Cost effectiveness of aortic valve therapies: a systematic review of the literature

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ABSTRACT

BACKGROUND: we performed a systematic review on the cost effectiveness of transcatheter aortic valve implantation (TAVI) to standard aortic valve replacement and medical management in high-risk elderly patients with severe aortic stenosis.

METHODS: in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analyses, a systematic review on current literature for cost-effectiveness of TAVI, standard aortic valve replacement, and medical management for elderly patients with high-risk severe aortic stenosis was performed. Incremental cost effectiveness ratio is used to measure effectiveness through life years gained or quality adjusted life years. Drummond checklist was used to further assess the quality of the included studies.

RESULTS: the systematic literature search identified 4 primary publications (derived from 52 citations) that fulfilled the inclusion criteria. Tremendous discrepancy in incremental cost effectiveness ratio is demonstrated with operable patients similar to Cohort A of the PARTNER trial (€ 749 416 and € 39 577). Inoperable patients similar to Cohort B of the PARTNER trial suggest notable differences in favour for transcatheter aortic valve implantation with an increase in quality adjusted life years (0.06 versus 1.6, respectively). With lifetime horizon to transcatheter aortic valve implantation there is a more comparable incremental cost effectiveness ratio in the literature (€ 38 260 and € 37 432). Lowest incremental cost effectiveness ratio witnessed in the technical inoperable group at € 26 482. Lifetime horizon of 10 years with transcatheter aortic valve implantation differ (€ 39 388 versus € 19 947). Overall, a review of the literature suggests TAVI usage in patients for severe aortic stenosis whom are not eligible for surgery. All the studies were overall judged of medium-high quality.

CONCLUSIONS: transcatheter aortic valve replacement is more cost effective with a lifetime horizon for the treatment of patients with high-risk aortic stenosis compared with medical management considering those ineligible for standard aortic valve replacement. Further cost effectiveness research is needed in the stratifications of patient risk and patient co-morbidities for those candidates eligible for surgery.

Key words: Aortic stenosis; Transcatheter aortic valve implantation; Cost effectiveness; Clinical effectiveness; Systematic review

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INTRODUCTION

Aortic stenosis (AS) is one of the most frequently encountered cardiovascular diseases and has a substantial socioeconomic burden; without valve replacement, symptomatic patients with severe AS have a mortality >70% within a few years of symptom onset [1]. In the coming decades, there will be a tremendous aging of the population in developed countries with a unique increase of inhabitants older than 80 years [2]. Depending on patient risk severity and operability, medical management for high risk patients with AS is performed. In spite of this, aortic valve replacement (AVR) has been proven to significantly prolong life expectancy and improve quality of life. Although AVR is regarded to be the mainstay for improved survival and symptom relief, not all patients, especially the elderly, are able to profit from this technique [2]. Transcatheter aortic valve implantation (TAVI) is rapidly gaining acceptance as a viable therapy for severe aortic stenosis for patients deemed at prohibitive or excessive surgical risk [3]. In 2002 Criber et al performed the first TAVI for patients with inoperable aortic stenosis [4]. As of June 2010, approximately 20 000 procedures have been performed worldwide with over 425 interventional centres, and this number experiences exponential growth [2, 5]. At present, two different TAVI valves have been accepted into the European market: the SAPIEN® valve of Edwards Lifesciences and CoreValve® of Medtronic. Presently, only one randomized control trial studying the safety and efficacy of TAVI was published in September 2010 with an additional analysis published in June 2011: Placement of AoRtic TraNscathetER valve (*PARTNER I and II*). Although patient selection, operator skills, and technology have improved, all previous TAVI studies have been observational registries, without standardization or endpoint definitions, without formal clinical events committees, and without independent echo core lab [5].

Health economic analysts have designed frameworks to evaluate the economic impact and value for improvements in health and longevity. This could have important decision making implications for usage to be justified for long term performance. Given the advanced age and multiple co-morbidities conditions that characterize patients with high surgical risk for surgical valve replacement, the question of whether TAVI can provide meaningful health benefits to the population at an acceptable cost is particularly germane [6]. New technologies into the market place are cited to contribute to increasing healthcare costs. Therefore, before a technology is adopted it is important to understand the clinical and economic implications up front, as it is more difficult to withdraw from usage once approved. To date, there is limited objective evidence measuring the cost effectiveness of TAVI compared to SAVR and standard medical treatment.

