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Original Article/Research

# Do economic evaluations of TAVI deal with learning effects, innovation, and context dependency? A review

Joost J. Enzing[a,b,*], Sylvia Vijgen[b], Saskia Knies[a,b], Bert Boer[a], Werner B.F. Brouwer[a]

[a] Erasmus School of Health Policy & Management, Erasmus University Rotterdam, Rotterdam, The Netherlands
[b] Zorginstituut Nederland, Diemen, The Netherlands

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ABSTRACT

*Introduction:* Most collectively funded healthcare systems set limits to their benefit package. Doing so requires judgements which may involve economic evaluations. Performing such evaluations brings methodological challenges, which may be more pronounced in non-pharmaceutical interventions. For example, for medical devices, the validity of assessment results may be limited by learning effects, incremental innovation of the devices and the context-dependency of their outcomes.

*Objective:* To review the extent to which "learning effects", "incremental innovation" (related to outcomes) and "context-dependency" are included and/or discussed in peer reviewed economic evaluations on medical devices using Transcatheter Aortic Valve Implementation (TAVI) as an example.

*Methods:* A systematic review was performed including full economic evaluations of TAVI for operable patients with aortic stenosis identified using the Pubmed database. Study characteristics, study results and text fragments concerning the aforementioned aspects were extracted. The quality of the studies was assessed using a quality checklist (CHEC-extended).

*Results:* Within 207 screened records, 15 studies were identified. Two studies referred to all three aspects, four studies referred to none. "Learning effects" were discussed in five studies, one of which described a method to cope with this challenge. “Incremental innovation” was described in seven studies. Limitations in generalizability of results related to context of care provision were discussed in seven studies.

*Conclusion:* The challenges related to economic evaluations of TAVI and their influence on the validity of reported results, are typically only partly discussed and rarely dealt within peer reviewed studies. It is important for better informed policy decisions that this improves.



## Introduction

Collectively funded healthcare systems in Western countries set limits to their benefit package. Setting these limits requires designated authorities to make judgements on whether specific healthcare interventions merit a claim on collective means. These policy judgements may be based on the assessment and appraisal of multiple aspects of health technologies, for instance on effectiveness, legal, social and ethical aspects [1]. Cost-effectiveness may be among these considered aspects. This aspect can be assessed using an economic evaluation. A growing number of these economic evaluations are conducted: i.e. until 2009 almost 2,500 cost-utility analyses (a specific form of economic evaluation) were published in English [2], in 2017 this number had grown to more than 7,000 [3]. Guidelines on how to perform economic evaluations in healthcare are available for many jurisdictions [e.g. 4]. However, despite the growing number of published evaluations, and the existence of guidelines, performing economic evaluations is still not without methodological challenges. As a result, estimates of interventions' incremental cost-effectiveness ratios (ICERs) may be inaccurate and thus policy makers may be misinformed. While some of the methodological challenges in performing economic evaluations are relevant to all types of healthcare, others are more pronounced in specific types of interventions. For medical devices three of such specific challenges have been repeatedly identified as important:

* Corresponding author at: Erasmus School of Health Policy & Management, Erasmus University Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, Rotterdam, The Netherlands.
*E-mail addresses:* enzing@eshpm.eur.nl (J.J. Enzing), sylviavijgen@hotmail.com (S. Vijgen), knies@eshpm.eur.nl (S. Knies), boer@eshpm.eur.nl (B. Boer), brouwer@eshpm.eur.nl (W.B.F. Brouwer).

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learning effects, incremental innovation and context-dependency of outcomes [5–9]. Although more specific challenges may exist, these three thus seem particularly relevant in the context of medical devices. The concept of learning effects, or learning curves, refers to the situation in which the (cost-)effectiveness of an intervention is related to the experience (and resulting competence) of care providers with using a particular procedure or device. Learning effects can be relevant when accumulating experience and knowledge of care providers, e.g. during a period of proctoring, lead to an increase in the average effectiveness and/or a decrease in the average costs. Incremental innovation refers to incremental changes through time of the medical device itself (e.g. alterations of its technical specifications) or its provision/use (e.g. alterations in the surrounding clinical pathway), which may cause changes in the efficacy and/or costs of the intervention as well. Finally, context-dependence of outcomes refers to a dependency of (cost-)effectiveness on the (organisational) context of care provision (e.g. organisational size or academic versus non-academic hospitals). All three aspects may thus influence the observed cost-effectiveness, leading to questions of whether this observed cost-effectiveness is generalisable in time, context and place, and therefore most relevant in informing a policy decision (which of course also depends on the policy problem that needs to be addressed). Flexible modelling and appropriate data collection may be among possible solutions to cope with these challenges [10]. Alternatively, researchers may provide a discussion of (the relevance of) these challenges to, at least, inform policy makers on limitations of their study, or present specific sensitivity analyses. Otherwise, when these aspects are (potentially) relevant yet ignored when conducting and reporting an economic evaluation, the reported results may misinform policy makers, who may not be aware of these specific challenges and their impact on the results. This raises the question to which extent "learning effects", "incremental innovation" (related to outcomes), and "context-dependence of outcomes" are accounted for in peer reviewed, full economic evaluations of medical devices. This review aims to answer this question, discuss some policy consequences of not dealing with these challenges, and through that to raise awareness about these challenges and their handling in applied economic evaluations, and ultimately improve the quality of economic evaluations of medical devices and decisions based upon these.

