expert roundtable »

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

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Discussants: **Carl J. Lavie, MD**[2]**; JoAnne M. Foody, MD**[3]**; Jeffrey S. Berger, MD, MS**[4]

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

The discussion focused primarily on: (1) The recent changes to the guidelines for 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, and evidence from recent clinical trials, on antiplatelet therapy and the use of antiplatelet agents in practice; and (3) the challenges surrounding implementation and maintenance of evidence-based therapy. (*Med Roundtable Cardiovasc Ed*. 2014;3(4):242–250)

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CAPRIE, CHARISMA, CURE, CURRENT-OASIS 7, CRUSADE, GWTG-CAD, PLATO, TRILOGY ACS,TRITON-TIMI 38

COMPOUNDS DISCUSSED:
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DR. FERDINAND: This is the second part of a two-part roundtable discussion series on the updated American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines on the management of ST-segment-elevation myocardial infarction (STEMI).[1] We're going to focus mainly on the implications for antiplatelet therapy. As you know, acute coronary syndromes (ACS) encompass a constellation of symptoms, including those related to unstable angina and non-ST-segment-elevation myocardial infarction (NSTEMI). For the purposes of this roundtable we're going to be discussing specifically STEMI.

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, Louisiana.

DR. FOODY: This is JoAnne M. Foody, MD. I'm an associate professor at Harvard Medical School and I'm director of the cardiovascular wellness center at Brigham and Women's Hospital in Boston, Massachusetts.

DR. BERGER: I'm Jeffrey Berger. I'm an assistant professor of medicine and surgery at NYU School of Medicine and director of cardiovascular thrombosis.

DR. FERDINAND: In STEMI, the infarct artery is almost always completely

occluded and the patients have more severe symptoms than they do with NSTEMI in which the artery is only partially occluded. Unstable angina and NSTEMI have certain clinical presentations, but with STEMI the complete occlusion means that it's urgent that the artery is recanalized as soon as possible and direct coronary intervention is considered the appropriate care.

Specifically as it relates to antiplatelet therapy, dual antiplatelet therapy both during and after reperfusion is recommended. We have, along with clopidogrel, newly available $P2Y_{12}$ inhibitors for patients undergoing primary percutaneous intervention. Only clopidogrel and prasugrel are recommended after fibrinolytic therapy and we will discuss why that may be—why ticagrelor is not indicated in that particular situation, whether it's something nuanced related to the drug itself or just to the clinical evidence on which the recommendations are based.

Let's go with some questions. The first one is similar to what we had when we discussed unstable angina and NSTEMI. What's the most significant change you see in the updated guidelines?

DR. LAVIE: Well, I think the most significant change is similar to what we discussed in the NSTEMI guidelines, which is the addition of ticagrelor, the newest oral antiplatelet agent that is indicated for the treatment of patients with STEMI, NSTEMI, as well as unstable angina, regardless of whether the patient is managed medically or with intervention/revascularization. If there's not the availability of care and immediate percutaneous intervention then they obviously need thrombolytic therapy, and at present, these patients would probably not get ticagrelor.

The reason is two-fold. One is that it was an exclusion criterion in the Platelet Inhibition and Patient Outcomes (PLATO) trial (no fibrinolytic therapy within 24 hours of randomization), which was probably due to concern that ticagrelor was more potent and that combining such a potent antiplatelet agent with fibrinolytic therapy might increase the risk of bleeding.

I think the initial thought was that ticagrelor was going to be associated with a lot more major bleeding compared to clopidogrel, and it was associated with a little bit more major bleeding, at least in those who were not managed with bypass.[2] There still was not very much difference between clopidogrel and ticagrelor, so maybe if they were doing the trial over again, maybe they would have allowed the thrombolytic therapy, but I think that right now since it was not used in the PLATO trial, the fact that it is a lot more potent and is at least associated with a modest increase in major bleeding (at least in those who did not receive bypass surgery), we probably should only use ticagrelor in the STEMI patient who is treated with percutaneous intervention.

"I would like to say there are many patients who get treated with clopidogrel. This applies to the PLATO trial as well. Since 46% of patients in the PLATO trial had already received clopidogrel administered in-hospital before getting randomized,[2] a clinician can still safely load with ticagrelor 180 mg followed by 90 mg twice daily."

