Clinical Outcomes of Primary Stenting versus Balloon Angioplasty in Patients with Myocardial Infarction: A Meta-analysis of Randomized Controlled Trials

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PURPOSE: To examine whether primary stenting as compared with primary balloon angioplasty reduces clinical outcomes in patients with myocardial infarction.

METHODS: Major medical databases from 1979 to March 2002 were searched for randomized controlled trials that compared primary stenting with balloon angioplasty in patients with myocardial infarction. Two independent reviewers selected and extracted data from identified trials. The outcomes were mortality at 30 days, 6 months, and 12 months; recurrent events; and bleeding.

RESULTS: Nine trials with a total of 4433 patients fulfilled the inclusion criteria. The odds ratios for mortality after stenting as compared with balloon angioplasty were 1.17 (95% confidence interval [CI]: 0.78 to 1.74) at 30 days, 1.07 (95% CI: 0.76 to 1.52) at 6 months, and 1.09 (95% CI: 0.80 to 1.50) at 12 months (*P* for heterogeneity >0.1 for each comparison). The odds ratios for reinfarction after stenting as compared with balloon angioplasty were 0.52 (95% CI: 0.31 to 0.87) at 30 days, 0.67 (95% CI: 0.45 to 1.00) at 6 months, and 0.67 (95% CI: 0.45 to 0.99) at 12 months; for target vessel revascularization, they were 0.46 (95% CI: 0.34 to 0.61) at 30 days, 0.42 (95% CI: 0.35 to 0.51) at 6 months, and 0.48 (95% CI: 0.39 to 0.59) at 12 months (*P* for heterogeneity >0.1 for all estimates with the exception of reinfarction at 12 months where $P = 0.08$). The odds ratio for postinterventional bleeding complications after stenting as compared with balloon angioplasty was 1.34 (95% CI: 0.95 to 1.88; *P* for heterogeneity >0.1).

CONCLUSION: Compared with balloon angioplasty, primary stenting is not associated with lower mortality, but is associated with a lower risk of reinfarction and target vessel revascularization. **Am J Med. 2004;116:253–262.** ©2004 by Excerpta Medica Inc.

In patients with myocardial infarction, balloon angioplasty reduces short-term death, nonfatal myocardial infarction, and stroke when compared with thrombolytic reperfusion (1). Still, the clinical efficacy of balloon angioplasty is limited by the development of late restenosis in up to 50% of patients, and by recurrent myocardial infarction in 3% to 5% of patients (2–5). Primary stenting may offer additional benefits. However, a recent meta-analysis of clinical trials found no difference in mortality and reinfarction rates among patients undergoing stenting or balloon angioplasty (6). We conducted a meta-analysis based on published and unpublished trial data to investigate whether primary stenting as compared with balloon angioplasty reduces mortality, recurrent events, and the risk of bleeding in patients with myocardial infarction.

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 that compared primary stenting with balloon angioplasty in patients with myocardial infarction. We used the following search terms: *angioplasty transluminal percutaneous coronary, stents, randomized controlled trials, clinical trials, coronary artery dilatation, transluminal coronary angioplasty,* and *random.* We also searched all references of relevant articles for additional trials. If necessary, authors of identified trials were contacted for additional information.

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Two reviewers independently selected the relevant trials; disagreements were resolved by consensus. The same reviewers extracted data from all trials that fulfilled the inclusion criteria.

Inclusion and Exclusion Criteria

Trials were included if they met the following criteria: randomization to primary stenting or balloon angioplasty prior to the invasive procedure; intervention in native coronary arteries within 24 hours after onset of symptoms of myocardial infarction; report of death or reinfarction; and follow-up of at least 1 month. We excluded trials in which randomization occurred after an invasive procedure had already been performed, as well as trials that exclusively included patients with cardiogenic shock.

Outcomes

The main outcome of interest was mortality at 30 days, 6 months, and 12 months of follow-up. Other endpoints were reinfarction; coronary artery bypass grafting; target vessel revascularization; a composite outcome of death and reinfarction at 30 days, 6 months, and 12 months; and procedure-related bleeding complications (defined as retroperitoneal, intracerebral, or fatal bleedings with the need for vascular repair or blood transfusion).

Assessment of Study Quality

Two reviewers independently assessed the quality of each included trial using a modified Jadad score (7). The methodologic quality of the included trials was rated based on the following items: randomization of participants; blinding of patients, caregivers, and those assessing outcome; and full description of withdrawals and dropouts. One point was given for each item if present. If randomization was concealed, and if the method of double-blinding was appropriate, one additional point was given to each item, yielding a total score of 0 to 5 points. Agreement between the reviewers was assessed by calculating the proportions of specific agreement for positive and negative ratings (8). Disagreements were resolved by consensus.