In this review Transcatheter Aortic Valve Implementation (TAVI) is used as a case study. TAVI is a recently developed, minimal invasive technology initially aimed at inoperable patients with symptomatic aortic valve stenosis. In this context, TAVI was shown to be cost-effective [11]. Currently, the indication of TAVI has broadened towards patients with aortic valve stenosis (AS) who are also eligible for surgical aortic valve replacement (SAVR) [11]. This review focuses on economic evaluations of TAVI with SAVR as comparator. For TAVI, as a complicated, recent and developing technique, each of the three challenges mentioned above is potentially relevant when performing an economic evaluation. Recent economic evaluations for TAVI in this context are available, making this intervention a suitable case for this study. In addition, the aforementioned, recently broadened indication of TAVI may have influenced its costs and outcomes, making TAVI, especially compared to SAVR, a currently relevant topic for policy makers.

As part of the MedtecHTA project Tarricone et al. [12] previously reviewed published economic evaluations (published until December 2014) in order to investigate how they handled four distinctive features of medical devices, including “learning effects” and “incremental innovation”. Based on two case studies, TAVI (for all indications) and implantable cardioverter defibrillators (ICD), it was concluded that general awareness of specific features of medical devices is low in the context of health technology assessments (HTA). Meanwhile, the results of the MedtecHTA project have been published and have informed methodological guidance for the assessment of medical devices issued by EUnetHTA [13]. The current review therefore updates the study by Tarricone et al. in the specific context of economic evaluations of TAVI with SAVR as comparator, enabling to assess whether the awareness about / inclusion of learning effects and incremental innovation has increased in published economic evaluations since 2015.

## Methods

### *Search strategy and inclusion criteria*

The systematic review was conducted according to PRISMA guidelines [14]. On November 12th 2018 PubMed was searched to identify publications which fulfilled the inclusion criteria: these publications should contain information on costs and benefits, aortic valve stenosis, transcatheter valve implantation, and surgery (see appendix I). No time restriction was applied. Subsequently, two reviewers (JE & SV) independently reviewed the results, excluding publications which did not report full economic evaluations of TAVI versus SAVR for patients with AS, based on the titles and abstracts of the identified publications. As a result, cost studies, editorials and letters to the editor were excluded. In case of differences between the reviewers, agreement was found through discussion between the two reviewers. Using the full articles of the remaining publications, the two reviewers independently determined whether articles could be regarded as full economic evaluations of TAVI versus SAVR for patients with AS. Again, differences were resolved through discussion between the two reviewers. Systematic reviews were excluded from this final selection, however, their references were cross-checked for relevant full economic evaluations. No search for grey literature was performed, also based on the assumption that policy makers would typically prefer to obtain evidence from peer reviewed studies in the decision making process.

### *Methodological quality assessment*

To determine the quality of the included economic evaluations, the extended Consensus Health Economic Criteria list (CHEC-extended) [15,16] was used. This tool was selected since it was developed to assess both trial based as model based full economic evaluations, both included in the review. The CHEC-extended list has twenty questions, with response options “yes” or “no”. The two reviewers separately scored the included economic evaluations using this checklist. In case of differences in scoring, agreement was found through discussion between the two reviewers. For each economic evaluation, a quality ratio was composed by relating the number of positive answers to the number of applicable questions. Since the impact of the individual questions on quality may be incomparable, this ratio must be interpreted with care.

### *Data extraction*

General study characteristics (e.g. perspective) were extracted using a data extraction form (JE, validated by SV). This data extraction form was designed by the authors and implemented in Microsoft Excel. Publications were read in full by the two reviewers and for each publication text-elements (and their section titles) were copied to the extraction form when they were regarded to concern:

- Learning effects: (potential) changes in the efficacy and/or costs of the intervention (TAVI) related to the cumulative experience of operators and/or centres;

