EDITORIAL

To Pretreat or Not to Pretreat (With Oral P2Y12 Antagonists)? That is the Question

Angela Lowenstern, MD; L. Kristin Newby, MD, MHS

The treatment of patients presenting with non-ST-segment elevation myocardial infarction (NSTEMI) continues to evolve. As advancing technical capabilities in the cardiac catheterization lab have expanded percutaneous revascularization options, medical treatments have also continued to progress, offering ongoing improvements in outcomes. The 2014 American Heart Association/American College of Cardiology guidelines reflect the importance of medical management, including platelet inhibition, and recommend treatment with both aspirin and a P2Y12 receptor inhibitor, either clopidogrel or ticagrelor, before coronary angiography and possible percutaneous coronary intervention (PCI).[1] However, because of the increased risk of bleeding, the guidelines also recommend subsequent discontinuation of the P2Y12 inhibitor 5 to 7 days before coronary artery bypass grafting (CABG) if surgical revascularization therapy is pursued. The management of antiplatelet therapy in patients with NSTEMI continues to change as further data are obtained regarding the optimal management of these patients.

As reflected in guidelines recommendations, treatment with P2Y12 inhibitors is a foundational element of therapy for patients presenting with NSTEMI. Before the mid-1990s, the benefit of treatment of coronary artery disease with percutaneous intervention was limited by stent thrombosis in the setting of aspirin alone or by bleeding among patients treated with intensive anticoagulation. In the mid-1990s, ticlodipine, a member of the thienopyridine family, became the first commercially available P2Y12 receptor inhibitor and data soon began to show benefit of dual antiplatelet therapy among stented patients.[2,3] Given hematological side effects associated with ticlodipine, clopidogrel, another member of the thienopyridine family, became an attractive alternative. The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial showed a 30% reduction in major adverse cardiovascular events when clopidogrel was added to aspirin for treatment of patients presenting with non-ST-segment elevation acute coronary syndrome.[4] Additionally, within a subset of patients in the CURE trial who were randomized to pretreatment with clopidogrel, results showed the benefits of clopidogrel within 24 hours of randomization and extending long term, without increased bleeding risk.[5,6] Prasugrel, a third-generation thienopyridine with increased potency compared with clopidogrel, was subsequently developed. The TRITON-TIMI (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction) 38 trial showed improved outcomes among patients treated with PCI who received prasugrel compared with clopidogrel.[7] However, the TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) trial showed that among medically managed patients, there was no significant difference between the 2 P2Y12 inhibitors.[8] Ticagrelor addressed some of the challenges with the thienopyridines, including inconsistent metabolism and irreversible binding. The PLATO (Platelet Inhibition and Patient Outcomes) trial showed a 1.9% absolute reduction in death from cardiovascular causes, myocardial infarction, or stroke among patients treated with ticagrelor compared with clopidogrel.[9] Cangrelor, the only intravenously administered P2Y12 inhibitor, is characterized by rapid onset and offset, with platelets regaining normal reactivity within 30 to 60 minutes of cessation,[3] making it an attractive treatment for patients undergoing procedures. Trials examining its routine use compared with clopidogrel showed that cangrelor improved outcomes when used during PCI, and reduced the risk of stent thrombosis and death among patients who received it periprocedurally.[10,11]

Large bodies of data all show the benefit of treatment with dual antiplatelet therapy including aspirin and a P2Y12 receptor inhibitor. Although the landscape of treatment with

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From the Division of Cardiology, Department of Medicine and the Duke Clinical Research Institute, Duke University Medical Center, Durham, NC.

Correspondence to: L. Kristin Newby, MD, MHS, Division of Cardiology, Department of Medicine and the Duke Clinical Research Institute, Duke University Medical Center, P.O. Box 17969, Durham, NC 27715-7969. E-mail: kristin.newby@duke.edu

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P2Y12 medications has evolved, the processes of care in the diagnosis and treatment of patients with NSTEMI have also progressed. At the time that the CURE trial was completed, patients underwent PCI at a median of 10 days following presentation and frequently did not have PCI until a second hospital stay, when the acute event was resolved. This is in stark contrast to current management and more-recent studies in which patients underwent coronary angiography largely within 48 hours. These changes in clinical practice may underlie discordance in results among studies examining outcomes among patients treated with P2Y12 therapy before coronary angiography. Whereas a substudy of the CURE trial showed benefit among patients pretreated with clopidogrel before coronary angiography, the small, randomized ARMYDA-5 (Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty-5) PRELOAD and PRAGUE-8 (PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis-8) trials showed no benefit.[5,12,13] The ACCOAST (Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction) trial similarly showed no benefit in pretreatment with prasugrel.

