THE IMPORTANCE AND ADDED VALUE OF HEALTH TECHNOLOGY ASSESSMENT AND ECONOMIC EVALUATIONS OF MEDICAL INTERVENTIONS TO SUPPORT REIMBURSEMENT DECISIONS: THE TAVI EXPERIENCE

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De Boeck Supérieur | « Reflets et perspectives de la vie économique »

2014/4 Tome LIII | pages 55 à 65
ISSN 0034-2971
ISBN 9782807301276

Article disponible en ligne à l'adresse :

https://www.cairn.info/revue-reflets-et-perspectives-de-la-vie-economique-2014-4-page-55.htm

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The importance and added value of Health Technology Assessment and economic evaluations of medical interventions to support reimbursement decisions: the TAVI experience

Mattias Neyt

Abstract – Health technology assessment (HTA) aims at providing support to decision makers in taking good decisions to keep the health care system accessible, of the highest quality as possible and durable. One element of HTA is the economic aspect considering whether an intervention offers value for money in comparison to other alternatives. In this article, we provide an introduction to HTA and economic evaluations and provide the example of transcatheter aortic valve implantation (TAVI).

Key words: Health technology assessment, economics, cost-benefit analysis, transcatheter aortic valve replacement.

Résumé – Les évaluations des technologies de santé (HTA) visent à apporter un support aux décideurs afin qu’ils puissent prendre les décisions adaptées au maintien d’un système de soins de santé accessible, qualitatif et durable. Un élément des HTA concerne l’aspect économique qui vérifie si une intervention offre une valeur pour l’investissement financier consenti en comparaison avec les autres alternatives. Dans cet article, nous fournissons une introduction aux HTA et aux évaluations économiques que nous illustrons par l’exemple de l’implantation transcutanée des valves aortiques (TAVI).

Mots clés : évaluations de technologies de santé, aspects économiques, analyse coûts-bénéfices, implantation transcutanée des valves aortiques.

JEL classification : D61, H51, I13, I18

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It does not need to be said that health care resources are limited and that there are many more interventions that (might) provide benefit to patients than society can afford. Choices have to be made. Only looking at benefits without taking into account the costs might result in more harm than good for the health of our population due to the opportunity cost of every decision. Health technology assessment (HTA) aims at providing support to decision makers in taking good decisions to keep the health care system accessible, of the highest quality as possible and durable. Not taking into account costs runs the risk of having a negative impact on the health care system’s accessibility or quality, e.g. by increasing patients’ contributions or taking away other interventions that provide more value for money to fund the interventions that are relatively too expensive. In this article, we provide an introduction to HTA and economic evaluations and provide the example of transcatheter aortic valve implantation (TAVI).

1 LIMITED RESOURCES AND OPPORTUNITY COSTS

The opportunity cost is the value of the best alternative forgone, or according to the dictionary: “the loss of potential gain from other alternatives when one alternative is chosen” (The New Oxford American Dictionary). There are not so many examples to illustrate this since the opportunity cost is often not made explicit. When reimbursement decisions are taken, it is not always clear where the money comes from to fund the decision. An illustrative example of almost ten years ago is the case of Herceptin, a drug for the treatment of a specific group of breast cancer patients. BBC news entitled: “Herceptin costs ‘threaten care’” (BBC News 24 November, 2006). At that time, evidence already clearly showed that this drug has an added value for patients (Huybrechts, Hulstaert et al., 2006). In the study BBC was referring to, researchers calculated that they have to find £1.9m (€2.9m) each year in drug costs alone to make Herceptin available to the 75 patients who may be eligible in their region to cure 3 extra patients. “The real cost lies in the services that will be cut to provide this money” (Barrett, Roques et al., 2006). To illustrate this, the researchers looked for different ways to find this budget. They “could fund Herceptin if we did not treat 355 patients receiving adjuvant treatment (16 of whom would be cured) or 208 patients receiving palliative chemotherapy, and if we found £0.5m from another source” (Barrett, Roques et al., 2006) This would results in more harm than good. This opportunity cost example shows the importance of taking into account both benefits and costs when taking reimbursement decisions.

