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Cost-efficacy in interventional cardiology

Results from the EPISTENT study

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Aims The EPISTENT study has demonstrated that the combined use of abciximab and stenting as an adjunct to PTCA leads to increased event-free survival compared to either using abciximab or stenting alone. However, this combined strategy may be costly and the additional costs have to be weighted against the additional effects.

Method and Results The 6-months efficacy data from the EPISTENT study are combined with Dutch estimates of unit costs. Adding a stent to a procedure with abciximab further decreases the number of revascularizations at an extra cost of Euros 12 000 (95% upper limit (u.l.) Euros 31 000) per additional major adverse cardiac event-free survivor. Adding abciximab to a stenting procedure decreases the incidence of myocardial infarctions at an extra cost of Euros 13 000 (95% u.l. Euros 27 000) per additional myocardial infarction-free survivor. In the subgroup of diabetics, adding abciximab improves revascularization rates as well, resulting in a cost-efficacy rate of Euros 2000 (95% u.l. Euros 25 000) per additional MACE-free survivor, with uncertainty regions indicating potential costs savings.

Conclusion The combination of stenting and abciximab costs about Euros 13 000 to avoid one event after PTCA. In diabetic patients the strategy may be cost-saving.
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Key Words: Cost-effectiveness, platelet aggregation inhibitors, stents, clinical trials, diabetes mellitus

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Introduction

Over the last decade at least two technologies have changed the face of interventional cardiology. First, intracoronary stents, which have been shown to reduce the need for repeat revascularizations by 20%–50%[1–7]. Second, the GP IIb/IIIa receptor blockers, most notably abciximab (ReoPro®), which have been shown to be effective in reducing the rate of myocardial infarction and the necessity for urgent revascularization in patients undergoing percutaneous transluminal coronary angioplasty (PTCA)[8–11]. Both technologies are now common practice, stents probably more than abciximab, as in most American and European institutions 60%–90% of all angioplasty cases now involve stent implantation[12].

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Given the 'separate' effects of stenting and abciximab — stents on revascularization-free and abciximab on myocardial infarction-free survival — the question that needed to be addressed was whether their combination would lead to a synergistic effect. This was done in the 'Evaluation of Platelet IIb/IIIa Inhibitor For Stenting Trial (EPISTENT)' study. Here, three treatments were compared: (1) elective stenting and placebo, (2) elective stenting and abciximab, and (3) balloon angioplasty with abciximab. The combined use of stents and abciximab turned out to be the superior treatment, showing both an effect on myocardial infarctions and early re-PTCAs due to the use of abciximab, and effects on late revascularizations due to the use of stents[13,14].

Nowadays, the fact that the combination, stents with abciximab, has been shown to lead to a significant improvement in event-free survival, or even survival, is not a guarantee for widespread use. Many hospitals, especially European hospitals, face budgetary constraints and the use of stents plus abciximab are associated with additional costs. In these cases,

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questions may be raised about the balance between the additional costs and the additional efficacy. Additionally, when assessing this balance, the question may not only be whether to treat patients with this combination, but also whom to treat. As such, finding that the combination of stenting and abciximab proved to be especially valuable in diabetic patients was important[15]. Diabetes is an important determinant of restenosis and the need for revascularizations after conventional PTCA. In a subgroup analysis of EPISTENT, however, diabetics in the stent–abciximab group had a similar target revascularization rate after 6 months compared with non-diabetic patients in the same group. In the diabetic cohort, there was a >50% reduction in the 6-month target revascularization rate for the stent–abciximab group compared to the stent–placebo group, while in the non-diabetics this reduction was <3%.

Here, we address the question on the balance between the costs and effects of combined use of abciximab and stenting using the 6-months efficacy data from the EPISTENT study, in combination with Dutch estimates of unit costs. We assess both the cost-efficacy of adding a stent to a procedure where the use of abciximab is planned, as well as the cost-efficacy of adding abciximab to a procedure where the use of a stent is planned. Special attention is given to the uncertainties surrounding the estimates, especially when breaking down the results between diabetics and non-diabetics.

Methods

The presented analysis can be labelled as a cost-efficacy analysis from a societal perspective in which only direct medical costs are taken into account. The analysis is based on individual data per patient with a time horizon of 6 months. The analysis includes a subgroup of diabetic and non-diabetic patients.

