



HAUTE AUTORITÉ DE SANTÉ

Assessment of drug-eluting stents

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Medical Devices Assessment Department

Healthcare Strategies Assessment Department

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SUMMARY

INTRODUCTION

In 2007, HAS undertook a reassessment of drug-eluting stents (DES) with the aim to analyse their efficacy and their security compared to bare-metal stent (BMS) following the publication of contradictory data reporting a greater incidence of delayed intrastent thrombosis in patients implanted with a DES. A medical and an economic evaluation were performed simultaneously.

SCOPE OF THE ASSESSMENT

This assessment covers DES that are on the reimbursement list: the CYPHER sirolimus-eluting stent, the TAXUS paclitaxel-eluting stent, the ENDEAVOR zotarolimus-eluting stent , the XIENCE V and PROMUS everolimus-eluting stents .

BACKGROUND

In addition to secondary prevention, the available therapies for the management of coronary disease consist of drugs and surgical techniques for myocardial revascularisation (coronary artery bypass graft surgery, CABG) or interventional techniques (angioplasty with a balloon alone or with stent implantation). The place of revascularisation differs depending on the type of the disease (stable angina, ST-segment elevation myocardial infarction, STEMI, or non ST-segment elevation, NSTEMI). In stable angina, it is limited to patients who remain symptomatic while on medication or have extensive myocardial ischaemia with a poor prognosis. In STEMI, the indication for angioplasty is based on an estimate of the delay in management of the patient between onset of symptoms and the performance of the intervention. In NSTEMI, the decision for revascularisation is based on the classification of the risk of acute thrombosis based on clinical data, the electrocardiogram and the biological markers for myocardial ischaemia.

Regardless of the form of the disease, the place of DES has not been clearly defined in the current recommendations of learned societies.

In France, DES are reimbursable over and above the payment made for a hospital stay in the treatment of coronary insufficiency that may be attributed to *de novo* lesions of native coronary arteries in patients with high risk of restenosis (especially lesions greater than 15 mm, vessels with a diameter of less than 3 mm, stenosis of the proximal left anterior descending artery or the presence of diabetes); restenosis within BMS and chronic total coronary occlusion. The current indications are based on the inclusion criteria of the first published trials.

In France, in 2007 70,000 DES were billed (42 % of stents implanted) at a cost of 106 million euros (67% of total costs). In 2008, DES accounted for 45% of all implanted stents.

AIMS

The principal aim is to define the indications for which:

- alternative strategies to angioplasty with DES implantation (CABG surgery and pharmacological treatments) are preferable;
- DES implantation is recommended rather than angioplasty without stent implantation or with implantation of a BMS;
- a particular DES should be recommended rather than another DES.

The second aim is to define the use of dual antiplatelet treatment at the time of stent implantation (treatment duration and management of the treatment in the context of any type of surgery).

MATERIALS and METHODS

The method used by the working group to evaluate the DES involved the following phases: 1) a critical analysis of the medical and medico-economic literature and of the clinical data supplied by the manufacturers; 2) the conduct of complementary studies by HAS (meta-analysis and medico-economic models); 3) the consultation of a review group.

Following an exhaustive search covering 2002 to 2008, the selection criteria used enabled the following to be retained: 1) for the clinical evaluation: 2 technological assessments, 10 recommendations and 70 clinical studies subsequent to the technological assessments of 2007 (corresponding to 17 meta-analyses, 14 randomised controlled studies and 39 registers), as well as 9 unpublished studies (data from 5 studies and 4 registers); 2) for the medico-economic evaluation: 5 pivotal studies and 18 models.

The principal clinical efficacy criterion adopted was new revascularisation of an already treated lesion (target lesion revascularisation, TLR) following the reappearance of clinical symptoms (clinically documented¹). The secondary efficacy criteria used were: an angiographic criterion based on the quantification of the phenomenon of restenosis (late loss) and another clinical criterion based on the global revascularisation of the patient (targeted or non-targeted revascularisation of the initial lesion). The principal safety criteria were death and thrombosis within the stents defined according to the *Academic Research Consortium* (ARC). Myocardial infarction and major adverse cardiac events (death, myocardial infarction, stroke) were analysed within the secondary criteria. The criterion of efficiency used was the cost by avoided target lesion revascularisation.