2 HEALTH TECHNOLOGY ASSESSMENT AND EVIDENCE-BASED MEDICINE

“Health technology assessment (HTA) is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues

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related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value. Despite its policy goals, HTA must always be firmly rooted in research and the scientific method” (www.eunethta.eu). The health technologies or interventions under assessment are not limited to drugs and devices, but include all possible interventions that can be used to improve health, prevent, diagnose or treat diseases or risks, to revalidate or provide long-term care, but also procedures and organisational or supportive systems. HTA tries to support policy makers in making good decisions by providing them with objective, transparent, and scientifically based information in order to encourage the use of safe, better and acceptable interventions.

In HTA, the most important part is in the first place the medical aspect. Researchers support the principle of evidence-based medicine (EBM): “Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research” (Sackett, Rosenberg et al., 1996). "External clinical evidence both invalidates previously accepted diagnostic tests and treatments and replaces them with new ones that are more powerful, more accurate, more efficacious, and safer" (Sackett, Rosenberg et al., 1996). In the medical part of an HTA report, safety and efficacy or effectiveness of the intervention versus alternatives are assessed. "Efficacy is the extent to which an intervention does more good than harm under ideal circumstances ("Can it work?"). Effectiveness assesses whether an intervention does more good than harm when provided under usual circumstances of healthcare practice ("Does it work in practice?")" (Haynes, 1999). Of course, this does not take into account costs. That’s when economic evaluations come up to the stage.

3 ECONOMIC EVALUATIONS

“Efficiency measures the effect of an intervention in relation to the resources it consumes ("Is it worth it?")” (Haynes, 1999). Economic evaluations of interventions are performed to support the efficient use of limited resources. They “tend to guide decision makers towards the maximisation of health gains within a resource constraint, regardless of which individuals or population groups may benefit from a health intervention or perhaps be penalised by that intervention” (Sassi, Archard et al., 2001). The link with the medical part is clear from the general definition of an economic evaluation: “the comparative analysis of alternative courses of action in terms of both their costs and consequences” (Drummond, Sculpher et al., 2005). In economic evaluations, the incremental cost-effectiveness ratio (ICER) is calculated applying the following general formula:

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\text{ICER} = \frac{\text{IC}}{\text{IE}} = \frac{\text{C}_{\text{Int}} - \text{C}_{\text{Comp}}}{\text{E}_{\text{Int}} - \text{E}_{\text{Comp}}}
\]

With C: costs; Comp: comparator; E: effects; IC: incremental cost; IE: incremental effect; Int: intervention.
This formula clearly shows the link with the medical part and the need for a critical assessment of all evidence. Outcomes are usually expressed in life-years gained (LYG) or quality-adjusted life years gained, the so-called QALYs. QALYs are a measure for health outcomes that includes both quantity and quality of life (QoL). They are calculated by estimating the total life years (gained) from a treatment and weighting each time period within these life years with a quality-of-life score or utility. These utilities are measured on a continuous scale from 0 (death) to 1 (perfect health). Negative values are also possible for very severe health states (e.g. coma or severe burn wounds). The most common and recommended way to measure these utilities is by measuring this indirectly applying a specific questionnaire, i.e. a so called generic utility instruments like EQ-5D. (EUnetHTA, 2013) This is a multidimensional construct measuring the physical, social and emotional aspects that are relevant and important to a patient’s well-being. (Cleemput, Neyt et al., 2008). There exist also specific scales for example for renal failure or respiratory diseases. 

