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). 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. 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. 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. Prasugrel, a third-generation thienopyridine with increased potency compared with clopidogrel, was subsequently developed. The TRILOGY 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. 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. 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. 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, 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.

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
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 Emer-
gency thrombolysis-8) trials showed no benefit.5,12,13 The
ACCOAST (Comparison of Prasugrel at the Time of Percuta-
eous 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 precatheter-
ization 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 catheter-
ization. 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,
future 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
causé 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.14 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 contin-
ued 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. Where 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 pretreatment treatment with a P2Y12 inhibitor may 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.

Disclosures

Newby reports modest research grant support from Amlylin/BMS, GlaxoSmithKline, Boehringer Ingelheim, and Sanofi.

References

1. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes D Jr, 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 antiaggregation versus antplatelet therapy in unplanned and elective coronary stenting. The full antiplatelet and ticagrelor (FANTASTIC) study. Circulation. 1998;97:1597–1603.
3. Laine M, Paganeli F, Bonello L. P2Y12-ADP receptor antagonists: days of future and past. World J Cardiol. 2016;8:327–332.
4. Yusuf S, Zhao M, Mehta SR, Chrolavicius S, Tognoni G, Fox K; Clopidogrel in Unstable Angina To Prevent Recurrent Events Trial Investigators. Effect 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 M, 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 M, 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. Viviotis 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, Cornell JR, Huth ET, Lincoff AM, Gibson CM, 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.
9. Harrington RA, Stone GW, McNulty S, White HD, Lincoff AM, Gibson CM, Pollack CV Jr, Montalescot G, Van Landeghem K, Kornowski R, Ciampi A, Bruckman P, Di Mario U, Ong AT, Lincoff AM, Girolami C, Alfonso F, Zito F; PCI Outcomes Group; PCI Outcomes Group. 2011. doi: 10.1161/JAHA.117.006508.
10. Roe MT, Armstrong PW, Fox KA, White HD, Prabhakaran D, Goodman SG, Cornell JR, Huth ET, Lincoff AM, Gibson CM, 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.
11. Harrington RA, Stone GW, McNulty S, White HD, Lincoff AM, Gibson CM, Pollack CV Jr, Montalescot G, Van Landeghem K, Kornowski R, Ciampi A, Bruckman P, Di Mario U, Ong AT, Lincoff AM, Girolami C, Alfonso F, Zito F; PCI Outcomes Group; PCI Outcomes Group. 2011. doi: 10.1161/JAHA.117.006508.
12. Widimsky P, Motovska Z, Simek S, Kala P, Pudil R, Holm F, Petr R, Bilkova D, SV, Widimsky P, Chew DP, Cura F, Manukov I, Tousek F, Jafar MZ, Arneja J, Skerjanec S, Bhatt DL. Platelet inhibition with cangrelor in patients undergoing PCI. N Engl J Med. 2009;361:1318–1329.
13. Widimsky P, Motovska Z, Simek S, Kala P, Pudil R, Holm F, Petr R, Bilkova D, SV, Widimsky P, Chew DP, Cura F, Manukov I, Tousek F, Jafar MZ, Arneja J, Skerjanec S, Bhatt DL. Platelet inhibition with cangrelor in patients undergoing PCI. N Engl J Med. 2009;361:1318–1329. doi: 10.1091/0022-0364.2001.13209.21.
14. Widimsky P, Motovska Z, Simek S, Kala P, Pudil R, Holm F, Petr R, Bilkova D, SV, Widimsky P, Chew DP, Cura F, Manukov I, Tousek F, Jafar MZ, Arneja J, Skerjanec S, Bhatt DL. Platelet inhibition with cangrelor in patients undergoing PCI. N Engl J Med. 2009;361:1318–1329. doi: 10.1091/0022-0364.2001.13209.21.
15. Di Sciascio G, Patti G, Pasceri V, Gatto L, Colonna G, Montinaro A; ARMYDA-5 Multicentre Trial 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.
16. Di Sciascio G, Patti G, Pasceri V, Gatto L, Colonna G, Montinaro A; ARMYDA-5 Multicentre Trial 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.
17. Badri M, Abdelbaky A, Li S, Chiswell K, Wang TY. Pretreatment 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 Disease Registry. J Am Coll Cardiol. 2010;56:550–557.
18. Badri M, Abdelbaky A, Li S, Chiswell K, Wang TY. Pretreatment 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 Disease Registry. J Am Coll Cardiol. 2010;56:550–557.
19. Badri M, Abdelbaky A, Li S, Chiswell K, Wang TY. Pretreatment 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 Disease Registry. J Am Coll Cardiol. 2010;56:550–557.
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, Hutrya M, Welsby IJ, Voeltz MD, Chandna H, Ramaih 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, Brillakis ES, Ohman EM, Chen AY, Wang TY, Peterson ED, Roe MT, Holper EM; GRUSADE 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 JK, Clare RM, Shaw LK, Lodge AJ, Smith PK, Jolicouer 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.

Key Words: Editorials • acute coronary syndrome • antiplatelet therapy • coronary artery bypass graft surgery