

Long term outcome and cost-effectiveness of stenting versus balloon angioplasty for acute myocardial infarction

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Abstract

Objective—To investigate the long term clinical outcome and cost-effectiveness of stenting compared with balloon angioplasty in patients with acute myocardial infarction.

Methods—Patients with acute myocardial infarction were randomly allocated to primary stenting (112) or balloon angioplasty (115). The primary end point was the cumulative first event rate of death, non-fatal reinfarction, or target vessel revascularisation. Secondary end points were restenosis at six months and the cost-effectiveness at follow up.

Results—After 24 months, the combined clinical end point of death/reinfarction was 4% after stenting and 11% after balloon angioplasty ($p = 0.04$). Subsequent target vessel revascularisation was necessary in 15 patients (13%) after stenting and in 39 (34%) after balloon angioplasty ($p < 0.001$). The cumulative cardiac event-free survival rate was also higher after stenting (84% *v* 62%, $p < 0.001$). The angiographic restenosis rate after stenting was less than after balloon angioplasty (12% *v* 34%, $p < 0.001$). Despite the higher initial costs of stenting (Dfl 21 484 *v* Dfl 18 625, $p < 0.001$), the cumulative costs at 24 months were comparable with those of balloon angioplasty (Dfl 31 423 *v* Dfl 32 933, $p = 0.83$).

Conclusions—Compared with balloon angioplasty, primary stenting for acute myocardial infarction results in a better long term clinical outcome without increased cost. (*Heart* 2001;85:667-671)

Keywords: stenting; angioplasty; myocardial infarction; cost-benefit analysis

The most important goal of the initial treatment of acute myocardial infarction is early and complete reperfusion of the infarct related coronary artery. Compared with thrombolytic treatment, primary angioplasty for acute myocardial infarction causes a decrease in recurrent infarction and death after both short term¹ and long term follow up.² These beneficial effects are mainly produced by a higher patency rate of the infarct related vessel after primary angioplasty.³ However, recurrent ischaemia, early reocclusion of the infarct related vessel, and late restenosis requiring subsequent target vessel revascularisation remain potential clinical problems after primary angioplasty.

There have been several randomised trials showing that the use of stents in primary angioplasty results in a better event-free survival than after primary angioplasty with balloon alone.⁴⁻⁹ In particular, the need for repeat target vessel revascularisation during follow up is less after the use of stents.

Angioplasty with the use of stents is more expensive than angioplasty with balloon alone, so there may be concerns that the high initial cost of stenting is a major limitation of this approach.¹⁰⁻¹² However, as patients with stents have fewer readmissions and revascularisation procedures during follow up, the long term costs may be comparable. Because long term clinical outcome and cost-effectiveness of stents in primary angioplasty have not been reported, we examined these variables in patients involved in our prospective

randomised trial of stents versus balloon angioplasty for acute myocardial infarction.⁹

Methods

The study protocol has been described previously.⁹ In brief, 227 patients with acute myocardial infarction presenting within six hours, and in whom the infarct related vessel was considered suitable for stenting, were randomised to primary stenting or balloon angioplasty. During the study period, a further 225 patients (50%) were excluded, mainly because of small and diffusely diseased infarct related vessels.³

Bare Palmaz-Schatz stents were hand mounted on the balloon used for predilatation. If necessary, high pressure inflation was performed with a bigger sized balloon. Angiographic success, subacute occlusion, and bail out stenting were defined as previously described.^{9 13} Quantitative coronary angiography of the target lesion was performed in all patients enrolled into the study on site, as well as by an independent core laboratory (Cardi-lysis, Rotterdam, Netherlands), blinded to all clinical data and outcome. The degree of stenosis (per cent) was assessed in the angiographic view in which the stenosis appeared most severe immediately before and after angioplasty, and at follow up angiography. Thrombolytic treatment, platelet glycoprotein IIb/IIIa receptor antagonists, and intravascular ultrasound were not used. Radionuclide ejection fraction was assessed at discharge and at six months.²

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Table 1 Baseline characteristics and in-hospital outcome of the 227 randomised patients

