group to which they were assigned?	☐	☐	☐
		b) Were deviations of the non-randomized cases reported that were included in the analysis?	☐	☐	☐
		c) Has the effect of missing values been analyzed?	☐	☐	☐

QB	3.	Have the effect estimates and their precision (e.g. confidence intervals) been reported for all primary and secondary outcomes for each group?	☒	☐	☐
	4.	Has the distinction between a priori defined analysis and exploratory analysis been made and was the problem of multiple testing of hypotheses considered?	☐	☒	☐
I	5.	Are the results presented in a graphical form and are the underlying values for the graphics expressed?	☒	☐	☐
	H	Discussion	Yes	No	?
	1.	Are the following points in respect to the interpretation of results sufficiently covered?			
		a) the reference to the study hypothesis	☒	☐	☐
		b) the sources of distortion	☒	☐	☐
		c) statistical uncertainties	☐	☒	☐
		d) hazard multiple testing	☐	☒	☐
	2.	Was the external validity (generalizability) of the study results discussed?	☒	☐	☐
	3.	Were the study results discussed in the context of current evidence?	☒	☐	☐
Final assessment: This publication is included ☒ excluded ☐					

Checklist 2a

Checklist 2a: Primary studies (RCTs / case-control studies / cohort studies / longitudinal studies / case series)					
Report No.: 9.5.1.1.4					
Title:	Transcatheter aortic valve implantation: Selection strategy is crucial for outcome				
Authors:	Al-Attar, N. et al. 2009				
Source:	Ann Thorac Surg 2009;87:1757-1763				
Document type	RCT: ☐ Cohort study: ☐ Case-control study: ☐ Longitudinal study: ☐ Case series: ☒ Other: ☐				
Clas	A	Selection of study participants	Yes	No	?
QA	1.	Are the inclusion and exclusion criteria for study participants sufficiently / clearly defined?	☐	☒	☐
QA	2.	Have the inclusion and exclusion criteria been defined before the intervention?	☒	☐	☐
QA	3.	Has the disease status been assessed in a valid and reliable manner?	☒	☐	☐
QBI	4.	Are the diagnostic criteria of the disease described?	☐	☒	☐
QB	5.	Is the study population / exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6.	For cohort studies: Were the study groups considered simultaneously?	☐	☒	☐
	7.	Has the determination of the sample size been specified?	☐	☒	☐
	8.	Are the period of recruitment and follow-up indicated?	☒	☐	☐
	B	Assignment and study participation	Yes	No	?
QA	1.	Do the exposed / cases and non-exposed/ controls come from a similar population?	☐	☐	☐
QA	2.	Are the intervention/ exposed group and the control/ non-exposed group comparable at baseline?			
		a) with respect to demographic characteristics	☐	☐	☐
		b) with respect to clinical characteristics	☐	☐	☐
QB	3.	Was the selection conducted randomized with a standard procedure?	☐	☒	☐
		a) was the allocation sequence generated by an accepted procedure?	☐	☐	☐
		b) was the allocation sequence concealed until the intervention?	☐	☐	☐
QC	4.	Was the randomization blinded?	☐	☐	☐
		a) for the patient	☐	☐	☐
		b) for the intervening physician	☐	☐	☐
QA	5.	Were known / possible confounders taken into account at the start of the study?	☐	☐	☒
	C	Intervention / Exposure	Yes	No	?
QA	1.	Were intervention or exposure recorded in a valid, reliable and similar manner?	☒	☐	☐
QB	2.	Were the intervention / control groups - with the exception of the intervention - treated alike?	☐	☐	☐
QB	3.	In case of different therapies, have they been recorded in a valid and reliable manner?	☐	☐	☐
QA	4.	For RCTs: Have placebos been used for the control groups?	☐	☐	☐
QA	5.	For RCTs: has the administration of placebos been documented?	☐	☐	☐
	D	Study Administration	Yes	No	?
QB	1.	Is there evidence of an "Overmatching"?	☐	☒	☐
QB	2.	In multicenter studies: were the diagnostic and therapeutic methods, and the outcome measurement identical in all participating centers?	☐	☐	☐
QA	3.	Was it ensured that study participants did not change between intervention and control groups?	☐	☐	☐
	E	Outcome measurement	Yes	No	?
I	1.	Were point-of-care outcome parameters used?	☐	☐	☒
QA	2.	Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3.	Was the outcome measurement blinded?	☐	☒	☐
QC	4.	In case series: was the distribution of prognostic factors adequately covered?	☐	☒	☐
	F	Drop Outs	Yes	No	?
QA	1.	Was the response rate in intervention / control groups high enough or in cohort studies: could a sufficiently large part of the cohort be followed-up over the entire study period?	☒	☐	☐
QA	2.	Were the reasons for the drop-outs of study participants listed?	☐	☐	☐
QB	3.	Were the outcomes of the drop-outs described and considered in the evaluation?	☐	☐	☐
QB	4.	If differences were found - are they significant?	☐	☐	☐
QB	5.	If differences were found - are they relevant?	☐	☐	☐
	G	Statistical analysis	Yes	No	?
QA	1.	Are the described analytical procedures correct and is that information sufficient for a proper evaluation?	☒	☐	☐
	2.	For RCT: was an intention-to-treat analysis conducted?	☐	☐	☐
		a) Were all randomized individuals analyzed within the group to which they were assigned?	☐	☐	☐
		b) Were deviations of the non-randomized cases reported that were included in the analysis?	☐	☐	☐
		c) Has the effect of missing values been analyzed?	☐	☐	☐

QB	3.	Have the effect estimates and their precision (e.g. confidence intervals) been reported for all primary and secondary outcomes for each group?	☐	☒	☐
	4.	Has the distinction between a priori defined analysis and exploratory analysis been made and was the problem of multiple testing of hypotheses considered?	☐	☒	☐
I	5.	Are the results presented in a graphical form and are the underlying values for the graphics expressed?	☒	☐	☐
	H	Discussion	Yes	No	?
	1.	Are the following points in respect to the interpretation of results sufficiently covered?			
		a) the reference to the study hypothesis	☒	☐	☐
		b) the sources of distortion	☒	☐	☐
		c) statistical uncertainties	☐	☒	☐
		d) hazard multiple testing	☐	☒	☐
	2.	Was the external validity (generalizability) of the study results discussed?	☒	☐	☐
	3.	Were the study results discussed in the context of current evidence?	☒	☐	☐
Final assessment: This publication is included ☒ excluded ☐					

Checklist 2a

Checklist 2a: Primary studies (RCTs / case-control studies / cohort studies / longitudinal studies / case series)					
Report No.: 9.5.1.1.5					
Title:	Results of transfemoral and transapical aortic valve implantation following a uniform assessment in high-risk patients with aortic stenosis				
Authors:	Himbert, D. et al. 2009				
Source:	JACC 2009;54:303-311				
Document type	RCT: ☐	Cohort study: ☐	Case-control study: ☐	Longitudinal study: ☐	
	Case series: ☒	Other: ☐			

Clas		A Selection of study participants	Yes	No	?
QA	1.	Are the inclusion and exclusion criteria for study participants sufficiently / clearly defined?	☒	☐	☐
QA	2.	Have the inclusion and exclusion criteria been defined before the intervention?	☒	☐	☐
QA	3.	Has the disease status been assessed in a valid and reliable manner?	☒	☐	☐
QBI	4.	Are the diagnostic criteria of the disease described?	☒	☐	☐
QB	5.	Is the study population / exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6.	For cohort studies: Were the study groups considered simultaneously?	☐	☐	☐
	7.	Has the determination of the sample size been specified?	☐	☒	☐
	8.	Are the period of recruitment and follow-up indicated?	☒	☐	☐
		B Assignment and study participation	Yes	No	?
QA	1.	Do the exposed / cases and non-exposed/ controls come from a similar population?	☐	☐	☐
QA	2.	Are the intervention/ exposed group and the control/ non-exposed group comparable at baseline?			
		a) with respect to demographic characteristics	☐	☐	☐
		b) with respect to clinical characteristics	☐	☐	☐
QB	3.	Was the selection conducted randomized with a standard procedure?	☐	☒	☐
		a) was the allocation sequence generated by an accepted procedure?	☐	☐	☐
		b) was the allocation sequence concealed until the intervention?	☐	☐	☐
QC	4.	Was the randomization blinded?	☐	☐	☐
		a) for the patient	☐	☐	☐
		b) for the intervening physician	☐	☐	☐
QA	5.	Were known / possible confounders taken into account at the start of the study?	☐	☐	☐
		C Intervention / Exposure	Yes	No	?
QA	1.	Were intervention or exposure recorded in a valid, reliable and similar manner?	☒	☐	☐
QB	2.	Were the intervention / control groups - with the exception of the intervention - treated alike?	☐	☐	☐
QB	3.	In case of different therapies, have they been recorded in a valid and reliable manner?	☐	☐	☐
QA	4.	For RCTs: Have placebos been used for the control groups?	☐	☐	☐
QA	5.	For RCTs: has the administration of placebos been documented?	☐	☐	☐
		D Study Administration	Yes	No	?
QB	1.	Is there evidence of an "Overmatching"?	☐	☒	☐
QB	2.	In multicenter studies: were the diagnostic and therapeutic methods, and the outcome measurement identical in all participating centers?	☐	☐	☐
QA	3.	Was it ensured that study participants did not change between intervention and control groups?	☐	☐	☐
		E Outcome measurement	Yes	No	?
I	1.	Were point-of-care outcome parameters used?	☐	☐	☒
QA	2.	Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3.	Was the outcome measurement blinded?	☐	☒	☐
QC	4.	In case series: was the distribution of prognostic factors adequately covered?	☒	☐	☐
		F Drop Outs	Yes	No	?
QA	1.	Was the response rate in intervention / control groups high enough or in cohort studies: could a sufficiently large part of the cohort be followed-up over the entire study period?	☒	☐	☐
QA	2.	Were the reasons for the drop-outs of study participants listed?	☐	☐	☐
QB	3.	Were the outcomes of the drop-outs described and considered in the evaluation?	☐	☐	☐
QB	4.	If differences were found - are they significant?	☐	☐	☐
QB	5.	If differences were found - are they relevant?	☐	☐	☐
		G Statistical analysis	Yes	No	?
QA	1.	Are the described analytical procedures correct and is that information sufficient for a proper evaluation?	☒	☐	☐
	2.	For RCT: was an intention-to-treat analysis conducted?	☐	☐	☐
		a) Were all randomized individuals analyzed within the group to which they were assigned?	☐	☐	☐
		b) Were deviations of the non-randomized cases reported that were included in the analysis?	☐	☐	☐
		c) Has the effect of missing values been analyzed?	☐	☐	☐

QB	3.	Have the effect estimates and their precision (e.g. confidence intervals) been reported for all primary and secondary outcomes for each group?	☒	☐	☐
	4.	Has the distinction between a priori defined analysis and exploratory analysis been made and was the problem of multiple testing of hypotheses considered?	☐	☒	☐
I	5.	Are the results presented in a graphical form and are the underlying values for the graphics expressed?	☒	☐	☐
	H	Discussion	Yes	No	?
	1.	Are the following points in respect to the interpretation of results sufficiently covered?			
		a) the reference to the study hypothesis	☒	☐	☐
		b) the sources of distortion	☒	☐	☐
		c) statistical uncertainties	☒	☐	☐
		d) hazard multiple testing	☒	☐	☐
	2.	Was the external validity (generalizability) of the study results discussed?	☒	☐	☐
	3.	Were the study results discussed in the context of current evidence?	☒	☐	☐
Final assessment: This publication is included ☒ excluded ☐					

Checklist 2a

Checklist 2a: Primary studies (RCTs / case-control studies / cohort studies / longitudinal studies / case series)					
Report No.: 9.5.1.1.6					
Title:	Characterization and outcome of patients with severe symptomatic aortic stenosis referred for percutaneous aortic valve replacement				
Authors:	Kapadia, S. R. et al. 2009				
Source:	J Thorac Cardiovasc Surg 2009;137:1430-1435				
Document type	RCT: ☐ Cohort study: ☒ Case-control study: ☐ Longitudinal study: ☐ Case series: ☐ Other: ☐				
Clas	A	Selection of study participants	Yes	No	?
QA	1.	Are the inclusion and exclusion criteria for study participants sufficiently / clearly defined?	☒	☐	☐
QA	2.	Have the inclusion and exclusion criteria been defined before the intervention?	☒	☐	☐
QA	3.	Has the disease status been assessed in a valid and reliable manner?	☒	☐	☐
QBI	4.	Are the diagnostic criteria of the disease described?	☒	☐	☐
QB	5.	Is the study population / exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6.	For cohort studies: Were the study groups considered simultaneously?	☐	☒	☐
	7.	Has the determination of the sample size been specified?	☐	☒	☐
	8.	Are the period of recruitment and follow-up indicated?	☒	☐	☐
	B	Assignment and study participation	Yes	No	?
QA	1.	Do the exposed / cases and non-exposed/ controls come from a similar population?	☒	☐	☐
QA	2.	Are the intervention/ exposed group and the control/ non-exposed group comparable at baseline?			
		a) with respect to demographic characteristics	☒	☐	☐
		b) with respect to clinical characteristics	☒	☐	☐
QB	3.	Was the selection conducted randomized with a standard procedure?	☐	☒	☐
		a) was the allocation sequence generated by an accepted procedure?	☐	☐	☐
		b) was the allocation sequence concealed until the intervention?	☐	☐	☐
QC	4.	Was the randomization blinded?	☐	☐	☐
		a) for the patient	☐	☐	☐
		b) for the intervening physician	☐	☐	☐
QA	5.	Were known / possible confounders taken into account at the start of the study?	☒	☐	☐
	C	Intervention / Exposure	Yes	No	?
QA	1.	Were intervention or exposure recorded in a valid, reliable and similar manner?	☒	☐	☐
QB	2.	Were the intervention / control groups - with the exception of the intervention - treated alike?	☐	☐	☒
QB	3.	In case of different therapies, have they been recorded in a valid and reliable manner?	☐	☐	☒
QA	4.	For RCTs: Have placebos been used for the control groups?	☐	☐	☐
QA	5.	For RCTs: has the administration of placebos been documented?	☐	☐	☐
	D	Study Administration	Yes	No	?
QB	1.	Is there evidence of an "Overmatching"?	☐	☒	☐
QB	2.	In multicenter studies: were the diagnostic and therapeutic methods, and the outcome measurement identical in all participating centers?	☐	☐	☐
QA	3.	Was it ensured that study participants did not change between intervention and control groups?	☐	☐	☒
	E	Outcome measurement	Yes	No	?
I	1.	Were point-of-care outcome parameters used?	☐	☐	☒
QA	2.	Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3.	Was the outcome measurement blinded?	☐	☒	☐
QC	4.	In case series: was the distribution of prognostic factors adequately covered?	☐	☐	☐
	F	Drop Outs	Yes	No	?
QA	1.	Was the response rate in intervention / control groups high enough or in cohort studies: could a sufficiently large part of the cohort be followed-up over the entire study period?	☒	☐	☐
QA	2.	Were the reasons for the drop-outs of study participants listed?	☐	☒	☐
QB	3.	Were the outcomes of the drop-outs described and considered in the evaluation?	☐	☒	☐
QB	4.	If differences were found - are they significant?	☐	☐	☐
QB	5.	If differences were found - are they relevant?	☐	☐	☐
	G	Statistical analysis	Yes	No	?
QA	1.	Are the described analytical procedures correct and is that information sufficient for a proper evaluation?	☒	☐	☐
	2.	For RCT: was an intention-to-treat analysis conducted?	☐	☐	☐
		a) Were all randomized individuals analyzed within the group to which they were assigned?	☐	☐	☐
		b) Were deviations of the non-randomized cases reported that were included in the analysis?	☐	☐	☐
		c) Has the effect of missing values been analyzed?	☐	☐	☐

QB	3.	Have the effect estimates and their precision (e.g. confidence intervals) been reported for all primary and secondary outcomes for each group?	☐	☒	☐
	4.	Has the distinction between a priori defined analysis and exploratory analysis been made and was the problem of multiple testing of hypotheses considered?	☐	☒	☐
I	5.	Are the results presented in a graphical form and are the underlying values for the graphics expressed?	☒	☐	☐
	H	Discussion	Yes	No	?
	1.	Are the following points in respect to the interpretation of results sufficiently covered?			
		a) the reference to the study hypothesis	☒	☐	☐
		b) the sources of distortion	☒	☐	☐
		c) statistical uncertainties	☐	☒	☐
		d) hazard multiple testing	☐	☒	☐
	2.	Was the external validity (generalizability) of the study results discussed?	☒	☐	☐
	3.	Were the study results discussed in the context of current evidence?	☒	☐	☐
Final assessment: This publication is included ☒ excluded ☐					

