A Meta-Analysis Of Randomized Controlled Trials With Coronary Drug-Eluting Stents Compared With Bare-Metal Stents

M Sondhi, A Jagannath, J Wong

Citation

Abstract
Background: We sought to quantify current risks and benefits of coronary drug-eluting stents compared with bare-metal stents.

Methods: We searched Medline 1996-2005 for randomized, controlled trials of drug-eluting stents. Data relating to death, death or myocardial infarction (MI), target lesion revascularization, restenosis, and need for repeat percutaneous coronary intervention (PCI) or coronary artery bypass grafting were extracted. Using the DerSimonian and Laird random effects models, risk differences were calculated with and without drug-eluting stents. Sensitivity analyses were done based on control rate, study quality, type of eluting drug and observation duration.

Results: In all, 12 trials involving 4902 patients were identified but not all contributed to each endpoint. Drug-eluting stents did not significantly affect the risk of death or death or MI compared with bare-metal stents. Drug-eluting stents, however, had a baseline risk of restenosis of 8% (CI 7% to 9%) a risk difference of -23% (CI -30% to -17%) compared with bare-metal stents. Drug-eluting stents required repeat target lesion revascularization in 4% (CI 3% to 5%) a risk difference of -11% (CI -15% to -7%) compared with bare-metal stents. Drug-eluting stents also had risk differences for CABG of -1.0% (CI -1.9% to -0.1%) and for subsequent repeat PCI of -11% (CI -16% to -6%). Contributors to statistical heterogeneity included control rate variation, study quality, type of eluting drug and observation duration.

Conclusions: Coronary drug-eluting stents significantly reduced the rates of restenosis and the need for repeat revascularization when compared with bare-metal stents.

Grant Support: In part by grant from the Agency for Healthcare Research and Quality, Rockville, Maryland; grant LM07092-12 from the National Library of Medicine, Bethesda, Maryland, and the Harold Williams Medical Student Research Fellowship, Tufts University School of Medicine.

Conflict of interest notification
We, the authors, report no conflicts of interest. For full disclosure, John Wong was a co-investigator in the Patient Outcome Research Team grant for Ischemic Heart Disease from the then Agency for Health Care Policy and Research from 1990-95 and is currently the content editor for Coronary Artery Disease for the non-profit Foundation for Informed Medical Decision Making. Manu Sondhi received a grant for fellowship from the National Library of Medicine. Amitha Jagannath received a summer research grant from the Tufts University School of Medicine. Dr. Wong, Dr. Sondhi and Ms. Jagannath had complete independence from the funding sources in study design, interpretation of data, report writing, and publication regardless of results.

INTRODUCTION
Since its introduction in 1977, percutaneous coronary intervention (PCI), a less invasive procedure than coronary artery bypass grafting (CABG), has been widely used for the treatment of coronary artery obstruction (1). In 2002, 657,000 PCI procedures were performed - a 324% increase from 1987 (2). However, following angioplasty with balloon
dilatation, many patients develop restenosis, often leading to another revascularization procedure. A recently published meta-analysis of randomized trials reported that the use of stents reduced the restenosis rate by about one-half (odds ratio 0.52, CI 0.37 to 0.69) and the need for repeat angioplasty by about 40% (odds ratio 0.59, CI 0.50 to 0.69) (3).

To reduce restenosis rates further, anti-stenotic drug coatings have been applied to bare-metal stents. The Food and Drug Administration (FDA) approved the use of sirolimus-eluting coronary stent in 2003 and paclitaxel-eluting coronary stent in 2004 (4). Randomized controlled trials (RCTs) involving drug-eluting stents (DES) have shown consistent reductions in restenosis, and a meta-analysis of these trials was recently published reporting reduced rates of restenosis with drug-eluting stents (odds ratio 0.18, CI 0.08 to 0.40) (5). However, this study did not examine differences in patient characteristics and potential effects of observation duration or study quality. We considered these factors by pooling updated RCT data published till mid-2005 and determined the effectiveness of drug-eluting stents compared with bare-metal stents in reducing clinically important endpoints such as death, myocardial infarction (MI), restenosis, and repeat revascularization. To explore sources of potential heterogeneity, we examined control rate, study quality, type of eluting drug and observation duration. Lastly, to facilitate understandability of the degree of benefit, we present our results not as odds ratios but as absolute risk, risk differences and number needed to treat (NNT) (6).