Examination of Publication Bias

A plot of standardized effect against precision was used to test for publication bias (9).

Data Analysis

STATA 7.0 (Stata Corporation, College Station, Texas) statistical software was used to calculate the odds ratios for the primary and secondary outcomes (10). To explore the stability of the overall treatment effect, we compared trials that used different types of stents and postinterventional antithrombotic/anticoagulant drug therapies, and trials with a crossover rate from balloon angioplasty to stenting that was below and above the median (crossover rate of 15%). In addition, we compared trials involving concealed randomization versus those that did not, and trials that had blinded outcome assessment versus those that did not. Analyses were repeated after excluding the results of unpublished trials.

RESULTS

Of the 603 potentially relevant publications, 10 met the inclusion criteria (11–20) (Figure 1). We did not include one trial in which patients were randomly assigned to provisional stenting or to no further intervention after balloon angioplasty had already been performed (21). Another publication that was excluded was a long-term follow-up of a previously published trial (13). Thus, nine trials with a total of 4433 patients were included in the meta-analysis (Tables 1 and 2). Five of these trials explicitly excluded patients with cardiogenic shock. Two trials allowed for the inclusion of patients with cardiogenic shock: 8 of 104 patients in the Gianturco-Roubin in Acute Myocardial Infarction (GRAMI) trial (14) and 6 of 44 patients in the Primary Stenting versus Angioplasty Acute Myocardial Infarction (PSAAMI) trial (19).

Abciximab was used routinely only in the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial (20). This trial had a two-by-two factorial design and randomly assigned patients to balloon angioplasty alone, balloon angioplasty plus abciximab, stenting alone, or stenting plus abciximab. In our primary analysis, we compared all patients randomly assigned to balloon angioplasty (with or without abciximab) with those randomly assigned to stenting (with or without abciximab).

Palmaz-Schatz stents were used in three trials (12,15,16), and were heparin coated in one trial (15). Two trials used Wiktor stents (17,18). All trials used more aggressive postinterventional antithrombotic/anticoagulant therapies in patients assigned to stenting. Patients treated with stents were given aspirin and ticlopidine, clopidogrel, or warfarin, whereas patients treated with balloon angioplasty were generally only given aspirin. In the CADILLAC trial (20), all patients randomly assigned to stenting and approximately 50% of patients randomly assigned to percutaneous transluminal coronary angioplasty received either ticlopidine or clopidogrel.

Plots of standardized effects against precision indicated a low probability of publication bias ($P = 0.68$) (9).

Agreement on Quality Rating

There was complete agreement between both reviewers for concealment of treatment allocation, and full description of follow-up. For blinded outcome assessment, agreement was 0.80 for positive ratings and 0.92 for negative ratings.