¹ i.e. the occurrence of myocardial infarction or unstable angina, recurrence of angina pectoris, evidence of extensive myocardial infarction.

RESULTS

The clinical data (26 studies, 80,150 patients followed-up for a maximum of 4 years) showed that DES were more effective² and at least as safe³ as BMS in the clinical studies, which most commonly selected patients with *de novo* lesions of the coronary arteries, and in the majority of comparative observational studies. However, in some observational studies with a follow-up lasting up to one year, the incidence of revascularisation of the target lesion, of death and of myocardial infarction was increased in those patient populations, who had received a DES outside of the selection criteria of the randomised studies. In economic terms, implantation of DES in this non-selected population generates an unjustified extra cost with respect to the benefit obtained in terms of avoided revascularisations and the quality of life⁴. Analysis of the literature therefore shows that there is a benefit from implanting a DES solely in selected subpopulations of patients.

Clinical and medico-economic data by clinical characteristics or by lesion.

Efficacy-safety ratio of DES

The methodological quality of data used is good, except in comparison with BMS for multi-vessel lesions, where the methodological quality is low to moderate. No data comparing a DES with pharmacological treatment was identified.

➤ *Risk factors for restenosis (lesions > 15 mm, vessels < 3 mm, diabetes)*

CYPHER and TAXUS stents were significantly more effective than BMS, the efficacy varying according to the risk factors investigated in 15 studies on a total of 7,026 patients: RRR⁵ of clinically documented TLR⁶ for up to 4 years in the longest follow-up period (CYPHER: from 67 % to 92 %, TAXUS: from 54 % to 60 %). ENDEAVOR, XIENCE V and PROMUS stents were more effective than BMS in 2 studies on 626 patients with lesions having broader characteristics than those with high risk of restenosis.

When the recommended duration of dual antiplatelet treatment was between 2 and 3 months, an additional risk of mortality was observed with CYPHER and TAXUS stents in two studies on 278 diabetic patients (risk ranged from 2.3 [1.18-5.12] to 2.9 [1.38-6.10]). When the recommended duration of dual antiplatelet treatment was reported for up to 1 year, the DES were as safe as the BMS (no difference in terms of thrombosis, death and myocardial infarction). For diabetic patients some data were in favour of CYPHER and TAXUS stents over BMS in 2 studies on 2,006 patients (RR of infarction was 0.48 [0.26-0.87]; absolute risk⁷ of myocardial infarction was -3.0 % [-5.6 ; -0.5] and of death -3.2 % [-6.0 ; -0.4]).

➤ *ST-segment elevation myocardial infarction*

CYPHER and TAXUS stents were significantly more effective than BMS in 9 studies on a total of 7,639 patients (RRR of clinically documented TLR⁶ for up to 2 years CYPHER: of the order of 55 %, TAXUS: of the order of 40 %).

The DES were also as safe as the BMS: no difference was observed in terms of death and myocardial infarction. After 1 year, the total number of certain or probable thrombosis did not differ between the two groups.

² Compared to BMS, the DES decreased the number of new TLR⁶ (at 1 year, a 75 % decrease in the randomised studies and a decrease of between 30 and 60 % in the observational studies).

³ Compared to BMS, the incidence of death and myocardial infarction is lower with DES, but the differences are not statistically significant. The incidence of intrastent thrombosis is, according to the ARC, slightly increased after 1 year (from 0.4 to 1.4 % versus from 0 to 0.6 %) without any difference being observed over the whole follow-up period.

⁴ None of the 5 pivotal studies and the 15 models reporting a cost-efficacy ratio demonstrated a dominance of DES over BMS in a large population.

⁵ The RRR is the reduction in relative risk (RR), it corresponds to $(1-RR)*100$ (RR is the ratio of percentages observed in the groups compared).

⁶ New revascularisation of an already treated lesion.

⁷ The absolute risk (AR) is the difference in the percentages observed in the two groups compared.

➤ *Treatment of BMS in-stent restenosis*⁸

CYPHER and TAXUS stents were significantly more effective than balloon angioplasty alone in 3 studies on a total of 730 patients (RR of clinically documented or not TLR⁶ for up to 1 year ranging from 0.35 [0.25-0.49] to 0.45 [0.26-0.77]).