The EPISTENT study

In the EPISTENT trial, 2399 patients (75% males, aged 60 ± 11 years) were enrolled at 63 hospitals in the U.S.A. and Canada between July 1996 and September 1997[13]. All patients had ischaemic heart disease and coronary artery lesions that had caused stenosis of at least 60%, amenable to balloon angioplasty or stenting. Patients were randomly assigned to stenting and placebo (n=809), stenting plus abciximab (n=794), or balloon angioplasty plus abciximab (n=796). The primary endpoint of the trial included any of the following events over the first 30 days after randomization: death from any cause, myocardial infarction or reinfarction, or severe myocardial ischaemia requiring urgent coronary-artery bypass surgery, stent placement or PTCA. Further details have been published elsewhere[13].

Efficacy

The analysis of cost-efficacy starts with the assumption that the results from the EPISTENT study can be extrapolated to Europe. The clinical end-point used in the EPISTENT trial and in three other large trials that have been conducted with abciximab, was 'event-free survival', including death, myocardial infarction and urgent revascularizations as events. From an economic perspective, there are various reasons why this outcome may be subject to criticism. Using this composite end-point, a repeat PTCA receives the same weight as a myocardial infarction, and a myocardial infarction has the same weight as dying. Moreover, revascularizations — even 'urgent' revascularizations — may be subject to clinicians' decisions. Ideally, one would want to use the number of Quality Adjusted Life Years (QALYs) gained through the use of abciximab. However, no data on the quality of life of the study population has been collected. Therefore, we followed the same approach as followed earlier in cost-efficacy studies with abciximab and stenting using two definitions of 'event-free survival'. The first is defined as the percentage of patients surviving 6 months without a myocardial infarction ('myocardial infarction-free survival'); the second is defined as the percentage of patients surviving 6 months with neither a myocardial infarction nor a revascularization procedure (major cardiac event-free survival or 'MACE-free survival'). It is noted that we include the urgent as well as the non-urgent revascularizations as events. As such, 'event-free survival' is used as the measure of efficacy, since all events that are included in the definition are very likely to be associated with quality of life and survival probabilities. Also, the various components do not change in opposite directions (in the sense that the use of abciximab would, for example, lead to fewer revascularizations but more deaths). Differences in effects are tested using the Chi-square test.

Costs

Costs are 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 based on the economic evaluation study from the BENESTENT II trial[5].

The costs of initial stenting procedures, including an average number of hospital days, are estimated higher than the costs for initial PTCA procedures. This difference results from the price of the stent, the use of additional balloons and other devices, and a slightly longer duration of the procedure[16]. The costs of the initial procedures are complemented with the costs of abciximab (blinded and open use), the costs associated with bail-out stent implantation, and the costs associated with additional stents.

During the follow-up period, the costs take into consideration open abciximab usage, revascularizations and the resources associated with myocardial infarctions. We estimated that patients experiencing a Q wave myocardial infarction required hospitalization for 2 days at a coronary care unit (CCU) and another 6 days at a

normal care unit. For non-Q wave myocardial infarction patients, we estimated half a CCU day plus half a day at a normal care unit. The costs for a re-PTCA or a repeat stent procedure are estimated higher than the costs for the initial procedures. While the latter does not include the costs for diagnostic procedures (visits, tests, and angiography), the first do. All costs are expressed in 1998 Euros. Differences in costs are tested using one-way ANOVA and contrasts.

Cost-efficacy

The balance between costs and effects is addressed by computing incremental cost-efficacy ratios, i.e. the additional costs per additional event-free survivor. We assess the cost-efficacy of adding stents to a procedure with abciximab by a comparison of the stent plus abciximab arm with the PTCA plus abciximab arm. The cost efficacy of adding abciximab to a stent procedure is assessed by a comparison between the stent plus abciximab arm and the stent plus placebo arm. Additionally, as in the clinical report about efficacy, a breakdown is presented distinguishing between diabetes and non-diabetes patients. The uncertainties surrounding the estimates are addressed by way of probability ellipses and by presenting upper 95% limits to the cost-efficacy ratios[17]. It is noted that the trial did not include any European patients and that the results are conditional on the assumption that the clinical findings can be extrapolated to a European context.