Checklist 2a

Checklist 2a: Primary studies (RCTs / case-control studies / cohort studies / longitudinal studies / case series)					
Report No.: 9.5.1.1.7					
Title:	Transcatheter aortic valve implantation in patients with very high risk for conventional aortic valve replacement				
Authors:	Thielmann, M. et al. 2009				
Source:	Ann Thorac Surg 2009;88:1468-1475				
Document type	RCT: ☐	Cohort study: ☐	Case-control study: ☐	Longitudinal study: ☐	
	Case series: ☒	Other: ☐			

Clas		A Selection of study participants	Yes	No	?
QA	1.	Are the inclusion and exclusion criteria for study participants sufficiently / clearly defined?	☒	☐	☐
QA	2.	Have the inclusion and exclusion criteria been defined before the intervention?	☒	☐	☐
QA	3.	Has the disease status been assessed in a valid and reliable manner?	☒	☐	☐
QBI	4.	Are the diagnostic criteria of the disease described?	☐	☒	☐
QB	5.	Is the study population / exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☐	☒	☐
QA	6.	For cohort studies: Were the study groups considered simultaneously?	☐	☐	☐
	7.	Has the determination of the sample size been specified?	☐	☒	☐
	8.	Are the period of recruitment and follow-up indicated?	☒	☐	☐
		B Assignment and study participation	Yes	No	?
QA	1.	Do the exposed / cases and non-exposed/ controls come from a similar population?	☐	☐	☐
QA	2.	Are the intervention/ exposed group and the control/ non-exposed group comparable at baseline?			
		a) with respect to demographic characteristics	☐	☐	☐
		b) with respect to clinical characteristics	☐	☐	☐
QB	3.	Was the selection conducted randomized with a standard procedure?	☐	☒	☐
		a) was the allocation sequence generated by an accepted procedure?	☐	☐	☐
		b) was the allocation sequence concealed until the intervention?	☐	☐	☐
QC	4.	Was the randomization blinded?	☐	☐	☐
		a) for the patient	☐	☐	☐
		b) for the intervening physician	☐	☐	☐
QA	5.	Were known / possible confounders taken into account at the start of the study?	☐	☐	☒
		C Intervention / Exposure	Yes	No	?
QA	1.	Were intervention or exposure recorded in a valid, reliable and similar manner?	☒	☐	☐
QB	2.	Were the intervention / control groups - with the exception of the intervention - treated alike?	☐	☐	☐
QB	3.	In case of different therapies, have they been recorded in a valid and reliable manner?	☐	☐	☐
QA	4.	For RCTs: Have placebos been used for the control groups?	☐	☐	☐
QA	5.	For RCTs: has the administration of placebos been documented?	☐	☐	☐
		D Study Administration	Yes	No	?
QB	1.	Is there evidence of an "Overmatching"?	☐	☒	☐
QB	2.	In multicenter studies: were the diagnostic and therapeutic methods, and the outcome measurement identical in all participating centers?	☐	☐	☐
QA	3.	Was it ensured that study participants did not change between intervention and control groups?	☐	☐	☐
		E Outcome measurement	Yes	No	?
I	1.	Were point-of-care outcome parameters used?	☐	☐	☒
QA	2.	Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3.	Was the outcome measurement blinded?	☐	☒	☐
QC	4.	In case series: was the distribution of prognostic factors adequately covered?	☒	☐	☐
		F Drop Outs	Yes	No	?
QA	1.	Was the response rate in intervention / control groups high enough or in cohort studies: could a sufficiently large part of the cohort be followed-up over the entire study period?	☒	☐	☐
QA	2.	Were the reasons for the drop-outs of study participants listed?	☐	☐	☐
QB	3.	Were the outcomes of the drop-outs described and considered in the evaluation?	☐	☐	☐
QB	4.	If differences were found - are they significant?	☐	☐	☐
QB	5.	If differences were found - are they relevant?	☐	☐	☐
		G Statistical analysis	Yes	No	?
QA	1.	Are the described analytical procedures correct and is that information sufficient for a proper evaluation?	☒	☐	☐
	2.	For RCT: was an intention-to-treat analysis conducted?	☐	☐	☐
		a) Were all randomized individuals analyzed within the group to which they were assigned?	☐	☐	☐
		b) Were deviations of the non-randomized cases reported that were included in the analysis?	☐	☐	☐
		c) Has the effect of missing values been analyzed?	☐	☐	☐

QB	3.	Have the effect estimates and their precision (e.g. confidence intervals) been reported for all primary and secondary outcomes for each group?	☐	☒	☐
	4.	Has the distinction between a priori defined analysis and exploratory analysis been made and was the problem of multiple testing of hypotheses considered?	☐	☒	☐
I	5.	Are the results presented in a graphical form and are the underlying values for the graphics expressed?	☒	☐	☐
	H	Discussion	Yes	No	?
	1.	Are the following points in respect to the interpretation of results sufficiently covered?			
		a) the reference to the study hypothesis	☒	☐	☐
		b) the sources of distortion	☒	☐	☐
		c) statistical uncertainties	☐	☒	☐
		d) hazard multiple testing	☐	☒	☐
	2.	Was the external validity (generalizability) of the study results discussed?	☒	☐	☐
	3.	Were the study results discussed in the context of current evidence?	☒	☐	☐
Final assessment: This publication is included ☒ excluded ☐					

Checklist 2a

Checklist 2a: Primary studies (RCTs / case-control studies / cohort studies / longitudinal studies / case series)					
Report No.: 9.5.1.1.8					
Title:	Transcatheter aortic valve implantation: impact on clinical and valve-related outcomes				
Authors:	Webb, J. G. et al. 2009				
Source:	Circulation 2009;119:3009-3016				
Document type	RCT: ☐ Cohort study: ☐ Case-control study: ☐ Longitudinal study: ☐ Case series: ☒ Other: ☐				
Clas	A	Selection of study participants	Yes	No	?
QA	1.	Are the inclusion and exclusion criteria for study participants sufficiently / clearly defined?	☒	☐	☐
QA	2.	Have the inclusion and exclusion criteria been defined before the intervention?	☒	☐	☐
QA	3.	Has the disease status been assessed in a valid and reliable manner?	☒	☐	☐
QBI	4.	Are the diagnostic criteria of the disease described?	☐	☒	☐
QB	5.	Is the study population / exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6.	For cohort studies: Were the study groups considered simultaneously?	☐	☐	☐
	7.	Has the determination of the sample size been specified?	☐	☒	☐
	8.	Are the period of recruitment and follow-up indicated?	☒	☐	☐
	B	Assignment and study participation	Yes	No	?
QA	1.	Do the exposed / cases and non-exposed/ controls come from a similar population?	☐	☐	☐
QA	2.	Are the intervention/ exposed group and the control/ non-exposed group comparable at baseline?			
		a) with respect to demographic characteristics	☐	☐	☐
		b) with respect to clinical characteristics	☐	☐	☐
QB	3.	Was the selection conducted randomized with a standard procedure?	☐	☒	☐
		a) was the allocation sequence generated by an accepted procedure?	☐	☐	☐
		b) was the allocation sequence concealed until the intervention?	☐	☐	☐
QC	4.	Was the randomization blinded?	☐	☐	☐
		a) for the patient	☐	☐	☐
		b) for the intervening physician	☐	☐	☐
QA	5.	Were known / possible confounders taken into account at the start of the study?	☐	☐	☒
	C	Intervention / Exposure	Yes	No	?
QA	1.	Were intervention or exposure recorded in a valid, reliable and similar manner?	☒	☐	☐
QB	2.	Were the intervention / control groups - with the exception of the intervention - treated alike?	☐	☐	☐
QB	3.	In case of different therapies, have they been recorded in a valid and reliable manner?	☐	☐	☐
QA	4.	For RCTs: Have placebos been used for the control groups?	☐	☐	☐
QA	5.	For RCTs: has the administration of placebos been documented?	☐	☐	☐
	D	Study Administration	Yes	No	?
QB	1.	Is there evidence of an "Overmatching"?	☐	☒	☐
QB	2.	In multicenter studies: were the diagnostic and therapeutic methods, and the outcome measurement identical in all participating centers?	☐	☐	☐
QA	3.	Was it ensured that study participants did not change between intervention and control groups?	☐	☐	☐
	E	Outcome measurement	Yes	No	?
I	1.	Were point-of-care outcome parameters used?	☐	☐	☒
QA	2.	Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3.	Was the outcome measurement blinded?	☐	☒	☐
QC	4.	In case series: was the distribution of prognostic factors adequately covered?	☒	☐	☐
	F	Drop Outs	Yes	No	?
QA	1.	Was the response rate in intervention / control groups high enough or in cohort studies: could a sufficiently large part of the cohort be followed-up over the entire study period?	☒	☐	☐
QA	2.	Were the reasons for the drop-outs of study participants listed?	☐	☐	☐
QB	3.	Were the outcomes of the drop-outs described and considered in the evaluation?	☐	☐	☐
QB	4.	If differences were found - are they significant?	☐	☐	☐
QB	5.	If differences were found - are they relevant?	☐	☐	☐
	G	Statistical analysis	Yes	No	?
QA	1.	Are the described analytical procedures correct and is that information sufficient for a proper evaluation?	☒	☐	☐
	2.	For RCT: was an intention-to-treat analysis conducted?	☐	☐	☐
		a) Were all randomized individuals analyzed within the group to which they were assigned?	☐	☐	☐
		b) Were deviations of the non-randomized cases reported that were included in the analysis?	☐	☐	☐
		c) Has the effect of missing values been analyzed?	☐	☐	☐

QB	3.	Have the effect estimates and their precision (e.g. confidence intervals) been reported for all primary and secondary outcomes for each group?	☒	☐	☐
	4.	Has the distinction between a priori defined analysis and exploratory analysis been made and was the problem of multiple testing of hypotheses considered?	☐	☒	☐
I	5.	Are the results presented in a graphical form and are the underlying values for the graphics expressed?	☒	☐	☐
	H	Discussion	Yes	No	?
	1.	Are the following points in respect to the interpretation of results sufficiently covered?			
		a) the reference to the study hypothesis	☒	☐	☐
		b) the sources of distortion	☐	☒	☐
		c) statistical uncertainties	☐	☒	☐
		d) hazard multiple testing	☐	☒	☐
	2.	Was the external validity (generalizability) of the study results discussed?	☒	☐	☐
	3.	Were the study results discussed in the context of current evidence?	☒	☐	☐
Final assessment: This publication is included ☒ excluded ☐					

Checklist 2a

Checklist 2a: Primary studies (RCTs / case-control studies / cohort studies / longitudinal studies / case series)					
Report No.: 9.5.1.1.9					
Title:	Transapical transcatheter aortic valve implantation: 1-year outcome in 26 patients				
Authors:	Ye, J. et al. 2009				
Source:	J Thorac Cardiovasc Surg 2009;137:167-173				
Document type	RCT: ☐	Cohort study: ☐	Case-control study: ☐	Longitudinal study: ☐	
	Case series: ☒	Other: ☐			

Clas			Yes	No	?
	A	Selection of study participants			
QA	1.	Are the inclusion and exclusion criteria for study participants sufficiently / clearly defined?	☒	☐	☐
QA	2.	Have the inclusion and exclusion criteria been defined before the intervention?	☒	☐	☐
QA	3.	Has the disease status been assessed in a valid and reliable manner?	☒	☐	☐
QBI	4.	Are the diagnostic criteria of the disease described?	☐	☒	☐
QB	5.	Is the study population / exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6.	For cohort studies: Were the study groups considered simultaneously?	☐	☐	☐
	7.	Has the determination of the sample size been specified?	☐	☒	☐
	8.	Are the period of recruitment and follow-up indicated?	☒	☐	☐
	B	Assignment and study participation	Yes	No	?
QA	1.	Do the exposed / cases and non-exposed/ controls come from a similar population?	☐	☐	☐
QA	2.	Are the intervention/ exposed group and the control/ non-exposed group comparable at baseline?			
		a) with respect to demographic characteristics	☐	☐	☐
		b) with respect to clinical characteristics	☐	☐	☐
QB	3.	Was the selection conducted randomized with a standard procedure?	☐	☒	☐
		a) was the allocation sequence generated by an accepted procedure?	☐	☐	☐
		b) was the allocation sequence concealed until the intervention?	☐	☐	☐
QC	4.	Was the randomization blinded?	☐	☐	☐
		a) for the patient	☐	☐	☐
		b) for the intervening physician	☐	☐	☐
QA	5.	Were known / possible confounders taken into account at the start of the study?	☐	☐	☒
	C	Intervention / Exposure	Yes	No	?
QA	1.	Were intervention or exposure recorded in a valid, reliable and similar manner?	☒	☐	☐
QB	2.	Were the intervention / control groups - with the exception of the intervention - treated alike?	☐	☐	☐
QB	3.	In case of different therapies, have they been recorded in a valid and reliable manner?	☐	☐	☐
QA	4.	For RCTs: Have placebos been used for the control groups?	☐	☐	☐
QA	5.	For RCTs: has the administration of placebos been documented?	☐	☐	☐
	D	Study Administration	Yes	No	?
QB	1.	Is there evidence of an "Overmatching"?	☐	☒	☐
QB	2.	In multicenter studies: were the diagnostic and therapeutic methods, and the outcome measurement identical in all participating centers?	☐	☐	☐
QA	3.	Was it ensured that study participants did not change between intervention and control groups?	☐	☐	☐
	E	Outcome measurement	Yes	No	?
I	1.	Were point-of-care outcome parameters used?	☐	☐	☒
QA	2.	Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3.	Was the outcome measurement blinded?	☐	☒	☐
QC	4.	In case series: was the distribution of prognostic factors adequately covered?	☒	☐	☐
	F	Drop Outs	Yes	No	?
QA	1.	Was the response rate in intervention / control groups high enough or in cohort studies: could a sufficiently large part of the cohort be followed-up over the entire study period?	☒	☐	☐
QA	2.	Were the reasons for the drop-outs of study participants listed?	☐	☐	☐
QB	3.	Were the outcomes of the drop-outs described and considered in the evaluation?	☐	☐	☐
QB	4.	If differences were found - are they significant?	☐	☐	☐
QB	5.	If differences were found - are they relevant?	☐	☐	☐
	G	Statistical analysis	Yes	No	?
QA	1.	Are the described analytical procedures correct and is that information sufficient for a proper evaluation?	☒	☐	☐
	2.	For RCT: was an intention-to-treat analysis conducted?	☐	☐	☐
		a) Were all randomized individuals analyzed within the group to which they were assigned?	☐	☐	☐
		b) Were deviations of the non-randomized cases reported that were included in the analysis?	☐	☐	☐
		c) Has the effect of missing values been analyzed?	☐	☐	☐

QB	3.	Have the effect estimates and their precision (e.g. confidence intervals) been reported for all primary and secondary outcomes for each group?	☐	☒	☐
	4.	Has the distinction between a priori defined analysis and exploratory analysis been made and was the problem of multiple testing of hypotheses considered?	☐	☒	☐
I	5.	Are the results presented in a graphical form and are the underlying values for the graphics expressed?	☒	☐	☐
	H	Discussion	Yes	No	?
	1.	Are the following points in respect to the interpretation of results sufficiently covered?			
		a) the reference to the study hypothesis	☒	☐	☐
		b) the sources of distortion	☐	☒	☐
		c) statistical uncertainties	☐	☒	☐
		d) hazard multiple testing	☐	☒	☐
	2.	Was the external validity (generalizability) of the study results discussed?	☒	☐	☐
	3.	Were the study results discussed in the context of current evidence?	☒	☐	☐
Final assessment: This publication is included ☒ excluded ☐					