~Carl J. Lavie, MD

DR. FERDINAND: Dr. Berger, do you agree that the guidelines seem to tease out this idea that with thrombolytic therapy ticagrelor should not be utilized, and it's not even listed as an alternative.

DR. FOODY: I'm sorry, just one more comment though, to clarify. The guidelines are very specific that with fibrinolytic therapy, only clopidogrel is recommended. Prasugrel can be used in the setting of percutaneous coronary intervention (PCI) following fibrinolytic therapy. There's a little bit of a nuance there.

DR. FERDINAND: Why don't you say it again, Dr. Foody? State it very clearly for the recording. What's the difference?

DR. FOODY: When using fibrinolytic therapy only, the only drug that's been studied in that setting is clopidogrel in conjunction with aspirin and heparin. In individuals who go on to PCI after fibrinolytic therapy, either for bailout or recurrent symptoms, both clopidogrel and prasugrel have been studied. In those hospitals where fibrinolytic therapy may be the primary reperfusion strategy, those individuals should be using per these guidelines, clopidogrel as their dual antiplatelet of choice.

DR. BERGER: Right. I think that is an excellent point. I think there were very few patients in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) who actually had previous fibrinolytic therapy before they underwent their PCI and STEMI. I think that in a patient who received thrombolytic therapy for reperfusion therapy, I would use aspirin and clopidogrel being my second antiplatelet drug. I would not use one of the more potent drugs for fear of just increasing the risk of bleeding too much.

DR. FERDINAND: Now, you're in New York City. I visited Manhattan many times and I am always impressed with how many people they have packed in such a small area. Do you ever have a person that needs to have fibrinolytic therapy vs direct PCI?

DR. BERGER: We do. I round in the coronary care unit at Bellevue Hospital. It is the flagship hospital of the New York City Health and Hospitals Corporation, which is a composite of many hospitals surrounding the city. We get a lot of patients who come in with a STEMI at one of these local hospitals. Depending upon how long it would take for them to be transferred to our hospital, many of them will get pharmacologic reperfusion if it will just take too long to transfer and we would not have a fast enough door-to-balloon time. So I actually see a handful of patients who undergo thrombolytic therapy for one reason or another.

DR. FERDINAND: I'm really surprised because you're talking about an island that's only 26 miles and it has hospitals, it seems to me, every ten blocks. That does happen?

DR. BERGER: Yes, it definitely happens. In fact, the population of patients we see is quite amazing. For one reason or another, patients could delay coming into the hospital hours or days following their symptom onset.

DR. FERDINAND: So some of it may be what we call health illiteracy and some of it may be patient preference. There are a lot of cultural barriers, especially in new immigrants and some ethnic minorities in terms of going to the hospital. That's the last thing you do, go to the hospital, so they may have delayed their presentation for almost a day.

DR. BERGER: Right.

DR. FERDINAND: Now, one of the things that I did notice in the new guidelines, they are a little sensitive about the aspirin dosage. We had talked about this in the unstable angina section, but even with primary PCI there's still a question of whether or not 81 mg is the preferred dose. They give it a Class IIa level of evidence B, suggesting that you don't have to use the 81 mg. Why do you think they nuanced that a little bit?

DR. BERGER: Right. I think this is very, very important. I think it's important to actually mention there's a randomized trial called CURRENT-OASIS 7 which randomized patients with an ACS to low- or high-dose aspirin after their initial dose. Every patient got a loading dose of aspirin and then they got 30 days of either 81 mg vs 325 mg. As we all know, there was no added benefit for aspirin 325 mg vs 81 mg.[3] Moreover, there was no benefit of using the higher aspirin dose even in those patients who underwent PCI. There was, however, significantly more minor bleeding, which was not so minor—it was gastrointestinal bleeding—in the group that got 325 mg.[3] I think because of that trial, that's why the guidelines came out and gave a stronger recommendation for aspirin 81 mg than we have seen previously.

"From my perspective in thinking about the STEMI patients, I think the most important thing is that time is of the essence, that there need to be systematic approaches in whatever hospital system one might exist, with respect to giving early therapy, whether it be fibrinolytic or PCI-based strategy in conjunction with dual antiplatelets. The key is that that's done in a systematic way that ensures that patients get evidence-based care."

~JoAnne M. Foody, MD

DR. LAVIE: I do not think there are that many trials in ACS and STEMI that have used 81 mg of aspirin. Most of the stent trials and the percutaneous transluminal coronary angioplasty (PTCA) trials for 20 years have used 325 mg aspirin in the United States. Not that 325 mg aspirin was shown to be better than 81 mg, nevertheless, it was just the standard dose used in all the initial stent trials.

