Pharmacy and Wellness Review

Volume 3 | Issue 1 Article 3

January 2012

The Emerging Role of Ticagrelor in Acute Coronary Syndromes

Jennifer Bauer
Ohio Northern University

Brittany Dye
Ohio Northern University

Kimberly Baucher
Ohio Northern University

Megan Keller
Ohio Northern University, m-keller@onu.edu

David Bright
Ohio Northern University

See next page for additional authors

The Emerging Role of Ticagrelor in Acute Coronary Syndromes

Authors

Jennifer Bauer, Brittany Dye, Kimberly Baucher, Megan Keller, David Bright, and Karen L. Kier

The Emerging Role of Ticagrelor in Acute Coronary Syndromes

Jennifer Bauer, fifth-year pharmacy student from St. Marys, Pa.; Brittany Dye, fourth-year pharmacy student from Tiro, Ohio; Kimberly Baucher, fourth-year pharmacy student from Findlay, Ohio; **Megan Keller**, PharmD '11, community pharmacy resident; David Bright, PharmD, BCACP, assistant professor of pharmacy practice; **Karen L. Kier**, BSPh '82, Ph.D., R.Ph., BCPS, BCACP, professor of clinical pharmacy, director of assessment

This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

ACPE Universal Activity Number (UAN): 0048-0000-11-051-H01-P

Objectives:
After completion of this program, the reader should be able to:

1. List the disease states associated with acute coronary syndromes (ACS) and general treatment approaches.
2. Describe the rationale behind the development of new antiplatelet drug therapies.
3. Explain the mechanisms of action of clopidogrel, prasugrel and ticagrelor.
4. List the advantages and disadvantages of treating ACS with either clopidogrel, prasugrel or ticagrelor.
5. Describe the appropriate patient populations indicated for each drug therapy.

Abstract
Antiplatelet therapy has become a mainstay in the treatment of acute coronary syndromes (ACS). Until recently, options were somewhat limited when it came to individualizing drug selection. Plavix® (clopidogrel) has been successfully used for many years but requires activation by CYP enzymes. Depending on an individual patient's genetic makeup, function of these CYP enzymes may be altered, which may increase the risk for clots. The recent approval of Effient® (prasugrel) and Brilinta® (ticagrelor) has provided physicians and pharmacists with more options and may hopefully lead to improved clinical outcomes. Ticagrelor specifically exhibits clinically different pharmacologic characteristics that require twice daily dosing, but also allows for faster onset and offset, as well as more predictable platelet inhibition as compared to clopidogrel. Additional postmarketing surveillance and treatment guidelines will hopefully continue to guide appropriate selection of antiplatelet therapies.

Introduction

Acute coronary syndromes, which include unstable angina (UA), non-ST elevated myocardial infarction (NSTEMI) and ST elevated myocardial infarction (STEMI) are among the leading causes of mortality today.[1] Platelets play a key role in atherothrombosis and may be a key contributor to ACS.[2] As a result, antiplatelet agents are commonly used as a preventive measure, particularly after a patient has suffered from ACS. Aspirin is often seen as the foundational antiplatelet agent. When Plavix® (clopidogrel) is combined with aspirin, the additive antiplatelet effect has been shown to provide further benefit. However, due to variability among patients in response level, as well as delayed onset, researchers are seeking to find new and better ways of implementing antiplatelet therapy for patients with ACS. Effient® (prasugrel) and Brilinta® (ticagrelor) are two viable alternatives to clopidogrel in the treatment of ACS. Ticagrelor specifically offers different characteristics than clopidogrel and prasugrel and shows promise as a part of the standard of care in ACS. The goal of this paper is to review the use of existing antiplatelet therapies and to highlight clinically relevant studies and strategies of care for ticagrelor.