METHODS

Eligibility criteria

The systematic review is based on published peer-reviewed full-text reports in randomized control trials as well as case studies, cohort studies and secondary literature from health technology institutes and reports from governing bodies. It is in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA), pre-established criteria for inclusion and exclusion into this review can be found in Table 1 [7]. Additional literature searches for clinical effectiveness of TAVI and AS along with learning curves and operative risk factors were used for a deeper comprehensive understanding of the disease and not factored into inclusion criteria.

Data Collection Process

The literature search was performed in MEDLINE, the search strategy consisted of vocabulary including titles, abstracts, keywords such as “cost effectiveness transcatheter aortic valve implantation” or “cost effectiveness transcatheter aortic valve replacement”, “review” or “systematic review”, and “health technology assessment”, and “cost effectiveness aortic stenosis”. The search was restricted to the English language but not to any specific time period. Findings from MEDLINE were last update on April 2nd 2012. These searches were complemented by searching the reference lists of key papers to identify any additional relevant studies. No limitations were based on the study type. For further searches, Agencies for Health Technology Assessment (INAHTA) electronic databases, National Institute for Health and

TABLE 1

INCLUSION AND EXCLUSION CRITERIA FOR PUBLICATIONS

CHARACTERISTIC	CRITERIA
Publication type	Peer-reviewed full-text publications that report cost-effectiveness outcomes, systematic reviews, publications from health technology institutes, and government agencies. Papers presented at conferences were excluded due to restricted access
Language	English
Intervention	Transcatheter aortic valve implantation (TAVI)
Study characteristics	Cost-effectiveness studies, including case reports
Economic/Health Outcome	Cost effectiveness, Quality adjusted life years (QALY) and life years gained (LYG)

Clinical Excellence (NICE) and supplemental databases of national governing body Canadian Agency for Drug and Technologies in Health (CADTH) were reviewed. Selection of literature was constructed in two ways: an initial screening of the literature search by title, abstract and keywords followed by full-text publications, health technology assessments, and reports. The rational for any exclusion criteria of data in the literature search is mainly due to lack of relevance to cost-effectiveness information.

Quality assessment

Drummond checklist was used to further evaluate the quality of the studies included in the systematic review [8]. The checklist was developed to assess the quality of an economic evaluation considering the following sections: study design, data collection, analysis and interpretation of results. All of the 35 items were explored by two independent reviewers (S.B., W.M.) per each included study.

RESULTS

Results of literature search

For the transparent reporting of this systematic review, the PRISMA statement consists of a 27-item checklist and a four phase flow diagram [7]. As illustrated in the flow chart in Figure 1 the original literature search identified a total of 52 citations (whereby 10 cost effectiveness TAVI/TAVR and 42 cost effectiveness aortic stenosis). Based on the screening of titles and abstracts 38 citations were excluded from the review and 13 potentially relevant publications were retrieved for full text screening. An additional 13 potentially relevant reports were retrieved through hand searching the reference list papers, 26 underwent a detailed full-text screening, yielding 4 [1, 4, 6, 9] primary publications for TAVI, SAVR, and medical management of AS.

Most of the data available with a cost effectiveness search tended to be prior to the PARTNER trial and mainly cost minimization analysis or cost of illness in specified hospital settings. Since the publication of PARTNER trial in September 2010, the 4 primary publications for this systematic review are in reference to select patient cohorts from this study. As highlighted by Leon et al., the key study characteristics and patient types for the PARTNER trial are described in Table 2. Most included studies were recently published with publication year from 2007 and as recent as March 2012.

Quality of the included studies

Table 3 reports qualitative evaluation assigned to each included study, according to the 35 items exploring study design, data collection and analysis and interpretation of results. All studies presented lack in the data collection section and in part explanation of analysis and interpretation of results, being adherent to almost all of the remaining items explored. Study design items were adherent for all of the studies, except for the choice of form of economic evaluation justification in relation to the questions addressed in Neyt et al. and Gada et al. studies [1, 9].