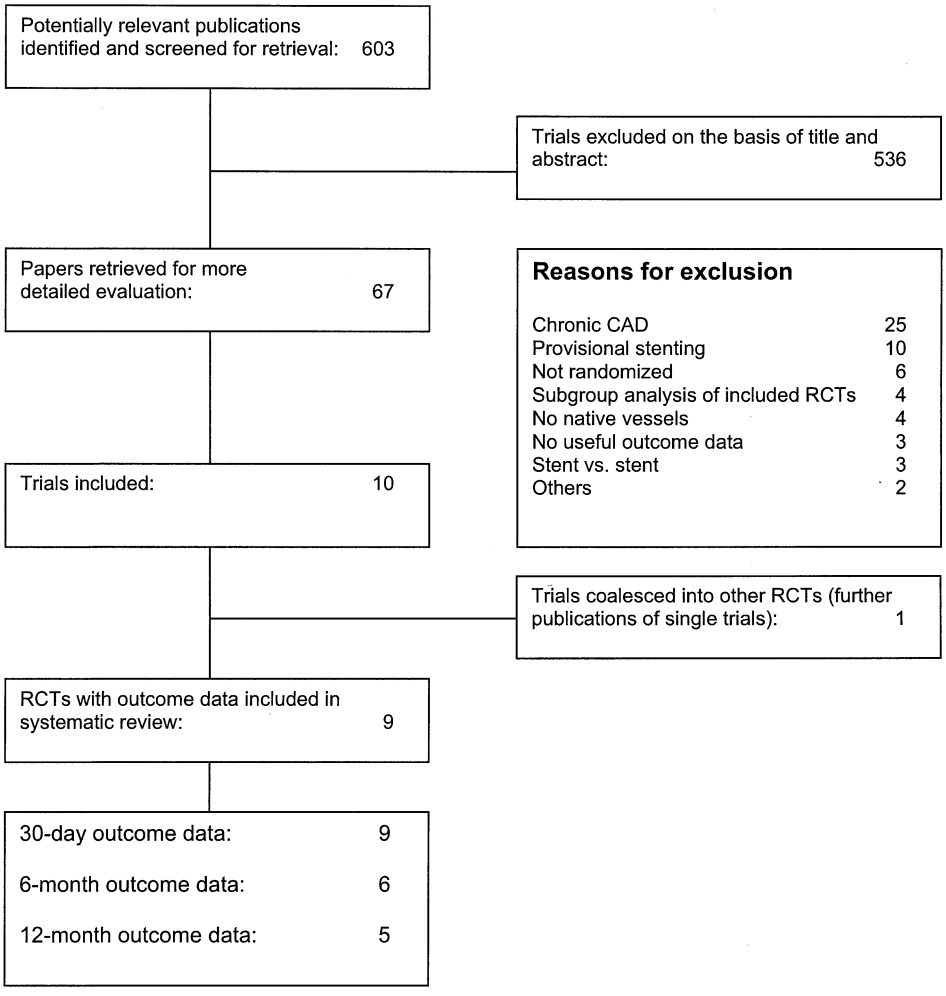

Figure 1. Flow diagram of eligible and included trials comparing routine primary stenting with balloon angioplasty in patients with myocardial infarction. CAD = coronary artery disease; RCT = randomized controlled trial.

Methodologic Quality of Trials

Random allocation was concealed in four trials (15,18–20) and possibly concealed in the remaining five trials (11,12,14,16,17). Blinded outcome assessment of clinical endpoints was reported only in three trials (12,15,20). In three trials (11,15,20), the description of follow-up and withdrawals was incomplete.

Clinical Outcomes

The odds ratios for postinterventional mortality slightly favored balloon angioplasty as compared with stenting at 30 days, 6 months, and 12 months (Table 3; Figure 2). Although the point estimates indicated slightly increased mortality with primary stenting, they were not statistically significant. There was no evidence of heterogeneity for all three estimates ($P > 0.1$). In contrast, the odds ratios for reinfarction favored primary stenting at the three time points during follow-up (Table 3; Figure 3), as did those for revascularization of the target vessel (Table 3; Figure 4). There was no evidence of heterogeneity ($P > 0.1$) for all but one summary estimate (reinfarction at 12 months, $P = 0.08$).

The odds ratios for coronary artery bypass grafting and the composite endpoint of reinfarction and mortality after primary stenting as compared with balloon angioplasty were not statistically significant (Table 3). The odds ratio for bleeding complications after primary stenting was 1.34 (95% CI: 0.95 to 1.88; P for heterogeneity >0.1).

Sensitivity Analyses

In trials that used Palmaz-Schatz stents, the odds ratios for mortality after primary stenting as compared with balloon angioplasty were 1.27 (95% confidence interval [CI]: 0.65 to 2.45) at 30 days, 1.21 (95% CI: 0.66 to 2.25)

Table 1. Baseline Characteristics and Type of Intervention in Randomized Controlled Trials Comparing Primary Stenting with Balloon Angioplasty in Patients with Myocardial Infarction

First Author (Reference)	Quality Score	Intervention	No. of Patients	Mean (±SD) Age (years)	Male Sex (%)	Mean Follow-up (months)	Stent Type	Differences in Postinterventional Antithrombotic/Anticoagulant Therapy	Criteria for the Need for Target Vessel Revascularization
Jaksch (11)*	1	Stenting Angioplasty	231 231	58 ± 12	72	6	Various	Ticlopidine for 4 weeks in stent group only	Not specified
Rodriguez (14)	3	Stenting Angioplasty	52 52	59 ± 10	84	12	Gianturco-Roubin	Ticlopidine 500 mg/d for 4 weeks in stent group only	Not specified
Suryapranata (12)	4	Stenting Angioplasty	112 115	58 ± 11	84	12	Palmaz-Schatz	Warfarin ≥3 months and ticlopidine 250 mg/d for ≥2 weeks in stent group only	Electrocardiographic or scintigraphic evidence of ischemia at rest or on exercise testing
Grines (15)	3	Stenting Angioplasty	452 443	60 ± 12	75	12	Heparin-coated Palmaz-Schatz	Ticlopidine in 93% of stent group and 88% of PTCA group	Clinical symptoms suggestive of ischemia or electrocardiographic changes during exercise
Saito (16)	3	Stenting Angioplasty	67 70	67 ± 11	72	12	Palmaz-Schatz	Ticlopidine 200 mg for 4 weeks in stent group only	Not specified
Kawashima (17)*	1	Stenting Angioplasty	110 112	NA	NA	6	Wiktor	No data	Not specified
Maillard (18)	4	Stenting Angioplasty	101 110	57 ± 12	82	12	Wiktor GX	Ticlopidine 500 mg/d for 4 weeks in stent group only	Not specified
Scheller (19)	4	Stenting Angioplasty	44 44	61 ± 10	76	24	Tensum III	Ticlopidine 500 mg/d for 4 weeks in stent group only, abciximab in 48% of patients in both groups	Not specified
Stone (20)	3	Stenting Angioplasty	1036 1046	60	73	12	Multi-Link and Multi-Link Duet	Ticlopidine 250 mg twice daily or clopidogrel 75 mg/d for 4 weeks in stent group only; abciximab for 50% of patients in both groups	Evidence of ischemia during functional testing or angina