Clopidogrel

Clopidogrel has been the standard of care for ACS for many years. Clopidogrel is a prodrug that must undergo a two-step metabolism in order to be converted to the active metabolite. Peak levels of the active metabolite are observed approximately three to four hours after administration. Cytochrome P450 (CYP450) enzymes, most notably CYP2C19, first convert clopidogrel to 2-oxo-clopidogrel, which is then hydrolyzed into the active metabolite responsible for irreversibly blocking ADP $P2Y_{12}$ receptors on the platelet surface, therefore inhibiting platelet aggregation.[1]

As CYP2C19 is involved in both steps of the biotransformation of clopidogrel, the CYP2C19 genotype is a significant contributing factor to response variability for clopidogrel. Genetics and ethnicity may lead to changes in the CYP enzymes, potentially resulting in clopidogrel resistance.[1] CYP2C19*1 is the wild-type, or common, allele while CYP2C19*2, CYP2C19*3 and CYP2C19*17 are examples of alternate alleles that may express reduced or increased enzymatic function. Alterations in CYP3A5 and ABCB1 may also affect clopidogrel metabolism.[3] Based on the genetic variability of the biotransformation process, the FDA is recommending genetic testing for patients on clopidogrel due to the potential for clopidogrel to not function fully (clopidogrel nonresponsiveness).[2,4]

Clopidogrel is used to reduce the rate of atherothrombotic events in patients with UA, NSTEMI or STEMI. In patients with STEMI who are managed medically, it can also reduce the mortality rate. The typical dose of clopidogrel is 300 mg as a loading dose followed by 75 mg every day accompanied by 75-162 mg of aspirin every day for patients with UA, NSTEMI or STEMI. In CYP2C19 poor metabolizers, a 600 mg loading dose with 150 mg per day has been utilized. Clopidogrel is contraindicated in any patient with known hypersensitivity to clopidogrel or any component of the product, and in any patient with active pathological bleeding such as GI

and/or intracranial bleeding.[5] Clopidogrel is not recommended for use in patients with reduced CYP2C19 function due to the decreased activation of clopidogrel. Adverse reactions to clopidogrel include dermatologic rash or pruritus, bruising, epistaxis and other bleeding that may be major or minor. These reactions occur in less than 10 percent of patients taking clopidogrel.

The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study was a randomized, double-blind, placebo-controlled trial in patients presenting with non-ST segment elevated ACS.[6,7] Patients were either placed in the clopidogrel or placebo group. The clopidogrel group received 300 mg as a loading dose followed by a 75 mg maintenance dose, while the placebo group received a matching placebo dosing regimen. Both groups received aspirin 75-325 mg daily as prescribed by the physician. Follow-up occurred at three-month intervals and continued up to one year, with an average duration of nine months. The primary outcome measured was a composite of cardiovascular death, myocardial infarction and stroke. In order to measure safety, bleeding complications were measured. Clopidogrel lead to a significant reduction in the primary outcome. The researchers also determined that the likelihood of benefit substantially outweighs the risks of life-threatening or major bleeding.

Prasugrel

Prasugrel also irreversibly blocks $P2Y_{12}$ receptors; however, it is 10 times more potent than clopidogrel. Prasugrel is a prodrug that is rapidly converted to an active metabolite via a single-step process using CYP3A4 and CYP2B6.[8] Peak plasma levels are reached approximately 30 minutes after administration.[9] Despite 70 percent of prasugrel being excreted renally, it does not require dosage adjustment for renal impairment.[10] Prasugrel has a more consistent and potent inhibition of platelet aggregation than clopidogrel. Therefore, prasugrel may be appropriate in a patient who does not respond to clopidogrel. However, prasugrel has an increased risk of bleeding, especially in patients with a history of stroke or patients over 75 years of age.

Prasugrel is recommended for use in patients who are being managed with percutaneous coronary intervention (PCI) for UA, NSTEMI or STEMI to reduce the rate of thrombotic cardiovascular events.[8] Patients with ACS managed with PCI are given a prasugrel loading dose of 60 mg no later than an hour following PCI.[11] Patients are then placed on a maintenance dose of 10 mg daily along with 81-325 mg of aspirin every day. This maintenance dosage is recommended to continue for 12 months in patients with UA, NSTEMI and STEMI. However, the clinician may choose to extend treatment duration to 15 months in UA and NSTEMI patients, unless the risk of bleeding outweighs the benefits. Prasugrel should not be given to patients who have active pathological bleeding or a history of transient ischemic attack or stroke. Furthermore, due to an increased risk of complications, the maintenance dose is suggested to be decreased to 5 mg once daily in patients who weigh less than 60 kg. Adverse reactions are rare, but can be fatal; as may be the case with bleeding. Other cardiovascular adverse reactions occurring in less than 10 percent of patients include hypertension, hypotension, atrial fibrillation, bradycardia, hyperlipidemia and epistaxis.

The Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation-Thrombolysis in Myocardial Infarction 44 (PRINCIPLE-TIMI 44) was a phase II, double-blind, randomized, crossover study comparing prasugrel and clopidogrel in patients referred for PCI.[12] Patients in the prasugrel group received 60 mg as a loading dose and 10 mg per day as a maintenance dose while the clopidogrel group received 600 mg as a loading dose and 150 mg per day as a maintenance dose. The maintenance dose lasted through the 28-day crossover period, with an inhibition of platelet aggregation (IPA) endpoint measurement after 14 days of either drug. The primary endpoint after the loading dose phase was IPA with 20 μmol/L ADP after six hours. The IPA of the prasugrel group was significantly higher than in the clopidogrel group. The study concluded prasugrel was the preferred treatment because of the increased platelet inhibition, but did not address clinical endpoints such as MI, stroke or CV death.

Prasugrel versus clopidogrel in patients with acute coronary syndromes (TRITON-TIMI 38) was a double-blind, randomized controlled trial in 30 countries with 13,608 people participating.[13] Patients in the clopidogrel group received 300 mg as a loading dose and a maintenance dose of 75 mg per day. Those in the prasugrel group received 60 mg as a loading dose followed by 10 mg per day as a maintenance dose. The primary efficacy endpoint was the composite of death from cardiovascular causes, nonfatal MI and nonfatal stroke. Overall, there was a significant reduction in the primary efficacy endpoint when using prasugrel as compared to clopidogrel with a hazard ratio (HR) of 0.81 with a 95 percent confidence interval (95% CI) of 0.73 to 0.90 ($P<0.001$). Key secondary endpoints for the follow-up were stent thrombosis and a composite of death due to cardiovascular events, nonfatal MI, nonfatal stroke or rehospitalization due to a cardiac ischemic event. The secondary endpoint of stent thrombosis was also significantly reduced (HR 0.48, 95% CI 0.36 to 0.64, $P<0.001$). The other secondary endpoint of death from cardiovascular causes, nonfatal MI, nonfatal stroke or rehospitalization for ischemia was again significantly reduced (HR 0.84, 95% CI 0.76 to 0.92, $P<0.001$). The study concluded prasugrel is more effective at reducing thrombotic cardiovascular events than clopidogrel for patients undergoing PCI with STEMI. However, clinicians should weigh these benefits against the increased risk of bleeds.

Ticagrelor

What Makes Ticagrelor Different?

On July 20, 2011, the FDA approved ticagrelor to reduce the rate of thrombotic cardiovascular events in patients with ACS.[14] This drug is the first in a novel chemical class, the cyclopentyltriazolapyramides.[15] Ticagrelor is unique as compared to clopidogrel and prasugrel in that it displays direct-acting $P2Y_{12}$ receptor antagonism, as well as reversible binding properties. Ticagrelor typically reaches peak levels in 1.5 hours. Also, there is at least one metabolite of ticagrelor that exhibits the same action as the parent compound.

The other notable difference between ticagrelor as compared with clopidogrel and prasugrel is seen in regard to binding properties. When clopidogrel and prasugrel bind, they are present throughout the entire life-span of the platelet. If the patient must discontinue the drug for any reason, most commonly for surgical preparation, it will take approximately one week for the effect of the drug to disappear.[2] Ticagrelor, on the other hand, is reversible, which leads to a quicker offset of action than other platelet-inhibiting therapeutic agents. The reversibility may prove advantageous for patients who need to have a Coronary Artery Bypass Graft (CABG). Although the manufacturer recommends a five-day waiting period before surgery, it could be theorized that ticagrelor could wear off faster than clopidogrel or prasugrel given the reversible properties of the drug.[16]