Characteristic	Treatment groups	
	Stent (n=112)	Balloon (n=115)
Age (years)	59 (11)	57 (11)
Male	93 (83%)	98 (85%)
Previous infarction	15 (13%)	15 (13%)
Killip class ≥ 2 at admission	25 (22%)	20 (17%)
Symptom onset to admission (min)	217 (222)	211 (242)
Admission to first inflation (min)	62 (82)	62 (63)
Symptom onset to admission < 3 h	75 (67%)	79 (69%)
Multivessel disease	49 (44%)	51 (44%)
Infarct artery:		
Left anterior descending	66 (59%)	70 (61%)
Right coronary	34 (30%)	35 (30%)
Circumflex	12 (11%)	10 (9%)
Initially occluded infarct artery	97 (87%)	96 (83%)
Angiographic success	110 (98%)	110 (96%)
Subacute occlusion	1 (1%)	5 (4%)
Crossover (bail out)	2 (2%)	15 (13%)*
Intra-aortic balloon pumping	18 (16%)	15 (13%)
Major bleeding complications	7 (6%)	3 (3%)
Death	2 (2%)	3 (3%)
Reinfarction	1 (1%)	5 (4%)

Values are mean (SD) or n (%).

* $p < 0.002$.

Table 2 Cumulative clinical outcome at 24 months

	Stent (n=112)	Balloon (n=115)	p Value
Death	3 (3%)	4 (3%)	1.00
Reinfarction	1 (1%)	10 (9%)	0.01
Death/reinfarction	4 (4%)	13 (11%)	0.04
Target vessel revascularisation	15 (13%)	39 (34%)	0.0003
Subsequent bypass surgery	7 (6%)	18 (16%)	0.033
Repeat angioplasty	8 (7%)	21 (18%)	0.016
Cumulative cardiac event-free survivor	94 (84%)	71 (62%)	0.0002

Values are n (%).

The primary study end point was the cumulative first event rate of death, non-fatal reinfarction, or the need for myocardial revascularisation of the target vessel at follow up, as previously defined.⁹ Myocardial infarction was defined as electrocardiographic signs of infarction combined with an increase in serum creatine kinase (CK) > 200 U/l and creatine kinase MB isoenzyme fraction/total creatine $\geq 10\%$.

Revascularisation was defined as angioplasty or bypass surgery performed because of restenosis of the target lesion. The indication for revascularisation had to be substantiated by symptoms and ECG or scintigraphic evidence of ischaemia at rest or during exercise. Subsequent revascularisation involving other vessels did not constitute an end point. Two cardiologists blinded to treatment assignments reviewed all events.

The secondary study end points consisted of angiographic restenosis at six months and cost-effectiveness at follow up. Angiographic restenosis was defined as at least 50% diameter stenosis of the target lesion on a follow up angiogram.^{9,13} Follow up assessment of resource use and health status was made through telephone interviews with the general practitioner of each patient and was conducted 24 months after the procedure. Patient reported clinical events and resource use during follow up were confirmed from hospital discharge summaries. The calculation of costs was based on the direct medical costs, including all aspects of medical care.^{14,15} These include resources use during the initial procedure, all hospital admissions (coronary care unit, intensive care unit, general ward), and other diagnostic or therapeutic procedures—including repeat angiography—during follow up. Follow up resource use was limited to cardiac hospital admissions and cardiac outpatient visits and diagnostic tests. Cardiac hospital admissions included those for any type of chest pain, congestive heart failure, arrhythmia, or any other cardiovascular diagnosis.

Costs per patient were calculated as the product of each patient's use of resources and the corresponding unit cost. All costs are given in Dutch guilders (Dfl). The balance between costs and effects was addressed by calculation of the incremental cost-effectiveness ratio (the

Table 3 Cumulative costs per patient in Dutch guilders (Dfl) during 24 months follow up

	Resource utilisation			Average cost/patient		
	Stent (n=112)	Balloon (n=115)	Unit cost (Dfl)	Stent (n=112)	Balloon (n=115)	p Value
<i>In hospital costs</i>						
PTCA procedure	1	1	8535	8535	8535	1
Stent	1.17	0.24	2200	2573	535	0.0001
IABP	0.16	0.13	1300	221	170	0.5
Angiography	0.02	0.03	3882	69	135	0.43
CABG	0.02	0.01	26052	465	227	0.55
Repeat PTCA	0.01	0.04	8535	76	371	0.11
CCU (days)	2.42	2.2	2200	5323	4840	0.82
Ward (days)	5.28	4.77	800	4221	3812	0.18
Total cost				21484	18625	0.0001
<i>Follow up costs</i>						
Angiography	0.88	0.85	3882	3397	3308	0.53
CABG	0.04	0.14	26052	930	3624	0.006
Repeat PTCA	0.10	0.14	8535	836	1187	0.15
Stent	0.03	0.12	2200	59	268	0.012
IABP	0.01	0	1300	12	0	0.31
CCU (days)	0.29	0.59	2200	648	1301	0.018
Ward (days)	3.94	4.62	800	3150	3694	0.34
Follow up visits	4.10	3.91	125	512	489	0.58
Echo	0.19	0.22	128	24	28	0.29
Stress test	0.71	0.84	115	81	97	0.26
EF	0.88	0.96	325	287	311	0.56
Total cost				9939	14308	0.028
Total cost per patient				31423	32933	0.83

