expert roundtable »

Updated ACCF/AHA Guidelines on the Management of UA/NSTEMI: Implications for Antiplatelet Therapy (Part I of II)

Moderated by Keith C. Ferdinand, MD
Discussants: Carl J. Lavie, MD; JoAnne M. Foody, MD; Jeffrey S. Berger, MD, MS

DR. FERDINAND: This is the first part of a two-part roundtable discussion series. The purpose of it is to reach out to clinical cardiology, both invasive and non-invasive, to discuss the updated American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines on unstable angina and non-ST-segment-elevation myocardial infarction (NSTEMI) and the second group of guidelines of the ACCF/AHA ST-segment-elevation myocardial infarction (STEMI). We’re really interested in focusing on the implications for antiplatelet therapy. The guidelines, as you know, are very comprehensive and reach across a broad spectrum of medical and nonmedical interventions, but we’re not going to try to comprehensively cover all of those areas.

I’m Keith C. Ferdinand, MD. I’m a professor of clinical medicine at the Tulane University School of Medicine in New Orleans, Louisiana.

DR. LAVIE: This is Carl “Chip” Lavie. I’m a medical director of cardiac rehabilitation and preventive cardiology and director of the exercise laboratories at the John Ochsner Heart and Vascular Institute, Ochsner Clinical School—The University of Queensland School of Medicine, in New Orleans, LA. I’m an associate professor at Tulane University School of Medicine and I’m going to try to comprehensively cover all of those areas.

I’m Jeffrey Berger. I’m an assistant professor of medicine and surgery at NYU School of Medicine and director of cardiovascular thrombosis.

The following Expert Roundtable Discussion was held on November 4, 2013.

The discussion focused primarily on: (1) The recent changes to the guidelines for unstable angina and non-ST-segment-elevation myocardial infarction, in particular, changes to antiplatelet therapy and the addition of prasugrel and ticagrelor to the therapeutic armamentarium; (2) the impact of the updated guidelines on antiplatelet therapy in clinical decision making and the use of antiplatelet agents in practice; (3) the potential application of genetic and/or platelet function testing in antiplatelet therapy; and (4) compliance issues. (Med Roundtable Cardiovasc Ed. 2014;3(4):234–241) ©2014 FoxP2 Media, LLC

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STUDIES DISCUSSED:
CURE, PLATO, TRILOGY ACS, TRITON-TIMI 38

COMPOUNDS DISCUSSED:
aspirin, clopidogrel, dipyridamole, prasugrel, ticagrelor

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Harvard Medical School and I’m director of the cardiovascular wellness center at Brigham and Women’s Hospital in Boston, Massachusetts.
DR. FERDINAND: Thank you very much. For the purpose of the platform of this discussion, we’re going to be discussing acute coronary syndromes (ACS). As we know, it’s a constellation of clinical symptoms compatible with acute myocardial ischemia. It includes ST-segment-elevation myocardial infarction, or STEMI, and non-ST-segment-elevation myocardial infarction, or NSTEMI, which also includes unstable angina. ACS mainly is the disruption of a vulnerable high-risk plaque and consequently disruption of blood flow through the affected artery. With unstable angina and NSTEMI, it is usually not a total occlusion vs STEMI. We’ll be discussing STEMI shortly, but at this time we’re going to focus mainly on unstable angina and NSTEMI in terms of the use of antiplatelet agents. And looking specifically at the recent updates to the ACCF/AHA guidelines for unstable angina and NSTEMI.

We’re also going to be focusing on the use of dual antiplatelet therapy. As you know, there is clopidogrel, which is time tested, but there are also two newer P2Y12 inhibitors which have been approved and have been included in the guidelines. Ticagrelor has been approved along with prasugrel.

So let’s do this as an open-ended discussion.

The first question is what do you see as the most significant changes in the guidelines?

DR. LAVIE: It seems like the biggest change in the guidelines is the addition of ticagrelor, or BRILINTA®. That is also a new antiplatelet therapy that has been shown to be effective in ACS. Actually, based on the PLATO trial and the current [US FDA] rulings, it’s the only antiplatelet agent that is superior to clopidogrel for reducing cardiovascular death following ACS. …

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DR. FERDINAND: How is that different, Dr. Lavie, from prasugrel?

