COST-EFFECTIVENESS OF A NOVEL SELF-APPOSING STENT IN ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION (STEMI) IN FRANCE

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ABSTRACT

The objective was to calculate the cost-effectiveness profile of STENTYS compared to conventional bare and drug-eluting stents (DES). Stents are widely used in the treatment of patients with ST-segment elevation myocardial infarction (STEMI). However, several reports point to the prevailing risk of coronary events such as recurrent myocardial infarction, some of which are related to in-stent thrombosis, possibly explained by poorly apposed stents. 1-year results of the self-apposing stent, STENTYS, are promising regarding the incidence of fatal and non-fatal cardiovascular (CV) events. A model was developed to simulate costs and quality-adjusted life years (QALYs) over 1-5 years. In the first 12 months, a decision tree framework was used to define different CV outcomes for STEMI patients receiving a stent. After 12 months, outcomes were categorised in a Markov stage of the model as myocardial infarction (MI), other CV events, revascularisation, and death. Cost of comparative treatments and follow-up in relation to CV events were calculated from the French health insurance perspective. The results indicated, in the base case, over a time horizon of 5 years, that STENTYS bare metal stent (BMS) is dominant (less costly and more QALYs) against conventional DES. The STENTYS DES is dominant compared with conventional DES and very cost-effective versus BMS. The results were robust for different variations in the input variables. This first analysis of the cost-effectiveness of STENTYS showed that it is dominant or very cost-effective as compared to conventional stents. Further comparative research and longer follow-up data are needed to expand on these results.

Keywords: Cost-effectiveness, self-apposing stent, France, quality-adjusted life year (QALY), STENTYS.

INTRODUCTION

Primary percutaneous coronary intervention (PCI) has been established as the treatment of choice for patients with acute ST-segment elevation myocardial infarction (STEMI).[1] In the 1990s it was shown that, compared to balloon angioplasty, stentsoffered better outcomes for patients at a reasonable extra cost.[2] Although the use of stents has led to an important reduction in major adverse cardiac events (MACE) and cardiac death, the risk of restenosis remains high with the use of bare metal stents (BMS). The use of drug-eluting stents (DES) was intended to reduce the risk of restenosis. Based on a systematic review, Greenhalgh et al.[3] concluded that there were significant reductions in composite outcomes such as MACE but no statistically significant differences in individual parameters such as death, acute myocardial infarction (MI), 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 long-term follow-up. Concerns had been raised about the cost-effectiveness of DES compared with BMS if only an effect on TVR

would be substantial,[4] but recent real-life data[5] and systematic reviews of the literature[1] suggest a benefit of DES compared with BMS, at least in the first year after the index event at minimum. However, concerns still remain about the risk of stent thrombosis and re-infarction after using DES that might be more pronounced among STEMI patients.[6] Heestermans et al.[7] investigated 5,842 STEMI patients treated with primary PCI, of which 201 (3.5%) presented with an early (<30 days) definite stent thrombosis. The strongest predictors of early stent thrombosis and re-infarction were post-procedural dissection, undersizing, and small stent diameter.

Recently a self-apposing stent, STENTYS, has been developed with the aim to provide a better fit to the vessel and therefore reduce the occurrence of re-infarctions. The first randomised study with STENTYS showed that it perfectly appose to the vessel, whereas 28% of conventional stents were malapposed (APPOSITION II).[8] The APPOSITION III study[9] evaluated the long-term clinical benefit of the STENTYS stent in STEMI patients in a real-life setting. This was a prospective, non-randomised, single-arm, multicentre study evaluating the safety and performance of the STENTYS stent in routine clinical practice in 965 STEMI patients. Both drug-eluting and bare-metal versions of the STENTYS stent were available and were used at the operator's discretion.[9] The primary endpoint at 12 months, presented at EuroPCR 2013,[10] was MACE, defined as cardiac death, target-vessel recurrent MI (re-MI), or clinically-driven TLR. Secondary endpoints were definite/probable stent thrombosis, all-cause mortality, any MI, and any TVR. 1-year cardiac death or target vessel re-MI was observed in only 3.2% of patients, and only 2.4% if post-dilation was applied. The trial results showed a lower all-death rate as compared to a meta-analysis of conventional stents. In the current healthcare environment, the need to allocate public money wisely has increased the interest in comparative effectiveness and cost-effectiveness research.[11] Hence, it is important in the development of new technologies not only to investigate their clinical effectiveness, but also to estimate potential cost savings of such technologies. The objective of this study was to calculate the cost-effectiveness of STENTYS (BMS and DES) in treating STEMI patients, and to identify the drivers of this cost-effectiveness.