Results

Efficacy

The results for all patients confirm that the main effect of abciximab on myocardial infarctions is mainly during the first month, and the main effect of stenting on the number of revascularizations is mainly after the first month. After 1 month, only 45 patients had either died or experienced a myocardial infarction after combined therapy, compared to 90 patients in the stent+placebo arm and 54 patients in the PTCA+abciximab arm. The number of revascularizations during the first month was 25 in the combined arm, 42 in the stent+placebo arm, and 41 in the PTCA+abciximab arm. The additional number of patients who either died or experienced a myocardial infarction during the subsequent months was six in the combined arm, 10 in the stent+placebo arm, and 15 in the PTCA+abciximab arm. The additional number of revascularizations during the subsequent months was 66 in the combined arm, 66 in the stent+placebo arm, and 98 in the PTCA+abciximab arm.

As such, a combination of stenting and abciximab leads to a significant improvement in efficacy, when compared with a procedure with stent implantation and when compared to a procedure with abciximab. The results in terms of survival, myocardial infarction-free survival and MACE-free survival are presented in Table 1.

The results — not using abciximab — confirm that stenting is associated with lower MACE-free survival in diabetics when compared to non-diabetics (73% vs 80%, $P=0{\cdot}07$). However, it appears that when abciximab is used, MACE-free survival after stenting is approximately equal for diabetics and non-diabetics. Thus, in diabetics the use of abciximab not only decreases the numbers of myocardial infarctions — as it does in non-diabetic patients — but it decreases the number of revascularizations as well, suggesting not only an additional effect to stent implantation but also a synergistic effect.

Costs

Table 2 presents the estimates of the average cost per patient for the different contributing factors after 6 months of treatment. The results differ slightly from those that would be obtained by simply multiplying the volumes with the unit costs. This is related to the fact that when two events were observed for one patient, this contributed only once to the efficacy measure, but twice to the costs. It is noted that 6 months after the initial procedure, 29% of the patients who were not planned to have a stent implanted had indeed received a stent, either by bail-out (18%) or during follow-up (11%).

The combination of both stenting and abciximab administration leads to higher costs for the initial procedure when compared to a procedure where only stenting or abciximab is used. However, a substantial part of the additional costs are compensated for by savings as a result of a decrease in revascularization procedures and myocardial infarctions. After 6 months, the net costs of adding abciximab to a stent procedure was estimated at Euros 764, after an initial increase of Euros 1012. After 6 months, the net costs of adding a stent to a procedure with abciximab was estimated at Euros 886, after an initial increase of Euros 1403.

Cost-efficacy

From the above results, it may be concluded that the combination of abciximab and stenting is not expected to be cost saving within the first 6 months. Table 3 presents the estimates of costs, effects and cost-efficacy ratios for all patients, diabetics and non-diabetics. The results show that adding stenting to a procedure where the use of abciximab is planned, may only be considered efficient when the goal is to prevent revascularizations, not so much when the goal is to improve myocardial infarction-free survival. The value of adding abciximab

Table 1 Efficacy at 1 month and 6 months for all patients, non-diabetics and diabetics

	Stent+placebo	Stent+abciximab	PTCA+abciximab	*P*-value when adding: abciximab	stenting
All patients					
n	809	794	796		
Survival					
1 month	99·38%	99·62%	99·25%	0·50	0·32
6 months	98·76%	99·50%	98·24%	0·19	0·02
MI-free survival					
1 month	88·88%	94·33%	93·22%	<0·001	0·36
6 months	87·64%	93·58%	91·33%	<0·001	0·09
MACE-free survival					
1 month	85·78%	92·32%	89·32%	<0·001	0·04
6 months	78·37%	83·75%	76·51%	0·006	<0·001
Non-diabetics					
n	636	632	640		
Survival					
1 month	99·69%	99·68%	99·22%	0·99	0·26
6 months	98·90%	99·53%	98·13%	0·21	0·02
MI-free survival					
1 month	89·15%	94·30%	92·81%	<0·001	0·28
6 months	87·74%	93·51%	91·25%	<0·001	0·13
MACE-free survival					
1 month	86·32%	92·09%	88·28%	<0·001	0·02
6 months	79·72%	83·54%	76·72%	0·08	<0·01
Diabetics					
n	173	162	156		
Survival					
1 month	98·27%	99·38%	99·36%	0·35	0·98
6 months	98·27%	99·38%	98·72%	0·35	0·54
MI-free survival					
1 month	87·86%	94·44%	94·87%	0·04	0·87
6 months	87·28%	93·83%	91·67%	0·04	0·46
MACE-free survival					
1 month	83·82%	93·21%	93·59%	<0·01	0·89
6 months	73·41%	84·57%	75·64%	0·01	<0·05