DR. LAVIE: I do not think prasugrel has any data to show that it significantly reduces cardiovascular death compared to clopidogrel. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) trial, there was a very small statistically significant reduction in cardiovascular death (7.4% in the prasugrel group vs 7.9% in the clopidogrel group; \( P = 0.001 \)). But I do not think there was a substantial reduction of risk of cardiovascular death. For every cardiovascular death that would have been prevented there was an equal fatal bleed. Prasugrel does not have FDA approval for reducing cardiovascular death compared to clopidogrel.

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DR. FERDINAND: Does anyone else want to comment on that nuance that Dr. Lavie just mentioned, that it appears that in terms of the evidence, ticagrelor has some data supporting a decrease in cardiovascular death as compared to prasugrel?

DR. BERGER: I think that’s a very important point. I think that both trials, TRITON as well as PLATO, showed a reduction in cardiovascular events when looking at the composite endpoint, but when looking at the specific end points there was that important distinction. I think that the major bleeding piece is also really important. As potent antiplatelet therapies, ticagrelor and prasugrel increase the risk of bleeding, you have to be very careful with the major bleeding definition used in each publication such that in TRITON there was a significant increase in the risk of the primary safety end point, TIMI non-coronary artery bypass graft (CABG)-related major bleeding (2.4% in the prasugrel group vs 1.8% in the clopidogrel group: \( P = 0.03 \)).

In PLATO, there was no increase in the trial’s primary assessment of major bleeding which was the PLATO major bleeding definition, but when you look at the primary bleeding definition used in TRITON (the TIMI major non-CABG definition), there was a significantly increased risk (2.8% in the ticagrelor group vs 2.2% in the clopidogrel group: \( P = 0.03 \)). Both drugs increase the risk of TIMI non-CABG related major bleeding, but prasugrel also increased fatal bleeding and life-threatening bleeding. So I think the excess bleeding risk that was seen with prasugrel in TRITON probably, most likely, counteracted or prevented the significant benefit in cardiovascular death as was seen in PLATO.

DR. FERDINAND: Dr. Foody, can you clarify—it appears that when you look at the guidelines for Class Ia evidence they’re talking on a platform of aspirin. All patients should get aspirin unless intolerant.
DR. FOODY: Correct.

DR. FERDINAND: Is that accurate?

DR. FOODY: Yes, and Keith, I just want to step back a little. I think your original question was really, “What did the new guidelines bring to light?” First and foremost, we have to step back and say that dual antiplatelet therapy is now without question recommended for all patients with ACS, and consists of a background of aspirin, as you mentioned, and any one of the three agents we’re talking about. In fact, as much as there are nuances between the three agents, the US guidelines do not specifically endorse one necessarily over the other. The real message is that all patients with unstable angina and NSTEMI should be considered candidates for dual antiplatelet therapy.

Now, there are subtleties within, and as we’ve moved from a simple aspirin-based strategy to clopidogrel and now moving to prasugrel and ticagrelor we continue to reduce ischemic events at the expense of bleeding. Again, many of these decisions need to be based on the risk of the given individual patient not only for ischemic events but also for their bleeding risk.

DR. FERDINAND: You know, one thing that is not really clear to me is why there are some nuances in the labeling for the drugs. I’m sure that someone can articulate how this is really based on evidence. It’s not new. It was in the older guidelines when they were first mentioning prasugrel, but they put this barrier of greater than or equal to 75 years of age not being recommended. What’s the benefit or harm of that?

DR. BERGER: Right. I think there are two very important points. One is when looking at the TRITON data there were three subgroups of patients with whom you have to be very careful when interpreting the data. One was in subjects who had a prior stroke or transient ischemic attack. The primary efficacy endpoint of death from cardiovascular causes, nonfatal MI and nonfatal stroke was higher with prasugrel vs clopidogrel treatment (19.1% vs 14.4% respectively), while the rate of TIMI non-CABG-related major bleeding was significantly higher (5.0% vs 2.9%, prasugrel vs clopidogrel respectively; \( P = 0.06 \)).

