INTRODUCTION

It has been well established by a number of randomized trials that drug-eluting stents (DES) is superior to plain balloon angioplasty and bare-metal stents (BMS) in terms of reducing restenosis and improve the effectiveness of percutaneous coronary intervention (PCI).1-3 The decrease in the need of revascularization has been previously reported in relatively short-term follow-up (6 months to 1 year). However, the long-term efficacy of DES requires evidence because of the delayed occurring stent thromboses (more than one year after stent implantation) and delayed healing of the stented arterial segment.4,5 The mechanism underlying the very late stent thromboses observed after DES implantation may be associated with the antiproliferative agents eluting by the stent and local inflammatory reaction, which eventually cause delayed endothelial healing.6,7 This prolonged healing alters the traditional duration of six to eight months required for endothelial recovery, so that the stent thromboses may appear beyond 1 year. DES has been linked to the very late stent thromboses observed after DES implantation may be associated with the antiproliferative agents eluting by the stent and local inflammatory reaction, which eventually cause delayed endothelial healing.6,7 This prolonged healing alters the traditional duration of six to eight months required for endothelial recovery, so that the stent thromboses may appear beyond 1 year.

META ANALYSIS

Long-term Outcomes of Paclitaxel-Eluting Versus Sirolimus-Eluting Stent for Percutaneous Coronary Intervention: A Meta-Analysis

Jie Kong, Peng Liu, Xueqiang Fan, Jianyan Wen, Jianbin Zhang, Yanan Zhen, Jinyong Li, Yiyao Cui, Xia Zheng and Zhidong Ye

ABSTRACT

The relative long-term efficacy and safety of sirolimus-eluting stents (SES) compared with paclitaxel-eluting stents (PES) in multiple comparative studies remains controversial. This report evaluates 29 randomized trials with 18,379 patients in whom long-term (more than 1 year) outcomes were evaluated. The primary outcomes were target lesion revascularization (TLR) and the secondary end points were death, cardiac death, myocardial infarction (MI), major adverse cardiac events (MACEs), target vessel revascularization (TVR) and stent thrombosis (ST). In comparison with PES, SES significantly reduced the long-term risk of TLR (RR=0.68; 95% CI=0.57 to 0.80, p<0.001), TVR (RR=0.69; 95% CI= 0.60 to 0.79, p<0.001) and MACE (RR=0.82; 95% CI= 0.77 to 0.88, p<0.001), while there were no significant difference with respect to death, cardiac death, MI and ST between the two groups. SES performance was significantly better for reducing the former three outcomes and comparable for the majority of the secondary end points when compared against PES.


INTRODUCTION

It has been well established by a number of randomized trials that drug-eluting stents (DES) is superior to plain balloon angioplasty and bare-metal stents (BMS) in terms of reducing restenosis and improve the effectiveness of percutaneous coronary intervention (PCI).1-3 The decrease in the need of revascularization has been previously reported in relatively short-term follow-up (6 months to 1 year). However, the long-term efficacy of DES requires evidence because of the delayed occurring stent thromboses (more than one year after stent implantation) and delayed healing of the stented arterial segment.4,5 The mechanism underlying the very late stent thromboses observed after DES implantation may be associated with the antiproliferative agents eluting by the stent and local inflammatory reaction, which eventually cause delayed endothelial healing.6,7 This prolonged healing alters the traditional duration of six to eight months required for endothelial recovery, so that the stent thromboses may appear beyond 1 year. DES has been linked to the very late stent thromboses that could not be identified in the short- to mid-term follow-up.8 However there have been limited data regarding the long-term outcome comparison between the two most common DES, newly sirolimus-eluting stent (SES) and the paclitaxel-eluting stent (PES) implanted in millions of patients worldwide. Significant differences exist between SES and PES in terms of stent platform, polymer coating and the antiproliferative agent used.9 A number of trials directly compared the two groups, but the results were debated. Some results showed the SES to be superior to PES in anti-restenotic efficacy,10,11 while others showed minor differences, and considered the two DES clinically equivalent. Whether different DES differ from each other on the risk of adverse rates over time is of major clinical interest, but it remains uncertain in the difference of long-term safety profile between SES and PES.