So US cardiologists, and in particular US interventional cardiologists, have primarily used 325 mg of aspirin. This explains why for the PLATO trial, you see that in the whole trial, which was almost 90% from non-North American and non-United States, these patients generally were treated with less than 100 mg of aspirin. However, in North America and the United States, it was something like 54% of patients who received doses above 300 mg of aspirin.[4]

I think that right now there is recognition that many patients are still getting 325 mg of aspirin in the United States. There are probably very little data, with the OASIS trial being one that shows the efficacy of 81 mg, but there are very little data on 81 mg and a lot more data, particularly the older data, where patients were treated with 325 mg of aspirin.

DR. FERDINAND: On the other hand, based on the updated guidelines and the 75–100 mg labeling for ticagrelor, that is the recommended maintenance dose, the 81 mg.

DR. FOODY: We have seen a change in paradigm as we have moved to more aggressive dual antiplatelet therapy with loading doses of these other agents. As much as OASIS randomized high (300–325 mg) vs low (75–100 mg) dose aspirin, we appreciate that in general the recommended maintenance dose of aspirin is 81 mg. The current guidelines come down pretty clear as to using 81 mg of aspirin, again, though, with the assumption that everyone is a candidate for

dual antiplatelet therapy unless there are major contraindications.

DR. FERDINAND: Very good. You know, I've practiced medicine a long time and Dr. Lavie, I know you have, too. I can remember when we didn't do a lot of loading with clopidogrel when it was first released, but looking at the adjunctive antithrombotic therapy in the new STEMI guidelines, they specifically give doses. Clopidogrel, they say 600 mg as early as possible or at the time of PCI; prasugrel, 60 mg, same thing, as early as possible or at the time; ticagrelor, 180 mg.

It appears now that the old idea of whether or not you need to load or not has been answered. Dr. Lavie?

DR. LAVIE: Yes I would agree. Even though the United States Food and Drug Administration (FDA) approved, at least in my understanding, the loading dose of clopidogrel as 300 mg, I think that most clinicians have been routinely using 600 mg load for a decade now. So if you are going to be using clopidogrel you should probably use a 600 mg loading dose, generally followed by 75 mg once daily.

I would like to say there are many patients who get treated with clopidogrel. This applies to the PLATO trial as well. Since 46% of patients in the PLATO trial had already received clopidogrel administered in-hospital before getting randomized,[2] a clinician can still safely load with ticagrelor 180 mg followed by 90 mg twice daily.

DR. BERGER: I actually think that is an extremely important point because in TRITON they excluded patients who were on baseline clopidogrel. It's less of a real world trial. There are no data that if somebody's on clopidogrel that prasugrel beats clopidogrel. The trial randomized patients who did not receive clopidogrel early on in the emergency department. I think that's an important distinction between the trials.

DR. FERDINAND: Let me just make a note for the purposes of our roundtable. The FDA labeling for clopidogrel specifically still mentions 300 mg. The alternative of 600 mg is in the guidelines, as early as possible or at the time of PCI with a Class I evidence B recommendation.

DR. FOODY: Keith, one more thing. Just to be clear, we talked about the medically managed patients in NSTEMI, but similarly in STEMI, in medically managed STEMI only ticagrelor and clopidogrel have been studied, but prasugrel was not looked at.

DR. LAVIE: Yes, and Dr. Foody said this in the NSTEMI discussion as well. Prasugrel only has data and is only approved in combination with PCI, since the TRITON study was all PCI patients. Then the following study was the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY-ACS) trial, and it did not show any benefit of prasugrel vs clopidogrel in medically managed patients. Therefore, I would totally agree that the only utilization for prasugrel should be in patients who are managed with PCI, with the only advantage compared with ticagrelor is once daily chronic dosing compared with twice daily with ticagrelor, whereas unlike prasugrel, ticagrelor is not contra indicated in patients with prior transient ischemic attack (TIA) or stroke and only ticagrelor has data for superiority over clopidogrel for cardiovascular and all-cause mortality (the official FDA indication includes the superior wording for cardiovascular death but not for all-cause mortality).