In fact, in that subgroup of patients, not only was there no net clinical benefit, there was actually net clinical harm. For that reason the FDA gave it a black box warning to avoid prasugrel in that group.

Then, they found two other subgroups. They found a group that was greater than or equal to 75 years of age or those with less than—I believe it was—60 kg.

DR. BERGER: Yes, 60 kg.

DR. FERDINAND: Yes, 60 kg.

DR. BERGER: In both of those groups there was no apparent benefit and the bleeding risk was elevated. For that reason the FDA came out and suggested that prasugrel is generally not recommended in patients \( \geq 75 \) years of age or body weight less than 60 kg.

DR. FERDINAND: You know, as we talk about the new agents, and I had taken the conversation back to aspirin and I’m going to stick with aspirin for a second, I can clearly remember there was a time when we thought at least 325 mg on a daily basis even after the first initial dose and some clinicians were using a higher dose. Within the data that were looked at, for instance, North American vs European data with ticagrelor, it appears that maybe the 325 mg dose is no longer the correct dose. Does anyone want to comment on that?

DR. LAVIE: I think that when you review most of the aspirin data from stable coronary disease and other syndromes, the weight of evidence is that the lower dose, doses of 100 mg and below, which is really the 81 mg in the United States, is providing equal or possibly a trend toward even greater efficacy than the higher dose. I think the doses are probably more equal statistically, but the lower dose is associated with less bleeding, particularly gastrointestinal bleeding. So when you consider that there is no added benefit for the higher dose and there are just more complications, the dose of aspirin for preventive cardiology probably should be 81 mg in most patients.

Now saying that, if one disagrees with that and feels that they have to use 325 mg, I believe we’re splitting hairs between 81 mg and 325 mg. I personally agree with the 81 mg, but if one wants to use 325 mg, the problem is that you cannot then use ticagrelor with high aspirin dose. Ticagrelor is contraindicated with higher doses of aspirin because in the PLATO trial, higher doses of aspirin were not associated with benefit and actually, were associated with a trend toward worse outcomes with ticagrelor compared to clopidogrel.
I do not think that anyone has given an adequate mechanism for this decreased effectiveness, but clearly ticagrelor demonstrated overall effectiveness in the whole trial. Now, realize in the entire PLATO trial only a very small number received the highest doses of aspirin, above 300 mg, and that was probably mostly people in the United States and in North America. In the United States, North America, and the entire trial, there appeared to be worse outcomes when combining ticagrelor with higher doses of aspirin compared with clopidogrel and high dose aspirin, whereas there was marked benefit compared to clopidogrel with aspirin doses of 100 mg or less.

I personally think whether one is prescribing ticagrelor or not, even if one is prescribing clopidogrel, if you go back to the old Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, the CURE data suggested that the lower doses of aspirin when combined with clopidogrel were just as good, but the higher doses of aspirin were associated with more bleeding. In fact, the higher doses of aspirin in the CURE trial were associated with more bleeding than with low dose aspirin combined with clopidogrel. High dose aspirin alone had more bleeding than low dose aspirin combined with clopidogrel (3.67% vs 2.97% respectively).

So even if we combined aspirin with clopidogrel, I think that we should be using the 81 mg, but this lower dose is required if one decides to prescribe ticagrelor.

DR. FERDINAND: Dr. Lavie, you know that’s a very clear analysis that you’ve given. I looked at the CURE data when we were preparing for this conversation and there was twice the rate of bleeding with the doses above 200 mg, 3.67% vs 1.86% in those taking less than 100 mg. It may not only be a question of efficacy but it also is a question of safety.

Dr. Foody, sometimes we hear of physicians who like to use the non-enteric coated aspirin acutely but then long-term feel that there is some benefit. Is there a benefit in enteric coated aspirin or is this somewhat of an old wives’ tale?

DR. FOODY: It could be an old wives’ tale, too. In general, particularly at these low doses, there doesn’t seem to be a particular difference in outcomes. Some have argued that, in the setting of ACS you do not want to use enteric coated, but that tends to be only anecdotal. I think in the current era of using dual antiplatelet approaches in patients with low-dose aspirin it probably doesn’t matter either way.

