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Clinical research

Clinical outcomes of stents versus balloon angioplasty in non-acute coronary artery disease

A meta-analysis of randomized controlled trials

Alain J. Nordmann[a]*, Peter Hengstler[b], Bernd M. Leimenstoll[c], Thomas Harr[b], James Young[a], Heiner C. Bucher[a]

[a] *Basel Institute for Clinical Epidemiology, University Hospital Basel, Base, Switzerland*
[b] *Medical Outpatient Clinic, Department of Internal Medicine, University Hospital Basel, Basel, Switzerland*
[c] *Department of Internal Medicine, University Hospital Basel, Basel, Switzerland*

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Coronary artery disease;
Stents;
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Meta analysis

Aims To evaluate whether stents as compared to balloon angioplasty reduce mortality in patients with non-acute coronary artery disease.
Methods and results We identified randomized controlled trials comparing stents to balloon angioplasty for the treatment of non-acute coronary artery disease by searching major medical databases from 1979 to March 2002. Two independent reviewers selected and extracted data from trials that had to report data on death and myocardial infarction. Nineteen trials, with a total of 8004 patients, fulfilled our inclusion criteria. For 1000 patients treated with stents rather than balloon angioplasty, 3 (95% CI 0–6), 5 (95% CI 0–9), and 6 (95% CI -1–12) additional lives were saved at 30 days, 6 and 12 months. At 12 months, for 1000 patients treated with stents rather than balloon angioplasty 46 (95% CI 25–66) additional target vessel revascularizations were avoided, but 25 (95% CI 15–34) additional bleeding complications with need for blood transfusion or surgical intervention occurred. In sensitivity analysis 11 (95% CI 2–20) and 2 (95% CI -4–7) deaths were avoided per 1000 patients treated with stents rather than PTCA in trials that routinely used compared to trials that did not use glycoprotein IIb/IIIa inhibitors.
Conclusion In non-acute coronary disease stents may reduce overall mortality, but this benefit seems to be limited to stents used in conjunction with glycoprotein IIb/IIIa inhibitors. Stents compared to PTCA reduce target vessel revascularizations, but increase the risk of bleeding complications.

Introduction

Since the introduction of the first stents in 1987[1] their use in patients with coronary artery disease has steadily increased. Today over 1 million coronary angioplasty procedures are performed every year in the USA.[2] In Europe stents are used in more than 70% of these procedures.[3] Clinical trials have shown that stents reduce restenosis and revascularization compared to simple balloon angioplasty.[4–6]

The introduction of sirolimus-and paclitaxel eluting stents is another breakthrough in the treatment of coronary artery disease. In a recent trial, 27% of patients treated with conventional uncoated stents, but none of

* Correspondence to: Alain J. Nordmann, MD MSc, Basel Institute for Clinical Epidemiology, University Hospital Basel, Hebelstrasse 10, 4031 Basel, Switzerland. Tel: +41 61 265 31 00; Fax: +41 61 265 31 09
E-mail address: nordmanna@uhbs.ch (A.J. Nordmann).

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the patients treated with sirolimus-eluting stents developed restenosis.[7] Major cardiac events were significantly reduced in the first year following treatment, but this effect was entirely due to a higher revascularization rate in the conventional stent group. Similarly, restenosis and intimal hyperplasia was more effectively reduced by paclitaxel-eluting as compared to conventional stents in another recent randomized trial.[8] However, it is still not known whether routine use of stents rather than balloon angioplasty in non-acute coronary heart disease reduces mortality and other clinical outcomes such as myocardial infarction.

In a meta-analysis of randomized controlled trials, we investigated whether routine use of stents rather than balloon angioplasty reduces mortality and improves clinical outcome in patients with non-acute coronary artery disease.

Methods

Data search and trial selection

We searched Medline, Embase, Pascal, Index medicus, the Cochrane library and abstracts from cardiology conferences from 1979 to March 2002 to identify all randomized controlled trials in non-acute coronary artery disease that compared stents with balloon angioplasty. We used the following search terms: Angioplasty-transluminal-percutaneous-coronary, Stents, Randomized-controlled-trials, Clinical-trials, Coronary-artery-dilatation, Transluminal-coronary-angioplasty, Random. In addition, we searched all references of relevant articles for additional trials and if necessary, contacted authors of identified trials to ask for additional information.

Two reviewers independently selected the relevant trials and resolved disagreement by consensus. The same reviewers extracted data from all trials that fulfilled our inclusion criteria.

Inclusion- and exclusion criteria

Trials were included if they met the following criteria: randomization to stents or balloon angioplasty prior to the invasive procedure, intervention in native coronary arteries, reporting death or myocardial infarction, and follow-up of at least 6 months. We excluded trials in patients with acute myocardial infarction where angioplasty was done within 48 h after diagnosis, trials that exclusively randomized patients to provisional stenting and trials where patients were randomized after angioplasty only.

Outcomes

The primary outcome was mortality at 30 days (including in-hospital mortality), and at 6 and 12 months after the intervention. Secondary outcomes were myocardial infarction, coronary artery bypass grafting (CABG), a composite outcome of death and myocardial infarction, target vessel revascularization, and bleeding complications with need of transfusion or surgery.

Assessment of study quality

Two reviewers independently assessed the quality of each included trial according to the following criteria: concealment of treatment allocation, blinded outcome assessment, and full description of follow-up. We summarized the quality rating and used a modified Jadad score (Table 1).[9] The score gives one point to each of five items (random allocation, blinding, blinded outcome assessment, full description of all losses of follow-up and withdrawals, and loss to follow-up <10%) if present. One additional point is given if randomization is concealed and one if double-blinding is appropriate. Since blinding to stent or balloon angioplasty was not possible, the score could range from 0 to 5 points. Agreement between the two reviewers was assessed by calculating proportions of specific agreement for positive and negative ratings.[10] Disagreement between reviewers was resolved by consensus.

Examination of publication bias

We used a plot of standardized effect against precision to test for the presence of publication bias.[11]

Data aggregation and sensitivity analysis

We used STATA 7.0 (Stata Corporation, Texas, USA) statistical software to calculate summary risk differences using a fixed effect model. While meta-analyses are often carried out on a relative scale, the risk difference scale is appealing for rare events because of its immediate interpretability and because trials with zero events in both treatment groups can be included in the analysis.[12] In our analysis, the use of summary risk differences was a reasonable approach since there was little difference between trials in event rates in the control group.[13,14] For easier interpretation, we report differences in event rates per 1000 patients. In addition, we report Peto odds ratios for the primary outcome. Simulation suggests that with rare events, meta-analysis underestimates the true effect of treatment over control, but Peto odds ratios are the least biased and most powerful method of pooling trial results among the methods in common use.[15,16] When events are at least moderately rare (i.e. one or two per 1000), odds ratios are a close approximation to the relative risk.[12]

To explore the stability of the overall treatment effect, we compared the primary outcome in predefined subgroups.[17,18] These subgroups were: different types of stents, intervention in vessels with large (≥3 mm) and small (<3 mm) diameters, different post-interventional antithrombotic/anticoagulant drug regimens, and use of glycoprotein IIb/IIIa inhibitors. In order to account for an any time-related effect, we performed an additional sensitivity analysis comparing trials starting enrolment of patients before the year 1996 and trials starting enrolment in 1996 or later.

