The Effectiveness and Safety of Triple-Antiplatelet Treatment Based on Cilostazol for Patients Receiving Percutaneous Coronary Intervention: A Meta-Analysis

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ABSTRACT

The combination of cilostazol, aspirin, and clopidogrel (triple therapy) after percutaneous coronary intervention has been considered as an alternative therapy. We performed a meta-analysis based on 8 randomized controlled trials with a total of 3332 patients to compare the effectiveness and safety of this triple therapy with traditional dual therapy (aspirin and clopidogrel). Our findings suggested that the triple therapy is more effective than dual therapy in preventing restenosis (odds ratio [OR]: 0.52, 95% confidence interval [CI]: 0.40–0.66, $P < 0.00001$), maintaining minimal lumen diameter (OR: 0.15, 95% CI: 0.10–0.20, $P < 0.00001$), and avoiding target-vessel revascularization (OR: 0.62, 95% CI: 0.47–0.82, $P = 0.001$). There is also no significant difference in major adverse cardiac and cerebrovascular events between the 2 therapies, except the smaller occurrence rate of target-lesion revascularization in the triple-therapy group (OR: 0.42, 95% CI: 0.26–0.69, $P = 0.0005$). However, the triple therapy is associated with a higher level of adverse drug events, including rash (OR: 2.45, 95% CI: 1.41–4.23, $P = 0.001$), gastrointestinal disorders (OR: 2.59, 95% CI: 1.26–5.30, $P = 0.009$), and drug discontinuation (OR: 3.80, 95% CI: 1.59–9.10, $P = 0.003$), but it has no difference in bleeding compared with the dual therapy (OR: 1.05, 95% CI: 0.71–1.55, $P = 0.80$).

Introduction

For patients with stenotic coronary arteries, percutaneous coronary intervention (PCI), also known as coronary angioplasty, is one of the therapeutic choices.^{1,2} The use of metallic stents in PCI has reduced the risk of both clinical and angiographic restenosis.³ Clinical restenosis involves a series of clinical outcomes, such as target-vessel revascularization (TVR), target-lesion revascularization (TLR), target-vessel failure, myocardial infarction (MI), and death.⁴ Angiographic restenosis is generally defined as 50%-diameter stenosis of the lumen that had a previously successful intervention.⁴ In this study, restenosis mainly refers to angiographic restenosis. Although a significant decrease in restenosis is observed, the remaining risk of restenosis (6-mo rates may be as high as 10%),⁵ as well

as other associated risks such as no flow⁶ after PCI, still pose serious threats to the patients. Neointimal hyperplasia, caused by immune and proliferative responses initiated due to PCI, is the major contributor to restenosis of coronary arteries.^{3,7}

In recent years, cilostazol, a phosphodiesterase III inhibitor that is primarily used for relief of intermittent claudication due to its antiplatelet and vasodilation function, has shown the additional effect of inhibiting neointimal hyperplasia and controlling smooth-muscle proliferation after endothelial injury.^{8,9} Moreover, some researchers also reported that the use of cilostazol after stent implantation or balloon angioplasty supported a significantly higher reduction of restenosis, in contrast with aspirin or ticlopidine.^{10–12} Stent thrombosis is also a major complication of PCI. Therefore, patients undergoing PCI face both the threat of in-stent restenosis and stent thrombosis. Traditionally, dual antiplatelet therapy that combines aspirin with clopidogrel has been applied to prevent stent thrombosis after PCI.¹³ Whether the combination of cilostazol, aspirin, and clopidogrel (triple therapy) after PCI with coronary stents improves outcomes is still not quite clear.

Additional Supporting Information may be found in the online version of this article.

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Although previous meta-analyses in this field identified some better outcomes associated with triple therapy compared with dual therapy, some recent randomized clinical trials (RCTs) have added new evidence to the comparison.^{14,15} To better understand the benefits of triple therapy and dual therapy, the authors of this study performed a meta-analysis of randomized trials comparing the triple and dual therapies.

Methods

Study Design

This study is a meta-analysis focusing on the RCTs comparing the effects of triple and dual therapy. Two reviewers (PW, SZ) independently assessed the eligibility of RCTs identified through search of relevant databases. Disagreements were resolved through group discussion. Data retrieved from the RCTs include details of publications and the characteristics of each trial, such as sample size, interventions, duration of follow-up, and key outcome index measured.