In the context of this changing landscape of diagnosis, medical management, and interventional treatment for NSTEMI, Badri et al examined the association of precatheterization use of P2Y12 therapy and timing of administration of these medications with outcomes among patients undergoing surgical revascularization therapy in this issue of *JAHA*.[14] The investigators used Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry data collected between 2009 and 2014 to identify patients diagnosed with NSTEMI who underwent left heart catheterization during the first 24 hours from admission and subsequently had CABG during the same hospitalization. In their analysis, nearly two thirds of patients were treated with a P2Y12 inhibitor before catheterization. Compared with patients who did not receive P2Y12 before catheterization, those who did had longer wait times to CABG, although still less than the labeled recommendations for 5 to 7 days following cessation of P2Y12 treatment, and longer total hospital stays. Additionally, they experienced higher rates of post-CABG bleeding and increased rates of transfusion. Despite the varying potencies across P2Y12 inhibitors, there was no difference in post-CABG bleeding among patients treated with clopidogrel, ticagrelor, or prasugrel. In the era of early catheterization for NSTEMI, the investigators bring into question the current practice of P2Y12 therapy preceding evaluation of coronary anatomy. However, ischemic end points were not evaluated in this study, and given its retrospective and observational nature, further data are needed in order to fully assess the balance of ischemic and bleeding risks associated with the timing of P2Y12 administration in the setting of NSTEMI.

As explored by Badri et al, when surgical revascularization is the intended strategy, pretreatment with a P2Y12 receptor inhibitor may lead to increased postoperative bleeding complications. Unfortunately, patient presenting features offer little insight into which patients will ultimately require surgical revascularization during their hospitalization. Thus, the early medical management of an NSTEMI requires careful consideration of the benefits and risks of these medications, timing of their use, and potential consequences of these decisions. As may be expected, the increasing potency of the P2Y12 inhibitors has been accompanied by a higher risk of bleeding, including procedure-related bleeding. Even when clopidogrel, the least potent of the P2Y12 inhibitors, was added to aspirin in the CURE study, the bleeding risk was significantly higher than with aspirin alone.[4] Similarly, with the progressive increase in potency of P2Y12 inhibitors, bleeding risk has increased—compared with clopidogrel, prasugrel caused increased risk of bleeding, including life-threatening bleeding, and ticagrelor increased the risk of non-CABG-related major bleeding.[7,9] Guidelines currently recommend that P2Y12 inhibitor therapy should be held for at least 5 days for clopidogrel or ticagrelor and 7 days for prasugrel before surgery (Class I, Levels of Evidence B and C, respectively). However, the guidelines also provide the recommendation that it is reasonable to perform surgery before these time points, and perhaps as early as 3 days from discontinuation.[1,15] These guidelines stem from the inherent properties of each medication, including their metabolism and clearance. For example, platelet inhibition with clopidogrel is irreversible and platelet reactivity is only regained with regeneration of new platelets, which occurs at a rate of ≈10% to 15% per day.[16] Conversely, given its very short half-life, cangrelor can safely be administered up to 1 to 6 hours pre-CABG without an increase in bleeding, compared with placebo therapy,[17] and offers an alternative P2Y12 treatment strategy that avoids the issues of pretreatment with an oral agent.

As new developments in P2Y12 inhibitors have led to increased potency, reversible platelet binding, and even the ability to administer a P2Y12 medication intravenously with rapid onset, in-hospital care of patients undergoing early coronary angiography and revascularization has also continued to evolve. Patients now frequently undergo coronary angiography within the first 24 to 48 hours of hospitalization; data from the ACTION Registry suggest that ≈60% of patients undergo coronary angiography within 48 hours.[18] In this setting, the benefit of pretreatment with P2Y12 therapy before coronary angiography that was observed in the CURE trial, where coronary angiography occurred a median of 10 days from presentation,[4] may no longer be directly applicable. A subanalysis of the CURE trial, however, argues

against this. It showed that the benefits of clopidogrel began within hours of randomization with a statistically significant benefit between groups in the first 24 hours, which was largely driven by reduction of in-hospital refractory ischemia.[6] Nonetheless, the benefit of pretreatment must be balanced with the possible delays and increased bleeding risks associated with a surgical revascularization.