* Published as abstract only.

NA = not available; PTCA = percutaneous transluminal coronary angioplasty.

Table 2. Event Rates in Randomized Controlled Trials Comparing Primary Stenting with Balloon Angioplasty in Patients with Myocardial Infarction

First Author (Reference)	Intervention	Crossover from Balloon Angioplasty to Stenting (%)	Successful Dilatation* (%)	Postinterventional Bleeding Complications (%)	Event Rates								
					Mortality (%)			Myocardial infarction (%)			Revascularization* (%)		
					30 days	6 months	12 months	30 days	6 months	12 months	30 days	6 months	12 months
Jaksch (11)†	Stenting	27	97	NA	1.3	2.2	–	1.2	1.2	–	1.7	3.0	–
	Angioplasty		97	NA	2.2	3.0	–	3.5	3.5	–	6.1	8.7	–
Rodriguez (14)	Stenting	25	98	1.9	3.8	–	–	0.0	–	–	0.0	–	3.0
	Angioplasty		92	1.9	7.8	–	–	7.7	–	–	5.8	–	4.3
Suryapranata (12)	Stenting	13	96	6.3	1.8	1.8	2.7	0.9	0.9	0.9	0.0	3.6	7.1
	Angioplasty		98	2.6	2.6	2.6	3.5	4.4	7.0	8.7	4.3	16.5	18.3
Grines (15)	Stenting	15	98	5.1	3.5	4.2	5.8	0.4	2.4	2.9	1.3	7.7	–
	Angioplasty		99	3.8	1.8	2.7	3.1	1.1	2.2	2.7	3.8	20.0	–
Saito (16)	Stenting	10	97	1.5	3.0	4.5	4.5	0.0	0.0	0.0	6.0	16.4	17.9
	Angioplasty		99	1.4	7.1	7.1	8.6	4.3	5.7	5.7	12.9	32.8	34.3
Kawashima (17)†	Stenting	1	NA	NA	0.0	–	–	–	–	–	22.7	–	–
	Angioplasty		NA	NA	0.9	–	–	–	–	–	34.0	–	–
Maillard (18)	Stenting	36	86	2.0	1.0	2.0	3.0	4.0	4.0	4.0	5.0	16.8	16.8
	Angioplasty		83	2.7	0.0	1.1	1.8	3.6	5.5	5.5	5.4	26.3	27.3
Scheller (19)	Stenting	27	61	9.0	4.5	–	9.1‡	0.0	–	2.3‡	0.0	–	15.9‡
	Angioplasty		91	13.6	2.3	–	18.1‡	2.3	–	9.0‡	9.0	–	34.1‡
Stone (20)	Stenting	16	96	4.0	2.4	3.6	4.2	0.9	1.9	2.1	2.3	6.7	8.7
	Angioplasty		95	2.8	1.8	3.4	4.3	0.8	2.2	2.5	4.5	14.7	16.8

* According to individual trials' criteria.
† Published as abstract only.
‡ 24-month follow-up data.
NA = not available.