> ***"I think following an ACS we have shown that dual antiplatelet therapy is effective at decreasing cardiovascular events for 12 months. That has been shown in medically treated ACS as well as following stent implanted ACS."***
>
> *~Jeffrey S. Berger, MD*

DR. BERGER: One minor thing. We were talking about the aspirin doses earlier and maybe I missed this, but clearly, in ACS the loading dose of aspirin can still be 325 mg. Even if one is using ticagrelor, the maintenance dose needs to be less than 100 mg per day and typically the 81 mg per day in the United States. The loading dose either in the urgent care clinic, in the medical office, or the emergency room is still 162 mg to 325 mg of aspirin.

DR. FERDINAND: You're absolutely correct. In the guidelines they give 162 mg to 325 mg, but clearly our whole discussion on the 81 mg as a preferred maintenance dose was specifically with ticagrelor but with other agents if desired. That was only a Class IIa. It's a Class Ib for 162 mg to 325 mg loading dose for all.

Let's go to maintenance doses and duration of therapy. Clopidogrel has been around a long time. It's generic and readily available. It's at 75 mg. We have prasugrel, 10 mg or 5 mg and ticagrelor, 90 mg (twice a day). The first question is, does duration of therapy make a difference, i.e. 12 months either for a drug-eluting stent or bare metal stent? Is there a difference for timing?

DR. LAVIE: I would say no.

DR. BERGER: Right, I agree. I think following an ACS we have shown that dual antiplatelet therapy is effective at decreasing cardiovascular events for 12 months. That has been shown in medically treated ACS as well as following stent implanted ACS. Don't

forget that in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, 20% of the patients underwent a stent implantation of which almost all were bare metal stents.[5] It was shown that in that small subgroup there was a very significant benefit in decreasing cardiovascular events. I think we have excellent data showing that whether it is a bare metal stent or a drug-eluting stent, that two drugs compared to one is significantly better for a year's duration.

DR. LAVIE: To add to that, Keith, I think that most people would have thought—and we have been practicing it—if a patient could not continue dual antiplatelet therapy for whatever reason, this would be a reason to use a bare metal stent, but a paper that just came out in the last month in *JAMA* suggested that bare metal stents and drug-eluting stents had about the same risk when dual antiplatelet therapy was discontinued.[6]

DR. FERDINAND: Dr. Foody, do you agree that the guidelines don't seem to make a difference for continued dual antiplatelet therapy whether it's a drug-eluting stent or a bare metal stent? Both had the same level.

DR. FOODY: All things being equal and as long as patients can tolerate dual antiplatelet therapy, we have strong evidence that at least a year provides better benefit. There are also some other nuances. In the setting of primary PCI ticagrelor or prasugrel are now given at presentation. There is also a tendency, although not supported in the guidelines, that when clopidogrel is chosen some may use a 600 mg bolus, followed by 150 mg daily and moving then to 75 mg daily after a week.

DR. FERDINAND: Recognizing that may be preferred, the guidelines are pretty silent on that one week of a higher dose.

DR. FOODY: Exactly.

DR. FERDINAND: Well, let's talk about personal preference. That may not be initially listed in the guidelines but perhaps in the future would be. Does anyone think we need a higher dose of clopidogrel for that first week?

DR. BERGER: I think that is actually based on OASIS 7 as well. OASIS 7 was a two-by-two comparison trial. We were just talking about the aspirin dose, but they also looked at an initial loading dose of clopidogrel of 600 mg and a week of 75 mg twice a day of clopidogrel vs a 300 mg loading dose and 75 mg a day.[3]

Now, importantly, and the reason why the guidelines did not adopt it is because it was a negative trial. In the overall population there was no significant benefit. However, among patients who underwent stent implantation there was a significant benefit in decreasing cardiovascular events and a significant decrease in stent thrombosis with the higher dose clopidogrel. I think because of that, many in the interventional field believe that using this higher loading dose and using this double dose clopidogrel is more effective for the first week.

DR. LAVIE: The question is, was it the higher loading dose or was it the higher one-week maintenance dose? I do not think that the trial separated these factors, did it, Dr. Berger?

DR. BERGER: No, it did not.

DR. FERDINAND: So recognizing that the guidelines are pretty much silent on that higher dose of clopidogrel, do you think that because there is the potential for benefit it's reasonable, recognizing that the guidelines don't explicitly note the twice a day clopidogrel?