PTCA=percutaneous transluminal coronary angioplasty; MI=myocardial infarction; MACE= major adverse cardiac event.

to a stenting procedure differs among subgroups. For the majority of patients, adding abciximab may be efficient in increasing myocardial infarction-free survival. However, in the subgroup of diabetic patients, adding abciximab affects revascularizations as well, and may be an efficient strategy in terms of myocardial infarction-free survival as well as MACE-free survival.

While there are substantial differences between the point estimates when comparing diabetics and non-diabetics, these differences are not evident when comparing the one-sided 95% upper limits. This is, of course, related to the fact that the subgroup of diabetic patients contained fewer patients. This is confirmed by Figs 1 and 2, which indicate both costs and effects in two-dimensional planes, together with the estimated uncertainties, for diabetic and non-diabetic patients. Figure 1 illustrates the value of adding abciximab to a procedure involving stent implantation, and Fig. 2 shows the added value of stenting when the use of abciximab was planned. Points in the right upper quadrant denote that the addition of abciximab (Fig. 1), respectively the addition of a stent (Fig. 2), is more effective and more costly; the right lower quadrant denotes the addition to be more effective and less costly; the left lower quadrant denotes lower efficacy and lower costs; and the left upper quadrant denotes both higher efficacy and higher costs.

It is noted that there is more uncertainty surrounding diabetic patients, and that there is a substantial probability that the combination of abciximab and stenting might result in cost savings (and more event-free survivors), especially when abciximab is added to a procedure where stenting is scheduled.

Discussion

The results of the EPISTENT study may help in deciding whether one should add abciximab to an elective stent procedure, or whether one should add a stent to a procedure planned with abciximab. As such, they do not answer the question should one use a stent or abciximab in the first place. For these questions, one should consider the results from the BENESTENT II study (for stenting)[5] or from the EPIC study[18]. In the BENESTENT II study, the costs for stenting were estimated at Euros 8 780 per MACE-free survivor[5]. For

Table 2 Costs after 6 months for all patients

	Incidence of events			Unit costs (Euros)	Costs per patient (Euros)		
	Stent/placebo	Stent/abciximab	PTCA/abciximab		Stent/placebo	Stent/abciximab	PTCA/abciximab
Initial procedure							
PTCA/stenting	98·52%	98·74%	98·62%	4505/5904	5816	5829	4442
Bail out stenting	0·00%	0·00%	18·34%	2211	0	0	406
Additional stents	0·38	0·30	0·00	1397	527	419	0
Initial no. vials abciximab	0	3·23	3·23	347	0	1122	1122
Open abciximab	1·85%	0·38%	0·25%	1121	21	4	3
					6363	7375	5972
Follow-up							
Open abciximab	1·40%	1·12%	1·01%	1121	15	13	11
Q-wave MI	1·85%	1·64%	2·51%	4753	88	78	131
Non-Q wave MI	9·39%	4·41%	4·90%	719	68	33	36
Re-PTCA	6·30%	4·79%	4·15%	7178	497	380	325
Re-stent	4·45%	3·78%	11·31%	7678	361	309	916
Re-bypass	4·57%	4·28%	3·89%	17 795	814	784	693
					1843	1597	2113
Average costs per patient					8207	8971*	8085

*Compared to stent/placebo $P=0·003$, compared to PTCA/abciximab $P<0·001$.
PTCA=percutaneous transluminal coronary angioplasty; MI=myocardial infarction.