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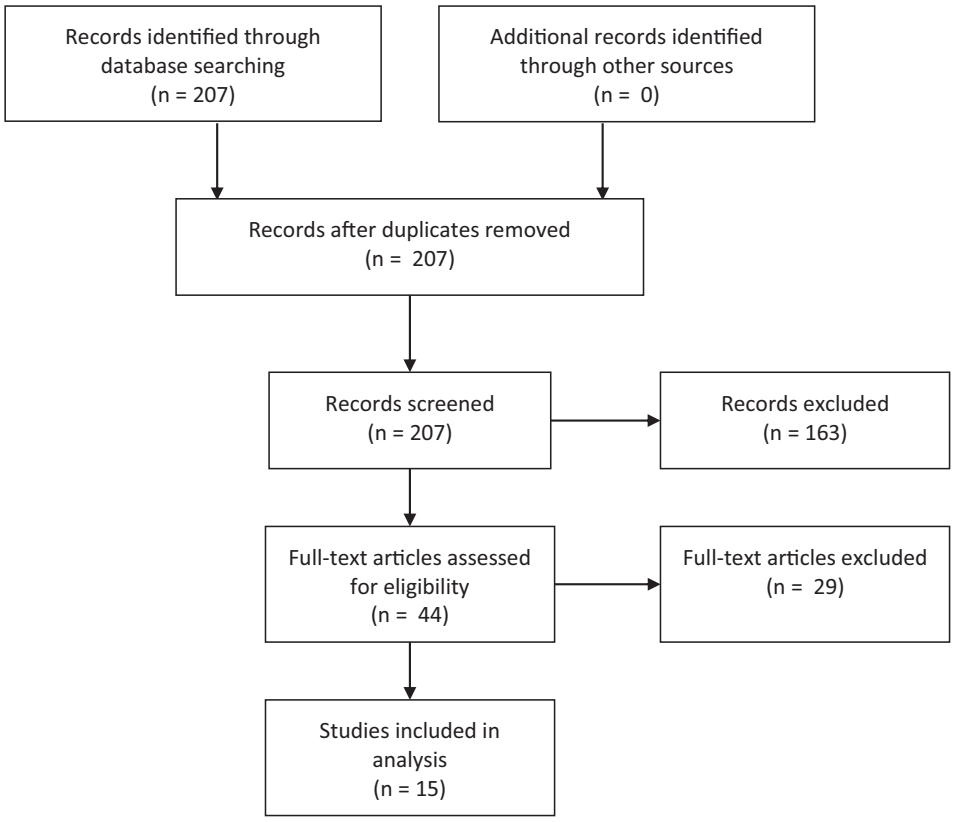


**Fig. 1.** PRISMA flow diagram.

- Incremental innovation related to outcomes: (potential) changes in the efficacy and/or costs of the intervention related to its (incremental) innovation through time;
- Context-dependency of outcomes: influence of personal characteristics of the care provider and/or the organisational context (e.g. organisational size and organisational structure) on the efficacy and/or costs of the intervention.

Based on the presence of text-elements on these methodological challenges, these challenges were regarded as undiscussed or discussed within a specific publication. Additionally, the reviewers determined whether any of the challenges mentioned in the text resulted in methodological choices to account for these challenges. If this was the case, this was noted as an analytical solution in our review. Differences between judgements were resolved after discussion between the two reviewers.

*Analyses*

Publications before and after 2015 were compared in terms of the number of challenges discussed per study.

As additional information the results of the economic evaluations (e.g. ICERs) were extracted, also to explore whether TAVI outcomes improved over time, which could suggest learning effects and/or incremental innovation in subsequent studies.

## Results

The literature search resulted in 207 studies, of which 15 studies were finally included (see Fig. 1). Studies were excluded for not being a full economic evaluation (e.g. cost studies) (n= 147), or subsequently for not concerning a comparison of TAVI to SAVR for operable AS patients. Ten systematic reviews were found and used to check their references to find additional peer reviewed full economic evaluations. This did not result in additional studies. Noteworthy, one included HTA-report [17] concerned an update of another included HTA-report [18] which is also described in a journal article [19]. This overlap was not considered problematic, so both were retained.

*Methodological quality assessment*

The assessment of methodological quality of the included studies using the extended CHEC-list resulted in scores ranging from 12/20 (60 percent) to 17/19 (89 percent). Ten of the checklist items did not differentiate between studies, e.g. all clearly described their study population. No study discussed each validation type required by the checklist. Studies differed in terms of their scores regarding appropriateness of their costs measurement and valuation. Some equated costs with an assumed reimbursement tariff [20]. Differences were also observed in the explicit indication of potential conflict of interest in the published papers. Ethical and distributional issues were rarely discussed.

