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Evidence for Use of Coronary Stents

A Hierarchical Bayesian Meta-Analysis

James M. Brophy, MD, PhD; Patrick Belisle, MSc; and Lawrence Joseph, PhD

Background: **Coronary stents are widely used in interventional cardiology, but a current quantitative systematic overview comparing routine coronary stenting with standard percutaneous transluminal coronary angioplasty (PTCA) and restricted stenting (provisional stenting) has not been published.**

Purpose: **To summarize results from all randomized clinical trials comparing routine coronary stenting with standard PTCA.**

Data Sources: **Electronic databases were searched by using the key words *angioplasty* and *stent*. References from identified articles were also reviewed. In addition, several prominent general medical and cardiology journals were searched and agencies known to perform systematic reviews were consulted.**

Study Selection: **All comparative randomized clinical trials were included, except those involving primary angioplasty for the treatment of acute myocardial infarction.**

Data Extraction: **A specified protocol was followed, and two of the authors independently extracted the data. Outcomes assessed were total mortality, myocardial infarction, angiographic restenosis, coronary artery bypass surgery, repeated PTCA, and freedom from angina.**

Data Synthesis: **The results were synthesized by using a Bayesian hierarchical random-effects model. A total of 29 trials involving 9918 patients were identified. There was no evidence for a difference between routine coronary stenting and standard PTCA in terms of deaths or myocardial infarctions (odds ratio, 0.90 [95% credible interval [CrI], 0.72 to 1.11]) or the need for coronary artery bypass surgery (odds ratio, 1.01 [CrI, 0.79 to 1.31]). Coronary stenting reduced the rate of restenosis (odds ratio, 0.52 [CrI, 0.37 to 0.69]) and the need for repeated PTCA (odds ratio, 0.59 [CrI, 0.50 to 0.68]). The trials showed a wide range of crossover rates from PTCA to stenting. By use of a multiplicative model, each 10% increase in crossover rate decreased the need for repeated angioplasty by approximately 8% (odds ratio multiplying factor, 1.08 [CrI, 0.98 to 1.18]). Routine stenting probably reduces the need for repeated angioplasty by fewer than 4 to 5 per 100 treated persons compared with PTCA with provisional stenting. Studies were not blinded and suggest a bias with a possible overestimation of this benefit.**

Conclusions: **In the controlled environment of randomized clinical trials, routine coronary stenting is safe but probably not associated with important reductions in rates of mortality, acute myocardial infarction, or coronary artery bypass surgery compared with standard PTCA with provisional stenting. Coronary stenting is associated with substantial reductions in angiographic restenosis rates and the subsequent need for repeated PTCA, although this benefit may be overestimated because of trial designs. The incremental benefit of routine stenting for reducing repeated angioplasty diminishes as the crossover rate of stenting with conventional PTCA increases.**

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For author affiliations, see end of text.

See editorial comment on pp 842-843.

Percutaneous transluminal coronary angioplasty (PTCA) is a common intervention that is used primarily to reduce the symptoms of angina pectoris; it has no discernible benefit for reducing rate of myocardial infarction or death when compared with other treatments (1). An important limitation of PTCA has been the occurrence of restenosis. Coronary stenting is a percutaneous technique involving the intraluminal introduction of metal scaffolding. Coronary stenting was introduced in 1989 to treat the acute complications of PTCA (2) but is now routinely used for most angioplasties. The elective stent era began with the publication in 1994 of two randomized clinical trials showing a reduced rate of restenosis with coronary stenting compared with ordinary PTCA (3, 4). Subsequently, the use of stents has increased exponentially; some consensus panels endorsed this clinical enthusiasm for coronary stenting even before a large body of high-quality evidence was available (5).

Recently, more randomized clinical trials comparing coronary stenting to ordinary angioplasty have been published. However, these trials have often had small sample sizes with low event rates; their focus, therefore, has been on composite outcomes. As a consequence, editorialists, citing selected studies, have arrived at opposite conclusions on the role of elective stenting in interventional cardiology (6, 7).

A systematic overview may better quantify the benefits of coronary stenting and provide meaningful insights into the separate clinical end points. Two studies have qualitatively evaluated the benefits of coronary stents (8, 9), but only one study, which was published in a nonclinical journal, has quantitatively reviewed this subject (10, 11). Because of the widespread use and cost of stents (an estimated $1.6 billion in 2002 for the United States market alone [12]), an updated quantitative synthesis of the risks and benefits of this technology seems appropriate.

Our paper adds three important elements to the assessment of stents. First, we update the earlier quantitative assessment by including several recent trials. Second, we use a more sophisticated statistical analysis that considers variability among studies. Finally, we provide a bias-adjusted result, which allows estimation of an upper limit of any possible bias.

Context

Although expensive, coronary stents are routinely used in angioplasties. However, are they better than balloon angioplasty?

Contribution

This meta-analysis of 29 randomized trials found that routine stenting reduced restenosis rates as compared with provisional stenting but did not affect rates of mortality or myocardial infarction or the need for bypass surgery. Routinely using stents instead of angioplasty with bailout stents for complications of or unsatisfactory results from angioplasties (provisional stenting) reduced the need for repeated revascularization procedures by at most 5 per 100 treated patients.

Implications

The benefits of routine stents versus angioplasty with provisional stents are modest.

