Does clopidogrel affect the efficacy of myocardial perfusion imaging?

Paco E. Bravo, MD,[a] and Marcelo F. Di Carli, MD[a]

[a] Noninvasive Cardiovascular Imaging Program, Divisions of Cardiovascular Medicine and Nuclear Medicine and Molecular Imaging, Departments of Medicine and Radiology, Heart and Vascular Institute, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Received Aug 25, 2015; accepted Aug 25, 2015
doi:10.1007/s12350-015-0280-7

See related article, pp. 773–779

Clopidogrel (Plavix) is an oral, anti-platelet agent of the thienopyridine-class that is an important part of the armamentarium in the management of acute coronary syndromes (ACS), as well as stable coronary artery disease (CAD), ischemic cerebrovascular disease, and peripheral arterial disease (PAD). It was initially approved by the Food and Drug Administration (FDA) in 1997 on the basis of the CAPRIE trial as an alternative anti-platelet drug to aspirin for the reduction of myocardial infarction (MI), stroke, and vascular death, in patients with atherosclerosis documented by recent stroke, recent MI, or established PAD.[1] A few years later, the FDA expanded its label to include ACS as an indication for treatment following evidence for the effectiveness of clopidogrel (in addition to aspirin) to reduce major cardiovascular events in patients with both non-ST—(CURE [2] trial) and ST-segment elevation (COMMIT[3] and CLARITY[4] trials) ACS independent of the downstream intervention (e.g., percutaneous or surgical revascularization or medical management alone). Perhaps the most common indication (albeit off-label) for clopidogrel use is that for the prevention of stent-associated thrombosis after percutaneous coronary or peripheral interventions. Depending on the type of stent, and clinical situation, the duration of clopidogrel therapy may be as short as 1 month (e.g., following elective bare-metal stenting), or more commonly 12 months after deployment of drug-eluting stents,[5] although, emerging evidence now suggests that this latter period may be extended to 30 months.[6] As a result of the large cumulative evidence since first introduced in 1997, clopidogrel has become one of the most commonly prescribed cardiovascular medications worldwide, and Plavix was for years the second biggest selling drug in the industry before going generic in 2012.[7]

Clopidogrel, as well as other thienopyridines, exerts its anti-platelet effect by conversion to active metabolites that bind irreversibly to the platelet $P2Y_{12}$ purinergic receptor, thereby inhibiting adenosine diphosphate (ADP)-mediated platelet activation and aggregation.[8,9] However, experimental evidence suggests that the beneficial effects of $P2Y_{12}$ inhibitors may extend beyond their capacity to inhibit platelet aggregation, as they also appear to display a direct thrombolytic effect in vivo,[10] and have been implicated in the modulation of vascular contractile responses,[11] and endothelium-dependent (nitric oxide-mediated) coronary vasodilation in vitro.[12] In fact, there is preliminary evidence that the use of ticlopidine (another potent thienopyridine) in patients with symptomatic CAD results in a significant reduction in the reported frequency of chest pain and number of episodes of ST-segment depression on ambulatory monitoring after 4 weeks of therapy.[13] Given the apparent anti-ischemic properties of thienopyridines reported in some of these studies, it is conceivable that their use could interfere with the efficacy of stress testing and potentially lead to underestimation of the presence and severity of inducible myocardial ischemia during stress radionuclide imaging.

In this issue of the Journal, Jovin et al. evaluated the effect of clopidogrel on myocardial ischemia detection by stress single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI). In this single-center study, they included 6,349 consecutive

Reprint requests: Marcelo F. Di Carli, MD, Brigham and Womenós Hospital, ASB-L1 037-C, 75 Francis Street, Boston, MA 02115; *mdicarli@partners.org*

J Nucl Cardiol 2016;23:780–2.
1071-3581/$34.00

Copyright © 2015 American Society of Nuclear Cardiology.

patients undergoing adenosine (43%) or exercise (57%) stress SPECT MPI within a 2-year period (2003-2005). The presence and extent of ischemia was assessed quantitatively. The authors identified 277 (4.4%) patients on clopidogrel at the time of the stress MPI. Compared to the 6,072 subjects (95.6%) not on clopidogrel at the time of imaging, those on clopidogrel were older, more likely to be men, and had a higher prevalence of established CAD, diabetes, and other cardiovascular risk factors. Not surprisingly, a higher proportion of these patients were on other cardiovascular medications including aspirin, blood pressure- and lipid-lowering drugs, as well as insulin and/or oral diabetic medications. In unadjusted analysis, patients on clopidogrel had a higher risk of demonstrating ischemic defects on stress MPI compared to those not on clopidogrel [odds ratio (OR) 2.75, 95% confidence interval (CI) 2.09-3.62; $P < .0001$]. The relative risk was higher with exercise (OR 4.59, 95% CI 2.62-8.03; $P < .0001$) than with vasodilator stress (OR 1.58, 95% CI 1.15-2.17; $P = .004$). Because assignment of patients to clopidogrel or other cardiovascular medications was made by physician choice, not as a result of randomization, the authors developed a propensity score for the use of clopidogrel to adjust for differences between groups. After multivariable adjustment for differences in baseline clinical characteristics and the propensity score, the relative risk of ischemic defects was similar between groups regardless of the stress test protocol used (*Exercise*, OR 1.60; 95% CI 0.85-3.00; $P = .14$; and *Adenosine*, OR 1.06, 95% CI 0.76-1.49; $P = .73$). Comparable results were also obtained in matched-pair analyses [OR 1.23 (95% CI 0.0-3.05; $P = .65$) for exercise, and OR 0.90 (95% CI 0.58-1.38; $P = .62$) for adenosine]. Compared to control patients, those on clopidogrel showed similar extent and severity of ischemia, as assessed by the summed difference score, regardless of stress protocol (adenosine, 1.24 ± 2.42 vs 1.16 ± 2.34, respectively; $P = .7$; exercise, 1.24 ± 2.28 vs 1.15 ± 2.57, respectively; $P = .8$). The authors concluded that clopidogrel use does not seem to decrease the efficacy of vasodilator or exercise stress SPECT MPI to detect myocardial ischemia, and that based on these observations, holding clopidogrel prior to stress testing is not warranted.