*Study characteristics*

Characteristics of the fifteen included studies are provided in Table 1. The studies were published from 2012 until 2018, most (12/15) were model based, and most used a payer's perspective (12/15). Most studies (10/15) were North American (Canada, USA) or European (four; United Kingdom, Belgium, Spain) and one was Japanese. Ten studies used a time horizon of ten years or more. Most studies (10/15) were based on the industry-sponsored, multicentre, randomized controlled Placement of Aortic Transcatheter Valves (PARTNER) trial. Studies targeted two types of operable patients: those with high surgical risk (11/15) and those with intermediate risk (4/15). Most studies investigated a TAVI valve system

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**Table 1**
Study characteristics.

| Author | Country | Target population | Interventions | Comparator | Analytic approach | Time horizon | Efficacy source | Cost source | Perspective | Discounting |
|---|---|---|---|---|---|---|---|---|---|---|
| Reynolds et al. [21] | USA | high surgical risk | TAVI (TF and TA) Edwards SAPIEN | SAVR | Trial based | 1 year | PARTNER A | US hospital billing and resource based accounting | US healthcare system | n/a |
| Neyt et al. [23] | Belgium | high surgical risk | TAVI (TF and TA) Edwards SAPIEN | SAVR | Model based | 1 year | PARTNER A Continued Acces study (non-published) | Belgian hospital billing data (n=183, treated with Edwards SAPIEN valve) | Belgian healthcare payer | n/a |
| Gada, Kapadia, Tuzcu, Svensson, & Marwick [20] | USA | high surgical risk | TAVI (TF) Edwards SAPIEN | SAVR | Model based | lifetime | Published reports, registries, European PARTNER | Reimbursement data, primarily published reports (DRG, Medicare payments). | Healthcare provider | 5% |
| Gada, Agarwal, & Marwick [25] | USA | high surgical risk | TAVI (TA) Edwards SAPIEN | SAVR | Model based | lifetime | Registries | Reimbursement data, registries, DRGs. Medicare payments | Healthcare funding body | 5% |
| Sehatzadeh et al. [18] | Canada | high surgical risk | TAVI (TF and TA) Edwards SAPIEN | SAVR | Model based | 20 years | PARTNER | Ontario Case Costing Initiative (OCCI) cost data | Canadian healthcare payer | 5% |
| Doble et al. [19] | Canada | high surgical risk | TAVI (TF and TA) Edwards SAPIEN | SAVR | Model based | 20 years | PARTNER US | Ontario Case Costing Initiative | Canadian healthcare payer | 5% (costs) |
| Fairbairn et al. [26] | UK | high surgical risk | TAVI (TF and TA) Edwards SAPIEN | SAVR | Model based | 10 years | Utility data from a UK high-risk AS population PARTNER A | UK costs UK care pathway | UK National Health Service | 3.5% |
| Sehatzadeh et al. [17] | Canada | high surgical risk | TAVI (TF and TA) Edwards SAPIEN | SAVR | *not stated* | *not stated* | 2-year follow-up of the PARTNER trial | Ontario Case Costing Initiative (OCCI) cost data | Canadian healthcare payer | 5% |
| Orlando et al. [27] | UK | high surgical risk | TAVI Edwards SAPIEN | mixture of SAVR (90%) and medical management (10%) | Model based | 25 years / lifetime | PARTNER B | Reference prices and literature | UK National Health Service | 3.5% |
| Ribera et al. [28] | Spain | intermediate surgical risk | TAVI (TF) Edwards SAPIEN Medtronic CoreValve | SAVR | Trial based | 1 year | Collected within study | Collected within study, cost accounting, reimbursement tarrifs | Spanish health service | n/a |
| Reynolds et al. [22] | USA | high surgical risk | TAVI Medtronic CoreValve | SAVR | Trial based | lifetime | CoreValve U.S. High Risk Pivotal Trial | CoreValve U.S. High Risk Pivotal Trial (resource utilization, hospital billing data) | US Healthcare system | 3% |
| Health Quality Ontario [29] | Canada | high surgical risk | TAVI Medtronic Corevalve | SAVR | Model based | 5 years | U.S. CoreValve Pivotal Trial | Ontario Case Costing Initiative | Canadian healthcare payer | 5% |
| Kodera et al. [30] | Japan | intermediate surgical risk | TAVI (TF) Edwards Sapien XT | SAVR | Model based | 10 years | PARTNER 2 cohory A Optimizes Catheter vAlvular iNtervention (OCEAN) TAVI registry | Previous studies, and estimations | Japanese public healthcare payers | 2% |
| Tam, Hughes, Fremes [24] | Canada | intermediate surgical risk | TAVI (TF and TA) Edwards Sapien XT | SAVR | Model based | lifetime | PARTNER 2 cohory A Optimizes Catheter vAlvular iNtervention (OCEAN) TAVI registry | Canadian Institue of Health Information, Ontario Schedule of Benefits / literature review | Canadian healthcare payer | 1.5% |
| Tam, Hughes, Wijeysundera & Fremes [31] | Canada | intermediate surgical risk | TAVI (TF and non-TF) Medtronic CoreValve Medtronic Evolut R | SAVR | Model based | lifetime | SURTAVI trial / CoreValve US High Risk Pivotal Trial (EQ-5D) | Canadian Institute of Health Information | Canadian healthcare payer | 1.5% |

TAVI = Transcatheter Aortic Valve Implantation, TF = transfemoral, TA = transapical, SAVR = Surgical Aortic Valve Replacement, n/a = not applicable

of Edwards LifeSciences (11/15), others investigated a TAVI valve system of Medtronic, Inc. (3/15), and one study investigated systems of both manufacturers. One of the studies was limited to transapical (TA) implantation of TAVI, the other studies investigated (the less-invasive) transfemoral (TF) implantation or a combination of both routes.