DR. FOODY: This is not guideline-based. There are studies of small subgroups of patients. In higher risk patients undergoing PCI not on a prasugrel or ticagrelor strategy, a higher dose clopidogrel strategy may be beneficial. However, to emphasize, this is not supported by the guidelines.

DR. FERDINAND: So now the plot thickens. We go to a patient who has a drug-eluting stent with a STEMI. We're beyond one year with clopidogrel, prasugrel, or ticagrelor. The guidelines now have dropped it down to a IIb and a level of evidence C, so it's almost expert opinion, meaning you could do it if you want, but we don't really know. Should we go beyond one year with dual antiplatelet therapy after a drug-eluting stent?

DR. LAVIE: I personally think that we would need a trial to answer this question. There is some evidence from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial showing that patients with prior thrombo embolic disease still had between a 15% and 20% benefit from continued clopidogrel.[7] We have all seen patients who have gone off their antiplatelet therapy past a year and soon afterward had an ACS.

Since the guidelines say we have to go one year with dual anti platelet therapy, it is not wrong to stop dual antiplatelet therapy at one year and then just continue aspirin alone. However, in the patient who has very severe disease, who has had multiple procedures or, for example, the patient who had the "widow maker" disease of proximal left anterior descending artery (LAD) or who had sudden death with their ACS, those would all be situations where I would be more favorable to continuing dual antiplatelet therapy indefinitely.

Now, when I do so, I would personally prescribe clopidogrel for my long-term dual antiplatelet therapy. At least there are some long-term studies with clopidogrel, whereas there are

no long-term studies with prasugrel or ticagrelor.

DR. FERDINAND: Didn't the Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial use a subset of people who stayed on it indefinitely who have peripheral vascular disease and diffuse vascular disease and they still had benefit?

DR. BERGER: CAPRIE was a very, very important trial. It compared clopidogrel monotherapy vs aspirin monotherapy and it showed a small but significant 9% reduction in the risk of cardiovascular events with clopidogrel.[8] As you point out, it was driven mostly by a 24% reduction in patients with peripheral artery disease.[8] That was using monotherapy, so that was not two drugs.

DR. FERDINAND: That doesn't mean it's without question.

DR. BERGER: Right. Nonetheless, I agree with Dr. Lavie. I think that there are some data, although it is a subgroup analysis of a negative trial, but there are some data that patients with established cardiovascular disease, that aspirin and clopidogrel may be better than aspirin alone. I think that we are really entering an area where there is a scarcity of data. There are a lot of ongoing important clinical trials in this area that will shed a lot of light on what to do with some of these patients, but I think we have to also remember the bleeding. I think that bleeding is not a benign event. Patients who bleed do very bad in the short- and long-term. I think we really need large clinical trials which are ongoing to sort of help us figure out who should be on two drugs vs one following a year after an ACS.

DR. FERDINAND: Dr. Foody, let's get your take on long-term dual antiplatelet therapy after STEMI with a drug-eluting stent or if you want to just make a general comment about long-term dual antiplatelet care.

DR. FOODY: Keith, the way I approach this is on an individual patient basis. I think we have suggestions from trials that there are certain groups of individuals, those with significant burden of atherosclerotic peripheral vascular disease who may benefit, but the studies are really lacking in post PCI patients long-term. I think the guidelines are relatively silent on this. I think, again, this goes back to a discussion about risk—risk of subsequent events relative to bleeding risk. Like most things, this is an individual decision on a case-by-case basis.

DR. FERDINAND: So we're in a real grey area here.

DR. FOODY: Right.

DR. FERDINAND: When we discussed the NSTEMI I mentioned that we always discuss what should be done, but I also like to look at harm because it's sometimes underdiscussed and it becomes a blind spot for a clinician because no one has brought it up. When I looked at the new guidelines specifically as they relate to patients with STEMI in prior stroke or TIA they give a Class III harm with direct notation evidence level B for prasugrel. Why is that? Does anyone have any take on that?

DR. LAVIE: Yes, Dr. Berger discussed that, Keith, when we were discussing the NSTEMI data, that in the patients who had previous TIA or stroke, in the TRITON trial they did considerably worse with the very high risk of fatal bleeding/hemorrhagic stroke if they received prasugrel, which led to prasugrel being contraindicated for TIA or stroke. This was not the case with ticagrelor in the PLATO trial, as these patients with prior TIA or stroke did better with ticagrelor than clopidogrel, with no more harm, similar to the benefit/harm noted in patients who did not have a previous TIA or stroke.