Checklist 2a

Checklist 2a: Primary studies (RCTs / case-control studies / cohort studies / longitudinal studies / case series)					
Report No.: 9.5.1.1.10					
Title:	Is transapical aortic valve implantation really less invasive than minimally invasive aortic valve replacement?				
Authors:	Zierer, A. et al. 2009				
Source:	J Thorac Cardiovasc Surg 2009;138:1067-1072				
Document type	RCT: ☐ Cohort study: ☒ Case-control study: ☐ Longitudinal study: ☐ Case series: ☐ Other: ☐				
Clas	A	Selection of study participants	Yes	No	?
QA	1.	Are the inclusion and exclusion criteria for study participants sufficiently / clearly defined?	☒	☐	☐
QA	2.	Have the inclusion and exclusion criteria been defined before the intervention?	☐	☒	☐
QA	3.	Has the disease status been assessed in a valid and reliable manner?	☒	☐	☐
QBI	4.	Are the diagnostic criteria of the disease described?	☐	☒	☐
QB	5.	Is the study population / exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6.	For cohort studies: Were the study groups considered simultaneously?	☐	☒	☐
	7.	Has the determination of the sample size been specified?	☐	☒	☐
	8.	Are the period of recruitment and follow-up indicated?	☒	☐	☐
	B	Assignment and study participation	Yes	No	?
QA	1.	Do the exposed / cases and non-exposed/ controls come from a similar population?	☒	☐	☐
QA	2.	Are the intervention/ exposed group and the control/ non-exposed group comparable at baseline?			
		a) with respect to demographic characteristics	☒	☐	☐
		b) with respect to clinical characteristics	☒	☐	☐
QB	3.	Was the selection conducted randomized with a standard procedure?	☐	☒	☐
		a) was the allocation sequence generated by an accepted procedure?	☐	☐	☐
		b) was the allocation sequence concealed until the intervention?	☐	☐	☐
QC	4.	Was the randomization blinded?	☐	☐	☐
		a) for the patient	☐	☐	☐
		b) for the intervening physician	☐	☐	☐
QA	5.	Were known / possible confounders taken into account at the start of the study?	☐	☐	☒
	C	Intervention / Exposure	Yes	No	?
QA	1.	Were intervention or exposure recorded in a valid, reliable and similar manner?	☒	☐	☐
QB	2.	Were the intervention / control groups - with the exception of the intervention - treated alike?	☒	☐	☐
QB	3.	In case of different therapies, have they been recorded in a valid and reliable manner?	☐	☐	☒
QA	4.	For RCTs: Have placebos been used for the control groups?	☐	☐	☐
QA	5.	For RCTs: has the administration of placebos been documented?	☐	☐	☐
	D	Study Administration	Yes	No	?
QB	1.	Is there evidence of an "Overmatching"?	☐	☒	☐
QB	2.	In multicenter studies: were the diagnostic and therapeutic methods, and the outcome measurement identical in all participating centers?	☐	☐	☐
QA	3.	Was it ensured that study participants did not change between intervention and control groups?	☐	☐	☐
	E	Outcome measurement	Yes	No	?
I	1.	Were point-of-care outcome parameters used?	☐	☐	☒
QA	2.	Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3.	Was the outcome measurement blinded?	☐	☒	☐
QC	4.	In case series: was the distribution of prognostic factors adequately covered?	☐	☐	☐
	F	Drop Outs	Yes	No	?
QA	1.	Was the response rate in intervention / control groups high enough or in cohort studies: could a sufficiently large part of the cohort be followed-up over the entire study period?	☒	☐	☐
QA	2.	Were the reasons for the drop-outs of study participants listed?	☐	☐	☐
QB	3.	Were the outcomes of the drop-outs described and considered in the evaluation?	☐	☐	☐
QB	4.	If differences were found - are they significant?	☐	☐	☐
QB	5.	If differences were found - are they relevant?	☐	☐	☐
	G	Statistical analysis	Yes	No	?
QA	1.	Are the described analytical procedures correct and is that information sufficient for a proper evaluation?	☒	☐	☐
	2.	For RCT: was an intention-to-treat analysis conducted?	☐	☐	☐
		a) Were all randomized individuals analyzed within the group to which they were assigned?	☐	☐	☐
		b) Were deviations of the non-randomized cases reported that were included in the analysis?	☐	☐	☐
		c) Has the effect of missing values been analyzed?	☐	☐	☐

QB	3.	Have the effect estimates and their precision (e.g. confidence intervals) been reported for all primary and secondary outcomes for each group?	☐	☒	☐
	4.	Has the distinction between a priori defined analysis and exploratory analysis been made and was the problem of multiple testing of hypotheses considered?	☐	☒	☐
I	5.	Are the results presented in a graphical form and are the underlying values for the graphics expressed?	☒	☐	☐
	H	Discussion	Yes	No	?
	1.	Are the following points in respect to the interpretation of results sufficiently covered?			
		a) the reference to the study hypothesis	☒	☐	☐
		b) the sources of distortion	☒	☐	☐
		c) statistical uncertainties	☐	☒	☐
		d) hazard multiple testing	☐	☒	☐
	2.	Was the external validity (generalizability) of the study results discussed?	☒	☐	☐
	3.	Were the study results discussed in the context of current evidence?	☒	☐	☐
Final assessment: This publication is included ☒ excluded ☐					

Checklist 2a

Checklist 2a: Primary studies (RCTs / case-control studies / cohort studies / longitudinal studies / case series)					
Report No.: 9.5.1.1.11					
Title:	Progress and current status of percutaneous aortic valve replacement: results of three device generations of the CoreValve Re-valving system				
Authors:	Grube, E. et al. 2008				
Source:	Circ Cardiovasc Intervent 2008;1:167-175				
Document type	RCT: ☐ Cohort study: ☐ Case-control study: ☐ Longitudinal study: ☐ Case series: ☒ Other: ☐				
Clas	A	Selection of study participants	Yes	No	?
QA	1.	Are the inclusion and exclusion criteria for study participants sufficiently / clearly defined?	☒	☐	☐
QA	2.	Have the inclusion and exclusion criteria been defined before the intervention?	☒	☐	☐
QA	3.	Has the disease status been assessed in a valid and reliable manner?	☒	☐	☐
QBI	4.	Are the diagnostic criteria of the disease described?	☒	☐	☐
QB	5.	Is the study population / exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6.	For cohort studies: Were the study groups considered simultaneously?	☐	☐	☐
	7.	Has the determination of the sample size been specified?	☐	☒	☐
	8.	Are the period of recruitment and follow-up indicated?	☒	☐	☐
	B	Assignment and study participation	Yes	No	?
QA	1.	Do the exposed / cases and non-exposed/ controls come from a similar population?	☐	☐	☐
QA	2.	Are the intervention/ exposed group and the control/ non-exposed group comparable at baseline?			
		a) with respect to demographic characteristics	☐	☐	☐
		b) with respect to clinical characteristics	☐	☐	☐
QB	3.	Was the selection conducted randomized with a standard procedure?	☐	☒	☐
		a) was the allocation sequence generated by an accepted procedure?	☐	☐	☐
		b) was the allocation sequence concealed until the intervention?	☐	☐	☐
QC	4.	Was the randomization blinded?	☐	☐	☐
		a) for the patient	☐	☐	☐
		b) for the intervening physician	☐	☐	☐
QA	5.	Were known / possible confounders taken into account at the start of the study?	☐	☐	☐
	C	Intervention / Exposure	Yes	No	?
QA	1.	Were intervention or exposure recorded in a valid, reliable and similar manner?	☒	☐	☐
QB	2.	Were the intervention / control groups - with the exception of the intervention - treated alike?	☐	☐	☐
QB	3.	In case of different therapies, have they been recorded in a valid and reliable manner?	☐	☐	☐
QA	4.	For RCTs: Have placebos been used for the control groups?	☐	☐	☐
QA	5.	For RCTs: has the administration of placebos been documented?	☐	☐	☐
	D	Study Administration	Yes	No	?
QB	1.	Is there evidence of an "Overmatching"?	☐	☒	☐
QB	2.	In multicenter studies: were the diagnostic and therapeutic methods, and the outcome measurement identical in all participating centers?	☐	☐	☐
QA	3.	Was it ensured that study participants did not change between intervention and control groups?	☐	☐	☒
	E	Outcome measurement	Yes	No	?
I	1.	Were point-of-care outcome parameters used?	☐	☐	☒
QA	2.	Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3.	Was the outcome measurement blinded?	☐	☒	☐
QC	4.	In case series: was the distribution of prognostic factors adequately covered?	☒	☐	☐
	F	Drop Outs	Yes	No	?
QA	1.	Was the response rate in intervention / control groups high enough or in cohort studies: could a sufficiently large part of the cohort be followed-up over the entire study period?	☒	☐	☐
QA	2.	Were the reasons for the drop-outs of study participants listed?	☐	☐	☐
QB	3.	Were the outcomes of the drop-outs described and considered in the evaluation?	☐	☐	☐
QB	4.	If differences were found - are they significant?	☐	☐	☐
QB	5.	If differences were found - are they relevant?	☐	☐	☐
	G	Statistical analysis	Yes	No	?
QA	1.	Are the described analytical procedures correct and is that information sufficient for a proper evaluation?	☒	☐	☐
	2.	For RCT: was an intention-to-treat analysis conducted?	☐	☐	☐
		a) Were all randomized individuals analyzed within the group to which they were assigned?	☐	☐	☐
		b) Were deviations of the non-randomized cases reported that were included in the analysis?	☐	☐	☐
		c) Has the effect of missing values been analyzed?	☐	☐	☐

QB	3.	Have the effect estimates and their precision (e.g. confidence intervals) been reported for all primary and secondary outcomes for each group?	☐	☒	☐
	4.	Has the distinction between a priori defined analysis and exploratory analysis been made and was the problem of multiple testing of hypotheses considered?	☐	☒	☐
I	5.	Are the results presented in a graphical form and are the underlying values for the graphics expressed?	☒	☐	☐
	H	Discussion	Yes	No	?
	1.	Are the following points in respect to the interpretation of results sufficiently covered?			
		a) the reference to the study hypothesis	☒	☐	☐
		b) the sources of distortion	☒	☐	☐
		c) statistical uncertainties	☐	☒	☐
		d) hazard multiple testing	☐	☒	☐
	2.	Was the external validity (generalizability) of the study results discussed?	☒	☐	☐
	3.	Were the study results discussed in the context of current evidence?	☒	☐	☐
Final assessment: This publication is included ☒ excluded ☐					

Checklist 2a

Checklist 2a: Primary studies (RCTs / case-control studies / cohort studies / longitudinal studies / case series)					
Report No.: 9.5.1.1.12					
Title:	Population characteristics, treatment assignment and survival of patients with aortic stenosis referred for percutaneous valve replacement				
Authors:	Otten, A. M. et al. 2008				
Source:	EuroIntervent 2008;4:250-255				
Document type	RCT: ☐	Cohort study: ☒	Case-control study: ☐	Longitudinal study: ☐	
	Case series: ☐	Other: ☐			
Clas	A	Selection of study participants	Yes	No	?
QA	1.	Are the inclusion and exclusion criteria for study participants sufficiently / clearly defined?	☒	☐	☐
QA	2.	Have the inclusion and exclusion criteria been defined before the intervention?	☒	☐	☐
QA	3.	Has the disease status been assessed in a valid and reliable manner?	☒	☐	☐
QBI	4.	Are the diagnostic criteria of the disease described?	☒	☐	☐
QB	5.	Is the study population / exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6.	For cohort studies: Were the study groups considered simultaneously?	☐	☒	☐
	7.	Has the determination of the sample size been specified?	☐	☒	☐
	8.	Are the period of recruitment and follow-up indicated?	☒	☐	☐
	B	Assignment and study participation	Yes	No	?
QA	1.	Do the exposed / cases and non-exposed/ controls come from a similar population?	☒	☐	☐
QA	2.	Are the intervention/ exposed group and the control/ non-exposed group comparable at baseline?			
		a) with respect to demographic characteristics	☒	☐	☐
		b) with respect to clinical characteristics	☒	☐	☐
QB	3.	Was the selection conducted randomized with a standard procedure?	☐	☒	☐
		a) was the allocation sequence generated by an accepted procedure?	☐	☐	☐
		b) was the allocation sequence concealed until the intervention?	☐	☐	☐
QC	4.	Was the randomization blinded?	☐	☐	☐
		a) for the patient	☐	☐	☐
		b) for the intervening physician	☐	☐	☐
QA	5.	Were known / possible confounders taken into account at the start of the study?	☐	☐	☐
	C	Intervention / Exposure	Yes	No	?
QA	1.	Were intervention or exposure recorded in a valid, reliable and similar manner?	☒	☐	☐
QB	2.	Were the intervention / control groups - with the exception of the intervention - treated alike?	☐	☐	☒
QB	3.	In case of different therapies, have they been recorded in a valid and reliable manner?	☐	☐	☒
QA	4.	For RCTs: Have placebos been used for the control groups?	☐	☐	☐
QA	5.	For RCTs: has the administration of placebos been documented?	☐	☐	☐
	D	Study Administration	Yes	No	?
QB	1.	Is there evidence of an "Overmatching"?	☐	☒	☐
QB	2.	In multicenter studies: were the diagnostic and therapeutic methods, and the outcome measurement identical in all participating centers?	☐	☐	☐
QA	3.	Was it ensured that study participants did not change between intervention and control groups?	☐	☐	☒
	E	Outcome measurement	Yes	No	?
I	1.	Were point-of-care outcome parameters used?	☐	☐	☒
QA	2.	Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3.	Was the outcome measurement blinded?	☐	☒	☐
QC	4.	In case series: was the distribution of prognostic factors adequately covered?	☐	☐	☐
	F	Drop Outs	Yes	No	?
QA	1.	Was the response rate in intervention / control groups high enough or in cohort studies: could a sufficiently large part of the cohort be followed-up over the entire study period?	☒	☐	☐
QA	2.	Were the reasons for the drop-outs of study participants listed?	☐	☐	☐
QB	3.	Were the outcomes of the drop-outs described and considered in the evaluation?	☐	☐	☐
QB	4.	If differences were found - are they significant?	☐	☐	☐
QB	5.	If differences were found - are they relevant?	☐	☐	☐
	G	Statistical analysis	Yes	No	?
QA	1.	Are the described analytical procedures correct and is that information sufficient for a proper evaluation?	☒	☐	☐
	2.	For RCT: was an intention-to-treat analysis conducted?	☐	☐	☐
		a) Were all randomized individuals analyzed within the group to which they were assigned?	☐	☐	☐
		b) Were deviations of the non-randomized cases reported that were included in the analysis?	☐	☐	☐
		c) Has the effect of missing values been analyzed?	☐	☐	☐

QB	3.	Have the effect estimates and their precision (e.g. confidence intervals) been reported for all primary and secondary outcomes for each group?	☐	☒	☐
	4.	Has the distinction between a priori defined analysis and exploratory analysis been made and was the problem of multiple testing of hypotheses considered?	☐	☒	☐
I	5.	Are the results presented in a graphical form and are the underlying values for the graphics expressed?	☒	☐	☐
	H	Discussion	Yes	No	?
	1.	Are the following points in respect to the interpretation of results sufficiently covered?			
		a) the reference to the study hypothesis	☒	☐	☐
		b) the sources of distortion	☒	☐	☐
		c) statistical uncertainties	☐	☒	☐
		d) hazard multiple testing	☐	☒	☐
	2.	Was the external validity (generalizability) of the study results discussed?	☒	☐	☐
	3.	Were the study results discussed in the context of current evidence?	☒	☐	☐
Final assessment: This publication is included ☒ excluded ☐					

7.7.2 Primary publications included for review on medical therapy of AS

Checklist 2a

Checklist 2a: Primary studies (RCTs / case-control studies / cohort studies / longitudinal studies / case series)										
Report No.: 9.5.1.2.1										
Title:		Severe aortic stenosis in a veteran population: treatment considerations and survival								
Authors:		Bakaeen, F. G. et al. 2010								
Source:		Ann Thorac Surg 2010;89:453-458								
Document type		RCT: ☐	Cohort study: ☒	Case-control study: ☐	Longitudinal study: ☐					
		Case series: ☐	Other: ☐							
Clas	A	Selection of study participants						Yes	No	?
QA	1.	Are the inclusion and exclusion criteria for study participants sufficiently / clearly defined?						☒	☐	☐
QA	2.	Have the inclusion and exclusion criteria been defined before the intervention?						☐	☒	☐
QA	3.	Has the disease status been assessed in a valid and reliable manner?						☒	☐	☐
QBI	4.	Are the diagnostic criteria of the disease described?						☐	☒	☐
QB	5.	Is the study population / exposed population representative of the majority of the exposed population or the "standard users" of the intervention?						☒	☐	☐
QA	6.	For cohort studies: Were the study groups considered simultaneously?						☐	☐	☒
	7.	Has the determination of the sample size been specified?						☒	☐	☐
	8.	Are the period of recruitment and follow-up indicated?						☒	☐	☐
	B	Assignment and study participation						Yes	No	?
QA	1.	Do the exposed / cases and non-exposed/ controls come from a similar population?						☒	☐	☐
QA	2.	Are the intervention/ exposed group and the control/ non-exposed group comparable at baseline?								
		a) with respect to demographic characteristics						☐	☒	☐
		b) with respect to clinical characteristics						☒	☐	☐
QB	3.	Was the selection conducted randomized with a standard procedure?						☐	☒	☐
		a) was the allocation sequence generated by an accepted procedure?						☐	☐	☐
		b) was the allocation sequence concealed until the intervention?						☐	☐	☐
QC	4.	Was the randomization blinded?						☐	☐	☐
		a) for the patient						☐	☐	☐
		b) for the intervening physician						☐	☐	☐
QA	5.	Were known / possible confounders taken into account at the start of the study?						☐	☐	☒
	C	Intervention / Exposure						Yes	No	?
QA	1.	Were intervention or exposure recorded in a valid, reliable and similar manner?						☒	☐	☐
QB	2.	Were the intervention / control groups - with the exception of the intervention - treated alike?						☐	☐	☒
QB	3.	In case of different therapies, have they been recorded in a valid and reliable manner?						☐	☐	☒
QA	4.	For RCTs: Have placebos been used for the control groups?						☐	☐	☐
QA	5.	For RCTs: has the administration of placebos been documented?						☐	☐	☐
	D	Study Administration						Yes	No	?
QB	1.	Is there evidence of an "Overmatching"?						☐	☒	☐
QB	2.	In multicenter studies: were the diagnostic and therapeutic methods, and the outcome measurement identical in all participating centers?						☐	☐	☐
QA	3.	Was it ensured that study participants did not change between intervention and control groups?						☐	☐	☒
	E	Outcome measurement						Yes	No	?
I	1.	Were point-of-care outcome parameters used?						☐	☐	☒
QA	2.	Were the outcomes recorded in a valid and reliable manner?						☒	☐	☐
Q B	3.	Was the outcome measurement blinded?						☐	☒	☐
QC	4.	In case series: was the distribution of prognostic factors adequately covered?						☐	☐	☐
	F	Drop Outs						Yes	No	?
QA	1.	Was the response rate in intervention / control groups high enough or in cohort studies: could a sufficient-ly large part of the cohort be followed-up over the entire study period?						☒	☐	☐
QA	2.	Were the reasons for the drop-outs of study participants listed?						☐	☐	☐
QB	3.	Were the outcomes of the drop-outs described and considered in the evaluation?						☐	☐	☐
QB	4.	If differences were found - are they significant?						☐	☐	☐
QB	5.	If differences were found - are they relevant?						☐	☐	☐
	G	Statistical analysis						Yes	No	?