*Cost-effectiveness results*

Cost-effectiveness outcomes as reported in the included studies are provided in Table 2. All studies reported incremental effects measured in QALY's, while one-third (5/15) also reported incremental effects measured in life-years-gained. The reported incremental effect of TAVI in QALY's was mostly positive (9/15), and most studies reported additional costs (12/15). All studies presented a sensitivity analysis to quantify uncertainties. Five studies reported that TAVI was dominated by SAVR, two studies reported SAVR was dominated by TAVI, the other studies reported TAVI to have an incremental cost-effectiveness ratio (ICER) ranging from (expressed in euros) €31,000 to €750,000 per QALY. The variation in the extracted cost-effectiveness results may partly be explained by observed differences in study characteristics, among which country, perspective and the cost and efficacy sources used were prominent ones. Furthermore, the reported incremental QALY's appeared to have an upward trend over time. All studies included some form of sensitivity analysis, among which one-way deterministic sensitivity analysis and probabilistic sensitivity analysis were the most common types of sensitivity analysis (in eleven and ten studies, respectively). None of the sensitivity analysis attempted to quantify the potential impact of learning effects or incremental innovation on the ICER. One of the analyses demonstrated the potential impact of context on cost-effectiveness by imputing country specific costs in two scenarios, changing the reported ICER from dominated in the base case to dominant in (some of) these scenarios [28].

*Methodological challenges*

Table 3 provides the results of the review per study. This table shows that each of the three methodological challenges was discussed in one or more of the studies. Two studies discussed all three challenges [21,22], while four studies discussed none [16,18,23,24]. The two studies which discussed all three were among the studies with the highest CHEC-list scores. Studies which discussed no or one challenge had a mean CHEC-score of 76%, studies which discussed two or three challenges had a mean CHEC-score of 85%, suggesting a potential relationship between number of discussed challenges and assessed methodological quality. Obviously, sample size prohibits formal testing or firm conclusions. Challenges were discussed in the "Discussion" (or "Comment") sections of the studies or, in one study, in the "Introduction" [27]. Two studies used 'analytical solutions' to deal with identified challenges. The first study was restrictive in the selection of registry data. It selected those registries that allowed inclusion of data after an initial learning effect, hence avoiding data from situations in which proper training and experience was not yet realized. This was highlighted in the "Discussion" section [25] of the publication. The second study concerned additional analyses to deal with (high-level) context dependency, i.e. an international comparison of results, by using information (i.e. imputing unit costs) from other countries and health care systems to understand cost-effectiveness in these contexts, rather than the country of origin. This issue was described in the "Methods" section [28] of the study. The results highlighted that cost-effectiveness estimates were quite sensitive to these country specific unit cost parameters.

**Table 2**
Reported cost-effectiveness outcomes.

| Author | Incremental effect (QALY) | Incremental costs | ICER | Sensitivity analysis |
|---|---|---|---|---|
| Reynolds et al. [21] | TAVI-TF: 0.068 TAVI-TA: -0.07 TAVI Overall: 0.027 | TAVI-TF: $ -1.250 TAVI-TA: $ 9.906 TAVI Overall: $ 2.070 | TAVI-TF dominates SAVR TAVI-TA is dominated by SAVR TAVI overall $76.877/QALY | Bootstrapping (and boundry testing valve pricescenarios) |
| Neyt et al. [23] | 0.03 | €20,400 | > €750,000/QALY | PSA and one-way sensitivity analysis |
| Gada, Kapadia, Tuzcu, Svensson, & Marwick [20] | 0.06 | $3,164 | $52,773/QALY | threshold analyses, one-way 2-way sensitivity analyses, PSA |
| Gada, Agarwal, & Marwick [25] | -0.04 | $ 100 | TA-TAVI is dominated by SAVR | PSA and one-way sensitivity analysis |
| Sehatzadeh et al. [18] | -0.102 | CAN $11,153 | TAVI is dominated by SAVR | Comprehensive sensitivity analyses |
| Doble et al. [19] | -0.102 | CAN $11,153 | TAVI is dominated by SAVR | DSA, PSA and scenario analyses |
| Fairbairn et al. [26] | 0.06 | £-1,350 | TAVI dominates SAVR | Deterministic and PSA |
| Sehatzadeh et al. [17] | -0.069 | CAN $ - 4,642 | CAN $66,985/QALY | 3-way deterministic sensitivity analyses |
| Orlando et al. [27] | -0.6087 | £7,963 | TAVI not available option dominates the TAVI available option/ patients suitable for SAVR | PSA and DSA (one-way sensitivity analysis) |
| Ribera et al. [28] | 0.036 (Edwards) -0.011 (Medtronic) | €8,800 (Edwards) €9,729 (Medtronic) | €148,525 (Edwards) Dominated by SAVR (Medtronic) | Bootstrapping |
| Reynolds et al. [21] | 0.32 | $17,849 | $55,090/QALY | One-way sensitivity analysis, bootstrapping |
| Health Quality Ontario [29] | 0.181 | CAN $9,412 | CAN $51,988/QALY | one-way and probabilistic sensitivity analyses, as well as scenario analyses. |
| Kodera et al. [30] | 0.22 | Y 1,723,516 | Y 7,523,821/QALY | PSA, one-way sensitivity analysis/DSA, threshold analysis |
| Tam, Hughes, Fremes, et al. [24] | 0.23 | CAN $10,548 | CAN $46,083/QALY (TF-TAVI CAN $24,790/QALY) | one-way DSA, PSA |
| Tam, Hughes, Wijeysundera, & Fremes [31] | 0.15 | CAN $11,305 | CAN $76,736/QALY | one-way DSA, PSA |