Cautions

Effects may vary depending on the lesions and vessels that are treated. Trials did not test new drug-eluting stents.

–The Editors

METHODS

Study Group

We attempted to identify all randomized studies published before 30 June 2002 that compared PTCA with routine coronary stenting (**Appendix Table**, available at www.annals.org). We searched the PubMed database by using the key words *angioplasty* and *stent*. The search was limited to clinical trials; review articles were excluded. Language of publication was not restricted. We identified a total of 578 articles. Trials of stenting in acute myocardial infarction and comparisons with other percutaneous, medical, or surgical techniques, as well as comparative studies of different stent models were excluded. A total of 29 randomized trials (3, 4, 13–39) were identified. All selected trials had at least 6 months of follow-up and reported the meaningful clinical end points of death, myocardial infarction, and repeated angioplasty of the target lesion. Two of the authors independently abstracted all data and resolved differences by consensus agreement.

We used a multifaceted approach to validate the search process. Using the criteria stated earlier, MEDLINE retrieved 2277 references but no additional studies. Finally, we hand-searched several prominent general medical and cardiology journals (*The Lancet*, *British Medical Journal*, *The New England Journal of Medicine*, *Journal of the American Medical Association*, *Annals of Internal Medicine*, *Circulation*, *Journal of the American College of Cardiology*, *American Journal of Cardiology*, and *Heart*), all references from the original articles, and recent review articles (8–10). No additional studies were identified.

Statistical Analysis

All analyses were intention-to-treat, so that patients requiring crossover were assessed in their originally assigned group. Rates of events are reported at 6 months, unless stated otherwise. It is unlikely, as implied by a fixed-effects meta-analysis model, that the effects of coronary stenting in each trial will be identical because of differences in trial methods, patients, and investigators. Therefore, we used a Bayesian hierarchical random-effects model (40, 41) to synthesize the results. In this model, the individual data in each trial and for each outcome are assumed to follow a binomial distribution; outcome probabilities are allowed to vary between the stent and PTCA groups within each study, and these parameters also vary among studies. The logarithm of the odds ratios among studies varies according to a normal distribution.

While this simple method models variability among trials, it does not attempt to explain any observed differences. The benefits of stents may depend on the anatomic lesion, the rate of crossover stenting, and the type of stent. Therefore, we added another level to our hierarchical model that included these explanatory variables. We allowed the logarithm of the odds ratio in each study to depend on a linear model that included the stated three variables. The coefficients of this linear model on the log odds scale were then interpreted as multiplicative factors on the original odds ratio scale. For example, an odds ratio multiplicative factor of 1.2 implies a change of 20% in the odds ratio. Thus, the effect is larger if the original odds ratio is greater than the null value of 1 or smaller if the original odds ratio is less than 1. Conversely, although an odds ratio multiplicative factor of 0.8 also implies a 20% change in the odds ratio, in this case, the effect is larger if the original odds ratio is less than 1 or smaller if the original odds ratio is greater than 1.

Another possible explanation for the observed differences is the possible bias introduced because the studies were not blinded (42). Therefore, we produced adjusted estimates by assuming that the rates of repeated PTCA, given the occurrence of restenosis, should be similar in the stent and PTCA groups. We estimated the proportion of patients with angiographic restenosis in the PTCA group who then underwent repeated PTCA and assumed that this rate should also apply to the stent group if the trials were blinded. This assumes that the entire effect of stents on repeated PTCA is due to a reduction in restenosis and not to other factors, such as an unwillingness among interventional cardiologists to attempt repeated PTCA in a patient with a stent and angiographic restenosis. This revised estimate probably provides an upper bound for the bias adjustment; the true odds ratio for repeated PTCA probably is somewhere between this upper bound and the original unadjusted estimate.

We estimated marginal posterior densities for all unknown parameters in our models by using the Gibbs sampler via BUGS software, version 0.6 for UNIX (Medical

