



NATIONAL PBM BULLETIN

December 17, 2014

DEPARTMENT OF VETERANS AFFAIRS
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP),
VISN PHARMACIST EXECUTIVES (VPEs), AND THE CENTER FOR MEDICAL SAFETY (VA MedSAFE)

FDA Reviews Long-Term Dual Antiplatelet Therapy as Preliminary Trial Data Shows Benefits but a Higher Risk of Non-Cardiovascular Death

I. ISSUE

A recent safety announcement from the Food and Drug Administration (FDA) describes findings from the Dual Antiplatelet Therapy (DAPT) trial which suggest that extending treatment with a thienopyridine and aspirin compared to aspirin alone beyond 1 year after percutaneous coronary intervention with drug-eluting stent placement reduced the risk of stent thrombosis and ischemic events, but was associated with an increase in bleeding events and non-cardiovascular death.

II. BACKGROUND

Dual antiplatelet therapy post-coronary stent placement prevents thrombotic complications. Current recommendations call for use of a P2Y₁₂-receptor inhibitor in combination with aspirin for 6-12 months after implantation of a drug-eluting coronary stent. The DAPT study was an international, multicenter, randomized, placebo-controlled trial designed by manufacturers in response to a request from the FDA to evaluate the risks and benefits of continuing dual antiplatelet therapy beyond 1 year after drug-eluting stent placement. In the DAPT trial, all patients received dual antiplatelet therapy for 12 months. Patients were then randomized to continue to receive either aspirin plus a thienopyridine [clopidogrel (Plavix) or prasugrel (Effient)] (N=5020) or to receive aspirin plus placebo (N=4941) for an additional 18 months to yield a total treatment period of 30 months.

III. DISCUSSION

Results from the DAPT study showed that continued thienopyridine therapy compared to placebo in patients who received a drug-eluting stent reduced the risk of stent thrombosis (0.4% versus 1.4%; hazard ratio, 0.29 [95% Confidence Interval {CI}, 0.17 to 0.48]; $p < 0.001$) and major adverse cardiovascular and cerebrovascular events (4.3% versus 5.9%; hazard ratio, 0.71 [95% CI, 0.59 to 0.85]; $p < 0.001$). Treatment benefit was influenced by a lower cumulative incidence of myocardial infarction (MI), notably MI unrelated to stent thrombosis. However, prolonged thienopyridine therapy in the treatment group compared to the placebo group was also associated with a greater risk of bleeding (2.5% versus 1.6%; hazard ratio 1.61 [95% CI, 1.21 to 2.16]; $p = 0.001$) even though no significant difference in severe or fatal bleeding prevailed between the study groups. Results further indicated that deaths from any cause during the treatment period in the group that continued to receive thienopyridine therapy exceeded the number in the group that received placebo (2.0% versus 1.5%; hazard ratio 1.36 [95% CI, 1.00 to 1.85]; $p = 0.05$). FDA continues to examine these preliminary trial findings as well as other available data and has not yet reached any conclusions.

IV. PROVIDER CONSIDERATIONS/RECOMMENDATIONS

FDA recommends that:

- Benefits of clopidogrel (Plavix) and prasugrel (Effient) therapy continue to outweigh their potential risks when used for



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approved indications.

- Patients should continue to take these drugs as directed to prevent ischemic events.
- Health care providers should not change the way they prescribe these drugs at this time.

Current VA guidance for use of clopidogrel (Plavix) or prasugrel (Effient) is available at: <http://www.pbm.va.gov/clinicalguidance/criteriaforuse.asp> . PBM is reviewing VA's dual antiplatelet guidance and will obtain input from the Cardiology Field Advisory Committee to provide further recommendations for VA in the near future.

V. REFERENCES

1. FDA Drug Safety Communication: FDA reviews long-term antiplatelet therapy as preliminary trial data shows benefits but a higher risk of non-cardiovascular death. <http://www.fda.gov/Drugs/DrugSafety/ucm423079.htm> . (Accessed 11/21/2014).
2. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 Months of Dual Antiplatelet Therapy After Drug-Eluting Stents. *New England Journal of Medicine*. Online ahead of print November 16, 2014.

ACTIONS

- **Facility Director** (or physician designee): Forward this document to the Facility Chief of Staff (COS).
- **Facility COS and Chief Nurse Executives**: Forward this document to all appropriate providers and health care staff (e.g., **primary care providers, and cardiologists, including contract providers, etc.**). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.
- **ACOS for R&D**: Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).