Antiplatelet Therapy for Secondary CVD Prevention

So Many Choices; What Should We Do?

FACULTY SLIDE REVIEW

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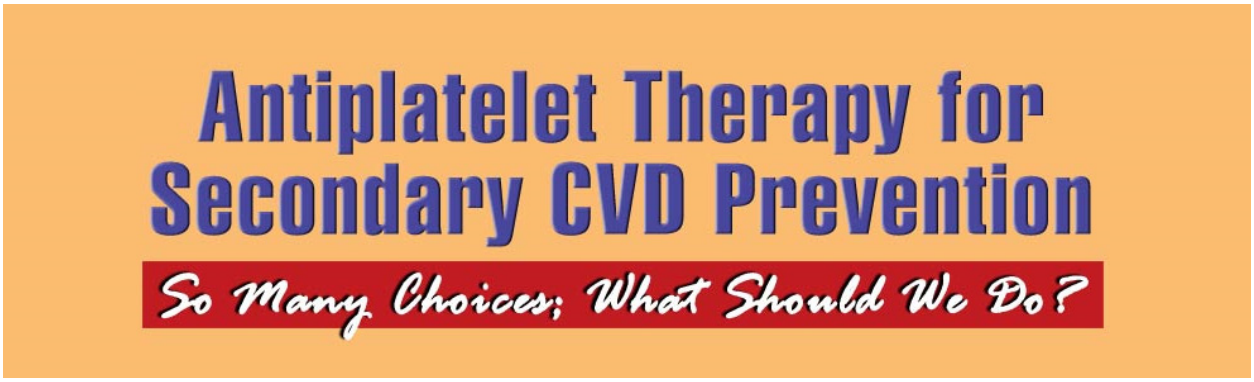

Slide 1 – Title Slide

Deepak Bhatt, MD: Welcome, everyone, to this CME-certified presentation called "Antiplatelet Therapy for Secondary Cardiovascular Prevention." This is Deepak Bhatt and I'm really fortunate to have my good friend and colleague Chris Cannon here, and we are going to go through some data as it pertains to topics in the antithrombotic world.

Slide 2 – Learning Objectives

The specific learning objectives of this activity are: to appraise the clinical data supporting long-term use of antithrombotics in patients with a history of cardiovascular disease; to analyze processes of switching therapies or employing concomitant therapies to achieve optimal balance of anti-ischemic protection versus the bleeding risks; and to customize longer-term therapies to the needs of particular patients, taking into consideration the evolving landscape of additional indications.

Slide 3 - Clinical Impact of Recurrent CVD; Therapeutic Opportunities

Let me first start off talking a bit about the clinical impact of recurrent cardiovascular disease and what the landscape shows.

Slide 4 - Patients with Prior MI Remain at High Risk for Ischemic Events

Data from the REACH Registry show that having had a prior myocardial infarction really puts patients at high risk for recurrent ischemic events. As you can see on the slide, patients who had prior ischemic events are at higher risk than those with stable atherosclerosis or those with risk factors only. And, in particular, those that have had prior ischemic events within the past year are at the highest risk, as sort of common clinical sense would also support.

Slide 5 - Secondary Prevention

This really sets the landscape for secondary prevention and the fact that, even once patients have gotten out of the acute phase of acute coronary syndrome, even in that phase where we call them stable, they still remain an elevated risk for ischemic events, and that's why things like lifestyle interventions are so important. Management of all their risk factors – their lipids, their blood pressure, if they're diabetic, their glucose – all those things are extremely important. We're going to focus in particular on antithrombotic therapies in terms of who to treat, which agents to use, and how long to treat, realizing that there are lots of options out there right now.

Slide 6 - 2º PREVENTION: Lifestyle Changes

Let me just say a couple of things about lifestyle.

Slide 7 - Lifestyle/Risk Factor Goals

There are a number of risk factors, of course, for cardiovascular disease, as listed on this slide here, and several different goals of therapy things like: smoking cessation; a careful diet, in particular one that is low in saturated and trans fats, probably also one that's low in sodium. In some people, lowering the cholesterol in the diet can also have an impact, albeit typically modest. Physical activity is important. Daily activity – at least 30 minutes a day – is a good goal. Maintenance of appropriate body weight or weight loss for patients that are overweight or obese seems to be important. Controlling blood pressure, particularly less than 140/90. LDL cholesterol is extremely important. Cardiovascular risk factor-intensive statin therapy has been shown to have a really important impact there, as well as, most recently, ezetimibe, as well, as Dr. Cannon showed in the IMPROVE-IT Trial. And management of diabetes also seems to be important for overall cardiovascular risk reduction, though the exact mechanism of doing that outside of lifestyle remains somewhat contentious.

Slide 8 - Lifestyle Interventions and Outcomes

The impact of lifestyle interventions on outcomes, is something that has been studied, is shown in this meta-analysis, and it does appear that there is an effect, as we all like to believe.

