

Drug eluting stents. Experts Consensus Document from the Société Française de Cardiologie. October 2007

Nicolas Danchin, Didier Blanchard, Bernard Chevalier, Hélène Eltchaninoff, Jean Ferrières, Philippe-Gabriel Steg, Jacques Machecourt,

Groupe de relecture : Loïc Belle, Yves Cottin, Thomas Lecompte, Jacques Puel, Emmanuel Teiger

Drug eluting stents, which are coated with a pharmacological antiproliferative agent that aims to combat restenosis, are now part of the therapeutic armamentarium in interventional cardiology. During recent months, doubts have been raised about the safety of these devices. In an attempt to clarify the situation and to provide clinical and interventional cardiologists with guidelines for their use, the Société Française de Cardiologie has deemed useful to examine the most recently published data on this subject. This document, drafted in October 2007 by a consensus of experts, will obviously need to be revised as further clinical data are produced in the coming months and years.

I.- What can be considered proven.

1° *With regard to effectiveness:* active stents reduce the incidence of clinical restenosis (« TLR ») by 75% on average in patients included in randomized studies (1,2), and there were no « Catch Up Phenomena » after 4 years of follow up (3). In routine clinical practice, the reduction in the TLR is situated between 55 and 65% (the difference between randomized controlled trials and « real world » studies can be explained by the use of angiographic control in randomized studies, which increases TLR by between 10 and 20% (4)). Subgroup analysis in pivotal studies, and specific randomized studies have shown that this difference in clinical efficacy is considerable in certain subgroups of patients with a high risk of restenosis: in diabetics (1,2, 5), in the case of lesions that are more than 15 mm long, in arteries with a diameter of less than 3 mm (6), in the treatment of restenosis in a bare metal stent (7), in the treatment of chronic (more than 1 month) total coronary occlusion (opinion of experts). This proof of the efficacy of active stents compared to bare metal stents lies at the heart of the recommendations for the use of coated stents published by the Haute Autorité de Santé and by the Société Française de Cardiologie.

2° *Safety of use:*

- As shown in a meta-analysis by Kastrati (8) and more recently in a meta analysis by Stettler (9) concerning 18,000 patients included in 38 randomized studies with a follow up of 4 years, there are no significant differences between drug-eluting and bare metal stents with regard to overall or cardiovascular-related mortality either in the acute phase or after 3 or 4years.
- In these randomized studies, there was no difference between the two stent types for the overall incidence of in-stent thrombosis at 1 month and 3 years after implantation.
- However, after one year, there was a slightly, though significantly, greater incidence of « very late » thrombosis in drug-eluting stents than in bare metal stents. This increased incidence of thrombosis, using the protocol definitions for stent thrombosis, was found for both Sirolimus and Paclitaxel-eluting stents at long-term follow-up in the pivotal studies (8, 10). However, when Academic Research Consortium criteria were used to define stent thrombosis, the difference remained significant only for paclitaxel-eluting stents beyond 30 days (10). The latter criteria include thromboses which occur at repeat interventions; these sometimes use techniques such as endocoronary brachytherapy, which by itself can cause thrombosis.

II.- What is under discussion.

1° *In terms of safety: high risk patients and « off-label » indications.*

The use of drug-eluting stents in so-called « off-label » indications presents a higher risk of in-stent thrombosis or death than does use in "on-label" indications (11,12). It must be pointed out, however, that it is difficult to characterize "on-" or "off-label" indications because they are based on regulations, which vary considerably depending on the period and the country. It is thus extremely difficult to take account of the results of studies based on such a classification. It seems preferable to consider either data from randomized studies and possibly subgroups in these studies or data from consecutive registries, taking into account specific sub-groups.

Randomized studies (cf Supra) have reported a likely but slight increase in the incidence of late thrombosis (more than 1 year) for active stents compared with bare metal stents. In the real world, it is impossible to demonstrate this as there are no appropriate control groups. In particular, when only bare metal stents existed, studies of in-stent thrombosis did not exceed one month (13). The predictors of acute or sub-acute in-stent thrombosis (< 1 month) are known: they are associated with either the difficulty of the procedure, or errors in the management of antiplatelet therapy, and there are no differences between

drug-eluting or bare metal stents in this regard. The predictors of late or very late thrombosis with drug-eluting stents are also quite well known (11,14): factors present at the time of implantation are highly calcified coronary lesions, diabetes notably insulin-dependent diabetes, renal insufficiency, the length of the implanted stent and the number of treated segments. Patients with an accumulation of risk factors (for example a diabetic patient with several diseased arteries) are at a significantly higher risk of developing in-stent thrombosis (11).

