Assessing Short-Term Risk in Acute Coronary Syndrome: The Role of P2Y12 Inhibition

Moderated by: Ajay J. Kirtane, MD, SM
Discussants: Sorin J. Brener, MD; Neal S. Kleiman, MD

DR. KIRTANE: It’s great to have both Sorin J. Brener, from New York Presbyterian Brooklyn Methodist Hospital, and Neal S. Kleiman, from Houston Methodist DeBakey Heart and Vascular Center, here today, and let’s just launch right into it. Maybe we’ll start just generically, and either of you can jump in. Tell me a little bit about what you worry most about in terms of patients with acute coronary syndrome (ACS) when they come to the hospital, with respect to both potential recurrent ischemia and bleeding, and what strategies might you use to mitigate some of those risks.

DR. BRENER: Maybe I’ll start. I think there are three levels of concern. The first is that we provide systematic guideline-directed therapy to patients with bona fide ACS, and I think it’s important to make sure that they really have the disease we’re aiming at. That’s number one. Number two is that they receive the therapy in a timely fashion, and number three is—because the length of hospitalization is so short these days—that we have in place immediately upon admission the mechanisms that are needed to ensure smooth transition to home, which means the right medications, appointments for follow-up and cardiac rehab, and so on. That’s why I think we need to attack all of those right upon admission, because it’s not going to be a long one.

The following Expert Roundtable Discussion was held on January 16, 2019.

The discussion focused primarily on (1) the importance of a correct acute coronary syndrome (ACS) diagnosis; (2) the importance of guideline-directed therapy for ACS; (3) strategies used to mitigate risks of ischemia and bleeding in ACS patients; (4) the role of P2Y12 antagonists immediately after ACS; (5) the appropriate and timely use of P2Y12 antagonists in ACS patients undergoing percutaneous coronary intervention (PCI); (6) patient risk factors such as unstable angina, ST-elevation myocardial infarction and non-ST-elevation myocardial infarction that may influence the use of P2Y12 antagonists in ACS patients undergoing PCI; (7) duration of dual antiplatelet therapy; (8) the role of antiplatelet regimens in patients who require concurrent anticoagulation; (9) minimizing bleeding risks in patients who have planned surgery; and (10) the use of P2Y12 reactivity testing. [Published online ahead of print April 8, 2019.] (Med Roundtable Cardiovasc Ed. 2019 April 8.) ©2019 FoxP2Media, LLC

This roundtable was supported by AstraZeneca. The discussants (authors) developed the discussion and reviewed the transcript for important intellectual content and approved the final version for publication. The authors maintained control of the discussion and the resulting content of this article.

STUDIES DISCUSSED: CURE, CREDO, ACCOAST, PRECISE-DAPT, PEGASUS-TIMI 54, ONSET/OFFSET, PARIS, ACSEND, and PLATO

COMPOUNDS DISCUSSED: aspirin, ticagrelor, clopidogrel, warfarin, heparin, morphine, fentanyl, and cangrelor

DRUG CLASSES DISCUSSED: glycoprotein IIb/IIa inhibitors, P2Y12 inhibitors, oral anticoagulants, direct thrombin or factor X inhibitors, opiates, and benzodiazepines

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Published online: www.themedicalroundtable.com • Search for ID: CV38395
DR. KLEIMAN: Yes, Sorin. I think you've hit on some of the really critical points. Number one, we've got to make sure we have the correct diagnosis. We've all been asked to see lots of patients for ACS who are started on a variety of meds that carry some benefit in the right patients and some risks in both the right and wrong patients. We all see that often patients who don't have the syndrome end up receiving medication and assume all the risks without the benefit, so number one is you've got to make sure you're treating the right patient group.

Number two, as Sorin said, is to make sure that the transition home is smooth, that medications are given properly, that instructions are given properly, that medications aren't interrupted, and that patients understand what they have and what they've got to do about it.

DR. KIRTANE: I think those are great overall summaries, and maybe we'll go directly into the specifics of when patients show up in the hospital, because it's important to sort take a step back and address what we're trying to do globally and then, perhaps, focus on specific therapies themselves. Maybe we can start with prevention of ischemic events. We do know that patients are coming in with ACS, or even percutaneous coronary intervention (PCI)—which in some respects is an iatrogenic ACS, where you're causing plaque rupture by blowing up a balloon. I think that people have been sort of going away from the thought that we need some antiplatelet protection during both those events, ACS as well as PCI.