METHODS

SEARCH STRATEGY

We searched for published randomized controlled trials comparing drug-eluting stents with bare-metal stents in Medline 1966-2005 (accessed 6/1/2005) using keywords: stents, sirolimus, paclitaxel, eluting, coated, trial and study (Figure 1) with exclusion of animal models and non-English studies. Review of the search results identified 78 citations reporting results from drug-eluting stent trials. Studies that were non-randomized, uncontrolled, published in abstract form only, contained a non-stent control, did not provide numerical data or full follow-up information were excluded. In all, 12 randomized controlled trials comparing drug-eluting stents with bare-metal stents were identified for our analysis. Prespecified data abstraction included demographic and clinical patient population characteristics and clinical outcomes: death, death or myocardial infarction (Q-wave or non-Q-wave), in segment restenosis, target lesion revascularization, need for CABG or repeat PCI, and persistent angina.

Figure 1

Figure 1: Flow diagram of study selection.

STATISTICAL METHODS

Statistical analyses in this study were performed using Meta-Analyst version 0.99 (Joseph Lau, Boston, MA). The endpoints from the trials were combined using the DerSimonian and Laird (7) random effects model to estimate the risk differences (RD) and corresponding 95% confidence intervals (CI) for each clinical outcome. The random effects model was chosen to provide estimates that consider variance both between and within studies. Heterogeneity testing applied the Q-statistic with p-values < 0.10 being considered significant. Studies that did not mention a specific outcome were excluded from the analysis for that endpoint. Although we looked for anginal outcomes, only Morice et al. reported angina leading to repeat revascularization (8). We examined study quality by determining the Jadad score, a well-established and validated scale (9) applying seven criteria (five for good and two for poor study quality) to obtain a numerical score between 0-5.
with 0 being the poorest and 5 being the highest design and reporting quality.

In addition, we calculated the number needed to treat (NNT), the number of patients that would need to be treated with drug-eluting stents instead of bare-metal stents to prevent one adverse outcome. Number needed to treat (NNT) is calculated as the reciprocal of the risk difference between drug-eluting and bare-metal stents for a particular clinical outcome. In general, NNTs between 2 and 5 indicate effective treatments, and NNTs of 20-40 may be useful in preventative treatments e.g. those that decrease mortality (10).

In the primary analysis, articles published in peer-reviewed journals were used. Sensitivity analyses explored factors potentially contributing to statistical heterogeneity such as control rates, length of study follow-up, type of stent, quality of study and duration of observation.

RESULTS

Our search identified 12 studies (8, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21) with 4902 patients comparing drug-eluting stents with bare-metal stents. Tables 1a and 1b list patient characteristics.

Figure 2
Table 1a: Patient Characteristics Data

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Table 1a Continued: Patient Characteristics Data

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Figure 3
Patients were mostly male (69% to 89%), between 56 and 66 years of age, hyperlipidemic (51% to 85%) except for ASPECT and RAVEL, hypertensive (45% to 79%), current non-smokers (54% to 78%), and most did not have diabetes mellitus (70% to 98%). Follow-up time varied from 6 months to 1 year, and Jadad scores ranged from 2 to 5.