As previously mentioned, the use of clopidogrel, as well as other thienopyridines, has increased significantly over the past 20 years. In the present study, ~28% of patients with known CAD were on clopidogrel. However, this estimate probably reflects clopidogrel use in 2003-2005, which is lower than more recent estimates of the use of $P2Y_{12}$ inhibitors (~35-45%) in patients with established CAD.[14] Therefore, the results of this study are important and quite pertinent to current nuclear cardiology practice. The lack of a significant effect of clopidogrel on the sensitivity of stress MPI to uncover ischemic defects is consistent with the results of a small randomized controlled trial of 31 male patients with documented CAD undergoing treatment for 2 weeks.[15]

This study has a few important limitations, primarily that treatment was chosen by physicians and not assigned randomly. Consequently, any difference or lack thereof in the frequency or magnitude of ischemic defects could be the result of residual selection bias that was uncorrected despite the careful statistical adjustment. Indeed, the propensity score method used in the study cannot adjust for data that were not recorded in the clinical database, such as renal function, or that was not assessed uniformly, such as left ventricular function, or the time elapsed between the last dose of clopidogrel and stress testing, or potential drug interactions of clopidogrel with other commonly used cardiovascular medications. Despite the large number of patients in the study, the number of patients on clopidogrel in this study was not large enough to provide definitive evidence that clopidogrel does not interfere with the efficacy of stress MPI. The authors did not report whether the use of clopidogrel may be associated with increased frequency of side effects (especially heart block) in patients undergoing adenosine stress, which is a real concern since $P2Y_{12}$ inhibitors (especially ticagrelor) can block adenosine reuptake by red blood cells,[16] and potentiate adenosine-mediated side effects. In fact, in the PLATO trial, patients assigned to ticagrelor experienced more dyspnea and asymptomatic ventricular pauses compared to clopidogrel.[17]

In summary, the use of clopidogrel does not appear to interfere with the efficacy of SPECT to assess the presence and magnitude of inducible ischemia during exercise or vasodilator stress MPI. Future studies will need to investigate whether the observations of Jovin et al. also hold true for the newer $P2Y_{12}$ inhibitors prasugrel, ticagrelor, and cangrelor. Importantly, future studies also need to address the safety of vasodilator stress in patients on $P2Y_{12}$ inhibitors to enhance the value of Jovin's conclusions, which at the moment solely speak to the efficacy issue.

Disclosure

The authors declare that they have no conflict of interest.

References

1. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996;348:1329-39.

2. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502.
3. Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: Randomised placebo-controlled trial. Lancet 2005;366:1607-21.
4. Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med 2005;352:1179-89.
5. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation 2011;124:e574-651.
6. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014;371:2155-66.
7. Maffrand JP. The story of clopidogrel and its predecessor, ticlopidine: Could these major antiplatelet and antithrombotic drugs be discovered and developed today? C R Chim 2012;15:737-43.
8. Hollopeter G, Jantzen HM, Vincent D, Li G, England L, Ramakrishnan V, et al. Identification of the platelet ADP receptor targeted by antithrombotic drugs. Nature 2001;409:202-7.
9. Foster CJ, Prosser DM, Agans JM, Zhai Y, Smith MD, Lachowicz JE, et al. Molecular identification and characterization of the platelet ADP receptor targeted by thienopyridine antithrombotic drugs. J Clin Invest 2001;107:1591-8.
10. Gryglewski RJ, Korbut R, Swies J, Kostka Trabka E, Bieron K, Robak J. Thrombolytic action of ticlopidine: Possible mechanisms. Eur J Pharmacol 1996;308:61-7.
11. Yang LH, Hoppensteadt D, Fareed J. Modulation of vasoconstriction by clopidogrel and ticlopidine. Thromb Res 1998;92:83-9.
12. Jakubowski A, Chlopicki S, Olszanecki R, Jawien J, Lomnicka M, Dupin JP, et al. Endothelial action of thienopyridines and thienopyrimidinones in the isolated guinea pig heart. Prostaglandins Leukot Essent Fatty Acids 2005;72:139-45.
13. Fox KM, Jonathan A, Selwyn AP. Effects of platelet inhibition on myocardial ischaemia. Lancet 1982;2:727-30.
14. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. N Engl J Med 2014;371:1208-17.
15. Perneby C, Wallen NH, Hofman-Bang C, Tornvall P, Ivert T, Li N, et al. Effect of clopidogrel treatment on stress-induced platelet activation and myocardial ischemia in aspirin-treated patients with stable coronary artery disease. Thromb Haemost 2007;98:1316-22.
16. Steg PG, James S, Harrington RA, Ardissino D, Becker RC, Cannon CP, et al. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. Circulation 2010;122:2131-41.
17. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57.