The Euros and sense of stents: do we get value for money?

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Introduction

Stents have become a cornerstone of the management of coronary disease. In the '90s it was shown that as compared to balloon angioplasty, stents offered better outcomes for patients at a reasonable extra cost. (Meads et al, 2000) Compared to surgery the situation is different and depends largely on the target population. In patients with diabetes or patients with multivessel disease CABG is more expensive in the short term but leads to better long term outcomes still justifying its cost.(Cohen et al, 2011)

But what do we mean by "justifying a cost"? When health economists use the term "cost-effectiveness" they mean the ratio between the extra cost of a technology as compared to standard care and the extra health effect (Annemans, 2008). If the ratio is good then it means that an acceptable amount of money is needed to gain one unit of health. If a lot of money is needed to gain one unit of health, then the ratio is bad or unacceptable. That's the principle, but obviously other questions immediately emerge: what is a unit of health? What is acceptable and what is not?

First of all, we should acknowledge that the main purpose of health care is to produce health. But as is the case in any sector of the economy, when we 'produce' something, it also means we have to be productive: health care must produce health in the most productive way and most efficient way. Why is it for instance not advisable to finance the use of cholesterol-reducing drugs for people who only have slightly raised cholesterol levels, without any other risk factors? Simply, because of risk-benefit issues but also because it is not efficient: the costs are too high in relation to the health gains. ((Ward et al, 2011) If we want to produce more health with the available (financial) resources, then we must allocate the money to those interventions and programs which produce most health per invested euro or dollar or pound; that is, to the most productive and efficient ones. Indeed, money

can only be spent once, and if we don't spend it wisely we miss the chance to do better things with that money.

It is noteworthy that governments and policymakers often devote more attention to making savings, without necessarily taking into account the ratio between input (money) and output (health), in other words without devoting the necessary attention to the price-quality ratio of treatments, interventions and care programmes. Annual budgets are still being presented and growth norms and savings are proposed in relation to these budgets. Nevertheless, the OECD (Organisation for Economic Cooperation and Development) clearly states that merely establishing growth norms has little or no relation with any notion of productivity or optimality. They must be replaced by measures based on health economic evaluations and by incentives to encourage efficient care. (Jacobzone, 2003)

The steps of evidence

Hence, we must aim for efficiency. Efficiency is sometimes considered by health economists as the 'third step of evidence'.

The first step of evidence is efficacy: if it can be demonstrated that a drug eluting stent is associated with less restenosis compared to a bare metal stent, then the stent is said to work better, to be more efficacious.

The second step is effectiveness. When it can be demonstrated in real situations (taking into account that the patient may have co-morbidities, is not always compliant with the drugs he/she has to take, etc.) that a technology produces health gains, it is said to be effective.REF Indeed, in real life, the average result may deviate from the original clinical studies. This explains the need for more registries in cardiology and in other fields of medicine. Effectiveness also means that it is necessary to look at relevant outcomes. In the example of stents, it should ideally be demonstrated that a better stent leads to less MACE, such as for example in Simsek et al (2011), where a 6 years follow up showed that the sirolimus eluting stent lead to less MACE as the bare metal stent.

So, the bridge from efficacy to effectiveness relates to two aspects: the circumstances in which the measurements are made (from an 'artificial' clinical study environment to 'real life' situations), and what is measured (from intermediary variables to clinically and socially relevant endpoints).

Suppose there is good evidence about the effectiveness of an intervention. Then it will only be considered to be efficient – the third step – when it can be demonstrated that the money spent on this intervention is money spent well. In other words, if it would have been possible to achieve greater health gains in any area of health with the same money by spending it on something else, the intervention being examined is relatively inefficient. (Annemans, 2008)

Hence , the crucial outcome is the ratio between the resources (money) needed to carry out the intervention and its health effects. This is called the cost-effectiveness ratio.

But, as already indicated above, it is difficult to determine what is money well spent and what is not. Of course, a treatment which is extremely expensive and provides virtually no health gains is clearly not, while a treatment which leads to many health gains for a very low price often is.