In the primary analysis (Table 2), involving 12 studies with 4902 patients (8, 11, 12, 13, 14, 15, 16, 17, 18, 19), drug-eluting stents did not significantly alter mortality alone or MI-free survival when compared with bare-metal stents (Table 2). With use of drug-eluting stents, the risk of death was 0.9% (CI 0.6% to 1.5%) and death or MI was 4% (CI 3% to 5%). The rate of restenosis (8, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20) for patients receiving drug-eluting stents was 8% (CI 7% to 10%), a significantly reduced risk of restenosis (RD –23%, CI –30% to –17%) (Figure 3a). Similarly, subsequent target lesion revascularization (8, 11, 12, 13, 14, 15, 16, 17, 18, 19) with drug-eluting stents was 3.7% (CI 2.9% to 4.7%) a statistically significant reduction compared with bare-metal stents (RD –11%, CI –15% to –6%) (Figure 3b). Drug-eluting stents reduced the likelihood of CABG (RD –1.0%, CI –1.9% to –0.1%) and repeat PCI (RD –11%, CI –16% to –6%) (Figures 3c).

Risk differences for restenosis (Figure 2a), target lesion revascularization (Figure 2b) and repeat percutaneous coronary intervention (Figure 2c) for drug-eluting stent (DES) versus bare-metal stent (Control). Study name and year published are given as well as the number of events and the number at risk. Control rates are given in the last column. Patient counts were estimated from percentages when not recorded. The figure displays the risk difference. The closed circles indicate the risk differences. The lines display the 95% confidence intervals for the risk difference. The pooled risk difference and confidence intervals are shown at the bottom of each figure. Results are statistically significant for all lines that do not cross zero.
A Meta-Analysis Of Randomized Controlled Trials With Coronary Drug-Eluting Stents Compared With Bare-Metal Stents

Figure 6
Figure 2a

Figure 7
Figure 2b

Figure 8
Figure 2c

Figures 3a to 3c display the risk differences for restenosis (3a), target lesion revascularization (3b) and repeat percutaneous coronary intervention (3c) for drug-eluting stent (DES) versus bare-metal stent (Control) at different duration of observation. Patient counts were estimated from percentages when not recorded. The figure displays the risk difference at different lengths of observation. The closed circles indicate the risk differences. The lines display the 95% confidence intervals for the risk difference. Results are statistically significant for all lines that do not cross zero.

Figure 9
Figure 3a

Figure 10
Figure 3b

Figure 11
Figure 3c

Based on the above risk differences, NNT calculations (Table 2) found that 4 (CI 3-6) patients would need to be treated with drug-eluting stents instead of with bare-metal stents to avoid one case of restenosis. Second, 9 (CI 7-15) patients would need to be treated with drug-eluting stents to avoid one target lesion revascularization. Finally, 100 (CI 53-1022) patients would need to be treated with drug-eluting stents to avoid one CABG, and 9 (CI 6-16) patients would need to be treated with drug-eluting stents to avoid one repeat PCI with bare-metal stents.
However, the likelihood of restenosis, target lesion revascularization and need for PCI varied across studies and yielded significant statistical heterogeneity. To explore sources for statistical heterogeneity, we performed a sensitivity analysis to determine the effect of control-rate variation. Studies with higher risk differences for the clinical outcomes of restenosis, target lesion revascularization, and need for PCI had higher control rates. Selective exclusion of studies with the highest and lower control rates decreased the statistical heterogeneity with no change in point estimates of risk difference and minimally smaller confidence intervals for these outcomes (Table 3a).

Stratifying studies using Jadad scores substantially reduced statistical heterogeneity, but heterogeneity continued to be significant (Table 3a). Studies with low Jadad score (2 and 3) suggesting lower quality of randomization compared to high Jadad scores (4 and 5) had a smaller risk difference for target lesion revascularization (~8%, p <0.003 vs. ~12%, p <0.001), for restenosis (RD ~17%, p 0.01 vs. ~28%, p <0.001) and for repeat PCI (RD ~8%, p = 0.06 vs. ~13%, p <0.001) when comparing drug-eluting stents with bare-metal stents.