CABG, bypass surgery; CCU, coronary or intensive care; echo, echocardiography; EF, radionuclide ejection fraction; IABP, intra-aortic balloon pumping; PTCA, percutaneous transluminal coronary angioplasty.

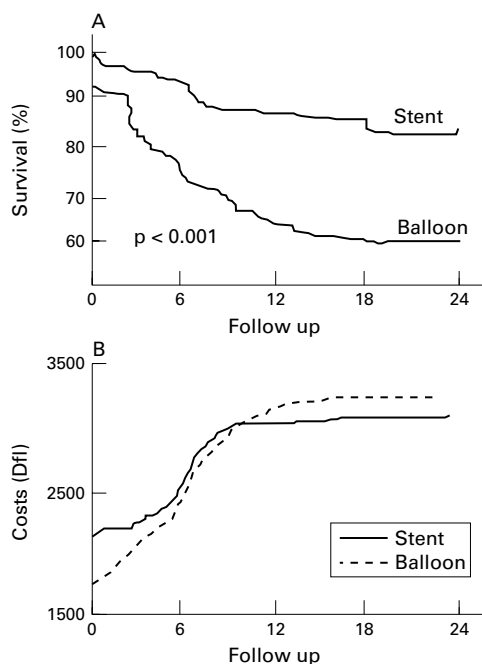


Figure 1 (A) Cumulative first event-free survival (no death, non-fatal reinfarction, or myocardial revascularisation during 24 months of follow up). (B) Cumulative costs per patient in Dutch guilders (Dfl) during follow up in both stent (solid line) and balloon (dotted line) groups.

average cost per patient in the stent group minus that in the balloon group divided by the percentage reduction in event-free survival) and the average cost-effectiveness ratios for both groups (the average costs per patient divided by the percentage of event-free survivors). No patient was lost to follow up.

DATA ANALYSIS

Sample size calculations have been described.⁹ Data were analysed according to the intention to treat principle. Continuous variables are expressed as means (SD) and were compared using the Student *t* test. The χ^2 test was used to compare proportions, or a Fisher's exact test when appropriate. Event-free survival was assessed by Kaplan-Meier method, using the

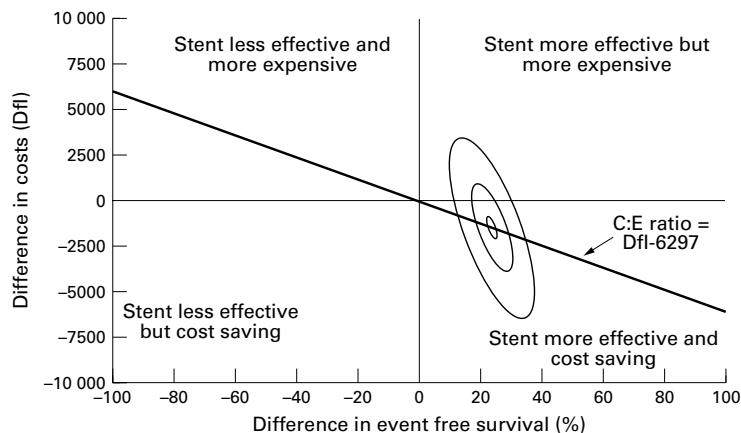


Figure 2 A bivariate normal distribution of differences in costs and effects in a two dimensional plane, together with the uncertainties surrounding the estimates. A 95% confidence ellipse, a simultaneous confidence region for both costs and effects, is depicted. The probability that the inner ellipse includes the true incremental costs and effectiveness is 5%. For the middle ellipse, this is 50%, and for the outer ellipse, 95%.

log rank test. Differences in costs were tested parametrically (*t* test) and non-parametrically (Mann-Whitney U test). Costs and effects are expressed in a two dimensional plane, and the uncertainties surrounding the estimates are expressed by confidence ellipses,¹⁵ assuming that the average costs and effectiveness approached a bivariate normal distribution. Relations were assessed using Pearson's correlation coefficient. A two sided probability value of $p < 0.05$ was considered significant.