Quality Adjusted Life Years

In order to enable a comparison of different health technologies, the QALY (Quality Adjusted Life Year) is often used as outcome parameter in cost-effectiveness studies. The principle of the QALY is that the quality and quantity of life can be combined in one concept. This is illustrated in Figure 1 (A, B, C, D). The Y axis in every case shows an index between 0 and 1, where 1 is equal to full health and 0 stands for no health. The index expresses the *utility* level, which can be considered – in simple terms – as a 'quality of life' level.

Imagine now that a patient with coronary heart disease has lived for 10 years from the time of receiving a revascularisation. Suppose that the average 'quality of life' during these 10 years had a value of 0.6 on this scale between 0 and 1. It is then said that this patient has had 0.6 x 10 = 6 QALYs. Indeed, each of the 10 years of life is assigned a 'weight' of 0.6, and the number of life years is adjusted to the quality of those life years, hence the term 'quality adjusted life years'. Thus the QALY is the result of multiplying the quantity and the quality of life. A patient who lived for 6 years in perfect health would also have 6 QALYs (6 years times 1).

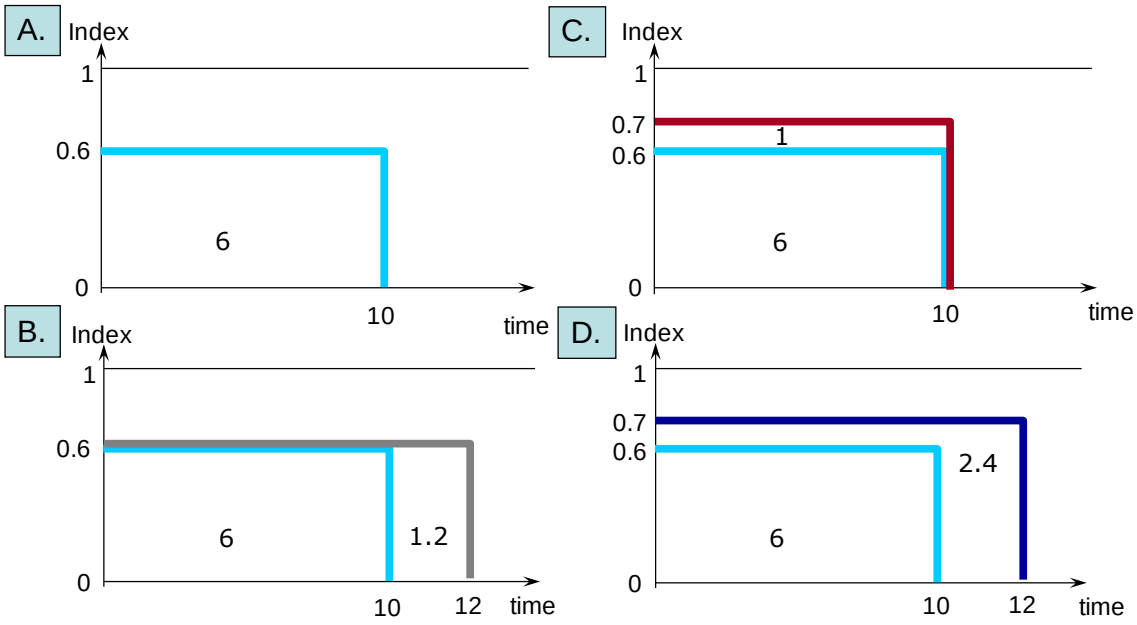
If it had been possible for the patient to live 2 years longer with a therapy to extend his life (e.g. CABG), but the quality of life expressed by the index does not change, the health gain would be 0.6 x 2 = 1.2 QALYs (Figure 1B). The gain in QALYs is equal to the difference between the surfaces under the two curves (7.2 -6 = 1.2).