Table 1. **Patient Characteristics***

Study (Reference)	Year	Patient Characteristics	Mean Age ± SD	Women	Diabetic Patients	Multivessel Disease	Clinical Follow-up
			y	← % →			*mo*
Serruys et al. (3)	1994	Stable angina	57.5 ± 9.5	19	6.5	NA	7
Fischman et al. (4)	1994	Stable angina	60 ± 10	22	15.5	34	6
Eeckout et al. (13)	1996	Stable angina	58 ± NA	66	11	NA	6
Sirnes et al. (14)	1996	Stable angina	58 ± 10	18	NA	38	6
Versaci et al. (15)	1997	Stable angina	56.5 ± 9.5	12.5	15	NA	12
Savage et al. (16)	1998	Stable angina	66 ± 9	19.5	29.5	NA	6
Erbel et al. (17)	1998	Stable angina	59.5 ± 9	19	17.5	32.5	6
Rubartelli et al. (18)	1998	Stable angina	57.7 ± 8.1	15.5	10	30	9
Hancock et al. (19)	1998	Stable angina, no AMI in previous 72 h	60.5 ± NA	37	NA	NA	6
Serruys et al. (20)	1998	Stable and unstable angina	54.5 ± 10.5	21.5	12	NA	12
Rodriguez et al. (21)	1998	Stable angina	57.3 ± 10	16.4	10.2	NA	6
Sievert et al. (22)	1999	Stable	60.5 ± 10	28.5	NA	NA	4
Hoher et al. (23)	1999	Stable angina	62 ± NA	30.8	34	58.4	6
Betriu et al. (24)	1999	Stable and unstable angina	59 ± NA	14	13.5	35	6
Buller et al. (25)	1999	Not described but no AMI	57.7 ± 10.5	18	16.5	NA	6
Lincoff et al. (26)	1999	Stable and unstable angina; recent AMI	59 ± 11	25.1	20.9	NA	6
Serruys et al. (27)	2000	Stable and unstable angina	59.5 ± 10.5	27.5	10	9.5	12
Di Mario et al. (28)	2000	Stable and unstable angina; no AMI in previous 24 h	60.4 ± 10.6	26.1	18.5	35.2	12
Kastrati et al. (29)	2000	Angina pectoris; no AMI in previous 72 h	65.8 ± 11.1	23.3	24.8	NA	7
Witkowski et al. (30)	2000	Symptomatic CAD; no AMI in previous 14 d	52.1 ± 11.2	17	3.4	NA	6
Lafont et al. (31)	2000	Stable and unstable angina; no AMI in previous 21 d	60 ± 10.7	17.9	15.6	NA	6
Fluck et al. (32)	2000	Symptomatic CAD; no AMI in previous 7 d	58.2 ± 9.2	24	9	NA	12
Dangas et al. (33)	2000	No rest angina within previous 24 h; no AMI in previous 72 h	62 ± 13	31	3	26	8
Weaver et al. (34)	2000	Stable and unstable angina	60.5 ± NA	26.5	18	30	6
Lotan et al. (35)	2000	Stable and unstable angina; no AMI in previous 10 d	59.1 ± 10.5	15.6	25	NA	6
Park et al. (36)	2000	Stable and unstable angina	60.9 ± 8.0	36.7	12.5	68.9	16
Koning et al. (37)	2001	Angina pectoris	62 ± 10	24	17	50	6
Doucet et al. (38)	2001	Stable and stabilized unstable angina	60 ± 10	33	20	NA	6
Moer et al. (39)	2001	Stable and unstable angina	63 ± 10	34	13	57	6

* AMI = acute myocardial infarction; CAD = coronary artery disease; NA = not available.

Research Council Biostatistics Unit, Cambridge, United Kingdom). All results are reported as posterior means with 95% equal-tailed credible intervals (CrIs). Credible intervals are the Bayesian analogue to confidence intervals.

Role of the Funding Sources

The funding sources had no role in the choice of topic; collection, analysis, or interpretation of the data; or in the decision to submit the manuscript for publication.

RESULTS

The search protocol identified 29 randomized studies involving 9918 patients that compared standard PTCA to routine coronary stenting (**Appendix Table**, available at www.annals.org). The studies examined patients with stable and unstable angina (**Table 1**) as well as various types of lesions: 15 studies in large native vessels (>3 mm), 5 studies in small native vessels (<3 mm), 7 studies of occluded vessels, and 1 study each of restenosed native arteries and bypass grafts. In addition, rates of crossover were studied (**Table 2**).

Methodologic quality of the studies was generally satisfactory. Although the randomization process was not always fully described, accountability for patients was excellent; almost no patients were lost to follow-up. The nature of coronary stenting does not permit blinding of investigators or patients. As will be discussed later, this inability to blind investigators may have influenced the outcome of repeated angioplasty.

Few patients died in either group (65 [1.2%] for the PTCA group; 39 [0.8%] for the stent group). The odds ratio for death was 0.69 (95% CrI, 0.43 to 1.05). **Figure 1** shows the combined death or myocardial infarction outcomes. Overall, the rates of death and myocardial infarction were similar in the two groups (odds ratio, 0.90 [CrI, 0.72 to 1.11]). Despite the large number of randomly assigned patients, the small number of events leads to a relatively wide credible interval. This implies that a 28% relative reduction or even an 11% increase in the combined death and myocardial infarction event rate with stenting cannot be excluded. In absolute terms, the effect was a difference of 0.38% (CrI, −0.81% to 0.05%) for death alone and 0.50% (CrI, −1.31% to 0.31%) for the combined event rate. Similarly, the need for coronary artery bypass surgery differed minimally between groups (146 of