"Dual antiplatelet therapy clearly improves both the short- and long-term (up to one year) prognosis of patients who are both conservatively or medically managed as well as patients undergoing revascularization. Our key challenge is to ensure that for both inpatients and outpatients, we apply these strategies consistently...."

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DR. BERGER: So even if we combined aspirin with clopidogrel, I think that we should be using the 81 mg, but this lower dose is required if one decides to prescribe ticagrelor.

DR. FERDINAND: Before we go back into some of the nuances of the anti-platelet therapy, specifically as it relates to the cytochrome P450 2C19, I’m not going to go into that right now but we’re going to get there. I wanted to talk about initial conservative vs invasive strategies that have been updated in the guidelines. They actually suggest with a Class I level of evidence B indication for invasive strategy. Early invasive strategy appears to give more benefit. Do you think that’s true? If a clinician is in a community hospital, and as we know, there are still a large number of community hospitals that don’t have the availability of interventional cardiology, are they doing something that’s harmful to a person that presents with unstable angina or NSTEMI? We’re not talking about direct percutaneous coronary intervention (PCI) for STEMI here.

DR. BERGER: When you look at the data in totality, you see that there is a significant benefit for a more invasive approach immediately, but as a practitioner I think it’s pretty interesting that you really need to look at the cumulative amount of data to show such a benefit. There have been few adequately powered studies that demonstrated a greater benefit for an invasive approach very early on vs a more delayed approach.

Personally, when I round in the coronary care unit, we are always looking at the benefit and risk of the person coming in with the ACS. Obviously we’re not talking about STEMI; we’re talking about an NSTEMI or unstable angina. We look at the individual’s risk profile and try to determine if the benefit is greater in individuals at higher risk. There have been some data to suggest that subjects at lower risk (e.g. without troponin elevation, lower risk score) may not get as much benefit.

I think it’s about the risk of the individual. I think that in somebody that’s
high risk, a more invasive approach is probably better, but I don’t think it is wrong to be more conservative as long as the patient and medical professional talk about this risk and benefit.

DR. FERDINAND: Dr. Berger, I think based on what the guidelines say, you’re right on, because reviewing it, there’s a Class IIa level of evidence B that says in patients not at high risk, a delayed invasive approach is reasonable. I would guess those doctors who are in community hospitals where certainly they can do electrocardiograms and get troponin and creatinine kinase MB levels and assess patients, they shouldn’t feel that they’re doing harm to their patients if it’s an unstable angina and they’re not at high risk. Is that what you’re basically saying?

DR. BERGER: Yes.

DR. FOODY: Keith, to echo that, I think we want to be really clear when we talk about the term early invasive strategy. We’re still talking NSTEMI and unstable angina at 24- to 48-hours. I think that’s why the guidelines have pulled back on that “very early” invasive strategy in non-ST-segment-elevation ACS (NSTEACS) patients no matter what.

So I think particularly now in the era of dual antiplatelet therapy we have a little bit of room now to move in this area as well.

DR. FERDINAND: Before we move on to the activity level of the antiplatelet responses related to genetic and functional testing, let me just note again that the guidelines respectfully reflect exactly what you guys are saying. In fact, they give a Class III no benefit for an early invasive strategy if the patient has a lot of serious comorbid conditions which are extensive and life-threatening, such as liver or pulmonary failure, cancer, etc, or if the patient has already said that they will not consent to revascularization. There’s no need to do a diagnostic angiogram in those particular situations. We have to be very careful that just because we can do a procedure, doesn’t mean it needs to be done in all patients.

DR. BERGER: I just want to make one point regarding the use of antiplatelet strategy in these different populations. This is actually where the guidelines do make an important distinction.

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–Jeffrey S. Berger, MD, MS

If a subject who has an ACS that is an NSTEMI or unstable angina and they undergo PCI, so they have an invasive approach, then the guidelines suggest you can use clopidogrel, ticagrelor, or prasugrel. Importantly, the guidelines state that if a subject does not undergo an invasive approach then you can only use clopidogrel or ticagrelor. In that case, prasugrel is not indicated. There was a trial called Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS).

It basically showed that in medically treated ACS, prasugrel was not effective at decreasing cardiovascular events. That’s a very important distinction because in TRITON, those patients were not included. Therefore, prasugrel should not be used in medically treated ACS patients.