On the contrary, some deficiencies have been highlighted referring to data collection section, details of the design and results of study

FIGURE 1

FLOW OF INFORMATION FOR SYSTEMATIC REVIEW

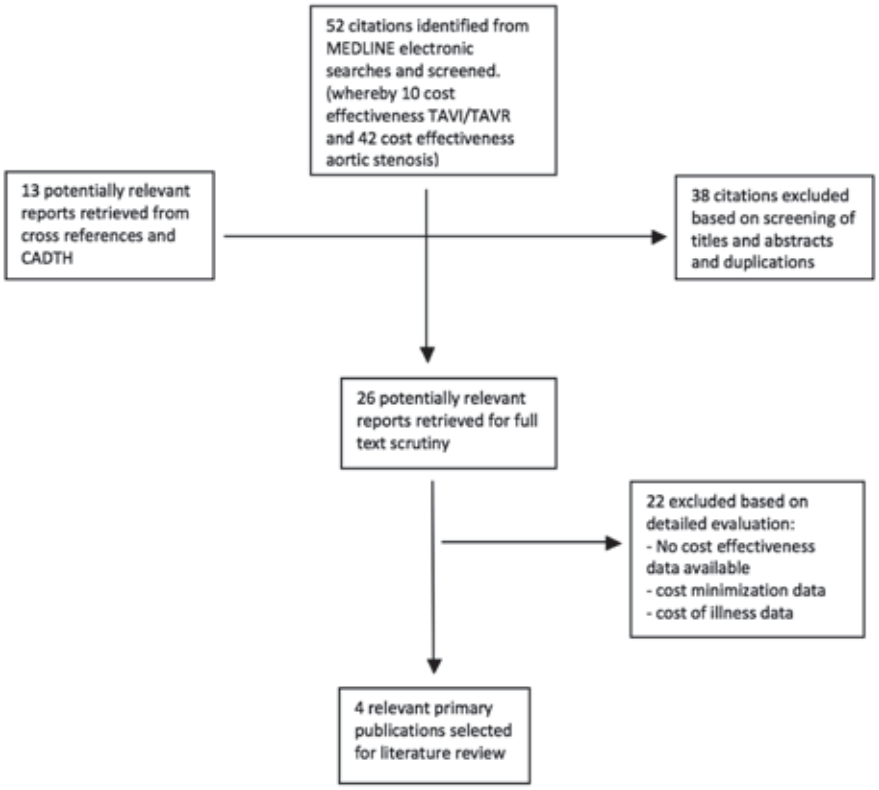

TABLE 2

PARTNER PATIENT COHORTS (PIVOTAL AND COMBINED ACCESS STUDY)

COHORT A	COHORT B
• High risk patients with an estimated operative mortality risk of at least 10% by the STS score, or at least 15% due to other severe problems not included in the STS score • Patients were randomised to transfemoral or transapical TAVI depending on whether or not transfemoral access was possible versus the classical surgical treatment (aortic valve replacement - AVR). In the analysis of the primary endpoint of the trial (all-cause mortality) both TAVI variants together were compared with surgery	• Patients considered as inoperable by at least two heart surgeons either due to anatomical factors (thoracic wall malformation, repeated previous thoracic surgeries, significant aortic calcification - so called porcelain aorta, sequelae of radiotherapy) or due to concomitant severe medical conditions • Patients with the possibility of a transfemoral access were randomized to transfemoral TAVI versus a standard therapy which, in addition to medication, generally involved balloon aortic valvuloplasty, a technique where the narrowed aortic valve is dilated with a balloon

Reference: Belgian Healthcare Knowledge Centre [9]

effectiveness, were not clearly given by Gada et al. [1]. The inconsistency for items 10 and from 13 to 19 documented some methodological limits for all of the four studies [1, 6, 9, 10].

Lastly, for items included in the analysis and interpretation of results, all studies stated a discounted rate but inconsistency for justifications of rate used and source of data for sensitivity analysis are not provided by Watt et al and Reynolds et al. [6, 10]. According to Drummond's checklist, studies were judged to be of medium-high quality, giving consistency to the systematic review.