TAVI = Transcatheter Aortic Valve Implantation, TF = transfemoral, TA = transapical, SAVR = Surgical Aortic Valve Replacement, PSA = Probabilistic Sensitivity Analysis, DSA = Deterministic Sensitivity Analysis, ICER = Incremental Cost Effectiveness Ratio, QALY = Quality-adjusted Life Year

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**Table 3**
Discussed challenges (1 = discussed, 0 = undiscussed).

| Author | Learning effects (discussed) | Incremental innovation (discussed) | Context dependence of results (discussed) |
|---|---|---|---|
| Reynolds et al. [21] | 1 | 1 | 1 |
| Neyt et al. [23] | 0 | 0 | 0 |
| Gada, Kapadia, et al. [20] | 0 | 1 | 0 |
| Gada, Agarwal, & Marwick [25] | 1 | 0 | 0 |
| Sehatzadeh et al. [18] | 0 | 0 | 0 |
| Doble et al. [19] | 0 | 1 | 1 |
| Fairbairn et al. [26] | 0 | 0 | 1 |
| Sehatzadeh et al. [17] | 0 | 0 | 0 |
| Orlando et al. [27] | 1 | 0 | 0 |
| Ribera et al. [28] | 0 | 0 | 1 |
| Reynolds et al. [22] | 1 | 1 | 1 |
| Health Quality Ontario [29] | 1 | 1 | 0 |
| Kodera, Kiyosue, Ando, & Komuro [30] | 0 | 1 | 1 |
| Tam, Hughes, Fremes, et al. [24] | 0 | 0 | 0 |
| Tam, Hughes, Wijeysundera, & Fremes [31] | 0 | 1 | 1 |
| **Total** | **5** | **7** | **7** |

*Learning effects*

Five studies discussed learning effects, three of which labelling it as "learning curves" or "learning curve effects". For example, Reynolds [21] wrote that "*most PARTNER sites did not perform enough TA-TAVR procedures to move beyond the point of learning curve effects*". The remaining two studies described a positive relation between experience and outcomes. For example, "*In centres experienced in conducting TAVIs, procedural success may be around 90% or more and closely linked to experience, with greater learning resulting in better patient selection and outcomes*" [27]. One of the five studies described how learning effects were taken into account in its model-based analysis: "*Given the recent development of transapical TAVI, we did not include data from registries emphasizing results of a 'learning curve'. Only registries that separated recent procedures, once proper proctoring and training had been completed, were included in the data employed in the model*" [25].

*Incremental innovation*

In seven of the included studies potential developments of TAVI or its comparator were explicitly related to (future) outcomes, costs and/or the ICER. For example, "*It is reasonable to expect that iterative improvements in TAVR technology in the short to intermediate term, coupled with increased clinical experience, will lead to reduced complication rates, more efficient care, reduced costs, and improved cost-effectiveness relative to SAVR, a much more mature therapy.*" [22]. No methodological solutions to cope with incremental innovation (e.g. specific sensitivity analysis) were found in the articles.

Besides these seven studies, three other studies contained a text fragment that implied that innovation of the intervention is continuing in daily practice, although without explicitly relating this phenomenon to (future) outcomes, costs and/or the ICER. As examples, Gada et al. labelled TAVI as "*a developing technique*" [25] and Orlando et al. stated that "*more sophisticated delivery systems have been developed.*" [27].

*Context dependent outcomes*

Seven studies discussed that their results may not be generalizable to other contexts

(e.g. jurisdictions or treatment settings). One study [28] conducted a scenario analysis to demonstrate results for additional countries by imputing observed unit costs, as highlighted above. Four of the seven studies specifically discussed the context of care provision (e.g. the specific hospital). For example, "*We recognize that there is substantial institutional heterogeneity with respect to procedural location and resources, and this factor may potentially affect the ICER.*" [31].