A meta-analysis of these randomized trials could increase the sample size and improve precision of treatment effects. Although there were some meta-analyses about the comparison between SES and PES,12-14 but few are focused on the long-term clinical results between different stents. Some trials about the head-to-head comparison between the two stents reported their 3~5 years follow-up results in recent years.15-20 Randomized controlled trials could control confounded factors and provide the most rigorous evidence, so the aim of this research was to analyse the randomized trials comparing the long-term clinical outcomes following PCI of the SES and PES.

METHODOLOGY

A computerized search was performed in the MEDLINE, Embase and the Cochrane Central Register of Controlled
Trials (CENTRAL) from their inception until February, 2016 for the randomized head-to-head trials between the SES and PES in patients with coronary artery disease (CAD). The trials were searched using the key words "sirolimus", "paclitaxel", "stent" and "random" or "randomly" or "randomized". Reference lists of retrieved literatures were scrutinized for the relevant studies. There was no restriction of the language or publication status. The trials selected were those which made direct comparisons of SES with PES in subjects who underwent PCI with at least 1-year follow-up and the result included the incidence of target lesion revascularization (TLR) as well as the follow-up data. A total of 29 randomized trials were included in this meta-analysis. The main features of the studied trials were shown in Table I.

Two investigators (JK and JZ) independently reviewed the titles/abstracts. The full text of the selected article was reviewed for assessing study eligibility. The data were extracted independently and disagreements were resolved by consensus. The variables included first author's name, name of trial, year of publication, total and subgroup sample size for both SES and PES, characteristics of the population, including the mean age, hypertension, diabetes, smoking, and the duration of the follow-up.

The primary outcome of interest was target lesion revascularization (TLR) which was defined as any repeat PCI of the target lesion or bypass surgery of the target vessel. Other clinical outcomes included myocardial infarction (MI), cardiac death, total death, stent thrombosis, target vessel revascularization (TVR), and major adverse cardiac events (MACE); the last included the composite of MI, death and TLR. The outcomes were grouped in accordance with the duration of follow-up into subgroup of 1–3 years (exclude 3 years) and subgroup of more than 3 years (include 3 years).

Cochrane Collaboration guidelines with Review Manager 5.3 were followed. The binary variables were the relative risks (RRs) and 95% confidence intervals (CIs). The continuous variables were estimated as weighted mean differences (WMDs) and 95% CIs. Frequency of TLR, TVR, MACE, death, cardiac death, MI and stent thrombosis in the two groups were presented as risk rate (RR) with 95% CI. The fixed-effects model was used in cardiac death, death, MACE, MI, stent thrombosis, TVR; while the TLR was calculated by the random-effects model because the study variability existed. Heterogeneity was checked with the Q test and I² statistic, and a cut-off value of P was 0.05 or I² was more than 50% suggested significant heterogeneity. Publication bias was evaluated by the funnel plot. The quality of studies was assessed by the Cochrane Collaboration's tool for assessing risk of bias including random sequence generation, allocation concealment, binding of participants and personnel, binding of outcome data, incomplete outcome data, selective reporting and other sources of bias. Statistical analyses were carried out through the Review Manager 5.3 software.

Table I: Clinical characteristics of included studies.

<table>
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<tr>
<th>First Author Year</th>
<th>Patient profile</th>
<th>FU (Y)</th>
<th>Sample size</th>
<th>Age (year) (n=18061)</th>
<th>Men (%) (n=18061)</th>
<th>DM (%) (n=18061)</th>
<th>HP (%) (n=17667)</th>
<th>Smoker (%) (n=17500)</th>
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DM = Diabetes mellitus, FU = Follow-up duration, HP = hypertension, STEMI = ST-segment elevation myocardial infarction; S = SES; P = PES
RESULT

Of the 571 articles with the potential of relevance were initially identified from EMBASE, Pubmed and CENTRAL, 29 articles met the selection criteria and were finally considered in the meta-analysis (Figure 1). A total of 18,379 patients (9,217 in SES arm, 9,162 in PES) were included. Basic characteristics of the patients enrolled in the studies are shown in Table I. The duration of follow-up ranged from 1 to 5 years and the sample size ranged from 44 to 3,426. The average age of the SES group and PES group ranged from 57.8±11.3 to 69.4±8.7 years and 59.3±11.2 to 69.2±9.1 years, respectively. The percentage of males ranged from 57% (n=76) to 86.4% (n=110) in SES group and from 55% (n=200) to 83% (n=100) in PES group. The percentage of patients with hypertension or diabetes in both groups is also shown in Table I. The results of bias assessment were shown in the Figures 2 and 3.