METHODS

Decision Model

We developed a health economic model in MS Excel 2010, inspired by previous health economic models of DES compared with BMS.[12-14] The model has a dual structure, with a decision tree reflecting the outcomes in the first 12 months (Figure 1, Part A). After 12 months, a Markov 'state transition' model presents and predicts the further evolution of patients over a period of 5 years (Figure 1, Part B). Indeed, in coronary heart disease patients, events that occur in the first year can lead to consecutive events in the following years. Therefore, reducing the events in the first year will also have an impact on the subsequent years. A similar approach was followed by Janzon et al.,[15] whereby even a lifetime extrapolation was applied. Nevertheless, in contrast to Janzon et al.,[15] we decided to not model further than 5 years because extrapolations beyond such a period would become too speculative.

In the model, the following strategies are compared:
- Conventional BMS
- Conventional DES
- STENTYS BMS
- STENTYS DES

As noted above, a decision tree is used to assess the first 12 months of patients in a given therapy. In those first 12 months, a patient can have a fatal or non-fatal re-infarction (the latter treated or not with revascularisation), another cardiovascular (CV) event (fatal or non-fatal), a revascularisation not related to MI, or die from another cause. Patients who survive the first 12 months continue in the Markov part of the model, which runs in years 2-5, and can have one of the following outcomes: death from any cause, MI, and revascularisation (not MI-related). Hence, from years 2-5, at the end of each year, patients can stay in the same state as they were before, or have an MI (fatal or non-fatal), need a revascularisation (not MI-related), or die from a CV event or other cause.

Clinical Data Input

Clinical data related to conventional stents are shown in Table 1.[12,16,17] Montalescot et al.[10] (ACTION study group, La Pitié-Salpêtrière Hospital, Paris, France) report the results of an analysis at 30 days and 1 year of the incidence of MACE and mortality in recent studies with conventional stents after STEMI. The authors did not report detailed data on separate outcomes such as MI, revascularisation

not related to MI, and CV death. Therefore, we also used data from Garg et al.,[12] reporting on the incidence of other CV events, and from a meta-analysis from Piscione et al.[16] reporting that 32% of all revascularisations after the use of BMS were associated with an MI. The probabilities of MI, revascularisation, and death beyond 1 year were also obtained from Garg et al.[12] Finally, since these data include a mix of approximately 50% BMS/50% DES, we adjusted the estimated number of events associated with BMS by accounting for the effect of DES, based on a meta-analysis from Suh et al.[1] Table 1 provides the key input data for the model applicable to conventional BMS. The relative risks (RR) of events associated with DES versus BMS were obtained from the most recent meta-analysis from Suh et al.[1] The RR for 1 year MI was 0.77 (95% CI 0.61-0.97) and the RR for 1 year TVR was 0.48 (95% CI 0.41-0.56). Comparing the results from APPOSITION III[9] with those of the above analysis, it was assumed in the base case that the RRs associated with BMS STENTYS versus conventional BMS were 0.50 for 30 day MI, 0.80 for 1 year MI, and 1 for 1 year TVR; for DES STENTYS versus conventional BMS, 0.70 for 1 year MI and 0.48 for 1 year TVR. The RR for re-infarction beyond 1 year was not known and therefore assumed to be 0.90 for STENTYS BMS and 0.80 for STENTYS DES(P). These assumptions were tested in sensitivity analyses (see results).