Slide 9 - 2º Prevention: Antithrombotic Therapies

Now let's move on to antithrombotic therapies.

Slide 10 - Atherothrombosis: Clinical Manifestations

Atherothrombosis is, of course, a problem that can manifest in the coronary arteries and results in acute coronary syndromes, but there are other places atherothrombosis can manifest such as peripheral artery ischemic events and cerebrovascular ischemic events. It appears that platelets are important in all these states and, therefore, antiplatelet therapy may have a role in all these states.

Slide 11 – Plaque Rupture

This diagram lists plaque rupture, either spontaneously with an acute coronary syndrome or iatrogenically when a stent is implanted into an atherosclerotic artery, and shows the cascade of events that are set off in terms of platelet activation, in terms of coagulation cascade being activated, all of which ultimately results in platelet-rich thrombus formation and, potentially, ischemic events.

Slide 12 - Antiplatelet Agents

Therefore, antiplatelet agents are important and, as shown on this slide, there are a number of different antiplatelets. Aspirin, of course, has been considered, really, the foundation antiplatelet therapy. The intravenous glycoprotein to IIb/III inhibitors have been studied extensively. And now in common use are the oral ADP receptor antagonists, in particular clopidogrel, prasugrel, and ticagrelor. And, more recently, the PAR-1 receptor antagonists have been evaluated and, of the two shown there, vorapaxar is the only one that's actually available.

Slide 13

This next slide shows some of the other interactions in the coagulation cascade, and lists the potential agents that could be used, not only warfarin, the old anticoagulant that has been used, but also the so-called novel or direct-acting oral anticoagulants, and now there are a number of them available for atrial fibrillation, and the direct thrombin inhibitors, also. So with these

different options – combining antiplatelets, potentially antithrombotics – life in the ACS world gets pretty complex, pretty quickly.

Christopher Cannon, MD: This slide and the previous one illustrate the subtitle of our program here of, "So many choices, what should we do?" And it's really remarkable how there has been such an explosion in the field of all these different mechanisms of antithrombotic therapy, a lot of good data for each one. And I think we'll try and sort through which mix of these things can really be helpful.

Dr. Bhatt: Yeah, I think, Chris, you've hit the nail on the head. It is a blessing and, in a sense, a curse; that is, it's really exciting to have so many options for patients. It, in theory, allows tailoring of therapy based on their risk factors, but it makes it really tough on physicians to really sort out what the right thing to do is for the right patient and at the right time.

Slide 14 - 2º PREVENTION: Antithrombotic Therapies: *Thromboxane-2 inhibition – Aspirin*
So let me move on to aspirin.

Slide 15 - Aspirin Evidence: Secondary Prevention
I won't linger for long because I don't think that there's much controversy for aspirin in secondary prevention. It's effective across the different subtypes of secondary prevention, as shown on this slide from the Antithrombotic Trialists' Collaboration.

Slide 16 - CURRENT-OASIS 7
But some relatively newer data with respect to aspirin have to do with aspirin dosing, such as from the CURRENT-OASIS 7 Trial. Part of that trial randomized patients to higher versus lower dose of aspirin and didn't find any benefit with respect to ischemic endpoints of the higher dosing of aspirin, but did find a little bit more GI bleeding. So, less GI bleeding with the low-dose of aspirin for chronic therapy in these post-ACS patients, and no obvious benefit with higher dosing. So most folks would interpret these data as being supportive of, in general, using lower-dose aspirin, in the U.S., 81 milligrams a day in the chronic phase of therapy.

Slide 17 - 2º PREVENTION: Antithrombotic Therapies: *P2Y12 Inhibition – Clopidogrel*
Let me move on to clopidogrel.

Slide 18 - CAPRIE
Clopidogrel was first really evaluated in the CAPRIE Trial, a head-to-head trial versus aspirin in high-risk secondary prevention in patients with recent ischemic stroke, recent MI, or symptomatic peripheral artery disease. And it was found to beat aspirin, an 8.7% relative risk reduction, and that is what led to the initial FDA approval of clopidogrel for patients who were post-MI or with ischemic stroke or symptomatic PAD.

Slide 19 - CAPRIE: Clopidogrel Provides Amplified Benefit in Patients with High Vascular Risk
Subsequent analyses from the CAPRIE Trial showed that there was an amplification of benefit in patients at even higher risk within that secondary prevention universe such as patients with multiple ischemic events shown on this slide, a larger relative risk reduction, largely absolute risk reduction in that cohort.

Slide 20 - CURE Study

The field then moved from a concept of more potent antiplatelet monotherapy to dual antiplatelet therapy, shown here as the CURE Study, acute coronary syndrome patients randomized to clopidogrel plus aspirin versus placebo plus aspirin, showing that dual antiplatelet therapy for a year was to become the standard of care in ACS management.

Slide 21 - CURE: Long-term Benefit of Clopidogrel

That benefit was evident in the first 30 days and significant, but it was also apparent and significant in a landmark analysis in that point between 30 days and one year, so both in early and later benefits.

