Active stents in diabetic patients

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SUMMARY
In the treatment of coronary stenosis, evolution after PTCA is not as good in diabetic patients compared to non diabetic ones, whatever the treatment used. We now have data of large clinical studies which show good results of drug loaded stents in diabetic patients, especially with either a cytostatic drug (sirolimus) or a cytotoxic one (paclitaxol). In the RAVEL study, among the 44 diabetic patients, 19 had sirolimus stenting with a restenosis rate of 0% vs a restenosis rate of 40% for the 25 patients with standard stents. In the 279 diabetic patient group of the SIRIUS study, the restenosis rate (50% or more stenosis rate) was 17.6% when sirolimus stenting was used vs 50.5% for the patients with standard stenting and at 9 months and target lesion revascularisation was from 22.3% with bare metal stents, compared to 6.9% with sirolimus eluting stents. In the TAXUS IV study, the advantage was evident in diabetic patients with a restenosis rate 80% lower in patients treated with oral anti diabetic therapy and 82% in patients treated with insulin. In the TAXUS VI study, the target lesion revascularisation rate of diabetic patients was 2.6% when taxus MR (modified release) was used, vs 22.6% with standard stents.

The event which until now made PTCA different from surgery was restenosis, especially in diabetic patients. The analysis of use of recent active stenting registries has shown that diabetic patients have now much better long term results than previously reported.

Key-words: Diabetes · Coronary stenosis · Percutaneous transluminal coronary angioplasty (PTCA) · Drug loaded stents.

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 RESUMÉ
Utilisation de stents actifs chez les patients atteints de diabète sucré

L’évolution après angioplastie percutanée transliminale pour sténose coronaire est moins bonne chez les diabétiques, quelque soit le traitement utilisé. Sont actuellement disponibles les résultats d’études portant sur des séries importantes, et montrant chez les diabétiques l’efficacité de stents actifs ou « coatés », avec des médicament cytostatique comme le sirolimus, ou cytotoxique comme le paclitaxol. Dans l’étude Ravel, parmi les 44 patients diabétiques, les 19 patients qui avaient un stent « coaté » au sirolimus avaient un taux de resténose de 0 %, alors que ce taux était de 40 % chez les 25 patients qui avaient reçu un stent non actif. Dans le groupe de 279 patients diabétiques de l’étude Sirius, le taux de resténose (50 % ou plus) était de 17,6 % avec un stent au sirolimus, et de 50,5 % avec un stent non actif. À 9 mois, le pourcentage de perméabilité de la lésion traitée était de 23,3 % avec les stents non actifs, et de 6,9 % avec les stents au sirolimus. Dans l’étude Taxus IV, le bénéfice était évident chez les diabétiques, avec un taux de resténose plus faible respectivement de 80 % chez les patients traités par antidiabétiques oraux et de 82 % chez les patients qui recevaient une insulinothérapie. Dans l’étude Taxus VI, chez les patients diabétiques, le taux de perméabilité de la lésion traitée était de 2,6 % avec le stent au taxus MR (libération modifiée), et de 22,6 % avec les stents standard.

L’événement qui faisait jusqu’alors la différence entre angioplastie transliminale et pontage coronaire était la resténose. L’analyse des registres des essais réalisés avec des stents actifs indique que le pronostic à long terme s’est considérablement amélioré chez les diabétiques, par rapport aux résultats antérieurs.

Mots-clés : Diabète · Sténose coronaire · Angioplastie percutanée transliminale · Stents actifs.

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If restenosis could be prevented, percutaneous transluminal coronary angioplasty (PTCA) would certainly be the treatment of choice for most patients including those with multivessel disease. Many studies have shown that clinical results post coronary bypass or post dilation after 1 to 2.5 years were the same for non diabetic patients, except for a restenosis rate of 20% post PTCA.

Diabetes is associated with a high risk of morbidity and mortality compared to non diabetic patients. In the treatment of coronary stenosis, evolution after PTCA is not as good in diabetic patients compared to non diabetic ones, whatever the treatment used. In diabetic patients, a prothrombotic state, endothelial dysfunction, expression of endothelial growth factors and matrivial expression are all more frequent. On the other hand, diabetes is more frequent every year among patients treated with PTCA: in our cathlab, more than 20% of the patients are diabetic. The large BARI study was the first showing a higher mortality in PTCA treated diabetic patients compared to those treated with coronary bypass surgery, or to non diabetic patients treated by PTCA [1]. The follow up was 1 to 8 years: the global mortality rate during this period was 33.7% in the PTCA treated diabetic patient group vs 18.9% in the surgically treated diabetic patients. The benefit in this latter group was essentially obtained in those patients treated with internal mammary arterial graft, and was not observed in the patients treated only with venous grafts. The same benefit was observed in other studies (EAST, CABRI) [2, 3]. Registry results showed less pronounced differences mostly because the choice between dilation and surgery was better adapted for the patients.