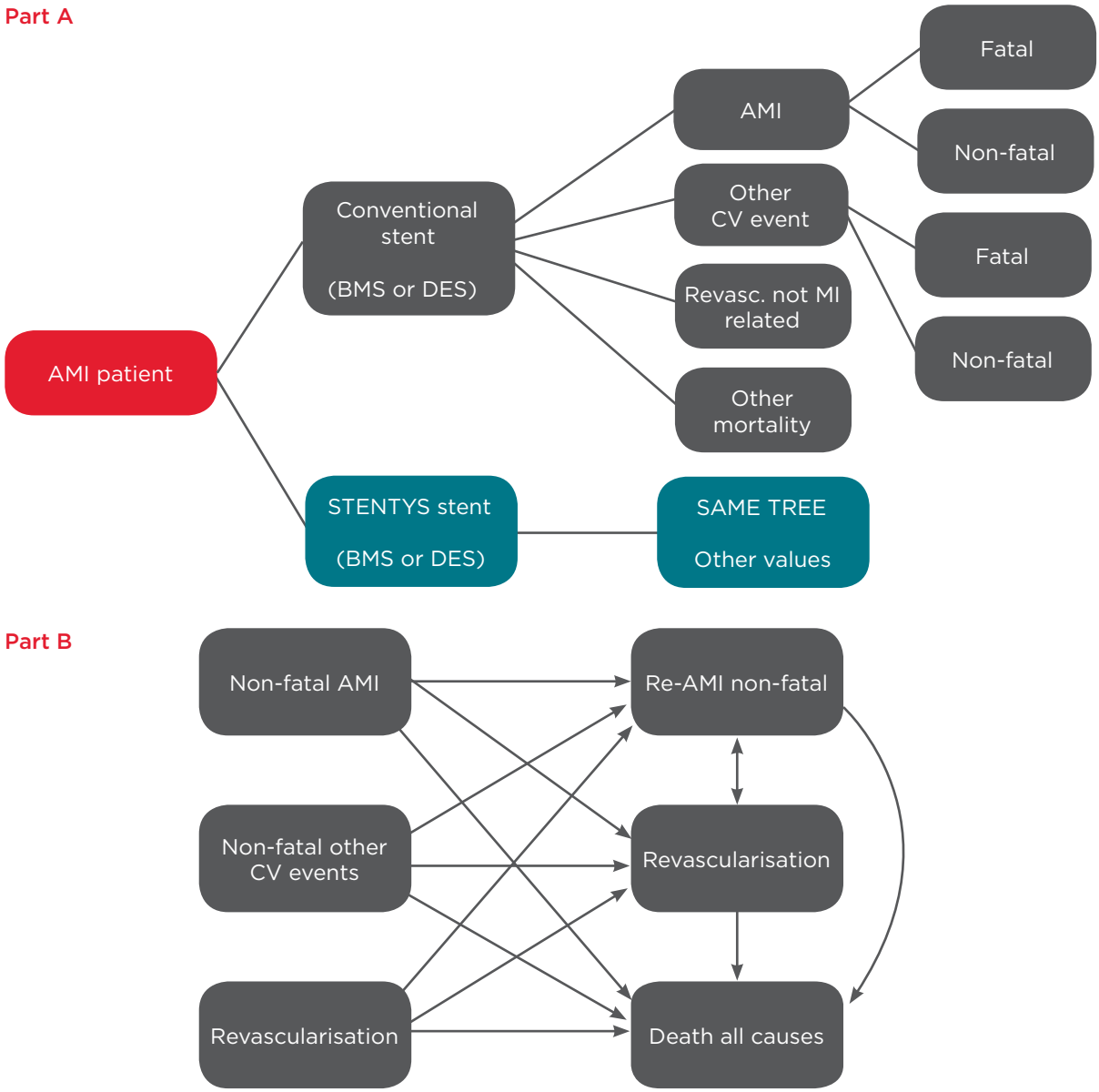

Figure 1: Graphical presentation of the health economic model.
Part A: first 12 months (decision tree); Part B: subsequent cycles of 12 months (Markov model)
AMI: acute myocardial infarction; BMS: bare metal stent; DES: drug-eluting stent; CV: cardiovascular.

