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Costs and effects of combining stenting and abciximab (ReoPro®) in daily practice

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Abstract

Aim: The combined use of stents and abciximab in percutaneous coronary intervention has been evaluated in the EPISTENT trial. However, the clinical and economic findings in trials are not necessarily generalisable to a general population setting. We conducted a study in daily clinical practice comparing stented and non-stented patients undergoing coronary angioplasty with abciximab administration. Furthermore, we compare our results with the findings of the EPISTENT trial. *Methods:* From 1995 to 1999, refractory unstable patients scheduled for angioplasty and receiving abciximab in a Dutch regional hospital were followed prospectively for 6 months. Total costs were considered in addition to 2 composite clinical endpoints: (1) death or myocardial infarction (MI); and (2) death, MI, or any revascularisation procedure (major adverse cardiac events, MACE). *Results:* Stented patients ($N=101$) experienced less MACE than non-stented patients ($N=83$) (6.9% vs. 16.9%, OR=0.37, $P=0.04$). The total costs were similar for stented and non-stented patients (EUR 7 844 vs. EUR 7 904, $P=0.93$). Adjustment for baseline characteristics yielded similar results, although significance subsided. The relative risk reduction of 44% that we found, closely resembles the 42% that was found in the EPISTENT trial. *Conclusions:* In everyday practice, as in the EPISTENT trial, the addition of a stent to abciximab treatment does seem to reduce the risk of MACE by about 40% at no additional costs.

Keywords: Angioplasty; Stents; Abciximab; Glycoprotein IIb/IIIa receptor blockade; Daily clinical practice; Economic evaluation

1. Introduction

A series of randomised controlled trials (RCTs), which directly compared elective stent implantation with balloon angioplasty, have shown that stenting reduces the need for repeat revascularisation procedures [1–7]. However, there is an ongoing debate about the respective merits of RCTs and observational studies in the assessment of treatments [8–12]. The results of RCTs are not necessarily generalisable to a general population setting. For example, it has been shown that patients included in RCTs of cardiovascular drugs have different characteristics from the people who use these products in daily practice [13], and also that the treatment effects of antihypertensive therapy in daily practice may be different from the effects in RCTs [14,15].

Also, the spectrum of patients undergoing a percutaneous coronary intervention in current practice may be much broader than the patients included in clinical trials, since the trials applied strict clinical

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and anatomical entry criteria. Therefore, it is important to evaluate the effectiveness of stenting under circumstances of everyday clinical practice [11,12]. This has been done already in several observational studies. These studies have found that the widespread use of coronary stents coincided with improved short-term outcomes and reduced or equal revascularisation rates during follow-up [16–18].

Over the recent years GP IIb/IIIa receptor blockers became available, most notably abciximab (ReoPro®). In RCTs abciximab has been shown to be effective in reducing the rate of myocardial infarction (MI) and the necessity for urgent revascularisation in patients undergoing percutaneous transluminal coronary angioplasty (PTCA). Given the ''separate'' positive effects of stenting and abciximab — stents on revascularisation-free and abciximab on MI-free survival — the ''Evaluation of Platelet IIb/IIIa Inhibitor For Stenting Trial (EPISTENT)'' study was performed to evaluate whether the combination of abciximab and stenting would lead to a synergistic effect. In this American/Canadian study, the combined use of stents and abciximab indeed turned out to be the superior treatment compared both to abciximab administration alone and to stenting alone [19].

However, again the question remains if this finding applies to everyday clinical practice in Europe as well. In daily practice, does the implantation of a stent have additional value when the patient is already receiving abciximab treatment? As far as we know, this question has not yet been addressed. Here we present a study which included all patients from a regional hospital in the Netherlands (Alkmaar) who were administered abciximab and who were subsequently transported to one of two specialised centres to undergo PTCA either with or without stent implantation. We compare cardiovascular outcome events and costs between stented and non-stented patients. Subsequently, we compare our findings to the findings in the EPISTENT study.

2. Methods

From June 1995 to June 1999, all PTCA patients that received abciximab were followed consecutively for 6 months. Characteristics such as age, gender, Braunwald score, previous PTCA and other related risk factors were registered at baseline. If the PTCA procedure involved the same vessel that had already been the target of a previous procedure, this is noted as ''restenosis''. Approximately 6 h after the intervention, creatine kinase and its MB isoenzyme levels in the blood were determined. At 1 month and at 6 months after the procedure the patients revisited the regional hospital for a clinical check-up, including an electrocardiogram (ECG).