Slide 22 - CURE: Life-threatening Bleeding

Now, of course, there was more bleeding with the addition of clopidogrel to aspirin, not surprising, in a placebo-controlled trial. There were increases in bleeding but, fortunately, not increases in stable or intracranial bleeding.

Slide 23 - CHARISMA: Primary Outcome

A trial that followed those observations was the CHARISMA Trial, to see if dual antiplatelet therapy with aspirin-clopidogrel would be a benefit, not just in ACS but in stable patients who are at high risk. And the overall trial did not find a significant benefit of dual antiplatelet therapy in a broad population of secondary and primary prevention but in patients who had been involved for secondary prevention indications.

Slide 24 – CHARISMA

In that subgroup of 12,000 patients, there was a significant reduction and, exploring that further on this slide, patients with prior MI seem to have a large reduction – 23% risk reduction. Patients with CAD, without prior MI, on the other hand, didn't seem to have any benefit at all versus just being on aspirin alone.

Slide 25 - CHARISMA: Primary Endpoint (MI/Stroke/CV Death) in Patients With Previous MI, IS, or PAD

Shown on this slide is a CAPRIE-like cohort, so these are patients with prior MI, ischemic stroke or symptomatic peripheral artery disease, sort of echoing back to the CAPRIE Trial I showed a few slides ago, of clopidogrel versus aspirin – but here, of course, it's clopidogrel *plus* aspirin versus aspirin – and there seemed to be a significant benefit with dual antiplatelet therapy over the course of about three years or so in this post hoc analysis.

Slide 26 – CHARISMA: *Timing of Severe or Moderate Bleeding*

Bleeding, in the CHARISMA Trial, was increased with dual antiplatelet therapy. All the trials show an increase with dual antiplatelet therapy versus aspirin monotherapy. Of course, reassuringly, it wasn't an excess in fatal bleeding, no excess in intracranial bleeding; the only increase was in transfusions, and it seemed to occur relatively early; by "early," I mean in the first nine to 12 months of therapy. After that, risk of bleeding with dual antiplatelet therapy was similar to that with aspirin alone.

Slide 27 - CURRENT-OASIS 7: Double versus Standard Dose Clopidogrel

I'll just mention briefly the CURRENT-OASIS 7 Trial. This was a trial of double- versus single-dose clopidogrel in ACS patients, and found that the higher dosing of clopidogrel was superior

to standard dosing; and, by "higher," I mean, a 600-milligram load and a 150 milligrams a day for the first week as opposed to a 75-milligram-a-day maintenance dose, so that higher dosing in the patients who underwent PCI was superior to just the regular 300-milligram load, 75-a-day of clopidogrel.

Now, some have said that the trial is negative because, overall, there was no significant difference; that's true, but at least in those patients who went on to PCI, a large subgroup, there did seem to be a difference. And, of course, one could recite that and say, "You don't know who is going to go on to PCI." In the emergency department, that's true, but I think the concept here, regardless of the statistics, is real; that is, in patients with ACS, who go on to PCI, in particular, those patients really do benefit from more potent antiplatelet therapy. Here, as in all the trials, there is a bit of a price to pay with respect to bleeding, and, with clopidogrel, that risk is largely an excess in transfusions.

Slide 28 - 2º PREVENTION: Antithrombotic Therapies *P2Y12 Inhibition – Prasugrel*

Let me move now to prasugrel, which is basically a more potent version of clopidogrel, and it was studied in the TRITON-TIMI 38 Trial.

Slide 29 - TRITON-TIMI 38 Efficacy and Safety

Again, these are ACS patients but, here, where there is a plan for PCI and, in these patients, a significant reduction in ischemic events over the course of 15 months with prasugrel versus clopidogrel. An excess in TIMI major bleeding also seen here. But, in terms of absolute number of events, you can see there is a lot more ischemic events than there is bleeding. So even though there is a bleeding price to pay, overall, in the trial, the net clinical benefit seemed to be good.

Slide 30 - Prasugrel vs Clopidogrel According to Clinical Scenario

And in terms of the types of events that were being prevented, this slide shows that it was events related to stent thrombosis, with events related to peri-procedural MI. But, importantly, it was also a reduction – a significant reduction – in spontaneous MI. So, sometimes, doctors think, "Oh, it's just small peri-procedural MIs that are being prevented by these antiplatelet agents that are more potent," but, no, in fact, it is important events like spontaneous MI, and it is not all stent-related, so a benefit in high-risk patients because of their underlying atherothrombotic risk.

Slide 31 - TRITON TIMI 38: *Net Clinical Benefit Prasugrel vs Clopidogrel Subgroups; Post hoc Analysis*

As far as the net clinical benefit goes, not all the patients benefited in this trial, so patients with prior stroke or TIA in the TRITON Trial actually had harm and, for that reason, prasugrel should not be used in patients with prior stroke or TI because of intracranial hemorrhage risk.