Table 1: Clinical input data for first 30 days and first 12 months after STEMI, applicable to conventional BMS.

Cardiovascular events post-STEMI treatment with a conventional BMS stent	Incidence (%) 30 days	Incidence (%) 1 year	Source
Non-fatal reinfarction	2.25%	3.72%	Montalescot 2013 (adjusted)[10]
Fatal reinfarction	3.10%	3.18%	Montalescot 2013 (adjusted)[10]
Non-fatal other cardiac event	0.34%	0.95%	Garg 2008[11]
Fatal other cardiac event	0.33%	0.71%	Garg 2008[11]
Mortality, other (non-cardiac)	0.08%	0.81%	French Lifetables[16]
Revascularisation excl. reinfarction	0.00%	2.53%	Garg 2008,[11] Piscioni 2010[15]
Total (excluding non-cardiac mortality)	6.02%	11.09%	

STEMI: ST-segment elevation myocardial infarction; BMS: bare metal stent.

Table 2: Cost data applied in the model.

Item	Cost (€)	Source
In-hospital reinfarction	1,449	Canoui-Poitrine 2009[4]
Non-fatal MI post-hospitalisation	4,815	Colin, 2007, adjusted for health index[17]
Fatal MI	4,610	Colin, 2007, adjusted for health index[17]
TVR	5,531	Haute Authorité de Santé (HAS)/SED/SEESP/2009, adjusted for health index[20]
Other CV event	3,984	Haute Authorité de Santé (HAS)/SED/SEESP/2009, adjusted for health index[20]
BMS	550	LegiFrance[21]; Canoui-Poitrine 2009[4]
DES	1,100	LegiFrance[21]
STENTYS BMS	840	Oral communication from STENTYS S.A.
STENTYS DES	1,200	Oral communication from STENTYS S.A.

MI: myocardial infarction; TVR: target vessel revascularisation; CV: cardiovascular; BMS: bare metal stent; DES: drug-eluting stent.

Cost Data Input

A French social insurance perspective was used, therefore productivity lost through illness or costs incurred directly by patients were not included. Discount rates of 3% are applied to both future costs and health benefits, consistent with prevailing guidelines. Cost data for all events are reported in Table 2.[18-20] The cost of re-infarction during the index hospitalisation was obtained from a study by Canoui-Poitrine et al.[4] and costs of re-infarctions after discharge (hence during the rest of the analytical period) were obtained from an earlier paper by Colin et al.[18] The cost of a fatal MI came from the latter source. Acute costs of revascularisation and other CV events were obtained from the French Health Authority. All costs were actualised to the year 2012. The costs of the STENTYS BMS and DES(P) were obtained from the company. In the model, an average of 1.2 stents per patient was assumed. The costs for current BMS and DES were obtained via the LegiFrance website. In the base case the cost data from 2012 were applied. In a sensitivity analysis, the most recently published costs for conventional DES were applied (€875 per stent).

Table 3: Utility data applied in the model.

Event/condition	Utility level		Source
First year after MI	0.80		Chevalier et al.[21]
Re-MI	0.70		Chevalier et al.[21]
TVR	0.70		Chevalier et al.[21]
Follow-up without events	0.85		Chevalier et al.[21]

MI: myocardial infarction; TVR: target lesion revasuclarisation.

Table 4a: Base case results at 1 year.