DR. FERDINAND: That’s interesting. I always like to point out when we have Class III evidence because sometimes we get so hung up on discussing with our colleagues and telling our referral agents, referring physicians, and clinicians what they should be doing, let’s talk about what should not happen.

Dipyridamole, which has been around for a long time and many of us thought it should always be used with aspirin as an antiplatelet agent, has Class III evidence in the new guidelines and is not recommended as an antiplatelet therapy post-unstable angina and NSTEMI and has not been shown to be effective.

Let’s move on to the idea of genetic testing and platelet function testing. I’ve done platelet function testing in terms of clinical studies. We don’t usually do it in usual clinical care. I know all of you are at major medical centers. What’s going on at your center and what do you think the evidence is for platelet function testing or genetic testing?

DR. LAVIE: This testing is not being routinely used at my place. I think that the guidelines are suggesting that one does not need to use this assessment in clinical practice. Although such testing may be theoretically helpful, the trial evidence has not panned out to either suggest that you can make better decisions using either the genetic testing or the platelet results.

DR. FERDINAND: So while they may have benefit, it remains selective and limited in terms of its use?

DR. LAVIE: I would think very limited from a clinical standpoint. Certainly, clinicians would not be wrong based on the guidelines to never be doing that testing in current practice.
DR. FERDINAND: So it should be taken in the context of your center and the patient as you see fit to do. Drs. Foody and Berger, just for practical reasons, we understand that these are generalizations and don’t necessarily fit each patient, but platelet function testing or genetic testing?

DR. FOODY: Currently I would not recommend routine testing of platelet function. The real question is, does platelet function and managing antiplatelets accordingly improve outcomes? Further, if you were to detect a difference and change a strategy, would you improve outcomes? The studies to date have not demonstrated that by having this kind of information, even if you were to dose accordingly, you would change outcomes. In general we are not testing platelet function in all but in very rare instances of stent thrombosis or, in very high-risk individuals.

DR. BERGER: Right. I would agree with that, with actually both of those comments. I think platelet activity testing has very limited use right now. I think that there are certain high risk groups—for example, patients who have had events despite being on the medicine and they’re known to be taking the medicine. I think that’s a reasonable group to consider it in, but I think you have to be very careful because as of today there are no data that making a decision based on any of these results would improve outcomes.

DR. FERDINAND: You know, I think all of you are exactly right. The new guidelines suggest that there may be some benefit, but either strategy may work—using them or not using them—and although there’s a level of evidence B recommendation for platelet function testing, it certainly doesn’t mean that someone is outside of appropriate clinical practice if they don’t use either genotype assessment or platelet function testing on a regular basis.

I think we have a lot to learn. I think that we have to be very careful and I think that we are sort of in the infancy of this field.

DR. FERDINAND: You know, Dr. Berger, your statements are very clear. I take them to heart. I would think that as we continue to use platelet function testing in clinical research that we may dampen our enthusiasm looking at the timing, the status of the patient, and so many other variables other than just doing a test.

DR. LAVIE: Keith, saying that, I would agree that we do not need to be doing it in clinical practice, but I do think that it's likely if you just make a comparison of clopidogrel vs ticagrelor, this may explain the reason why ticagrelor appears to be superior.

I think if you just compare ticagrelor to clopidogrel, one of the reasons why ticagrelor could be superior to clopidogrel is that it's faster, it's more potent, meaning greater inhibition of platelet aggregation (IPA), and the effect is less variable. For example, if clopidogrel gets a 40% IPA at 2 hours and ticagrelor is getting a 40% IPA at 30 minutes, that could partly explain ticagrelor's superior clinical efficacy. I believe it typically has close to a 90% IPA after

Clinical Implications

- Dual antiplatelet therapy improves both short- and long-term prognosis for UA/NSTEMI patients who are medically managed or undergoing PCI.
- All UA/NSTEMI patients should be considered for dual antiplatelet therapy.
- The selection and use of a specific dual antiplatelet therapy is at the discretion of the prescriber; the medical history of the individual should be considered.
2 hours and in steady state and 90% of the patients have an IPA of greater than 70% on ticagrelor which may explain why ticagrelor is a more potent agent and more effective agent than clopidogrel and also could explain why it has slightly more major bleeding than clopidogrel, at least among patients who do not get treated with bypass surgery.