Table 2. **Lesion and Stent Characteristics***

Study (Reference)	Lesion Inclusion Characteristics	PTCA	Stent	Stent Crossover	Type of Stent	Angiographic Substudy Follow-up†
		n		*n (%)*		*mo*
Serruys et al. (3)	> 3 mm (diam), < 15 mm (length)	257	259	13 (5)	Palmaz-Schatz	6
Fischman et al. (4)	> 3 mm (diam), < 15 mm (length)	202	205	14 (7)	Palmaz-Schatz	6
Eeckout et al. (13)	RCA, > 3 mm (diam), < 15 mm (length)	42	42	0	Wiktor	6
Sirnes et al. (14)	Chronic occlusion	59	58	0	Palmaz-Schatz	6
Versaci et al. (15)	Proximal LAD artery, > 3 mm (diam), < 15 mm (length)	60	60	2 (3)	Palmaz-Schatz	12
Savage et al. (16)	Aortocoronary venous bypass grafts	107	108	7 (7)	Palmaz-Schatz	6
Erbel et al. (17)	Restenotic lesion, < 10 mm (length)	176	178	12 (7)	Palmaz-Schatz	6
Rubartelli et al. (18)	Chronic occlusion	54	56	1 (2)	Palmaz-Schatz	9
Hancock et al. (19)	Occlusion > 3 d	30	30	0	Palmaz-Schatz	6
Serruys et al. (20)	> 3 mm (diam), < 18 mm (length)	410	413	55 (13)	Heparin-coated Palmaz-Schatz	6
Rodriguez et al. (21)	> 2.5 mm (diam), < 20 mm (length)	59	57	8 (14)	Variable	6
Sievert et al. (22)	Chronic occlusion	55	55	0	Variable	6
Hoher et al. (23)	Chronic occlusion	43	42	7 (16)	Wiktor	6
Betriu et al. (24)	> 3 mm (diam), < 15 mm (length)	223	229	25 (11)	Palmaz-Schatz	6
Buller et al. (25)	Chronic occlusion	208	202	20 (10)	Heparin-coated Palmaz-Schatz	6
Lincoff et al. (26)	Not fully described	796	794	154 (19)	Palmaz-Schatz	6
Serruys et al. (27)	< 25 mm (length)	511	97	318 (65)	Not specified	Not performed
Di Mario et al. (28)	"Suitability of lesions for stenting"	365	370	206 (55)	Not specified	Not performed
Kastrati et al. (29)	Small lesions, 2.0–2.8 mm (diam)	200	204	33 (17)	Multilink	6
Witkowski et al. (30)	> 2.5 mm (diam), < 15 mm (length)	196	192	19 (10)	Palmaz-Schatz	6
Lafont et al. (31)	> 2.7 mm (diam), < 15 mm (length)	126	125	61 (48)	Palmaz-Schatz	6
Fluck et al. (32)	> 3 mm (diam)	146	154	44 (30)	Wiktor	6
Dangas et al. (33)	> 3 mm (diam), < 15 mm (length)	66	31	24 (36)	Palmaz-Schatz	6
Weaver et al. (34)	> 3 mm (diam), < 20 mm (length)	248	229	93 (37)	Palmaz-Schatz	Not performed
Lotan et al. (35)	Chronic occlusion	48	48	0	AVE Micro Stent	6
Park et al. (36)	Small lesions, < 3 mm (diam)	60	60	12 (20)	7-cell NIR	6
Koning et al. (37)	Small lesions, < 3 mm (diam), < 15 mm (length)	189	192	45 (22.7)	beStent Small	6
Doucet et al. (38)	Small lesions, 2.3–2.9 mm (diam), < 12 mm (length)	182	169	37 (20.3)	beStent-Artist	6
Moer et al. (39)	Small lesions, 2.1–3.0 mm (diam), < 15 mm (length)	71	74	10 (14.1)	Heparin-coated BeStent	6

* diam = diameter; LAD = left anterior descending; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery.
† Angiographic substudies were performed at 6 months for all studies except Versaci et al. (15) (12 months) and Rubartelli et al. (18) (9 months). Serruys et al. (27), Di Mario et al. (28), and Weaver et al. (34) did not include a planned mandatory angiographic substudy.

5190 [2.8%] for the PTCA group; 143 of 4728 [3.0%] for the stent group) (odds ratio, 1.01 [CrI, 0.79 to 1.31]).

The most striking differences between PTCA and routine planned coronary stenting were the rates of angiographic restenosis and recurrent angioplasty. Twenty-six of the 29 studies had a systematic angiographic control at 6 months and reported the results in a standardized manner (number of patients with a recurrent blockage exceeding 50% at the site of the original intervention). One trial had an angiographic substudy but did not report the number of patients with more than 50% restenosis; therefore, it could not be included in the analysis of this outcome (26). Stenting was associated with an approximate 48% reduction in the restenosis rate (odds ratio, 0.52 [CrI, 0.37 to 0.69]) (**Figure 2**). In absolute terms, stenting reduces the angiographic restenosis rate by 14.5% (CrI, 11.6% to 17.5%). This difference in angiographic restenosis rates substantially affects the need for repeated PTCA (**Figure 3**). The number of repeated angioplasties was markedly reduced in the stent group (odds ratio, 0.59 [CrI, 0.50 to 0.68]). In absolute terms, this represents a 6.8% (CrI, 5.1% to 8.4%) reduction in the need for repeated PTCA.

Figures 2 and **3** show study variations, which were further investigated. Different types of lesions and stents may a priori be expected to respond in a pathophysiologically distinct manner to the angiographic restenosis associated with stent implantation. Compared with stenting of nonoccluded lesions, stenting of occluded lesions resulted in larger reductions in angiographic restenosis (odds ratio multiplicative factor, 0.34 [CrI, 0.17 to 0.57]) and repeated angioplasties (odds ratio multiplicative factor, 0.64 [CrI, 0.42 to 0.93]). We could not show any additional differences between other lesion or stent groups (Palmaz-Schatz vs. other types of stents), although wide credible intervals preclude definitive conclusions.