If you look at the rates, for instance, of preloading that occur in the United States, they are quite low, even though guidelines recommend preloading with antiplatelet agents (eg, P2Y12 inhibitors) prior to PCI in ACS patients.1

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DR. KLEIMAN: If you look at the rates, for instance, of preloading that occur in the United States, they are quite low, even though guidelines recommend preloading with antiplatelet agents (eg, P2Y12 inhibitors) prior to PCI in ACS patients.1 Even for elective PCI, there are many patients who come into the cath lab and are only getting loaded with antiplatelet agents such as P2Y12 inhibitors on the table or afterward. Why do you think that is? Is that what you both do in your practices? Maybe talk us through both those scenarios.

DR. KIRTANE: Sorin, what do you think, and what do you actually do?

DR. BRENER: Doing and thinking are different, because doing is depending on who does what. In New York, it's more open and everybody has opinions, and they act on them. In general, I think this is a case where the logic seems to be at odds with the data, so it would make perfect sense that preloading patients before PCI with or without ACS would be beneficial.

It's just that we haven't been able to muster the data, and I think that since the CREDO2 days, which is almost two decades ago, and the CURE3 days, which is two decades ago, we really haven't been able to generate good data to support it. That's the reason that I think you're right; there is a decline in the rate of preloading prior to arrival to the cath lab, which I think is unfortunate in the case of ACS. It may be a little less so in the case of stable coronary disease.

That being said, part of it has to do with the fact that the technique and technology have improved so much that for the practicing physician, there may be years elapsing between bad outcomes that are directly related to the lack of platelet inhibition at the time of PCI. I think that the memory is just not sufficiently strong for that. That's why I'm a big proponent of guidelines and of order sets. I use them extensively, and I don't allow people to get on the cardiac catheterization table without those order sets being followed appropriately, certainly for ACS patients.

DR. KIRTANE: I think it's very interesting. Back in the days of the IIb/IIIa inhibitors, there was such a heavy focus on platelet inhibition at the time of the PCI, and perhaps even ACS. But then with some of the negative trial data with the upstream use of IIb/IIIa inhibition, and even more focus on bleeding and the surgical issue that Neal rightly mentioned, I don't think there's as great an emphasis in the present day on platelet inhibition at the time of PCI and even ACS.

DR. KLEIMAN: I mean, look, the real truth is that it hasn't diminished in importance one iota, but it's no longer the topic that generates the most excitement at our meetings. That doesn't make it less important, but it makes it a little less prominent. It really should be second nature, but we all like to say that we're forward-looking and like to think about newer, more exciting technology, but this stuff's awfully important. Sometimes that's not easy to remember.
DR. KLEIMAN: That’s a great point. Let’s focus a little bit upon what can be done after ACS. What are you doing at your institutions with P2Y12 inhibitors? Virtually everyone is getting aspirin. Typically, people are getting loaded with 325 mg. It is important in light of some of the data in the last year to recognize that aspirin for people who actually have true coronary disease (eg, ACS, PCI, and secondary prevention scenarios) does have real benefits. But for P2Y12 inhibition, what are you giving, when are you giving it—before, during, and after PCI?

DR. BRENER: I think you are referring to the patients with ACS or to those with stable coronary disease?

DR. KIRTANE: ACS predominantly.

DR. BRENER: So, as I said, we’re using order sets that are very specific. All patients get aspirin and ticagrelor upon admission without room for consideration. The physician has the option to click a box where they say that they prefer to give clopidogrel rather than ticagrelor, and then they have to put a reason, so it can’t be left blank. It hasn’t happened in the last few years. I monitor all of those, so it just doesn’t happen. That’s at the front end, I would say, very close to 100 percent compliance with that part.

At hospital discharge, obviously some patients are switched to clopidogrel if they are on an anticoagulant, on either warfarin or a direct thrombin or factor X inhibitor with various permutations of dual or triple therapy. A small proportion are switched from ticagrelor to clopidogrel either because of terrible side effects or because of financial issues, but I would say that about 80 plus percent of people leave the hospital on aspirin and ticagrelor, at least for the first month pretty consistently.

