SCIENTIFIC LETTER

Complementary effects of sirolimus-eluting stents and glycoprotein IIb/IIIa inhibitors for percutaneous coronary intervention in diabetic patients: one-year follow up of a single-centre registry

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Patients with diabetes mellitus have an increased risk of cardiac events after percutaneous coronary intervention (PCI). As drug-eluting stents (DES) reduce restenosis and glycoprotein (Gp) IIb/IIIa inhibitors reduce the risk of death and myocardial infarction, the use of both treatments may be complementary and be a powerful tool for reducing cardiac events after PCI in diabetic patients. On the other hand, there are some concerns about the rate of stent thrombosis with DES, and some recent reports have pointed to diabetes as one of the risk factors.¹

We therefore tested the hypothesis that Gp IIb/IIIa inhibitors may reduce the rate of major cardiac events after PCI with sirolimus-eluting stents (SES) in patients with diabetes mellitus.

METHODS

This was a prospective non-randomised single-centre registry, including all consecutive patients with diabetes undergoing PCI with at least one SES at our institution from April 2002 to April 2003.

One-year clinical follow up was assessed in all patients. Patients were divided into two subgroups according to the periprocedural use of Gp IIb/IIIa inhibitors (99 patients in the group with Gp IIb/IIIa inhibitors and 104 in the group without).

The intervention strategy was entirely dependent on the operator and was performed according to standard guidelines. Patients were given a loading dose of 300 mg of clopidogrel immediately after the procedure and were taking aspirin and clopidogrel daily thereafter, for at least three months.

We evaluated a clinical end point defined as the combined incidence of the major adverse cardiac events (MACE) death, non-fatal myocardial infarction and target vessel revascularisation (TVR) at the one-year follow up.

Data were statistically analysed with SPSS V.11.0 software (SPSS Inc, Chicago, Illinois, USA) by χ^2 test, Student's unpaired t test, log rank test and Cox proportional hazards models as appropriate.

RESULTS

Of 1310 patients undergoing PCI at our institution from April 2002 to April 2003, 203 (15.5%) had diabetes and were treated with at least one SES. The Gp IIb/IIIa inhibitor used most often was abciximab (83%). Patients with acute coronary syndromes were given eptifibatide (13%) and tirofiban (4%) upstream before going to the cath lab.

The two groups of patients did not differ significantly in the baseline characteristics. However, more of the patients treated with Gp IIb/IIIa inhibitors were current smokers

(20.4% v 12.1%, $p = 0.16$) and had PCI in the setting of an acute coronary syndrome (40.8% v 28.3%, $p = 0.08$), and fewer of them had peripheral arterial disease (9.7% v 18.2%, $p = 0.12$) or a previous stroke (2.9% v 10.1%, $p = 0.07$).

Regarding the angiographic characteristics, patients treated with Gp IIb/IIIa inhibitors had a higher rate of PCI on a total occlusion (16.3% v 4.0%, $p = 0.008$), a higher mean total stent length (42.6 v 29.3 mm, $p = 0.002$) and more stents ≥ 33 mm implanted (41.3% v 24.2%, $p = 0.015$). Other important differences between the two groups of patients were the higher numbers of implanted stents (2.5 v 1.9, $p = 0.021$) and SES (2.1 v 1.6, $p = 0.028$) per patient in the group treated with Gp IIb/IIIa inhibitors.

Complete one-year follow-up information was available for all patients. The cumulative incidence of MACE at one year was significantly lower in the patients treated with Gp IIb/IIIa inhibitors (8.7% v 23.2%; hazard ratio (HR) 0.34, 95% confidence interval (CI) 0.16 to 0.74, $p = 0.006$). There was a trend for a lower combined incidence of death and non-fatal myocardial infarction (4.8% v 12.1%; HR 0.38, 95% CI 0.14 to 1.09, $p = 0.072$) and for a lower target lesion revascularisation rate (1.9% v 7.1%; HR 0.26, 95% CI 0.05 to 1.23, $p = 0.089$) in the Gp IIb/IIIa inhibitor treated group. The rate of TVR, which includes lower target lesion revascularisation, was significantly lower in the Gp IIb/IIIa inhibitor group (4.8% v 13.1%; HR 0.34, 95% CI 0.12 to 0.95, $p = 0.040$). Two insulin-requiring patients in the group not treated with Gp IIb/IIIa inhibitors presented with subacute stent thrombosis (2.02%), on day 6 and day 8 after the procedure. Both patients had a loading dose of 300 mg of clopidogrel immediately after the procedure and were taking aspirin and clopidogrel daily thereafter. No further thrombotic stent occlusion or unexplained sudden cardiac deaths were observed in the late follow up.