Table 3. Odds Ratios for Clinical Endpoints in Patients with Myocardial Infarction Who Were Treated with Primary Stenting Compared with Balloon Angioplasty

Endpoint	30 Days Odds Ratio (95% Confidence Interval)	*P* Value*	6 Months Odds Ratio (95% Confidence Interval)	*P* Value*	12 Months Odds Ratio (95% Confidence Interval)	*P* Value*
Mortality	1.17 (0.78–1.74)	0.43	1.07 (0.76–1.52)	0.73	1.09 (0.80–1.50)	0.28
Reinfarction	0.52 (0.31–0.87)	0.11	0.67 (0.45–1.00)	0.14	0.67 (0.45–0.99)	0.08
Revascularization of target vessel	0.46 (0.34–0.61)	0.48	0.42 (0.35–0.51)	0.76	0.48 (0.39–0.59)	0.90
Coronary artery bypass grafting	0.48 (0.20–1.11)	0.54	0.47 (0.20–1.11)	0.11		
Reinfarction and death	0.95 (0.70–1.29)	0.03	0.87 (0.67–1.14)	0.07		
Severe bleeding complications	1.34 (0.95–1.88)	0.86				

* Test of heterogeneity.

at 6 months, and 1.35 (95% CI: 0.79 to 2.31) at 12 months. The odds ratios were slightly lower in trials that used other types of stents (30 days: odds ratio [OR] = 1.11, 95% CI: 0.67 to 1.83; 6 months: OR = 1.01, 95% CI: 0.66 to 1.52; 12 months: OR = 0.97, 95% CI: 0.66 to 1.44; *P* for heterogeneity >0.1).

Because all trials used more potent postinterventional antithrombotic therapies in patients treated with stenting, a sensitivity analysis for this prespecified criterion was not possible. To adjust for a potential treatment interaction of abciximab, we repeated the analysis, excluding all patients treated with abciximab from the CADILLAC trial. In this analysis, the odds ratios for mortality after primary stenting as compared with balloon angioplasty were 1.20 (95% CI: 0.80 to 1.80) at 30 days, 0.91 (95% CI: 0.61 to 1.36) at 6 months, and 1.04 (95% CI: 0.69 to 1.56) at 12 months (*P* for heterogeneity >0.1).

In trials with lower crossover rates from balloon angioplasty to stenting (≤15%), the odds ratios for mortality after primary stenting as compared with balloon angioplasty were 1.19 (95% CI: 0.62 to 2.29) at 30 days, 1.21 (95% CI: 0.66 to 2.21) at 6 months, and 1.35 (95% CI: 0.79 to 2.31) at 12 months, as compared with odds ratios of 1.15 (95% CI: 0.70 to 1.90) at 30 days, 1.01 (95% CI: 0.66 to 1.55) at 6 months, and 0.97 (95% CI: 0.66 to 1.44) at 12 months in trials with crossover rates of >15% (*P* for heterogeneity >0.1).

In trials reporting concealment of treatment allocation, odds ratios for mortality after primary stenting as compared with balloon angioplasty were 1.72 (95% CI: 1.13 to 2.63) at 30 days, 1.20 (95% CI: 0.81 to 1.76) at 6 months, and 1.12 (95% CI: 0.74 to 1.68) at 12 months. The corresponding odds ratios in trials not reporting concealment of treatment allocation were 0.60 (95% CI: 0.28 to 1.28) at 30 days, 0.81 (95% CI: 0.38 to 1.74) at 6 months, and 0.62 (95% CI: 0.23 to 1.68) at 12 months (*P* for heterogeneity >0.1 for all comparisons with the exception of 12-month mortality in trials with concealed treatment allocation where $P = 0.09$).

In trials reporting blinded outcome assessment, the odds ratios for mortality after primary stenting as compared with balloon angioplasty were 1.45 (95% CI: 0.91 to 2.30) at 30 days, 1.15 (0.78 to 1.68) at 6 months, and 1.07 (95% CI: 0.71 to 1.60) at 12 months. The corresponding odds ratios in trials not reporting blinded outcome assessment were 1.17 (95% CI: 0.63 to 2.18) at 30 days, 0.95 (95% CI: 0.43 to 2.11) at 6 months, and 0.79 (95% CI: 0.27 to 2.30) at 12 months (*P* for heterogeneity >0.1 for all comparisons with the exception of 12-month mortality in trials with concealed treatment allocation where $P = 0.08$).

After exclusion of the two unpublished trials, the odds ratios for mortality after primary stenting as compared with balloon angioplasty were 1.27 (95% CI: 0.83 to 1.93) at 30 days and 1.12 (95% CI: 0.78 to 1.81) at 6 months (*P* for heterogeneity >0.1). The odds ratios for reinfarctions after primary stenting as compared with balloon angioplasty after exclusion of these two unpublished trials were 0.55 (95% CI: 0.31 to 0.99) at 30 days, 0.71 (95% CI: 0.47 to 1.09) at 6 months, and 0.67 (95% CI: 0.45 to 0.99) at 12 months (*P* for heterogeneity >0.1).