DR. FERDINAND: Okay. There is an excellent algorithm for reperfusion therapy with STEMI. We now know that there are still a lot of patients who will be seen at a local community hospital where direct PCI is not available. They suggest that if your door in/door out time is less than 30 minutes you still should transfer them to a primary PCI hospital. Drs. Berger, Foody, and Lavie, all of you are in major metropolitan areas. For a STEMI, do you see that there will be any reason for a small community hospital to hold on to that patient once they have diagnosed an ST-segment myocardial infarction?

DR. FOODY: Keith, I think it's difficult for us to imagine sitting in academic centers, but in fact, I think the last count was that 90% of hospitals in the United States do not have 24/7 PCI capable catheterization labs.[9] So it's surprising, as much as we talk about an invasive strategy, that there really are a very significant proportion of Americans who present to hospitals without traffic 90 minutes away from a center. Clearly, these are the recommendations. We would rather, certainly, if there were an approach that could get individuals to a catheterization lab within that timeframe, that's great, but even in a place like New York, where Dr. Berger is, traffic and other issues, transfers, may make that exceedingly difficult.

DR. FERDINAND: So in that particular case the algorithm clearly says to administer fibrinolytic therapy within 30 minutes if it's expected that you will not be able to get to a device within 120 minutes. Drs. Berger and Lavie, what do you think about that? What Dr. Foody seems to be saying is that although we've discussed at length the need for PCI in these patients and what medicines should be used, that especially in widespread geographic

areas and even sometimes within an urban center it may not be realistic to get that person to a device within less than 120 minutes and at that time fibrinolytic agents can be used with a Class I level of evidence B. You think the guidelines are reasonable at that point?

DR. LAVIE: I would think so Keith. We have a pretty sophisticated helicopter system with the referral hospitals in the region, but even then sometimes the helicopter may be out transporting another patient and sometimes the weather prevents the helicopter from flying. So there are definitely still needs for patients in the community hospitals to receive fibrinolytic therapy.

DR. FERDINAND: Dr. Berger?

DR. BERGER: I completely agree. I also think we have to remember that if you can administer fibrinolytic therapy very quickly the data are very good. It's just that once you sort of miss that very short window then clearly a PCI strategy is significantly better.

DR. FERDINAND: Very good. As we talked about with unstable angina and the NSTEMI, while it's important to talk about which drug and whether the person should get direct PCI or be transferred to an academic center or a major medical center for direct PCI, the thing that really plays a major component in how these patients live and die is medication adherence and timely follow-up by their healthcare team.

As I have practiced cardiology for many years, I've been more and more impressed that, while which medication and which device remains important, diet, physical activity, and compliance for secondary prevention is probably more important as a public health intervention and it's a challenge that we should never forget that we do a procedure, write a prescription, or send an electronic prescription to a local pharmacy and think that our job is completed.

My take home message is we should continue to try to look at the guidelines and the updated guidelines for direction but we can't forget that we're treating the patient and we're not just treating the lesion.

DR. FOODY: Keith, from my perspective in thinking about the STEMI patients, I think the most important thing is that time is of the essence, that there need to be systematic approaches in whatever hospital system one might exist, with respect to giving early therapy, whether it be fibrinolytic or PCI-based strategy in conjunction with dual antiplatelets. The key is that that's done in a systematic way that ensures that patients get evidence-based care.

DR. FERDINAND: Dr. Berger?

DR. BERGER: I would say that I think this is an area where there are a lot of data. We have a lot of very effective therapies and once again, I would agree with what you just said, which is that I think that there are so many different therapies and devices that are effective in this patient population and I think we just need to spend a little more time making sure that our patients take whichever therapy they are on. I think that we need to do a

Clinical Implications

- For patients receiving fibrinolytic therapy, clopidogrel is recommended as the secondary agent of choice following aspirin, given the slightly higher bleeding risk with the more potent $P2Y_{12}$ inhibitors, prasugrel and ticagrelor.
- The universal use of a loading dose of antiplatelet agent (including the newly added recommendation of ticagrelor 180 mg) administered as early as possible or at the time of primary PCI is recommended.
- Dual antiplatelet therapy for 12 months following stent implantation is recommended, regardless of the stent type (bare metal or drug eluting).
- Following a STEMI ACS, invasive therapy is the preferred therapy; however, geographical location and patient access to catheterization facilities may influence the treatment strategy available.
- In order to provide consistent, evidence-based care, physicians should refer to the details of the guidelines, however to ensure strategy success, discharge care must be maintained with patient education and referral to cardiac rehabilitation programs.

better job basically telling our patients why they are taking their therapy. They need to understand how important it is. I think that patients need to know that their health and their future really lie in their hands and that they can effectively have a very significant impact on their outcomes if they take their medicine and follow a really good healthy lifestyle.