Search Strategy

The Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and PubMed/MEDLINE databases were searched for RCTs using the terms “percutaneous coronary intervention” (or “PCI”), “cilostazol,” “randomized,” and “stent restenosis” in the title and abstract. Only studies published in English and before December 2011 were included. References of original manuscripts and review articles were manually searched to avoid possible omission of eligible RCTs.

Selection Criteria

Studies that met the following inclusion criteria were selected: studies were RCTs; study targets were patients who received PCI; patients were randomly assigned to triple- and dual-therapy groups; studies included outcomes measured during a follow-up ≥ 6 months; and ≥ 50 patients were enrolled. The bias risk of included publications was evaluated based on the *Cochrane Handbook for Systematic Reviews of Interventions*, version 5.0.1.¹⁶ The major quality components include (1) sequence generation of the allocation; (2) allocation concealment; (3) blinding of participants, personnel, and outcome assessors; (4) incomplete outcome data; (5) selective outcome reporting; and (6) other sources of bias.¹⁶ Trials were classified into 3 levels according to their risk of bias. Trials with appropriate and sufficient support of index of outcome assessment and with minimal risk of bias are classified into the A level; trials with ≥ 1 high or unclear risk of bias among the quality components and with a medium-level risk of bias are in the B level; and trials with ≥ 3 high or unclear risks of bias among the quality components and with the highest-level risk of bias are in the C level. Because this study only involved 8 RCTs, the funnel plot graph to show publication bias was not used.

Data Extraction

The RCTs included were identified with the first author and the year of publication. Data extracted from the trials

were checked for internal consistency. Study design and baseline characteristics of patients were compared to assess the heterogeneity. The incidence of restenosis, MLD, and TVR measured during follow-up were analyzed to compare the effects of triple and dual therapy. Major adverse cardiac and cerebrovascular events and adverse drug events were analyzed to compare the safety of the 2 therapies.

Statistical Analysis

Review Manager 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used to perform this analysis. Study-specific estimates (odds ratios [OR]) used Mantel-Haenszel methods in fixed-effects or random-effects model with 95% confidence intervals (CI). A P value ≤ 0.05 was used to denote statistical significance. Heterogeneity between studies was assessed using χ^2 tests.¹⁶ Primary assessment was performed with a fixed model. $P \geq 0.05$ and $I^2 \leq 50\%$ means the trials have no significant heterogeneity and a fixed effect model was adopted, whereas $P \leq 0.05$ and $I^2 > 50\%$ suggests the trials have significant heterogeneity.¹⁷ The source of the heterogeneity was then further analyzed. If there was no significant clinical heterogeneity, a secondary confirmatory analysis was done with a random-effects model. Otherwise, descriptive analysis was performed. Where necessary, sensitivity analyses were performed to test the stability of identified outcomes.

Results

Literature Search

From the PubMed/MEDLINE, Embase, and Cochrane databases, 178 potentially relevant studies were identified. Among them, 152 non-RCTs and 26 non-PCI studies were excluded. Fifteen studies were retrieved for more detailed assessment. Then, 3 studies were excluded due to involvement of other agents, 2 were excluded due to comparison of single and dual agents, and 1 updated study was excluded. Finally, 8 RCTs were selected for this meta-analysis: Chen 2006,¹⁸ Douglas 2005,¹⁹ Min 2007,²⁰ Lee 2007,²¹ Lee 2008,²² Lee 2011,²³ Han 2009,²⁴ and Ahn 2011.¹⁵ The entire search process followed the QUOROM-type flow chart, as shown in Supplementary Figure 1. Summary results and selected characteristics of the included RCTs are shown in Table 1.

Restenosis at the Sixth or Eighth Month

Six studies reported restenosis at the sixth or eighth month. The rate of restenosis after PCI in the triple-therapy group was significantly lower than in the dual-therapy group (11.2% vs 19.2%, respectively; OR: 0.52, 95% CI: 0.40–0.66, $P < 0.00001$; figure 1). Moreover, this trend has no significant heterogeneity among the trials ($P = 0.97$).

Minimal Lumen Diameter

Six studies assessed minimal lumen diameter (MLD) at the sixth or eighth month after PCI in the triple- and dual-therapy groups. The MLD of the triple-therapy group was significantly higher than that of the dual-therapy group at the sixth or eighth month after PCI (OR: 0.15, 95% CI:

Figure 1. A meta-analysis of restenosis. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

0.10–0.20, $P < 0.00001$; figure 2). Thus, compared with dual therapy, triple therapy helps to increase MLD after PCI.