DISCUSSION

Our meta-analysis found no evidence that primary stenting in patients with myocardial infarction reduced overall mortality compared with balloon angioplasty. However, primary stenting reduced the risk of reinfarction and target vessel revascularization, as compared with balloon angioplasty. At 1 year, an average of 12 (95% CI: 1 to 23) reinfarctions and 144 (95% CI: 66 to 223) target vessel revascularizations were avoided per 1000 patients with myocardial infarction who were treated with primary stenting instead of balloon angioplasty.

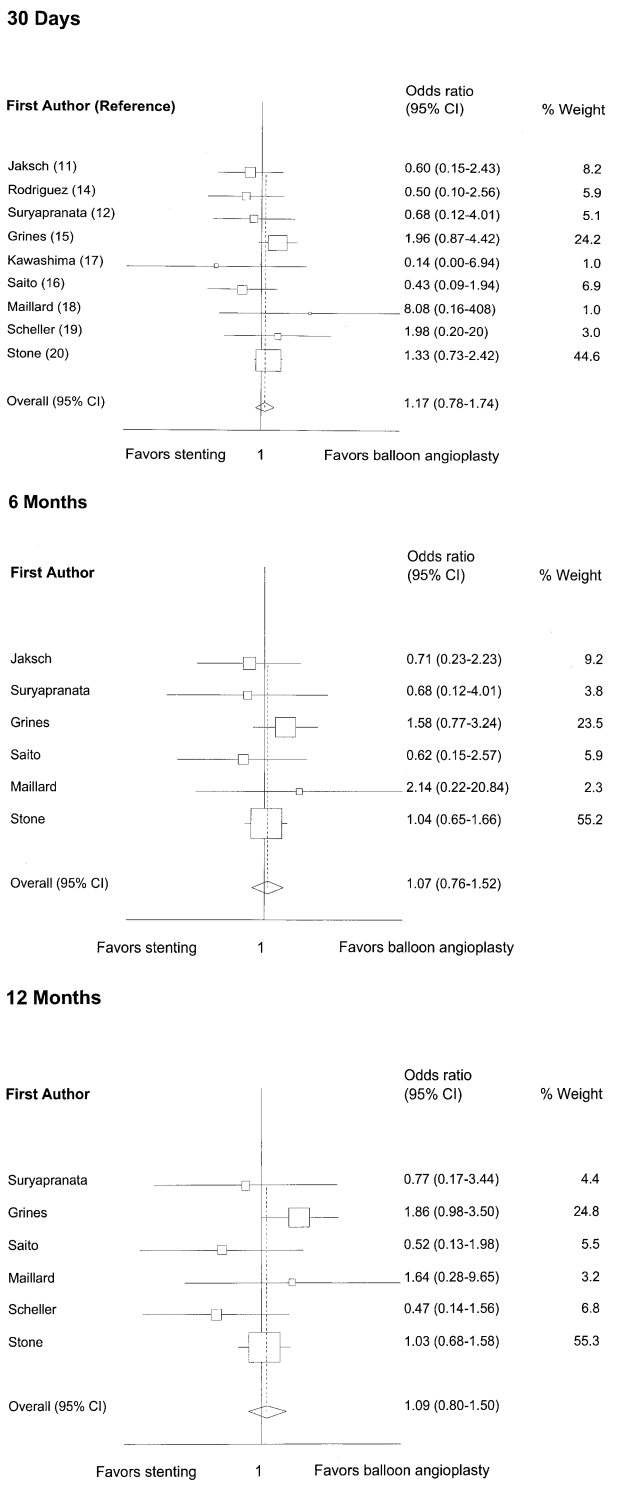

Figure 2. Odds ratios for mortality in patients with myocardial infarction who were treated with primary stenting versus balloon angioplasty. CI = confidence interval.