Role of the funding source

The funding source was not involved in study design, collection, analysis, or interpretation of data and had no impact on writing the manuscript or on the decision to submit the paper.

Results

Trials characteristics

Of 602 potentially relevant publications, 24 met our inclusion criteria (Fig. 1). Five of these publications were long-term follow-up reports of previously published trials[5,19–22] and so 19 trials with a total of 8004 patients

Table 1 Baseline characteristics and type of intervention in randomised controlled trials comparing stenting to balloon angioplasty (BA)

Author (year)	Intervention and number of individuals	Mean age (±SD)	Male (%)	Previous MI (%)	Stenosis (mean %)	Target vessel % LAD	% LCX	% RCA	Stent type	Differences in Postinterventional Antithrombotic/ Anticoagulant Therapy	Bleeding compli-cations[a] (%)	Successful dilatation[b] (%)	Crossover (%)	Quality score
Fischman 1994[4]	Stent 205	60±10	83	37	75	47	16	37	Palmaz–Schatz	Dipyridamol 75 mg/day	9	96	3	2
	BA 202		73	36	75	48	13	39		and warfarin for 1 month in stent-group	5	90	7	
Serruys 1994[30]	Stent 259	57±10	80	20	64	64	13	23	Palmaz–Schatz	No difference	14	98	5	4
	BA 257		82	19	64	62	10	28			3	97	5	
Eeckhout 1996[56]	Stent 42	58±4	88	36	72	0	0	100	Wiktor	Aspirin 100 mg/day in PTCA	21	95	2	4
	BA 42		74	38	71	0	0	100		Aspirin 325 mg/day+dipyridamol 75 mg/day in stent group	0	93	7	
Versaci 1997[36]	Stent 60	57±10	92	28	77	100	0	0	Palmaz–Schatz	Warfarin for 3 months in	7	95	0	4
	BA 60		83	29	78	100	0	0		stent-group	0	93	3	
Serruys 1998[34]	Stent 413	55±10	77	25	63	50	19	31	Palmaz–Schatz	Ticlopidine 250 mg/day for	1	99	0	5
	BA 410		80	28	63	52	19	30		4 weeks in stent group only	1	99	19	
Topol 1998[5]	Stent 794	60±11	75	50					Palmaz–Schatz	Abciximab for all,	5	97	4	3
	BA 796		75	49						ticlopidine 250 mg bid in stent-group only	5	81	10	
Betriu 1999[35]	Stent 239	59±7	87	32	74	51	14	26	Palmaz–Schatz	Dipyridamol 100 mg	4	95	1	4
	BA 233		85	32	73	54	13	30		tid+warfarin for 2 to 3 months in stent-group only	1	84	37	
Buller 1997[57]	Stent: 202	58±11	84	67	100	38	21	46	Heparin-coated	Ticlopidin in 57% of	NA	95	2	4
	BA 208		80	67	100	38	13	48		PTCA-and 93% of stent-group	NA	88	10	
Dangas 1999[29]	Stent: 31	62±13	69		79	42			Palmaz–Schatz	Ticlopidine for 2 to 4 weeks	NA	90	2	4
	BA 66		69		76	19				in stent group only	NA	45	30	
Niazi 1999[26]	Stent 96	55±11	83	59	82	51	29	20	Jo-2 heparin-coated	No information	NA			1
	BA 106		74	62	80	46	34	20			NA			

Table 1 (continued)

Author (year)	Intervention and number of individuals	Mean age (±SD)	Male (%)	Previous MI (%)	Stenosis (mean %)	Target vessel % LAD	% LCX	% RCA	Stent type	Differences in Postinterventional Antithrombotic/ Anticoagulant Therapy	Bleeding compli-cations[a] (%)	Successful dilatation[b] (%)	Crossover (%)	Quality score
Di Mario 2000[31]	Stent 370	61±11	75	40	69	41	24	35	Not specified	Ticlopidine 250 mg bid for 4	NA	100	0	2
	BA 365		73	38	69	38	23	39		weeks in stent group only	NA	57	11	
Fluck 2000[33]	Stent: 154	58±9	76		68				Wiktor	Warfarin and later ticlopidin	6	96	7	4
	BA 146		76		70					in stent group only	2	96	26	
Kastrati 2000[25]	Stent 204	66±11	78	35	76	42	38	20	Multi-link	Abciximab for all,	4	99	0	2
	BA 200		76	39	78	40	41	20		ticlopidine for 4 weeks in stent-group, for 2 weeks in balloon angioplasty-group	1	99	57	
Park 2000[27]	Stent 60	61±8	62	15	77	45	33	22	NIR	Ticlopidine 250 mg bid for 1	NA	100	2	3
	BA 60		65	10	74	55	30	15		month in stent group only	NA	100	13	
Weaver 2000[6]	Stent: 230	61	75	44	89	32	21	45	Palmaz–Schatz	No difference	NA	89	3	3
	BA 249		72	41	89	33	20	47			NA	78	23	
Witkowski 2000[32]	Stent 192	52±11	74	49	78	60	13	27	Palmaz–Schatz	No difference	0	98	0	3
	BA 196		72	42	77	56	15	29			0	99	20	
Doucet 2001[23]	Stent: 169	60±11	66	32	63	43	34	23	Be-stent Artist	Ticlopidine 250–500 mg/day	NA	98	4	3
	BA 182		67	35	62	47	34	20		for 1 month in stent-group only	NA	98	17	
Koning 2001[28]	Stent 192	62±10	73	32	68	24	19	10	Be-stent small	Ticlopidine 500 mg/day in	0	98	4	3
	BA 189		79	43	66	26	22	13		stent group only	0	94	14	
Moer 2001[24]	Stent 74	63±11	67	42	59	38	46	16	Heparin-coated	Thienopyridine for 4 weeks	NA	100	NA	4
	BA 71		73	46	57	39	44	17		instent-grouponly	NA	96	NA	

BA=balloon angioplasty; NA=not available

[a]Need for blood transfusion or surgical intervention.
[b]As defined by individual trial criteria.

