DAPT in STEMI

A panel of experts weighs in on STEMI pharmacology, transmission of prehospital ECGs by emergency medical services, and STEMI best practices for 2016.

MODERATOR

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Moderator: Two comparative effectiveness analysis trials (TRITON TIMI 28 and PLATO) have shown the newer P2Y12 agents to be more effective than clopidogrel. Is there any role for clopidogrel in contemporary STEMI?

Dr. Berger: Yes. Certain groups of patients would be most appropriately treated with clopidogrel. An easy example would be a patient with a previous transient ischemic attack or stroke who experiences an inferior myocardial infarction complicated by second-degree heart block. Another might be a patient who has recent or current major bleeding. Generally speaking, however, I think that clopidogrel is no longer the best choice in the acute setting.

I will add that it may be appropriate to switch a patient from a more rapidly acting and potent agent to clopidogrel in the days or weeks after a procedure, if he or she is at high risk of bleeding and the coronary anatomy and procedure suggest a low risk of throm-

bosis within the stent or elsewhere in the coronary circulation.

Dr. Gurbel: Evidence-based medicine would support the use of ticagrelor or prasugrel over clopidogrel in patients treated with PCI. The evidence base in the setting of fibrinolytic therapy is less robust with the new P2Y12 inhibitors. There was numerically less mortality in the TRITON trial in STEMI patients treated with prasugrel, which makes one wonder whether this potential signal would have reached significance had TRITON included a larger STEMI population.

Dr. Pollack: I think not. I think for continuing maintenance therapy, there are economic issues that sometimes intervene, but for that pre-primary PCI dose, I think data from both TRITON and PLATO show that prasugrel and ticagrelor, respectively, have better activity and better utility, and are generally equivalent in safety compared to clopidogrel. For maintenance after primary PCI, the data favor continuing ticagrelor to achieve the mortality benefit seen in PLATO. I think it makes sense, with the immediate life threat posed by STEMI, to use a more potent agent.

One thing I would add is that there are still situations (they're unusual, particularly in urban areas, but they do happen every day) in which lysis is still the preferred approach for STEMI management. The reason I bring this up is that the only antiplatelet drug with which we have experience in the lytic-treated STEMI patient is clopidogrel. So, there is a very limited role for clopidogrel in the primary PCI-treated STEMI patient, but in a patient who needs fibrinolytic therapy, CLARITY showed that lytic therapy can be optimized by adding clopidogrel to the lytic cocktail of anticoagulation and lysis. I don't see ticagrelor looking to expand into that area because lysis is used so infrequently. Because of bleeding concerns, I wouldn't see prasugrel as a reasonable alternative there. So, that's still clopidogrel's world. It's a very small world, but it is an important one for patients who can't get to primary PCI in a timely fashion.

Dr. Cohen: The short answer to that question is no. The bottom line is that the two studies show a better strategy than clopidogrel and, in an ideal world, if everybody had easy access to either agent, especially the agent that showed the mortality advantage, there wouldn't be much need for any discussion. The only time that the question of clopidogrel comes up is that it is generic, and some patients in some settings have more access to generic medications than to the proprietary prasugrel and/or ticagrelor. But from a science point of view and from a clinical trial point of view, these newer drugs should become the standard in the field.

Moderator: With regard to timing, because an AMI is happening now, and 99% of patients will undergo primary PCI in the first 24 hours as the primary revascularization strategy, why do we wait for patients to get to the emergency department to get loaded or even on the table?

Dr. Cohen: That is more of a legal worry/issue. You want to feel very confident that the diagnosis is acute STEMI and not aortic dissection or a perforating duodenal ulcer. In the United States, we are very sensitive to making a possible mistake in diagnosis and then being sued and under pressure from a legal point of view. However, in a world in which the level of confidence is high that this patient is having a STEMI, and the signs and the symptoms are not likely to be anything other than a STEMI, the answer to the question with regard to timing is we shouldn't wait. If we are confident in the diagnosis, there is no medical or scientific reason to wait.

Dr. Pollack: That's kind of a philosophical question. I think increasingly around the United States (parts of Western Europe are ahead of us), we have the capability and ability to interpret prehospital electrocardiograms (ECGs) either by the computerized algorithm of the machine or by telemetry to a base hospital. Because of this capability, we are doing a better job of identifying STEMI early on. What that is typically accomplishing is change to advance notice to the receiving emergency department and if, in fact, the emergency department is part of an interventional hospital, then the path to primary PCI can be much faster.

However, another potential use of that earlier identification of STEMI would be to get both anticoagulation and antiplatelet therapy onboard. Anticoagulation is a bit more challenging because it requires an IV and typically an ongoing infusion, whereas ticagrelor or prasugrel are pills to swallow. Given the time sensitivity with the treatment of STEMI, it would make sense to try to move in that direction.