TABLE 3

QUALITY OF INCLUDED STUDY					
	REFEREE'S CHECKLIST	STUDY ID			
	ITEM	NEYT 2011	WATT 2012	GADA 2012	REYNOLDS 2012
Study design	(I) The research question is stated	Y	Y	Y	Y
	(2) The economic importance of the research question is stated	Y	Y	Y	Y
	(3) The viewpoint(s) of the analysis are clearly stated and justified	Y	Y	Y	Y
	(4) The rationale for choosing the alternative programmes or interventions compared is stated	Y	Y	Y	Y
	(5) The alternatives being compared are clearly described	Y	Y	Y	Y
	(6) The form of economic evaluation used is stated	Y	Y	Y	Y
	(7) The choice of form of economic evaluation is justified in relation to the questions addressed	NC[1]	Y	NC[5]	Y
Data collection	(8) The source(s) of effectiveness estimates used are stated	Y	Y	Y	Y
	(9) Details of the design and results of effectiveness study are given (if based on a single study)	Y[2]	Y	NC	Y
	(10) Details of the method of synthesis or meta-analysis of estimates are given (overview)	N	NC[4]	NC[6]	N[7]
	(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Y	Y	Y	Y
	(12) Methods to value health states and other benefits are stated	Y	Y	Y	Y
	(13) Details of the subjects from whom valuations were obtained are given	NC	NC	NC	Y
	(14) Productivity changes (if included) are reported separately	N	N	N	N
	(15) The relevance of productivity changes to the study question is discussed	N	N	N	N
	(16) Quantities of resources are reported separately from their unit costs	N	N	N	Y
	(17) Methods for the estimation of quantities and unit costs are described	NC[3]	N	N	NC[8]
	(18) Currency and price data are recorded	Y	Y	Y	Y
	(19) Details of currency of price adjustments for inflation or currency conversion are given	NC	N	N	N
	(20) Details of any model used are given	Y	Y	Y	Y
	(21) The choice of model used and the key parameters on which it is based are justified	Y	Y	Y	Y
Analysis and interpretation of results	(22) Time horizon of costs and benefits is stated	Y	Y	Y	Y
	(23) The discount rate(s) is stated	Y	Y	Y	Y
	(24) The choice of rate(s) is justified	Y	N	N	N
	(25) An explanation is given if costs or benefits are not discounted	N	N	N	N
	(26) Details of statistical tests and confidence intervals are given for stochastic data	Y	Y	Y	Y
	(27) The approach to sensitivity analysis is given	Y	Y	Y	Y
	(28) The choice of variables for sensitivity analysis is justified	Y	N	Y	N
	(29) The ranges over which the variables are varied are stated	Y	Y	Y	Y
	(30) Relevant alternatives are compared	Y	Y	Y	Y
	(31) Incremental analysis is reported	Y	Y	Y	Y
	(32) Major outcomes are presented in a disaggregated as well as aggregated form	Y	Y	Y	Y
	(33) The answer to the study question is given	Y	Y	Y	Y
	(34) Conclusions follow from the data reported	Y	Y	Y	Y
	(35) Conclusions are accompanied by the appropriate caveats	Y	Y	Y	Y

Legend: Y= yes; N= not; NC= not clear

1 HTA although mainly clinical & economic evaluations

2 Based on PARTNER trial and Belgian TAVI Data

3 Section 6.1.1 redirects to 4.2 and 4.3: no specifics

4 Literature review - no methods to review discussed

5 Decision analytic model used - Markov Model

6 Published reports & data used from registries (Table 2)

7 Based on PARTNER Trial

8 TAVR procedure costs - average acquisition costs

Synthesis of results

The literature review conducted by Gada et al. in patients with high surgical risk TAVI, whom AVR is the current procedure of choice, appears to provide similar surgical outcomes for those of AVR [1]. The costs for TAVI and AVR are higher than medical management, although the outcomes are also superior to those of medical management. The cost-effectiveness ratio of TAVI and AVR was € 29 988/QALYs and € 29 475/QALYs, respectively [1]. An additional gain of 0.06 QALYs with the use of TAVI over AVR is observed. The cost of TAVI was greater than that of AVR (€ 44 649 vs. € 42 275), yielding an ICER of € 39 577/QALYs [1]. A threshold analysis is implemented suggesting the variation in net monetary benefit is influenced mainly in relation to TAVI. The net monetary benefit from AVR exceeded TAVI at a threshold TAVI cost of € 41 356 [1]. Using the PARTNER costs with transition probabilities and mortality rates outlined in the Gada et al. review the ICER of TAVI is € 24 003/QALYs [1]. As illustrated in Table 4, observations in the PARTNER trial (Cohort A) analyses the difference in lifetime costs were minimal and a small net health benefit using TAVI compared to AVR is demonstrated, the differences in utilities were not noted.