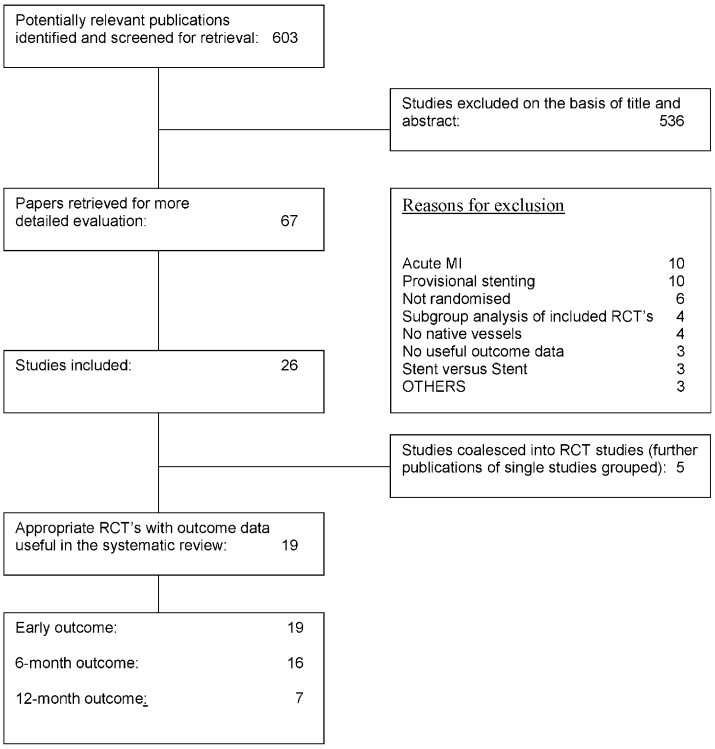


Fig. 1 Flow diagram of systematic review.

were included in our meta-analysis (Table 1). Six different stent types were used in the 19 trials. In 13 trials the target vessel size was ≥3 mm, and in six trials <3 mm.[23–28] Three trials included only patients with stable coronary artery disease,[29–31] the remaining trials included patients with stable and unstable angina.

Definitions of acute myocardial infarction varied across trials. Only four trials mentioned pre-specified criteria for the need of target vessel revascularization (Table 2).

Only three trials used the same post-interventional antithrombotic/anticoagulant therapy in both groups.[6,30,32] All other trials used a more aggressive post-interventional therapy in the stent group.

Only two trials used a glycoprotein IIb/IIIa inhibitor (abciximab) as a co-intervention in both treatment arms.[5,25] The EPISTENT-trial had three treatment arms: we used data from two arms-stents with abciximab and PTCA with abciximab.[5] We did not use data from the third arm (stents with placebo) because there was no comparison group (balloon angioplasty with placebo).

Plots of standardized effects against precision indicated a low probability for the presence of publication bias (P=0.28).[11]

Agreement on quality rating

Proportions of specific agreement for positive and negative ratings were 0.92 and 0.94 for concealment of treatment allocation, 0 and 0.83 for blinded outcome assessment, and 0.91 and 0.75 for full description of loss of follow-up. Proportions of specific agreement give the probability that one assessment is positive (or negative) given that the other assessment is also positive (or negative). Few trials were thought to have blinded outcome assessment by one reviewer or the other, and reviewers never agreed; hence the positive specific agreement of zero for this item. Both reviewers concluded that all trials lost 10% or fewer patients to follow-up and that all trials had open intervention.

Methodologic quality of trials

Random allocation was concealed in 13 trials and possibly concealed in the other six trials.[5,27,30,32–34] In all trials, interventions were not blinded for obvious reasons. After consensus, no trial was found to explicitly mention blinded outcome assessment. In all trials, follow-up data were reported for at least 90% of the patients. In all but five trials, a full description of follow-up and withdrawals was given.[4,26,31,34,35]

Clinical outcomes

Primary outcome

At 30 days, three (95% CI 0 to 6) additional lives were saved per 1000 patients treated with stents rather than balloon angioplasty (Table 3, Fig. 2). Early deaths occurred only in six of 19 trials. For these six trials, the odds ratio for mortality with stents rather than balloon angioplasty was 0.34 (95% CI 0.15–0.81).

Table 2 Endpoint definitions and policy for repeated angiography in included trials

	Definition of endpoints		
Author (year)	Myocardial infarction	Need for target vessel revascularization	Systematically repeated angiography
Fischman 1994[4]	New pathological Q waves or a creatine kinase level or MB fraction of at least twice upper limit of normal	Restenosis of target lesion in association with recurrent angina or in objective evidence of ischaemia	Yes
Serruys 1994[30]	New pathological Q waves or increase in creatine kinase more than twice normal value plus pathological increase in myocardial isoenzymes	Not prespecified	Yes
Eeckhout 1996[56]	Not defined	Not prespecified	Yes
Versaci 1997[36]	Definite electrocardiographic changes and documentation of abnormal cardiac enzyme levels	Not prespecified	Yes
Serruys 1998[34]	New pathological Q waves or increase in creatine kinase more than twice normal value plus pathological increase in myocardial isoenzymes	Not prespecified	Yes
Topol 1998[5]	New pathological Q-waves or increase in creatine kinase or its MB isoenzyme to at least twice the upper limit of normal	Not prespecified	No (34% of patients)
Betriu 1999[35]	New pathological Q waves or increase in creatine kinase/CK-MB levels at least twice upper limit of normal	Not prespecified	Yes
Buller 1999[57]	CK-MB elevation above normal range	Not prespecified	Yes
Dangas 1999[29]	Not defined	Not prespecified	No (62% of patients)
Niazi 1999[26]	Not defined	Not prespecified	Yes
Di Mario 2000[31]	New pathological Q waves in territory of treated artery or increase in creatine kinase MB fraction	Occlusion or restenosis at site of initial lesion or within 5 mm	No
Fluck 2000[33]	New pathological Q waves or increase in creatine kinase to at least twice upper limit of normal	Not prespecified	Yes
Kastrati 2000[25]	New pathological Q waves or increase in creatine kinase or its MB isoenzme to at least three times upper limit of normal	Angiographic restenosis and symptoms or signs of ischaemia	Yes
Park 2000[27]	New electrocardiographic changes or chest pain ≥30 min and increase in cardiac enzymes more than three times upper limit of normal	Not prespecified	Yes
Weaver 2000[6]	New pathological Q waves or symptoms associated with rise in creatine kinase or CK-MB to more than twice normal values	Not prespecified	No
Witkowski 2000[32]	New pathological Q wave and/or creatine kinase or MB fraction at least twice upper limit of normal	Not prespecified	Yes
Doucet 2001[23]	New pathological Q waves or elevation of creatine kinase to greater than twice upper limit of normal with elevated MB fraction	Recurrent angina or signs of ischaemia	Yes
Koning 2001[28]	Not defined	Not prespecified	Yes
Moer 2001[24]	Two of three criteria: prolonged chest pain of cardiac origin not relieved by nitroglycerin, rise in creatine kinase more than twice upper limit of normal, or new pathological Q waves	Not prespecified	Yes

At 6 months, deaths had occurred in 16 trials. On average 5 (95% CI 0 to 9) additional lives were saved per 1000 patients treated with stents rather than balloon angioplasty. The odds ratio for mortality with stents rather than balloon angioplasty was 0.57 (95% CI 0.34–0.96).