DR. KIRTANE: Neal, what do you do?

DR. KLEIMAN: We’ve got a mix that’s closer to 50/50. Large institution, State of Texas, people are very independent-minded, so getting agreement to use an order set is more difficult than it is in many institutions—but it’d be very nice if we could. I think we’d see a lot more ticagrelor use. We don’t see as much as we should in the emergency room either, and I think that’s got a little bit to do with built-in institutional complexities of getting the stuff ordered and getting it through pharmacy.

DR. KIRTANE: Yes. At least in our institution, we tend to favor for ACS the more potent agents, either ticagrelor or prasugrel. I do think that because of the ACCOAST data, we are not preloading with prasugrel, and so that agent would only be used post-PCI. Thus, in a lot of cases, other agents may be favored, at least in our institution.

As far as the preloading issue goes, we have a somewhat unique protocol in the sense that if there’s a long delay to getting to the cath lab—for instance, the patient comes in Friday night and is stable—those patients will often get preloaded with a P2Y12 inhibitor, but if the patients are going to the cath lab rapidly, we often don’t preload, and we’ll use more intensive platelet inhibition such as cangrelor at the time of PCI and then transition them to ticagrelor simply because that’s an easier transition because of the lack of drug–drug interactions at the level of P2Y12 receptor. I will say, though, that there are scenarios where we won’t use more potent agents. Those are patients perhaps at the highest risk of bleeding or other issues such as those, but by and large, we try to use more potent agents just because of data such as those from PLATO.

For elective PCI, I think the jury is a little bit out, but we do—even for our elective PCIs—preload typically with clopidogrel two hours prior to the PCI unless the stress test is super high-risk or there’s valvular disease that we’re worried about.

It is interesting—among the three of us, while there are some differences, there are many similarities, because I think the three of us are attuned to the fact that we want platelet inhibition as prevention of ischemic events.

DR. KLEIMAN: You know, it’d be really nice if we actually had a study in which patients were stratified according to bleeding risk, and then P2Y12 inhibitors were selected, probably at random, based on the bleeding risk stratification.

DR. KIRTANE: I agree.

DR. KLEIMAN: I think it would generate lots of excitement.

DR. BRENER: We kind of have that in the PRECISE study, at least part of it is retrospective, but we kind of have it.

DR. KLEIMAN: And we all kind of do it, and we all think we’re pretty savvy about it. I think I’m pretty savvy about it, but I may well be wrong. It’d be great to see a study like that. I think people would eat it up.

DR. KIRTANE: Any differences based upon patient risk? Let’s go from unstable angina to non-ST-elevation myocardial infarction (NSTEMI) to ST-elevation myocardial infarction (STEMI) in terms of what agent you use and when. Let’s take STEMI for instance. Tell us what you’re doing with STEMI.

DR. BRENER: We have again an order set, the Pyxis (Becton, Dickinson and...
Company) in the emergency department—a little bag with aspirin and ticagrelor, 4000 units of heparin, crush ticagrelor, avoid morphine. Lately, I’m trying to avoid fentanyl as well. I thought initially that there is much less inhibition of absorption with fentanyl than there was with morphine, but it turns out that it’s about the same. We crush for everybody, even those who are perfectly fine, and then go to the cath lab.

DR. KIRTANE: Neal, what do you do?

DR. KLEIMAN: Mostly, my concern is to make sure they get something in the emergency room. You know, it’s variable depending on where they’re coming from. I like to see it crushed. I like for it to be ticagrelor. I don’t always get what I want, but as Sorin said, there are many things that we’re doing at once. I just want to make sure they get the right med. I want to make sure they get a P2Y12 antagonist and aspirin quickly, and I want to make sure that they’re triaged appropriately.

DR. KLEIMAN: You know, some people have reservations in the STEMI population of loading with a P2Y12 inhibitor. My take on this is that, by and large, patients are almost never going to go for surgery. Also, there is delayed absorption of these agents. That’s why, I think, Sorin, you mentioned crushing as a way of overcoming that. But the key thing is that if we don’t give it upstream and early, then it’s really not going to take effect until later. One could use intravenous agents to bridge that, but in general, I think most people have fewer issues giving the P2Y12 inhibitor up front and early in the STEMI cases.