A number of other important points must also be considered. Many patients do not undergo early coronary angiography and would miss the early benefit of P2Y12 inhibitor observed in CURE. Furthermore, only 11% to 13% of patients admitted with NSTEMI will ultimately be found to have anatomy that necessitates CABG.[19] With a low rate of CABG and the benefits observed with P2Y12 pretreatment, perhaps it is better to tolerate the inherent surgical delays and bleeding risks associated with P2Y12 pretreatment in the small subset of patients who ultimately undergo CABG, rather than to miss the benefits of P2Y12 pretreatment for all patients. Finally, management of additional factors that are more strongly associated with CABG-related bleeding than the use and timing of P2Y12 inhibitors may also afford a better balance of benefit and risk for early use of P2Y12 inhibitors among patients requiring CABG. Whereas medications presurgery are an important factor to consider when evaluating bleeding risk, it is essential to also recognize that numerous other variables contribute to bleeding, including patient age, sex, renal function, the surgeon who performs the procedure, and the definition of bleeding that is used.[20]

The treatment of patients with NSTEMI is a field that continues to evolve. Although we know patients benefit from treatment with dual antiplatelet therapy, the timing of initiation of P2Y12 therapy remains unclear. Potency of platelet inhibition is offset by bleeding risk, particularly among patients undergoing CABG therapy, and precatheterization treatment with a P2Y12 inhibitor may to lead to increased time to CABG, increased length of stay, and increased bleeding risk with CABG. Large, randomized trials are needed to fully understand the optimal timing of P2Y12 inhibitor therapy and how timing affects outcomes related to surgical revascularization.