Multivariable Cox proportional hazards analysis identified Gp IIb/IIIa inhibitor use to be independently associated with a reduced risk of MACE (adjusted HR 0.30, 95% CI 0.13 to 0.67, $p = 0.003$) (fig 1) and of death and myocardial infarction (adjusted HR 0.34, 95% CI 0.12 to 0.99, $p = 0.048$).

The incidence of death, non-fatal myocardial infarction and TVR was consistently lower in patients treated with Gp

Abbreviations: CARDia, Coronary Artery Revascularization in Diabetes; DES, drug-eluting stents; Gp, glycoprotein; HR, hazard ratio; ISAR-REACT, Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention; RESEARCH, Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital; SES, sirolimus-eluting stents; TVR, target vessel revascularisation

Figure 1 Major adverse cardiac event-free survival at one year. CI, confidence interval; Gp, glycoprotein.

IIb/IIIa inhibitors across the different subgroups analysed. The benefit was higher in insulin-treated patients.

DISCUSSION

This was a clinical study with consecutive patients in routine daily practice that evaluated the benefit of Gp IIb/IIIa inhibition in the context of SES in patients with diabetes mellitus. The use of Gp IIb/IIIa inhibitors was associated with a reduction in the combined incidence of death and myocardial infarction and the overall combined MACE. To the best of our knowledge, no other data have been published on this issue.

Although DES are a powerful tool against restenosis, they are not expected to have a significant impact on the rate of death and myocardial infarction after PCI.² Gp IIb/IIIa inhibitors, by having a favourable effect on these major events, can therefore exert an important complementary effect, especially in high-risk patients with diabetes. In the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) registry, there was a 16% rate of Gp IIb/IIIa inhibitor administration. Diabetes mellitus was an independent predictor of both MACE and TVR, and patients with diabetes were one of the subgroups in which the benefit of SES did not reach significance.³ In the ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment) study, which found no benefit of abciximab in low- to intermediate-risk patients undergoing elective PCI after pretreatment with 600 mg of clopidogrel, patients with diabetes under medical treatment were excluded from enrolment.⁴

Insulin-treated patients with diabetes have been one of the most difficult groups of patients to treat with DES. In our registry, the benefit of the Gp IIb/IIIa inhibitor was higher in the insulin-treated patients and in other high-risk subgroups such as patients with multivessel disease or acute coronary syndromes and patients receiving 33 mm or longer stents. Insulin-requiring patients mainly have type 2 diabetes who became insulin dependent in a later stage of disease progression. This is a particularly diseased subgroup of patients, with a more extensive burden of atherothrombotic disease. In these patients, the high incidence of death, myocardial infarction and repeat PCI at different sites may offset the benefit of local interventions, even with very effective DES that, at best, reduce restenosis.

Although in randomised clinical trials the reported rate of DES thrombosis has been within the expected range, a substantially higher incidence was recently reported in registries of real-world patients, and diabetes was identified as one of the independent predictors.¹ In our registry, the two cases of stent thrombosis were observed in the group undergoing PCI without a Gp IIb/IIIa inhibitor, and the patients were treated with insulin. Although this study is underpowered to look for differences in this infrequent event, the lack of a single case of SES thrombosis in the high-risk group of patients with diabetes taking Gp IIb/IIIa inhibitors underscores the potential benefit of these agents in this context.

In the CARDia (Coronary Artery Revascularization in Diabetes) trial, up-to-date coronary artery bypass grafting is being compared with optimal PCI, in which the use of abciximab was recommended.⁵ This is one of the ongoing randomised trials designed to evaluate the best revascularisation strategy in patients diabetes that are expected to consider these issues in a more definite manner.

This was a single-centre registry and not a randomised study with a 2 × 2 factorial design, which would have been better suited for evaluating the complementary effects of two different interventions. The baseline characteristics of the two groups were well matched but there were some differences in the angiographic and procedural characteristics. Nevertheless, these differences were in favour of the group not receiving a Gp IIb/IIIa inhibitor, and this could have underestimated the benefit of these agents.

The use of Gp IIb/IIIa inhibitors in the context of SES in patients with diabetes gave superior clinical results, due to a significant reduction in the combined incidence of death, myocardial infarction and TVR. This benefit was greater in insulin-treated patients with diabetes. This, and the lack of a single case of SES thrombosis in this high-risk group of patients who were given a Gp IIb/IIIa inhibitor during stenting, seems to warrant a randomised controlled trial to examine this issue.

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