	COST (€)	QALY	INCR COST versus BMS (€)	INCR QALY versus BMS	ICER (€/QALY)	INCR COST versus DES (€)	INCR QALY versus DES	ICER (€/QALY)
Conventional BMS	1268.3	0.7681						
Conventional DES	1741.2	0.7717	472.9	0.0036	**131,067**			
STENTYS BMS	1550.3	0.7764	282.0	0.0083	**33,839**	-190.9	0.005	**dominant**
STENTYS DES	1838.2	0.7777	569.9	0.0096	**59,606**	97.0	0.006	**16,291**

INCR: incremental; QALY: quality-adjusted life year; ICER: Incremental Cost-Effectiveness Ratio; BMS: bare metal stent; DES: drug-eluting stent.

Table 4b: Base case results at 5 years.

	COST (€)	QALY	INCR COST versus BMS (€)	INCR QALY versus BMS	ICER (€/QALY)	INCR COST versus DES (€)	INCR QALY versus DES	ICER (€/QALY)
BMS	3471.9	3.5207						
DES	3822.2	3.5723	350.4	0.0516	**6,793**			
STENTYS BMS	3613.3	3.6123	141.4	0.0916	**1,543**	-208.9	0.040	**dominant**
STENTYS DES	3813.7	3.6346	341.8	0.1139	**3,001**	-8.5	0.062	**dominant**

INCR: incremental; QALY: quality-adjusted life year; ICER: Incremental Cost-Effectiveness Ratio; BMS: bare metal stent; DES: drug-eluting stent.

UTILITY DATA

In order to calculate quality-adjusted life years (QALYs), utility data are required. The QALY is a common measure of health improvement used in cost-effectiveness analyses. It combines mortality and quality of life gains by adjusting the number of years a person lives at the appropriate quality level (called utility) during those years. The maximum utility value is 1 and a value of 0 is assigned to death.[21] We applied utility values reported by Chevalier et al.[22] (Table 3).

RESULTS

Base Case

Table 4a and 4b show the base case results of our analysis for a time horizon of 1 year (hence not accounting for any additional benefits for STENTYS stents beyond 1 year) and 5 years, respectively. After 1 year, the STENTYS BMS is borderline cost-effective in comparison with conventional BMS and dominant (costing less and adding QALYs) against DES. The STENTYS DES is cost-effective compared

to conventional DES (€16,291/QALY) but not cost-effective versus conventional BMS. DES (all) are not cost-effective compared to BMS (all). After 5 years, assuming a continued benefit on re-MI as described in the methods, the STENTYS BMS is very cost-effective against conventional BMS and dominant against conventional DES. The STENTYS DES is very cost-effective against conventional BMS and moreover dominant versus conventional DES.

Sensitivity Analysis

Sensitivity analyses showed that, as expected, the relative benefit of STENTYS stents in the short and long-term are the key drivers of the results. The recently reduced costs of conventional BMS and DES strongly influence the Year 1 results but have a modest effect on the Year 5 results. In Table 5, the impact of different variables on the ICER (Incremental Cost-Effectiveness Ratio) is shown for the 5 year analysis.

DISCUSSION

Although huge progress has been made in the management of STEMI patients, not least with the introduction of BMS and DES, there is still a clear need for further improvement in the treatment of STEMI, with currently >10% MACE in the first year. The Self-Apposing STENTYS stent showed favourable 1 year clinical outcomes in a real-life STEMI population, supporting the hypothesis that correct stent sizing and elimination of malapposition after primary PCI may lead to improved long-term results. This model shows that under the current assumptions, the STENTYS DES(P) is already cost-effective at 1 year compared with conventional DES. However, applying the most recent price reductions of conventional stents, this conclusion no longer holds. Both the STENTYS BMS and DES(P) are very cost-effective if outcomes to 5 years are simulated, even with reduced prices of conventional stents. Yet, given this preliminary evidence, our model could still be called an 'early economic evaluation'. This practice of economic models in the early development phase of technologies has existed for more than a decade,[23,24] but has been largely applied only over the last few years.[25] The idea is clear: based on anticipated or preliminary results from a new technology and its costs to the healthcare system, the potential cost-effectiveness can be estimated, hence advising all stakeholders – manufacturers, policy makers, physicians, and patient advocacy groups – about what to expect from market access of the technology.