If it had been possible to improve the quality of the patient's life to 0.7, for instance by applying a stent, and do so for a period of 10 years, a gain of health would have been achieved equal to (0.7-0.6) x 10 = 0.1 x 10 = 1QALY (Figure 1C). Hence, it is also possible for someone to gain QALYs without increasing his/her life expectancy! Obviously, if an effect is achieved both with regard to the quality and the quantity of life, more QALYs are gained. If the patient had lived for 12 years with a quality of 0.7, the total number of QALYs would be 0.7 x 12 = 8.4, 2.4 more QALYs than in the starting situation (Figure 1D).

It is of key importance to understand that a QALY has an economic value. According to the WHO, the economic value of a QALY is at least the value of the Gross Domestic Product per head of the population. In Western societies, this value is about €30000. In other words, one year in good quality of life has an economic value of +/- €30000.

This also means that if a treatment costs €10000, and it leads to 0.5 extra QALYs, this comes down to investing €20000 to gain 1 QALY (10000/0.5 = 20000). So we pay €20000 to gain something that is in fact worth €30000, which means we obtained value for money.

Figure 1: Graphical representation of the QALY (based on Annemans, 2008)



Starting from the above concepts and principles, we explored the literature on the cost-effectiveness of stents. We found 42 articles based on the following search terms in Medline: ("stent"[title] OR "stents"[title]) AND "cost effectiveness"[All Fields] AND (heart OR coronary) [All Fields] AND (qaly OR quality) [All Fields], and after excluding those that were not economic evaluation studies.

Bare metal stents (BMS)

In 2000, Meads et al conducted a systematic review on the use of stents in the management of coronary heart disease, looking into their effectiveness and cost-effectiveness.

They found the following key effects in the comparison with PTCA:

1. Elective stent insertion versus PTCA in subacute IHD:
   - event rates (generally death, MI, repeat PTCA and CABG) – odds ratio (OR), 0.68 (95% confidence interval [CI], 0.59 to 0.78)
   - repeat PTCA – OR, 0.57 (95% CI, 0.48 to 0.69)
2. Elective stent insertion versus PTCA in AMI for:
   - event rates (generally death, MI, repeat PTCA and CABG) – OR, 0.39 (95% CI, 0.28 to 0.54)
   - repeat PTCA – OR, 0.44 (95% CI, 0.26 to 0.74).

There was insufficient evidence to draw any conclusions on the effectiveness of elective stent insertion versus CABG in subacute IHD. There was moreover wide variation in the estimates of cost,

and cost-effectiveness. The analyses generally reported cost/QALY estimations in the range of £20,000–£30,000.

Interestingly, apart from the Meads et al review, no additional evidence in terms of costs and QALYs was identified.

Drug eluting stents (DES)

When DES became available, the use of BMS was already quite established and health economic evaluations of DES were then also to be conducted in comparison with BMS and not in comparison with PTCA. Several authors have investigated the cost-effectiveness of DES vs BMS and up till now, no clear conclusions have been reached.

The first evaluations were rather promising. For instance, Cohen et al (2004), based on the SIRIUS trial, found that after a follow up of 1 year, the incremental cost-effectiveness ratio for SES was 1650 dollars per repeat revascularization event avoided or 27,540 dollars per QALY gained. The authors concluded that these values compared reasonably with other accepted medical interventions.

In further studies, these rather positive results were not systematically confirmed, on the contrary. Kuukasjärvi et al (2007), based on 13 economic evaluations concluded that there is a large inconsistency in the results of these studies. The authors made an attempt to estimate an overall cost-effectiveness ratio as compared to BMS and found an average value of almost €100,000 per QALY pointing to the absence of cost-effectiveness.

Based on their systematic review, Greenhalgh et al (2010) concluded that there were significant reductions in composite outcomes such as MACE but no statistically significant differences in individual parameters such as death, AMI or thrombosis between DES and BMS. Reductions in Target Lesion Revascularisation (TLR) and Target Vessel Revascularisation (TVR) were evident with all types of DES, and were demonstrated in longer term follow up. The authors concluded, without going in detail on cost-effectiveness analyses, that "the increased cost of drug-eluting stents and lack of evidence of their cost-effectiveness means that various health funding agencies are having to limit or regulate their use in relation to price premium."