Prevention of restenosis with active stents

Sirolimus stents

This stent delivers a medication which stops the cellular cycle in the G1 phase and prevents smooth cell proliferation. Sirolimus (rapamycin) is a micro organism first used as an antibiotic. Its development was stopped due to its immune suppressive action. It is cytostatic and not cytolytic. Novel uses include perfusion during kidney transplantation (anti inflammatory and anti proliferation effect) and certain oncological indications. It also blocks the effects of cytokines. It has a long half life and is active at low concentrations, much lower than the concentrations used in oncology, which may explain the absence of toxic effects. Sirolimus is put on the surface of the stent using a polymer. No special care is necessary in using this stent. 3 large clinical series studied this stent.

a) A first study was performed in men by 2 groups, one from Brazil and one from the Netherlands [4]. Forty five patients were included. The clinical, angiographic and intracoronary ultrasound follow up showed that the cellu-lar antiproliferative effect of sirolimus is spectacular, since coronary restenosis was absent in the 45 patients. The mean obstruction rate seen by ultrasound examination was 2% of the cross sectional area at 12 months. At 2 years, the follow up was very good with one secondary revascularisation of the studied vessel out of 30 patients, one death due to cerebral vascular attack, and one acute myocardial infarction due to the evolution of the coronary disease on a different artery than the one which had been treated. In this 45 patient series, 14% were diabetics, with no particularity compared to large evaluation series.

b) RAVEL (RAandomised VElocity artery Lesion) [5]: this randomised study included 238 patients with a mean follow-up of 5 years. Only one de novo lesion was present. The vessel diameters were 2.5 to 3.5 mm and the lengths of the lesions were lower than or equal to 18 mm. One hundred and twenty patients were in the active stenting group and 118 in the non active stenting group. The published results showed the following data:

- no decrease of diameter in the treated group compared to the control group (0.01 ° 0.33 vs -0.8 ° -0.53 mm P < 0.0001)
- no restenosis in the treated group (0 vs 26% P < 0.0001)
- spectacular reduction of adverse effects (death, myocardial infarction, revascularisation): 3.3% in the treated group vs 27.1% in the control group
- at 1 year, the revascularisation rate of the dilated vessels was 0% in the sirolimus treated group vs 22.9% in the control group. The rate of major cardiovascular events was 6% vs 29.3% (P < 0.001). Among the 44 diabetic patients, 19 had sirolimus stenting with a restenosis rate of 0% vs a restenosis rate of 40% for the 25 treated with standard stents.

c) SIRIUS [6]: 1058 patients were included in this US study. At 6 months, the inside the stent restenosis rate was 3.2% in the sirolimus stenting group vs 35.4% in the control group. The total restenosis rate was still much lower when near the stent restenosis was taken in account (8.9 vs 36.3%). In the 279 diabetic patients group, 131 received sirolimus-eluting stents and 148 patients received bare metal stents. The restenosis rate (50% or more stenosis rate) was 17.6% when sirolimus stenting was used vs 50.5% for the patients with standard stenting. At 9 months, target lesion revascularisation was reduced in diabetic patients from 22.3% with bare metal stents to 6.9% with sirolimus eluting stents (P < 0.001). Major adverse cardiac events were reduced in diabetic patients from 25% with bare metal stents to 9.2% with sirolimus eluting stents (P < 0.001). However, among patients receiving sirolimus-eluting stents, there remained a trend towards a higher frequency of repeat interventions in diabetic patients (6.9%) compared to non diabetic ones (2.9%), particularly in insulin requiring patients (6).

Paclitaxol stents

Contrary to sirolimus, paclitaxol is a cytotoxic drug and not a cytostatic one. Paclitaxol (Taxol) is fixed to the stent either directly or with the use of a biocompatible polymer.
Paclitaxel is a drug that links to the tubular system and stabilises microtubules, preventing polymerisation and cell division. This drug is not soluble in water and the used doses are 32 to 400 mg, which are well below toxic levels. The best results until now were those with the Taxus stent from Boston Scientific, published in several studies.