Table 5: Sensitivity analysis.

Simulation 1 year	**STENTYS DES versus conventional BMS**	**STENTYS DES versus conventional DES**
Basecase	€59,606/QALY	€16,291/QALY
Patient risk level -50%	€137,606/QALY	€35,677/QALY
Cost of events -50%	€70,593/QALY	€18,225/QALY
Cost of conventional BMS and DES resp. €500 and €875	€65,882/QALY	€61,647/QALY
RRR MI STENTYS -50%	€129,924/QALY	€126,362/QALY
Simulation 5 years	**STENTYS DES versus conventional BMS**	**STENTYS DES versus conventional DES**
Basecase	€3,001/QALY	dominant
Patient risk level -50%	€9,085/QALY	€1,628/QALY
Cost of events -50%	€4,925/QALY	€894/QALY
Cost of conventional BMS and DES resp. €500 and €875	€3,528/QALY	€4,196/QALY
RRR MI STENTYS -50%	€7,981/QALY	€16,171/QALY

QALY: quality-adjusted life year; BMS: bare metal stent; DES: drug-eluting stent; RRR: relative risk reduction; MI: myocardial infarction.

Early economic models have some limitations, as is also the case for the current one. Firstly, the key model input is based on non-comparative data. Confirmation of the results of APPOSITION III in a comparative setting is required to verify our results. The APPOSITION V, FDA-approved randomised study will bring a more definite answer to the comparative evidence, and will allow the assessment of the predictive validity of the current analysis. Even then, longer follow-up data are required to confirm the predicted over a period beyond 1 year. This should ideally be the case for all innovative technologies for which only rather short-term data exist. The model was based on a recently presented systematic literature search which was performed to find the most relevant effectiveness and complication data related to conventional stents. The search suffered from the lack of transparent reporting of the individual events in most of the studies in the review. Often events such as in-stent thrombosis, MI, and revascularisation are reported without clearly showing how many of the MIs were related to in-stent thrombosis, and how many revascularisations were related to MIs. We needed to rely on other data to obtain more granular estimates of the different individual events. Moreover, some studies in the systematic review were rather old, and others reported only 30 day data and no 1 year data, while other studies showed the reverse. We performed a secondary analysis thereby looking only at recent trials and imputing missing 1 year data based on the principle of proportionality. In that analysis, the total number of events at 30 days and 1 year became 5.39% and 10.70% and the number of CV deaths became slightly higher than in our base case analysis. However, the final results were not affected.

The model comparison did not adjust for baseline characteristics. In the systematic review, the average patient age was 61.4 years which is comparable with the mean age of 60 years in the APPOSITION III study.[9] However, other population baseline and procedural characteristics such as thrombolysis in myocardial infarction flow at baseline, culprit lesion location, thromboaspiration use, and novel P2Y12 use, although sometimes similar, do vary between trials in the review and also in comparison with the APPOSITION III trial. Finally, since the perspective of this analysis was the social health insurance in France, we did not account for possible savings due to reduced productivity. Patients with MI are often still at a productive age and therefore societal losses occur due to their absence from work. Annemans et al.[26] reported that the productivity related costs of CV events are at least as high as the direct medical costs. Taking these into account would lead to even more possible savings due to a new stent with improved features.

CONCLUSION

In conclusion, the current analyses in the French setting suggest favourable cost effectiveness of the STENTYS BMS and DES in comparison to conventional stents in patients with STEMI, when a time horizon beyond 1 year is applied. These conclusions are based on a 1 year prospective trial with STENTYS and a systematic review of current stents. Long-term and comparative clinical data are required to confirm these results.

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