The DES were as safe as balloon angioplasty alone: no difference was observed between the groups in terms of the criteria of death and myocardial infarction. The cases of intrastent thrombosis were not reported according to the definition of the ARC in this study.

➤ *Total coronary occlusion (> 72 hours)*

The CYPHER stents were significantly more effective than the BMS in 100 patients at the end of one randomised study (after 6 months RRR of TLR⁶ with planned angiographic follow-up of 79 %; associated with a reduced late loss of 1.04 mm).

CYPHER stents were as safe as BMS: no difference in terms of death, myocardial infarction or stroke was observed.

➤ *Multi-vessel lesions and/or unprotected left main stenosis*

CABG surgery was significantly more effective than CYPHER and TAXUS stents in 9 studies on a total of 13,576 patients with complex lesions and a low to moderate surgical risk (including 7,016 diabetic patients). In fact, patients with DES, who were followed-up for between 10 months and 3 years, had a risk of revascularisation that was 2 to 3 times greater than patients who had undergone CABG surgery (RR of global revascularisation without planned angiographic follow-up of 2.05 [1.12-3.75] to 2.81 [2.11-3.75], RR of TLR⁶ 2.98 [1.15-7.75]).

There was difference between DES and CABG in the incidence of death and myocardial infarction (relative risk ranged from 1.2 to 1.5 except in diabetic patients, for whom the RR of death and myocardial infarction ranged from 1.20 [0.99-1.45] to 1.89 [0.89-3.97]). The incidence of stroke was significantly increased at 12 months in the CABG group (from 2.2 to 4 % *versus* from 0 to 0.6 %). Data on intrastent thrombosis were fragmentary and showed a global incidence of 1.1 % to 2.7 %.

Following medical-surgical consultation when angioplasty was adopted (in particular when the surgical risk was elevated), TAXUS and CYPHER stents were significantly more effective than BMS in 4 studies on a total of 1,028 patients (RRR of TLR⁶ for a follow-up of 6 months to 3 years without planned angiographic follow-up was between 80 and 88 %). CYPHER and TAXUS stents were as safe as BMS, because no difference was observed with respect to death, myocardial infarction or stroke.

➤ *Vein graft stenosis*

CYPHER and TAXUS stents were not superior to BMS in 4 studies in a total of 392 patients (between 1 and 3 years: RR of TLR⁶ with planned angiographic follow-up was 2.27 [0.64-8.13], of death, myocardial infarction or intrastent thrombosis was 1.5 [0.5-4.7] to 3.4 [0.8-15.4]). A study on a small population even reported an excess of death at 15 months following implantation of a DES (29 % *versus* 0; $p < 0.001$).

➤ *Stenosis of the proximal left anterior descending artery and bifurcation lesions*

No comparative data between DES and BMS was considered. The data (non-comparative or between DES) did not enable any benefit to be demonstrated for DES in patients with lesions of this type.

⁸ Resulting in clinical manifestations of myocardial ischaemia.

Comparison between DES

In all the studies (10 in total), CYPHER stents were more effective than TAXUS stents in a total of 7,450 patients with high risk of restenosis. In fact, the comparisons between CYPHER and TAXUS stents show a RR of clinically documented TLR⁶ up to 4 years of between 0.27 [0.09-0.75] and 0.78 [0.50-1.14]. In a population of 13,102 patients not selected for clinical or lesion characteristics, the data were significantly in favour of CYPHER stents in 4 studies (RR of clinically documented TLR⁶ of the order of 0.7 [0.6-0.8]). The results are consistent in terms of late loss (between 6 and 9 months, 0.09 to 0.12 mm *versus* 0.19 to 0.31 mm).

With respect to the other DES, ENDEAVOR, XIENCE V and PROMUS stents, the comparisons with CYPHER stents involved a total 13,741 patients who were not definitively selected for clinical and/or lesion characteristics (results from 2 studies). The CYPHER stents were as or even more effective over a follow-up not exceeding 2 years (RR of clinically documented TLR⁶ *versus* ENDEAVOR: of 0.24 [0.12-0.48] to 0.44 [0.28-0.70] and *versus* XIENCE V: 1.47 [0.90-2.44]).