There are different types of economic evaluations. First, in cost-minimization analyses (CMA) only costs are compared because the alternative interventions have equal effects. The requirement for this type of analysis is that there is sufficient certainty that the alternatives are equivalent, otherwise it is a pure cost analysis which cannot be categorized as a full economic evaluation looking at both costs and effects of several alternatives. Next, in cost-effectiveness analyses (CEA) the outcomes are expressed in life-years gained or a disease-specific outcome. In cost-utility analyses (CUA) preferences are taken into account and outcomes are expressed in extra costs per QALY gained. In some cases it may be difficult to translate a variety of outcomes in LY or QALYs. In such cases cost-consequences analyses (CCA) can be performed separately presenting incremental costs and these various outcomes (e.g. Neyt, Hulstaert et al., 2014: number of children born with Down syndrome, number of invasive tests and related miscarriages, etc.). Finally, in a cost-benefit analyses (CBA), a monetary value is also assigned to the benefits. However, due to difficulties of translating outcomes in monetary values, this approach is usually not applied by health economists. It is preferable to express results in extra costs per LY and QALY gained since impact on mortality and morbidity are eventually the most important outcomes for patients and these outcomes allow comparisons of results across indications. This is very difficult if disease-specific outcomes are applied. For example, how is a policy maker going to compare the extra costs to avoid a cardiac event versus avoiding a cancer to become metastatic? The importance of measuring the impact on costs, mortality and/or quality of life should already been taken into account when setting up study protocols.

The results of a full economic evaluation can be represented graphically on a cost-effectiveness plane (CE-plane, Figure 1). This visualises the cost difference (Y-axis) and effect difference (X-axis) between an intervention and its comparator. The comparator can be no intervention, the current situation or a relevant cost-effective alternative intervention for the same condition. Working on the so-called efficiency frontier, an intervention should be compared with the previous most cost-effective alternative (Neyt & Van Brabandt, 2011).
LY: life years; QALYs: quality-adjusted life-years. The cloud of dots in this figure is caused by the uncertainty around the input variables (costs, treatment effect, QoL, etc.) which, after 1000 Monte Carlo simulations, translates into the uncertainty around the ICER. The slope of the dotted lines represents the 2.5% and 97.5% ICER (average ICER = €22 141/QALY gained; 95% credibility interval: €16 785 – €29 005).

4 WHAT IS ACCEPTABLE?

In the end, when the ICER is calculated and if policy makers want to take economic considerations into account, they have to decide whether the result is acceptable or not. Such conclusions require a comparison with a reference value for the ICER, above which an intervention would not be considered cost-effective (because the additional cost for an additional unit of effect is considered too high) and below which it would be considered cost-effective, the so-called ICER threshold (Cleemput, Neyt et al., 2008). The theoretical health maximisation model to determine this ICER threshold value cannot be applied in real life due to several reasons, the most important one being lack of full information on the ICERs of all possible health care interventions, which is utopian. As concluded by the KCE report on this topic “The ICER threshold value against which the ICERs of interventions should be compared is unknown and is variable over time. This is not, however, an argument against the use of economic considerations in health care decision making. Neglecting economic considerations is unethical as spending resources on one health programme reduces the resources available for other health programmes” (Cleemput, Neyt et al., 2008).
The higher the ICER, the higher the probability that an intervention is not considered acceptable and vice versa. There is only one national guideline that makes their threshold ($\lambda$) explicit and that is the National Institute for Health and Care Excellence (NICE) in the UK (NICE, 2013). For interventions with an ICER <£20 000/QALY gained, decisions will primarily be guided by cost-effectiveness considerations. In principle, the recommendation will be to provide this intervention, unless there are major doubts about the plausibility of and/or certainty around the estimated ICER. For interventions with an ICER between £20 000/QALY gained and £30 000/QALY gained, NICE takes account of the following factors: degree of (un)certainty about the ICER; whether the assessment of QoL has inadequately been captured, and may therefore misrepresent the health utility gained; the innovative nature of the technology; whether the technology meets the criteria for special consideration as a 'life-extending treatment at the end of life'; and aspects that relate to non-health objectives of the NHS (NICE, 2013). This idea can be applied to the cost-effectiveness acceptability curve (Figure 2), which is deduced from the CE-plane. This curve represents the probability of an intervention being cost-effective (Y-axis), given different values for the ICER threshold value (X-axis) and reflects the uncertainty around the ICER estimate (Cleemput, Neyt et al., 2008). For example, with e.g. the £20 000 (€22 800) threshold, the intervention in Figure 2 (deduced from Figure 1) would have a 61% probability of being considered as an acceptable intervention, and 100% with a threshold of £30 000 (€34 200).