The following events were recorded: death, myocardial infarction (MI), repeated transluminal coronary intervention, and coronary artery bypass graft (CABG). We used the same criteria as in the CAPTURE and the EPISTENT trial to define a MI [19,20]. Two composite endpoints were considered: (1) death or MI; and (2) death, MI, or any revascularisation procedure (major adverse cardiac events, MACE). Costs were calculated by multiplying the number of events recorded in the trial database by the estimates of costs per event. The estimates of these unit costs are derived from The Netherlands and are based on the economic evaluation study from the BENESTENT II trial [3].

Baseline characteristics, outcomes and costs were compared using Fisher's Exact test and the Student's *t*-test. (Adjusted) odds ratios for outcomes were estimated using logistic regression.

3. Results

From 1995 to 1999, 184 patients were administered abciximab and then transported for PTCA. Of these patients 83 underwent plain balloon angioplasty and 101 were stented. Baseline characteristics are shown in Table 1. There were no significant differences. However, patients receiving a stent tended to be more often male, hypercholesterolemic, diabetic and smoker. On the other hand, in this group there is also a tendency towards fewer patients with restenosis or a previous MI.

Cardiovascular outcomes for stented and non-stented patients are shown in Table 2. The risk of MACE is significantly lower for stented patients compared to patients who received only balloon angioplasty (6.9% vs. 16.9%, OR=0.37, $P=0.04$). This improved outcome is mainly driven by a decrease in the number of revascularisations. Age,

Table 1
Baseline characteristics of non-stented and stented patients in our study[a]

	Non-stented	Stented	*P*-value
Number	83	101	
Age (years)	63.5±2.4	62.8±2.2	0.67
Male (%)	68.7%	80.2%	0.09
Braunwald score			0.18
1b	0.0%	3.0%	
2b	16.9%	25.7%	
2c	24.1%	24.8%	
3b	27.7%	26.7%	
3c	31.3%	19.8%	
Number of vessels	1.58±0.16	1.64±0.15	0.81
Hypertension (%)	32.5	27.7	0.52
Hypercholesterolemia treatment (%)	60.2	66.3	0.44
Diabetes (%)	6.0	9.9	0.42
Smoking (%)	30.1	36.6	0.43
Family history (%)	43.4	48.5	0.55
Previous MI (%)	60.2	56.4	0.65
Previous PTCA (%)	14.5	7.9	0.23
Restenosis (%)	6.0	2.0	0.25
Previous CABG (%)	8.4	11.9	0.48

[a] MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft.

gender, Braunwald score, previous PTCA, restenosis, previous CABG and previous MI were identified as confounders and were subsequently adjusted for. After adjustment the occurrence of MACE after stenting is still decreased compared to plain balloon angioplasty, although not statistically significant (OR=0.56, $P=0.28$). General risk factors for developing cardiovascular diseases (CVD), such as hypertension, diabetes, smoking, and a history of CVD in the family, were not adjusted for, since their influence was negligible.

Table 3 shows that, although the implantation of a stent increases the cost of the initial procedure with about EUR 1250 per patient (from EUR 3 959 to EUR 2 718), the total costs after 6 months of follow-up are similar for stented and non-stented patients (EUR 7 844 and EUR 7 904 respectively, $P=0.93$).

In Table 4 the baseline characteristics of the patients in our study are compared to the patients in the EPISTENT trial. In our study there are less patients with hypertension or diabetes, and more patients who had had a previous MI. Nonetheless, the baseline rate of events without stent implantation is similar in our study as in EPISTENT (death/MI 3.6% respectively 7.8%, $P=0.27$; MACE 16.9% respectively 20.4%, $P=0.56$). As shown in Table 5, the relative risk reductions (RRR) and the numbers needed to treat to avoid one event (NNT) that we found in our study are similar to the findings in EPISTENT. Looking at death and MIs, 35–43 patients need to be stented to avoid one event; if revascularisations are considered as well, about 13 patients need to be stented to avoid one event.

4. Discussion

In our observational study in daily clinical practice, the number of MACE during 6 months of follow-up improved by about 44% after stenting compared to plain balloon angioplasty, whereas the direct medical costs are similar in both groups. Our results correspond very well to the findings in the EPISTENT trial, where a reduction of 42% was found in the incidence of death, MI and target-vessel revascularisations. The difference between our study including

Table 2
Odds ratios for clinical endpoints at 6 months of stented compared to non-stented patients in our study[a]

	Non-stented	Stented	OR unadjusted	OR adjusted[b]
Deaths (%)	1.2	0.0	–	
MIs (%)	2.4	1.0	0.41 (0.03–4.5)	0.30 (0.02–4.4)
Re-PTCA/re-stent (%)	9.6	5.0	0.49 (0.15–1.6)	0.73 (0.19–2.7)
CABG (%)	6.0	2.0	0.32 (0.06–1.7)	0.48 (0.06–4.0)
Death or MI (%)	3.6	1.0	0.27 (0.03–2.6)	0.20 (0.01–2.8)
MACE (%)	16.9	6.9	0.37 (0.14–0.96)	0.56 (0.19–1.7)
Costs (EUR)	7908	7844		

[a] MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft; MACE, major adverse cardiac event.
[b] Adjusted for age, gender, Braunwald score, previous PTCA, restenosis, prev. CABG and prev. MI.