- TAXUS 1 [7]: 61 patients were included in this randomised study involving native arteries. At 12 months, only 1 revascularization of the treated artery was observed in the paclitaxol group due to atheromatous progression away from the stent. The restenosis rate was 3.2% in the paclitaxol group vs. 13.3% in the control group with a standard metallic stent.

- TAXUS 2 [8]: in this trial, 3 groups were present: gr1 (131 patients with slow release of paclitaxol); gr2 (136 patients with standard stenting); gr3 (135 patients with paclitaxol stents and shorter release). The revascularisation rates due to restenosis of the treated arteries were 6% (gr1), 16% (gr2) and 4% (gr3) and the rates of evolution without events were 91.1% (gr1), 80.2% (gr2) and 92.2% (gr3).

- TAXUS 3 [9]: 30 patients with coronary restenosis were included in this non randomised study, with a follow-up for 28 patients: no intrastent thrombosis was observed, the binary rate of restenosis was 16% (4/25), 3 times occurring on a non paclitaxol stent or between 2 stents. The rate of deleterious events at 6 months was 28.6%.

- TAXUS 4 was a double blind randomised US study comparing slow release paclitaxol stenting vs normal stents in 1326 patients. The 9 month restenosis rate was 4.7% with the paclitaxol stent vs 12% with the standard stent (revascularisation rate 3% vs 11.3%, death + myocardial infarction + target vessel revascularisation 8.5% vs 15%). In diabetic patients, the benefit was very high, with a restenosis rate 80% lower in patients treated with oral anti diabetic therapy and 82% in patients treated with insulin.

- TAXUS 5 included 1108 patients, with a taxus stent treated subgroup.

- TAXUS 6 evaluated the results in long lesions. Eighty-nine patients out of 446 were diabetic. The target lesion revascularisation rate of the diabetic patients was 2.6% when taxus MR (moderate release) was used, vs 22.6% with standard stents (P < 0.0103). These good results are present in both patients treated with oral anti diabetic therapy and in patients treated with insulin (not published).

**What can be concluded from those results which seem to open a new era in the history of coronary angioplasty?**

It is well known that first results may not be confirmed in the long term due to new events which were not observed early on. The first results with bioactive stents are very good, with the use of sirolimus and paclitaxel (fig. 1). This was not the case with the use of batimastat and actinomycin D. We are waiting for the results with tacrolimus. On the other hand, studies are now being performed to evaluate the use of insulin in long term follow-up after PTCA. In a recent randomised study of 93 diabetic patients, a positive effect on restenosis has been reported with rosiglitazone, the restenosis rate being 47% in the control group vs 12% in the treated group (P < 0.001) [10].

To date, no large series with diabetic patients have been published, and the optimal duration of antiplatelet therapy to prevent the risk of thrombosis due to delay in re-endothelialization is still discussed. It is now clear that antiplatelet

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**Figure 1**

Long diffuse 30 mm stenosis of the proximal and middle segments of the left anterior descending artery, before dilatation (A) and 6 months after dilatation using 2 long active stents. No restenosis (B).
therapy using clopidogrel must be used with aspirin for at least 9 months. In the 2 preliminary studies with sirolimus, no events were reported within the 2 first months, and there was no difference during the follow up at both 18 months and 2 years. However ultrasound examinations have shown a delay of re-endothelialization and the problem of thrombosis is not completely solved because of reported individual cases during the 2 months following stenting.

If other randomised studies could confirm the quasi non-occurrence of restenosis (the a-sirius study for longer stenosis and many other studies being now performed), the use of PTCA would then be completely changed. Limitations which may exist for the treatment of multivessel or diabetic patients would no exist due to the non-occurrence of restenosis, although the evolution of the atheromatous and thrombotic lesions would still have to be managed with medication. Many of the recent studies comparing the long term results of bypass surgery and PTCA have shown no differences for the death rate and the reinfarction rate. The event which until now made PTCA different from surgery was restenosis, especially in diabetic patients. The analysis of recent active stenting registries shows that diabetic patients have much better long term results than previously reported. With the use of the new anti-platelet therapy, long term results of PTCA treatment are very similar to the results of surgery, without the risk of long term venous graft degeneration.

Lastly, the use of PTCA may allow for delaying of surgery which may be of great benefit for these patients. If these data are confirmed, PTCA cardiology would once more benefit from recent progress and go beyond its previous limitations. All those expectations seem real and should be confirmed, with the desire that the prohibitive price of these new stents will not limit their use.

References

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