An up-dated meta-analysis of major adverse cardiac events on triple versus dual antiplatelet therapy after percutaneous coronary intervention in patients with type 2 diabetes mellitus

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This meta-analysis is conducted to assess the efficiency and safety of triple antiplatelet therapy in patients with type 2 diabetes mellitus (T2DM) who have received coronary stents implantation. The risk of major adverse cardiac events (MACEs), target vessel revascularization (TVR), target lesion revascularization (TLR), myocardial infarction (MI) and bleeding events were evaluated in this meta-analysis. Eight randomized controlled trials incorporating 1700 participants were included. During a follow-up of 12 months after stents implantation, the risk of TVR, TLR and MACEs in Triple group were lower than that of Dual group. There was no significant difference in the comparison of stent thrombosis and bleeding events between the two groups. Triple antiplatelet therapy is effective in reducing adverse cardiovascular outcomes in T2DM patients after stents implantation, without increasing the risk of bleeding events. Advanced designed and large-scale trails are deserved in the future.

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1. Data

Dual antiplatelet therapy consisting of aspirin and clopidogrel is a cornerstone of management for coronary artery disease (CAD) patients, especially for those who have received stents implantation. Previous studies have found that addition of cilostazol was an effective and relatively safe strategy in preventing major adverse cardiac events (MACEs) in type 2 diabetes mellitus (T2DM) patients. The value of triple antiplatelet therapy had not been well proved. Therefore, this meta-analysis was conducted to systematically evaluate the efficiency and safety of this strategy in the treatment of T2DM patients.

![Flow diagram](image)

**Fig. 1.** Flow diagram of the literature search process of this meta-analysis.
| Study  | Country | Number Dual / Triple | Mean age (yrs) Dual / Triple | Male (%) Dual / Triple | Hypertension (%) Dual / Triple | Hypercholesterolemia (%) Dual / Triple | Current smoker (%) Dual / Triple | Multivessel disease (%) Dual / Triple | Follow-up (m) Dual / Triple |
|--------|---------|---------------------|-----------------------------|-----------------------|-------------------------------|--------------------------------------|-----------------------------------|---------------------------------|-----------------------------|
| Gao [9] | China   | 156/162             | 64.3/65.2                   | 55.8/54.9             | 43.6/45.1                     | 46.2/53.1                           | 48.7/50.6                        | 59.5/48.2                       | 1                           |
| Lee [8]  | Korea   | 84/92               | 62.1/60.9                   | 71.5/70.0             | 64.7/58.4                     | 45.0/42.4                           | 30.1/30.4                        | 37.3/34.8                       | 12                          |
| Li 2010 [6] | China | 30/30               | NA                          | NA                    | NA                            | NA                                   | NA                                | NA                             | 9                           |
| Shen [7] | China   | 80/80               | 69.6/67.9                   | 75/73.8               | 62.5/68.8                     | 38.8/36.2                           | 46.2/43.8                        | NA                             | 12                          |
| Han [2] | China   | 122/141             | 59.6/59.5                   | 77.0/71.6             | 72.1/70.9                     | 55.7/53.9                           | 43.4/44.7                        | 72.1/80.1                       | 12                          |
| Lee [5] | Korea   | 200/200             | 60.7/61.0                   | 57.0/59.0             | 59.5/59.5                     | 28.5/30.5                           | 31.5/24.8                        | 62.5/65.5                       | 9                           |
| Lu [4]  | China   | 79/78               | 61.0/61.0                   | NA                    | NA                            | NA                                   | NA                                | NA                             | 6                           |
| Lee [3] | Korea   | 81/85               | 61.2/60.9                   | 63.6/64.8             | 55.2/54.8                     | 28.4/30.0                           | 37.2/37.6                        | 59.6/66.8                       | 9                           |

NA: not available.
Fig. 2. Forest plot of the risk of TVR. The risk of TVR in Triple group was lower than that of Dual group during a follow-up of 12 months after stents implantation.

Fig. 3. Forest plot of the risk of TLR. Compared to Dual group, the risk of TLR in Triple group was reduced significantly.

Fig. 4. Forest plot of the risk of MACEs. Compared to Dual group, the risk of MACEs was reduced significantly in Triple group after stents implantation.

Fig. 5. Forest plot of the risk of bleeding events. The risk of bleeding events were similar in Dual and Triple group during a follow-up of 12 months after stents implantation.
2. Experimental design, materials and methods

2.1. Design, materials and methods

Relevant studies were identified from PubMed, Cochrane Library, Wanfang Database, Science Direct and Embase. The key words included cilostazol, stent, percutaneous coronary intervention and diabetes. A total of 1403 relevant publications were found in the initial internet retrieval. One of the articles [1] was excluded because it was a sub-study of another one [2] and was conducted by the same research group. Finally, eight randomized controlled trials (RCTs) [2–9] met the inclusion criteria and were enrolled (Fig. 1). The dosage of cilostazol was 200 mg per day for 6 months. Data including the first author’s surname, publication year, region, case number, gender, age, demographic data, target population, treatment protocol, follow-up period, efficacy outcomes and safety outcomes were extracted (Table 1). The primary efficacy outcome was MACEs which was defined as a composite of cardiac death, myocardial infarction (MI), stroke, target vessel revascularization (TVR), target lesion revascularization (TLR), or stent thrombosis.