Dr. Gurbel: Only one trial, the ATLANTIC trial, prospectively and adequately tested the hypothesis that pre-PCI loading (with ticagrelor) produced better outcomes versus administration at the time of PCI. The coprimary endpoints involved infarct-related artery patency and ST-segment resolution; the result of the trial was nega-

tive. One potential explanation was the short median time interval between the pre-PCI load given in the ambulance and that given during the PCI (31 min). Not surprisingly, with no difference in the pharmacodynamic effects between the groups at the time of PCI, there was also no demonstrable difference in bleeding between the groups. It is uncertain whether a benefit would have been observed if the interval between loading and PCI were longer.

Dr. Berger: It isn't true that 99.9% of patients with STEMIs get a PCI; many undergo lytic therapy or no reperfusion therapy, unfortunately. It isn't even true that 99.9% of patients taken to the cath lab for immediate angiography undergo PCI or that 99.9% of patients who are confirmed to have an acute coronary occlusion undergo PCI.

But regarding pretreatment, which I agree makes sense for many reasons (especially when a radial approach is utilized, which reduces the risk of bleeding at the arterial access site), the ATLANTIC trial studied pretreatment with ticagrelor and found it not to be beneficial. Pretreatment hasn't been studied with the other two P2Y12 inhibitors, although it was found to increase harm in NSTEMI patients when prasugrel was administered.

I suspect that in properly designed trials, especially using a radial approach, pretreatment with ticagrelor (and possibly prasugrel) in STEMI patients with a significant interval between diagnosis and the PCI would be superior. But, that is only a guess, and it is not supported yet by existing data.

I will also add that if I experienced a STEMI today, with what is currently known, I would want pretreatment with ticagrelor the moment a STEMI is confirmed, and I would want radial access. Remember, it wasn't harmful in ATLANTIC, it just wasn't beneficial. And there were important secondary endpoints that appeared to be reduced by ticagrelor, although that should be viewed as encouraging and hypothesis generating because it may well have been the play of chance.

Moderator: We give prehospital aspirin, and in certain systems, we give prehospital tPA. Why do we withhold P2Y12 for 20 to 30 minutes and, in some cases, especially if the patient arrives at a non–PCI-capable hospital?

Dr. Pollack: I think this is a great question. It's not just the non–PCI-capable hospital; even when the patient arrives at a PCI-capable hospital, sometimes there is a surrounding rural area, and the transport time can be long (20 or 30 minutes, or even longer). There's not a lot of prehospital tPA being given around the country, but in someone who has chest pain and isn't obviously bleeding, aspirin is standard of care everywhere. You're right, it is typically done in the ambulance upon presentation with that complaint.

While aspirin does carry a measurable bleeding risk, aspirin plus a P2Y12 inhibitor carries a greater bleeding risk, and I think there may be some concern that paramedics aren't in a position to risk stratify the bleeding risks of therapies given to patients in the EMS setting. One could easily make the argument that one loading dose is not going to have much of an impact on a patient's bleeding risk, but I think there may be some safety concerns that need to be looked at objectively and can probably be dispensed with. I think the balance in terms of safety and efficacy would clearly suggest that the earlier we give the P2Y12, the better.

Dr. Gurbel: There are no randomized data to support the safety or efficacy of prehospital therapy in the era of the new, more potent, faster-acting P2Y12 inhibitors. Tissue plasminogen activator reperfuses the myocardium by fibrinolysis and has been shown to salvage myocardium; this agent should not be equated with a P2Y12 inhibitor. Although there are some data to support that P2Y12 inhibition disaggregates platelets and may facilitate reperfusion, the evidence is scant.

Dr. Berger: Because there are no randomized data yet that support pretreatment, the question raised is if and when we should do things that make sense that haven't been proven or that have been disproven. Remember, in the ACCOAST trial using prasugrel in NSTEMI patients, pretreatment was actually harmful. And again, pretreatment with those agents in STEMI patients will increase procedural bleeding. Prehospital tPA has been studied and has been shown to improve outcome in most trials. Aspirin wasn't routinely given to STEMI patients until it was shown to improve outcome in randomized trials (ie, in ISIS-2).

Dr. Cohen: There is still lingering concern on the part of some interventional cardiologists that patients coming in having an emergency catheterization may end up with multivessel disease and therefore may end up needing bypass surgery. Realistically, the likelihood of a STEMI patient needing emergency bypass surgery has decreased to close to zero in the last couple of years; it is very unlikely that anybody coming in with a STEMI is going to end up undergoing bypass surgery in the first couple of days. There may still be some physicians out there who are worried that loading with dual-antiplatelet therapy ruins

the surgical option for patients with left main disease. The truth is you haven't ruined the surgical option. In the setting of acute coronary syndrome, you should proceed to open the acute infarct-related artery percutaneously with balloon pump or Impella (Abiomed, Inc.) support if necessary, and then negotiate the optimal timing for CABG. The patient will be a lot better off than if he or she had surgery in the throes of this catastrophic AMI situation.

So there really should not be any hesitation or any logical reason to withhold dual-platelet therapy in the current era.

Moderator: Should there be a focused nationwide improvement in systems of care that allows for every EMS ambulance to perform and transmit prehospital ECGs?