As far as patients older than 75 or less than 60 kilograms, there, the prasugrel wasn't *worse* than clopidogrel but it wasn't better and, for that reason – concerns about bleeding and cost – many would say clopidogrel would be preferred in those particular subgroups, that is, patients 75 years of age or older, or that are less than 60 kilograms, in these underweight patients.

Slide 32 - TRILOGY: Primary Efficacy Endpoint and TIMI Major Bleeding Through 30 Months

Let me just mention the TRILOGY Trial. This was a trial of the medical management of ACS – so somewhat parallel to, or complementary to, the TRITON Trial, which was ACS treated with PCI – here with TRILOGY with ACS treated medically. And, in the overall trial, no significant difference between prasugrel and clopidogrel. Numerically, there seems to be a lower event rate with the prasugrel, but this didn't reach statistical significance. There was more TIMI major bleeding with prasugrel, but that also didn't reach statistical significance.

Slide 33 - TRILOGY: Primary Efficacy Endpoint to 900

The interesting part, I think, of the TRILOGY Trial was the analysis shown here. The patients who underwent angiography or didn't go under angiography prior to randomization, so pre-randomization variable, a legitimate subgroup to examine. And those patients who did not undergo angiography derived no benefit from prasugrel versus clopidogrel, whereas those that *did* undergo angiography did seem to have a benefit that was statistically significant and, actually, large and absolute drops.

Now, both subgroups of patients had high event rates, so these were high-risk patients, for sure. But potentially – and this is just conjecture on my part, but, potentially, those patients who underwent angiography were patients where the doctor thought, "Oh, you really do have an acute coronary syndrome, and you need a cath because you have an acute coronary syndrome, and that should be the standard of care"; whereas the patient who *didn't* undergo angiography, maybe they had some sort of chest syndrome and, perhaps, a positive biomarker, but maybe that was a heart failure exacerbation or a transient bout of AFib, or something else that wasn't well characterized, and they were *entered* into this ACS trial but, in the doctor's opinion, didn't have a real ACS; that's why the doctor didn't do an angiogram on these. So that's one explanation; it could be other things, too. But, nevertheless, if you interpret it the way I did, and this trial is consistent with all the others, an appropriately risk-stratified ACS patients with real CAD, more potent antiplatelet therapy which provides incremental benefit.

Dr. Cannon: You know, I think, Deepak, you've done a very nice summary there of this concept, that making a good diagnosis – and this was done angiographically in the TRITON Trial, where you had to be in the cath, about to have a PCI, a really *big* benefit –and then supported by this information here. And, as you've just said, if you have a real patient, especially for prasugrel people who've had a cath and are undergoing PCI, this is really a step forward.

Dr. Bhatt: And, in fact, that statement was based on work, of course, that you did many years ago with the TACTICS Trial where it clearly showed that, in appropriate risk-stratified ACS patients, an early invasive approach is the way to go. So I think there's a lot to be said for delineating the coronary anatomy, even if the ultimate decision isn't to revascularize, because it does help identify those patients who maybe *don't* need intensification even of their medical therapy.

Slide 34 - PLATO

So let me move on now to a trial that, in fact, Dr. Cannon really helped lead – the PLATO Trial. And this was a study of ACS patients, again, more of an all-comer trial so not just PCI, not just medically managed, not just surgically managed, but all of the above. And these patients were randomized to ticagrelor or clopidogrel for a year, obviously on top of aspirin and other good

therapy. And the trial found a significant reduction in ischemic events for ticagrelor versus clopidogrel, clearly consistent with all the other studies of antiplatelet therapy.

Slide 35 - PLATO: *Secondary Efficacy Endpoints Over Time*

But what was *interesting* and a distinguishing feature about this trial is what's shown here, that is, there was a significant reduction in cardiovascular death, not just in myocardial infarction, not just in stent thrombosis but also in cardiovascular death, for that matter, also all-cause mortality that was significant, about 1:100 patients less likely to die if they were randomized to ticagrelor versus clopidogrel. So that really is a major advance in the world of ACS.

Slide 36 - PLATO

And I think subsequent analyses that are particularly informative from the PLATO Trial are shown here, supporting the benefit of ticagrelor in patients who are initially managed in a non-invasive fashion or, as is much more common in places like the U.S., were managed with an initial invasive strategy, as shown by Dr. Cannon in the *Lancet,* a significant reduction in ischemic events. So regardless of the practice pattern or style of management, which, again in the U.S., is an early invasive approach, it appears that ticagrelor provides significant benefit over just clopidogrel.

Slide 37 - PLATO: Stent Thrombosis

As I mentioned, that reduction in ischemic events includes reductions in stent thrombosis for ticagrelor versus clopidogrel, and that benefit also extends to those patients who undergo CABG. So whether they're managed with medicines, initially, with a stent, or with surgery, in all those cases, it appears that ticagrelor is a better antiplatelet agent than clopidogrel.