Seven trials reported mortality data at 12 months.[4,17,20,29,31,32,34] Six (95% CI −1 to 12) additional lives were saved per 1000 patients treated with stents rather than balloon angioplasty. The odds ratio for mortality with stents rather than balloon angioplasty was 0.62 (95% CI 0.36–1.05). In each analysis, there was no evidence of heterogeneity (P>0.1).

Secondary outcomes

At 30 days there was no evidence from summary risk differences that stents were superior to balloon angioplasty for myocardial infarction, CABG, target

Table 3 Additional events prevented per 1000 patients treated with stents rather than balloon angioplasty in non-acute coronary artery disease (test for heterogeneity $P>0.1$ for all comparisons)

Additional events prevented per 1000 (*n*= number of trials)	30 days (95% CI) *n*=19	6 months (95% CI) *n*=16	12 months (95% CI) *n*=7
Primary outcome			
Mortality	3 (0 to 6)	5 (0 to 9)	6 (−1 to 12)
Secondary outcomes			
Revascularisation of target vessel	3 (−2 to 8)	55 (40 to 71)	46 (25 to 66)
Myocardial infarction	1 (−7 to 9)	2 (−7 to 10)	10 (−4 to 20)
Coronary artery bypass grafting	−1 (−6 to 4)	3 (−5 to 10)	0 (−10 to 10)
Myocardial infarction and death	4 (−4 to 10)	7 (−4 to 20)	10 (2 to 20)
Severe bleeding complications (n=11)	−25 (−15 to −34)		

vessel revascularization, and the composite outcome of death and myocardial infarction (Table 3).

At 6 months, 55 (95% CI 40 to 71) target vessel revascularizations were avoided per 1000 patients treated with stents rather than balloon angioplasty. Summary risk differences for myocardial infarction and CABG suggested some benefit from stents over balloon angioplasty, but these differences were not statistically significant.

At 12 months, 46 (95% CI 25 to 66) target vessel revascularizations were avoided per 1000 patients treated with stents rather than balloon angioplasty, and 10 (95% CI 2 to 20) additional deaths or myocardial infarctions were prevented for 1000 patients treated with stents rather than balloon angioplasty. Summary risk differences at 12 months indicated benefit from stenting for all secondary outcomes—with the exception of CABG—but were not statistically significant. In each analysis, there was no evidence of heterogeneity ($P>0.1$).

Data on post-interventional bleeding complications with need for blood transfusion or surgical intervention were available from 11 trials. The bleeding complication rate ranged from 0 to 21% in patients randomized to stenting, and from 0 to 5% in patients randomized to balloon angioplasty (Table 1). On average, there were 25 (95% CI 15 to 34) additional bleeding complications per 1000 patients treated with stents rather than balloon angioplasty (test of heterogeneity $P>0.1$).

Sensitivity analyses

With few early deaths and few trials reporting 12-month mortality, sensitivity analysis for the primary outcome was only appropriate at 6 months. We compared trials using different stent types, trials with interventions in large and small vessels, trials with different post-interventional antithrombotic/anticoagulant drug therapies in both treatment arms and trials routinely using respectively not using glycoprotein IIb/IIIa inhibitors.

The average number of additional lives saved per 1000 patients treated with stents rather than PTCA was: five (95% CI 0 to 10) in trials using Palmaz–Schatz stents and four (95% −5 to 10) in trials using other stents; five (95% CI 0 to 10) in trials with intervention in large vessels and five (95% CI −5 to 20) in trials with intervention in smaller vessels; six (95% CI 0 to 10) in trials with more aggressive post-interventional antithrombotic/anticoagulant drug therapies in the stent group and one (95% CI −7 to 9) in those three trials with identical post-interventional therapies in both groups;[5,28,30]; 11 (95% CI 2 to 20) in those two trials[5,25] routinely using a glycoprotein IIb/IIIa inhibitor in both treatment groups and two (95% CI −4 to 7) in all other trials not routinely using a glycoprotein IIb/IIIa inhibitor; −1 (95% CI −9 to 7) in trials starting patient enrolment before 1996 and seven (95% CI 1 to 13) in trials starting patient enrolment in 1996 or later (test of heterogeneity for all comparisons $P>0.1$).

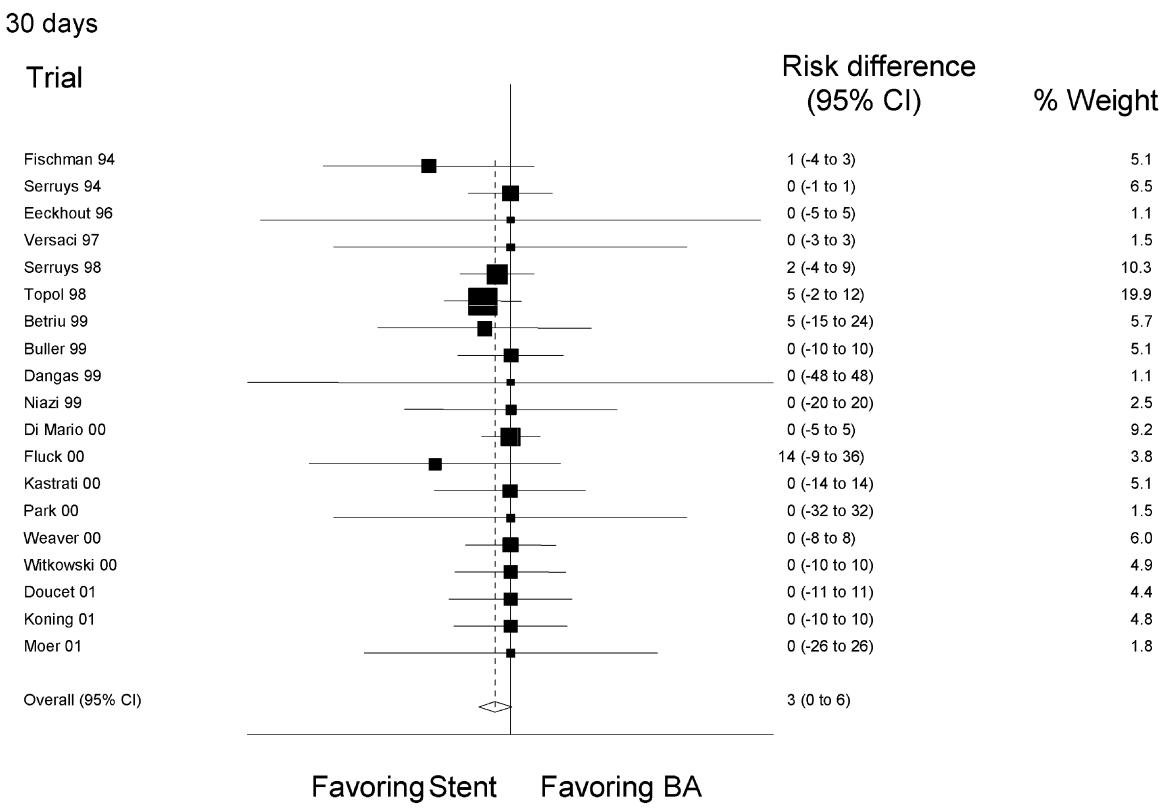
In order to differentiate between the effects of time-related improvements in stenting technique and the use of a glycoprotein IIb/IIIa inhibitors, we repeated our analysis of trials enrolling patients from 1996 and later after exclusion of those two trials routinely using glycoprotein IIb/IIIa inhibitors. By doing so, the average number of additional lives saved per 1000 patients treated with stents rather than PTCA was four (95% CI −3 to 11).