According to the literature review conducted by Reynolds et al. the results were relatively insensitive to changes in the discount rate or the assumed acquisition cost of the study device or the exclusion of costs associated with balloon valvuloplasty procedures from the control group [6]. The estimated difference in discounted lifetime medical care costs of € 60 859 and a gain in discounted life expectancy of 1.6 years resulted in an ICER of € 38 260 [6]. In reference to Table 4, with a decrease in time horizon from lifetime to 10 years and 5 years there is an increase ICER from € 38 260 to € 39 388 and € 43 742, respectively. As the time horizon increases so does the QALYs or life years (LY) expressed to suggest an overall increase with TAVI than when compared to the control group. However, due to lack of standardization amongst cost effectiveness reviews it can be misleading. Conceivably measurement for effectiveness in QALYs presents no assumed improvement over time in the baseline utility scores for either group, as a result the ICER for TAVI became less favourable at approximately € 63 191 [6]. Reynolds et al. suggest that although expert panels recommend the use of QALYs as a standard effectiveness measure in health economic analysis this guidance is not universally accepted both because of imprecision in the methods used to estimate QALYs and because there is both philosophical and political opposition to the notion that life-years for one group might be valued differently than life-years for another group due to age, disability or chronic health problems [6].

Furthermore in the literature review conducted by Watt et al. a cost effectiveness model is used to compare the costs and benefits over a 10 year time horizon of medical management versus TAVI in patients with inoperable aortic stenosis [4]. Similarly, the results presented in the PARTNER trial (Cohort B) are implemented into the cost effectiveness model. To note, 83% of individuals in the medical management arm were assumed to receive a balloon aortic valvuloplasty (BAV) procedure and all incurred the costs of pharmacological treatment [4]. In comparison to medical management, individuals in the TAVI arm incurred an additional 1.56 QALY's at 10 year cost per patient of € 30 296 suggesting a base case ICER of € 19 467 per QALY gained [4]. As observed in the PARTNER trial (Cohort B), using pooled input parameters, there is an additional 1.54 QALY's at 10 year cost per patient of € 30 777 suggesting a base case ICER of € 19 947 per QALY gained. The majority of TAVI related costs correspond to the initial implant operation (€ 22 846) or perioperative intensive care unit (ICU) care (€ 3 006), although saving are avoided in terms of BAV procedures (-€ 2885) [4]. The overall total procedure costs are the lowest amongst the reviews and possibly this can partially account for the significantly lower ICER relative to other centres.

The fourth principle publication used for this systematic review is the TAVI Health Technology Assessment completed by the Belgian Health Care Knowledge Centre, referenced as Belgian HTA report [9] for costs and reimbursements in Belgium. In reference to Table 5, reviewing the base case results and various scenario analyses, the cost effectiveness calculated for Cohort A suggests a substantial incremental cost for TAVI versus AVR. The average ICER is about € 750 000

TABLE 4

COST EFFECTIVENESS LITERATURE REVIEWS FOR TAVI TREATMENT COMPARED TO AVR AND MEDICAL MANAGEMENT

PUBLICATION (YEAR)	TYPE OF ECONOMIC EVALUATION AND TIME HORIZON	PERSPECTIVE AND COUNTRY	POPULATION / SAMPLE	TREATMENT	MEASURE OF OUTCOME	RESULTS
GADA ET AL. (2012)	Cost Effectiveness Analysis Time Horizon: Lifetime	Economic and Clinical USA	10 000 simulations	Reference case (operable AVR candidates) TAVI AVR	ICER (€/QALY) Direct Medical Costs: Inpatient treatment costs (DRG), TAVI and AVR annual follow-up plus 1 outpatient visit. Medical management annual costs post diagnosis.	Base Case: € 39 577 +0.06
				PARTNER costs TAVI AVR		PARTNER Costs: € 24 003 +0.06
				Alternative Scenario PARTNER (Cohort A) TAVI AVR		Alternative Scenario: NA +0.01
					Indirect: Not considered	Sensitivity Analysis: MonteCarlo simulation (probabilistic) - Cost effectiveness plane less robust with AVR when compared to TAVI.
REYNOLDS ET AL. (2012)	Cost Effectiveness Analysis Time Horizon: Lifetime, 10 years, and 5 years	Economic and Clinical USA	TAVR (n=179) Standard Therapy (n=179)	PARTNER (Cohort B - lifetime) TAVI MM	(€/LYG) Direct Medical Costs: Medical Management costs from hospital billing. TAVI costs for in-hospital treatment. Follow-up hospital care costs (MS-DRG) Rehabilitation facility costs included when available. Physician fees included for TAVI.	Base Case: (lifetime horizon) € 38 260 +1.59
				PARTNER (Cohort B - 10 years) TAVI MM		Base Case: (10 year horizon) € 39 388 +1.52
				PARTNER (Cohort B - 5 years) TAVI MM		Base Case: (5 years) € 43 742 +1.27
					Indirect: Not Considered	Sensitivity Analysis: Sensitivity analysis performed but type not stated. € 63 191 ICER
WATT ET AL. (2012)	Cost Effectiveness Analysis/ Cost Benefit Analysis Time Horizon: 30 days, 10 years	Economic and Clinical UK/Germany	2 interlinked Markov models used: short term - 30 days long term - 10 years. Number of cycles not stated.	Base Case TAVI MM	ICER (€/QALY) Direct Medical Costs: Drug costs, treatment specific costs, all procedure and device costs for TAVI taken from costing study,	Base Case: € 19 467 +1.56
						Alternative Scenario: € 19 947 +1.54
				Alternative Scenario PARTNER (Cohort B) TAVI MM	Indirect: Not Considered	Sensitivity Analysis: MonteCarlo simulation (probabilistic) and deterministic analysis. Robust to changes in hospitalization costs and adverse events, very sensitive to changes in short-term treatment effect and cost of initial operation.