Table 3
Costs at 6 months of stented compared to non-stented patients in our study[a]

	Incidence of events		Unit costs (EUR)	Costs per patient (EUR)	
	Non-stented	Stented		Non-stented	Stented
Initial procedure			2718/3959[b]	2718	3959
Abciximab (3 vials)			1041	1041	1041
Additional stents	0	0.20	1354	0	268
Hospital stay (days per patient)					
CCU or ICU	0.92	0.68	969	887	662
other	5.17	3.38	469	2424	1583
Revascularisation	9.64%	4.95%	3304/3222[b]	318	160
CABG	6.02%	1.98%	8622	519	171
				7908	7844

[a] CCU, coronary care unit; ICU, intensive care unit; CABG, coronary artery bypass graft.
[b] Unit costs for non-stented and stented patients respectively.

Table 4
Baseline characteristics of patients in our study and of patients in the EPISTENT trial[a]

	Our study	EPISTENT	*P*-value
Number	184	1590	
Age (years)	63.2±1.6	60±0.5	
Male (%)	75.0	75.3	0.93
Hypertension (%)	29.9	51.1	<0.001
Diabetes (%)	8.2	20.0	<0.001
Smoking (%)	33.7	35.7	0.63
Previous MI (%)	58.2	48.9	0.02
Previous CABG (%)	10.3	8.0	0.26

[a] MI, myocardial infarction; CABG, coronary artery bypass graft.

all revascularisations in the composite endpoint, and EPISTENT including only target-vessel revascularisations, is negligible since the vast majority of all revascularisations are indeed target-vessel revascularisations [19,21,22]. The fact that the reduction of MACE in our study does not remain significant after adjustment for baseline characteristics is most likely due to the small sample size. The indication as such, that the combined usage of stents and abciximab leads to improved event-free survival in daily practice in Europe, is not a guarantee for widespread use. Many hospitals face budgetary constraints and the use of stents initially is associated with increased costs. However, our study suggests that these additional costs are off-set by savings through a reduction in the number of revascularisations and MIs during follow-up.

An important limitation of our study is that stenting was not randomly assigned, but decided upon by physicians. This may have introduced bias. Despite adjustment for a large number of potential confounding factors, residual confounding due to unmeasured factors cannot be excluded.

In sensitivity analyses of the influence of differences in baseline characteristics on the estimates of the odds ratios, it turned out that previous coronary interventions or MIs have more influence than general risk factors for developing CVD, such as hypertension, smoking and a family history of CVD. Adjustment for diabetes did not influence the OR either. Diabetes is often mentioned as an indicator for inferior outcomes after PTCA [23,24]. In our study

Table 5
Relative risk reduction (RRR), 6 months absolute risk (AR_{6m}), and 6 month number-needed-to-treat (NNT_{6m}) for combined events in our study and in the EPISTENT trial[a]

	Our study			EPISTENT[b]		
	RRR (%)	AR_{6m} (%) non-stented/ stented	NNT_{6m}	RRR (%)	AR_{6m} (%) non-stented/ stented	NNT_{6m}
Death/MI	80 (−180–99)	3.6/0.72	35 (8-NA)	31 (−5–54)	7.8/5.5	43 (24-NA)
MACE	44 (−70–81)	16.9/9.5	13 (7-NA)	42 (24–56)	20.4/12.8	13 (9–20)

[a] MI, myocardial infarction; MACE, major adverse cardiac event; NA, not applicable since OR included one.
[b] In EPISTENT only target-vessel revascularisations are included in MACE, while we included all revascularisations in our study.

group there are 15 diabetes patients; the percentage of MACE occurring among them did not differ significantly from the non-diabetics (11.8% in non-diabetics vs. 6.7% for diabetics, $P=1.0$).

The issue of the additional value, in actual clinical practice, of stent implantation in PTCA patients who are already administered abciximab, remains an important topic to be addressed. In a relatively small study we found a beneficial effect of stenting, which is very comparable to the findings in the EPISTENT trial. In everyday practice, the addition of a stent to abciximab treatment does seem to yield additional benefit. However, this finding needs to be confirmed in larger scale studies.

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