It is still debatable whether in such patients the risks associated with stenting are greater than those associated with surgery. There have been no comparative randomized studies on this subject (two are in progress); only the ARTS II study (15), which matched a group of patients treated with drug-eluting stents with a « historical » group from the ARTS I randomized study, which compared CABG with angioplasty using bare metal stents. The study reported that in terms of mortality and efficacy drug-eluting stents were comparable to CABG in patients with multivessel disease.

2° In terms of safety: management and length of antiplatelet treatment after implantation of a drug-eluting stent.

“Premature” interruption of antiplatelet therapy is a strong predictor of thrombosis with drug-eluting stents (13,16). In the PREMIER registry, mortality was significantly increased in the case of premature interruption of the treatment with clopidogrel. This increased risk may be explained by the delayed endothelialisation that occurs with drug-eluting stents compared to bare metal stents (17). This led the American Heart Association/American College of Cardiology and the Food and Drug Administration to recommend that the treatment be continued for 12 months provided there was no high risk of bleeding with dual antiplatelet therapy (18, 19). This recommendation is in keeping with the recommendations for the use of dual antiplatelet therapy in acute coronary syndromes, whatever the management strategy employed. Such patients account for almost half of those treated by angioplasty (20). The recommended length of dual antiplatelet treatment of at least one year after the implantation of a drug-eluting stent is empiric and pragmatic. There have been no specific studies that deal with the problem of stopping the treatment after one year, and uncertainty about the optimal duration of dual antiplatelet therapy remains. The results of the CHARISMA study (21), involving 15 000 patients at a high risk for atherothrombosis (but most of whom were not treated with either drug-eluting or bare metal stents) are not in favor of prolonged dual antiplatelet therapy beyond one year (the risk of hemorrhage increases, with no improvement in efficacy); in this trial, however,

the excess risk of hemorrhage appeared mainly at the beginning of the treatment and after the first months of treatment the risk was no higher than that found in patients on aspirin alone (22). In contrast, there have been a number of isolated cases of very late in-stent thrombosis (up to 4 years after the implantation of a drug-eluting stent) at the moment when antiplatelet therapy is interrupted, notably prior to non-cardiac surgery; the incidence of late or very late thrombosis is about 0.6%/year (23). However, cases of late thrombosis (> 1 year) have been reported in patients still receiving dual anticoagulation therapy (24). The strategy of long-term antiplatelet therapy and the possible role of monitoring platelet function need to be investigated in prospective studies. Currently, it is not possible to give a formal recommendation to prolong or to avoid prolonging dual antiplatelet therapy to beyond a year.

3° Sub groups:

Diabetics:

The risk of restenosis after implantation of a bare metal stent and the benefits of drug-eluting stents, in terms of prevention of restenosis, are both higher in diabetic than in non-diabetic patients. In contrast, the risk of thrombosis is also greater than in non-diabetics (11). According to a meta-analysis by Stettler (9), mortality among diabetic patients during the first 4 years after the implantation of an active stent is slightly higher, but the difference is not statistically significant (OR: 1.16 for paclitaxel stents, $p = 0.55$; OR: 1.24 for sirolimus stents, $p = 0.29$, compared with bare metal stents).

Acute ST-elevation myocardial infarction:

Restenosis is less frequent following primary angioplasty for acute MI than following angioplasty for other reasons (25, 26). Implanting a drug-eluting stent to prevent restenosis therefore seems to be less necessary in these circumstances (27). Randomized studies and registries have not revealed any significant difference between drug-eluting stents and bare metal stents for mortality at one-year. Beyond one year, as shown in the data of the GRACE registry (Steg PG, presentation during the European Society of Cardiology congress 2007), a potentially increased risk among patients with a drug-eluting stent cannot be excluded.

Moreover, as primary angioplasty is performed as an emergency intervention, it is more difficult to evaluate at the time of the intervention the medium and long-term risk of hemorrhage and the ability of patients to follow the prescribed antiplatelet therapy. All of

the above data suggest that caution is required when considering the implantation of a drug-eluting stent in this particular indication.

Left main coronary artery:

Coronary artery surgery is the treatment of choice for stenosis of the left main coronary artery (28). Multicentre registries show satisfactory clinical results with drug-eluting stents during the first year (29, 30). However, until the results of ongoing randomized studies that compare drug-eluting stents with surgery become available, the use of angioplasty must remain an exception, and assessed on a case-by-case basis according to the clinical and anatomical context of each patient, notably for patients with a very high risk score for surgery (EUROSCORE or other). When angioplasty is chosen, drug-eluting stents seem to give better results in the medium term compared to conventional stents and thus seem to be preferable. As is the case for the general use of stents, the benefit/risk ratio for long-term dual antiplatelet therapy has to be assessed.