TLR was the primary measure of efficacy. PCI with SES had significant reduced incidence of TLR compared with PES at overall-term follow-up (RR=0.68; 95% CI= 0.57 to 0.80, P<0.001). SES significantly lowered the TLR than PES in both subgroups as shown in Figure 4a. The RR of subgroup 1~3 years and subgroup more than 3 years were 0.63 and 0.75, respectively. The test of heterogeneity showed I²=51%, P=0.001, so the random-effect model was used. There was no evidence of publication bias with respect to TLR in the funnel plot.

Twenty-three studies provided the data of death from all causes, showing no significant difference between the two groups (RR=1.00; 95% CI= 0.85 to 1.17, p=0.97). No difference was found in the subgroup analysis, too (Figure 4b). The fixed-effect model was used because of reasonable homogeneity between the trials (p=0.92, I²=0%), and no publication bias.

The meta-analysis of 23 included trials showed patients assigned to SES group did not have significantly different incidence of cardiac death than those in PES group (RR=1.05; 95% CI= 0.86 to 1.28, p=0.99, I²=0%) on fixed-effect model. Data on myocardial infarction were available for 26 randomized trials with no publication bias. There was no difference in the incidence of myocardial infarction between SES and PES (RR=0.96; 95% CI= 0.82 to 1.13, P=0.64) (Figure 4d). Test of heterogeneity among studies showed P=0.98 and I²=0%, so fixed-effect model was used.

A total of 17 randomized controlled studies provided data for TVR meta-analysis. TVR was significantly reduced in
subjects treated with SES than those treated with PES (RR=0.69; 95% CI= 0.60 to 0.79, p<0.001, Figure 4e). Again, there was neither significant heterogeneity among studies (p=0.17, I²=25%) requiring fixed-effect model nor publication bias.

MACE data were provided by 29 randomized controlled studies. The SES arm has significant lower incidence of MACE than the PES arm by the fixed-effect model (RR=0.82; 95% CI= 0.77 to 0.88, p<0.001, Figure 4f), t-test of heterogeneity showing (p=0.47, I²=0%) and no publication bias.

Stent thrombosis is the primary safety end point and was reported in 29 randomized trials. ST in SES group was not significantly different from that in the PES group (RR=0.85; 95% CI= 0.69 to 1.05, P=0.14) (Figure 4g). There was no significant heterogeneity (p=0.90 and I²=0%) so fixed-effect model was used. There was no publication bias.

**DISCUSSION**

This meta-analysis evaluated 29 randomized controlled trials and compared the long-term clinical outcomes (from 1 year to 5 years) of SES with PES in percutaneous coronary intervention. SES use significantly decreased the incidence of TLR, TVR, MACE compared with PES; and that effect sustained for up to 5 years follow-up, so that efficacy for prevention of restenosis SES reached at least 5 years. There was no significant difference in the frequency of all-cause death, cardiac death, myocardial infarction among patients treated with SES or PES for up to 5 years. The overall frequent of stent thrombosis was not different from each other. These conclusions are based on robust data from the rigorously designed and conducted randomized trials for diminishing the selection bias and confounding bias. These findings corroborate the previous studies that have suggested that SES could reduce the need for repeated revascularization and indicated that effect could last for at least 5 years.