Safety and Efficacy

One of the first studies to evaluate the safety and efficacy of ticagrelor versus clopidogrel in patients with NSTEMI was the Safety, Tolerability, and Initial Efficacy of AZD6140, the First Reversible Oral Adenosine Diphosphate Receptor Antagonist, Compared with Clopidogrel, in Patients with Non–ST-Segment Elevation Acute Coronary Syndrome: the DISPERSE-2 Trial. The study compared major and minor bleeding between the groups. The study found no significant difference in major bleeding. However, there was a significant difference in minor bleeding with ticagrelor having a higher incidence than clopidogrel. Also, the doses of ticagrelor yielded a level of platelet inhibition nearly double that of clopidogrel.[17] Furthermore, patients who discontinued ticagrelor one to five days prior to undergoing CABG experienced a lower rate of procedure-related bleeding than patients who had been in the clopidogrel group. This study paved the way for other studies to take place to analyze the efficacy of ticagrelor in ACS.

One landmark study was the Study of Platelet Inhibition and Patient Outcomes (PLATO) that was conducted to determine whether ticagrelor was superior to clopidogrel for the prevention of vascular events and death.[18] Patients were assigned to receive ticagrelor or clopidogrel with aspirin given to both treatment arms at a dose of 75-100 mg daily, unless the patient was unable to tolerate it. Ticagrelor was given as a 180 mg loading dose, followed by 90 mg twice daily. Clopidogrel was given as a 300 mg loading dose for patients who had not already been taking it, followed by 75 mg daily. The primary endpoint of this study was a composite of deaths from vascular causes, or any other cause. At the end of one year, it was discovered that the primary endpoint occurred less in the ticagrelor group (9.8 percent) than in the clopidogrel group (11.7 percent). The difference in the effect of the treatment was apparent from day 30 of the study and remained consistent. Secondary endpoints evaluated were death due to individual types of events, such as MI or stroke, and there was a reduction in deaths from MI individually as well as vascular events. Additionally, there was a reduction in the risk of stent thrombosis; however, there were more deaths from hemorrhagic stroke in the ticagrelor group compared to the clopidogrel group (0.2 percent versus 0.1 percent, respectively). This study showed there was no benefit of ticagrelor use in patients weighing less than the median weight for their sex, taking lipid lowering drugs or living in North America. There was also a higher rate of non-procedure related bleeding, as well as a higher rate of dyspnea in patients who received ticagrelor. It should be noted the risk of dyspnea was relatively low and does not mean the clear benefits of ticagrelor in regard to prevention of death should be disregarded. Despite the negative results shown in patients in North America, the FDA still chose to approve the drug. Potential considerations include the small sample size of North American study participants in the PLATO study and a different aspirin dosing regimen observed in North America.[19] Therefore, ticagrelor may still be used in North American patients as long as aspirin doses are maintained below 100 mg daily.

The genetic polymorphisms affecting clopidogrel action in different patients, specifically the CYP2C19 genotype, do not impact the effects of ticagrelor.[2] Therefore, if ticagrelor is used instead of clopidogrel, it would eliminate the need for the genetic testing currently recommended by the FDA for clopidogrel. Another PLATO substudy focused on patients who were scheduled to receive non-invasive treatment. The substudy found ticagrelor consistently reduced ischemic events in ACS patients whether or not they were scheduled for invasive stent placement or non-invasive treatment, implying that the intensified effects are beneficial in either management strategy.[20] At this time, head-to-head studies comparing prasugrel and ticagrelor have not been conducted. Therefore, it is difficult to discern if there is greater benefit shown when using prasugrel vs. ticagrelor.

As clopidogrel nonresponsiveness has become a clinical concern, the Response to Ticagrelor in Clopidogrel Nonresponders and Responders and Effect of Switching Therapies (RESPOND) Study set out to determine the feasibility of switching patients who fail clopidogrel treatment to ticagrelor. Ninety-eight patients were given 300 mg of clopidogrel and were then assessed for response via light transmittance aggregometry.[4] Once the patient was determined to be a responder or nonresponder to clopidogrel, he was randomly assigned to receive either clopidogrel 75 mg per day or ticagrelor 90 mg twice a day for two weeks. After two weeks, all nonresponders switched treatments and half of the responders switched treatments. The patients who tested nonresponsive to clopidogrel were responsive to ticagrelor. The platelet aggregation of these patients fell from 59 ± 9 percent to 35 ± 11 percent when switching from clopidogrel to ticagrelor and rose from 36 ± 14 percent to 56 ± 9 percent when switching from ticagrelor to clopidogrel. Therefore, ticagrelor was determined to be effective in overcoming clopidogrel nonresponsiveness. In the responder group, platelet aggregation showed statistically significant improvement in patients treated with ticagrelor. Additionally, it was found patients were able to switch directly from clopidogrel to ticagrelor without any reduction in antiplatelet effect. Therefore, ticagrelor is a promising therapeutic option for dealing with patients who experience clopidogrel nonresponsiveness.