QA	1.	Are the described analytical procedures correct and is that information sufficient for a proper evaluation?	☒	☐	☐
	2.	For RCT: was an intention-to-treat analysis conducted?	☐	☐	☐
		a) Were all randomized individuals analyzed within the group to which they were assigned?	☐	☐	☐
		b) Were deviations of the non-randomized cases reported that were included in the analysis?	☐	☐	☐
		c) Has the effect of missing values been analyzed?	☐	☐	☐
QB	3.	Have the effect estimates and their precision (e.g. confidence intervals) been reported for all primary and secondary outcomes for each group?	☒	☐	☐
	4.	Has the distinction between a priori defined analysis and exploratory analysis been made and was the problem of multiple testing of hypotheses considered?	☐	☒	☐
I	5.	Are the results presented in a graphical form and are the underlying values for the graphics expressed?	☐	☒	☐
	H	Discussion	Yes	No	?
	1.	Are the following point in respect to the interpretation of results sufficiently covered?			
		a) the reference to the study hypothesis	☒	☐	☐
		b) the sources of distortion	☒	☐	☐
		c) statistical uncertainties	☐	☒	☐
		d) hazard multiple testing	☒	☐	☐
	2.	Was the external validity (generalizability) of the study results discussed?	☒	☐	☐
	3.	Were the study results discussed in the context of current evidence?	☒	☐	☐
Final assessment: This publication is included ☒ excluded ☐					

Checklist 2a

Checklist 2a: Primary studies (RCTs / case-control studies / cohort studies / longitudinal studies / case series)					
Report No.: 9.5.1.2.2					
Title:	Prognostic benefit of transcatheter aortic valve implantation compared with medical therapy in patients with inoperable aortic stenosis				
Authors:	Rajani, R. et al. 2010				
Source:	Catheter Cardiovasc Interv. 2010;75:1121–1126				
Document type	RCT: ☐ Cohort study: ☒ Case-control study: ☐ Longitudinal study: ☐ Case series: ☐ Other: ☐				
Clas	A	Selection of study participants	Yes	No	?
QA	1.	Are the inclusion and exclusion criteria for study participants sufficiently / clearly defined?	☒	☐	☐
QA	2.	Have the inclusion and exclusion criteria been defined before the intervention?	☒	☐	☐
QA	3.	Has the disease status been assessed in a valid and reliable manner?	☒	☐	☐
QBI	4.	Are the diagnostic criteria of the disease described?	☐	☒	☐
QB	5.	Is the study population / exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6.	For cohort studies: Were the study groups considered simultaneously?	☒	☐	☐
	7.	Has the determination of the sample size been specified?	☐	☒	☐
	8.	Are the period of recruitment and follow-up indicated?	☒	☐	☐
	B	Assignment and study participation	Yes	No	?
QA	1.	Do the exposed / cases and non-exposed/ controls come from a similar population?	☒	☐	☐
QA	2.	Are the intervention/ exposed group and the control/ non-exposed group comparable at baseline?			
		a) with respect to demographic characteristics	☒	☐	☐
		b) with respect to clinical characteristics	☒	☐	☐
QB	3.	Was the selection conducted randomized with a standard procedure?	☐	☒	☐
		a) was the allocation sequence generated by an accepted procedure?	☐	☐	☐
		b) was the allocation sequence concealed until the intervention?	☐	☐	☐
QC	4.	Was the randomization blinded?	☐	☐	☐
		a) for the patient	☐	☐	☐
		b) for the intervening physician	☐	☐	☐
QA	5.	Were known / possible confounders taken into account at the start of the study?	☐	☐	☒
	C	Intervention / Exposure	Yes	No	?
QA	1.	Were intervention or exposure recorded in a valid, reliable and similar manner?	☒	☐	☐
QB	2.	Were the intervention / control groups - with the exception of the intervention - treated alike?	☐	☐	☒
QB	3.	In case of different therapies, have they been recorded in a valid and reliable manner?	☐	☐	☒
QA	4.	For RCTs: Have placebos been used for the control groups?	☐	☐	☐
QA	5.	For RCTs: has the administration of placebos been documented?	☐	☐	☐
	D	Study Administration	Yes	No	?
QB	1.	Is there evidence of an "Overmatching"?	☐	☒	☐
QB	2.	In multicenter studies: were the diagnostic and therapeutic methods, and the outcome measurement identical in all participating centers?	☐	☐	☐
QA	3.	Was it ensured that study participants did not change between intervention and control groups?	☐	☐	☒
	E	Outcome measurement	Yes	No	?
I	1.	Were point-of-care outcome parameters used?	☐	☐	☒
QA	2.	Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
Q B	3.	Was the outcome measurement blinded?	☐	☒	☐
QC	4.	In case series: was the distribution of prognostic factors adequately covered?	☐	☐	☐
	F	Drop Outs	Yes	No	?
QA	1.	Was the response rate in intervention / control groups high enough or in cohort studies: could a sufficiently large part of the cohort be followed-up over the entire study period?	☒	☐	☐
QA	2.	Were the reasons for the drop-outs of study participants listed?	☐	☒	☐
QB	3.	Were the outcomes of the drop-outs described and considered in the evaluation?	☐	☒	☐
QB	4.	If differences were found - are they significant?	☐	☐	☐
QB	5.	If differences were found - are they relevant?	☐	☐	☐
	G	Statistical analysis	Yes	No	?
QA	1.	Are the described analytical procedures correct and is that information sufficient for a proper evaluation?	☒	☐	☐
	2.	For RCT: was an intention-to-treat analysis conducted?	☐	☐	☐
		a) Were all randomized individuals analyzed within the group to which they were assigned?	☐	☐	☐
		b) Were deviations of the non-randomized cases reported that were included in the analysis?	☐	☐	☐
		c) Has the effect of missing values been analyzed?	☐	☐	☐

QB	3.	Have the effect estimates and their precision (e.g. confidence intervals) been reported for all primary and secondary outcomes for each group?	☒	☐	☐
	4.	Has the distinction between a priori defined analysis and exploratory analysis been made and was the problem of multiple testing of hypotheses considered?	☐	☒	☐
I	5.	Are the results presented in a graphical form and are the underlying values for the graphics expressed?	☒	☐	☐
	H	Discussion	Yes	No	?
	1.	Are the following point in respect to the interpretation of results sufficiently covered?			
		a) the reference to the study hypothesis	☒	☐	☐
		b) the sources of distortion	☒	☐	☐
		c) statistical uncertainties	☐	☒	☐
		d) hazard multiple testing	☐	☒	☐
	2.	Was the external validity (generalizability) of the study results discussed?	☒	☐	☐
	3.	Were the study results discussed in the context of current evidence?	☒	☐	☐
Final assessment: This publication is included ☒ excluded ☐					

Checklist 2a

Checklist 2a: Primary studies (RCTs / case-control studies / cohort studies / longitudinal studies / case series)					
Report No.: 9.5.1.2.3					
Title:	Evaluation of patients with severe symptomatic aortic stenosis who do not undergo aortic valve replacement				
Authors:	Bach, D. S. et al. 2009				
Source:	Circ Cardiovasc Qual Outcomes 2009;2:533-539				
Document type	RCT: ☐	Cohort study: ☒	Case-control study: ☐	Longitudinal study: ☐	
	Case series: ☐	Other: ☐			
Clas	A	Selection of study participants	Yes	No	?
QA	1.	Are the inclusion and exclusion criteria for study participants sufficiently / clearly defined?	☒	☐	☐
QA	2.	Have the inclusion and exclusion criteria been defined before the intervention?	☐	☒	☐
QA	3.	Has the disease status been assessed in a valid and reliable manner?	☒	☐	☐
QBI	4.	Are the diagnostic criteria of the disease described?	☒	☐	☐
QB	5.	Is the study population / exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6.	For cohort studies: Were the study groups considered simultaneously?	☐	☐	☒
	7.	Has the determination of the sample size been specified?	☒	☐	☐
	8.	Are the period of recruitment and follow-up indicated?	☒	☐	☐
	B	Assignment and study participation	Yes	No	?
QA	1.	Do the exposed / cases and non-exposed/ controls come from a similar population?	☒	☐	☐
QA	2.	Are the intervention/ exposed group and the control/ non-exposed group comparable at baseline?			
		a) with respect to demographic characteristics	☒	☐	☐
		b) with respect to clinical characteristics	☒	☐	☐
QB	3.	Was the selection conducted randomized with a standard procedure?	☐	☒	☐
		a) was the allocation sequence generated by an accepted procedure?	☐	☐	☐
		b) was the allocation sequence concealed until the intervention?	☐	☐	☐
QC	4.	Was the randomization blinded?	☐	☐	☐
		a) for the patient	☐	☐	☐
		b) for the intervening physician	☐	☐	☐
QA	5.	Were known / possible confounders taken into account at the start of the study?	☐	☐	☒
	C	Intervention / Exposure	Yes	No	?
QA	1.	Were intervention or exposure recorded in a valid, reliable and similar manner?	☒	☐	☐
QB	2.	Were the intervention / control groups - with the exception of the intervention - treated alike?	☐	☐	☒
QB	3.	In case of different therapies, have they been recorded in a valid and reliable manner?	☐	☒	☐
QA	4.	For RCTs: Have placebos been used for the control groups?	☐	☐	☐
QA	5.	For RCTs: has the administration of placebos been documented?	☐	☐	☐
	D	Study Administration	Yes	No	?
QB	1.	Is there evidence of an "Overmatching"?	☐	☒	☐
QB	2.	In multicenter studies: were the diagnostic and therapeutic methods, and the outcome measurement identical in all participating centers?	☐	☐	☒
QA	3.	Was it ensured that study participants did not change between intervention and control groups?	☐	☐	☒
	E	Outcome measurement	Yes	No	?
I	1.	Were point-of-care outcome parameters used?	☐	☐	☒
QA	2.	Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
Q B	3.	Was the outcome measurement blinded?	☐	☒	☐
QC	4.	In case series: was the distribution of prognostic factors adequately covered?	☐	☐	☐
	F	Drop Outs	Yes	No	?
QA	1.	Was the response rate in intervention / control groups high enough or in cohort studies: could a sufficiently large part of the cohort be followed-up over the entire study period?	☒	☐	☐
QA	2.	Were the reasons for the drop-outs of study participants listed?	☐	☒	☐
QB	3.	Were the outcomes of the drop-outs described and considered in the evaluation?	☐	☒	☐
QB	4.	If differences were found - are they significant?	☐	☐	☐
QB	5.	If differences were found - are they relevant?	☐	☐	☐
	G	Statistical analysis	Yes	No	?
QA	1.	Are the described analytical procedures correct and is that information sufficient for a proper evaluation?	☒	☐	☐
	2.	For RCT: was an intention-to-treat analysis conducted?	☐	☐	☐
		a) Were all randomized individuals analyzed within the group to which they were assigned?	☐	☐	☐
		b) Were deviations of the non-randomized cases reported that were included in the analysis?	☐	☐	☐
		c) Has the effect of missing values been analyzed?	☐	☐	☐

QB	3.	Have the effect estimates and their precision (e.g. confidence intervals) been reported for all primary and secondary outcomes for each group?	☒	☐	☐
	4.	Has the distinction between a priori defined analysis and exploratory analysis been made and was the problem of multiple testing of hypotheses considered?	☐	☒	☐
I	5.	Are the results presented in a graphical form and are the underlying values for the graphics expressed?	☒	☐	☐
	H	Discussion	Yes	No	?
	1.	Are the following points in respect to the interpretation of results sufficiently covered?			
		a) the reference to the study hypothesis	☒	☐	☐
		b) the sources of distortion	☒	☐	☐
		c) statistical uncertainties	☐	☒	☐
		d) hazard multiple testing	☒	☐	☐
	2.	Was the external validity (generalizability) of the study results discussed?	☒	☐	☐
	3.	Were the study results discussed in the context of current evidence?	☒	☐	☐
Final assessment: This publication is included ☒ excluded ☐					

Checklist 2a

Checklist 2a: Primary studies (RCTs / case-control studies / cohort studies / longitudinal studies / case series)					
Report No.: 9.5.1.2.4					
Title:	Therapeutic decisions for patients with symptomatic severe aortic stenosis: room for improvement?				
Authors:	van Geldorp, M. W. A. et al. 2009				
Source:	Eur J Cardiothorac Surg 2009;35:953-959				
Document type	RCT: ☐ Cohort study: ☒ Case-control study: ☐ Longitudinal study: ☐ Case series: ☐ Other: ☐				
Clas	A	Selection of study participants	Yes	No	?
QA	1.	Are the inclusion and exclusion criteria for study participants sufficiently / clearly defined?	☒	☐	☐
QA	2.	Have the inclusion and exclusion criteria been defined before the intervention?	☐	☒	☐
QA	3.	Has the disease status been assessed in a valid and reliable manner?	☒	☐	☐
QBI	4.	Are the diagnostic criteria of the disease described?	☐	☒	☐
QB	5.	Is the study population / exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6.	For cohort studies: Were the study groups considered simultaneously?	☒	☐	☐
	7.	Has the determination of the sample size been specified?	☒	☐	☐
	8.	Are the period of recruitment and follow-up indicated?	☒	☐	☐
	B	Assignment and study participation	Yes	No	?
QA	1.	Do the exposed / cases and non-exposed/ controls come from a similar population?	☒	☐	☐
QA	2.	Are the intervention/ exposed group and the control/ non-exposed group comparable at baseline?			
		a) with respect to demographic characteristics	☒	☐	☐
		b) with respect to clinical characteristics	☒	☐	☐
QB	3.	Was the selection conducted randomized with a standard procedure?	☐	☒	☐
		a) was the allocation sequence generated by an accepted procedure?	☐	☐	☐
		b) was the allocation sequence concealed until the intervention?	☐	☐	☐
QC	4.	Was the randomization blinded?	☐	☐	☐
		a) for the patient	☐	☐	☐
		b) for the intervening physician	☐	☐	☐
QA	5.	Were known / possible confounders taken into account at the start of the study?	☐	☐	☒
	C	Intervention / Exposure	Yes	No	?
QA	1.	Were intervention or exposure recorded in a valid, reliable and similar manner?	☒	☐	☐
QB	2.	Were the intervention / control groups - with the exception of the intervention - treated alike?	☐	☐	☒
QB	3.	In case of different therapies, have they been recorded in a valid and reliable manner?	☐	☐	☒
QA	4.	For RCTs: Have placebos been used for the control groups?	☐	☐	☐
QA	5.	For RCTs: has the administration of placebos been documented?	☐	☐	☐
	D	Study Administration	Yes	No	?
QB	1.	Is there evidence of an "Overmatching"?	☐	☒	☐
QB	2.	In multicenter studies: were the diagnostic and therapeutic methods, and the outcome measurement identical in all participating centers?	☐	☐	☒
QA	3.	Was it ensured that study participants did not change between intervention and control groups?	☐	☐	☐
	E	Outcome measurement	Yes	No	?
I	1.	Were point-of-care outcome parameters used?	☐	☐	☒
QA	2.	Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
Q B	3.	Was the outcome measurement blinded?	☐	☒	☐
QC	4.	In case series: was the distribution of prognostic factors adequately covered?	☐	☐	☐
	F	Drop Outs	Yes	No	?
QA	1.	Was the response rate in intervention / control groups high enough or in cohort studies: could a sufficiently large part of the cohort be followed-up over the entire study period?	☒	☐	☐
QA	2.	Were the reasons for the drop-outs of study participants listed?	☐	☒	☐
QB	3.	Were the outcomes of the drop-outs described and considered in the evaluation?	☐	☒	☐
QB	4.	If differences were found - are they significant?	☐	☐	☐
QB	5.	If differences were found - are they relevant?	☐	☐	☐
	G	Statistical analysis	Yes	No	?
QA	1.	Are the described analytical procedures correct and is that information sufficient for a proper evaluation?	☒	☐	☐
	2.	For RCT: was an intention-to-treat analysis conducted?	☐	☐	☐
		a) Were all randomized individuals analyzed within the group to which they were assigned?	☐	☐	☐
		b) Were deviations of the non-randomized cases reported that were included in the analysis?	☐	☐	☐
		c) Has the effect of missing values been analyzed?	☐	☐	☐