Target-Vessel Revascularization

Five studies reported TVR measured from the sixth to the 24th month among the patients after PCI. The triple therapy was more beneficial in preventing TVR than the dual therapy (6.08% vs 9.42%, respectively; OR: 0.62, 95% CI: 0.47–0.82, $P = 0.001$; Figure 3).

Major Adverse Cardiac and Cerebrovascular Events

Major adverse cardiac and cerebrovascular events (MA CCE) are defined as the set of cardiac death, MI, TLR, and stroke. Because a patient may suffer several MACCEs simultaneously, this study took the total number of events into calculation, rather than the total number of patients. Based on data of the RCTs involved, this study found no significant difference between the triple and dual therapy in cardiac death (OR: 0.75, 95% CI: 0.41–1.39, $P = 0.036$), MI (OR: 1.02, 95% CI: 0.56–1.85, $P = 0.95$), and stroke (OR: 0.78, 95% CI: 0.34–1.78, $P = 0.56$; Figure 4). However, it seems the triple therapy is more beneficial in the prevention of TLR compared with dual therapy (OR: 0.42, 95% CI: 0.26–0.69, $P = 0.0005$; Figure 4).

Adverse Drug Events

Because a patient also may suffer several adverse drug events simultaneously, this analysis took the total number of events into calculation.

As to adverse drug events, the triple therapy and dual therapy exhibited a similar rate of bleeding occurrence (OR: 1.05, 95% CI: 0.71–1.55, $P = 0.80$; Supplementary Figure 2). However, the triple-therapy group reported a higher rate of rash (OR: 2.45, 95% CI: 1.41–4.23, $P = 0.001$), gastrointestinal disorder (OR: 2.59, 95% CI: 1.26–5.30,

$P = 0.009$), and drug discontinuation (OR: 3.80, 95% CI: 1.59–9.10, $P = 0.003$; Supplementary Figure 2).

Discussion

The rationale to use cilostazol after PCI is based on its anti-inflammatory and antiproliferation effects. Ahn et al¹⁵ measured the inflammatory markers high-sensitivity C-reactive protein, interleukin 6, and tumor necrosis factor α in a 2-year follow-up among acute coronary syndrome patients who received the triple and dual therapy after PCI. Significant decreases in interleukin 6 (-2.79 ± 2.83 pg/mL and -2.14 ± 3.36 pg/mL, $P = 0.010$, respectively) and tumor necrosis factor α (-2.81 ± 1.97 pg/mL and -2.21 ± 2.68 pg/mL, $P = 0.029$, respectively) were observed in the follow-up. This suggests that the triple therapy has a better anti-inflammatory effect than the dual therapy.

Cilostazol is a phosphodiesterase III inhibitor that plays the role of increasing cyclic adenosine monophosphate within platelets and thus leads to reduced aggregation of platelets. This mechanism of action is different from that of aspirin, which inhibits the aggregation of platelets through irreversible inhibition of cyclooxygenase-1, and clopidogrel, which inhibits P2Y₁₂, an adenosine diphosphate chemoreceptor on the membrane of platelets.²⁵ Thus, these 3 drugs would be expected to synergistically inhibit platelet aggregation. In addition to the antiplatelet effect, cilostazol also can inhibit neointimal formation. First, phosphodiesterase III enzymes are abundantly present in endothelial cells and smooth-muscle cells.²⁶ Higher expression of cyclic adenosine monophosphate in vascular smooth-muscle cells caused by cilostazol can lead to up-regulated expression of p53 and p21 as well as hepatocyte growth factor.^{27,28} The p53 protein has an antiproliferative effect through blocking the cell cycle and inducing cell apoptosis, and hepatocyte growth factor stimulates regeneration of endothelial cells. Therefore,