Globally, there was no difference between CYPHER and the other stents in terms of the incidence of mortality, myocardial infarction and intrastent thrombosis (thrombosis from 0 % to 2.1 %).

Cost-efficacy ratio (efficiency) of DES

Published medico-economic data enable it to be estimated that the rate of angioplasty with implantation of a DES should concern between 3 % and 40 % of interventions, if one takes into account the results for DES in terms of avoided TLR⁶ and the costs of care.

➤ *By clinical and lesion characteristics (CYPHER and TAXUS stents)*

The simultaneous presence of several risk factors improves the cost-efficacy ratio of DES compared to BMS (3 models).

With respect to *de novo* lesions of a native coronary artery (2 studies), implantation of a DES compared to a BMS is cost-effective in the case of vessels with a small diameter (dominance if < 2.5 mm) and long lesions (dominant or cost-effective if > 20 mm). In a real population (2 studies), this result was confirmed for vessels of small diameter.

The efficiency of a DES in diabetes which is not associated with another risk factor (3 studies, 3 models) has not been demonstrated. On the one hand, diabetes does not appear systematically as an independent factor for a high risk of restenosis in the medico-economic analyses (1 study, 1 model), and this result has been confirmed by analysis of the medical literature. On the other hand, the medico-economic results are contradictory: 2 studies, of good methodological quality, demonstrate that it is not more cost-effective to implant a DES in a diabetic patient than in a non-diabetic patient; 1 study and 2 models of lower methodological quality show an improved cost-efficacy ratio in diabetic patients compared to non-diabetic patients.

When the patient has other risk factors (artery with a small diameter, multi-vessel lesions, acute coronary syndrome), the cost-efficacy ratio of a DES compared to a BMS stent is improved in diabetic patients compared to non-diabetic patients (1 study, 3 models).

In patients with complex lesions, DES are cost-effective compared to BMS in the case of STEMI (1 study) and in the case of multi-vessel lesions when surgery is not an alternative (3 models).

Globally, the efficacy of DES is low due to: 1) the relatively low gain in efficacy in terms of the number of patients in the target population avoiding target lesion revascularisation; 2) the difference in price between the two categories of stents.

Indeed, according to data in the medical and economic literature, of 100 patients treated with a DES, between 7 and 14 will avoid a new revascularisation. This proportion was found in the French EVASTENT study performed in routine practice: 6 to 12 diabetic patients out of 100 patients treated with a DES derived benefit in terms of avoiding new revascularisation, depending on whether they had single- or multi-vessel lesions. This benefit represents less than 5 % of non-diabetic patients.

Furthermore, the difference in price between DES and BMS has a major impact on the efficiency of DES. The current French tariff for DES does not permit a cancelling out of the difference in the cost of management at 12 months between the DES (more expensive with a longer dual antiplatelet treatment) and the BMS (costs associated with new target lesion revascularisation).

Medical data relating to dual antiplatelet therapy in the use of a DES

Data from the literature do not make it possible to define the optimum duration of dual antiplatelet treatment required when a DES is implanted. The minimum duration recommended by the learned societies is 12 months.

This results in difficulties when the patient has to undergo an intervention with a risk of bleeding. This may cause certain interventions to be postponed. When it is not possible to postpone the intervention, the decision to interrupt or continue the treatment consists of assessing between the risk of intrastent thrombosis (if the dual antiplatelet therapy is interrupted) and the risk of bleeding (if the dual antiplatelet therapy is continued).

Current data do not permit the quantification of risks associated with continuing or interrupting the treatment with respect to the type of intervention. Some learned societies have defined rules of practice without establishing formal recommendations. They recommend a multidisciplinary discussion on a case by case basis about how to proceed and on informing the patient.

WORKING GROUP OPINION

The working group consisted of four interventional cardiologists, three anaesthetists/resuscitators, two thoracic and cardiovascular surgeons, two radiologists/interventional cardiologists, one methodologist and one health economist. Of these thirteen experts, nine were active in the public sector and four in the private sector.

The opinion of the working group is based on a combined analysis of clinical and economic data.