QB	3.	Have the effect estimates and their precision (e.g. confidence intervals) been reported for all primary and secondary outcomes for each group?	☒	☐	☐
	4.	Has the distinction between a priori defined analysis and exploratory analysis been made and was the problem of multiple testing of hypotheses considered?	☐	☒	☐
I	5.	Are the results presented in a graphical form and are the underlying values for the graphics expressed?	☒	☐	☐
	H	Discussion	Yes	No	?
	1.	Are the following points in respect to the interpretation of results sufficiently covered?			
		a) the reference to the study hypothesis	☒	☐	☐
		b) the sources of distortion	☒	☐	☐
		c) statistical uncertainties	☐	☒	☐
		d) hazard multiple testing	☐	☒	☐
	2.	Was the external validity (generalizability) of the study results discussed?	☒	☐	☐
	3.	Were the study results discussed in the context of current evidence?	☒	☐	☐
Final assessment: This publication is included ☒ excluded ☐					

Checklist 2a

Checklist 2a: Primary studies (RCTs / case-control studies / cohort studies / longitudinal studies / case series)					
Report No.: 9.5.1.2.5					
Title:	Characterization and outcome of patients with severe symptomatic aortic stenosis referred for percutaneous aortic valve replacement				
Authors:	Kapadia, S. R. et al. 2009				
Source:	J Thorac Cardiovasc Surg 2009;137:1430-1435				
Document type	RCT: ☐ Cohort study: ☒ Case-control study: ☐ Longitudinal study: ☐ Case series: ☐ Other: ☐				
Clas	A	Selection of study participants	Yes	No	?
QA	1.	Are the inclusion and exclusion criteria for study participants sufficiently / clearly defined?	☒	☐	☐
QA	2.	Have the inclusion and exclusion criteria been defined before the intervention?	☒	☐	☐
QA	3.	Has the disease status been assessed in a valid and reliable manner?	☒	☐	☐
QBI	4.	Are the diagnostic criteria of the disease described?	☒	☐	☐
QB	5.	Is the study population / exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6.	For cohort studies: Were the study groups considered simultaneously?	☐	☒	☐
	7.	Has the determination of the sample size been specified?	☐	☒	☐
	8.	Are the period of recruitment and follow-up indicated?	☒	☐	☐
	B	Assignment and study participation	Yes	No	?
QA	1.	Do the exposed / cases and non-exposed/ controls come from a similar population?	☒	☐	☐
QA	2.	Are the intervention/ exposed group and the control/ non-exposed group comparable at baseline?			
		a) with respect to demographic characteristics	☒	☐	☐
		b) with respect to clinical characteristics	☒	☐	☐
QB	3.	Was the selection conducted randomized with a standard procedure?	☐	☒	☐
		a) was the allocation sequence generated by an accepted procedure?	☐	☐	☐
		b) was the allocation sequence concealed until the intervention?	☐	☐	☐
QC	4.	Was the randomization blinded?	☐	☐	☐
		a) for the patient	☐	☐	☐
		b) for the intervening physician	☐	☐	☐
QA	5.	Were known / possible confounders taken into account at the start of the study?	☒	☐	☐
	C	Intervention / Exposure	Yes	No	?
QA	1.	Were intervention or exposure recorded in a valid, reliable and similar manner?	☒	☐	☐
QB	2.	Were the intervention / control groups - with the exception of the intervention - treated alike?	☐	☐	☒
QB	3.	In case of different therapies, have they been recorded in a valid and reliable manner?	☐	☐	☒
QA	4.	For RCTs: Have placebos been used for the control groups?	☐	☐	☐
QA	5.	For RCTs: has the administration of placebos been documented?	☐	☐	☐
	D	Study Administration	Yes	No	?
QB	1.	Is there evidence of an "Overmatching"?	☐	☒	☐
QB	2.	In multicenter studies: were the diagnostic and therapeutic methods, and the outcome measurement identical in all participating centers?	☐	☐	☐
QA	3.	Was it ensured that study participants did not change between intervention and control groups?	☐	☐	☒
	E	Outcome measurement	Yes	No	?
I	1.	Were point-of-care outcome parameters used?	☐	☐	☒
QA	2.	Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3.	Was the outcome measurement blinded?	☐	☒	☐
QC	4.	In case series: was the distribution of prognostic factors adequately covered?	☐	☐	☐
	F	Drop Outs	Yes	No	?
QA	1.	Was the response rate in intervention / control groups high enough or in cohort studies: could a sufficiently large part of the cohort be followed-up over the entire study period?	☒	☐	☐
QA	2.	Were the reasons for the drop-outs of study participants listed?	☐	☒	☐
QB	3.	Were the outcomes of the drop-outs described and considered in the evaluation?	☐	☒	☐
QB	4.	If differences were found - are they significant?	☐	☐	☐
QB	5.	If differences were found - are they relevant?	☐	☐	☐
	G	Statistical analysis	Yes	No	?
QA	1.	Are the described analytical procedures correct and is that information sufficient for a proper evaluation?	☒	☐	☐
	2.	For RCT: was an intention-to-treat analysis conducted?	☐	☐	☐
		a) Were all randomized individuals analyzed within the group to which they were assigned?	☐	☐	☐
		b) Were deviations of the non-randomized cases reported that were included in the analysis?	☐	☐	☐
		c) Has the effect of missing values been analyzed?	☐	☐	☐

QB	3.	Have the effect estimates and their precision (e.g. confidence intervals) been reported for all primary and secondary outcomes for each group?	☐	☒	☐
	4.	Has the distinction between a priori defined analysis and exploratory analysis been made and was the problem of multiple testing of hypotheses considered?	☐	☒	☐
I	5.	Are the results presented in a graphical form and are the underlying values for the graphics expressed?	☒	☐	☐
	H	Discussion	Yes	No	?
	1.	Are the following points in respect to the interpretation of results sufficiently covered?			
		a) the reference to the study hypothesis	☒	☐	☐
		b) the sources of distortion	☒	☐	☐
		c) statistical uncertainties	☐	☒	☐
		d) hazard multiple testing	☐	☒	☐
	2.	Was the external validity (generalizability) of the study results discussed?	☒	☐	☐
	3.	Were the study results discussed in the context of current evidence?	☒	☐	☐
Final assessment: This publication is included ☒ excluded ☐					

Checklist 2a

Checklist 2a: Primary studies (RCTs / case-control studies / cohort studies / longitudinal studies / case series)					
Report No.: 9.5.1.2.6					
Title:	Outcomes of patients aged 80 and over with symptomatic, severe aortic stenosis: impact of patients' choice of refusing aortic valve replacement on survival				
Authors:	Kojodjojo, P. et al. 2008				
Source:	QJM 2008;101:567-573				
Document type	RCT: ☐ Cohort study: ☒ Case-control study: ☐ Longitudinal study: ☐ Case series: ☐ Other: ☐				
Clas	A	Selection of study participants	Yes	No	?
QA	1.	Are the inclusion and exclusion criteria for study participants sufficiently / clearly defined?	☒	☐	☐
QA	2.	Have the inclusion and exclusion criteria been defined before the intervention?	☒	☐	☐
QA	3.	Has the disease status been assessed in a valid and reliable manner?	☒	☐	☐
QBI	4.	Are the diagnostic criteria of the disease described?	☐	☒	☐
QB	5.	Is the study population / exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6.	For cohort studies: Were the study groups considered simultaneously?	☒	☐	☐
	7.	Has the determination of the sample size been specified?	☒	☐	☐
	8.	Are the period of recruitment and follow-up indicated?	☒	☐	☐
	B	Assignment and study participation	Yes	No	?
QA	1.	Do the exposed / cases and non-exposed/ controls come from a similar population?	☒	☐	☐
QA	2.	Are the intervention/ exposed group and the control/ non-exposed group comparable at baseline?			
		a) with respect to demographic characteristics	☒	☐	☐
		b) with respect to clinical characteristics	☒	☐	☐
QB	3.	Was the selection conducted randomized with a standard procedure?	☐	☒	☐
		a) was the allocation sequence generated by an accepted procedure?	☐	☐	☐
		b) was the allocation sequence concealed until the intervention?	☐	☐	☐
QC	4.	Was the randomization blinded?	☐	☐	☐
		a) for the patient	☐	☐	☐
		b) for the intervening physician	☐	☐	☐
QA	5.	Were known / possible confounders taken into account at the start of the study?	☒	☐	☐
	C	Intervention / Exposure	Yes	No	?
QA	1.	Were intervention or exposure recorded in a valid, reliable and similar manner?	☒	☐	☐
QB	2.	Were the intervention / control groups - with the exception of the intervention - treated alike?	☐	☐	☒
QB	3.	In case of different therapies, have they been recorded in a valid and reliable manner?	☐	☐	☐
QA	4.	For RCTs: Have placebos been used for the control groups?	☐	☐	☐
QA	5.	For RCTs: has the administration of placebos been documented?	☐	☐	☐
	D	Study Administration	Yes	No	?
QB	1.	Is there evidence of an "Overmatching"?	☐	☒	☐
QB	2.	In multicenter studies: were the diagnostic and therapeutic methods, and the outcome measurement identical in all participating centers?	☒	☐	☐
QA	3.	Was it ensured that study participants did not change between intervention and control groups?	☐	☐	☒
	E	Outcome measurement	Yes	No	?
I	1.	Were point-of-care outcome parameters used?	☐	☐	☒
QA	2.	Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3.	Was the outcome measurement blinded?	☐	☒	☐
QC	4.	In case series: was the distribution of prognostic factors adequately covered?	☐	☐	☐
	F	Drop Outs	Yes	No	?
QA	1.	Was the response rate in intervention / control groups high enough or in cohort studies: could a sufficiently large part of the cohort be followed-up over the entire study period?	☒	☐	☐
QA	2.	Were the reasons for the drop-outs of study participants listed?	☐	☐	☐
QB	3.	Were the outcomes of the drop-outs described and considered in the evaluation?	☐	☐	☐
QB	4.	If differences were found - are they significant?	☐	☐	☐
QB	5.	If differences were found - are they relevant?	☐	☐	☐
	G	Statistical analysis	Yes	No	?
QA	1.	Are the described analytical procedures correct and is that information sufficient for a proper evaluation?	☒	☐	☐
	2.	For RCT: was an intention-to-treat analysis conducted?	☐	☐	☐
		a) Were all randomized individuals analyzed within the group to which they were assigned?	☐	☐	☐
		b) Were deviations of the non-randomized cases reported that were included in the analysis?	☐	☐	☐
		c) Has the effect of missing values been analyzed?	☐	☐	☐

QB	3.	Have the effect estimates and their precision (e.g. confidence intervals) been reported for all primary and secondary outcomes for each group?	☐	☒	☐
	4.	Has the distinction between a priori defined analysis and exploratory analysis been made and was the problem of multiple testing of hypotheses considered?	☐	☒	☐
I	5.	Are the results presented in a graphical form and are the underlying values for the graphics expressed?	☒	☐	☐
	H	Discussion	Yes	No	?
	1.	Are the following points in respect to the interpretation of results sufficiently covered?			
		a) the reference to the study hypothesis	☒	☐	☐
		b) the sources of distortion	☒	☐	☐
		c) statistical uncertainties	☒	☐	☐
		d) hazard multiple testing	☒	☐	☐
	2.	Was the external validity (generalizability) of the study results discussed?	☒	☐	☐
	3.	Were the study results discussed in the context of current evidence?	☐	☒	☐
Final assessment: This publication is included ☒ excluded ☐					

Checklist 2a

Checklist 2a: Primary studies (RCTs / case-control studies / cohort studies / longitudinal studies / case series)					
Report No.: 9.5.1.2.7					
Title:	Population characteristics, treatment assignment and survival of patients with aortic stenosis referred for percutaneous valve replacement				
Authors:	Otten, A. M. et al. 2008				
Source:	EuroIntervent 2008;4:250-255				
Document type	RCT: ☐	Cohort study: ☒	Case-control study: ☐	Longitudinal study: ☐	
	Case series: ☐	Other: ☐			
Clas	A	Selection of study participants	Yes	No	?
QA	1.	Are the inclusion and exclusion criteria for study participants sufficiently / clearly defined?	☒	☐	☐
QA	2.	Have the inclusion and exclusion criteria been defined before the intervention?	☒	☐	☐
QA	3.	Has the disease status been assessed in a valid and reliable manner?	☒	☐	☐
QBI	4.	Are the diagnostic criteria of the disease described?	☒	☐	☐
QB	5.	Is the study population / exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6.	For cohort studies: Were the study groups considered simultaneously?	☐	☒	☐
	7.	Has the determination of the sample size been specified?	☐	☒	☐
	8.	Are the period of recruitment and follow-up indicated?	☒	☐	☐
	B	Assignment and study participation	Yes	No	?
QA	1.	Do the exposed / cases and non-exposed/ controls come from a similar population?	☒	☐	☐
QA	2.	Are the intervention/ exposed group and the control/ non-exposed group comparable at baseline?			
		a) with respect to demographic characteristics	☒	☐	☐
		b) with respect to clinical characteristics	☒	☐	☐
QB	3.	Was the selection conducted randomized with a standard procedure?	☐	☒	☐
		a) was the allocation sequence generated by an accepted procedure?	☐	☐	☐
		b) was the allocation sequence concealed until the intervention?	☐	☐	☐
QC	4.	Was the randomization blinded?	☐	☐	☐
		a) for the patient	☐	☐	☐
		b) for the intervening physician	☐	☐	☐
QA	5.	Were known / possible confounders taken into account at the start of the study?	☐	☐	☐
	C	Intervention / Exposure	Yes	No	?
QA	1.	Were intervention or exposure recorded in a valid, reliable and similar manner?	☒	☐	☐
QB	2.	Were the intervention / control groups - with the exception of the intervention - treated alike?	☐	☐	☒
QB	3.	In case of different therapies, have they been recorded in a valid and reliable manner?	☐	☐	☒
QA	4.	For RCTs: Have placebos been used for the control groups?	☐	☐	☐
QA	5.	For RCTs: has the administration of placebos been documented?	☐	☐	☐
	D	Study Administration	Yes	No	?
QB	1.	Is there evidence of an "Overmatching"?	☐	☒	☐
QB	2.	In multicenter studies: were the diagnostic and therapeutic methods, and the outcome measurement identical in all participating centers?	☐	☐	☐
QA	3.	Was it ensured that study participants did not change between intervention and control groups?	☐	☐	☐
	E	Outcome measurement	Yes	No	?
I	1.	Were point-of-care outcome parameters used?	☐	☐	☒
QA	2.	Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3.	Was the outcome measurement blinded?	☐	☒	☐
QC	4.	In case series: was the distribution of prognostic factors adequately covered?	☐	☐	☐
	F	Drop Outs	Yes	No	?
QA	1.	Was the response rate in intervention / control groups high enough or in cohort studies: could a sufficiently large part of the cohort be followed-up over the entire study period?	☒	☐	☐
QA	2.	Were the reasons for the drop-outs of study participants listed?	☐	☐	☐
QB	3.	Were the outcomes of the drop-outs described and considered in the evaluation?	☐	☐	☐
QB	4.	If differences were found - are they significant?	☐	☐	☐
QB	5.	If differences were found - are they relevant?	☐	☐	☐
	G	Statistical analysis	Yes	No	?
QA	1.	Are the described analytical procedures correct and is that information sufficient for a proper evaluation?	☒	☐	☐
	2.	For RCT: was an intention-to-treat analysis conducted?	☐	☐	☐
		a) Were all randomized individuals analyzed within the group to which they were assigned?	☐	☐	☐
		b) Were deviations of the non-randomized cases reported that were included in the analysis?	☐	☐	☐
		c) Has the effect of missing values been analyzed?	☐	☐	☐