2.2. Meta-analysis

All statistical tests were performed with Review Manager 5.2 from the Cochrane Collaboration. Odds ratio (OR) with 95% confidence interval (CI) was used. The pooled OR was performed for dominant model. P value ≤ 0.10 was considered to be significant for statistical heterogeneity. Random-effect model was chosen in this study to reduce the potential bias. According to the funnel plot (Suppl. 1) and risk of bias graph (Suppl. 2), the reporting biases of this study was acceptable. The data here showed that the risk of TVR (5.2% vs. 10.5%, OR 0.46 [0.30, 0.71], P = 0.0004, [Fig. 2]), TLR (3.4% vs. 7.8%, OR 0.42 [0.22, 0.81], P = 0.009, [Fig. 3]) and MACEs (5.9% vs. 12.1%, OR 0.44 [0.29, 0.68], P = 0.0002, [Fig. 4]) in Triple group were lower than that of Dual group. There was no significant difference in the comparison of stent thrombosis and bleeding events between the two groups (4.1% vs. 3.5%, OR 1.16 [0.69, 1.95], P = 0.57, [Fig. 5]).

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Transparency document. Supporting information

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.dib.2018.06.091.

References

[1] H. Zang, Y. Han, Y. Li, J. Deng, Q. Jing, S. Wang, Y. Ma, B. Luan, G. Wang, Long-term effect of triple antiplatelet therapy for diabetic patients after percutaneous coronary intervention, Med. J. Chin. People’s Lib. Army 33 (2008) 931–934.
Y. Han, Y. Li, S. Wang, Q. Jing, Z. Wang, D. Wang, Q. Shu, X. Tang, Cilostazol in addition to aspirin and clopidogrel improves long-term outcomes after percutaneous coronary intervention in patients with acute coronary syndromes: a randomized, controlled study, Am. Heart J 157 (2009) 733–739.

S.W. Lee, S.W. Park, Y.H. Kim, S.C. Yun, D.W. Park, C.W. Lee, M.K. Hong, H.S. Kim, J.K. Ko, J.H. Park, J.H. Lee, S.W. Choi, I.W. Seong, Y.H. Cho, N.H. Lee, J.H. Kim, K.J. Chun, S.J. Park, and Investigators DE-LS. Comparison of triple versus dual antiplatelet therapy after drug-eluting stent implantation (from the DECLARE-Long trial), Am. J Cardiol. 100 (2007) 1103–1108.

Y. Lu, Y. Chen, S. Lv, Study of using cilostazol for preventing restenosis after stenting in patients with diabetes mellitus, Chin. J. Diabetes 15 (2007) 35–37.

S.W. Lee, S.W. Park, Y.H. Kim, S.C. Yun, D.W. Park, C.W. Lee, M.K. Hong, H.S. Kim, J.K. Ko, J.H. Park, J.H. Lee, S.W. Choi, I.W. Seong, Y.H. Cho, N.H. Lee, J.H. Kim, K.J. Chun, S.J. Park, Drug-eluting stenting followed by cilostazol treatment reduces late restenosis in patients with diabetes mellitus the DECLARE-Diabetes Trial (A Randomized Comparison of Triple Antiplatelet Therapy with Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation in Diabetic Patients), J Am. Coll. Cardiol. 51 (2008) 1181–1187.

G. Li, Efficacy of triple antiplatelet therapy in aged patients with diabetes mellitus combined with coronary heart disease after percutaneous coronary intervention, Chin. J. Cardiovasc. Rehabil. Med. 19 (2010) 426–428.

J. Shen, H. Jin, Z. Liu, W. Wang, W. Yang, D. Wang, Z. Wang, H. Yu, Long-term effect of triple antiplatelet therapy for treatment of patients with diabetes and acute coronary syndrome after drug-eluting stent implantation, Shanghai Med. J. 33 (2010) 566–569.

S.W. Lee, S.W. Park, Y.H. Kim, S.C. Yun, D.W. Park, C.W. Lee, S.J. Kang, S.J. Park, J.H. Lee, S.W. Choi, I.W. Seong, N.H. Lee, Y.H. Cho, W.Y. Shin, S.J. Lee, S.W. Lee, M.S. Hyon, D.W. Bang, Y.J. Choi, H.S. Kim, B.K. Lee, K. Lee, H.K. Park, C.B. Park, S.G. Lee, M.K. Kim, K.H. Park, W.J. Park, Investigators D-US, A randomized, double-blind, multicenter comparison study of triple antiplatelet therapy with dual antiplatelet therapy to reduce restenosis after drug-eluting stent implantation in long coronary lesions: results from the DECLARE-Long II (Drug-Eluting Stenting Followed by Cilostazol Treatment Reduces Late Restenosis in Patients with Long Coronary Lesions) trial, J Am. Coll. Cardiol. 57 (2011) 1264–1270.

Q. Gao, L. Lv, M. Wang, H. Wei, Y. Li, G. Zhang, Y. Wang, K. Zhou, T. Liu, Impact of triple anti-platelet therapy on activation of platelet and short-term outcomes in CHD patients with diabetes undergoing PCI, Clin. Focus. 29 (2014) 1334–1338.