Table 1. Summary of Trials

Trial	Quality Components	Quality Level	No.	PCI Type	Triple Therapy	Dual Therapy
Chen et al, 2006 ¹⁸	R, DB, BR, F, C	B	106	BMS	Aspirin: 100 mg/d, indefinitely; cilostazol: 100 mg BID, 6 mo; clopidogrel: 75 mg/d, 6 mo	Aspirin: 100 mg/d, indefinitely; clopidogrel: 75 mg/d, 6 mo
Douglas et al, 2005 ¹⁹	R, DB, F, C	B	526	BMS	Aspirin: unclear; clopidogrel: 75 mg/d, 1 mo; cilostazol: 100 mg BID, 6 mo	Aspirin: unclear; clopidogrel: 75 mg/d, 1 mo, or placebo: 100 mg BID, 6 mo
Min et al, 2007 ²⁰	R, NB, BR, F, C	C	59	BMS	Aspirin: 100 mg/d; clopidogrel: 75 mg/d or ticlopidine: 250 mg/d, 1 mo; cilostazol: 100 mg BID, 6 mo	Aspirin: 100 mg/d; clopidogrel: 75 mg/d or ticlopidine: 250 mg/d, 1 mo
Lee et al, 2007 ²¹	R, ST, NB, BR, F, C	C	500	DES	Aspirin: 200 mg/d; clopidogrel: loading dose 300 mg, then 75 mg/d, ≥ 6 mo; cilostazol: loading dose 200 mg, then 100 mg BID, 6 mo	Aspirin: 200 mg/d; clopidogrel: loading dose 300 mg, then 75 mg/d, ≥ 6 mo
Lee et al, 2008 ²²	R, ST, NB, BR, F, C	C	400	DES	Aspirin: 200 mg/d; clopidogrel: loading dose 300 mg, then 75 mg/d, ≥ 6 mo; cilostazol: loading dose 200 mg, then 100 mg BID, 6 mo	Aspirin: 200 mg/d; clopidogrel: loading dose 300 mg, then 75 mg/d, ≥ 6 mo
Lee et al, 2011 ²³	R, ST, DB, F, C	B	399	DES	Aspirin: 200 mg/d, indefinitely; clopidogrel: loading dose 300 mg, then 75 mg/d, ≥ 12 mo; cilostazol: loading dose 200 mg, then 100 mg BID, 8 mo	Aspirin: 200 mg/d, indefinitely; clopidogrel: loading dose 300 mg, then 75 mg/d, ≥ 12 mo
Han et al, 2009 ²⁴	R, NB, F, C, ITT	C	1212	BMS/DES	Aspirin: 300 mg/d, 1 mo and 100 mg/d, indefinitely; clopidogrel: loading dose 300–600 mg, then 75 mg/d, 3–12 mo; cilostazol: 100 mg BID, 6 mo	Aspirin: 300 mg/d, 1 mo and 100 mg/d, indefinitely; clopidogrel: loading dose 300–600 mg, then 75 mg/d, 3–12 mo
Ahn et al, 2011 ¹⁵	R, NB, BR, F, C	B	130	DES	Aspirin: loading dose 200 mg, then 100 mg/d, 24 mo; clopidogrel: loading dose 300 mg, then 75 mg/d, 24 mo; cilostazol: 100 mg BID, 24 mo	Aspirin: loading dose 200 mg, then 100 mg/d, 24 mo; clopidogrel: loading dose 300 mg, then 75 mg/d, 24 mo
Abbreviations: BID, twice daily; BMS, bare-metal stents; BR, blind reviewer; C, controlled; DB, double-blind; DES, drug-eluting stents; F, follow-up; ITT, intent-to-treat; NB, nonblind; PCI, percutaneous coronary intervention; R, randomized; ST, stratification.						

the combined function of inhibiting abnormal vascular smooth-muscle cells and enhanced growth of endothelial cells can directly decrease neointimal formation. Second, cilostazol can inhibit expression of stent-induced P-selectin and the subsequent Mac-1-mediated leukocyte activation that is the trigger of restenosis after PCI surgery.²⁹ These mechanisms can be used to explain the better effect of the triple therapy in preventing restenosis, maintaining MLD, and avoiding TVR. The benefits of triple therapy are also independent of the type of stent planted (the studies reviewed used both drug-eluting stents and bare-metal stents). The Cilostazol: A Study in Long-term Effects (CASTLE) study³⁰ reported that cilostazol has no beneficial effect in reducing cardiovascular mortality among patients with peripheral arterial disease. However, a recent meta-analysis has suggested that cilostazol-based triple therapy may be associated with a mortality benefit over the dual therapy after PCI.³¹ Thus, whether cilostazol has long-term benefits should be further discussed.