QB	3.	Have the effect estimates and their precision (e.g. confidence intervals) been reported for all primary and secondary outcomes for each group?	☐	☒	☐
	4.	Has the distinction between a priori defined analysis and exploratory analysis been made and was the problem of multiple testing of hypotheses considered?	☐	☒	☐
I	5.	Are the results presented in a graphical form and are the underlying values for the graphics expressed?	☒	☐	☐
	H	Discussion	Yes	No	?
	1.	Are the following points in respect to the interpretation of results sufficiently covered?			
		a) the reference to the study hypothesis	☒	☐	☐
		b) the sources of distortion	☒	☐	☐
		c) statistical uncertainties	☐	☒	☐
		d) hazard multiple testing	☐	☒	☐
	2.	Was the external validity (generalizability) of the study results discussed?	☒	☐	☐
	3.	Were the study results discussed in the context of current evidence?	☒	☐	☐
Final assessment: This publication is included ☒ excluded ☐					

Checklist 2a

Checklist 2a: Primary studies (RCTs / case-control studies / cohort studies / longitudinal studies / case series)					
Report No.: 9.5.1.2.8					
Title:	Decision-making and outcomes in severe symptomatic aortic stenosis				
Authors:	Charlson, E. et al. 2006				
Source:	J Heart Valve Dis 2006;15:312-321				
Document type	RCT: ☐	Cohort study: ☒	Case-control study: ☐	Longitudinal study: ☐	
	Case series: ☐	Other: ☐			
Clas	A	Selection of study participants	Yes	No	?
QA	1.	Are the inclusion and exclusion criteria for study participants sufficiently / clearly defined?	☒	☐	☐
QA	2.	Have the inclusion and exclusion criteria been defined before the intervention?	☐	☒	☐
QA	3.	Has the disease status been assessed in a valid and reliable manner?	☒	☐	☐
QBI	4.	Are the diagnostic criteria of the disease described?	☒	☐	☐
QB	5.	Is the study population / exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6.	For cohort studies: Were the study groups considered simultaneously?	☐	☐	☒
	7.	Has the determination of the sample size been specified?	☒	☐	☐
	8.	Are the period of recruitment and follow-up indicated?	☒	☐	☐
	B	Assignment and study participation	Yes	No	?
QA	1.	Do the exposed / cases and non-exposed/ controls come from a similar population?	☒	☐	☐
QA	2.	Are the intervention/ exposed group and the control/ non-exposed group comparable at baseline?			
		a) with respect to demographic characteristics	☐	☒	☐
		b) with respect to clinical characteristics	☒	☐	☐
QB	3.	Was the selection conducted randomized with a standard procedure?	☐	☒	☐
		a) was the allocation sequence generated by an accepted procedure?	☐	☐	☐
		b) was the allocation sequence concealed until the intervention?	☐	☐	☐
QC	4.	Was the randomization blinded?	☐	☐	☐
		a) for the patient	☐	☐	☐
		b) for the intervening physician	☐	☐	☐
QA	5.	Were known / possible confounders taken into account at the start of the study?	☐	☒	☐
	C	Intervention / Exposure	Yes	No	?
QA	1.	Were intervention or exposure recorded in a valid, reliable and similar manner?	☒	☐	☐
QB	2.	Were the intervention / control groups - with the exception of the intervention - treated alike?	☐	☐	☒
QB	3.	In case of different therapies, have they been recorded in a valid and reliable manner?	☐	☐	☒
QA	4.	For RCTs: Have placebos been used for the control groups?	☐	☐	☐
QA	5.	For RCTs: has the administration of placebos been documented?	☐	☐	☐
	D	Study Administration	Yes	No	?
QB	1.	Is there evidence of an "Overmatching"?	☐	☒	☐
QB	2.	In multicenter studies: were the diagnostic and therapeutic methods, and the outcome measurement identical in all participating centers?	☐	☐	☒
QA	3.	Was it ensured that study participants did not change between intervention and control groups?	☐	☐	☒
	E	Outcome measurement	Yes	No	?
I	1.	Were point-of-care outcome parameters used?	☐	☐	☒
QA	2.	Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3.	Was the outcome measurement blinded?	☐	☒	☐
QC	4.	In case series: was the distribution of prognostic factors adequately covered?	☐	☐	☐
	F	Drop Outs	Yes	No	?
QA	1.	Was the response rate in intervention / control groups high enough or in cohort studies: could a sufficiently large part of the cohort be followed-up over the entire study period?	☒	☐	☐
QA	2.	Were the reasons for the drop-outs of study participants listed?	☐	☐	☐
QB	3.	Were the outcomes of the drop-outs described and considered in the evaluation?	☐	☐	☐
QB	4.	If differences were found - are they significant?	☐	☐	☐
QB	5.	If differences were found - are they relevant?	☐	☐	☐
	G	Statistical analysis	Yes	No	?
QA	1.	Are the described analytical procedures correct and is that information sufficient for a proper evaluation?	☒	☐	☐
	2.	For RCT: was an intention-to-treat analysis conducted?	☐	☐	☐
		a) Were all randomized individuals analyzed within the group to which they were assigned?	☐	☐	☐
		b) Were deviations of the non-randomized cases reported that were included in the analysis?	☐	☐	☐
		c) Has the effect of missing values been analyzed?	☐	☐	☐

QB	3.	Have the effect estimates and their precision (e.g. confidence intervals) been reported for all primary and secondary outcomes for each group?	☐	☒	☐
	4.	Has the distinction between a priori defined analysis and exploratory analysis been made and was the problem of multiple testing of hypotheses considered?	☐	☒	☐
I	5.	Are the results presented in a graphical form and are the underlying values for the graphics expressed?	☐	☒	☐
	H	Discussion	Yes	No	?
	1.	Are the following points in respect to the interpretation of results sufficiently covered?			
		a) the reference to the study hypothesis	☒	☐	☐
		b) the sources of distortion	☒	☐	☐
		c) statistical uncertainties	☐	☒	☐
		d) hazard multiple testing	☐	☒	☐
	2.	Was the external validity (generalizability) of the study results discussed?	☒	☐	☐
	3.	Were the study results discussed in the context of current evidence?	☐	☒	☐
Final assessment: This publication is included ☒ excluded ☐					

Checklist 2a

Checklist 2a: Primary studies (RCTs / case-control studies / cohort studies / longitudinal studies / case series)					
Report No.: 9.5.1.2.9					
Title:	Survival in elderly patients with severe aortic stenosis is dramatically improved by aortic valve replacement: results from a cohort of 277 patients aged ≥80 years				
Authors:	Varadarajan, P. et al. 2006b				
Source:	Eur J Cardiothorac Surg 2006;30:722-727				
Document type	RCT: ☐ Cohort study: ☒ Case-control study: ☐ Longitudinal study: ☐ Case series: ☐ Other: ☐				
Clas	A	Selection of study participants	Yes	No	?
QA	1.	Are the inclusion and exclusion criteria for study participants sufficiently / clearly defined?	☒	☐	☐
QA	2.	Have the inclusion and exclusion criteria been defined before the intervention?	☐	☒	☐
QA	3.	Has the disease status been assessed in a valid and reliable manner?	☒	☐	☐
QBI	4.	Are the diagnostic criteria of the disease described?	☒	☐	☐
QB	5.	Is the study population / exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6.	For cohort studies: Were the study groups considered simultaneously?	☐	☐	☒
	7.	Has the determination of the sample size been specified?	☒	☐	☐
	8.	Are the period of recruitment and follow-up indicated?	☒	☐	☐
	B	Assignment and study participation	Yes	No	?
QA	1.	Do the exposed / cases and non-exposed/ controls come from a similar population?	☒	☐	☐
QA	2.	Are the intervention/ exposed group and the control/ non-exposed group comparable at baseline?			
		a) with respect to demographic characteristics	☒	☐	☐
		b) with respect to clinical characteristics	☒	☐	☐
QB	3.	Was the selection conducted randomized with a standard procedure?	☐	☒	☐
		a) was the allocation sequence generated by an accepted procedure?	☐	☐	☐
		b) was the allocation sequence concealed until the intervention?	☐	☐	☐
QC	4.	Was the randomization blinded?	☐	☐	☐
		a) for the patient	☐	☐	☐
		b) for the intervening physician	☐	☐	☐
QA	5.	Were known / possible confounders taken into account at the start of the study?	☒	☐	☐
	C	Intervention / Exposure	Yes	No	?
QA	1.	Were intervention or exposure recorded in a valid, reliable and similar manner?	☒	☐	☐
QB	2.	Were the intervention / control groups - with the exception of the intervention - treated alike?	☐	☐	☒
QB	3.	In case of different therapies, have they been recorded in a valid and reliable manner?	☐	☐	☒
QA	4.	For RCTs: Have placebos been used for the control groups?	☐	☐	☐
QA	5.	For RCTs: has the administration of placebos been documented?	☐	☐	☐
	D	Study Administration	Yes	No	?
QB	1.	Is there evidence of an "Overmatching"?	☐	☒	☐
QB	2.	In multicenter studies: were the diagnostic and therapeutic methods, and the outcome measurement identical in all participating centers?	☐	☐	☐
QA	3.	Was it ensured that study participants did not change between intervention and control groups?	☐	☐	☒
	E	Outcome measurement	Yes	No	?
I	1.	Were point-of-care outcome parameters used?	☐	☐	☒
QA	2.	Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3.	Was the outcome measurement blinded?	☐	☒	☐
QC	4.	In case series: was the distribution of prognostic factors adequately covered?	☐	☐	☐
	F	Drop Outs	Yes	No	?
QA	1.	Was the response rate in intervention / control groups high enough or in cohort studies: could a sufficiently large part of the cohort be followed-up over the entire study period?	☒	☐	☐
QA	2.	Were the reasons for the drop-outs of study participants listed?	☐	☐	☐
QB	3.	Were the outcomes of the drop-outs described and considered in the evaluation?	☐	☐	☐
QB	4.	If differences were found - are they significant?	☐	☐	☐
QB	5.	If differences were found - are they relevant?	☐	☐	☐
	G	Statistical analysis	Yes	No	?
QA	1.	Are the described analytical procedures correct and is that information sufficient for a proper evaluation?	☒	☐	☐
	2.	For RCT: was an intention-to-treat analysis conducted?	☐	☐	☐
		a) Were all randomized individuals analyzed within the group to which they were assigned?	☐	☐	☐
		b) Were deviations of the non-randomized cases reported that were included in the analysis?	☐	☐	☐
		c) Has the effect of missing values been analyzed?	☐	☐	☐

QB	3.	Have the effect estimates and their precision (e.g. confidence intervals) been reported for all primary and secondary outcomes for each group?	☒	☐	☐
	4.	Has the distinction between a priori defined analysis and exploratory analysis been made and was the problem of multiple testing of hypotheses considered?	☒	☐	☐
I	5.	Are the results presented in a graphical form and are the underlying values for the graphics expressed?	☒	☐	☐
	H	Discussion	Yes	No	?
	1.	Are the following points in respect to the interpretation of results sufficiently covered?			
		a) the reference to the study hypothesis	☒	☐	☐
		b) the sources of distortion	☒	☐	☐
		c) statistical uncertainties	☒	☐	☐
		d) hazard multiple testing	☒	☐	☐
	2.	Was the external validity (generalizability) of the study results discussed?	☒	☐	☐
	3.	Were the study results discussed in the context of current evidence?	☒	☐	☐
Final assessment: This publication is included ☒ excluded ☐					

Checklist 2a

Checklist 2a: Primary studies (RCTs / case-control studies / cohort studies / longitudinal studies / case series)					
Report No.: 9.5.1.2.10					
Title:	Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery?				
Authors:	Iung, B. et al. 2005				
Source:	Eur Heart J 2005;26:2714-2720				
Document type	RCT: ☐	Cohort study: ☒	Case-control study: ☐	Longitudinal study: ☐	
	Case series: ☐	Other: ☐			
Clas	A	Selection of study participants	Yes	No	?
QA	1.	Are the inclusion and exclusion criteria for study participants sufficiently / clearly defined?	☒	☐	☐
QA	2.	Have the inclusion and exclusion criteria been defined before the intervention?	☐	☒	☐
QA	3.	Has the disease status been assessed in a valid and reliable manner?	☒	☐	☐
QBI	4.	Are the diagnostic criteria of the disease described?	☒	☐	☐
QB	5.	Is the study population / exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6.	For cohort studies: Were the study groups considered simultaneously?	☐	☐	☒
	7.	Has the determination of the sample size been specified?	☒	☐	☐
	8.	Are the period of recruitment and follow-up indicated?	☒	☐	☐
	B	Assignment and study participation	Yes	No	?
QA	1.	Do the exposed / cases and non-exposed/ controls come from a similar population?	☒	☐	☐
QA	2.	Are the intervention/ exposed group and the control/ non-exposed group comparable at baseline?			
		a) with respect to demographic characteristics	☒	☐	☐
		b) with respect to clinical characteristics	☒	☐	☐
QB	3.	Was the selection conducted randomized with a standard procedure?	☐	☒	☐
		a) was the allocation sequence generated by an accepted procedure?	☐	☐	☐
		b) was the allocation sequence concealed until the intervention?	☐	☐	☐
QC	4.	Was the randomization blinded?	☐	☐	☐
		a) for the patient	☐	☐	☐
		b) for the intervening physician	☐	☐	☐
QA	5.	Were known / possible confounders taken into account at the start of the study?	☒	☐	☐
	C	Intervention / Exposure	Yes	No	?
QA	1.	Were intervention or exposure recorded in a valid, reliable and similar manner?	☒	☐	☐
QB	2.	Were the intervention / control groups - with the exception of the intervention - treated alike?	☐	☐	☒
QB	3.	In case of different therapies, have they been recorded in a valid and reliable manner?	☐	☐	☒
QA	4.	For RCTs: Have placebos been used for the control groups?	☐	☐	☐
QA	5.	For RCTs: has the administration of placebos been documented?	☐	☐	☐
	D	Study Administration	Yes	No	?
QB	1.	Is there evidence of an "Overmatching"?	☐	☒	☐
QB	2.	In multicenter studies: were the diagnostic and therapeutic methods, and the outcome measurement identical in all participating centers?	☐	☐	☒
QA	3.	Was it ensured that study participants did not change between intervention and control groups?	☐	☐	☒
	E	Outcome measurement	Yes	No	?
I	1.	Were point-of-care outcome parameters used?	☐	☐	☒
QA	2.	Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3.	Was the outcome measurement blinded?	☐	☒	☐
QC	4.	In case series: was the distribution of prognostic factors adequately covered?	☐	☐	☐
	F	Drop Outs	Yes	No	?
QA	1.	Was the response rate in intervention / control groups high enough or in cohort studies: could a sufficiently large part of the cohort be followed-up over the entire study period?	☒	☐	☐
QA	2.	Were the reasons for the drop-outs of study participants listed?	☐	☐	☐
QB	3.	Were the outcomes of the drop-outs described and considered in the evaluation?	☐	☐	☐
QB	4.	If differences were found - are they significant?	☐	☐	☐
QB	5.	If differences were found - are they relevant?	☐	☐	☐
	G	Statistical analysis	Yes	No	?
QA	1.	Are the described analytical procedures correct and is that information sufficient for a proper evaluation?	☒	☐	☐
	2.	For RCT: was an intention-to-treat analysis conducted?	☐	☐	☐
		a) Were all randomized individuals analyzed within the group to which they were assigned?	☐	☐	☐
		b) Were deviations of the non-randomized cases reported that were included in the analysis?	☐	☐	☐
		c) Has the effect of missing values been analyzed?	☐	☐	☐