To assess in a general fashion whether the awareness, measured as being discussed, of the three challenges increased since the end of 2015, we compared publications before and after 2015 in terms of the number of challenges discussed per study. Ten studies were published in 2015 or before. In these ten studies on average one challenge was discussed (see Table 3). Five studies were published after 2015. These studies on average discussed 1.8 challenges (i.e. nine in total). Notwithstanding the low numbers and rough indicator, this may suggest at least an increase in awareness of the challenges related to the economic evaluation of TAVI. Whether this increased awareness is representative for other medical devices, or e.g. results from the elapsed time since the introduction of TAVI (time effect) requires further research.

## Discussion

This paper reviewed the extent to which three methodological challenges of particular importance to medical devices, were discussed in peer reviewed full economic evaluations of TAVI, and whether analytical solutions were provided. It was observed that these challenges and their influence on the validity of reported results of economic evaluations, are typically only partly discussed and rarely quantitatively dealt with in the reviewed economic evaluations of TAVI. This seems inappropriate from a general HTA perspective. Within an HTA process, economic evaluations are part of the information which is systematically collected and synthesized during the assessment, to inform a subsequent appraisal phase. During the latter, the available evidence is critically appraised in terms of validity, significance and relevance, along with known uncertainties and all societal and ethical considerations deemed relevant. Information on methodological challenges, both resolved and unresolved, is needed to inform these deliberations. It seems this information is mostly lacking in reports on economic evaluations of TAVI.

For each of the three challenges, this observed absence of information may have specific consequences for policy makers. First, only one study explicitly corrected for the influence of accumulated experience on outcomes. However, the literature highlights that significant learning effects exist in TAVI care provision, both effectiveness as costs are influenced by experience [32–35]. Consequently, when care providers' experience levels within trials used in economic evaluation differ from those in current or expected practice, the reported ICERs may not reflect actual clinical practice. For example, ICERs, which may aim to represent long-term cost-effectiveness of the use of an intervention, may be overestimated when short-term trial results are extrapolated without correcting for short-term inefficiencies such as learning effects [36].

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Given that readily available techniques to deal with these issues are lacking, one may argue that it cannot be expected from applied economic evaluations that they deal with or correct for this issue in a quantitative fashion. However, the relevance of (the potential influence of on outcomes of) learning effects also mostly remained undiscussed, which could result in unawareness about these issues among policy makers, and lead to an overestimation of the validity of the reported ICER by them. As an illustration of the potential impact of this issue, a combination of strong confidence with an overestimated ICER may result in rejecting an intervention that might be cost-effective in the longer run. Moreover, discussing the potential discrepancy between short-term and long-term efficiency may also avoid disappointment with short-term results after implementation of the intervention [37]. Second, none of the studies provided or applied an explicit analytical solution to cope with incremental innovation which may influence outcomes, and numerous studies did not discuss this aspect. However, multiple innovations which influenced TAVI outcomes have occurred, for examples new generations of valves and new strategies for procedure optimization were introduced [38,39]. Furthermore, new innovations, including those concerning alternative access routes, are expected. Such incremental innovations may be relevant for policy makers. As an illustration, one could consider the extremely divergent cost-effectiveness outcomes of the transfemoral (dominant) and the transapical access route (dominated) reported within a single study [21]. As a consequence of incremental innovation, reported ICERs may be especially relevant in the short-term. This aspect often is not mentioned explicitly, and remained undiscussed in almost half of the studies. It is clear that one should try to avoid evaluations reporting on already obsolete technologies or application procedures to inform reimbursement decisions that do not pertain (only) to the studied interventions but also those currently in place. Policy makers therefore need to be aware of this, to avoid suboptimal reimbursement decisions. Awareness of incremental innovation may lead policy makers to apply a more adaptive approach to health technology assessment [40] which may help in dealing with this challenge. Third, except for one of the reviewed studies (which highlighted a scenario analysis for other countries) [28] none of the studies provided or used an analytical solution approach to cope with the dependence of outcomes on the context of care provision, and most did not discuss this dependency. Nonetheless, context dependency of outcomes is of relevance for TAVI; e.g. hospitals differ in their mix of access routes, in devices used, and in operation settings [41], which are elements affecting the 'local ICER'. For example, Ribera et al. presented ICERs for both major valve manufacturers (Edwards Lifesciences and Medtronic) separately, suggesting differences between these ICERs [28]. It can be argued that the challenge of context dependency has been mitigated to a certain extent by using parameters from the PARTNER trial as these are based on multiple centres. However, although PARTNER was a multicentre RCT, it was limited to valves of Edwards Lifesciences. Moreover, reported average ICERs may still not be valid for all contexts and in centres with other characteristics than the included ones. This limitation mostly remained undiscussed, potentially leaving policy makers unaware of risks in generalising the results of the studies to the context of the relevant policy question at hand. However, the potential policy relevance of this issue may be illustrated by considering the different scenario's reported by Ribera et al. [28], ranging from dominated (a policy argument to reject reimbursement) to dominant (a policy argument to allow reimbursement).