4° The cost/benefit ratio for active stents: the absence of any improvement in mortality makes it impossible to establish a cost/benefit ratio in terms of increased life expectancy. The cost/benefit ratio is thus calculated with regard to the marginal cost of avoiding myocardial revascularisation, or to the resulting improvement in quality of life. Depending on the way cost analysis is modeled in such studies, the health costs in the different countries and the acceptable marginal cost threshold to avoid an adverse event, the use of a drug-eluting stent seems to be cost-effective in the overall population of stented patients (SIRIUS medico-economic study, 31), cost-effective only in certain sub groups of patients (for example in the BASKET study in patients with multivessel disease, long lesions and narrow vessels, 32) or not cost-effective in most clinical situations (NICE 2007,3). There is still great uncertainty on this issue.

5° Not all active stents are identical

In terms of efficacy, if we consider only drug-eluting stents that are subject to reimbursement because they have been shown beneficial in terms of prevention of restenosis compared with bare metal stents, there are probable differences: the intermediate angiographic criterion « late loss », which reflects the degree of secondary proliferation either inside the stent or at the border, and which appears to correlate strongly with the « TLR » (33) is greater for paclitaxel than for sirolimus stents, significantly greater for the zotarolimus (ENDEAVOR) than the sirolimus stent (ENDEAVOR III study (34)), significantly lower for everolimus (Xience, promus) stents

than for paclitaxel stents (Spirit II and III studies (35)). These results are contested by some, notably because the difference between sirolimus and paclitaxel stents in the REALITY study (36) with regard to binary restenosis was not significant. However, with regard to the « TLR » the sirolimus stent was more effective than the paclitaxel stent (8), tended to be more effective than the zotarolimus stent (34), and again with regard to the TLR the everolimus stent was more effective than the paclitaxel stent. Finally, the results presented to the TCT 2007 congress on the direct comparison between zotarolimus and paclitaxel stents showed that the paclitaxel stent was no better than the zotarolimus stent in terms of "target vessel failure" and "TLR".

In terms of safety, because of the low power of the studies and the insufficient follow-up it is impossible to confirm or deny that an active stent is safer than another in terms of the risk of in-stent thrombosis.

6° General guidelines

Though drug-eluting stents are an incontestably effective means to reduce the risk of restenosis, real doubts remain about the risk of late thrombosis and the optimal duration of antiplatelet treatment. Because of these doubts it is necessary to weigh the benefits against the risks for every patient particularly carefully. The estimated risk of restenosis, the long-term risk of hemorrhage and the ability of the patient to follow the antiplatelet therapy meticulously must all be taken into account. By the same token, it is essential to check whether the patient is likely to undergo surgery (cardiovascular or general) in the year following stent implantation. It is also advisable to assess the risk of emergency surgery according to the status of the patient (the annual incidence of a surgical intervention among the elderly is high, while the risk of trauma-related surgery should be taken into account for certain populations at risk). The recommendations issued by Learned Societies (37) and health authorities, which are regularly updated to keep in step with studies that show the safety and efficacy of a new indication, must be the reference for everyday clinical practice. Moreover, it is essential that hospital records and discharge letters specifically mention the precise description of stent used and its type (drug-eluting or bare metal) as well as the need for combined anticoagulant therapy for at least one year, which is in keeping with the current consensus. However, in the absence of any formal scientific facts about the optimal duration of dual antiplatelet therapy, it may be reasonable to propose a shorter course of treatment (6 months) in certain specific instances, after a careful and justified assessment of the benefit/risk ratio on a case-by-case basis. Likewise, whether dual antiplatelet therapy should be continued for longer than a year must be considered for each patient. Until more precise data become

available, treatment could be prolonged in patients with particular risk factors for thrombosis, or those in whom the onset of acute thrombosis would lead to a particularly high clinical risk (stenosis of the proximal left anterior descending artery, for example), if there is no increased risk of hemorrhage. Patients with particular risks should be issued with cards carrying this information. Finally, it must be explained to patients who have received a drug-eluting stent that their antiplatelet therapy must under no circumstances be interrupted without the prior agreement of a cardiologist. All of the above implies that a structured comprehensive discussion must take place between the patient and the interventional cardiologist: in every case, the cardiologist must bear in mind that he or she is treating a patient, and not just his/her coronary arteries.

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