QB	3.	Have the effect estimates and their precision (e.g. confidence intervals) been reported for all primary and secondary outcomes for each group?	☒	☐	☐
	4.	Has the distinction between a priori defined analysis and exploratory analysis been made and was the problem of multiple testing of hypotheses considered?	☒	☐	☐
I	5.	Are the results presented in a graphical form and are the underlying values for the graphics expressed?	☒	☐	☐
	H	Discussion	Yes	No	?
	1.	Are the following points in respect to the interpretation of results sufficiently covered?			
		a) the reference to the study hypothesis	☒	☐	☐
		b) the sources of distortion	☒	☐	☐
		c) statistical uncertainties	☒	☐	☐
		d) hazard multiple testing	☒	☐	☐
	2.	Was the external validity (generalizability) of the study results discussed?	☒	☐	☐
	3.	Were the study results discussed in the context of current evidence?	☒	☐	☐
Final assessment: This publication is included ☒ excluded ☐					

Checklist 2a

Checklist 2a: Primary studies (RCTs / case-control studies / cohort studies / longitudinal studies / case series)					
Report No.: 9.5.1.2.11					
Title:	Natural history of candidates for balloon aortic valvuloplasty				
Authors:	O'Keefe, J. H., JR et al. 1987				
Source:	Mayo Clin Proc 1987;62:986-991				
Document type	RCT: ☐ Cohort study: ☐ Case-control study: ☐ Longitudinal study: ☐ Case series: ☒ Other: ☐				
Clas	A	Selection of study participants	Yes	No	?
QA	1.	Are the inclusion and exclusion criteria for study participants sufficiently / clearly defined?	☒	☐	☐
QA	2.	Have the inclusion and exclusion criteria been defined before the intervention?	☐	☒	☐
QA	3.	Has the disease status been assessed in a valid and reliable manner?	☒	☐	☐
QBI	4.	Are the diagnostic criteria of the disease described?	☒	☐	☐
QB	5.	Is the study population / exposed population representative of the majority of the exposed population or the "standard users" of the intervention?	☒	☐	☐
QA	6.	For cohort studies: Were the study groups considered simultaneously?	☐	☐	☒
	7.	Has the determination of the sample size been specified?	☒	☐	☐
	8.	Are the period of recruitment and follow-up indicated?	☒	☐	☐
	B	Assignment and study participation	Yes	No	?
QA	1.	Do the exposed / cases and non-exposed/ controls come from a similar population?	☐	☐	☐
QA	2.	Are the intervention/ exposed group and the control/ non-exposed group comparable at baseline?			
		a) with respect to demographic characteristics	☐	☐	☐
		b) with respect to clinical characteristics	☐	☐	☐
QB	3.	Was the selection conducted randomized with a standard procedure?	☐	☒	☐
		a) was the allocation sequence generated by an accepted procedure?	☐	☐	☐
		b) was the allocation sequence concealed until the intervention?	☐	☐	☐
QC	4.	Was the randomization blinded?	☐	☐	☐
		a) for the patient	☐	☐	☐
		b) for the intervening physician	☐	☐	☐
QA	5.	Were known / possible confounders taken into account at the start of the study?	☐	☐	☒
	C	Intervention / Exposure	Yes	No	?
QA	1.	Were intervention or exposure recorded in a valid, reliable and similar manner?	☒	☐	☐
QB	2.	Were the intervention / control groups - with the exception of the intervention - treated alike?	☐	☐	☐
QB	3.	In case of different therapies, have they been recorded in a valid and reliable manner?	☐	☐	☐
QA	4.	For RCTs: Have placebos been used for the control groups?	☐	☐	☐
QA	5.	For RCTs: has the administration of placebos been documented?	☐	☐	☐
	D	Study Administration	Yes	No	?
QB	1.	Is there evidence of an "Overmatching"?	☐	☒	☐
QB	2.	In multicenter studies: were the diagnostic and therapeutic methods, and the outcome measurement identical in all participating centers?	☐	☐	☐
QA	3.	Was it ensured that study participants did not change between intervention and control groups?	☐	☐	☐
	E	Outcome measurement	Yes	No	?
I	1.	Were point-of-care outcome parameters used?	☐	☐	☒
QA	2.	Were the outcomes recorded in a valid and reliable manner?	☒	☐	☐
QB	3.	Was the outcome measurement blinded?	☐	☒	☐
QC	4.	In case series: was the distribution of prognostic factors adequately covered?	☐	☒	☐
	F	Drop Outs	Yes	No	?
QA	1.	Was the response rate in intervention / control groups high enough or in cohort studies: could a sufficiently large part of the cohort be followed-up over the entire study period?	☒	☐	☐
QA	2.	Were the reasons for the drop-outs of study participants listed?	☐	☐	☐
QB	3.	Were the outcomes of the drop-outs described and considered in the evaluation?	☐	☐	☐
QB	4.	If differences were found - are they significant?	☐	☐	☐
QB	5.	If differences were found - are they relevant?	☐	☐	☐
	G	Statistical analysis	Yes	No	?
QA	1.	Are the described analytical procedures correct and is that information sufficient for a proper evaluation?	☒	☐	☐
	2.	For RCT: was an intention-to-treat analysis conducted?	☐	☐	☐
		a) Were all randomized individuals analyzed within the group to which they were assigned?	☐	☐	☐
		b) Were deviations of the non-randomized cases reported that were included in the analysis?	☐	☐	☐
		c) Has the effect of missing values been analyzed?	☐	☐	☐

QB	3.	Have the effect estimates and their precision (e.g. confidence intervals) been reported for all primary and secondary outcomes for each group?	☒	☐	☐
	4.	Has the distinction between a priori defined analysis and exploratory analysis been made and was the problem of multiple testing of hypotheses considered?	☐	☒	☐
I	5.	Are the results presented in a graphical form and are the underlying values for the graphics expressed?	☒	☐	☐
	H	Discussion	Yes	No	?
	1.	Are the following points in respect to the interpretation of results sufficiently covered?			
		a) the reference to the study hypothesis	☒	☐	☐
		b) the sources of distortion	☒	☐	☐
		c) statistical uncertainties	☐	☒	☐
		d) hazard multiple testing	☐	☒	☐
	2.	Was the external validity (generalizability) of the study results discussed?	☐	☒	☐
	3.	Were the study results discussed in the context of current evidence?	☒	☐	☐
Final assessment: This publication is included ☒ excluded ☐					

7.7.3 Secondary publications on TAVI

Checklist 1a

Checklist 1a: context documents/ HTA					
Report no.: 9.5.2.6					
Title:	Percutaneous heart valve implantation in congenital and degenerative valve disease. A rapid health technology assessment.				
Author:	van Brabandt, H. and Neyt, M. 2008				
Source:	Online publication (Belgian KCE): http://www.kce.fgov.be/index_en.aspx?SGREF=5212&CREF=12220				
Document type: HTA report ☒ guideline ☐ other document ☐					
Target recipients: decision makers ☒ clinicians ☒ patients ☐ other ☐					
Clas	A	Research question and context	Yes	No	?
I	1.	Are the motive and objections of the publication presented in terms of a "policy question"?	☒	☐	☐
QA	2.	Is the research question for the intervention (of interest) precisely formulated within a broader context?	☒	☐	☐
I	3.	Does the publication include information on the following aspects:			
I		a) epidemiology of the target disease	☒	☐	☐
I		b) (development) state of technology	☒	☐	☐
I		c) efficacy	☐	☒	☐
I		d) effectiveness	☒	☐	☐
I		e) side effects	☐	☒	☐
I		f) indications	☒	☐	☐
I		g) contraindications	☐	☒	☐
I		h) practice variation	☐	☒	☐
I		i) supply structures	☐	☒	☐
I		j) cost considerations	☒	☐	☐
I		k) socio-economic, ethical and legal impact	☐	☒	☐
Clas	B.	Methods of information gathering	Yes	No	?
QA	1.	Are the sources used documented?	☒	☐	☐
QB	2.	Are the search strategies documented?	☒	☐	☐
QB	3.	Are the inclusion criteria defined?	☐	☒	☐
QB	4.	Are the exclusion criteria defined?	☒	☐	☐
Klas	C	Methods of evaluation and documentation	Yes	No	?
QA	1.	Are validity criteria taken into account?	☐	☐	☒
QC	2.	Was the assessment conducted independently by several people?	☐	☐	☒
QC	3.	Are excluded studies documented with their reasons for exclusion?	☐	☒	☐
QC	4.	Is the data extraction documented in a comprehensive manner?	☒	☐	☐
QC	5.	Was the data extraction conducted by several people independently?	☐	☐	☒
Clas	D	Methods of information synthesis	Yes	No	?
I		Quantitative information syntheses (please fill out the included checklist 1b on meta-analysis).	☐	☒	☐
I		Qualitative information syntheses (please fill out the included checklist 1b on information synthesis)	☒	☐	☐
I		Were proprietary surveys conducted to complement the available data?	☐	☒	☐
Clas	E	Results / Conclusions	Yes	No	?
QB	1.	Is the existing evidence consistently transferred into the conclusions?	☐	☐	☒
QA	2.	Are methodological limitations of the evidence critically discussed?	☒	☐	☐
I	3.	Are recommendations for action provided?	☒	☐	☐
I	4.	Is there a grading of the recommendation?	☐	☒	☐
QC	5.	Did the publication undergo an external review process before being published?	☐	☐	☒
I	6	Is a future update of the publication planned?	☐	☐	☒
Clas	F	Transferability of international/ foreign results and conclusions	Yes	No	?
		Do differences exist in respect to the:			
		a) epidemiology of the target condition?	☐	☒	☐
		b) development state of the technology?	☐	☒	☐
		c) indication?	☐	☒	☐
		d) health care contexts, conditions, processes?	☒	☐	☐
		e) compensation schemes?	☒	☐	☐
		f) socio-economic consequences?	☐	☐	☒
		g) patient and provider preferences?	☐	☐	☒
Final assessment: This publication is: included ☒ excluded ☐					

Checklist 1b

Checklist 1b: systematic reviews and meta-analyses				
Report no.: 9.5.2.1				
Title:	Transcatheter aortic valve implantation for high-risk patients with severe aortic stenosis: A systematic review			
Authors:	Yan, T. D. et al. 2010			
Source:	J Thorac Cardiovasc Surg, 139:1519-1528			
This document contains: qualitative information synthesis ☒ quantiative information synthesis ☐				
Clas	A Research question	Yes	No	?
QA	1. Is the research question relevant to your own question?	☒	☐	☐
Clas	B information retrieval	Yes	No	?
	1. Documentation of the literature search:			
QA	a) have the sources used been documented?	☒	☐	☐
QB	b) have the search strategies been documented?	☒	☐	☐
QB	2. Were the inclusion criteria define?	☒	☐	☐
QB	3. Were the exclusion criteria defined?	☒	☐	☐
	C Evaluation of information	Yes	No	?
	1. Documentation of the study evaluation:			
QA	a) Have criteria of validity been taken into account?	☒	☐	☐
QB	b) Was the evaluation conducted independently by several people?	☒	☐	☐
QC	c) Were excluded studies documented with their reasons for exclusion?	☐	☒	☐
QC	2. Is the documentation of data extraction comprehensible?	☒	☐	☐
QC	3. Was the data extraction conducted independently by several people?	☒	☐	☐
	D Information synthesis	Yes	No	?
	1. Quantitative Information synthesis:			
QA	a) Was the method for the meta-analysis specified?	☐	☐	☐
QB	b) Were heterogeneity tests conducted?	☐	☐	☐
QC	c) Were the results examined for robustness in a sensitivity analysis?	☐	☐	☐
	2. Qualitative information syntheses:			
QA	a) Is the synthesis of information clearly documented?	☒	☐	☐
QB	b) Is there an evaluation of existing evidence?	☐	☒	☐
	E Conclusions	Yes	No	?
QB	1. Is the research question answered?	☒	☐	☐
QB	2. Is the existing evidence consistently transferred into the conclusions?	☒	☐	☐
QA	3. Are methodological limitations related to the significance of results critically discussed?	☒	☐	☐
I	4. Are recommendations for action provided?	☐	☒	☐
I	5. Is there a grading of the recommendations?	☐	☒	☐
I	5. Are further research needs identified?	☐	☒	☐
I	6. Is a future update of the review planned?	☐	☐	☒
	F Transferability of international/ foreign results and conclusions	Yes	No	?
	Do differences exist in respect to the:			
	a) epidemiology of the target condition?	☐	☒	☐
	b) development state of the technology?	☐	☒	☐
	c) indication?	☐	☒	☐
	d) health care contexts, -environment, -processes?	☐	☐	☒
	e) compensation schemes?	☐	☐	☒
	f) socio-economic consequences?	☐	☐	☒
	g) patient and provider preferences?	☐	☒	☐
Final assessment: This publication is included ☒ excluded ☐				

Checklist 1b

Checklist 1b: systematic reviews and meta-analyses				
Report no.: 9.5.2.2				
Title:	Safety of percutaneous aortic valve insertion. A systematic review			
Authors:	van Brabandt, H. and Neyt, M. 2009			
Source:	BMC Cardiovasc Disord 9: 45-51			
This document contains: qualitative information synthesis ☒ quantiative information synthesis ☐				
Clas	A Research question	Yes	No	?
QA	1. Is the research question relevant to your own question?	☒	☐	☐
Clas	B information retrieval	Yes	No	?
	1. Documentation of the literature search:			
QA	a) have the sources used been documented?	☒	☐	☐
QB	b) have the search strategies been documented?	☒	☐	☐
QB	2. Were the inclusion criteria define?	☒	☐	☐
QB	3. Were the exclusion criteria defined?	☒	☐	☐
	C Evaluation of information	Yes	No	?
	1. Documentation of the study evaluation:			
QA	a) Have criteria of validity been taken into account?	☐	☐	☒
QB	b) Was the evaluation conducted independently by several people?	☐	☐	☒
QC	c) Were excluded studies documented with their reasons for exclusion?	☒	☐	☐
QC	2. Is the documentation of data extraction comprehensible?	☒	☐	☐
QC	3. Was the data extraction conducted independently by several people?	☒	☐	☐
	D Information synthesis	Yes	No	?
	1. Quantitative Information synthesis:			
QA	a) Was the method for the meta-analysis specified?	☐	☐	☐
QB	b) Were heterogeneity tests conducted?	☐	☐	☐
QC	c) Were the results examined for robustness in a sensitivity analysis?	☐	☐	☐
	2. Qualitative information syntheses:			
QA	a) Is the synthesis of information clearly documented?	☐	☒	☐
QB	b) Is there an evaluation of existing evidence?	☐	☒	☐
	E Conclusions	Yes	No	?
QB	1. Is the research question answered?	☒	☐	☐
QB	2. Is the existing evidence consistently transferred into the conclusions?	☒	☐	☐
QA	3. Are methodological limitations related to the significance of results critically discussed?	☒	☐	☐
I	4. Are recommendations for action provided?	☐	☒	☐
I	5. Is there a grading of the recommendations?	☐	☒	☐
I	5. Are further research needs identified?	☐	☒	☐
I	6. Is a future update of the review planned?	☐	☐	☒
	F Transferability of international/ foreign results and conclusions	Yes	No	?
	Do differences exist in respect to the:			
	a) epidemiology of the target condition?	☐	☒	☐
	b) development state of the technology?	☐	☒	☐
	c) indication?	☐	☒	☐
	d) health care contexts, -environment, -processes?	☐	☐	☒
	e) compensation schemes?	☐	☐	☒
	f) socio-economic consequences?	☐	☐	☒
	g) patient and provider preferences?	☐	☒	☐
Final assessment: This publication is included ☒ excluded ☐				

