NAVEEN PEREIRA: Greetings. My name is Naveen Pereira. I'm Assistant Professor of Cardiology and Pharmacology at the Mayo Clinic. And today on theheart.org, we'll be discussing adjunctive pharmacotherapy in coronary artery disease, specifically with an emphasis on anticoagulation and antiplatelet drugs, with my colleague Dr. Guri Sandhu, who is the Director of the Cardiac Catheterization Laboratory at Mayo Clinic Rochester and who specializes in percutaneous coronary intervention and structural heart disease intervention. Welcome, Dr. Sandhu.

GURPREET SANDHU: Thank you, Naveen. We definitely have some pretty topical medications to discuss today. They have both been in the news.

NAVEEN PEREIRA: Fantastic. So we'll get right into the news. So first of all, we know about all the traditional antiplatelet drugs that we've been using for acute coronary syndromes after percutaneous intervention and stable coronary artery disease.

Aspirin seems to be the mainstay. Aspirin irreversibly acetylates the platelets, and then we have the P2Y12 inhibitors. Specifically, more commonly used is clopidogrel and the newer ones, ticagrelor and prasugrel. But there's a new kid on the block, if you may, and that is Vorapaxar. And Vorapaxar is a protease-activated receptor inhibitor.

GURPREET SANDHU: Right.

NAVEEN PEREIRA: Dr. Sandhu, can you elaborate on this newer mechanism of an antiplatelet agent and tell us a little bit about Vorapaxar and its mechanism of action.

GURPREET SANDHU: So this is an entirely new class of agents, and Vorapaxar was recently approved by the FDA for clinical use. This medication, as you just mentioned, works via the protease-activator receptor pathway. And the mechanism is basically, once the coagulation system gets activated, thrombin will irreversibly activate this receptor. And that starts off the usual G protein-based intracellular activation that activates the platelets. So the hope is by inhibiting this receptor, we will reduce platelet activation. And this medication has been approved for secondary prevention.

NAVEEN PEREIRA: Wonderful. And it basically has come into the news recently because the FDA approved Vorapaxar and my understanding is the approval came after a consensus. There was a vote 10 to 1 in favor of approving Vorapaxar for patients for secondary prevention in coronary artery disease and peripheral arterial disease. The basis of this approval came from the TRA secondary prevention TIMI 50 Trial.

GURPREET SANDHU: Correct.

NAVEEN PEREIRA: Dr. Sandhu, could you tell us a little bit about this trial, the kind of patients that were involved, and the basic findings of this trial.

GURPREET SANDHU: So essentially, this was a pretty large trial. They had about 26,000 patients, all with stable atherosclerotic disease. And they had three subgroups. The first subgroup was patients who had had an MI within the past one year. The second subgroup was cerebrovascular disease. So patients who had had a TIA or a nonhemorrhagic stroke in the past year. The third subgroup was patients with peripheral arterial disease.

So these patients were placed on either a placebo or Vorapaxar, and the usual outcomes of MACE, death, stroke, need for urgent revascularization, and other criteria were looked at.

NAVEEN PEREIRA: And were they allowed to take other medications?

GURPREET SANDHU: They were also on their usual medications, and one confounding issue here which was brought up repeatedly was that about 16,000 of these were on thienopyridines, primarily clopidogrel. So that may have affected their overall outcomes and results.

NAVEEN PEREIRA: So more than 60% of these patients were on clopidogrel and so Vorapaxar was given in addition to clopidogrel in a large proportion of the patients in this trial.

GURPREET SANDHU: Exactly.

NAVEEN PEREIRA: OK.

GURPREET SANDHU: And as the trial unfolded, DSMB actually stopped one arm of the trial. Those are the patients who had had a previous ischemic stroke or TIA because of a higher signal of bleeding, both moderate-to-severe bleeding as well as intracerebral bleeds.

NAVEEN PEREIRA: OK. And was there a certain weight range? I know with prasugrel, for example, patients of a certain weight were excluded because of higher risk of bleeding. Was the same applicable in this trial?

GURPREET SANDHU: Exactly. So it is pretty much the same. So when this drug was approved, the two groups that were excluded from using this drug, were patients below 60 kilograms in weight and also patients who had had a previous cerebrovascular event.