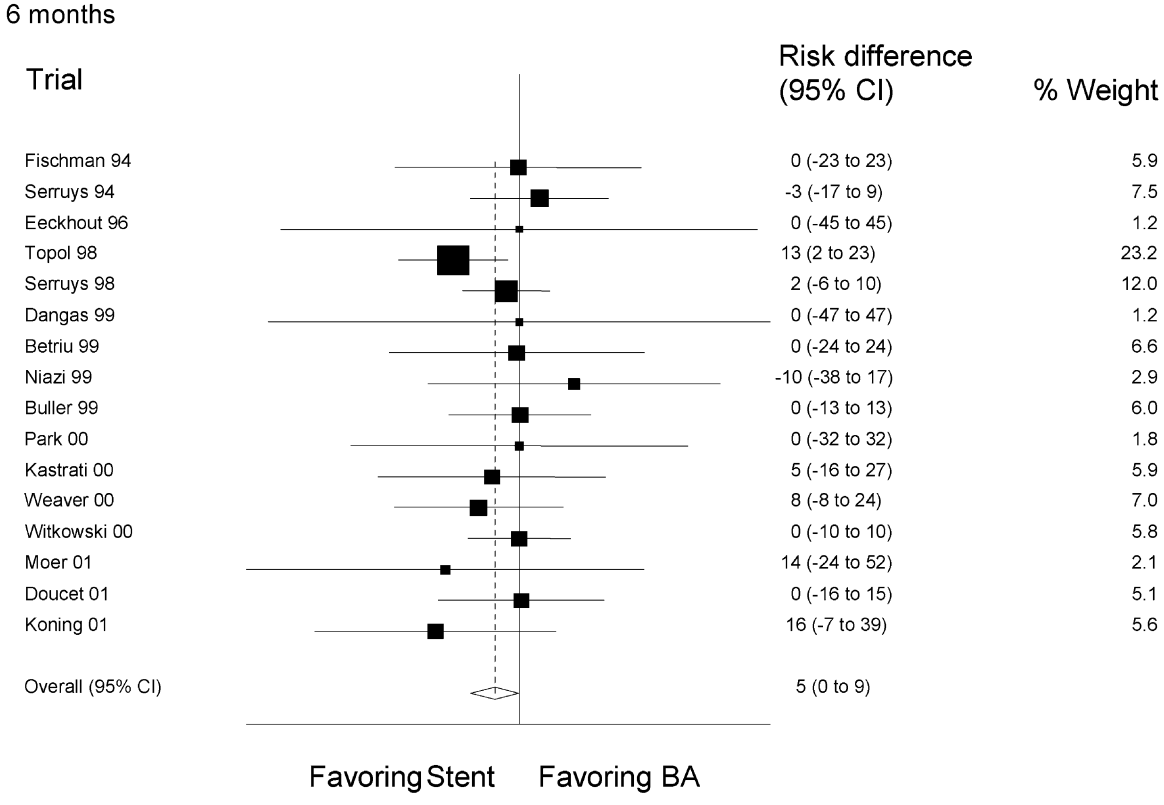
Discussion

Our meta-analysis shows that routine use of stents rather than balloon angioplasty reduces overall mortality at 6 months in patients with non-acute coronary artery disease. This benefit, however, is small and corresponds to five (95% CI 0 to 9) additional saved lives per 1000 patients treated. The benefit seems to persist at 12 months with six (95% CI −1 to 12) additional saved lives per 1000 patients. At 12 months, patients treated with stents rather than balloon angioplasty required between 25 and 66 fewer target vessels revascularizations per 1000 patients treated. This benefit, however, is tempered by a higher risk of post-interventional bleedings (15 to 34 additional bleedings per 1000 patients treated with stents rather than balloon angioplasty).

The evidence that stents reduce mortality is weaker when measured with risk differences than when measured with odds ratios. Simulation suggests that both measures will underestimate the true effect of stents

(a)


30 days
Trial
Risk difference (95% CI)
% Weight
Fischman 94 1 (-4 to 3) 5.1
Serruys 94 0 (-1 to 1) 6.5
Eeckhout 96 0 (-5 to 5) 1.1
Versaci 97 0 (-3 to 3) 1.5
Serruys 98 2 (-4 to 9) 10.3
Topol 98 5 (-2 to 12) 19.9
Betriu 99 5 (-15 to 24) 5.7
Buller 99 0 (-10 to 10) 5.1
Dangas 99 0 (-48 to 48) 1.1
Niazi 99 0 (-20 to 20) 2.5
Di Mario 00 0 (-5 to 5) 9.2
Fluck 00 14 (-9 to 36) 3.8
Kastrati 00 0 (-14 to 14) 5.1
Park 00 0 (-32 to 32) 1.5
Weaver 00 0 (-8 to 8) 6.0
Witkowski 00 0 (-10 to 10) 4.9
Doucet 01 0 (-11 to 11) 4.4
Koning 01 0 (-10 to 10) 4.8
Moer 01 0 (-26 to 26) 1.8
Overall (95% CI) 3 (0 to 6)
Favoring Stent
Favoring BA


6 months
Trial
Risk difference (95% CI)
% Weight
Fischman 94 0 (-23 to 23) 5.9
Serruys 94 -3 (-17 to 9) 7.5
Eeckhout 96 0 (-45 to 45) 1.2
Topol 98 13 (2 to 23) 23.2
Serruys 98 2 (-6 to 10) 12.0
Dangas 99 0 (-47 to 47) 1.2
Betriu 99 0 (-24 to 24) 6.6
Niazi 99 -10 (-38 to 17) 2.9
Buller 99 0 (-13 to 13) 6.0
Park 00 0 (-32 to 32) 1.8
Kastrati 00 5 (-16 to 27) 5.9
Weaver 00 8 (-8 to 24) 7.0
Witkowski 00 0 (-10 to 10) 5.8
Moer 01 14 (-24 to 52) 2.1
Doucet 01 0 (-16 to 15) 5.1
Koning 01 16 (-7 to 39) 5.6
Overall (95% CI) 5 (0 to 9)
Favoring Stent
Favoring BA