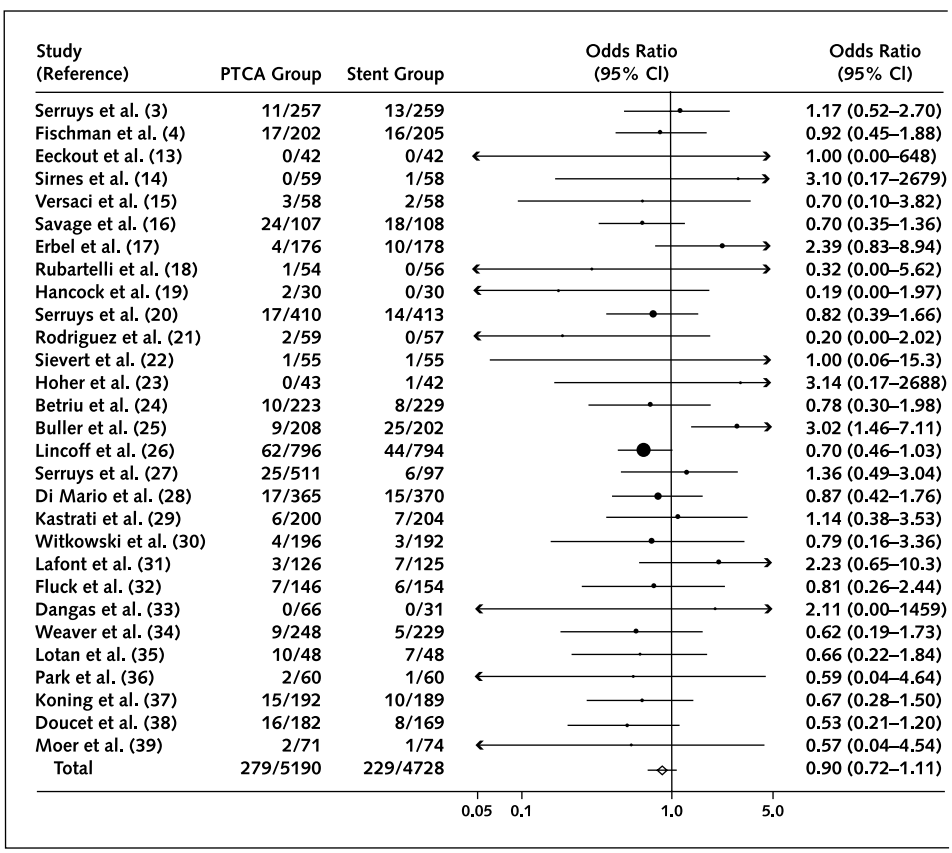
The comparisons of PTCA and stent results are complicated by the issue of "moving targets"; indications, techniques, and adjunct therapy for both treatments have evolved over the time frame in which these studies have been performed. Stents are now accepted for the treatment of acute complications (dissections, abrupt vessel closure) arising from standard PTCA and, increasingly, for operator-defined suboptimal results (often the persistence of a substantial residual stenosis); such a policy is called provi-

sional stenting. This explains the increasing number of patients in the PTCA groups who crossed over to stenting in the more recent trials. Therefore, we investigated whether an association existed between the crossover rate and the benefits of decreased need for repeated angioplasty. Our model predicted that a 10% increase in crossover stenting was associated with a tendency for an 8% reduction in the need for repeated angioplasty (odds ratio multiplier, 1.08 [CrI, 0.98 to 1.18]). **Figure 4** is a plot of the number of repeated angioplasties avoided with routine stenting, as a function of the crossover rate in the standard PTCA groups. This graph suggests that the number of repeated angioplasties avoided levels off at about 5 per 100 patients treated once a baseline crossover rate of approximately 20% to 40% is attained.

If the interventional cardiologists in these trials treated restenosis independently of the presence of a coronary stent, one would expect an equal number of patients with angiographic restenosis to have repeated PTCA in each treatment group. However, of patients originally assigned to PTCA, 847 of 1089 (77.8%) with documented angiographic restenosis had a second percutaneous intervention, whereas only 509 of 742 (68.6%) in the stent group had a second intervention (difference, 9.2 percentage points [CrI, 4.9 to 13.4 percentage points]). Chance alone is most unlikely to be responsible for such differences, suggesting that interventional cardiologists in these clinical trials may have treated restenosis differently on the basis of whether or not a stent was present. Thus, the softer end point of repeated PTCA may be biased because the trials were not blinded, perhaps leading to overestimates of the benefit of stenting in reducing the need for repeated PTCA. Modeling to correct for this potential bias, by assuming a constant ratio of repeated angioplasties–to–angiographic restenoses in each group, suggests that the advantage of stents in reducing repeated angioplasty may be closer to 10% (odds ratio, 0.90 [CrI, 0.68 to 1.18]). In absolute terms, this could imply a reduction in the number of avoided angioplasties to 2.1 per 100 patients treated (CrI, −1.6 to 6.0).