Another trial, a randomized, double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study, provided further clinical support for the use of ticagrelor.[21] ONSET/OFFSET was a study encompassing 123 patients with stable coronary artery disease who received either 90 mg ticagrelor twice daily, 75 mg clopidogrel once daily or placebo for six weeks. Ultimately, greater platelet inhibition occurred with ticagrelor at all times tested and a faster onset of action was noted. Also, there was a faster offset of action when the patients were taken off the drug at the end of week six. The level of platelet inhibition of ticagrelor after the third day of being taken off the medication was comparable to day five of the clopidogrel patients. The faster offset of action could be beneficial if the patient needed surgery or if they had to discontinue their antiplatelet medication for any other reason. Despite this evidence, as mentioned previously, the drug manufacturer still recommends discontinuing ticagrelor five days prior to surgery.[17]

Clinical Considerations

Although ticagrelor shows great promise in the treatment of ACS, there are several drawbacks to consider. The first is that ticagrelor has been shown to have an increased risk of fatal intracranial bleeding and higher rates of GI-related bleeding as compared to clopidogrel; however, it should be considered that the percentage of intracranial bleeding and GI bleeds may not outweigh the benefits of improved cardiovascular outcomes.[2] Clinicians may want to keep these bleeding risks in mind and carefully monitor patients at a higher risk for bleeding if ticagrelor is chosen. Also, dyspnea was noted at an increase of about 6 percent compared to clopidogrel. Dyspnea may impact long-term adherence and should be monitored. Additionally, a slightly greater increase in serum creatinine and uric acid levels was noted in the PLATO trial, regarding ticagrelor compared to clopidogrel. Serum uric acid levels increased with ticagrelor compared to clopidogrel, but reports of gout did not differ between groups.[18] Serum creatinine increased in patients taking ticagrelor compared to clopidogrel. Due to the increase in serum creatinine, renally impaired patients should be monitored when either antiplatelet agent is administered. In regard to other medications, ticagrelor increases levels of drugs metabolized through CYP3A4, such as simvastatin. CYP3A4 inhibitors, such as diltiazem, increase the levels of ticagrelor and reduce the speed of offset.[22]

Ticagrelor prescribing information states that it is recommended for use in all forms of ACS.[16] Ticagrelor is taken in conjunction with aspirin, though aspirin doses above 100 mg have been shown to decrease the effectiveness of the drug. Treatment starts with a 180 mg loading dose followed by 90 mg twice daily. Aspirin is delivered as a 325 mg loading dose and then 75-100 mg daily. Ticagrelor is contraindicated in patients with a history of intracranial hemorrhaging, active pathological bleeding or severe hepatic impairment.[14] Patients may experience dyspnea and may be at a greater risk for non-procedural related bleeding, easier bruising, longer bleeding times and an increased likelihood of epistaxis.

Conclusion

Although clopidogrel has been the standard of care for the treatment of ACS for several years, the recent approval of prasugrel and ticagrelor now allows for alternative therapies. Ticagrelor specifically exhibits clinically different pharmacologic characteristics that require twice daily dosing, but also allows for faster onset and offset, as well as more predictable platelet inhibition as compared to clopidogrel. It is important to individualize antiplatelet therapy to ensure the best possible therapeutic outcomes. Additional postmarketing surveillance and treatment guidelines will hopefully continue to guide appropriate selection of antiplatelet therapies.