Separate analyses of clinical outcomes for paclitaxel and sirolimus studies were done (Table 3b). Because there is a slower and prolonged elution in polymer based stents e.g. 10% elution in paclitaxel SR stent over 30 days versus non-polymer coated stents that elute 40% of the drug during stent delivery, paclitaxel-eluting stents were separated into polymer-based or non-polymer based and compared with bare-metal stents (a). Risk differences for polymer-based paclitaxel-eluting stents were larger than for non-polymer studies. Compared with bare-metal stents, polymer-based stents reduced the risk of restenosis from 23% to 7% (p <0.001) and target lesion revascularization from 12% to 3% (p <0.001), while risk differences for need for CABG and PCI were not statistically significant. Risk differences for non-polymer based paclitaxel stents compared with bare-metal stents were not statistically significant for any of the outcomes except for a reduced risk of restenosis from 23% to 9% (p = 0.02).
A Meta-Analysis Of Randomized Controlled Trials With Coronary Drug-Eluting Stents Compared With Bare-Metal Stents

Figure 14
Table 3b: Sensitivity Analyses of Clinical Outcome Drug-Eluting Stents vs. Bare-Metal Stents

Polymer-based sirolimus-eluting stents compared with bare-metal stents significantly reduced the risk of restenosis from 38% to 4% (p<0.001), target lesion revascularization from 20% to 4% (p<0.001), need for CABG from 1.5% to 0.7% (p=0.08) and need for PCI from 20% to 4% (p<0.001) (Table 3b). Note that the control rates were higher for the sirolimus studies than for the paclitaxel polymer studies, so analysis by type of drug-eluting stent revealed reduced statistical heterogeneity for restenosis, target lesion revascularization and repeat PCI. These analyses suggest absolute risk reduction with sirolimus-eluting stents greater than those with polymer-based paclitaxel-eluting stents.

To explore potential reasons for the differences between paclitaxel and sirolimus studies, we compared patient characteristics, lesion characteristics, angiographic analysis techniques and ratios of stent to lesion length. There were no significant differences in patient characteristics including gender, history of diabetes, hypertension, current smoker and previous MI between the paclitaxel and sirolimus studies except for a significantly higher percentage of patients with hyperlipidemia in sirolimus studies (Figure 4a) perhaps accounting in part for the higher control rates with sirolimus.

Analysis of paclitaxel-eluting stent (PES) studies versus sirolimus-eluting stent (SES) studies comparing (Figure 4a) patient characteristics, (Figure 4b) lesion classification, (Figure 4c) location of stenosis and (Figure 4d) quantitative angiographic measures. The bars indicate indicative weighted averages. White vertical bars represent paclitaxel-eluting stents and gray bars represent sirolimus-eluting stents. The lines display the 95% confidence intervals for these values. LAD indicates left anterior descending coronary artery, RCA, right coronary artery, LCx, left circumflex coronary artery, RVD, reference vessel diameter and MLD, minimum lumen diameter.

Figure 15
Table 3c

Polymer-based sirolimus-eluting stents compared with bare-metal stents significantly reduced the risk of restenosis from 38% to 4% (p<0.001), target lesion revascularization from 20% to 4% (p<0.001), need for CABG from 1.5% to 0.7% (p=0.08) and need for PCI from 20% to 4% (p<0.001) (Table 3b). Note that the control rates were higher for the sirolimus studies than for the paclitaxel polymer studies, so analysis by type of drug-eluting stent revealed reduced statistical heterogeneity for restenosis, target lesion revascularization and repeat PCI. These analyses suggest absolute risk reduction with sirolimus-eluting stents greater than those with polymer-based paclitaxel-eluting stents.

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Figure 16
Figure 4a
When comparing the types of coronary lesions, paclitaxel studies had a significantly greater percentage of patients with type A and type B1 (angiographically favorable lesions) and hence fewer patients with type B2 and type C coronary lesions as compared with sirolimus studies (Figure 4b). No differences were found between paclitaxel and sirolimus studies in location of stenosis (Figure 4c), lesion length, reference vessel diameter and percentage of stenosis.

Finally, there were no differences in lesion characteristics post procedure including in-stent diameter, in-segment diameter and final reference vessel diameter (Figure 4d). Angiographic evaluation in the paclitaxel and sirolimus studies used different computer-based systems including CAAS II and MEDIS. Stent-length to lesion-length ratios ranged from 1.6 - 1.8:1 in the sirolimus-eluting studies (11, 18). In the paclitaxel-eluting studies this ratio was not consistently reported but when found was mostly lower, in the 1.3 - 1.5:1 range (11, 12, 15, 19, 20). As above, the higher proportion of patients with unfavorable characteristics in the sirolimus studies support the observed higher control rates in those studies. Additionally, the high stent to lesion ratio may account for the sirolimus benefit.