Slide 38 - PLATO Invasive

Is there any price to pay for that? Yes, there is an increase in bleeding, as shown on this slide, as significant increases in non-CABG, PLATO, or TIMI major bleeding.

Slide 39 – PLATO *Non-CABG and CABG-related Major Bleeding*

But what's interesting and, again, different from the prasugrel versus clopidogrel trials, and different from the clopidogrel versus placebo trials, is that there was no excess in CABG-related major bleeding, which is actually pretty interesting because one would expect a more potent antiplatelet agent to cause more bleeding and to cause even *more* bleeding in the setting of bypass surgery. But, here, the more potent agent *isn't* causing more bleeding in the context of surgery, and this likely has to do with the fact that, biologically speaking, it's a reversible agent. Now, that doesn't mean, if you stop ticagrelor, it's out of your system in five minutes; it's an oral agent, of course, and it is dosed b.i.d., but, in general, it wears out sooner than does clopidogrel, on average, about three days versus five days, realizing, with clopidogrel, there's a fair amount of variability in response, and sometimes it wears out sooner or later. But, nevertheless, these pharmacodynamic properties appear to be a particular advantage in that patient who might ultimately go on to CABG.

Dr. Cannon: This has been, as you highlighted at the mortality benefits seen in this ACS population with this agent, has certainly captured a lot of attention and pushed people towards saying, "Well, maybe this really is an advance we need to try and offer." And, as you point out, that reversibility may explain how it fits in a little bit better with people who need to go off for CABG. So, again, a nice advance that we can offer for our patients.

Dr. Bhatt: Yeah, so, very, very well put and, of course, you had a lot to do with those advances.

Slide 40 - 2º PREVENTION: Antithrombotic Therapies: *PAR-1 Thrombin Inhibitor – Atopaxar*
Let me now shift a little bit to a different type of drug, a PAR-1 receptor antagonist, a thrombin inhibitor. Thrombin is, of course, the most potent plate agonist there is, and one agent that had been studied, that was an antagonist is atopaxar. Though, let me just remind you this drug isn't available, and I don't think it will be just given various issues of patent, license, and so forth. But, nevertheless, I think there are some useful things that were learned in its extensive phase II development that may be applicable to the class.

Slide 40 - LANCELOT-ACS: Atopaxar
So it was studied in the LANCELOT-ASC Trial phase II trial, really designed for safety, but, for what it's worth, it did seem like or numerical trends to lower ischemic events.

Slide 42 - LANCELOT-ACS: *Incidence of Holter-Detected Ischemia*
But, more importantly, then, the actual efficacy – which phase II was really hard to find, to assess; they are designed to safety – was this study of LANCELOT-ACS where Holter-detected ischemia was determined for eight hours after the loading dose of the drug was given. And what was found was a significant reduction in ischemia with this oral antiplatelet versus a placebo.

And I thought this was a pretty interesting finding because it just showed that an oral antiplatelet agent can indeed, at least in this early ACS population, lead to reductions in ischemia, not just in clinical events like with hard MI or stent thrombosis, or, or that sort of thing but, in fact, also just ischemia. And it goes back to some of the older data showing things like cyclic flow, a variation in arteries that were platelet-mediated phenomena. So an interesting way, I think, of tying together some of that older preclinical work with some human observations.

Slide 43 - LANCELOT-ACS: Atopaxar: *Incidence of Any TIMI Bleeding*
With respect to bleeding and atopaxar, of course it is a ponent antithrombotic agent. There wasn't any statistically significant excess in any TIMI bleeding there's shown here, but, numerically, it looked like there was probably something going on, and I think it was just an issue of power, why there wasn't any clearer signal. On the other hand, it might have to do with this mechanism of action compared with other approaches to antagonizing the platelet, but I think it probably is just a limited sample size.

Slide 44 - 2º PREVENTION: Antithrombotic Therapies: *Factor Xa Inhibitor – Rivaroxaban*
So let me move on now, and I'll return to PAR-1 receptor antagonists, but let me now just move on to some other developments occurring in parallel in the field of ACS and atherothrombosis, and turn to Factor Na inhibition with rivaroxaban.

Slide 44 - RIVAROXABAN: ATLAS ACS 2 TIMI 51
This was studied in the ATLAS 2 Trial. Again, ACS patients, this case randomized rivaroxaban through different doses, both of which are lower than the, Afib dose, versus placebo, and the trial on the significant reduction in ischemic events favoring rivaroxaban.

Slide 46 - RIVAROXABAN: ATLAS ACS 2 TIMI 51: *Efficacy Endpoints: Very Low Dose*
Importantly, with the very low dose of rivaroxaban that was studied – 2.5 b.i.d. – there was a significant reduction in ischemic events, as in the overall trial. But also with this lower dose – a

significant reduction in cardiovascular death that favored the rivaroxaban. So, similar to PLATO, once again another trial showing that, in ACS patients, moving beyond just standard aspirin plus clopidogrel is able to reduce cardiovascular events, MRIs, and thrombosis, that sort of thing, but also, importantly, reduce cardiovascular death.