**DR. FERDINAND:** I’m going to wrap up this part of the conversation and say that I always find it informative and we like talking to each other because we learn from each other, although I recognize for the purposes of the roundtable discussion some of this on platelet and genotype testing may not actually meet the criteria for the final document. I find it very enlightening and individual variability and responses to clopidogrel is noted in the guidelines so there may be, in the future, some use of genetic testing and some use for antiplatelet testing or functional testing. At the present time, if a clinician is not doing that they’re certainly not outside the guidelines.

The high point that I wanted to make is when we review the guidelines and we get through the differences and the nuances in antiplatelet therapy, etc., and intervention, invasive vs noninvasive, sometimes we don’t get to the end. The end was a new section on quality care and outcomes. It mentioned the need for the development of regional systems for unstable angina and NSTEMI. It mentioned the use of standardization of quality of care and data registries designed to track and measure outcomes, complication, and adherence. Certain things such as the National Cardiovascular Data Registry (NCDR), the action registry, get with the guidelines. They’re all listed there.

I think it’s important that as we read guidelines and we nuance which agent vs another, invasive vs noninvasive, the timing of various interventions, that we don’t forget that many of us are practicing not evidence-based medicine, not guideline-based medicine, but how we feel on a certain day, and we probably should pay more attention to these large broad quality improvement initiatives that sometimes we think are intrusive to our clinical care but may actually help the public.

If anyone wants to give a one-minute highlight or take-home, something that we may want to quote you directly on, feel free. Then we’ll close.

**DR. LAVIE:** I think one thing that we did not discuss when we were discussing prasugrel was that even before when it was just prasugrel and clopidogrel, I did not use a lot of prasugrel. But besides only being able to be used in combination with PCI and not in patients treated medically—we commented on the group that did very poorly, those who had a transient ischemic attack or prior stroke where it’s contraindicated and that if patients are over 75 or under 60 kg, they also do not do any better with prasugrel than clopidogrel—the one group that seemed to at least trend a bit better on prasugrel compared with clopidogrel was the diabetic subgroup of patients.

Of the three agents, I think currently ticagrelor is the one with the best evidence, at least based on the PLATO trial, and the only one that the FDA has said is superior to clopidogrel for reducing cardiovascular death. The number needed to treat to do so was only about 90 patients to reduce one more cardiovascular death (and only 54 patients to reduce one more cardiovascular death, MI, or stroke combined), which is impressive overall efficacy.

**DR. FERDINAND:** That’s where the registries come into play, because they tell us what we’re doing regardless of how we think we’re doing.

**DR. FOODY:** Absolutely.

**DR. FERDINAND:** Dr. Berger, you have the last comment.

**DR. BERGER:** Sure. I would just make one final comment basically echoing what Dr. Foody said, which is that we have many excellent therapies. I really think we need to pay very careful attention to adherence. I think that regardless of the strategy a physician chooses, we have excellent drugs, but we need to stress the importance to our patients of actually taking these disease modifying therapies. I think that we, as a profession, need to do a better job at making sure patients understand how important it is to be taking their therapies.

**DR. FERDINAND:** Well, that ends our roundtable discussion on unstable angina and NSTEMI. We’ll have a second discussion on the ACCF/AHA guidelines on STEMI and the implications, again, for antiplatelet therapy. I’d like to thank the panel members, Drs. Berger, Foody, and Lavie for their input.

Faculty disclosures: Keith C. Ferdinand, MD is a speaker and consultant for AstraZeneca, and a consultant for Sanofi, Forest, and Daiichi Sankyo. Jeffrey Berger, MD, MS serves on an executive committee for a trial sponsored by AstraZeneca, studying ticagrelor in peripheral artery disease. JoAnne Foody, MD is a consultant for Merck, Pfizer, Jansen, and Zeneca, studying ticagrelor in peripheral artery disease.
BMS, and Sanofi. Carl Lavie, MD is a consultant and speaker for AstraZeneca, GlaxoSmithKline, Abbott, and Amarin.

REFERENCES


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