Note: XE Universal Currency Converter (April 2 2012): 1 Euro = 0.83 GBP, 1 Euro = 1.33 USD
Gada et al. EuroSCORE patient risk of TAVI & AVR > 15%. STS patient risk of TAVI & AVR > 10%, discounted at 5%, lifetime horizon
Reynolds et al. New York Heart Association functional class ≥ 2, high surgical risk based on STS, costs discounted at 3%, EQ-5D measurement for QALY (*QALYs or LY)
Watt et al. EuroSCORE patient risk of TAVI & AVR > 15%. STS patient risk of TAVI & AVR > 10%, discounted at 3.5%, time horizon 10 years

per life years gained (LYG) or per QALY gained [9]. Even with a decrease in the TAVI device cost from € 18 000 to € 10 000 the average ICER remains above € 450 000 per LYG or QALY gained [9]. The cost effectiveness calculated for Cohort B suggests with a lifetime treatment effect the average ICER is about € 37 400 per QALY. When taking into account a mortality time horizon scenario of 3 years, the average ICER increases to € 71 573 per QALY. It is suggested that the net monetary health costs contribute largely to the cost of the device at € 18 000. Lowering the TAVI device cost to € 10 000 brings down the ICER to roughly € 30 000 per QALY and small increments with little impact are illustrated with an increase in additional fees.

As stated in Table 6, in the Pivotal study (PARTNER I), the Belgian HTA report suggests a similar ICER with a lifetime horizon as observed by Reynolds et al. at approximately € 38 000. With additional patients in the continued access study (PARTNER II) it did not show as favourable findings with an increased lifetime ICER of € 44 932. Through stratification of the data in inoperable patients of Cohort B there is a demonstrative difference in ICER. Although a reduction in mortality is observed in both subgroups, those inoperable patients due to technical reasons suggest the most advantageous ICER of € 26 482 per QALY vs. the non-technical group at € 42 285 per QALY [9].

DISCUSSION

From an economic perspective, comparing the Belgian HTA report to Gada et al. suggests significant differences in cost effectiveness outcomes regardless of device costs. With a 10 year lifetime horizon, the literature review conducted by Gada et al. suggests a reference case ICER of € 39 577 compared to Belgian HTA report [9] outcome of € 749 416 for patients of high-risk severe AS who are still operable. Furthermore, factoring a scenario analysis with a reduced TAVI cost from € 18 000 to € 10 000 the data continues to suggest a drastic difference in ICER at € 455 461. Using the scenario results from PARTNER costs in Gada et al., further illustrates a tremendous discrepancy with an ICER of € 24 012. Limited information is provided by the Belgian HTA report on the summation of costs. Health economic evaluations should be designed with more costs transparency to accurately compare consumption of resources. At this time further investigation is needed to clarify significant differences.

In the same way for high-risk patients who are inoperable due to anatomical factors, significant aortic calcification, or medical conditions the base case results between Watt et al. and Reynolds et al. suggest an ICER with a € 20 000 difference at a 10 year time horizon. Watt et al. ICER of € 19 467 or PARTNER (Cohort B) of € 19 947 is significantly less compared to the ICER results demonstrated with the Reynolds et al. PARTNER (Cohort B) at an ICER of € 39 388 with the intent of a similar patient population. Similar to above, bearing in mind factors attributed to the cost of TAVI medical device and the contributions to the total costs of the procedure will vary, all direct medical and indirect costs relevant to the perspective chosen for the study should be clearly defined in unit quantities and prices for comparability.

