News and Views From the Literature

Percutaneous Coronary Intervention

Cardiovascular Outcomes and Long-Term Clopidogrel Use After PCI in Patients With Diabetes

Reviewed by Christopher P. Cannon, MD, FACC,* Subroto Acharjee, MBBS†

**TIMI Study Group, Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; †Division of Cardiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA*

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Long-Term Outcomes by Clopidogrel Duration and Stent Type in a Diabetic Population With De Novo Coronary Artery Lesions

Brar SS, Kim J, Brar SK, et al.

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The use of percutaneous coronary intervention (PCI) is growing for many groups of patients, and much attention has been focused on how to optimize adjunctive antiplatelet therapy. For ST-elevation myocardial infarction (MI), primary PCI, especially with stenting, is superior to fibrinolytics in patients with diabetes,[1,2] although event-free survival in this population is lower than in patients without diabetes.[2] Similarly, for elective PCI, worse short-term and long-term outcomes are noted in patients with diabetes than in patients without diabetes, despite similar procedural success.[3-5] Stent restenosis and stent thrombosis have been considered important factors responsible for this poor outcome.

Currently, drug-eluting stents (DES) are preferentially used in diabetes patients undergoing PCI, largely because of their demonstrated ability to lower stent restenosis.[6,7] The benefit of reduced rates of restenosis and target vessel revascularization with DES over bare-metal stents (BMS) in patients with diabetes has been seen in subgroup analyses from individual trials[8,9] as well as in larger studies,[10-12] although not in a network meta-analysis.[13] However, DES are associated with an increased incidence of late stent thrombosis, particularly when clopidogrel is discontinued prematurely.[14-19] Several studies suggest that diabetes is, in fact, a predictor of late stent thrombosis.[20,21] Thus, patients with diabetes who are treated with DES are at very high risk for developing late stent thrombosis and, therefore, constitute an ideal group for studying how long clopidogrel should be continued after PCI with DES.

A Survival Analysis

To evaluate the effects of stent type and duration of clopidogrel use on long-term outcomes in patients with diabetes, Brar and colleagues[22] performed a survival analysis among 749 consecutive diabetes patients who underwent initial PCI with a BMS or DES at the Kaiser Permanente Los Angeles Medical Center in California. Patients were excluded from the study if they received both stent types during this index PCI, had undergone prior coronary artery bypass grafting, had moderate-to-severe valvular disease, or were not a member of a health

plan. Medication use, including clopidogrel, was assessed from prescription refill data, which were available in the Kaiser Permanente system. Compliance with clopidogrel was high (95%) in the overall cohort, and mean duration of clopidogrel use was greater in the DES group (10.1 months vs 9 months; $P = .03$).

Patients were divided into DES and BMS groups, which were further stratified into longer-duration clopidogrel users (> 180 days after initial PCI) and short-duration users. At baseline, indication for PCI, insulin use, hemoglobin A_{1c}, stent location, and number of diseased arteries were similar. Cumulative stent length was greater and stent diameter and number were lower in the DES group versus the BMS group. Longer-duration clopidogrel users had higher use of statins, β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers.

Within the initial 180 days post-PCI, no difference was noted between the DES and BMS groups in the cumulative incidence of the primary endpoint (death and nonfatal MI). Thereafter, a lower event rate was seen in the DES group ($P = .05$). Among subjects event-free at 6 months, a trend towards a lower incidence was seen in the DES group (3.1% vs 6.2%; $P = .08$).

Patients treated with longer-duration clopidogrel in the BMS group had significantly lower rates of death and nonfatal MI compared with short-duration users (3.5% vs 12.2%, respectively; $P = .01$), and a similar trend was seen among DES-treated subjects (2.2% vs 5.5%, respectively; $P = .07$). The cumulative incidence of death alone was lower among longer-duration clopidogrel users compared with short-duration users in the BMS group (2% vs 6.8%, respectively; $P = .07$) and the DES group (1.0% vs 3.9%, respectively; $P = .03$).

The authors also used a multivariate model to determine the risk of death and nonfatal MI after adjusting for baseline differences. Taking BMS clopidogrel short-duration users as the referent group, the hazard ratios (HRs) (and 95% confidence intervals) were 0.25 (0.08-0.81) for BMS clopidogrel longer-duration users, 0.39 (0.13-1.13) for DES clopidogrel short-duration users, and 0.22 (0.08-0.62) for DES clopidogrel longer-duration users. Further analysis was performed to compare longer-duration clopidogrel users with short-duration users within the 2 stent types. The HR was low in both groups but statistically significant only in the BMS group (0.21; $P = .01$) and not in the DES group (0.48; $P = .48$).

To further examine the effect of duration of clopidogrel, the authors grouped the entire cohort by duration of clopidogrel use and analyzed the event rates. Death and MI, or death alone, was lowest in those using clopidogrel for longer than 9 months. For death/MI, the event rate was 16.5% in those using clopidogrel for less than 6 months, 9.4% in the 6-to-9–month group, and 3.2% in those using clopidogrel for longer than 9 months ($P < .001$). A similar result was seen for death alone, with event rates of 10.0% for those using clopidogrel for less than 6 months, 4.3% for those using clopidogrel for 6 to 9 months, and 0.5% those using clopidogrel for longer than 9 months ($P < .001$). Both results were significant even when analysis was confined to subjects who were event-free at 6 months.

Thus, this study underlines the importance of extended clopidogrel therapy after placement of coronary stents[23] and provides confirmatory data supporting the findings of a previous observational analysis regarding the benefits of extended clopidogrel use in patients with DES.[19]

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Continued use of clopidogrel is considered vital among DES-treated patients, given the risk of late stent thrombosis. Initially, the US Food and Drug Administration (FDA) recommended that clopidogrel be used for at least 3 months (for sirolimus-coated stents) or 6 months (for paclitaxel-coated stents) following DES implantation.[24-26] However, the increasing utilization of DES for high-risk off-label use in complex patients and lesions led the American College of Cardiology, American Heart Association, and Society of Cardiovascular Angiography and Interventions (ACC/AHA/SCAI) to recommend extending clopidogrel use to 1 year except in patients with a high risk of bleeding.[27] The FDA labeling was also updated subsequently to reflect this recommendation.

Issues to Consider

Some important issues need to be considered when interpreting the results of these data. Post-PCI clopidogrel use in this study was less than the recommended 1 year for DES. The potential limitation to extended clopidogrel therapy is the risk of bleeding; the authors do not mention if rates of bleeding were increased with longer duration of clopidogrel. Antiplatelet therapy resistance is higher among patients with diabetes[28] and, thus, could affect the results. No information regarding platelet function among clopidogrel users was provided in the study. The results from this single-center retrospective observational analysis might not be generalizable to other populations. All participants were insured health plan

members; appropriate cardiovascular risk management and access to care might have altered the rates of adverse events. The high compliance with clopidogrel might be difficult to achieve in other patient groups. Clopidogrel use was determined by prescription records and not by performing pill-counts. Also, data about aspirin use (dose and duration) were not available.

Conclusion

This study highlights the benefits of extended clopidogrel use post-PCI. The ideal duration of therapy for patients with diabetes is yet to be specifically studied, but this trial provides further observational data supporting a longer duration (about 1 year) over a shorter duration (about 6 months). Further observational studies and prospective, randomized trials should help clarify this important issue. ■

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