NAVEEN PEREIRA: So they looked at a composite endpoint of that myocardial infarction, stroke, coronary revascularization. So can you elaborate a little more on the relative risk and the absolute risk reduction? I think that's important, because the relative risk reduction always sounds impressive, but when you look at the absolute risk reduction, we may not be that impressed.

GURPREET SANDHU: So the relative risk reduction was 13%, and the number--

NAVEEN PEREIRA: With the use of Vorapaxar.

GURPREET SANDHU: With the use of Vorapaxar. So the number needed to treat was 53.

NAVEEN PEREIRA: OK.

GURPREET SANDHU: In terms of absolute risk reduction, it was basically about 1%-- between 10% to 9%.

NAVEEN PEREIRA: OK. OK. And so there's some adjunctive benefit, it appears, but there may be an increased risk of bleeding.

GURPREET SANDHU: Yes.

NAVEEN PEREIRA: And so what's your take-home from this FDA approval and the results of the trial? Do you think it's going to change your practice, Dr. Sandhu?

GURPREET SANDHU: Not immediately, because the biggest concern is the risk of bleeding. There was a 4.2% rate of bleeding with the medication compared to placebo, which was 2.5%. So in balance, the risk of bleeding seems to neutralize any obvious benefit across the larger population. However, having said that, this is potentially a medication that could be individualized. So I think as we have more data, more evidence coming forward, we will probably find the right patient population. At this time, it is still an early stage medication. I think we need more evidence before we have any definitive conclusions.

NAVEEN PEREIRA: Right. And it would be nice not to have clopidogrel as a confounding factor in terms of antiplatelet agents.

GURPREET SANDHU: Correct. Absolutely.

NAVEEN PEREIRA: OK. So Dr. Sandhu, let's move to another interesting topic of anticoagulation. We use unfractionated heparin commonly in acute coronary syndrome, so low-molecular weight heparin. There's this big controversy of whether we should use Bivalirudin. There's a trial that addressed this issue, the HEAT trial. Can you tell us briefly about this trial and give us the key findings.

GURPREET SANDHU: So the HEAT trial was done in the UK with the randomized patients with ST-elevation MI to unfractionated heparin versus Bivalirudin. They had about 1,800 patients, and their findings were a little bit controversial. Previously, Bivalirudin had been shown to reduce the risk of bleeding. In this trial, they showed that there was no difference between using unfractionated heparin versus Bivalirudin. And on the other hand, the risk of stent thrombosis was a little bit higher with the use of Bivalirudin. So this created a large amount of controversy and discussion. And I think the jury's still out on where this is going to go.

NAVEEN PEREIRA: So no differences in bleeding between unfractionated heparin and Bivalirudin.

GURPREET SANDHU: Exactly.

NAVEEN PEREIRA: Any effects and MACE?

GURPREET SANDHU: So the effect on MACE seemed to be slightly lower with heparin. And coming back to the bleeding issue, all the previous studies with Bivalirudin had mostly compared unfractionated heparin plus an intravenous glycoprotein inhibitor versus Bivalirudin alone. And we know for a fact that glycoprotein inhibitors increase the risk of bleeding. So those are utilized less commonly nowadays. So that is one issue that has been taken off the table in this comparison.

The other issue is also radial access is gaining predominance. Femoral access management is better. So overall bleeding rates across the board are going down. So the difference is potentially less than it was seen in the previous studies.

NAVEEN PEREIRA: So what do we do at Mayo, in general, for patients with STEMI, in terms of using heparin versus low-molecular weight heparin versus Bivalirudin?

GURPREET SANDHU: So at Mayo, our practice for any acute coronary event is to use dual antiplatelet loading up front. So everyone will get aspirin with either ticagrelor or clopidogrel. And then in terms of the anticoagulant, our preferred approach is unfractionated heparin with appropriate levels of ACT. And we will also selectively use an intravenous 2B3A agent for patients with slow flow and thrombus.

NAVEEN PEREIRA: That's great. Thank you, Dr. Sandhu. So the HEAT trial results substantiate and validate the approach used here.

GURPREET SANDHU: They do seem to fit in with what we have.

NAVEEN PEREIRA: So thanks to Dr. Sandhu for these great insights. And thank you, our viewers. We hope that you will continue to check out future content on Mayo Clinic's page at theheart.org on Medscape.