DR. FERDINAND: Very good. Dr. Lavie, you have the last word. I'm going to ask for an addendum. Each of you can think about this. We didn't say anything about women. Is the evidence good for women? You can make the addendum to the NSTEMI or STEMI. Is there some nuance we should say about women? Dr. Lavie?

DR. LAVIE: I think obviously we should emphasize evidence-based therapy and we need to get patients on beta blockers. I personally think the evidence supports carvedilol. We should get patients on ACE inhibitors, especially if they have left ventricular systolic dysfunction or significant hypertension. Most diabetic patients should also receive an ACE inhibitor or angiotensin receptor blocker, and I think the evidence mostly supports the ACE inhibitor, ramipril. We not only have to get patients on statins but we need high, intense doses of statins (e.g. atorvastatin 80 mg/day). Obviously, we discussed mostly today dual antiplatelet therapy, and I think that in that regard maintenance therapy with 81 mg baby aspirin and with the more potent dual antiplatelet drug, particularly ticagrelor, in combination with baby aspirin appears to be preferable for the reduction of cardiovascular death.

The one thing we did not discuss in either the NSTEMI or the STEMI discussion today is that patients need to be routinely referred to and strongly encouraged to attend formal cardiac rehabilitation programs following acute coronary events.

DR. FERDINAND: I know this is an important consideration for which you have a high degree of interest and experience.

DR. LAVIE: That is evidence-based therapy proven to prolong survival, and there are national efforts being made by the AHA, the American College of Cardiology, and by other organizations to not only assure that patients are referred to cardiac rehabilitation programs but that we have a much greater number of patients actually attending and completing these programs.

DR. FERDINAND: So the utilization of cardiac rehabilitation is as of as much importance as the acute interventions in terms of the long-term outcomes and is often overlooked, unfortunately.

DR. LAVIE: Yes.

DR. FERDINAND: Anything specific on women? Dr. Foody?

DR. FOODY: Across a wide range of patients, including women and African-Americans and various racial and ethnic groups, these evidence-based strategies apply across all of them, but we know that they are inefficiently and incompletely applied. That's really where our challenge is, again, to ensure that we provide evidence-based therapy for all those who are likely to benefit.

For patients presenting with either STEMI or UA/NSTEMI, while the current ACCF/AHA guidelines recommend universal strategies that apply to both males and females, there are gender-specific considerations that must be taken into account with respect to female patients. At symptomatic presentation, female patients are often older, have comorbidities such as diabetes mellitus and hypertension and may present anginal-equivalent or atypical symptoms. As a result, STEMI is often underdiagnosed and the treatment is delayed. Analysis of the Get With the Guidelines-Coronary Artery Disease (GWTG-CAD) Registry results revealed that, in patients presenting with STEMI, in-hospital mortality was significantly higher in both younger (≤45 years) and older (>45 years) women compared to age-matched males (≤45 years cohort, 3.23% vs 1.17%; $P=0.03$ and >45 years cohort, 8.56% vs 5.34%; $P<0.0001$).[10] Gender differences in response to treatment strategies should also be noted. The Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) trial reported a higher risk of bleeding with antiplatelet therapy in females, risk which persisted even when adjusted for a number of confounding factors including age, weight, and blood pressure.[11]

DR. FERDINAND: This conversation has been very interesting for me—particularly as a follow up to our previous expert roundtable discussion on unstable angina and NSTEMI. I look forward to reading both of these and sharing with our colleagues. Of course, we have done our best to clearly delineate where we have given personal opinion outside of guidelines. I don't think that there's any conflict there as a result.

Thank you, Drs. Berger, Foody, and Lavie, for all of your remarks. I think our colleagues will find it interesting and informative. That closes our roundtable.

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, Janssen, BMS, and Sanofi. Carl Lavie, MD is a consultant

and speaker for AstraZeneca, GlaxoSmith-Kline, Abbott, and Amarin.

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