Lastly, we explored differences in follow-up duration as a source of statistical heterogeneity for the outcomes of death, death or MI, target vessel restenosis, target lesion revascularization, need for CABG and repeat PCI divided into 4 time frames: <1 month, 6 months, 8-9 months and 1 year (Table 2). The results were not statistically significantly different for death alone and for death or MI in any of the 4 time periods. In addition, in the <1 month group, target lesion revascularization, need for CABG and repeat PCI were not statistically significantly different. Drug-eluting stents, however, significantly reduced the risk of restenosis (RD –17%, p <0.001) over 6 months, and the effect was even greater (RD –28%, p <0.001) in the 8-9 month subgroup (Figure 3a). For target vessel revascularization, the risk difference was –5% (p 0.02) in the 6 month subgroup, –11% (p <0.001) in the 8-9 month subgroup and –13% (p <0.001) in the 1 year subgroup (Figure 3b). The risk difference for need for CABG was –1.5% (p = 0.001) in the 8 to 9 month subgroup; but the RD was not statistically significant in the 1 year subgroup. In addition, the risk difference for repeat PCI was –11% (p <0.001) in the 8 to 9 month subgroup and –13% (p <0.001) in the 1 year subgroup (Figure 3c). Analysis by differences in follow-up duration reduced heterogeneity in restenosis, target lesion revascularization and need for repeat PCI.

**DISCUSSION**

As a new technology, drug-eluting stents have now emerged as an important innovation in reducing coronary restenosis. To provide a precise estimate of their clinical benefit and to explore sources of statistical heterogeneity, we performed a meta-analysis of randomized controlled trials involving currently available drug-eluting stents using a DerSimonian
and Laird random effects model. Our meta-analysis found no significant reduction in mortality or MI-free survival from the use of drug-eluting stents. However, drug-eluting stents clearly reduced the risk of restenosis by 23% and the risk for target lesion revascularization by 11% in the primary analysis. This is similar in magnitude to the benefit found for stents compared to balloon angioplasty \((1)\). The need for revascularization after DES was 3.7% that is similar to the 3.8% observed after coronary artery bypass grafting and much lower than the 21% with bare-metal stents \((29)\).

Our analysis found significant statistical heterogeneity for the outcomes of restenosis, target lesion revascularization and need for PCI. Subgroup analyses found that control rate variation, study quality, type of drug-eluting stent and follow-up duration contributed to the heterogeneity. Control rate can be considered as a proxy surrogate marker for patient risk factors, and variation in it may reflect across study differences in risk factors in these patient populations, length of study follow-up and treatment delivery \((33)\).

Although control rate as a predictor of risk differences can yield a false positive result, when excluding studies based on control rate, we found a statistically homogenous result. Generally studies with low quality scores produced significantly larger risk differences \((11)\), but we found that studies with lower Jadad scores had a smaller treatment effect. Third, stratifying by type of drug-eluting stents reduced statistical heterogeneity. Finally, analyzing studies by difference in duration of follow-up also reduced heterogeneity.

When we examined paclitaxel and sirolimus stent outcomes separately, the event rates were similar in the intervention arms. Although the control rates were much higher in the sirolimus studies, yet the risk differences or benefit with sirolimus were more substantial than with polymer-based paclitaxel stent when each was compared to bare-metal stent controls. To determine if patient or lesion characteristics could account for the differences in control rate events, we compared characteristics in published paclitaxel studies to those in sirolimus ones and found that sirolimus patients had a higher proportion with hyperlipidemia and with less favorable B2 and C lesions. An additional potential reason for greater observed benefit with sirolimus stents was their higher stent-length to lesion-length ratios \((25)\).