This study confirmed the low bleeding potential of the triple therapy. Only 6 out of the 8 RCTs reported bleeding-event rate (triple-therapy group, $n = 1627$; dual-therapy group, $n = 1640$). Patients receiving the triple therapy had a similar bleeding-event rate to those in the dual-therapy group (OR: 1.05, 95% CI: 0.71–1.55, $P = 0.80$). Four studies^{15,21–24} offered detailed and consistent definitions of both major and minor bleeding, and one¹⁹ gave a detailed definition of major bleeding. The similar definitions help to reduce the heterogeneity of this finding. Because this analysis identified a significantly higher rate of rash, gastrointestinal disorders, and drug discontinuation among patients in the triple-therapy group, doctors need to monitor these events and adjust medication timely to avoid drug discontinuation. As common practice, most ST-elevation MI patients are treated with reperfusion therapies such as thrombolysis or PCI, whereas non-ST-elevation MI patients are managed with medication, although PCI is also done in some cases.³² What the differences are between the clinical outcomes of

Figure 2. A meta-analysis of MLD. Abbreviations: CI, confidence interval; MLD, minimal lumen diameter; SD, standard deviation.

Figure 3. A meta-analysis of TVR. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel; TVR, target-vessel revascularization.

patients receiving the triple therapy and dual therapy after PCI in these 2 groups should be assessed in future trials.

Study Limitations

One major limitation of this study is that all the RCTs involved were limited to relatively low-risk candidates; whether the benefits of triple therapy can apply to high-risk patients, such as those with left-main disease, graft-vessel

disease, and/or renal dysfunction, is still not clear. In addition, only 8 suitable RCTs, covering a total of 3332 patients, were available because the triple therapy currently is only tested among low-risk patients. Therefore, the total number of patients involved in this meta-analysis is relatively small. However, this meta-analysis observed the promising effects of triple therapy and the similar bleeding-event rate to that of the dual therapy. More RCTs with larger sample sizes are feasible and are required

Figure 4. A meta-analysis of MACCE. Abbreviations: CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events; M-H, Mantel-Haenszel; MI, myocardial infarction; TLR, target-lesion revascularization.

to confirm findings of this study and to assess whether the triple therapy can be applied routinely in patients undergoing PCI.

Significant heterogeneity in the duration of therapies and lengths of follow-up of the involved RCTs hampered reliability of the findings. However, except for the evaluation of drug discontinuation that had $I^2 > 50\%$ (Supplementary Figure 2), the rest of the comparisons all had $I^2 < 50\%$, suggesting the influence of heterogeneity is limited and acceptable. Although the dose of aspirin varies in the RCTs, previous meta-analysis confirmed that low- or medium-dose aspirin (≤ 325 mg per d) has similar preventive efficacy in patients after a transient ischemic attack or nondisabling stroke,³³ suggesting that the low or medium dose has a similar antiplatelet effect. Thus, the heterogeneity caused by the difference of aspirin dose is limited.

Only RCTs published in English were searched, which may contribute to language bias. Although this meta-analysis is subjected to publication bias, the empirical

study of Sutton et al³⁴ confirmed the limited and small impact of publication bias on meta-analysis.

Conclusion

This is a meta-analysis of 8 RCTs of patients undergoing coronary stenting comparing the efficacy and safety of triple and dual antiplatelet agents for the prevention of MACCEs. From a total of 3332 patients, it was found that the addition of cilostazol to aspirin + clopidogrel reduced the rate of restenosis, improved MLD, and prevented TVR. The authors attributed the benefit to cilostazol's additional antiplatelet, anti-inflammatory, and antiproliferative actions. Bleeding complications were not increased, and there was no significant difference in cardiac death, MI, and stroke between the triple- and dual-therapy groups. The triple therapy is more beneficial in preventing TLR compared with dual therapy. However, the occurrence rates of rash, gastrointestinal disorder, and drug discontinuation were substantially higher with the triple therapy. Despite its

potential efficacy, the use of cilostazol in clinical practice is still restricted due to important safety issues. In fact, it is associated with a high incidence of side effects, which results in discontinuation of the drug in a substantial proportion of patients. Thus, the exact effect of the triple therapy should be further assessed. In future studies, the mechanism of why cilostazol is superior where glycoprotein IIb/IIIa inhibitors have failed in preventing restenosis in patients undergoing coronary stenting should also be investigated.

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