Table 3 Incremental cost-efficacy ratios at 6 months for all patients, non-diabetics and diabetics

	Stent/placebo	Stent/abciximab	PTCA/abciximab
All patients			
n	809	764	796
Costs (Euros)	8207	8971	8085
MI-free survivors	87·64%	93·58%	91·33%
MACE-free survivors	78·37%	83·75%	76·51%
Non-diabetics			
n	636	632	640
Costs (Euros)	8047	8955	8029
MI-free survivors	87·74%	93·51%	91·25%
MACE-free survivors	79·72%	83·54%	76·72%
Diabetics			
n	173	162	156
Costs (Euros)	8792	9034	8317
MI-free survivors	87·28%	93·83%	91·67%
MACE-free survivors	73·41%	84·57%	75·64%

	Incremental CE-ratio adding abciximab (one-sided 95% upper limit)		Incremental CE-ratio adding stents (one-sided 95% upper limit)	
All patients				
MI-free survival	12 876	(27 366)	39 463	(1 438 868)
MACE-free survival	14 198	(49 873)	12 228	(30 597)
Non-diabetics				
MI-free survival	15 713	(36 381)	40 936	(ns)
MACE-free survival	23 717	(487 232)	13 570	(40 555)
Diabetics				
MI-free survival	3695	(42 521)	33 219	(ns)
MACE-free survival	2167	(25 246)	8040	(91 103)

PTCA=percutaneous transluminal coronary angioplasty; MI=myocardial infarction; MACE=major adverse cardiac event; ns=if efficacy is not significant at 10% then no upper limit for the cost-efficiency ratio is calculated.

abciximab, the costs per additional myocardial infarction-free survivor were estimated in the EPIC study at Euros 2900[19].

The result confirm the hypothesis, given that one already has decided to use abciximab, that stenting will further decrease the number of revascularizations in both diabetics and other patients. The costs per additional MACE-free survivor are estimated at Euros 12 000 (95% upper limit (u.l.) Euros 31 000); for diabetics at Euros 8000 (95% u.l. Euros 91 000). Additionally, the result confirms the hypothesis, given that one will use a stent, that use of abciximab will decrease the incidence of myocardial infarctions. The additional costs per additional myocardial infarction-free survivor are estimated at Euros 13 000 (95% u.l. Euros 27 000); for diabetics at Euros 3700 (95% u.l. Euros 46 000). Most notably, in the subgroup of diabetic patients, adding abciximab not only improves myocardial infarction-free survival, but also decreases the revascularization rate. This results in a cost-efficacy rate of Euros 2000 per MACE-free survivor (95% u.l. Euros 25 000), and even the possibility of cost savings.

The calculations presented here are obtained by combining event rates in the EPISTENT study with estimated costs from the Dijkzigt hospital in the Netherlands. It is emphasized that the results presented here need to be interpreted with some care since: (1) only direct medical costs have been included, (2) no data on health-related quality of life have been included, and (3) no analysis of costs per life year gained has been performed. The trial was not powered to analyse differences in survival, although the 6 month results show a significant difference due to stenting. The recently reported 12 month results confirm this difference, and also show a significant survival difference at that point in time, due to abciximab[20]. These results could be used to calculate an extrapolated survival difference, to estimate future costs and to estimate costs per life year gained. However, we feel that these estimates would need to be surrounded with lots of uncertainties, in light of the limited power and the fact that, until now, stents have never been able to convincingly show a decrease in mortality[21].

Also, a number of assumptions have been made in the analysis. Most notably, it has been assumed that the results from the EPISTENT trial can be reproduced in The Netherlands. This assumption may not be correct, especially when certain treatment decisions affect the costs and effects. For example, it should be appreciated that the average number of PTCAs per 100 000 citizens is between 115 and 143 in the United States, while it is only about 70 in the Netherlands[22]. Another concern is