Typical illustration of the latter are the papers by Bischof et al (2009) and Neyt et al (2009) where it was concluded, based on the results of several RCTs that DES are not at all cost-effective as compared to BMS. Goeree et al (2009) came to the same conclusion based on one large prospective trial.

However, when assessing cost-effectiveness, one should look further than the mere time horizon of a clinical trial and one should also attempt to make simulations based on real life data rather than on artificial clinical trial circumstances.

With regards to time horizon , a recent paper by Remak et al (2010) pointed out that if a time horizon of at least 4 years is applied, by extrapolating clinical trial results the use of DES (in this paper the zotarolimus stent) a very good cost-effectiveness ratio of less than £,4,000 per QALY is obtained.

With regard to the inclusion of real life data, results might change in the good or the bad direction. Filion et al (2009) point to the occurrence of late stent thrombosis as observed in registries and conclude that if these are accounted for in the economic evaluations, the results become even worse. This finding confirms the need for stents that offer the same clinical benefits but reduce the rates of stent thrombosis. (Amoroso et al, 2011)

A recent paper by Norwegian researchers (Wisløff et al, 2011) confirms the importance to look into real life data but finds data of a totally different order of magnitude and much more in favour of DES. The cost effectiveness of replacing bare metal stents (BMS) by drug-eluting stents (DES) was simulated based on both trial data ánd registry data, whereby the authors simulated the outcomes of a virtual cohort of 60-year-old patients undergoing PCI for acute or subacute coronary artery disease. The patients were followed in the simulation until death or 100 years of age. On using trial data, it was found that sirolimus-eluting stents (SES) yield 0.003 greater life expectancy and $3300 lower costs than do BMS, meaning that the gain in quality adjusted life expectancy is after all very modest but that in the end net savings can be obtained. Paclitaxel-eluting stents (PES) yield 0.148 more life years than do SES at additional lifetime costs of $2800 , which comes down to $21,400 per life year gained. On using registry data, the cost per life year gained was found to be $4900 when replacing BMS with DES, which is very cost-effective. Here, the authors were not able to distinguish the different types of DES.

Regardless of the difference between RCT and real life data, the long time horizon is likely explaining these better results.

What is sometimes missed in the overall discussion is the right selection of patients. Ekman et al (2006) investigated the cost-effectiveness of the paclitaxel eluting stent in the Swedish setting and concluded that it was cost-effective in high risk patients and provided sufficient follow up time. Lord et al (2005), in an Australian review and assessment come to similar conclusions: “DESs are effective in reducing revascularisation. Estimates of cost-effectiveness are very sensitive to changes in estimates of their true effects in clinical practice, market price and the number of stents used per patient. Decisions to limit DESs to only patients at the highest risk of restenosis may improve their cost-effectiveness but will need to be reassessed when evidence is available to compare absolute benefits between patient groups.” Also the BASKET trial, after a follow up of 1.5 years, concluded that the result in high risk patients was clearly better than the overall result. (Brunner-La Rocca et al, 2007)

Hill et al (2009) reviewed 10 economic evaluations and also concluded that DES are more cost-effective in higher risk patients. They found that, all patients considered together, the calculated cost per QALY ratios are high (183,000-562,000 pounds) and outside the normal range of acceptability, but that in patients with small vessels and a history of PCI, the results are markedly better. The price premium, numbers of stents used in the index procedure and absolute risk reduction in repeat interventions most significantly influence the cost-effectiveness ratios.

Venkitachalam et al (2011) build further on this very important aspect of the correct use of technologies. They found, based on data from the EVENT registry that a “liberal” use of DES as compared to selected use, lead to a marginal benefit, associated with a cost per QALY of more than

$400000. This is an illustration of 2 key aspects: first , that one never can call any technology “cost-effective” without clearly specifying how and in which patients it is used. DES is cost-effective if used in a clearly selected way. Second, we have arrived at the so called “flat of the curve”: when a lot of health gain has already been achieved in a disease area, it becomes more and more difficult to add additional value at a reasonable cost.