Figure 2: The cost-effectiveness acceptability curve

The probability that an intervention is considered cost-effective depends on the willingness-to-pay (WTP) for a health effect. In this example, with a WTP of €22 800 per QALY, there is a 61% probability that the intervention is considered cost-effective. There is a direct link between figure 2 and figure 1, for a higher ICER threshold, the slope of the dotted line of figure 1 (representing the ICER threshold) is also higher and the proportion of dots falling below the line becomes also higher. This explains why the curve is continuously increasing in this example.
Of course, economic considerations are only one element in the decision-making process. Other elements might have an influence on the willingness-to-pay (e.g., economic crisis, unmet medical need, lobby, etc.) and decision makers may sometimes not just wish to maximise health (in LY or QALYs) and give more weight to other criteria. It would in fact seem, on the very short term, easy if stakeholders and policy makers don’t need to take into account economic considerations. However, ignoring the economic reality that resources are limited would, in the longer term, endanger the accessibility and quality of the health care system. As with the ‘prudent man’ principle, economic reality should be faced and not neglected.

5 AN EXAMPLE: THE TAVI CASE

The heart has four valves, one of them being the aortic valve which lies between the left ventricle and the aorta. Due to aortic stenosis (AS), the valve fails to open fully and thereby obstructs blood flow out from the heart. Depending on the severity of this stenosis, this might require an aortic valve replacement (AVR) which requires an open heart surgery. More than a decade ago, an alternative technique, the transcatheter aortic valve implantation (TAVI) was developed. With this less invasive surgical procedure, the new valve is implanted using a catheter without open heart surgery (http://en.wikipedia.org/wiki/Aortic_valve).

5.1 CPG: the perspective of the clinicians and patients

Physicians try to do the best possible for their patients and try to select the best management strategies. Clinical practice guidelines (CPG) aim at guiding decisions taken by health care professionals. These guidelines are based on an examination of current evidence within the paradigm of EBM (http://en.wikipedia.org/wiki/Medical_guideline).

In the case of TAVI, the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) published guidelines on the management of valvular heart disease mentioning the following (Joint Task Force on the Management of Valvular Heart Disease of the European Society of European Association for Cardio-Thoracic et al., 2012).

- High-risk operable patients: “TAVI should be considered in high-risk patients with severe symptomatic AS who may still be suitable for surgery, but in whom TAVI is favoured by a ‘heart team’ based on the individual risk profile and anatomic suitability” (recommendation class IIa, level of evidence B).

- Inoperable patients: “TAVI is indicated in patients with severe symptomatic AS who are not suitable for AVR as assessed by a ‘heart team’ and who are likely to gain improvement in their quality of life and to have a life expectancy of more than 1 year after consideration of their comorbidities” (recommendation class I, level of evidence B).
– Class I means the intervention is recommended and class IIa means the intervention should be considered. Level of evidence B in this case refers to data derived from a single randomized clinical trial (RCT), the PARTNER trial, which randomized both high-risk operable patients (cohort A (Smith, Leon et al., 2011)) and inoperable patients (cohort B (Leon, Smith et al., 2010)).

5.2 HTA: the perspective of the government and tax payers

The Belgian Health Care Knowledge Centre (KCE), an independent federal institution providing advice to policymakers on decisions relating to health care and health insurance (www.kce.fgov.be), made an HTA report on this intervention (Neyt, Van Brabandt et al., 2011). For high-risk operable patients, the researchers recommended not to reimburse TAVI. For inoperable patients, a distinction was made between the underlying reasons for being inoperable. Both medical and anatomic factors may lead to the surgeons’ conclusion of inoperability. Medical conditions include e.g. highly compromised respiratory disease or advanced multi-system dysfunction. These patients may benefit from a correction of the aortic stenosis, but this will usually not solve the problems linked to the presence of other serious medical co-morbid conditions. Anatomic conditions include porcelain aorta, chest wall deformity, and multiple previous interventions. These patients not necessarily have serious non-cardiac comorbidities (Neyt, Van Brabandt et al., 2011). The KCE HTA report only provided a positive reimbursement recommendation for this group:

– “Patients with symptomatic severe aortic stenosis in whom correction of the aortic stenosis is considered as possibly beneficial but who are considered to be inoperable due to anatomical factors by a heart surgeon who is independent of the heart team treating the patient are eligible for treatment with and reimbursement of TAVI with the Sapien® valve, if one is prepared to pay a relatively high price for TAVI.”