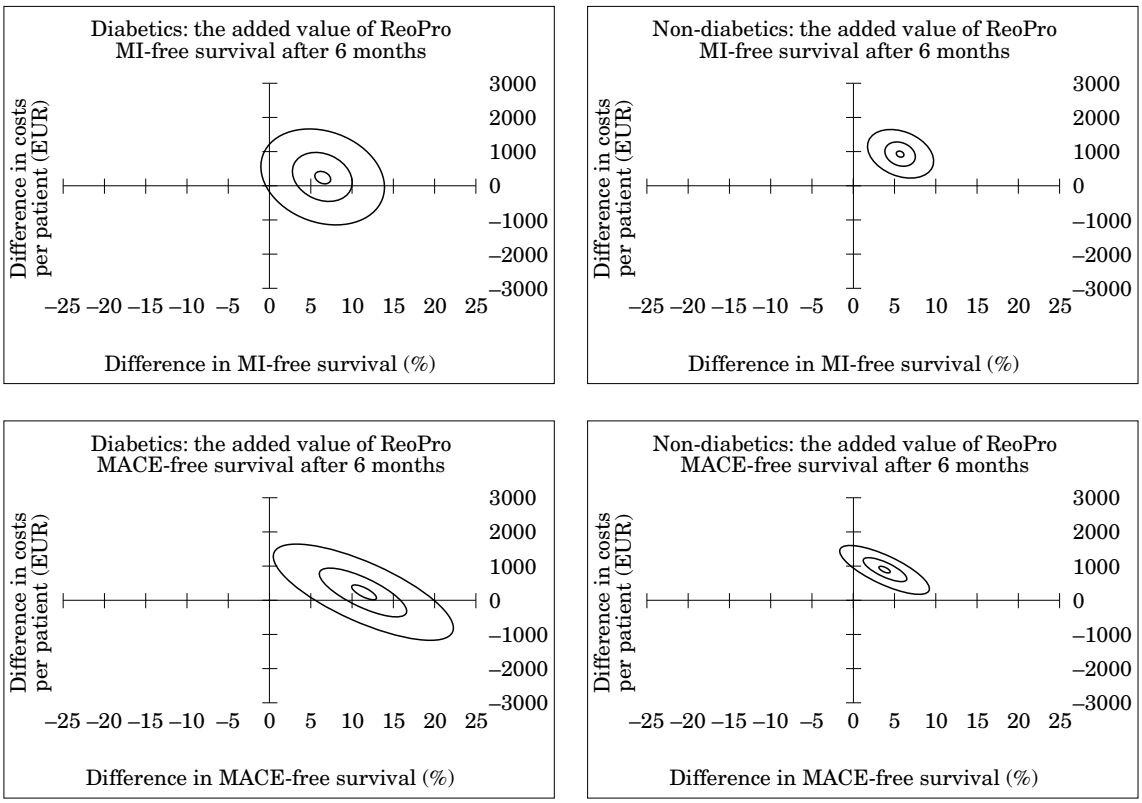

Figure 1 **The added value of abciximab; diabetics and non-diabetics. Outer ellipse=smallest area containing, with 95% probability, average costs and effects; middle ellipse=that area with 50% probability; inner ellipse=that area with 5% probability. Centre of ellipse=point estimate of both average costs and effects.**

the definition of efficacy. The analysis includes death, myocardial infarctions and revascularization procedures in the outcome measure without any distinction with respect to the severity of the various events. This can only be labelled as a very rough approach. When additional research is initiated, it would be worthwhile to incorporate quality of life measures in the assessment of the effects. Additionally, to calculate quality adjusted life years gained, it would be worthwhile to incorporate a utility measure, such as the EuroQol or a patient preference method.

The question can now be raised, how can these results be translated into clinical practice? Clinicians might ask themselves whether these incremental cost-efficacy ratios are acceptable. Is it worth Euros 13 000 to prevent a myocardial infarction (in most cases a non-Q wave myocardial infarction), and is it worth Euros 12 000 to prevent a revascularization? The answers are difficult to give and may also depend on the possibility of finding additional funds. One way may be to limit the combined strategy to diabetic patients for whom the cost-efficacy ratios are much lower, with the need for correspondingly less funds. On the one hand, this is due to the fact that fewer patients are treated, and on the other hand, to the reduced need for repeat interventions in these patients. However, the latter needs to be interpreted with care. A reduction in the revascularization rate was demonstrated only in the EPIC trial[9], while in other trials (including the overall results from EPISTENT) this finding could not be replicated. More important than whether this finding is coincidental, may be the question whether one should stent a diabetic patient in the first place. The literature does not present any uniform conclusions about efficacy, let alone about cost-efficacy[23,24]. In such cases, the cost-efficacy ratio of combined use of stenting and abciximab should be calculated against a plain PTCA procedure or even better, with diabetic patients, against bypass surgery. Indeed, if one buys a Ferrari, it is better to buy one with wheels; however, the question is, of course, whether one should have bought a Ferrari in the first place. As such, a further refinement of whom to stent and who should be given abciximab in the first place, may prompt the creation of an additional budget for treating patients with the combination of the two.