Less widespread are the comparison of ICER's at lifetime horizon for patients considered inoperable between Belgian HTA reports with an ICER of € 37 432 to Reynolds et al. lifetime horizon with an ICER of € 38 260. In both cases, with a reduced time horizon scenario of 3 years and 5 years this ICER increases to € 71 573 in the Belgian HTA report with a parallel increase of € 43 742 amongst the Reynolds et al. review respectively. The choice of time horizon used in these economic analysis's are reflected in the respective increases in ICER, fundamentally further consideration to the age and average life expectancy of the patient population studied should be taken into account for health policy decisions. The Belgian HTA report continues to illustrate with inoperable (Cohort B) patients' economic outcomes with reduced device costs from € 18 000 to € 10 000 and factoring variable inclusive TAVI device fees. Savings are demonstrated by lowering the cost per device resulting in an ICER close to € 30 000 and after initial rise of device fees of € 500 minimal impact is attributed to further increases in device fees. When TAVI is compared to medical management the incremental cost effectiveness over lifetime horizon is more advantageous and likely recommended. Short term survival can represent a major drawback to the cost effectiveness of TAVI, however if economic evaluations can be reproduced transparently different viewpoints and perspectives may influence policy decisions.

TABLE 5

BELGIAN HTA REPORT, BASE CASE RESULT AND SCENARIO ANALYSES FOR TAVI

PUBLICATION (YEAR)	TYPE OF ECONOMIC EVALUATION AND TIME HORIZON	PERSPECTIVE AND COUNTRY	POPULATION / SAMPLE	TREATMENT	MEASURE OF OUTCOME	RESULTS
BELGIAN HEALTH CARE KNOWLEDGE CENTRE (2011)	Health Technology Assessment Cost effectiveness analysis, Cost utility analysis Time Horizon: Lifetime, 3 years	Economic, Clinical Belgium	1000 TAVI eligible patients Markov model simulation	Cohort A TAVI € 18 000 Base case (lifetime horizon)	ICER (€/LYG) ICER (€/QALY) Direct Medical Costs: From perspective of healthcare payer. TAVI - Treatment costs during hospitalization and ambulatory costs, device costs. AVR – hospitalization costs, no ambulatory costs.	Cohort A TAVI € 18 000 € 759 072 or € 749 416 +0.03 (LYG and QALY)
				Cohort A TAVI € 10 000 Scenario analysis (3 year horizon)		Cohort A TAVI € 10 000 € 461 360 or € 455 461 +0.03 (LYG and QALY)
				Cohort B Base case (lifetime horizon)		Cohort B Base case € 31 856 or € 37 432 +1.16 (LYG) +0.92 (QALY)
				Cohort B (3 year horizon)		Cohort B € 68 208 € 71 573 0.55 (LYG) 0.47 (QALY)
				Cohort B TAVI € 10 000		Cohort B TAVI € 10 000 € 24 735 or € 29 117 1.16 (LYG) 0.92 (QALY)
						TAVI device fee € 500 €30 945 or € 36 368 +1.16 (LYG) +0.92 (QALY)
					Indirect: Not considered	TAVI device fee € 1 000 € 31 400 or € 36 900 +1.16 (LYG) +0.92 (QALY)
				Cohort B With TAVI device fee € 500 With TAVI device fee € 1 000		Cohort B (base case) TAVI device fee € 1 500 € 31 856 or € 37 432 +1.16 (LYG) +0.92 (QALY)
				Cohort B (base case) With TAVI device fee € 1 500		Sensitivity Analysis: MonteCarlo Simulation (probabilistic). Cost effectiveness plan for Cohort A measures life years gained vs Cohort B measures QALY. Cohort B illustrates more robust results

Reference: Belgian Healthcare Knowledge Centre [9]

TABLE 6

STRATIFICATION OF DATA WITH THE BELGIAN HEALTHCARE KNOWLEDGE CENTRE					
PIVOTAL AND CONTINUED ACCESS	**INCREMENTAL COST**	**INCREMENTAL EFFECT (LYG)**	**INCREMENTAL EFFECT (QALY)**	**ICER (€/LYG)**	**ICER (€/QALY)**
Cohort B - Pivotal (baseline)	€ 34 590 (€ 29 881 – € 38 631)	1.16 (0.65 – 1.75)	0.92 (-0.29 – 1.90)	€ 31 856 (€ 20 259 – € 51 554)	€ 37 432
Cohort B - Combined	€ 33 243 (€ 27 452 – € 37 773)	0.88 (0.39 – 1.41)	0.74 (-0.44 – 1.69)	€ 42 647 (€ 23 655 – € 86 311)	€ 44 932
TECHNICAL VS NON-TECHNICAL INOPERABLE PATIENTS	**INCREMENTAL COST**	**INCREMENTAL EFFECT (LYG)**	**INCREMENTAL EFFECT (QALY)**	**ICER (€/LYG)**	**ICER (€/QALY)**
Cohort B Non-technical inoperable	€ 34 285 (€ 29 229 – € 38 647)	(0.45 – 1.64)	0.81 (-0.30 – 1.77)	€ 34 301	€ 42 285
Cohort B Technical inoperable	€ 36 123 (€ 30 350 – € 41 850)	1.78 (0.60 – 3.27)	1.36 (-0.15 – 2.88)	€ 24 270 (€ 11 942 – € 53 898)	€ 26 482