Results

In all, 227 patients were included in the study, of whom 112 were randomised to primary stenting and 115 to balloon angioplasty. The baseline characteristics and in hospital outcome are listed in table 1. There were no differences in the baseline characteristics between the two groups. In two patients (2%) allocated to stenting, the target lesion could not be crossed by the stent owing to proximal vessel tortuosity, but the result was excellent after balloon angioplasty. Bail out stenting was needed in 15 patients (13%) allocated to balloon angioplasty, as a result of major dissection with threatening vessel occlusion.

Tables 2 and 3 show the clinical outcome and the total costs during follow up. After a follow up period of 24 months the occurrence of reinfarction and the combination of death or non-fatal reinfarction was lower in patients treated with primary stenting. In fig 1, the event-free survival curves and the cumulative costs during follow up are depicted. Despite the higher initial costs of stenting on admission, the cumulative costs after 24 months were similar between the groups. The efficiency of both treatment modes can be assessed from the average costs per event-free survivor. The average cost-effectiveness ratio (calculated from the average total costs and the event-free survival) was Dfl 37 408 in the stent group and Dfl 53 117 in the balloon group ($p < 0.001$). The incremental cost-effectiveness ratio was estimated at Dfl -6297 (95% confidence interval Dfl -18 828 to Dfl 16 390). The uncertainties of this estimate are indicated in fig 2, where both differences in costs and effects are depicted as a bivariate normal distribution in a two dimensional plane.

Follow up angiography was obtained in 197 patients (87%). Five patients died (three after stenting and two after balloon angioplasty), and eight underwent bypass surgery before scheduled angiography (one after stenting and seven after balloon angioplasty); seven patients in the stent group and 10 in the balloon group refused angiography. Matched quantitative analyses, obtained from the independent core laboratory, are shown in table 4 and fig 3, which were comparable to those analysed on site. Matched ejection fractions, obtained before discharge and at six months, increased significantly in both groups, from (mean (SD)) 43.4 (10.5)% to 45.8 (11.0)% ($p = 0.023$) after stenting, and from 45.0 (10.7) to 46.1 (11.6)% ($p = 0.019$) after balloon angioplasty.

Table 4 Core laboratory quantitative angiographic results

Matched analysis	Stent (n=101)	Balloon (n=96)	p Value
Time to follow up (months)	6.90 (2.36)	6.32 (2.32)	0.084
Minimum lumen diameter (mm)			
Pre	0.24 (0.46)	0.33 (0.51)	0.20
Post	2.56 (0.38)*	2.17 (0.48)*	< 0.0001
Follow up	2.04 (0.63)*	1.64 (0.83)*	0.0002
Diameter stenosis (%)			
Pre	91.5 (15.4)	89.1 (16.7)	0.28
Post	18.0 (6.5)*	29.1 (9.2)*	< 0.0001
Follow up	33.4 (18.8)*	47.3 (23.6)*	< 0.0001
Reference diameter (mm)			
Post	3.15 (0.47)	3.11 (0.55)	0.25
Follow up	3.08 (0.44)	3.09 (0.56)	0.68
Restenosis (diameter stenosis > 50%)	12 (11.9%)	33 (34.4%)	0.0002

Values are means (SD) or n (%).

*p < 0.0001 versus pre and/or post procedure.

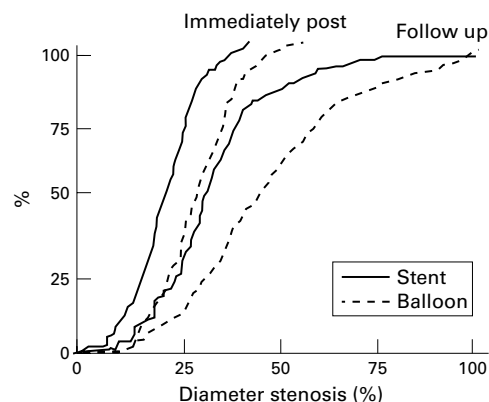


Figure 3 Cumulative frequency of diameter stenosis (%) in both groups, as obtained from the independent core laboratory.