The meta-analysis could combine data from many inadequately powered studies for assessing the superiority or inferiority of low frequency event (death, MI, or stent thrombosis). It could result in a lesser degree of heterogeneity and higher degree of confidence in the conclusions that included only randomized trials in the meta-analysis. There were some prior meta-analyses comparing the 2 stent systems. Gurm analyzed 12 studies that randomized 7,455 patients undergoing PCI by SES or PES and concluded that SES is more effective than PES for reducing the incidence of TLR or TVR. But the follow-up duration of that meta-analysis was relatively short and not sufficient to evaluate the incidence of late stent
Figure 4: (4a) Forest plot of RR and 95% CI for TLR after PCI in patients receiving SES compared PES. SES significantly decreased the incidence of TLR for 1~3 year (RR=0.63; 95% CI= 0.48 to 0.83, P=0.001), 3~5 years (RR=0.75; 95% CI= 0.62 to 0.91, P=0.004) and overall-term (RR=0.68; 95% CI=0.57 to 0.80, P<0.0001) follow-up. CI = confidence interval; PES = paclitaxel-eluting stents; RR = relative risk; SES = sirolimus-eluting stent; TLR = target lesion revascularization.

(4b) Forest plot of RR and 95% CI for all-cause death after PCI in patients receiving SES compared PES. SES is similar to PES in the incidence of death for 1~3 year (RR = 1.04 ; 95% CI= 0.80 to 1.36, P=0.75), 3~5 years (RR=0.97; 95% CI= 0.80 to 1.18, P=0.77) and overall-term (RR=1.00; 95% CI= 0.85 to 1.17, P=0.97) follow-up. CI = confidence interval; PES = paclitaxel-eluting stents; RR = relative risk; SES = sirolimus-eluting stent.

(4c) Forest plot of RR and 95% CI for cardiac death after PCI in patients receiving SES compared PES. SES is similar to PES in the incidence of cardiac death for 1~3 year (RR = 1.12 ; 95% CI= 0.74 to 1.68, P=0.60), 3~5 years (RR = 1.03; 95% CI= 0.82 to 1.30, P=0.60) and overall-term (RR=1.05; 95% CI= 0.86 to 1.28, P=0.63) follow-up. CI = confidence interval; PES = paclitaxel-eluting stents; RR = relative risk; SES = sirolimus-eluting stent.

(4d) Forest plot of RR and 95% CI for MI after PCI in patients receiving SES compared PES. SES is similar to PES in the incidence of MI for 1~3 year (RR = 0.92; 95% CI= 0.75 to 1.13, P=0.44), 3~5 years (RR = 1.03; 95% CI= 0.80 to 1.31, P=0.83) and overall-term (RR=0.96; 95% CI= 0.82 to 1.13, P=0.64) follow-up. CI = confidence interval; PES = paclitaxel-eluting stents; RR = relative risk; SES = sirolimus-eluting stent; MI = myocardial infarction.

(4e) Forest plot of RR and 95% CI for TVR after PCI in patients receiving SES compared PES. SES significantly decreased the incidence of TVR for 1~3 year (RR=0.67; 95% CI= 0.55 to 0.81, P=0.0001), 3~5 years (RR=0.71; 95% CI= 0.59 to 0.85, P=0.0002) and overall-term (RR=0.69; 95% CI= 0.60 to 0.79, P<0.0001) follow-up. CI = confidence interval; PES = paclitaxel-eluting stents; RR = relative risk; SES = sirolimus-eluting stent; TVR = target vessel revascularization.

(4f) Forest plot of RR and 95% CI for MACE after PCI in patients receiving SES compared PES. SES significantly decreased the incidence of MACE for 1~3 year (RR=0.78; 95% CI= 0.70 to 0.88, P=0.0001), 3~5 years (RR=0.85; 95% CI= 0.78 to 0.94, P=0.0009) and overall-term (RR=0.82; 95% CI= 0.77 to 0.88, P<0.0001) follow-up. CI = confidence interval; PES = paclitaxel-eluting stents; RR = relative risk; SES = sirolimus-eluting stent; MACE = major adverse cardiac event.