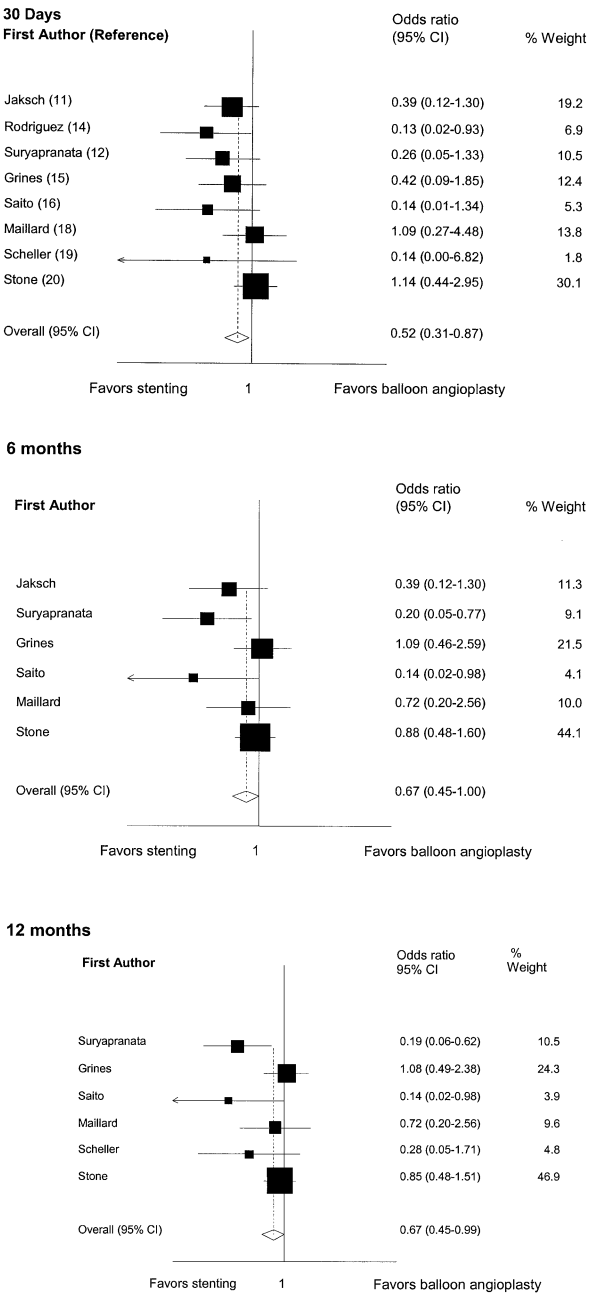

Figure 3. Odds ratios for reinfarction in patients with myocardial infarction who were treated with primary stenting versus balloon angioplasty. CI = confidence interval.

This meta-analysis was based on a comprehensive literature search that included unpublished data from individual trials. Although formal testing indicated no publication bias, we cannot completely rule out such a bias. We explored heterogeneity between trials according to criteria defined a priori, but lack of data precluded the detailed sensitivity analysis that we had sought. For the remaining criteria, we found no evidence of heterogeneity. However, the test for heterogeneity has low power (22), particularly in meta-analyses of uncommon events (23), and this may explain our failure to detect heterogeneity.