DR. KLEIMAN: There are issues with the opiates that Sorin brought up. The data to me are pretty convincing that they delay drug absorption, but on the other hand, patients are in pain. As physicians, we’re supposed to alleviate pain, at least as far as I can remember. The other truth is that if you have elderly patients who you take into the cath lab, you see fewer paradoxical reactions with opiates than benzodiazepines. The last thing you want is to have an unstable patient with an acute myocardial infarction (MI) and also to be struggling to keep the patient calm. I’m well aware of those data, but I’m not sure what to do with them. We have cangrelor on formulary. That’s a recent addition, and I have not used it yet.

I was always a proponent of preloading in NSTEMI. I realize that the data are not there to support that. I accept that. I am not oblivious to the fact that I cannot actually quote a study that really shows that it’s beneficial, but I think it’s not detrimental, and I’m impressed by the fact that people don’t go to the cath lab as early as we would like them to go.

I think that there is an element of delay which is more common among patients arriving on the weekend who don’t go to cath until Monday, and there’s usually no reason that they should go. I cannot predict up front, and I cannot review every single patient to predict up front who’s going to go right away and who’s not, so I prefer to preload them unless there is an overwhelming reason not to, such as known preexisting surgical disease, where the patient was supposed to come for coronary artery bypass grafting (CABG) and now comes with another ACS. We know that, but otherwise, I just can’t find a reason not to, and for simplicity so that the emergency department always does the same thing, and they don’t have to think about it, it seems to me the right thing to do.

DR. KIRTANE: That makes sense. Let’s transition a little bit to duration of therapy. I know we briefly mentioned it. How long do you continue on these agents? What are you doing with these agents? Is there down-titration, either through dose or different agents? What are you doing after these patients come in?

DR. KLEIMAN: I send them home ... actually, all of us here send them home on whatever they were getting in hospital. I think the fewer things you change, the more likely the patient is to be compliant.

DR. KIRTANE: Sorin, same for you?

DR. BRENER: I couldn’t agree more. I think we have ... when I was at the Cleveland Clinic, I used to give people a yellow card that said “if you stop this
We do the same. We ac-

I think also that it does

Let’s just transition

I’m pretty committed

The interesting thing

Oh, really? I was going

Neal, what do you do?

You know, I’ve been im-

As far as the clopidogrel and down-

DR. KIRTANE: Yes. We have a similar practice, too. I think that in trying to resolve what a patient is going to go home on and not have to change is really important, so sometimes there is switching that happens, even in the hospital if an insurance can’t cover a specific agent, for example. But most of the time nowadays, we can resolve these issues in-house, and folks will go home on what they were treated with at the hospital. For the higher-risk ACS, that’s typically going to be a potent agent such as ticagrelor.

The one thing that we’ll typically do in the ACS setting is that we are pretty programmatic about down-titration at a year. For example, if I am going to extend the duration of therapy, I will down-titrate from 90 mg to 60 mg of ticagrelor, which is, I think, a nice facet of that specific agent, with the data from the PEGASUS trial,9 in particular, showing that there’s less bleeding associated with the 60-mg dose, so that’s what we do.

DR. BRENER: We do the same. We actually have it in the electronic medical records, so when you renew the prescription, it asks you whether it’s more than one year or less than one year, and then it automatically alerts you to the need to down-titrate.

DR. KIRTANE: The interesting thing that’s been happening a little bit—I’ve just noticed anecdotally more recently—is that some patients, when they tolerate it, they’re happy to be on it, and they’re a little reluctant to stop it, but they’re more okay stopping aspirin. Absent data, something that I’ve occasionally done is continue them on the P2Y12 inhibitor and drop the aspirin at a year to lower bleeding risk.

As far as the clopidogrel and down-titration of that, we have the same issue that sometimes we do have to do it. The dyspnea component, at least of ticagrelor, should be discussed briefly. I do think that you can treat through it, but from a practical standpoint, for patients it’s sometimes more reassuring to them to just switch, and so I’ve employed both strategies, and it’s definitely something one sees in clinical practice, so you should know how to deal with it. Any other thoughts on that?