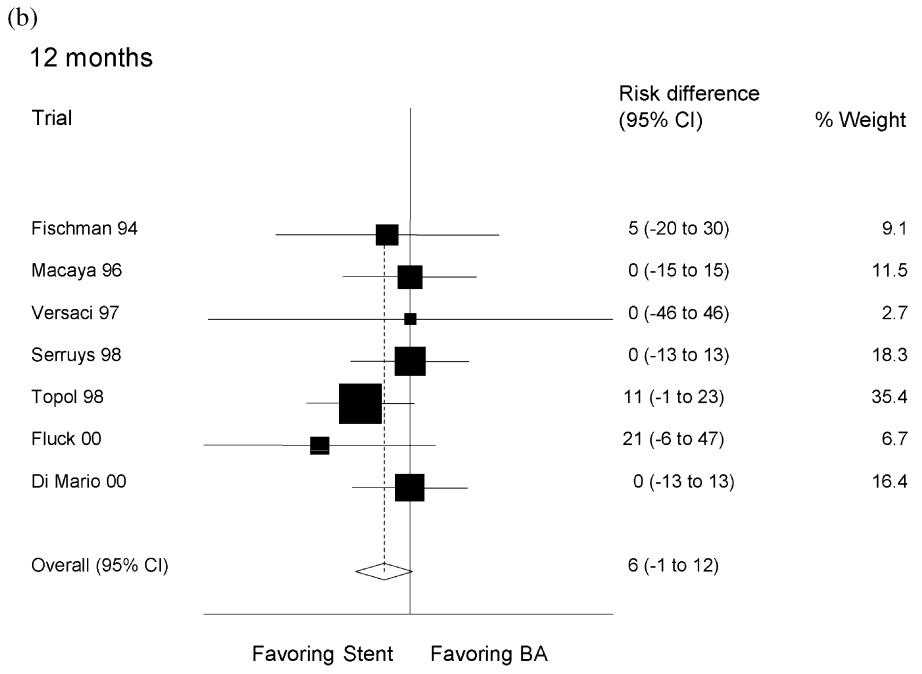


Fig. 2 Additional lives saved per 1000 patients treated with stents as compared to balloon angioplasty in non-acute coronary artery disease (BA).

rather than balloon angioplasty.[15] While Peto odds ratios may be less biased than risk differences when events are rare, the implications of excluding trials with no events in both groups has never been fully investigated.[12] Using risk differences, which include such trials, is therefore a conservative approach.

Following a comprehensive literature search, we included additional unpublished data from individual trials by contacting authors of published trials to provide information not readily available form the published trials and of one trial that had been published only in abstract form.[26] We have no evidence of a publication bias, although such a bias is always possible. We explored heterogeneity between trials according to a priori defined criteria but found no evidence for heterogeneity. A lack of power could be a reason for our failure to detect heterogeneity. The usual test for heterogeneity has low power,[37] particularly in meta-analyses of rare events.[12] However, various clinical trials comparing different stent types have not shown any difference on clinical outcomes such as mortality and reinfarction rates.[38–44] There may be a higher risk of restenosis and revascularization with the Gianturco–Roubin flex stent,[45] but this stent was not used in any of the trials in our analysis.

Given that stents seem to be associated with a lower mortality than balloon angioplasty, we would have expected a lower rate of myocardial infarction in patients treated with stents. Possibly, stents reduce acute plaque rupture of high-risk lesions and so reduce sudden death, but have less effect on non-fatal myocardial infarction. Unfortunately, we do not have the necessary data on sudden death to test this hypothesis.

This meta-analysis has some limitations. Cross-over rates from balloon angioplasty to stents in the included trials were substantial and ranged from 0 to 57% (Table 1). Thus, we may underestimate the true effects of stents. None of the included trials were found to report blinded outcome assessment. While blinded outcome assessment is irrelevant for mortality, the primary endpoint of our study, its absence limits the reliability of results for the secondary outcomes.

Pre-specified comparisons for relevant subgroup analysis of stent types and vessel size remained inconclusive due to lack of power. Only three trials used the same post-interventional antithrombotic/anticoagulant therapy in both groups.[6,30,32] All other trials used a more aggressive post-interventional therapy in the stent group. Our sensitivity analysis lacked power to detect what could be a clinically significant difference in mortality between trials with balanced and unbalanced co-intervention. Therefore, we can not be sure that the reduced mortality in patients treated with stents is really due to stenting and not to unbalanced co-intervention.

The beneficial effect of stenting on mortality was only seen in trials that started patient enrolment in 1996 or later. This implies that advances in stenting technique over the past few years may account for the reduction in mortality. However, the concomitant use of glycoprotein IIb/IIIa inhibitors seems to be the most important factor responsible for the observed benefit of stenting on mortality as demonstrated by our sensitivity analysis. Even modern stenting techniques do not seem to reduce mortality in comparison to balloon angioplasty in the absence of concomitant use of a glycoprotein IIb/IIIa inhibitor. Importantly, the concomitant use of glycoprotein IIb/IIIa inhibitors does not seem to be associated with a higher risk of bleeding complications. In the Epistent trial[5] major bleeding episodes were not higher in

patients treated with stents or balloon angioplasty plus abciximab than in patients treated with stents plus placebo.

The generally higher bleeding risk associated with stenting observed in this meta-analysis may be due to inclusion of earlier trials that used more aggressive anticoagulant therapy. Recently, high levels of procedural anticoagulation with heparin were found to increase haemorrhagic complications without improving clinical outcome in cardiac patients treated with stents.[46] Based on these results, activated clotting times within a range of 150 to 275 s seem to be associated with the lowest risk of bleeding complications.

The external validity of our findings may be limited. Many trials were conducted in specialized high volume centres and some of them included highly pre-selected patients. Therefore, our results may not necessarily apply to patients treated in other centres or settings. We were not able to get individual patient data and therefore unable to evaluate the effects of stenting in important subgroups such as women, diabetic and elderly patients. Women, diabetic and elderly patients were clearly under-represented in the trials included into our meta-analysis. More data on the effects of stenting in these patients are required, especially in the elderly, since angioplasty is increasingly used in older patients with severe angina because it is less invasive than bypass surgery.

We excluded trials that exclusively randomized patients to provisional stenting, a technique that may be less effective, but also less costly than routine stenting.[47] Finally, the trials included into our meta-analysis were of relatively short duration and there is a clear need for more data on the long-term benefits of stents in coronary angioplasty. Cohort studies and national or regional registries could be used to collect this important information.