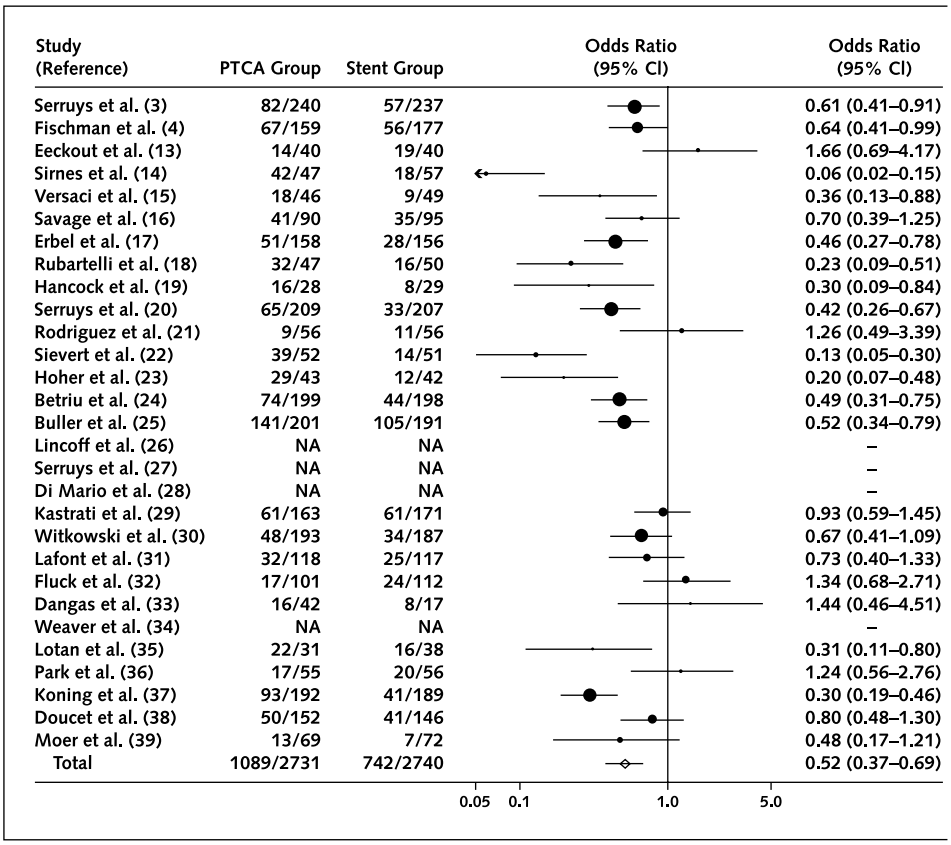
Most trials (23 of 29) did not report on quality-of-life measures, including angina status. However, in the 6 studies that did assess these measures, angina disappeared or was reduced in 67% of patients (1032 of 1540) in the stent group compared with 61% of patients (952 of 1551) in the angioplasty alone group (difference, 6 percentage points [CrI, 3 to 9 percentage points]).

Figure 1. **Forest plot comparing the rate of death or myocardial infarction in the elective stenting and standard percutaneous transluminal coronary angioplasty (*PTCA*) groups for the 29 trials.**



Values in the second and third columns are number of patients sustaining outcome of interest/number of patients in treatment group.

Figure 2. **Forest plot comparing the rate of angiographic restenosis in the elective stenting and standard percutaneous transluminal coronary angioplasty (*PTCA*) groups for the 25 trials with an angiographic follow-up end point.**



Values in the second and third columns are number of patients sustaining outcome of interest/number of patients in treatment group.

DISCUSSION

Because the current literature is unclear about the benefits of routine coronary stenting in interventional cardiology, we have attempted to quantify and compare the risks and benefits of routine coronary stenting and standard angioplasty. The trials that we identified in our systematic overview did not compare the use of stents with no use of stents; instead, they compared two different strategies for using stents—routine elective stenting and an evolving but more restrained (or provisional) approach. The latter approach treats not only the acute complications of angioplasty but also increasingly suboptimal results.

We identified 29 published randomized trials, involving 9918 patients, that compared routine coronary stenting with standard PTCA in patients with stable and unstable coronary syndromes. The results of these trials confirm the safety of coronary stenting and no increased risk for death, myocardial infarction, or coronary artery bypass surgery. On the other hand, evidence does not support a reduction in these outcomes. In contrast, the clinical benefits of using coronary stents as a bailout procedure for complications of angioplasty are so striking that clinical trials in this area would be unnecessary and unethical (44).

Our quantitative overview confirms that stenting greatly reduces rates of angiographic restenosis and repeated angioplasty; this reduction is clinically important. The benefit of reduced rates of angiographic restenosis is especially evident among patients with a totally occluded artery who are undergoing a percutaneous intervention. Overall, the best estimate from the aggregate clinical trials is that rates of restenosis are reduced by 48% and rates of repeated angioplasty are reduced by 41%. The result is 7 fewer repeated angioplasties per 100 patients receiving stents. However, the reduction in repeated revascularizations diminishes as the rate of crossover stenting increases in the PTCA group. The data suggest that once a 20% to 40% rate of stenting is achieved (to allow for treatment of acute complications of angioplasty and suboptimal results in some cases), the number of repeated angioplasties avoided decreases to approximately 5 per 100 patients treated.

We have identified a possible systematic bias associated with the obligatory nonblinded trial designs that may lead to overestimation of the number of avoided repeated angioplasties. Among patients with more than 50% restenosis, fewer patients with stents went on to have repeated angioplasty compared with those who did not have an initial stent. The clinically recognized increased difficulty of treating in-stent restenosis is consistent with these observa-

tions. Although it is impossible to know the exact severity and clinical consequences of each case, this lower rate does suggest a potential bias in the use of repeated angioplasty as a clinical outcome. An upper limit for this bias is attained mathematically by assuming equal rates of repeated PTCA, assuming restenosis in both groups. Thus, routine stenting may reduce use of subsequent angioplasties by fewer than 5 per 100 patients treated.