Checklist 1b

Checklist 1b: systematic reviews and meta-analyses				
Report no.: 9.5.2.3				
Title:	Minimal-invasiver perkutaner Aortenklappenersatz. Systematischer Review – 1. Update 2009			
Authors:	Wild, C. and Geiger-Gritsch, S. 2009			
Source:	Online publication (LBI Austria) http://eprints.hta.lbg.ac.at/766/2/DSD_18_Update2009.pdf			
This document contains: qualitative information synthesis ☒ quantiative information synthesis ☐				
Clas	A Research question	Yes	No	?
QA	1. Is the research question relevant to your own question?	☒	☐	☐
Clas	B information retrieval	Yes	No	?
	1. Documentation of the literature search:			
QA	a) have the sources used been documented?	☒	☐	☐
QB	b) have the search strategies been documented?	☒	☐	☐
QB	2. Were the inclusion criteria define?	☒	☐	☐
QB	3. Were the exclusion criteria defined?	☒	☐	☐
	C Evaluation of information	Yes	No	?
	1. Documentation of the study evaluation:			
QA	a) Have criteria of validity been taken into account?	☒	☐	☐
QB	b) Was the evaluation conducted independently by several people?	☐	☐	☒
QC	c) Were excluded studies documented with their reasons for exclusion?	☐	☒	☐
QC	2. Is the documentation of data extraction comprehensible?	☒	☐	☐
QC	3. Was the data extraction conducted independently by several people?	☐	☐	☒
	D Information synthesis	Yes	No	?
	1. Quantitative Information synthesis:			
QA	a) Was the method for the meta-analysis specified?	☐	☐	☐
QB	b) Were heterogeneity tests conducted?	☐	☐	☐
QC	c) Were the results examined for robustness in a sensitivity analysis?	☐	☐	☐
	2. Qualitative information syntheses:			
QA	a) Is the synthesis of information clearly documented?	☒	☐	☐
QB	b) Is there an evaluation of existing evidence?	☒	☐	☐
	E Conclusions	Yes	No	?
QB	1. Is the research question answered?	☒	☐	☐
QB	2. Is the existing evidence consistently transferred into the conclusions?	☒	☐	☐
QA	3. Are methodological limitations related to the significance of results critically discussed?	☒	☐	☐
I	4. Are recommendations for action provided?	☒	☐	☐
I	5. Is there a grading of the recommendations?	☒	☐	☐
I	5. Are further research needs identified?	☐	☒	☐
I	6. Is a future update of the review planned?	☐	☐	☒
	F Transferability of international/ foreign results and conclusions	Yes	No	?
	Do differences exist in respect to the:			
	a) epidemiology of the target condition?	☐	☒	☐
	b) development state of the technology?	☐	☒	☐
	c) indication?	☐	☒	☐
	d) health care contexts, -environment, -processes?	☐	☐	☒
	e) compensation schemes?	☐	☐	☒
	f) socio-economic consequences?	☐	☐	☒
	g) patient and provider preferences?	☐	☒	☐
Final assessment: This publication is included ☒ excluded ☐				

Checklist 1b

Checklist 1b: systematic reviews and meta-analyses				
Report no.: 9.5.2.4				
Title:	Pose de bioprothèses valvulaires aortiques par voie artérielle fémorale et par abord transapical			
Authors:	Blanchard, S. 2008			
Source:	Online publication (HAS France) http://www.has-sante.fr/portail/upload/docs/application/pdf/document_avis_valves_2008.pdf			
This document contains: qualitative information synthesis ☒ quantiative information synthesis ☐				
Clas	A Research question	Yes	No	?
QA	1. Is the research question relevant to your own question?	☒	☐	☐
Clas	B information retrieval	Yes	No	?
	1. Documentation of the literature search:			
QA	a) have the sources used been documented?	☒	☐	☐
QB	b) have the search strategies been documented?	☐	☒	☐
QB	2. Were the inclusion criteria define?	☐	☒	☐
QB	3. Were the exclusion criteria defined?	☐	☒	☐
	C Evaluation of information	Yes	No	?
	1. Documentation of the study evaluation:			
QA	a) Have criteria of validity been taken into account?	☐	☐	☒
QB	b) Was the evaluation conducted independently by several people?	☐	☐	☒
QC	c) Were excluded studies documented with their reasons for exclusion?	☐	☐	☐
QC	2. Is the documentation of data extraction comprehensible?	☐	☐	☐
QC	3. Was the data extraction conducted independently by several people?	☐	☐	☐
	D Information synthesis	Yes	No	?
	1. Quantitative Information synthesis:			
QA	a) Was the method for the meta-analysis specified?	☐	☐	☐
QB	b) Were heterogeneity tests conducted?	☐	☐	☐
QC	c) Were the results examined for robustness in a sensitivity analysis?	☐	☐	☐
	2. Qualitative information syntheses:			
QA	a) Is the synthesis of information clearly documented?	☐	☒	☐
QB	b) Is there an evaluation of existing evidence?	☒	☐	☐
	E Conclusions	Yes	No	?
QB	1. Is the research question answered?	☒	☐	☐
QB	2. Is the existing evidence consistently transferred into the conclusions?	☒	☐	☐
QA	3. Are methodological limitations related to the significance of results critically discussed?	☒	☐	☐
I	4. Are recommendations for action provided?	☒	☐	☐
I	5. Is there a grading of the recommendations?	☐	☒	☐
I	5. Are further research needs identified?	☒	☐	☐
I	6. Is a future update of the review planned?	☒	☐	☐
	F Transferability of international/ foreign results and conclusions	Yes	No	?
	Do differences exist in respect to the:			
	a) epidemiology of the target condition?	☐	☒	☐
	b) development state of the technology?	☐	☒	☐
	c) indication?	☐	☒	☐
	d) health care contexts, -environment, -processes?	☐	☐	☒
	e) compensation schemes?	☐	☐	☒
	f) socio-economic consequences?	☐	☐	☒
	g) patient and provider preferences?	☐	☒	☐
Final assessment: This publication is included ☒ excluded ☐				

Checklist 1b

Checklist 1b: systematic reviews and meta-analyses				
Report no.: 9.5.2.5				
Title:	Interventional procedure overview of transcatheter aortic valve implantation for aortic stenosis			
Authors:	National Institute for Health and Clinical Excellence (NICE) 2008			
Source:	Online publication (NICE UK) http://www.nice.org.uk/nicemedia/live/11914/39663/39663.pdf			
This document contains: qualitative information synthesis ☒ quantiative information synthesis ☐				
Clas	A Research question	Yes	No	?
QA	1. Is the research question relevant to your own question?	☒	☐	☐
Clas	B information retrieval	Yes	No	?
	1. Documentation of the literature search:			
QA	a) have the sources used been documented?	☒	☐	☐
QB	b) have the search strategies been documented?	☒	☐	☐
QB	2. Were the inclusion criteria define?	☒	☐	☐
QB	3. Were the exclusion criteria defined?	☒	☐	☐
	C Evaluation of information	Yes	No	?
	1. Documentation of the study evaluation:			
QA	a) Have criteria of validity been taken into account?	☒	☐	☐
QB	b) Was the evaluation conducted independently by several people?	☐	☐	☒
QC	c) Were excluded studies documented with their reasons for exclusion?	☒	☐	☐
QC	2. Is the documentation of data extraction comprehensible?	☒	☐	☐
QC	3. Was the data extraction conducted independently by several people?	☐	☐	☒
	D Information synthesis	Yes	No	?
	1. Quantitative Information synthesis:			
QA	a) Was the method for the meta-analysis specified?	☐	☐	☐
QB	b) Were heterogeneity tests conducted?	☐	☐	☐
QC	c) Were the results examined for robustness in a sensitivity analysis?	☐	☐	☐
	2. Qualitative information syntheses:			
QA	a) Is the synthesis of information clearly documented?	☒	☐	☐
QB	b) Is there an evaluation of existing evidence?	☐	☒	☐
	E Conclusions	Yes	No	?
QB	1. Is the research question answered?	☐	☐	☒
QB	2. Is the existing evidence consistently transferred into the conclusions?	☒	☐	☐
QA	3. Are methodological limitations related to the significance of results critically discussed?	☐	☒	☐
I	4. Are recommendations for action provided?	☐	☒	☐
I	5. Is there a grading of the recommendations?	☐	☒	☐
I	5. Are further research needs identified?	☐	☒	☐
I	6. Is a future update of the review planned?	☐	☐	☒
	F Transferability of international/ foreign results and conclusions	Yes	No	?
	Do differences exist in respect to the:			
	a) epidemiology of the target condition?	☐	☒	☐
	b) development state of the technology?	☐	☒	☐
	c) indication?	☐	☒	☐
	d) health care contexts, -environment, -processes?	☐	☐	☒
	e) compensation schemes?	☐	☐	☒
	f) socio-economic consequences?	☐	☐	☒
	g) patient and provider preferences?	☐	☒	☐
Final assessment: This publication is included ☒ excluded ☐				

Checklist 1b

Checklist 1b: systematic reviews and meta-analyses				
Report no.: 9.5.2.6				
Title:	Percutaneous heart valve implantation in congenital and degenerative valve disease. A rapid health technology assessment.			
Authors:	van Brabandt, H. and Neyt, M. 2008			
Source:	Online publication (Belgian KCE): http://www.kce.fgov.be/index_en.aspx?SGREF=5212&CREF=12220			
This document contains: qualitative information synthesis ☒ quantiative information synthesis ☐				
Clas	A Research question	Yes	No	?
QA	1. Is the research question relevant to your own question?	☒	☐	☐
Clas	B information retrieval	Yes	No	?
	1. Documentation of the literature search:			
QA	a) have the sources used been documented?	☒	☐	☐
QB	b) have the search strategies been documented?	☒	☐	☐
QB	2. Were the inclusion criteria define?	☒	☐	☐
QB	3. Were the exclusion criteria defined?	☒	☐	☐
	C Evaluation of information	Yes	No	?
	1. Documentation of the study evaluation:			
QA	a) Have criteria of validity been taken into account?	☐	☐	☒
QB	b) Was the evaluation conducted independently by several people?	☐	☐	☒
QC	c) Were excluded studies documented with their reasons for exclusion?	☒	☐	☐
QC	2. Is the documentation of data extraction comprehensible?	☒	☐	☐
QC	3. Was the data extraction conducted independently by several people?	☐	☐	☒
	D Information synthesis	Yes	No	?
	1. Quantitative Information synthesis:			
QA	a) Was the method for the meta-analysis specified?	☐	☐	☐
QB	b) Were heterogeneity tests conducted?	☐	☐	☐
QC	c) Were the results examined for robustness in a sensitivity analysis?	☐	☐	☐
	2. Qualitative information syntheses:			
QA	a) Is the synthesis of information clearly documented?	☐	☒	☐
QB	b) Is there an evaluation of existing evidence?	☐	☒	☐
	E Conclusions	Yes	No	?
QB	1. Is the research question answered?	☒	☐	☐
QB	2. Is the existing evidence consistently transferred into the conclusions?	☐	☐	☐
QA	3. Are methodological limitations related to the significance of results critically discussed?	☒	☐	☐
I	4. Are recommendations for action provided?	☒	☐	☐
I	5. Is there a grading of the recommendations?	☐	☒	☐
I	5. Are further research needs identified?	☒	☐	☐
I	6. Is a future update of the review planned?	☐	☐	☒
	F Transferability of international/ foreign results and conclusions	Yes	No	?
	Do differences exist in respect to the:			
	a) epidemiology of the target condition?	☐	☒	☐
	b) development state of the technology?	☐	☒	☐
	c) indication?	☐	☒	☐
	d) health care contexts, -environment, -processes?	☐	☐	☒
	e) compensation schemes?	☐	☐	☒
	f) socio-economic consequences?	☐	☐	☒
	g) patient and provider preferences?	☐	☐	☒
Final assessment: This publication is included ☒ excluded ☐				

Checklist 1b

Checklist 1b: systematic reviews and meta-analyses				
Report no.: 9.5.2.7				
Title:	Minimal-invasiver perkutaner Aortenklappenersatz. Systematischer Review			
Authors:	Wild, C. et al. 2008			
Source:	Online publication (LBI Austria) http://eprints.hta.lbg.ac.at/1/DSD_18.pdf			
This document contains: qualitative information synthesis ☒ quantiative information synthesis ☐				
Clas	A Research question	Yes	No	?
QA	1. Is the research question relevant to your own question?	☒	☐	☐
Clas	B information retrieval	Yes	No	?
	1. Documentation of the literature search:			
QA	a) have the sources used been documented?	☒	☐	☐
QB	b) have the search strategies been documented?	☒	☐	☐
QB	2. Were the inclusion criteria define?	☒	☐	☐
QB	3. Were the exclusion criteria defined?	☒	☐	☐
	C Evaluation of information	Yes	No	?
	1. Documentation of the study evaluation:			
QA	a) Have criteria of validity been taken into account?	☒	☐	☐
QB	b) Was the evaluation conducted independently by several people?	☒	☐	☐
QC	c) Were excluded studies documented with their reasons for exclusion?	☐	☒	☐
QC	2. Is the documentation of data extraction comprehensible?	☒	☐	☐
QC	3. Was the data extraction conducted independently by several people?	☒	☐	☐
	D Information synthesis	Yes	No	?
	1. Quantitative Information synthesis:			
QA	a) Was the method for the meta-analysis specified?	☐	☐	☐
QB	b) Were heterogeneity tests conducted?	☐	☐	☐
QC	c) Were the results examined for robustness in a sensitivity analysis?	☐	☐	☐
	2. Qualitative information syntheses:			
QA	a) Is the synthesis of information clearly documented?	☒	☐	☐
QB	b) Is there an evaluation of existing evidence?	☒	☐	☐
	E Conclusions	Yes	No	?
QB	1. Is the research question answered?	☒	☐	☐
QB	2. Is the existing evidence consistently transferred into the conclusions?	☒	☐	☐
QA	3. Are methodological limitations related to the significance of results critically discussed?	☒	☐	☐
I	4. Are recommendations for action provided?	☒	☐	☐
I	5. Is there a grading of the recommendations?	☒	☐	☐
I	5. Are further research needs identified?	☐	☒	☐
I	6. Is a future update of the review planned?	☐	☐	☒
	F Transferability of international/ foreign results and conclusions	Yes	No	?
	Do differences exist in respect to the:			
	a) epidemiology of the target condition?	☐	☒	☐
	b) development state of the technology?	☐	☒	☐
	c) indication?	☐	☒	☐
	d) health care contexts, -environment, -processes?	☐	☐	☒
	e) compensation schemes?	☐	☐	☒
	f) socio-economic consequences?	☐	☐	☒
	g) patient and provider preferences?	☐	☒	☐
Final assessment: This publication is included ☒ excluded ☐				

8 Table of abbreviations

ACC	*American College of Cardiology*
ACE	Angiotension-converting enzymes
AHA	American Heart Association
AI	Aortic insufficiency
AR	Aortic regurgitation
AS	Aortic stenosis
AVA	Aortic valve area
AVR	Aortic valve replacement
BAV	Balloon aortic valvuloplasty
CABG	Coronary Artery Bypass Grafting
CDSR	Cochrane Database of Systematic Reviews
CI	Confidence interval
cm^2	Square centimeter
CRD	Center for Reviews and Dissemination
DGK	German Society of Cardiology
DGTHG	German Society for Thoracic and Cardiovascular Surgery
ESC	European Society of Cardiology
EQ-5D™	Trademark of the EuroQoL Group (Descriptive system of health-related quality of life states consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression))
EU	European Union
EuroSCORE	European System for Cardiac Operative Risk Evaluation
e.g.	exempli gratia (for example)

et al.	Et alii (and other [team members])
GSWG	German Scientific Working Group Technology Assessments for Health Care
HAS	Haute Autorité de Santé (France)
HTA	Health Technology Assessment
ICU	Intensive care unit
i.e.	id est (that is)
INAHTA	International Network of Agencies for Health Technology Assessment
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Germany)
KCE	Health Care Knowledge Center (Belgium)
LBI	Ludwig-Bolzmann-Institut (Austria)
LVEF	Left ventricular ejection fraction
M	Medical therapy
m²	Square meter
MACCE	Major adverse cardiac and cerebrovascular events
MeSH	Medical Subject Headings
MI	Myocardial infarction
mmHg	Millimeters of mercury
N/ n	Number of patients
NA	Not available
NICE	National Institute for Health and Clinical Excellence (UK)
NYHA	New York Heart Association
PARTNER	Placement of Aortic Transcatheter Valves Trial
PPM	Permanent pacemaker

QoL	Quality of Life
RCT	Randomized controlled trial
SD	Standard deviation
STS	Society of Thoracic Surgeons
TAVI	Transcatheter aortic valve implantation
TA	Transapical
TV	Transvascular
UK	United Kingdom
USA	United States of America
www	World wide web

9 Acknowledgements

At this point I would like to take the opportunity to thank those people that were of particular importance for the realization of this work.

First of all, my special thanks go to my supervisor PD Dr. med. Till Neumann who supported the planning and execution of the project and provided critical guidance and patient support over the entire course of this work.

In addition, I would like to thank Dr. med. Dr. rer. pol. Anja Neumann for her expert opinion and advice on the methodology of systematic reviews as well as her guidance on the structure of the publication manuscript.

Beyond the scope of work, I would like to thank my husband, my parents, and my parents-in-law who ensured the most important prerequisite for this project, i.e. took care of the twins.

10 Curriculum vitae

The CV has been removed from the online publication due to data protection purposes.