Reference: Belgian Healthcare Knowledge Centre [9]

The technique of TAVI is a risky procedure consequently the learning curve should also be considered to clinical outcomes and cost effectiveness. The combination of operator experience, patient selection, and technological advancements can have important implications on procedural complications and potentially cost effectiveness outcomes. The minimum volume of training for each operator to eliminate the learning curve is important, and further study is required to determine the minimum number of yearly procedures required to maintain TAVI competency [3]. The Belgian HTA report advises to guarantee a sufficient workflow TAVI treatment the procedure should be limited to 1 or 2 Belgian centres [9]. To sustain operator experience, minimize procedural complications and impact costs of the procedure, future considerations to the number of centres undertaking this cardiac procedure can be further contemplated. In the same way organizational structure and impact on how care is delivered warrants further discussion (hybrid context vs. operating room) when evaluating cost effectiveness. In regards to patient selection and stratification, furthermore two different methods of predicting the level of operative mortality risk are used in the four studies included, EuroSCORE and Society of Thoracic Surgeons (STS) risk score. A review is reasonable for comparability to patient selection and stratification across studies. Literature suggests, with experience and increased procedural acceptance by referring physicians and cardiothoracic surgeons, it is likely the pendulum will swing from only truly inoperable patients to those who are potentially otherwise operable albeit at a higher risk [3]. Overall, disclosure of information on costs and differences in economic evaluations limit the making of reliable analysis. Although the four studies included in the systematic review are of good quality, some deficiencies have been documented in the data collection section and future studies will need to take better account of the items from a methodological point of view. This is also necessary to perform economic evaluations comparable and scientifically based.

This is a rapidly evolving technology amongst the medical community and only recently implemented for use in many countries. As stated in the PARTNER trial, on the basis

of a rate of death from any cause at 1 year there was evidence of 20 percentage points lower with TAVI than with standard therapy, suggesting balloon-expandable TAVI should be the new standard of care for patients with aortic stenosis who are not suitable candidates for surgery [10]. Edwards SAPIEN® valve is FDA approved and available for use in the USA market and initiated in 2010, the FDA approved a randomized controlled trial studying the Medtronic CoreValve® which is still ongoing. To date, there is no head to head comparison between the different percutaneous valves.

CONCLUSIONS

In conclusion, this systematic review followed the methodology recommended by PRISMA to objectively assess the cost effectiveness of TAVI compared with AVR and medical management. Although, it is largely based on the patient outcome results achieve in the PARTNER trial whereby this systematic review suggests greater cost effectiveness benefit in Cohort B. According to Leon et al., additional randomized trials are needed to compare TAVI with aortic-valve replacement among high-risk patients with aortic stenosis for whom surgery is a viable option and among low-risk patients with aortic stenosis [10]. As seen from the results in Cohort A of the PARTNER trial, the smaller the difference between incremental cost effectiveness in life years gained and quality adjusted life years the more you need to perform an RCT to illustrate superiority. In view of scarcity of resources, cost effectiveness research is needed with improved standardization to aggregated and disaggregated cost effectiveness endpoints allowing for transparency to itemized costs and accountability for variations to costs across hospitals, countries and health systems. It could be argued the major attraction of TAVI relates to the benefits of a shorter hospital stay and recovery, but this is not incorporated into the model [1]. The type of economic evaluation and what this entails should be clearly stated to accurately compare across studies. Combined with limited objective data available at present it proved to be challenging when attempting to make direct comparisons. Given the projected life expectancy of an 83 year old in the US is roughly 7 years, the scope of this systematic review suggests a start to further comprehensive analyses. In that direction researchers should improve the production of high-quality economical evaluation studies, which is the assumption to better support the decision-making process.

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