Taken together, the distinctive features of medical devices result in methodological challenges which were typically not accounted for in economic evaluations of TAVI. As a result, dealing with these challenges is, mostly implicitly, passed on to policy makers. When policy makers are unaware of these challenges, they may overestimate the relevance of reported cost-effectiveness results for their decision context. This could result in non-optimal decisions regarding funding these technologies or to a lack of additional information gathering to come to more relevant and up-to-date estimates of cost-effectiveness.

It could be suggested that the three methodological challenges were omitted in the included economic evaluations because of a presumed small impact on the ICER. However, this would require a quantification of their impact which was not provided within these evaluations. Also, some of the examples above suggest that their influence can indeed be substantial.

Exploring the impact on ICERs of dealing with (any of) the three challenges is hampered by the fact that only one study reported handling learning effects [25]. This study reported an incremental effect (-0.04 QALY) slightly below the average (0.02 QALY) but falling well within the range of incremental effects (-0.61 QALY to 0.23 QALY) reported in the included studies. The incremental costs reported in this study also fell within the range of reported values.

It should be noted that it may be unreasonable to expect individual economic evaluations to find and use technical solutions for the fundamental and complicated challenges highlighted here, without clear guidance how to do so. Although ready to use technical solutions may not be available, in current international methodological guidance on the assessment of medical devices (e,g. [13]) and in national HTA guidelines (e.g. England, France, the Netherlands, and Sweden) [42] the specific methodological challenges are extensively acknowledged. Consequently, it could be reasonably expected that studies would at least mention these challenges and particularly their potential impact on the results, also to inform policy makers who may use the results of studies. Reporting study details on the level of operators' experience, organisational context and interventions, would allow policy makers to judge their similarity with health provision in their own context.

While our results suggest some improvement over time, they also show that still not all current studies mention these challenges and their potential impact. To stimulate further improvement, policy makers could enforce submitters of economic evaluations to specify how they handled specific methodological challenges of the intervention concerned. Moreover, future research could contribute to the further development of methodology dealing with these challenges, and the development of best practices to illustrate how to do so in economic evaluations.

As mentioned, the consideration of learning effects and incremental innovation in economic evaluations of TAVI has been subject of previous research. Tarricone and colleagues [12] showed in their review among other results that a minority of HTA-reports and journal articles on TAVI considered "learning curves" (42 percent of included publications) and "incremental innovation" (37 percent of included publications). Our results were in line with their results, showing moderate improvement over time in terms of the consideration of these challenges. Based on their results, combined with comparable results for economic evaluations of implantable cardioverter defibrillators (ICD), they concluded that the general awareness of specific features of medical devices is low in the context of economic evaluation. Our review confirms their conclusion, despite the developments in this field since their study, including the publication of specific guidance. Hence, more effort is needed to increase the awareness about these challenges, their explicit mentioning in economic evaluations, and the availability of methodological techniques to deal with these issues.

As an additional observation, acknowledging the low number of included studies, an upward trend appears to be observed over time, in terms of the reported incremental QALY's gained. This potential trend may suggest a relative improvement of TAVIs effectiveness over time. However, it needs to be noted that the fifteen studies included in our review differed in terms of the risk class of

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their target population as well as the applied time horizon (ranging from 1 year to lifetime). Such differences warrant caution in the interpretation of these effectiveness results.

## Limitations of this review

A number of limitations of this review deserve mentioning. First, this review only dealt with one particular medical device: TAVI. Hence, generalisations to other medical devices cannot be made, especially since medical devices consist of a large and heterogeneous collection of technologies [43]. For example, while TAVI is an artificial body part implanted by a medical procedure, other devices may concern assistive devices directly used by patients. In the latter category, in contrast to TAVI, a learning curve on patient side may be expected. For diagnostic technologies other methodological challenges may apply compared to therapeutic technologies like TAVI. Finally, for pragmatic reasons the search for this study was limited to one digital database (Pubmed) although several other digital databases (e.g. Embase, Web of Science) are available. However, given that the identified systematic reviews and the study of Tarricone et al. did not include peer reviewed studies that did not show up in our results, this suggests our search strategy was quite adequate in retrieving relevant studies.

## Conclusion

The challenges related to economic evaluations of medical devices and their influence on the validity of reported cost-effectiveness results, are typically discussed incompletely and rarely dealt with in peer reviewed studies on TAVI. It is important for research and policy that this improves. Best practices should be developed to support the application of technical solutions, and policy makers should require submitters to at least reflect on specific methodological challenges of the intervention concerned.

## Declaration of Competing Interest

None declared.

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