Dr. Pollack: Yes, there should be; from a scientific or clinical standpoint, there's not much doubt about it. The problem is that there is an associated expense, and in most places, the EMS is taxpayer supported. In other places, it is funded through donation and volunteer support, so there's a real patchwork of targets to which to roll this out.

There are also some logistical challenges. Across the 50 states, there are 50 different EMS boards, and adding drugs or strategies to their formularies and treatment plans can be problematic and time consuming. But, it seems to me like a reasonable goal because if one can identify STEMI in the field, particularly in areas where there are longer transport times, it makes sense to go ahead and start as much treatment as one can prior to getting the patient into the emergency department for formal evaluation and treatment.

Dr. Gurbel: Yes, absolutely. The earlier the care team knows the condition of the suspected infarct artery, the better prepared they are for the procedure.

Dr. Berger: Absolutely yes. Definitely. With appropriate exclusions of complicated patients (uncertain diagnosis, do not resuscitate orders, patients with dementia or abnormal mental status, etc.) bypassing the emergency department based on a prehospital ECG shortens time to treatment and improves outcomes.

Dr. Cohen: I think this question has been answered very clearly. Obtaining, transmitting, and using prehospital ECG information literally cuts a minimum of 20 minutes in unnecessary delay in making a diagnosis and subsequently a delay in treatment. I would agree wholeheartedly that the prehospital ECG is a scientifically validated concept, and it's a shame that it's not a standard throughout the entire country.

In the United States, dealing with patients in an ambulance setting is still not routine. We all recognize what the Europeans and other countries have done in terms of triaging and treating patients in an ambulance, but it's not something that has been established in the United States. I think it is time to do a major prospective trial in the United States in which we test different models relating to health care delivery by EMS as an initial step to expedite the treatment of STEMI patients. We have to start with science and validate it scientifically, then the onus is on the states that refute the science or ignore the science. In that way, the political heat gets much greater once the science is pointing in a certain direction.

Moderator: What are STEMI best practices in 2016?

Dr. Pollack: Acknowledging my bias as an emergency physician, I believe best practice has to involve a close collaboration between emergency medicine and cardiology. In the STEMI world, if there's capability for primary PCI, then the emergency physician is a key component of timely care and notification of the cath lab, marshalling the appropriate resources.

There also has to be significant and meaningful participation by the emergency physician in facilities where primary PCI is not a core capability, because the decision has to be made whether to stabilize, package, and ship the patient for primary PCI or whether instead the patient should be evaluated for lytic therapy. The answer is not always clear-cut, it may depend on traffic conditions, weather, availability of helicopters, how busy the potential receiving site is, etc. The emergency physician at a non–PCI-capable hospital needs to be aware of all the options at any given time. A lot of what we need to do to improve STEMI care is built around what we've already talked about in the EMS environment, with getting prehospital ECGs and potentially getting prehospital antiplatelet loading and then having the emergency physician feel very comfortable and confident with the backup in the institution to captain the ship. Then, once the patient arrives, quick management and transition of care to the consulting cardiologist can proceed.

Dr. Berger: I think the following are absolutely best practices: (1) prehospital ECG in the ambulance, (2) preactivation of the cath lab for clear-cut STEMIs, (3) bypass of the emergency department (if the cath lab team has arrived) for all patients without strong relative or abso-

lutely contraindications to PCI, and (4) transport by EMS to the most appropriate hospital (a PCI center in most cases) rather than the nearest hospital.

While there is much discussion (appropriate discussion) about which P2Y12 inhibitor to use and which anticoagulant to use, these practices would have far more impact at improving outcome than if we used "the best" P2Y12 inhibitor and procedural anticoagulant instead of "the worst."

Dr. Cohen: I would start by developing a multistep construct. The first step would be creation of a national awareness campaign for the early detection on the part of a spouse or significant other or a friend or neighbor who is aware enough of the signs and symptoms of STEMI such that if someone were having crushing chest pain, he or she could start therapy or administer an aspirin.

The next step of this construct would be early diagnosis and a mandate that all EMS personnel have the capacity to transmit a 12-lead ECG wirelessly to effect early diagnosis.

The third step would be early treatment based on the wireless telemetered ECG; once the diagnosis is made from the ECG, give authority to the EMS staff to initiate therapy with heparin or with dual-antiplatelet therapy.

The last step of this construct would be early transfer. Patients diagnosed with STEMI should be quickly and immediately transferred to the closest primary PCI facility. It is reasonably well established that going straight to a primary PCI center saves a lot of time and trouble and may be more effective than stopping at a nonprimary PCI center first and then getting triaged and moved later to a PCI center.

Dr. Gurbel: To make every effort for early diagnosis and arrival in the cath lab—the old adage that "time is myocardium" still remains true. To treat the patient with evidence-based medicine—there is a substantial body of data supporting the use of prasugrel or ticagrelor in favor of clopidogrel in the majority of patients with STEMI. Don't forget the importance of aspirin and its effect in blocking COX-1 that synergizes the effect of all P2Y12 inhibitors. ■