For the particular case of ST segment elevation myocardial infarction (STEMI), the STRATEGY study compared the overall costs and cost effectiveness ratio of sirolimus-eluting stents (SES) implantation and tirofiban infusion with abciximab and bare metal stent (BMS) in patients undergoing primary intervention for acute STEMI. (Valgimigli et al, 2008). After a follow up of two years whereby all data on cardiovascular medical resource use was collected, it was found that the rate of TVR was significantly lower in the SES group , leading to net savings of about €1100 per patient.

Importantly, the authors admittedly reported that the TVR rates in the study were likely overestimated due to mandatory angiographic follow up in the trial, leading to protocol driven medical resource use. However, it was calculated that even if the number of interventions in the trial would be 60% higher than in real life, the savings with SES would still be more than €800. Nevertheless, the authors recommend that studies are needed to evaluate the cost effectiveness ratio of DES implantation in the setting of STEMI when clinical follow-up alone is carried out. Moreover, studies with larger sample sizes and longer follow up are required.

Pedersen et al (2011) recently reported the results of such a study, carried out in Denmark, in 1725 patients followed up for 4 years in a real life setting, comparsing SES with BMS in a 2 to 1 ratio. The authors concluded that the TLR rate was significantly reduced with SES whereas there was a trend towards increased incidence of stent thrombosis. Economic evaluations alongside this study have not yet been reported.

Regardless of the choice for BMS or DES, a Swedish research team recently showed that primary PCI in STEMI patients is cost-effective and even dominant (less costs better outcomes) as compared to thrombolysis. (Aasa et al, 2011) The study was carried out in Sweden in 205 patients followed up for one year. In total , on average $1,500 per patients was saved, and a small QALY gain of 0.03 was observed.

With regard to the comparison with bypass surgey, Shimizu et al (2010) conclude based on interim) results from a comparative trial between DES and CABG, in patients with unprotected left main coronary artery (ULMCA) that the MACCE-free survival rate was better in the CABG group (CABG: 82.2% and DES: 62.6% at 2 years) (P=0.033), and that total hospitalization costs were lower (P=0.013) in the CABG group (median: 3,225 thousand yen) than in the DES group pointing to dominance (less cost, more health) of CABG in this indication. Cohen et al (2011) conclude – however based on a 1 year follow up –that DES is economically attractive over the first year for patients with low and moderate angiographic complexity, while CABG is favored among patients with high angiographic complexity.

In conclusion

In conclusion, the answer to the question “are stents value for money?” must obviously be a nuanced one. Health technology assessment is about evaluating a technology but more so about evaluating its right use.

As compared to PTCA, stents have shown to be cost-effective. In comparison to CABG, the latter is still preferred in subtypes of patients (diabetes, 3-vessel disease, …). The cost-effectiveness of DES has been largely investigated. This is typical for a technology for which a higher price is claimed: that price premium should only be granted if it can be shown that the technology also offers an additional therapeutical value that is in good proportion to its additional cost. The controversy about the cost-effectiveness of DES vs BMS remains. There is a trend towards a narrowing of the price gap between BMS and DES which is obviously in favour of the cost-effectiveness of the latter. Apart from the price, the key issues are the time horizon of the analysis, the need to apply real life data, and the right selection of patients. The good approach in European countries should have been to pay the same price for DES as for BMS until more and clear evidence of their cost-effectiveness existed and only then to reward this extra value. Cardiology guidelines should account for cost-effectiveness data in order to have more fine tuned recommendations.

Of note is also that the comparison with CABG has been very poorly investigated, certainly in terms of cost-effectiveness.

In the future, decision makers should faster detect potentially cost-effective technologies, give them the benefit of the doubt, and make them subject of risk sharing agreements with the manufacturers, whereby the money granted to the technology is made dependent on its performance in real life.

Word count = 3190

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