Our analysis is limited in its ability to compare different drug-eluting stents directly. An indirect comparison of sirolimus-eluting stent versus polymeric paclitaxel-eluting stent showed a nonsignificant reduction in target lesion revascularization and a highly statistically significant reduction in binary in-stent restenosis rate; both favoring sirolimus-eluting stents \((13)\). However, the strength of inference associated with indirect comparisons is limited even when lacking demonstrable sources of bias \((3)\).

Initially, the results of head-to-head trials comparing sirolimus-eluting to paclitaxel-eluting stents were conflicting. In one trial, sirolimus-eluting stents reduced restenosis in patients with in-stent stenosis \((19\) ), but the two stents were found to be equivalent in 202 patients followed clinically for six months \((10)\). Two new studies have now found lower restenosis rates for sirolimus-eluting stents \((24, 25)\). In patients with diabetes mellitus and coronary artery disease, sirolimus-eluting compared with paclitaxel-eluting stents had decreased late luminal loss, suggesting a reduced risk in restenosis \((34)\). In another study, sirolimus-eluting stents resulted in fewer major adverse cardiac events, primarily by decreasing the rates of clinical and angiographic restenosis as compared with paclitaxel-eluting stents \((33)\). A meta-analysis of randomized trials with sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease found that patients receiving sirolimus-eluting stents had a significantly lower risk of restenosis and target vessel revascularization compared with those receiving paclitaxel stents while rates of death, death or MI, and stent thrombosis were similar \((28)\).

For all of these studies, knowledge of angiographic results (in the absence of clinical indications such as angina or abnormal stress test for angiography) likely contributed to higher rates of repeat target lesion revascularization in the control bare-metal stent arms and hence higher observed risk differences \((23, 28)\).

Our analysis based on endpoint follow-up duration, however, suggests that the risk difference for target vessel revascularization increases from 6 months to 8-9 months to 1-year follow-up. The studies we included had a maximum follow-up of 1 year while published abstracts are now available with longer follow-up \((25)\). Results from TAXUS-III with 2 year angiographic and ultrasound follow-up failed to demonstrate any “catch-up” with the TAXUS stent. Additional trials with extended follow-up should be performed.

Does the restenosis benefit of drug-eluting stents justify their higher cost? SIRIUS investigators performed a preliminary
cost-effectiveness analysis of the sirolimus-eluting stent (1) and found it to be “cost-effective” for complex lesions and not for larger vessels and discrete lesions. This analysis, however, was based on one clinical trial and was performed prior to FDA approval. A disease-state model simulating use of drug-eluting stents found that the proposed Medicare reimbursement increase might not totally offset the costs (13). In addition, low reimbursement for these higher costing stents and decreased hospital revenues from loss of repeat catheterization and revascularization may affect utilization of these stents (14,20). Indeed, in actual clinical practice, among patients undergoing PCI irrespective of indication, use of drug-eluting stents were associated with higher total costs of about 900 euros (23). Despite 44% lower major adverse cardiac event rates versus a third-generation bare-metal stents, drug-eluting stents have a cost-effectiveness ratio exceeding 50,000 euros over a 6-month time horizon. Similarly, in a cost-effectiveness analysis of drug-eluting stents used in patients with high-risk lesions in Australia, drug-eluting stents were found to be cost neutral only if the premium for drug-eluting stents decreased from the actual $A1500 to $A600 (24). Further cost-effectiveness analyses using data from head-to-head comparisons within drug-eluting stents and updated stent costs due to increased competition should be performed over longer time horizons.

In conclusion, our meta-analysis suggests that patients treated with drug-eluting stents have lower rates of repeat revascularization and restenosis than those treated with bare-metal stents even in the presence of statistical heterogeneity that can be attributed to control-rate variation, study quality, type of eluting drug and duration of study observation. These findings support the clinical use of this new technology, but further investigation into patient selection criteria, alternative clinical populations, lesion characteristics (25) and differences among drug-eluting stents should be performed. Because, as with all treatments, not everyone experiences the same benefits as others, the final test of these stents lies in their efficacy and utility in actual clinical practice.

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