Slide 47 - RIVAROXABAN: ATLAS ACS 2 TIMI 51: *Treatment Emergent Fatal Bleeds and ICH*

Now, these data, I think, are quite strong. There was a bleeding issue, though, as shown on this slide where there was a significant increase in bleeding. Now, shown in blue is the 5-milligram b.i.d. dose, the so-called "low dose," the 2.5 in yellow – 2.5 b.i.d., which is a very low dose, and there did seem to be a step increase in intracranial hemorrhage going from placebo to the very low dose of rivaroxaban, to the low dose, but still, overall, a reduction in CV and all-cause mortality with that 2.5-milligram dose. I thought a reasonable net clinical benefit, but regardless of my opinions, this isn't an FDA-approved regimen for ACS; though, in Europe, it is approved, though I don't think frequently used for ACS.

Slide 48 - Rivaroxaban – Clinical Trial Design of COMPASS

However, there is an ongoing trial with rivaroxaban; it's a CHARISMA-like trial examining stable CAD or PAD patients randomized to aspirin once a day, the control arm; or to rivaroxaban, 5 milligrams twice a day, alone, an experimental arm; or rivaroxaban at a very low dose, 2.5 milligrams twice day, plus aspirin. So the idea is to compare an antiplatelet to anticoagulant, to the combination. So I think, regardless of what that trial shows, it'll be very, very interesting.

Slide 49 - DAPT Study: Continuation of Thienopyridine:*12 Months after PCI: Efficacy*

Let me now move on to review some of the very recent DAPT trials including the DAPT Study. So this was a trial of stented patients who were randomized to 12 or 30 months of dual antiplatelet therapy, and the overall trial found a significant reduction in the two co-primary endpoints of MACE and stent thrombosis favoring longer-duration therapy. About a quarter to a third or so of the patients had an acute coronary syndrome.

Slide 50 - Risk of Cardiovascular and Bleeding Endpoints

This slide breaks down some of the leading endpoints showing, of course, the significant excess in bleeding with longer duration of DAPT – that's not surprising – but, fortunately no excess in fatal bleeding or an intracranial hemorrhage.

Slide 51 - DAPT Study: Continuation of Thienopyridine

There were some issues with the trial, where there was actually an increase in all-cause mortality in the longer-duration DAPT, and that seemed to be confined to the non-ACS patients; whereas, the ACS patients seemed to have a good clinical benefit. So I think there's a bit of subtlety in interpreting the study. But, at least, in the context of this talk, with ACS patients, the ACS subgroup from DAPT looked quite good.

Dr. Cannon: And I'd just like to note it, I'll just point out, on the prior slide, there was about two-thirds clopidogrel, one-third prasugrel where we have data on, and it was pretty consistent regardless of which agent was used for the longer-duration, so nice evidence for both those antiplatelet agents.

Dr. Bhatt: Yeah, that's a really good point.

Slide 50 - PEGASUS-TIMI 54: Ticagrelor

The PEGASUS Trial is a trial that was presented and published in the past year, and this was a trial of long-term ticagrelor meant to really be similar to a CHARISMA Trial or at least those subgroups from CHARISMA that looked good, such as the post-MI subgroup. And there were two different doses of ticagrelor – 90 milligrams twice a day – that's the ACS-approved dose; 60 milligrams twice a day, which is the very recently approved dose of ticagrelor for stable MI patients; or placebo, so a three-arm study. Of course, everybody got aspirin and other good background therapy. And over the median follow-up with 33 months, a significant reduction in ischemic events favoring either ticagrelor dose versus placebo.

Slide 53 - PEGASUS-TIMI 54: *Components of Primary Endpoint*

This slide shows the breakdown by different dose of ticagrelor, pretty consistent, as well as the full doses. As I mentioned, significant reduction in overall ischemic events, that is, cardiovascular death, MI, or stroke. Now, sort of trends towards reduction of cardiovascular death but not statistically significant; MI, of course, very significantly reduced by both doses, in particular the full dose gives a lot of events and a lot of statistical power.

Interestingly, stroke also reduced with the 60-milligram dose and in the full doses. And people often forget that the CHARISMA Trial had a reduction of stroke that was significant, and I don't mean any particular subgroup; I mean in the overall trial there was a significant reduction. So I think this finding here is a real finding, that is, in patients at high atherothrombotic risk because of a prior MI, they're at high risk of ischemic stroke, as well, and antiplatelet therapy seems to be able to modulate that risk.

Slide 54 - PEGASUS: Bleeding

Now, bleeding, of course, in the placebo-controlled trial, is increased with both doses of ticagrelor – the 60 and the 90 b.i.d., both TIMI major and TIMI minor bleeding increased by about two- to threefold, so not small increases. But, fortunately, no excess in fatal bleeding, no excess in intracranial hemorrhage with ticagrelor versus placebo, so largely transfusions that were increased. Not to trivialize that, but at least it's not stable bleeding.

