

SARASCHANDRA Hello, and welcome back to the Mayo Clinic Medscape video series. I'm Dr. Sarachandra Vallabhajosyula. I'm
VALLABHAJOSYULA: a cardiology fellow here at the Mayo Clinic. Today, we'll be discussing the Twilight study, which was recently published in *The New England Journal of Medicine*. I'm joined today by my colleague, Dr. Patricia Best, who's a consultant interventional cardiologist and an Associate Professor of Medicine at the Mayo Clinic. Welcome, Dr. Best.

PATRICIA BEST: Thank you.

SARASCHANDRA So Dr. Best, this Twilight study was recently published in *The New England Journal of Medicine* and caused
VALLABHAJOSYULA: quite an impact in the clinical practice. Could you tell us a little bit about the study?

PATRICIA BEST: This study was primarily done by Dr. Roxana Mehran and her colleagues looking at patients who are at high risk for traumatic complications after their percutaneous coronary intervention, who were randomized after three months of DAP therapy with ticagrelor and aspirin to either ticagrelor and aspirin or ticagrelor alone.

And so the randomization occurred at the three month time period, and then there was 12 more months of one or the other therapies. And then they looked at outcomes. Their main outcome was looking at bleeding events. But they also had a very high focus on ischemic events because they also didn't want to-- they wanted to know whether or not those ischemic events were higher when you got rid of the aspirin.

SARASCHANDRA Can you tell us briefly about the population that was included and how they went about executing that plan?
VALLABHAJOSYULA:

PATRICIA BEST: Yeah, the study population is always very important because that tells you whether or not their results are transferable to your population. So they took patients who had clinical features that were higher risk-- so patients who are over the age of 65, women, patients who had troponin positive acute coronary syndrome-- and, in fact, over a third of the patients were in that category. They had patients who had non-ST-elevation myocardial infarction, which was about 25% of the population. So again, very high-risk features from a clinical population standpoint, or they'll also include patients with chronic kidney disease which has had a GFR less than 60.

Then, they also looked at the angiographic features. And they also had to have one of the higher risk and geographic features as well. The angiographic features included left main coronary artery disease. It included proximal left anterior descending coronary artery stenosis. It included bifurcation stenting, where they had to use two stents for the bifurcation disease or very long stenting, such as greater than 30 millimeters of stent or multi vessel disease that they were treating.

And so by looking at having both of these factors as part of their inclusion criteria, they were at much higher risk for more thrombotic and ischemic complications later. Some of those factors that were put into the study, also, when you look at the higher risk of thrombotic complications, some of the clinical factors also put them at higher risk of bleeding complications, such as the chronic kidney disease population and women.

SARASCHANDRA That's definitely like you said, a very select and an appropriate population to do the study in. So can you tell
VALLABHAJOSYULA: us briefly what the findings of this study were-- the main findings?

PATRICIA BEST: The main findings of the study was looking at barc-- 2, 3, and 5 bleeding complications. And in those bleeding complications, there was a lower risk of bleeding in the patients who had ticagrelor alone in the three to 15 months after their PCI, compared to those who had dual antiplatelet therapy. That was decreased from 7.1% to 4%, so about a 40% reduction in bleeding events. And that was very significant.

Along with that, then, they looked at ischemic complications. And in the patients who had ischemic complications, there was absolutely no difference between the groups. And ticagrelor alone was not inferior to dual antiplatelet therapy. When you look at the trial, one of the other things in the trial design is that they didn't randomize patients until after the three months that they had to successfully make through the three months without major complications. So it is excluding those patients as well.

SARASCHANDRA Now this is obviously an important finding. Can you, given your expertise on the subject, having transacted **VALLABHAJOSYULA:**with these patients both the clinic and the hospital, how do you contextualize these results to our patient populations? And in light of prior studies, what are your perspectives on where the study fits the bill?

PATRICIA BEST: So prior studies have looked-- such as the Smart Choice and Smart DAP studies-- they had looked at lower-risk populations. They also were not looking at necessarily ticagrelor as the second agent in the dual antiplatelet therapy. So it could be any agent. And it was looking at a lower-risk population. They were, again, looking at dropping the dual antiplatelet therapy at three months and comparing those. And those studies also looked like it was favorable to using a single agent.

That is compared against one of the other studies-- the Global Leader Study, which was a larger study that was done in a mixed population. So there were some non-ST-elevation myocardial infarction patients as well as those patients who were more going undergoing routine PCI. It was a large study. But it looked at dropping the dual antiplatelet therapy at one month. It was, again, using ticagrelor. And then looking at 24 months to see their outcomes. That study was looking for superiority of ticagrelor over dual antiplatelet therapy and was a negative outcome.

Importantly, in that study, was that when you looked at follow up and actually compliance to ticagrelor, it was actually much lower. It was in the 70% range, versus the 90% range for aspirin in those patients. And so that what you're finding is that one of the downsides to this much more potent and effective dual antiplatelet therapy with ticagrelor is that you're also having the downside of it being a twice-a-day agent.

SARASCHANDRA Now these a very interesting observations, Dr. Best. How do you see this study in light of prior studies **VALLABHAJOSYULA:**influencing our practice in the Cath lab and in the clinic?

PATRICIA BEST: I think what it's showing us is certainly in the lower-risk population and now also in the higher-risk population, particularly when ticagrelor is being used, and when there's good compliance with the ticagrelor, after three months of dual antiplatelet therapy, we are safe to remove the aspirin and leave patients on a single ticagrelor lower during that time period, it will lower our bleeding risk, which is what is expected.

However, what we yet don't know is some of the higher-risk populations that were excluded out of the Twilight study, such as ST-elevation myocardial infarction and cardiogenic shock. So those populations just haven't been studied yet. So that we need to be a little bit careful that we're not expanding our thoughts on this to all patients, because they haven't been studied yet. Although, obviously, sometimes we don't have studies for everything.

And so that we want to think about what is safest for our patients and so that better understanding the patient's bleeding risk versus their thrombotic risk and tailoring individually to patients will be helpful. And I think more patients will be on a single antiplatelet agent at three months after this study, after their PCI compared to prior to this study.

SARASCHANDRA Now Dr. Best, obviously this has been well-received in the interventional community. Dr. Mehran's work was well-received at TCT and subsequently, the publication in *The New England Journal*. Now obviously, there are limitations to every study. So what are the limitations and caveats of this study that you think are fertile ground for future research in this field?

PATRICIA BEST: So the fertile ground is really looking at do we need three months of dual antiplatelet therapy? So that when you look at dual antiplatelet therapy, that's how all of the original PTCA and bare metal stents studies-- once we were using dual antiplatelet therapy with the sense studies and not using anticoagulation with aspirin-- how they've all gone is maintaining aspirin as part of it. And the question is, do we need aspirin early on? And given the very powerful antiplatelet agents we now have available, is aspirin adding to it? Or is it just adding to the bleeding risk? And we don't know some of those data.

And other places that are interesting and also grounds for potential research would be whether or not we can switch off of ticagrelor to other agents. So ticagrelor-- although it is very beneficial in preventing thrombotic events and ischemic events, it is also a twice-a-day agent. It also has the risks of shortness of breath in our patient population as a side effect, and that's obviously not an ideal side effect to have with it.

We know that compliance goes down dramatically when you go from once-a-day dosing to twice-a-day dosing. And then cost is the other factor.

SARASCHANDRA Dr. Best, thank you for your excellent thoughts and sharing such amazing insights into this important study.
VALLABHAJOSYULA: Thank you for joining us today on heart.org Medscape Cardiology. Thank you.