– “Patients with symptomatic severe aortic valve stenosis and severe comorbidities who are considered inoperable due to medical factors are not eligible for reimbursement of TAVI.”

For high-risk operable patients, also no reimbursement was recommended. At first sight, this might seem quite different than the recommendations in the clinical guideline. Nevertheless, the medical assessment in this HTA report is based on the same RCTs and comes to the same conclusions: similar outcomes for both mortality and quality of life after one year in the high-risk operable group and better outcomes for the inoperable group (Neyt, Van Brabandt et al., 2011). However, adding economic considerations has a major impact on the reimbursement recommendations:

– High-risk operable patients (Figure 3): “reimbursement of a procedure that is not better but is indeed more costly (€43,600 for the TAVI procedure, including €18,000 for the Sapien® valve, versus €23,700 for AVR) would
naturally result in inefficient use of limited available resources. Even if the (non-significant) differences in 30-day and 1-year mortality are taken into account, the incremental cost-effectiveness ratio (ICER) remains on average above €750,000 per quality-adjusted life year (QALY) gained [incremental cost (IC): €20,400; incremental effect (IE): 0.03 QALYs] (In high-risk patients (Cohort A)). This conclusion would only change if the price of TAVI were to approach that of AVR and/or if TAVI were to perform better than AVR in the future” (Neyt, Van Brabandt et al., 2011).

Inoperable patients (Figure 3): in this population, with a life-long extrapolation of the mortality benefit, an ICER of €44,900 per QALY (IC: €33,200; IE: 0.74 QALYs) was calculated. In Belgium, there is no explicit cost-effectiveness threshold. If the previously mentioned NICE threshold of £20,000 (~€22,800) to £30,000 (~€34,200) per QALY gained was applied, this resulted in a 9.2% to 36.7% chance that TAVI could be considered as cost-effective in inoperable patients (Neyt, Van Brabandt et al., 2011).

Figure 3: TAVI’s cost-effectiveness in Belgium

TAVI: Transcatheter Aortic Valve Implantation. We refer to the full report (Neyt M, Van Brabandt H et al. 2011) and publication of the economic evaluation (Neyt, Van Brabandt et al. 2012) for further details on this project and a transparent presentation of all input variables.

Instead of just giving a negative advice based on these economic considerations, the KCE researchers looked further and obtained the impact on mortality for both anatomic and medical inoperable patients from the study sponsor. In both groups, there was a positive impact on survival (Neyt, Van Brabandt et al., 2011); however, in the anatomic group this was relatively larger resulting in an ICER that was around €11,000 lower, while it was around €5,000 higher in medically inoperable patients. This explains the recommendation to restrict
reimbursement to the anatomical inoperable patients, which was followed by the National Institute of Health and Disability Insurance (RIZIV/INAMI).\(^2\)

### 6 CONCLUSION

Performing an economic evaluation has nothing to do with cost cutting and rationing of healthcare. It’s there to support doing as much as possible with our limited resources for the total population. Looking at the medical added value of an intervention is of utmost importance and comes at the first place. Economic evaluations link this added value to costs to see whether an intervention also offers value for money.

For policy makers, it is not easy to use economic arguments to refuse reimbursement of a medical intervention, especially when these interventions are recommended in practice guidelines. Providing all stakeholders further insights into the different perspectives applied in clinical practice guidelines and HTA is desirable to convince them of the importance of HTA to pursue a health care system with a high accessibility, of the highest quality as possible and which is durable in the long term. Taking not only benefits, but also costs and opportunity costs, into account is certainly an ethical way to make choices in healthcare.

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\(^2\) Information on reimbursement criteria is available in Dutch and French: http://www.inami.fgov.be/nl/professionals/individuelezorgverleners/verstrekkers-van-implantaten/akkoord/Paginas/klepstent-aortapositie.aspx#.VOSBQi5e_gC