References

1. Yukhanya L, Freynhofer MK, Siller-Matula J, Schror K, Huber K. Genetic variability in response to clopidogrel therapy and its clinical implications. *Thromb Haemost.* 2011;105(Suppl 1):S55-9.
2. Lombo B, Diez JG. Ticagrelor: the evidence for its clinical potential as an oral antiplatelet treatment for the reduction of major adverse cardiac events in patients with acute coronary syndromes. *Core Evid.* 2011;6:31-42.
3. Terpening C. Clopidogrel: a pharmacogenomic perspective on its use in coronary artery disease. *Clin Med Insights Cardiol.* 2010;4:117-28.
4. Gurbel PA, Bliden KP, Butler K, Antonino MJ, Wei C, Teng R, et al. Response to ticagrelor in clopidogrel nonresponders and responders and effect of switching therapies: The RESPOND study. *Circulation.* 2010;121:1188-99.
5. Plavix® (clopidogrel) [product information]. Bridgewater, NJ: Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, 2011. Available from: http://products.sanofi.us/plavix/plavix.html.
6. Gerschutz GP, Bhatt DL. The CURE trial: using clopidogrel in acute coronary syndromes without ST-segment elevation. *Cleve Clin J Med.* 2002;69(5):377-85.
7. Fox KAA, Mehta SR, Peters R, Zhao F, Lakkis N, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the clopidogrel in unstable angina to prevent recurrent ischemic events (CURE) trial. *Circulation.* 2004;110:1202-8.
8. Prasugrel [monograph on the Internet]. Tampa (FL): Gold Standard/ Elsevier; 2011 [cited 2011 Oct 19]. Available from: www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=3477&n=Prasugrel.
9. Schafer JA, Kjesbo NK, Gleason PP. Critical review of prasugrel for formulary decision makers. *J Manag Care Pharm.* 2009;15(4):335-43.
10. Farid NA, Smith RL, Gillespie TA, Rash TJ, Blair PE, et al. The disposition of prasugrel, a novel thienopyridine, in humans. *Drug Metab Dispos.* 2007;35(7):1096-1104.
11. Effient® (prasugrel) [product information]. Indianapolis, IN: Daiichi Sankyo, Inc. and Eli Lilly Company, 2010. Available from: http://pi.lilly.com/us/effient.pdf.
12. Wiviott SD, Trenk D, Frelinger AL, O'Donoghue M, Neumann F, Michelson AD, et al. Prasugrel compared with high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the prasugrel in comparison to clopidogrel for inhibition of platelet activation and aggregation-thrombolysis in myocardial infarction 44 trial. *Circulation.* 2007;116:2923-32.
13. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2007;357(20):2001-15.
14. FDA approves new medicine BRILINTA (ticagrelor) for use in the US. AstraZeneca Web Site. [cited 2011 September 30]. Available from: www.astrazeneca.com/Media/Press-releases/Article/20110720-fda-approves-brilinta-us.
15. Abergel E, Nikolsky E. Ticagrelor: An investigational oral antiplatelet treatment for reduction of major adverse cardiac events in patients with acute coronary syndrome. *Vasc Health Risk Manag.* 2010;6:963-77.
16. Brilinta® (ticagrelor) [product information]. Wilmington, DE: AstraZeneca LP, 2011. Available from: www1.astrazeneca-us.com/pi/brilinta.pdf.
17. Cannon CP, Husted S, Harrington RA, Scirica BM, Emanuelsson H, Peters G, et al. Safety, tolerability, and initial efficacy of AZD6140, the

first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non–ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. *J Am Coll Cardiol.* 2007;50:1844-51.
18. 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(11):1045-57.
19. Ohman EM, Roe MT. Explaining the unexpected: insights from the PLATelet inhibition and clinical outcomes (PLATO) trial comparing ticagrelor and clopidogrel. *Thromb Haemost.* 2011;105:763-5.
20. James SK, Roe MT, Cannon CP, Cornel JH, Horrow J, Husted S, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management: substudy from prospective randomised PLATelet inhibition and patient Outcomes (PLATO) trial. *BMJ.* 2011;342:1-11.
21. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: The ONSET/OFFSET study. *Circulation.* 2009;120:2577-85.
22. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the task force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2011;1-56.