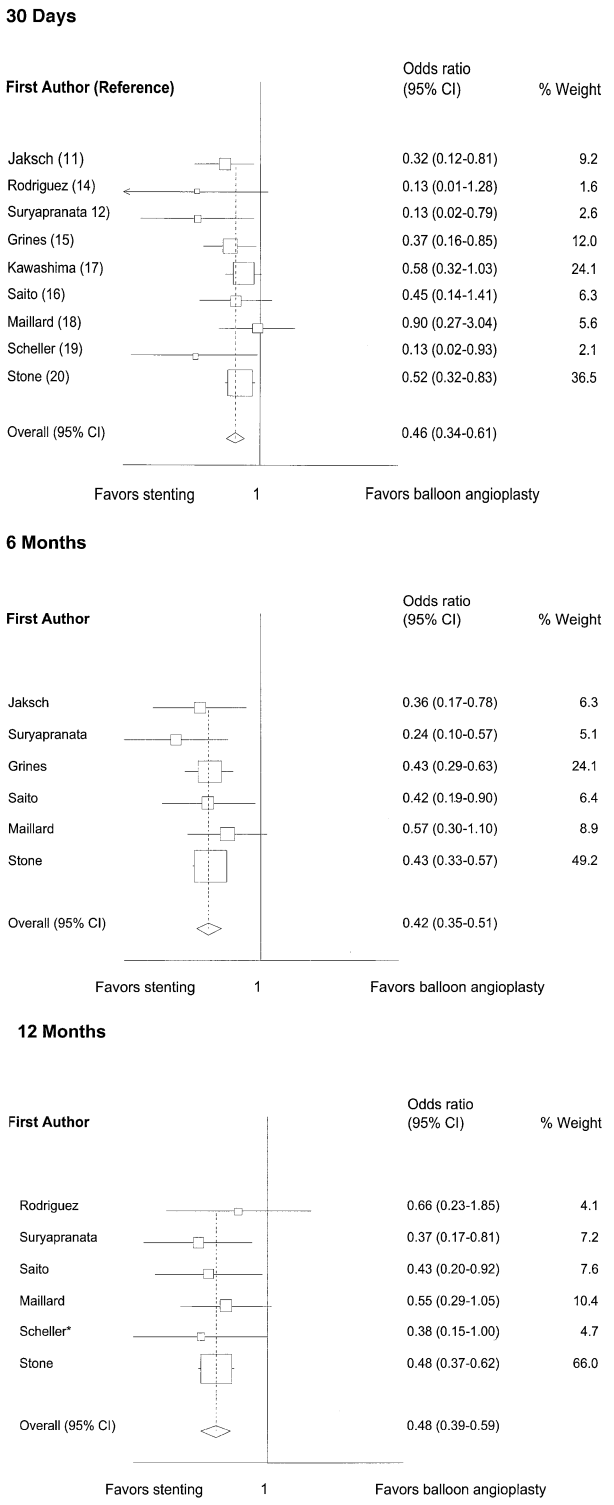

Figure 4. Odds ratios for revascularization in patients with myocardial infarction who were treated with primary stenting versus balloon angioplasty. CI = confidence interval. *24-month data.

We were not able to obtain individual patient-level data and had to rely on summary reports. The quality of included trials varied substantially. Only four trials reported concealed treatment allocation and three reported blinded outcome assessment. Summary estimates in trials without reported concealed treatment allocation and without blinded outcome assessment indicated benefit from primary stenting, whereas both summary estimates in trials with higher quality indicated harm from routine stenting. Although our sensitivity analysis was inconclusive as 95% confidence intervals overlapped, this might be an indication that trial quality may have affected our summary estimates. By including trials of poorer quality, we may have underestimated the harmful effect of routine stenting on mortality in patients with myocardial infarction.

Crossover rates from balloon angioplasty to stenting in some trials were substantial and ranged from 1% (17) to 36% (18). A sensitivity analysis comparing trials with lower ($\leq$15%) and higher ($>$15%) crossover rates failed to reveal any difference in mortality. It is therefore unlikely that the crossover rates influenced the validity of our findings.

All trials used more aggressive postinterventional antithrombotic/anticoagulant therapies in patients assigned to stenting. The addition of an adenosine diphosphate P2Y12 receptor antagonist (ticlopidine or clopidogrel) to aspirin following stenting has repeatedly been shown to offer greater protection from thrombotic complications than aspirin alone (24–28). Thus, unbalanced cointervention might have introduced bias in favor of stenting and may explain the reduced risk of reinfarction and target vessel revascularization in this group. However, it is not clear whether the addition of antithrombotic or anticoagulant drugs to aspirin is similarly beneficial in patients treated with balloon angioplasty without stent placement. In the Total Occlusion Study of Canada (TOSCA) trial, ticlopidine added to aspirin did not improve clinical outcomes in patients treated with balloon angioplasty (29), but coumarin added to aspirin prevented acute and late complications after angioplasty in another trial (30). Further studies are needed to identify which antithrombotic strategy is most likely to be beneficial in stent recipients.

The external validity of our findings may be limited. Many trials were conducted in specialized high-volume centers and some included highly preselected patients. Additionally, women and elderly patients were underrepresented.

Contrary to a previous meta-analysis (6), we found a substantial reduction in reinfarction rates in patients treated with primary stenting, owing to a difference in the inclusion of eligible trials. A previous systematic review included a large trial in which there was no difference in reinfarction rates in the two treatment strategies (21). This trial did not meet our inclusion criteria because it did not compare primary stenting with balloon angioplasty per se, but with optimal balloon angioplasty. In

addition, our analysis included data from a relatively large unpublished trial (11) in which the reinfarction rate was lower in patients treated with stents.

Stent technology has developed considerably over the last few years. There is now a wide variety of stents with different physical and antithrombotic properties. Future trials comparing sirolimus-eluting stents with balloon angioplasty may show similar benefits of primary stenting in patients with myocardial infarction as in those with chronic coronary artery disease (31). However, these benefits have been limited to a reduction in restenosis and a reduced need for target vessel revascularizations, but not to a reduction of other endpoints such as myocardial infarction or mortality. New stent types are more expensive, and cost-effectiveness analyses and additional data on long-term reliability will be important in justifying their use.

In conclusion, evidence from existing trials suggests that primary stenting in patients with myocardial infarction does not reduce mortality when compared with balloon angioplasty, but is associated with a reduced risk of reinfarction and target vessel revascularization. Additional trials based on the use of modern sirolimus-eluting stents with extended follow-up periods and balanced antithrombotic therapies in both stent and balloon angioplasty arms are needed to better define the role of stents in the management of patients with myocardial infarction.

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