Discussion

This is the first randomised trial to report the cost-effectiveness and long term clinical and angiographic outcome of primary stenting for acute myocardial infarction. Primary stenting results in a better long term clinical outcome and is more cost-effective than conventional balloon angioplasty in selected patients with acute myocardial infarction. Our results also confirm the long term safety and efficacy of stenting without ultrasound guidance and without conventional anticoagulant treatment.¹⁶ Thus the major advantage of primary stenting in this setting is that these patients can be managed more efficiently and more definitively during the acute stage of myocardial infarction, as the combined clinical end point of death or recurrent myocardial infarction and the need for subsequent reintervention are significantly reduced when compared with balloon angioplasty.

The overall mortality (3%) and recurrent myocardial infarction rates (4%) at 24 months are comparable with those reported in our previous trial of thrombolysis versus primary angioplasty.² This favourable outcome may reflect the short time delay from admission to first inflation (62 minutes), and the fact that most patients were admitted within three hours after symptom onset (table 1). However, no difference in mortality could be observed as it would be unlikely that stenting could further

reduce the extremely low mortality achieved by balloon angioplasty. The reduction in the need for target vessel revascularisation after stenting is mainly because of a significant reduction in restenosis (12%), which is quite favourable when compared with elective cases.¹³ This favourable outcome probably reflects the fact that patients selected in this trial had a larger vessel size than in other trials.¹³ The restenosis rate of 34% after balloon angioplasty is quite similar to our previous trial.¹⁷ To address the potential analysis bias, quantitative angiography was analysed not only by our own but also by an independent core laboratory.

The favourable results of stenting in our study are expressed not only by the efficacy data but also by the cost-effectiveness analysis. The present data indicate that—at least in the setting of a Dutch general hospital with an existing infrastructure for primary angioplasty and stenting—the cumulative costs at 24 months after stenting are similar to those of balloon angioplasty (fig 1). The differences in the costs of the initial procedure are mainly related to the longer hospital stay after stenting and the cost of the stent itself (table 3). However, the costs of stenting procedure are relatively low in our setting, because of the use of a single balloon for predilatation, stent delivery, and post-stenting dilatation. The relatively longer hospital stay in the stent group in our study, resulting in a higher initial cost, is related to the use of anticoagulant treatment in the initial phase of our trial, before the post-stent regimen was modified.⁹ The use of only aspirin and ticlopidine after stenting has led to a shorter hospital stay. However, the higher in-hospital costs of stenting are compensated for by the lower costs during follow up, making primary stenting a good investment. In fact, the primary stenting strategy is more cost-effective than balloon angioplasty, owing to a significantly lower incidence of target vessel revascularisation. Thus the concern that stenting would be more expensive than balloon angioplasty^{10–12} was not confirmed in our study. These cost-effectiveness data are comparable to more recent studies of the costs of stents in daily practice.^{18, 19}

Several limitations of this study must be considered.⁹ The present cost-effectiveness analysis is based on a single centre trial. Thus it might not be universally applicable to other hospitals or health care facilities. However, it can be extensively modified according to the economic standards in other European or US hospitals. Estimates can be obtained by using local unit cost estimates and the corresponding data on use of resources. As our hospital has a high volume of primary angioplasty, the clinical outcome in both treatment groups in our study may be better than in hospitals with less frequent primary angioplasty.²⁰ The trial could not of course be blinded, and because follow up angiography was performed as an integral part of the trial, this might have affected the occurrence of reinterventions.²¹ However, a cardiac team consisting of both cardiologists and thoracic surgeons had to make the decision for reintervention in our setting, based on ECG or

scintigraphic evidence of ischaemia at rest or during exercise. As patients receiving stents in our study had fewer readmissions and fewer symptoms, our current estimates of costs could have underestimated the economic benefits of stenting, as we did not include indirect costs associated with, for example, loss of employment.

Several issues remain to be addressed before primary stenting can be adopted routinely. Although the potential benefits of platelet glycoprotein IIb/IIIa receptor antagonists²²⁻²⁴ and the promising results of heparin coated stents²¹ have been reported, their definitive role in the setting of acute myocardial infarction is still uncertain. Furthermore, to define a subgroup of patients who will have most benefit from stenting and to determine whether similar results could also be obtained in smaller and diffusely diseased infarct related vessels, all patients are now randomised before angiography in our current ongoing trial.

CONCLUSIONS

Our randomised study of stents versus conventional balloon angioplasty in acute myocardial infarction showed, after a follow up period of two years, that coronary stenting leads to improved patient outcomes without increased long term costs.

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