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References

1. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DRJr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ; ACC/AHA Task Force Members; Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:2354–2394.
2. Bertrand ME, Legrand V, Boland J, Fleck E, Bonnier J, Emmanuelson H, Vrolix M, Missault L, Chierchia S, Casaccia M, Niccoli L, Oto A, White C, Webb-Peploe M, Van Belle E, McFadden EP. Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting. The full anticoagulation versus aspirin and ticlopidine (FANTASTIC) study. *Circulation*. 1998;98:1597–1603.
3. Laine M, Paganelli F, Bonello L. P2Y12-ADP receptor antagonists: days of future and past. *World J Cardiol*. 2016;8:327–332.
4. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. 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.
5. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001;358:527–533.
6. Yusuf S, Mehta SR, Zhao F, Gersh BJ, Commerford PJ, Blumenthal M, Budaj A, Wittlinger T, Fox KA; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Early and late effects of clopidogrel in patients with acute coronary syndromes. *Circulation*. 2003;107:966–972.
7. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM; TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001–2015.
8. Roe MT, Armstrong PW, Fox KA, White HD, Prabhakaran D, Goodman SG, Cornel JH, Bhatt DL, Clemmensen P, Martinez F, Ardissino D, Nicolau JC, Boden WE, Gurbel PA, Ruzyllo W, Dalby AJ, McGuire DK, Leiva-Pons JL, Parkhomenko A, Gottlieb S, Topacio GO, Hamm C, Pavlides G, Goudev AR, Oto A, Tseng CD, Merkely B, Gasparovic V, Corbalan R, Cinteza M, McLendon RC, Winters KJ, Brown EB, Lokhnygina Y, Aylward PE, Huber K, Hochman JS, Ohman EM; Trilogy ACS Investigators. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *N Engl J Med*. 2012;367:1297–1309.
9. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA; PLATO Investigators, Freij A, Thorsen M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–1057.
10. Harrington RA, Stone GW, McNulty S, White HD, Lincoff AM, Gibson CM, Pollack CV Jr, Montalescot G, Mahaffey KW, Kleiman NS, Goodman SG, Amine M, Angiolillo DJ, Becker RC, Chew DP, French WJ, Leisch F, Parikh KH, Skerjanec S, Bhatt DL. Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med*. 2009;361:2318–2329.
11. Bhatt DL, Lincoff AM, Gibson CM, Stone GW, McNulty S, Montalescot G, Kleiman NS, Goodman SG, White HD, Mahaffey KW, Pollack CV Jr, Manoukian SV, Widimsky P, Chew DP, Cura F, Manukov I, Tousek F, Jafar MZ, Arneja J, Skerjanec S, Harrington RA; CHAMPION PLATFORM Investigators. Intravenous platelet blockade with cangrelor during PCI. *N Engl J Med*. 2009;361:2330–2341.
12. Widimsky P, Motovska Z, Simek S, Kala P, Pudil R, Holm F, Petr R, Bilkova D, Skalicka H, Kuchynka P, Poloczek M, Miklik R, Maly M, Aschermann M; PRAGUE-8 Trial Investigators. Clopidogrel pre-treatment in stable angina: for all patients > 6 h before elective coronary angiography or only for angiographically selected patients a few minutes before PCI? A randomized multicentre trial PRAGUE-8. *Eur Heart J*. 2008;29:1495–1503.
13. Di Sciascio G, Patti G, Pasceri V, Gatto L, Colonna G, Montinaro A; ARMYDA-5 PRELOAD Investigators. Effectiveness of in-laboratory high-dose clopidogrel loading versus routine pre-load in patients undergoing percutaneous coronary intervention: results of the ARMYDA-5 PRELOAD (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty) randomized trial. *J Am Coll Cardiol*. 2010;56:550–557.
14. Badri M, Abdelbaky A, Li S, Chiswell K, Wang TY. Precatheterization Use of $P2Y_{12}$ Inhibitors in Non-ST-Elevation Myocardial Infarction Patients Undergoing Early Cardiac Catheterization and In-Hospital Coronary Artery Bypass Grafting: Insights From the National Cardiovascular Data Registry®. *J Am Heart Assoc*. 2017;6:e006508. doi: 10.1161/JAHA.117.006508.
15. Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Brown JR, Despotis GJ, Hammon JW, Reece TB, Saha SP, Song HK, Clough ER; Society of Cardiovascular Anesthesiologists Special Task Force on Blood Transfusion, Shore-Lesserson LJ, Goodnough LT, Mazer CD, Shander A, Stafford-Smith M, Waters J; International Consortium for Evidence Based Perfusion, Baker RA, Dickinson TA, FitzGerald DJ, Likosky DS, Shann KG. 2011

update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. *Ann Thorac Surg*. 2011;91:944–982.

16. Weber AA, Braun M, Hohlfeld T, Schwippert B, Tschope D, Schror K. Recovery of platelet function after discontinuation of clopidogrel treatment in healthy volunteers. *Br J Clin Pharmacol*. 2001;52:333–336.
17. Angiolillo DJ, Firstenberg MS, Price MJ, Tummala PE, Hutyra M, Welsby IJ, Voeltz MD, Chandna H, Ramaiah C, Brtko M, Cannon L, Dyke C, Liu T, Montalescot G, Manoukian SV, Prats J, Topol EJ; BRIDGE Investigators. Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: a randomized controlled trial. *JAMA*. 2012;307:265–274.
18. Roe MT, Messenger JC, Weintraub WS, Cannon CP, Fonarow GC, Dai D, Chen AY, Klein LW, Masoudi FA, McKay C, Hewitt K, Brindis RG, Peterson ED, Rumsfeld JS. Treatments, trends, and outcomes of acute myocardial infarction and percutaneous coronary intervention. *J Am Coll Cardiol*. 2010;56:254–263.
19. Parikh SV, de Lemos JA, Jessen ME, Brilakis ES, Ohman EM, Chen AY, Wang TY, Peterson ED, Roe MT, Holper EM; CRUSADE and ACTION Registry-GWTG Participants. Timing of in-hospital coronary artery bypass graft surgery for non-ST-segment elevation myocardial infarction patients results from the National Cardiovascular Data Registry ACTION Registry-GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With The Guidelines). *JACC Cardiovasc Interv*. 2010;3:419–427.
20. Kim JH, Newby LK, Clare RM, Shaw LK, Lodge AJ, Smith PK, Jolicoeur EM, Rao SV, Becker RC, Mark DB, Granger CB. Clopidogrel use and bleeding after coronary artery bypass graft surgery. *Am Heart J*. 2008;156:886–892.

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