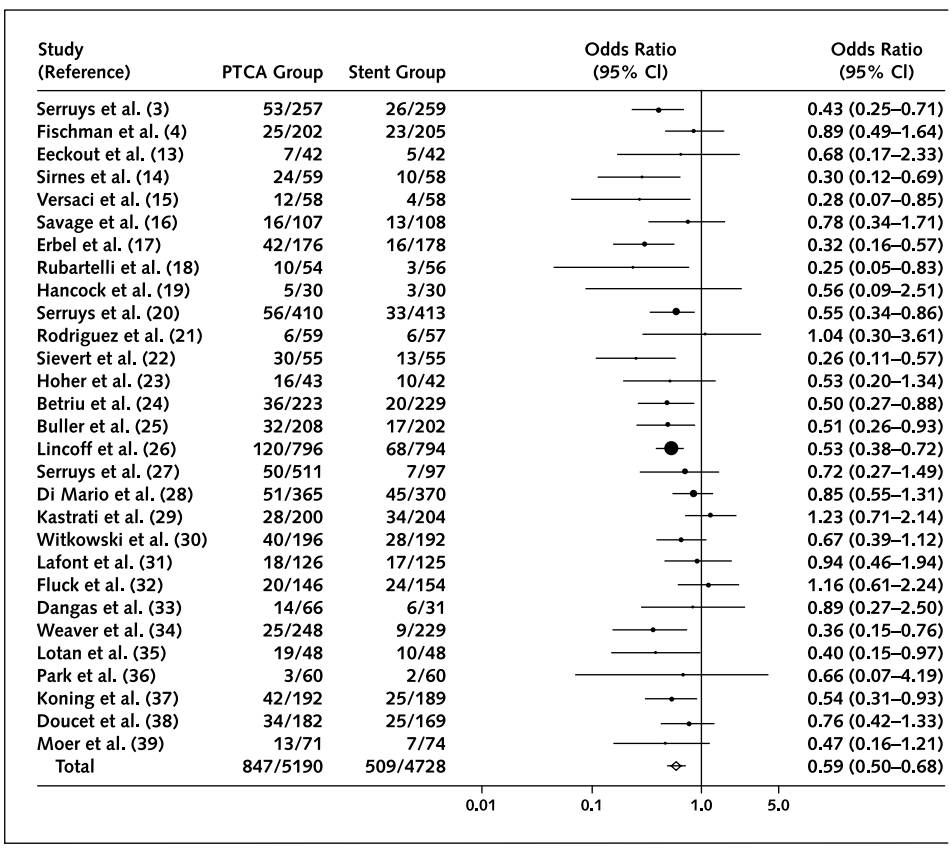
The design of most of the trials mandated obligatory angiography at 6 months, which may have introduced an additional bias to the estimation of repeated angioplasties avoided. A randomized substudy of the Benestent II trial showed that a 6-month routine angiography follow-up compared with a clinical assessment alone led to twice as many repeated revascularization procedures in the following 6 months (45). Therefore, in the trials that we identified, which mostly focused on angiography, the benefit from stenting in reducing repeated angioplasties may be overstated and not applicable in routine practice, where systematic angiography is not performed at 6 months. Although the Benestent II study was well designed, we did not attempt to model these results into our analysis because it is the only study of its kind. It does, however, suggest that our estimate of avoided angioplasties is probably optimistic and that the true benefit in clinical practice could be even lower.

The results of this overview raise several questions: 1) Why are the major clinical end points not reduced in the routine stent group? 2) What additional factors might be driving the near ubiquitous use of stents? 3) What is the optimal rate of coronary stenting?

Stenting has improved the safety of angioplasty by providing a reliable technique for treating acute or threatened occlusion and thereby reducing the potential for same-day emergency bypass surgery (46–48). Stenting has become a mandatory tool for interventional cardiologists. Positive experiences with stenting are reflected in the increased use of crossover stenting in the control groups. Crossover patients were probably initially at the highest risk for an adverse event, and by crossing over, any clinical advantage of elective stenting compared with PTCA would be diluted.

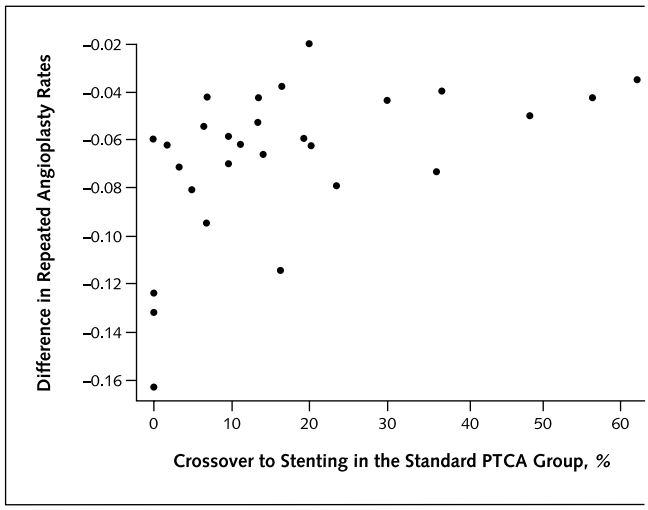
The reasons why stents do not improve clinical outcomes may be related to pathophysiology. Although stents improve acute gain in vessel diameter by reducing recoil and negative remodeling, they increase platelet and neutrophil activation and late neointimal proliferation (49), as well as endothelial dysfunction (50). Endothelial dysfunc-