Opinion concerning the literature

- 1- DES do not provide a gain in terms of survival compared to BMS.
- 2- DES are not a cause of an increased risk of intrastent thrombosis, death or myocardial infarction during follow-up over at least 4 years.
- 3- In patients for whom angioplasty is preferable to a CABG surgery, and in comparison with BMS, DES are of benefit in the case of some clinical characteristics and types of lesion: they reduce the need for revascularisation of the target lesion with it being necessary to treat on average 7 to 14 patients in order to avoid one such event.
- 4- DES are not identical in terms of clinical benefit.
- 5- The efficacy of DES is low due to: 1) the relatively low gain in efficacy in terms of the number of patients in the target population avoiding new target lesion revascularisation; 2) the difference in price between the two categories of stents.

Opinion concerning the indications

Whether the current recommendations for myocardial revascularisation are respected, the working group distinguishes two areas of indications for DES.

The first area concerns the treatment of coronary insufficiency due to *de novo* lesions in native coronary arteries in some subgroups of patients with high risk of restenosis (lesions > 15 mm, diameter of affected vessel < 3 mm or some diabetic patients without multi-vessel lesions). The devices selected were the CYPHER, TAXUS, ENDEAVOR stents as well as the XIENCE V and PROMUS stents. Only the CYPHER and TAXUS stents may be used in STEMI in patients with high risk of restenosis.

The second area concerns limited indications arising from a multidisciplinary medical-surgical consultation⁹ in the treatment of coronary insufficiency:

- the first intrastent restenosis in a BMS (i.e., the reappearance of ischaemic symptoms leading to a new revascularisation of the artery) for CYPHER and TAXUS stents. Apart from this situation, all the therapeutic options should be considered (a CABG surgery should be favoured in particular during a second restenosis with extensive myocardial ischaemia or if the lesions appears to be poorly accessible);
- total occlusion of native coronary arteries (> 72 hours) in a situation where there is prior evidence of ischaemia and when the lesion appears accessible with a reasonable success rate for the CYPHER stents;
- some *de novo* multi-vessel lesions of native coronary arteries following a medical-surgical consultation on the alternatives for revascularisation and taking into account the risk factors assessed. CABG surgery remains the standard treatment with complete revascularisation of the ischaemic regions when angioplasty does not appear a reasonable possibility (high SYNTAX score). While complete revascularisation by angioplasty is possible, stent implantation might be preferable in a case of very high surgical risk (high EUROSCORE). CYPHER and TAXUS stents are therefore recommended for lesions > 15 mm, for an affected vessel with diameter < 3 mm or for diabetic patients;
- unprotected left main stenosis following medical-surgical consultation. In the majority of cases, a CABG remains the standard treatment. In some cases where angioplasty could be envisaged, CYPHER stents are recommended. Since they are contraindicated in the CE marking, TAXUS stents may not be used.

Overall, of patients are likely to receive a DES, approximately 50,000 will receive a XIENCE V/PROMUS stents or ENDEAVOR stent, 66,000 a TAXUS stent and 69,000 a CYPHER stent.

In the absence of demonstrative data, bifurcation lesions and stenosis of the proximal left anterior descending artery may not in themselves be considered as indications for the use of DES.

Venous graft stenosis is not an indication for the use of DES.

Opinion concerning the therapeutic benefit

⁹ The medical-surgical team should include at least one interventional cardiologist, one cardiac surgeon, and ideally the referring cardiologist and an anaesthetist.

- The clinical effect of DES is moderately superior compared to BMS and balloon angioplasty alone;
- compared to CABG in multi-vessel lesions and unprotected left main stenosis, DES are slightly superior when the lesions are accessible to angioplasty in patients with a high surgical risk (although CABG remains the standard treatment). They are superior in the absence of a therapeutic alternative if the patient is not suitable for surgery;
- compared to CYPHER stents, the other DES are inferior with respect to the angiographic criterion (late loss) and are comparable with respect to the clinical criterion (target lesion revascularisation).

Opinion concerning contraindications

These include left ventricular ejection fraction < 30 %, intolerance to antiplatelet treatment with heparin, to the metal of the stent platform or to an angiographic contrast medium, as well as pregnant women. Lesions with calcifications, which cannot be predilated by means of a balloon or rotational atherectomy are also excluded.