Slide 55 - ANTITHROMBOTIC THERAPIES: Longer-term Protection *PAR-1 Antagonist – Vorapaxar*

So now we turn to vorapaxar, a PAR-1 antagonist.

Dr. Cannon: Deepak, on PEGASUS, that just has just been FDA-approved, that 60-milligram dose, so definitely a new advance in option. And, as you were presenting, and I have to admit I had not really paid as much attention to the stroke finding that you nicely highlighted, that may be the first time in a long time that, in a cardiac set of patients, more intensive therapy has been helpful. There has certainly been a lot of trouble and, as you highlighted earlier with prasugrel as compared to clopidogrel and ACS, that got worse, hemorrhagic stroke. So I think a very interesting additional benefit that's seen there in PEGASUS.

Dr. Bhatt: I agree with you. That is something that I think had largely been overlooked. In fact, as I mentioned, many people have forgotten that CHARISMA showed that, as well. And I think, now that we have a second trial – in fact, I'd say even a third trial that supports that concept – that it's a real finding.

And speaking of that third trial, let me move on to that now as I shift to speak a little bit about vorapaxar, a PAR-1 receptor antagonist. I mentioned atopaxar before. This is another drug in that same class, so this one *is* FDA-approved in patients with a previous MRI or peripheral artery disease. And that was based on the TRA 2ºP-TIMI 50 Trial.

Slide 56 - Vorapaxar

Shown here are the results and, specifically in the population of which the drug was approved, the overall trial was positive. But I'm showing here specifically those patients where the drug was approved by the FDA, so this excludes patients with a stroke or TIA in whom vorapaxar shouldn't be used because of intracranial hemorrhage risk. But in the study of the patients with the CAD or with, rather, MI or PAD as their entry criteria taking patients with stroke or TIA, the drug performed quite well, a significant reduction – about a 20-ish percent – with a risk reduction with vorapaxar versus placebo over long-term follow-up. There was an increase in GUSTO moderate/severe bleeding similar to all these trials that look at more potent antiplatelet strategies.

Slide 57 - Vorapaxar: Secondary Prevention (MI Cohort)

This slide here shows that this reduction in ischemic events occurred early – by that, I mean in the first year after randomization – but also late for several years, post-randomization. And it's about a 20-ish percent relative risk reduction in both cases, about a 1% absolute risk reduction in both cases; of course, the second curve is over a longer duration of follow up. So it's an ongoing risk that these patients face, and it does appear that more potent antiplatelet therapy really does help reduce that risk in the post-MI, post-ACS patient.

Also, not shown on this slide is the patient's risk. Prior MI here, there was actually a reduction in ischemic stroke in those patients with vorapaxar versus placebo, so that's what I meant a couple of minutes ago when I said there are really three trials supporting that concept – CHARISMA, PEGASUS, and TRA 2ºP – all showing that, in appropriate patients, there does appear to be a reduction in ischemic stroke with more potent antiplatelet therapy.

Slide 58 - Optimal Duration of DAPT?

So how can all this be integrated? It's a lot of data, a lot of trials, lots of recent approval drugs with the recent approval of the 60 b.i.d. of ticagrelor, relatively recent approval of vorapaxar, lots of different options here. Well, the first question is what to do with DAPT. How long should it be? And this slide attempts to summarize some of the thinking about durations of DAPT. And I'd say, overall, in the ACS patient, in general, if they're not at high bleeding risk, they probably ought to be on DAPT for longer than 12 months. In patients who are a high bleeding risk or actually have bleeding occurring during that first year, then it might make sense to curtail their duration of DAPT. Many other factors go into that calculus: whether the patient has diabetes, renal dysfunction, previous stent thrombosis, heart failure, PAD, all things that might push towards protracting the duration of DAPT. Or if they've got a single short lesion, stable CAD, second-generation DES, maybe, there, a duration even *shorter* than 12 months might be prudent. And there are ongoing studies to determine if there are patients where we can *decrease* their duration of DAPT. But those are largely stable patients getting second-generation DES.

I think the primary sort of predictor of who might benefit from well-protracted DAPT is the ACS patient.

Slide 59 - Guideline Recommendations

And we've got to see what the guidelines will say to all these new data, but the current duration of therapy after ACS, as summarized on this slide, is around 12 months per the different guidelines that are out there, that opine on this topic.

Slide 60 - 2012 ACCF/AHA Focused Update on UA/NSTEMI

And with respect to the guidelines, clopidogrel, prasugrel, ticagrelor – all three are guideline-endorsed with some preference now given to prasugrel over clopidogrel in invasively managed ACS patients, and preference given to ticagrelor over clopidogrel in conservatively or invasively managed patients, so in both cases.