Figure 3. **Forest plot comparing the rate of repeated percutaneous transluminal coronary angioplasty (*PTCA*) in the elective stenting and standard PTCA groups for the 29 trials.**



Values in the second and third columns are number of patients sustaining outcome of interest/number of patients in treatment group.

Figure 4. **Plot of the difference between the elective stenting and standard percutaneous transluminal coronary angioplasty (*PTCA*) groups for the outcome of repeated PTCA as a function of the stent crossover rate in the standard PTCA groups.**



tion, in particular, has been shown to predict atherosclerotic disease progression and future cardiac events (51, 52).

What is the basis for the cardiovascular community's acceptance of elective stenting? Our overview suggests that any clinical benefits beyond a strategy of provisional stenting are modest. One can only speculate, but a combination of factors may be involved. The positive effects achieved in treating acute complications of angioplasties (historically, about 5% of cases) and a preoccupation with angiographic images may have unduly influenced practice patterns beyond the strength of the data on clinical outcomes (53). The use of relative rather than absolute measures of efficacy and of composite end points can also inflate the importance of these results. Cardiologists may also not appreciate that standard PTCA has improved over time (32). Standard statistical analysis using often-misunderstood *P* values also tends to overestimate the perception of the strength of any conclusions (54, 55). The impact of peer pressure from the interventional community or the device industry on the high rates of stent use cannot be evaluated.

The ideal rate for stenting is difficult to determine, but our analysis suggests diminishing returns once a provisional stenting rate exceeds approximately 20% to 40%. Is the additional reduction in repeated angioplasties adequate justification for full elective stenting? There is no unique response to this question, which must consider not only efficacy and risks but also patient expectations and costs. The evidence is convincing that elective stenting modestly reduces the need for repeated revascularizations. However, coronary stenting is associated with substantial procedure costs and increased difficulty in managing in-stent restenosis. Individual health care systems must evaluate whether these well-defined but limited health benefits are worth the additional costs of routine coronary stenting. Similar assessments will be needed to determine the future role of drug-eluting stents.

Any meta-analysis is limited by the quality of the original studies. The studies in our analysis were generally of good quality and had no selection or attribution biases. As discussed, we did detect and offer a rough correction for a possible performance bias. As with all meta-analyses, the possibility of missing studies, mostly resulting from a publication bias against negative studies, must be considered. The pertinence and validity of our meta-analysis may be questioned because stent technology is continually evolving and because the included studies often used different protocols, particularly in selecting the patient population and in deciding on the need for crossover stenting. However, the disparate methods reflect the diversity of practice settings to which clinical trial results must always be extrapolated. Another limitation of our study is the absence of studies with drug-eluting stents. Although some studies used heparin-coated stents, no trials have compared standard angioplasty without stents to the promising drug-eluting stents (56). A complete assessment of drug-eluting stents will require a clear appreciation of the baseline benefits of routine stenting, which our study does provide.

From McGill University, Montreal, Quebec, Canada.

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Requests for Single Reprints: James Brophy, MD, PhD, Division of Epidemiology, McGill University Health Center (MUHC), Royal Victoria Hospital, 687 Pine Avenue West, Room 4.12, Montreal, Quebec H3A 1A1, Canada; e-mail, james.brophy@mcgill.ca.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Dr. Brophy: Division of Epidemiology, McGill University Health Center (MUHC), Royal Victoria Hospital, 687 Pine Avenue West, Room 4.12, Montreal, Quebec H3A 1A1, Canada.
Mr. Belisle and Dr. Joseph: Division of Clinical Epidemiology, Montreal General Hospital, McGill University, 1650 Cedar Avenue, Montreal, Quebec H3G 1A4, Canada.

Author Contributions: Conception and design: J.M. Brophy, L. Joseph.
Analysis and interpretation of the data: J.M. Brophy, P. Belisle, L. Joseph.
Drafting of the article: J.M. Brophy, L. Joseph.
Critical revision of the article for important intellectual content: J.M. Brophy, P. Belisle, L. Joseph.
Final approval of the article: J.M. Brophy, P. Belisle, L. Joseph.
Statistical expertise: J.M. Brophy, P. Belisle, L. Joseph.
Obtaining of funding: J.M. Brophy.
Administrative, technical, or logistic support: J.M. Brophy
Collection and assembly of the data: J.M. Brophy, L. Joseph.

Appendix Table. **Search Strategy**

Search	Database	Key Words	Studies Selected	Time Range	References, *n*	Randomized, controlled trials, *n*
Search A	PubMed	Angioplasty, stent	Clinical trials only	1/1/93–6/30/02	578	29
Search B	MEDLINE	Angioplasty, stent	Clinical trials only	1/1/93–6/30/02	2277	29