Opinion concerning prescription and use

The number of reimbursable units is 1 stent per patient except in the case of acute occlusive dissection. In multi-vessel lesions after a medical-surgical consultation, a maximum of 3 CYPHER or TAXUS stents per patient could be reimbursed. Concerning the associated dual antiplatelet therapy, information must be given to the patient prior to the intervention about the need to continue the treatment for one year and the difficulties associated with the procedure. A card should be given to the patient. This will define the type of stent, the date of its implantation and the subsequent anti platelet treatment (with duration). In the event of surgical procedures occurring within the year following stent implantation, a multidisciplinary consultation between the surgeon, anaesthetist and cardiologist concerning the procedures to be followed should be organised.

Opinion concerning request for reimbursement

For every modification of a reimbursed DES in terms of drug dose, drug concentration or polymer, for any new DES or for any new indication, it is necessary to provide at least one randomised clinical study. The trial should be methodologically correct, of sufficient size and power and may address a principal clinical or angiographic criterion (such as late loss). If the study focuses on an angiographic criterion and is performed in a limited number of patients, a register should be established with a sufficient number of patients to make it possible to evaluate the clinical parameters of safety and efficacy with a minimum planned follow-up of 5 years. The results after 1 year follow up must be supplied. Analyses of sub-groups could be accepted on condition that they derive from a randomised study, have been specified in the protocol and concern a sufficient number of analysed patients.

CONCLUSION – THE OPINION OF HAS

In comparison to BMS, DES are of confirmed but moderate benefit in terms of reducing the incidence of restenosis and revascularisation procedures. They are not a cause of an increased risk of intrastent thrombosis, death or myocardial infarction during follow-up over up to 4 years when they are used with long-term anti platelet treatment. DES provide some clinical benefit, but this benefit is obtained at the cost of prolonged dual antiplatelet therapy, continued for a minimum of 12 months.

Economic data show that the efficiency of DES varies according to the clinical characteristics of the patients and the lesions and is strongly dependent on the difference in price between DES and BMS.

HAS considers that there are no benefits in implanting DES in a non-selected patient population. Whether the current recommendations for myocardial revascularisation are respected, HAS recommends to limit the use of DES to the following indications:

- treatment of coronary insufficiency attributable to *de novo* lesions in native coronary arteries in some subgroups of patients at high risk of restenosis (lesions > 15 mm, diameter of affected vessel < 3 mm or in diabetic patients). The devices recommended are the CYPHER, TAXUS, ENDEAVOR stents as well as the XIENCE V and PROMUS stents.
- some situations of coronary insufficiency require a multidisciplinary consultation involving a medical-surgical team:
 - treatment of total coronary occlusion (> 72 hours) in a situation where there is evidence of ischaemia and when the lesion appears accessible with a reasonable success rate. The recommended devices are the CYPHER and TAXUS stents.
 - treatment of the first clinical intrastent restenosis in a BMS (i.e., the reappearance of ischaemic symptoms leading to a new revascularisation of the artery). The recommended devices are the CYPHER and TAXUS stents.
 - treatment of some *de novo* multi-vessel lesions in native coronary arteries (lesions > 15 mm, diameter of affected vessel < 3 mm or in diabetic patients), which are accessible to angioplasty when the surgical risk is very high. This situation should be the object of a medical-surgical discussion about the revascularisation alternatives, taking into account the risk factors assessed (EUROSCORE and SYNTAX score). CYPHER and TAXUS stents are recommended.
 - treatment of unprotected left main stenosis. The recommended device is the CYPHER stent.

This evaluation confirms the benefit of DES compared to BMS in some indications. The clinical benefit (reduction of new revascularisation of lesion already treated with a DES) is less than previously expected and bears a cost in the need for antiplatelet treatment using a combination of salicylic acid and clopidogrel for 1 year. Economic data demonstrate a low efficiency of DES.

In other indications for angioplasty, BMS should be favoured. DES require prolonged dual antiplatelet therapy and their cost is much higher than that of BMS. In the future, it will be desirable to have data documenting more precisely the efficiency of DES according to the indications, particularly in diabetic patients.