In conclusion, there are still unanswered questions about which treatment is the most efficient for patients scheduled for revascularization. Potentially, the main problem may be that a PTCA is already a very efficient procedure and it will always be difficult to improve on something that is already so good. As such, one might conclude that interventional cardiologists are being punished for their own success. However, and this may offer some comfort, there are probably many specialists who would like to be in this position.

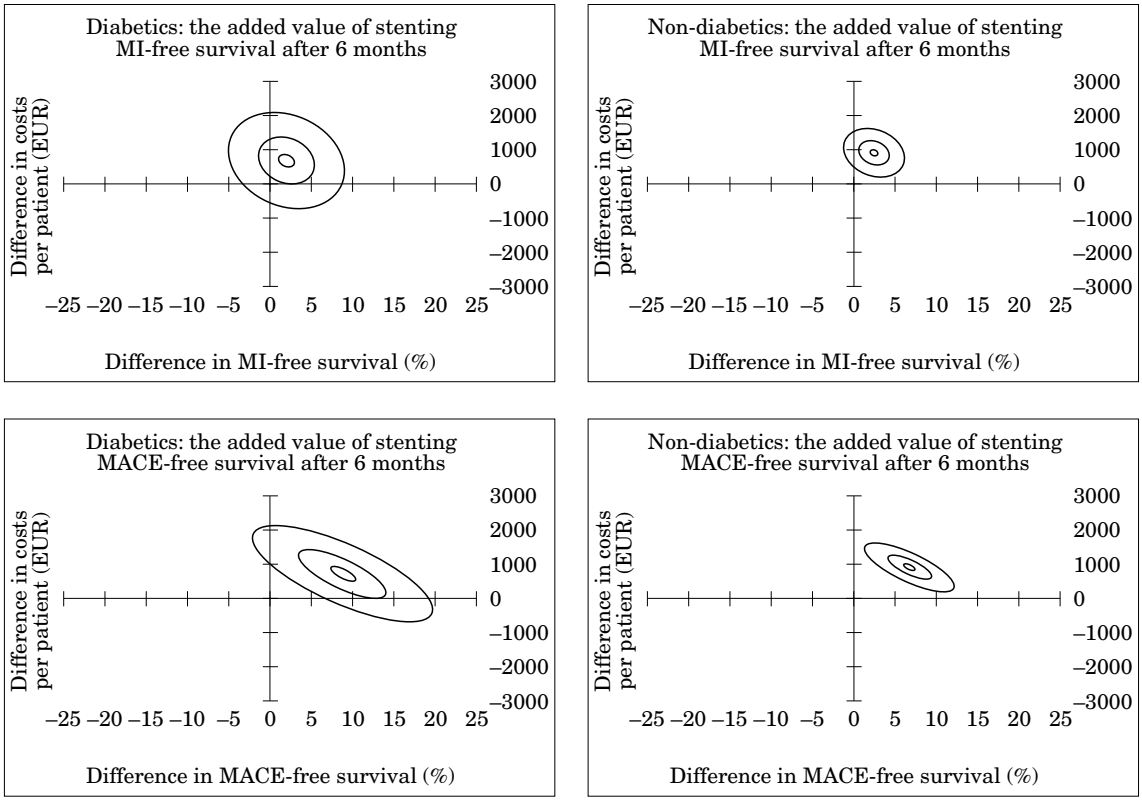

Figure 2 **The added value of stenting; diabetics and non-diabetics. Outer ellipse = smallest area containing, with 95% probability, average costs and effects; middle ellipse = that area with 50% probability; inner ellipse = that area with 5% probability. Centre of ellipse = point estimate of both average costs and effects.**

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