A recent meta-analysis comparing routine coronary stenting to balloon angioplasty concluded that stenting is safe but probably not associated with important reductions in rates of mortality and acute myocardial infarction.[48] However, this meta-analysis also included trials that randomized patients to stents only after balloon angioplasty had already been performed successfully. This may lead to an underestimation of the true effects of stenting since only patients with optimal balloon angioplasty results served as controls. Furthermore, the beneficial effect of the conjunctive use of glycoprotein IIb/IIIa inhibitors to stents was missed, because no evaluation of the impact of different antithrombotic co-interventions was performed in that study. Another recent meta-analysis that included data derived from stent registries failed to demonstrate any difference in mortality and infarction rates between patients treated by stenting and balloon angioplasty.[49] Inadequate power due to insufficient sample size and lack of inclusion of trials using glycoprotein IIb/IIIa inhibitors may explain why no significant differences were observed in that meta-analysis.

A meta-analysis comparing stents to balloon angioplasty in patients with acute myocardial infarction and with similar follow-up times failed to show any statistically significant difference in mortality (OR 1.04, 95% CI 0.75 to 1.44 for stents versus balloon angioplasty).[50] This could be due to the higher baseline risk of procedure- and non-procedure-related mortality in acute compared to non-acute coronary artery disease.

Stent technology has developed considerably over the last few years. There is now a broad variety of stents with different physical and antithrombotic properties. Clinical trials are needed comparing different stent types or stents with and without new co-interventions such as drug-eluting stents or endoluminal beta-emitting radiation therapy.[7,8,51] Trials with longer follow-up are needed comparing stents with other promising revascularization procedures such as minimally invasive bypass surgery.[52] Some cost-effectiveness studies have clearly favoured stents over balloon angioplasty[53] while others have been inconclusive.[54,55] It is clear that stents will become more economically attractive as their in-hospital costs decrease. New stent types are likely to be associated with higher in-hospital cost and so cost-effectiveness analyses will be needed to justify their use.

In conclusion, routine use of stents rather than balloon angioplasty in the treatment of non-acute coronary artery disease is associated with a reduced risk of both mortality and revascularization up to 6 months of follow-up. The benefit on mortality seems to be limited to stenting with concomitant use of glycoprotein IIb/IIIa inhibitors. These benefits outweigh a higher risk of post-interventional bleeding complications in patients treated with stents.

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References

1. Sigwart U, Puel J, Mirkovitch V et al. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. *N Engl J Med* 1987;**316**:701–6.
2. Curfman GD. Sirolimus-eluting coronary stents. *N Engl J Med* 2002; **346**:1770–1.
3. Eeckhout E, Wijns W, Meier B et al. Indications for intracoronary stent placement: the European view. Working Group on Coronary Circulation of the European Society of Cardiology. *Eur Heart J* 1999; **20**:1014–9.
4. Fischman DL, Leon MB, Baim DS et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *N Engl J Med* 1994;**331**:496–501.
5. The EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. *Lancet* 1998; **352**:87–92.