Assessment Questions

1. Clopidogrel is not recommended in patients with reduced _____ function, due to decreased activation of the drug.
    a. CYP2C19
    b. Platelet
    c. Kidney
    d. All of the above
    e. B and C

2. Ticagrelor's primary mechanism of action can be described as:
    a. Conversion by liver metabolism to form an active metabolite that will bind to the $P2Y_{12}$ receptor
    b. Direct binding to the $P2Y_{12}$ receptor
    c. Conversion by liver metabolism to form an active metabolite that will bind directly to CYP3A4
    d. Direct binding to CYP3A4

3. Due to differences in binding, ticagrelor has a slower onset of action than clopidogrel.
    a. True
    b. False

4. The genetic polymorphisms affecting the action of clopidogrel in different patients do not impact the effects of ticagrelor.
    a. True
    b. False

5. BT is a 68-year-old female who is 5'2" and 67 kg. Platelet function testing shows BT is unresponsive to clopidogrel. Which of the following is/are appropriate alternative therapy?
    a. prasugrel
    b. ticagrelor
    c. Either A or B
    d. None of the above

6. Ticagrelor offers decreased risk of intracranial bleeding over clopidogrel.
    a. True
    b. False

7. Patient compliance due to twice daily dosing may be an issue with:
    a. clopidogrel
    b. prasugrel
    c. ticagrelor
    d. All of the above

8. Adverse effects associated with ticagrelor include:
    a. Dyspnea
    b. GI bleeding
    c. Intracranial bleeds
    d. All of the above
    e. A and C

9. Ticagrelor is contraindicated in patients with:
    a. Bradyarrythmia
    b. Under 60 kg
    c. History of asthma
    d. None of the above

10. Which of the following drugs increases the level of other medications metabolized through CYP3A4?
    a. ticagrelor
    b. prasugrel
    c. clopidogrel
    d. All of the above

Ohio Northern University is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program is eligible for credit until 11/29/14.

To receive continuing education credit for this program, you must answer the above questions and fill out the evaluation form. Please visit www.onu.edu/pharmacy to enter the required information. Please allow two to three weeks for electronic distribution of your continuing education certificate, which will be sent to your valid email address in PDF format.

To receive continuing education credit for this program, visit ***www.onu.edu/pharmacy/CE*** OR fill out the form below including your indicated answers to the assessment questions and return to:

Office of Continuing Education at the Raabe College of Pharmacy
Ohio Northern University
525 South Main Street
Ada, Ohio 45810

Ohio Northern University Continuing Education Registration & Evaluation Form
Raabe College of Pharmacy Continuing Education Evaluation Form

Program Title: **The Emerging Role of Ticagrelor in Acute Coronary Syndromes**
UAN: 0048-0000-11-051-H01-P CEUs: 0.1

All information must be printed CLEARLY to ensure accurate record keeping for attendance and the awarding of continuing education credit. Certificates will be distributed as a PDF document to a valid email address.

Name:

Address:

City: **State:** **Zip:**

Phone: **E-mail:**

Pharmacy License #: **State:** **ONU Alumni?** **Y** **N**

Program Content:	Strongly Disagree				Strongly Agree
The program objectives were clear.	1	2	3	4	5
The program met the stated goals and objectives:					
List the disease states associated with acute coronary syndromes and general treatment approaches.	1	2	3	4	5
Describe the rationale behind the development of new antiplatelet drug therapies.	1	2	3	4	5
Explain the mechanisms of action of clopidogrel, prasugrel and ticagrelor.	1	2	3	4	5
List the advantages and disadvantages of treating ACS with either clopidogrel, prasugrel or ticagrelor.	1	2	3	4	5
Describe the appropriate patient populations indicated for each drug therapy.	1	2	3	4	5
The program met your educational needs.	1	2	3	4	5
Content of the program was interesting.	1	2	3	4	5
Material presented was relevant to my practice.	1	2	3	4	5

Comment/Suggestions for future programs:

Thank you!

Answers to Assessment Questions—Please Circle Your Answer

1. **A B C D E**
2. **A B C D**
3. **A B**
4. **A B**
5. **A B C D**
6. **A B**
7. **A B C D**
8. **A B C D E**
9. **A B C D**
10. **A B C D**

Any questions/comments regarding this continuing education program can be directed to Lynn Bedford, Advanced Administrative Assistant for the Office of Continuing Education (email: l-bedford@onu.edu, phone 419-772-1871).

Ohio Northern University is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program is eligible for credit until 11/29/14.