DR. KLEIMAN: You know, I’ve been impressed that we see less dyspnea than we expect to. I really can count on one hand the number of patients in whom I’ve attributed dyspnea to ticagrelor.

DR. BRENER: I totally agree.

DR. KIRTANE: Oh, really? I was going to say after hearing Neal’s response that Texans might not complain as much as the New Yorkers! I tend to see it more frequently than reported in PEGASUS, which is around 14 percent. Clearly there is some patient and practice variability.

DR. BRENER: I think also that it does help—at least, the way I handle this is to say it may be from that. Give it a month. Usually, it goes away in most people. It’s worth it, because I think there are some benefits in reduction in clinical events, and I think that does it for most people. I agree with … my experience is the same as Neal’s, that I needed to switch very few people because really they just can’t handle this sensation of dyspnea, which I think is very different than the regular heart failure dyspnea. It doesn’t seem to be that much of a deal, I think.

DR. KIRTANE: Let’s just transition quickly to oral anticoagulants (OACs). What do you do in that situation? This is an increasingly prevalent population. What do you think?

DR. BRENER: I’m pretty committed to following the guidelines,10 which is that we should use only clopidogrel with OACs, and I follow pretty much the algorithm, using triple therapy rarely and briefly, if at all, and I use the OAC with clopidogrel alone in most folks. In the young ones who are really at low risk of bleeding, I would use triple therapy, but for most, I go with the guidelines.

DR. KIRTANE: Neal, what do you do?

DR. KLEIMAN: I do the same. They get aspirin for a day or two after they’ve had a PCI, then they come off aspirin. They go home on clopidogrel and an OAC. The problem is that getting that message out is not easy. Some people are really stubborn about it. I’m trying to be polite since we’re on tape, but it gets me angry sometimes.

DR. KIRTANE: No, I know. For me as well, it’s actually, interestingly, one of
A downside of ticagrelor is that it has bid dosing, but the upside is that because it’s reversible and has a shorter half-life, that may be helpful in that scenario. That may explain some of the bleeding differences that were seen in the trials of ticagrelor compared with other agents. By the way, this may be another scenario where—and I don’t want to be a total advocate of P2Y12 reactivity testing—one can use that testing to determine when patients are not inhibited anymore and therefore expedite the surgery. This approach is one that has been discussed in anesthesia guidelines.\(^\text{15}\)

**Clinical Implications**

- Therapies to mitigate bleeding and ischemic events need to be guideline-directed and administered in a timely manner.
- Early inhibition of platelets remains critical to preventing ischemic events in patients with ACS.
- There are differences between P2Y12 inhibitors with respect to potency as well as onset.
- Drug interactions need to be considered when switching between P2Y12 inhibitors. Ticagrelor may be easier to transition to because it does not have drug-drug interactions.
- DAPT can be continued for high-risk patients with possible down-titration at a year.
- In patients with a higher bleeding risk, down-titration can be considered earlier.
there is a certain risk of actual events occurring—we learned that from the PARIS trial. Interruptions are relatively benign, but it’s not zero, so there’s no point to wait another three, four, five days before you go to surgery when it’s not necessary. If you can go, you should go get it done and resume, if necessary, the antiplatelet therapies. So, it’s on both ends of the spectrum.

**DR. KIRTANE:** All right. With that, I think we’ve covered a broad range of topics. Just some brief take-homes.

I think first is that, at least in ACS and PCI, it is important to recognize the importance of platelet inhibition. Also, to recognize that there are differences between P2Y12 inhibitors with respect to potency as well as the onset of these agents. Additionally, when the patient is done with the procedure, if one is using other intravenous agents (particularly cangrelor), there may be issues transitioning between these agents. Typically, I think there was consensus that we try to continue dual antiplatelet therapy for patients particularly at the highest risk, with possible down-titration at a year. Obviously, we will consider down-titration earlier in patients at higher bleeding risk. I think we covered a lot of topics with respect to side effects, discontinuation, and also even concomitant antiocoagulant therapy, too. With that, I thank you both, Sorin and Neal, for doing this and look forward to doing this again!

**REFERENCES**