(4g) Forest plot of RR and 95% CI for ST after PCI in patients receiving SES compared PES. SES is similar to PES in the incidence of ST for 1~3 year (RR = 0.68; 95% CI= 0.46 to 1.02, P=0.06), 3~5 years (RR = 0.93; 95% CI= 0.73 to 1.19, P=0.59) and overall-term (RR=0.85; 95% CI= 0.69 to 1.05, P=0.14) follow-up. CI = confidence interval; PES = paclitaxel-eluting stents; RR = relative risk; SES = sirolimus-eluting stent; ST = stent thrombosis.
thrombosis. Schomig studied 8,695 patients enrolled in 16 randomized controlled studies and concluded that SES could more effectively reduce the need for repeat coronary intervention and stent block than PES without affecting the mortality. Zhang analyzed both randomized trials and observational studies. Long-term follow-up about the comparison between SES and PES has been reported in recent years. To the best of authors' knowledge, this is the largest study that included the longest duration of follow-up focused on the long-term outcomes of comparison between SES and PES.

SES and PES were the first two commercially available drug-eluting stents and widely used in the treatment of coronary artery disease. Both DES could effectively suppress smooth muscle cell proliferation; however, they are different from each other with respect to the coated agent, drug-elution kinetics, polymer, and the micro-mechanism of action. SES has sirolimus which is an immuosuppressive agent that arrests the cell-cycle in the G1/S phase and has anti-inflammatory properties. Paclitaxel is a cytotoxic agent and arrests the cell-cycle in the G2/M phase. The therapeutic range of paclitaxel is narrower than sirolimus. The drug-eluting kinetics of sirolimus is more effective than that of paclitaxel because siromilus could distribute homogeneously throughout the vascular wall while paclitaxel binds to microtubules and stays predominantly in the subintimal. The local distribution of paclitaxel might promote the presence of thrombus. The closed-cell design of a SES favors uniform local delivery and allows for elution of 100% of the agent within 1 month while the open-cell design of a PES is less effective and elutes only 10% of the agent over 2 months. These factors might explain that the SES is more effective than PES in curbing intimal hyperplasia recurrence and late lumen narrowing. The latter effect is correlated with a greater reduction in the need for revascularization, and a greater clinical benefit of SES over PES has been primarily driven by the reduction of re-intervention. The decrease in TLR has been previously reported in relatively short-term follow-up (6 months to 1 year). The authors hereby compared the long-term clinical outcomes of the two and noted the lower incidence of TLR, TVR and MACE in SES group over at least 1-year follow-up. In the subgroup analyses, such a decrease could sustain for up to 5 years of follow-up and the incidence of TLR, TVR, and MACE in the SES-treated group was lower than that in the PES-treated group during 3–5 years of follow-up.

It is increasingly recognized that DES undergo late stent thrombosis, which is because of systematic delayed healing of the stented arterial segment and preventing complete coverage of stent struts. The delayed arterial wall healing after DES implantation could be found on autopsy as well as in clinical observational studies. The delayed healing interrupts the temporal course of neointimal and endothelial formation, so that the restenosis could present beyond 1 year. There is concern regarding higher risk of very late stent thrombosis, but there was a paucity of such events in RCTs make the precise statistical quantification of the difference. Previous published meta-analyses of SES and PES showed no evidence of different risk of ST between the two DES during relative short-term follow-up. In this analysis, there was no significant difference in the rate of stent thrombosis between SES and PES on subgroup analyses including 6,455 patients. SES was found to be as safe as PES and is not associated with increased mortality or MI during 3–5 years follow-up. This is in accordance with previous observations. This assessment of trials' quality showed low heterogeneity, which makes the above conclusion robust.

There are still several limitations in this study. This meta-analysis was based on the group estimates in published data rather than individual data. Not every study included all of the outcomes analyzed in this analysis; therefore, there may be selective reporting bias. The definitions of MACE varied among studies and may have an impact on the conclusions of this meta-analysis. The follow-up duration varied among the trials, so subgroup analysis had to be done according to the duration of follow-up to reduce the heterogeneity.

CONCLUSION

In this direct comparative meta-analysis of 29 randomized trials, SES group showed significantly lower long-term incidence of TLR, TVR and MACE compared than PES; while the risk of death, cardiac death, myocardial infarction and stent thrombosis was not significantly different between them.

Additional Information: This work was supported by grants from International S&T Cooperation Program (2013DFA31900), the National Natural Science Foundation of China (Nos. 81670443, 81670275).

REFERENCES