6. Weaver WD, Reisman MA, Griffin JJ et al. Optimum percutaneous transluminal coronary angioplasty compared with routine stent strategy trial (OPUS-1): a randomised trial. *Lancet* 2000; **355**:2199–203.
7. Morice MC, Serruys PW, Sousa JE et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;**346**:1773–80.
8. Park SJ, Shim WH, Ho DS et al. A paclitaxel-eluting stent for the prevention of coronary restenosis. *N Engl J Med* 2003;**348**:1537–45.
9. Jadad AR, Moore RA, Carroll D et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;**17**:1–12.
10. Cicchetti DV, Feinstein AR. High agreement but low kappa: II. Resolving the paradoxes. *J Clin Epidemiol* 1990;**43**:551–8.
11. Egger M, Davey SG, Schneider M et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629–34.
12. Sutton A, Cooper N, Lambert P et al. Meta-analysis of rare and adverse event data [abstr]. *Pharmacoecon Outcom Res* 2002;**2**:367.
13. Smeeth L, Haines A, Ebrahim S. Numbers needed to treat derived from meta-analyses — sometimes informative, usually misleading. *BMJ* 1999;**318**:1548–51.
14. Engels EA, Schmid CH, Terrin N. Heterogeneity and statistical significance in meta-analysis: an empirical study of 125 meta-analyses. *Stat Med* 2000;**19**:1707–28.
15. Deeks J, Bradburn M, Localio R et al. Much ado about nothing: Meta-analysis for rare events. 6th Cochrane Colloquium Baltimore, MD,USA 0 AD.
16. Sweeting M, Sutton A, Lambert P What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of rare events, July 2, 2002; 4th symposium on systematic reviews: pushing the boundaries. Oxford, UK.
17. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–88.
18. Fleiss JL. The statistical basis of meta-analysis. *Stat Methods Med Res* 1993;**2**:121–45.
19. Macaya C, Serruys PW, Ruygrok P et al. Continued benefit of coronary stenting versus balloon angioplasty: one-year clinical follow-up of Benestent trial. Benestent Study Group. *J Am Coll Cardiol* 1996; **27**:255–61.
20. Kiemeneij F, Serruys PW, Macaya C et al. Continued benefit of coronary stenting versus balloon angioplasty: five-year clinical follow-up of Benestent-I trial. *J Am Coll Cardiol* 2001;**37**:1598–603.
21. Lincoff AM, Califf RM, Moliterno DJ et al. Complementary clinical benefits of coronary-artery stenting and blockade of platelet glycoprotein IIb/IIIa receptors. Evaluation of Platelet IIb/IIIa Inhibition in Stenting Investigators. *N Engl J Med* 1999;**341**:319–27.
22. George CJ, Baim DS, Brinker JA et al. One-year follow-up of the Stent Restenosis (STRESS I) Study. *Am J Cardiol* 1998;**81**:860–5.
23. Doucet S, Schalij MJ, Vrolix MC et al. Stent placement to prevent restenosis after angioplasty in small coronary arteries. *Circulation* 2001;**104**:2029–33.
24. Moer R, Myreng Y, Molstad P et al. Stenting in small coronary arteries (SISCA) trial. A randomized comparison between balloon angioplasty and the heparin-coated beStent. *J Am Coll Cardiol* 2001; **38**:1598–603.
25. Kastrati A, Schomig A, Dirschinger J et al. A randomized trial comparing stenting with balloon angioplasty in small vessels in patients with symptomatic coronary artery disease. ISAR- SMART Study Investigators. Intracoronary Stenting or Angioplasty for Restenosis Reduction in Small Arteries. *Circulation* 2000;**102**:2593–8.
26. Niazi K. Stents in small coronary vessels: A prospective, randomized study [abstr]. *Circulation* 1999;**Supplement I**:I-510.
27. Park SW, Lee CW, Hong MK et al. Randomized comparison of coronary stenting with optimal balloon angioplasty for treatment of lesions in small coronary arteries. *Eur Heart J* 2000;**21**:1785–9.
28. Koning R, Eltchaninoff H, Commeau P et al. Stent placement compared with balloon angioplasty for small coronary arteries: in-hospital and 6-month clinical and angiographic results. *Circulation* 2001;**104**:1604–8.
29. Dangas G, Ambrose JA, Rehmann D et al. Balloon optimization versus stent study (BOSS): provisional stenting and early recoil after balloon angioplasty. *Am J Cardiol* 2000;**85**:957–61.
30. Serruys PW, de Jaegere P, Kiemeneij F et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med* 1994;**331**:489–95.
31. Di Mario C, Moses JW, Anderson TJ et al. Randomized comparison of elective stent implantation and coronary balloon angioplasty guided by online quantitative angiography and intracoronary Doppler. DESTINI Study Group (Doppler Endpoint STenting INternational Investigation). *Circulation* 2000;**102**:2938–44.
32. Witkowski A, Ruzyllo W, Gil R et al. A randomized comparison of elective high-pressure stenting with balloon angioplasty: six-month angiographic and two-year clinical follow-up. On behalf of AS (Angioplasty or Stent) trial investigators. *Am Heart J* 2000; **140**:264–71.
33. Fluck DS, Chenu P, Mills P et al. Is provisional stenting the effective option? The WIDEST study (Wiktor stent in de novo stenosis). Widest Trial Investigators' Group. *Heart* 2000;**84**:522–8.
34. Serruys PW, van Hout B, Bonnier H et al. Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). *Lancet* 1998;**352**:673–81.
35. Betriu A, Masotti M, Serra A et al. Randomized comparison of coronary stent implantation and balloon angioplasty in the treatment of de novo coronary artery lesions (START): a four-year follow-up. *J Am Coll Cardiol* 1999;**34**:1498–506.
36. Versaci F, Gaspardone A, Tomai F et al. A comparison of coronary-artery stenting with angioplasty for isolated stenosis of the proximal left anterior descending coronary artery. *N Engl J Med* 1997; **336**:817–22.
37. Hardy RJ, Thompson SG. Detecting and describing heterogeneity in meta-analysis. *Stat Med* 1998;**17**:841–56.
38. Baim DS, Cutlip DE, O'Shaughnessy CD et al. Final results of a randomized trial comparing the NIR stent to the Palmaz–Schatz stent for narrowings in native coronary arteries. *Am J Cardiol* 2001; **87**:152–6.
39. Baim DS, Cutlip DE, Midei M et al. Final results of a randomized trial comparing the MULTI-LINK stent with the Palmaz–Schatz stent for narrowings in native coronary arteries. *Am J Cardiol* 2001; **87**:157–62.
40. Heuser R, Lopez A, Kuntz R et al. SMART: The microstent's ability to limit restenosis trial. *Cathet Cardiovasc Interv* 2001;**52**:269–77.
41. Nageh T, de Belder AJ, Thomas MR et al. A randomised trial of endoluminal reconstruction comparing the NIR stent and the Wallstent in angioplasty of long segment coronary disease: results of the RENEWAL Study. *Am Heart J* 2001;**141**:971–6.
42. Han RO, Schwartz RS, Kobayashi Y et al. Comparison of self-expanding and balloon-expandable stents for the reduction of restenosis. *Am J Cardiol* 2001;**88**:253–9.
43. Miketic S, Carlsson J, Tebbe U. Randomized comparison of J&J Crown stent versus NIR stent after routine coronary angioplasty. *Am Heart J* 2001;**142**:E8.
44. Mehilli J, Kastrati A, Dirschinger J et al. A randomized trial comparing the hand-mounted JoStent with the premounted Multi-Link Duet stent in patients with coronary artery disease. *Cathet Cardiovasc Interv* 2001;**54**:414–9.
45. Lansky AJ, Roubin GS, O'Shaughnessy CD et al. Randomized comparison of GR-II stent and Palmaz–Schatz stent for elective treatment of coronary stenoses. *Circulation* 2000;**102**:1364–8.
46. Ashby DT, Dangas G, Aymong EA et al. Relation between the degree of procedural anticoagulation and complications after coronary stent implantation. *Am J Cardiol* 2003;**92**:319–22.
47. Yock CA, Boothroyd DB, Owens DK. Projected long-term costs of coronary stenting in multivessel coronary disease based on the experience of the Bypass Angioplasty Revascularization Investigation (BARI). *Am Heart J* 2000;**140**:556–64.
48. Brophy JM, Belisle P, Joseph L. Evidence for use of coronary stents. A hierarchical bayesian meta-analysis. *Ann Intern Med* 2003; **138**:777–86.
49. Mercado N, Maier W, Boersma E et al. Clinical and angiographic outcome of patients with mild coronary lesions treated with balloon angioplasty and coronary stenting. Implications for mechanical plaque sealing. *Eur Heart J* 2003;**24**:541–51.
50. Zhu MM, Feit A, Chadow H et al. Primary stent implantation compared with primary balloon angioplasty for acute myocardial infarction: a meta-analysis of randomized clinical trials. *Am J Cardiol* 2001; **88**:297–301.

51. Keller PF, Verin V, Ziegler T et al. Gamma-irradiation markedly inhibits the hydrated collagen gel contradiction by arterial smooth muscle cells. *J Investig Med* 2001;**49**:258–64.
52. Diegeler A, Thiele H, Falk V et al. Comparison of stenting with minimally invasive bypass surgery for stenosis of the left anterior descending coronary artery. *N Engl J Med* 2002;**347**:561–6.
53. Van Hout BA, van der WT, de Jaegere PP et al. Cost effectiveness of stent implantation versus PTCA: the BENESTENT experience. *Semin Interv Cardiol* 1996;**1**:263–8.
54. Cohen DJ, Krumholz HM, Sukin CA et al. In-hospital and one-year economic outcomes after coronary stenting or balloon angioplasty. Results from a randomized clinical trial. Stent Restenosis Study Investigators. *Circulation* 1995;**92**:2480–7.
55. Peterson ED, Cowper PA, DeLong ER et al. Acute and long-term cost implications of coronary stenting. *J Am Coll Cardiol* 1999;**33**:1610–8.
56. Eeckhout E, Stauffer JC, Vogt P et al. Comparison of elective Wiktor stent placement with conventional balloon angioplasty for new-onset lesions of the right coronary artery. *Am Heart J* 1996;**132**:263–8.
57. Buller CE, Dzavik V, Carere RG et al. Primary stenting versus balloon angioplasty in occluded coronary arteries: the Total Occlusion Study of Canada (TOSCA). *Circulation* 1999;**100**:236–42.