Slide 61 - Antithrombotic Agents: *Comparative Clinical Attributes*

This slide summarizes a lot of the different data that Dr. Cannon and I have just been discussing. The clopidogrel data and the value of longer-term clopidogrel, as evidenced in CHARISMA and CAPRIE, and DAPT; the prasugrel data and the superiority over clopidogrel with respect to ischemic events and thrombosis, not all-cause mortality but other important cardiovascular events; the data for ticagrelor showing a reduction of ischemic events and thrombosis but also cardiovascular mortality and including benefits in patients who've ultimately gone to CABG and, most recently, the value of longer-term ticagrelor, in particular that 60-milligram b.i.d. dose in post-ACS/post-MI patients; and then, finally, the PAR-1 receptor antagonist and the only one that's actually been on is vorapaxar, which, for patients with a history of ACS and not directly covered in today's talk, also patients with CAD seems to provide additional protection beyond just standard antiplatelet therapy.

Slide 62 - Antithrombotics in Longer-term 2º Prevention: *Current/Future Issues and Opportunities*

For the future, there's a lot of different issues that need to be sorted out. As Dr. Cannon mentioned, when you think about it, there are a lot of different combinations, so antiplatelets, potentially going into anticoagulants, PAR-1 receptor antagonists, different durations of those different drugs. There are probably hundreds of different combinations if we did a sort of factorial calculation. And some of the issues that will need to be sorted out in coming years is how long to continue different therapies, whether we should switch from one to another, whether we should try to tailor therapy to the individual based just on high risk ischemic or bleeding features. Is there is potentially any role that will ultimately be validated for platelet function testing or genotyping? Are there other high-risk populations where we should be expanding the intensity and/or duration of antiplatelet therapy, PAD, ischemic stroke? And studies are ongoing in all those different areas.

So, Chris, what do you think? Where is the field heading? Where does it stand now? What should physicians on the front line do with all these trials and guideline recommendations?

Dr. Cannon: Well, just an amazing summary that you have. And I think the one short message is that we now have good evidence supporting more intensive antiplatelet therapy, on the one hand, and longer-duration antiplatelet therapy. And the key is to target that to patients who are at higher risk of ischemic events and, ideally, watch and avoid people who are high risk for bleeding; you know, that's easier said than done. But looking at the high ischemic risk to older patients and various other risk factors, to think about any of these different options to increase

over and above just aspirin, we have good evidence to do that where that will translate into reductions in major cardiovascular events.

The longer-duration, I think, in DAPT and PEGASUS looks very promising and, the most recent approval in this area. And so thinking about longer duration, we've actually been doing it since your CHARISMA Trial that the higher-risk patients were worried about. We continued the dual antiplatelet therapy, and now we have more evidence to support it. And I think being on the watch for bleeding and being sensitive to that as potentially stopping it if there are early signs of, of bleeding is what I do in my practice. So I've certainly looked to be more intensive and am looking for longer in the higher-risk patient.

Dr. Bhatt: Yeah, maybe I could ask you – because, of course, you highlighted the fact that there is a new approval of ticagrelor 60 b.i.d. – in whom might you use just clopidogrel beyond a year, which post-MI patient versus ticagrelor, realizing that, CHARISMA that's based on some subgroup data, a ticagrelor is based on an overall positive trial – PEGASUS. But, on the other hand, ticagrelor is a lot more expensive than clopidogrel. Clopidogrel now obviously has multiple generics andit's once a day; ticagrelor is twice a day. How do you decide which one to do in your own practice?

Dr. Cannon: Certainly, the 60 milligrams – I've yet to give that new dose, because it's just been, a week or so, but the idea of continuing therapy is someone were on ticagrelor post ACS, there, I would see that as a natural way to continue ticagrelor.

Cost becomes an issue for some patients. There are different ways that one can mitigate that cost, but the lower-cost option is certainly there, and so continuing some type of antiplatelet therapy is key. The higher level of antiplatelet therapy I think of in the higher-risk patients. So all of those factors, I think, factor in.

On the other hand, avoiding just having people floating around on just aspirin, I think all these different trials show that keeping the dual antiplatelet therapy in the higher-risk patient for a few years looks like a very good way to prevent a cardiovascular event.

Dr. Bhatt: Yeah. No, I agree. I mean, that's probably the most important message, that, for high ischemic risk, the patients who aren't at too-high bleeding risk, aspirin alone, if they're post MI or post ACS, is probably not sufficient.

And how do you see vorapaxar fitting in, especially with the clopidogrel or ticagrelor also potentially in the mix? That is, if you've got a patient that's several months post MI and, let's say, for some reason, just on aspirin but didn't have any particularly high bleeding risk, which of those three might you use, and what would determine that?

Dr. Cannon: Well, I have to say the bleeding profile for vorapaxar has been a little more worrisome, so I think aiming for people at lower risk for bleeding is where I'd open the door for adding that as an option. But it's a difficult balance because, as we know, the people who are at high risk of ischemic events, unfortunately, in the older, renal dysfunction, diabetes, who turn out to be the same risk factors for bleeding. But it certainly has very robust data over a several-year period there in that early post-MI period that looks very favorable.

Dr. Bhatt: Right, and also in PAD, though not directly the topic of our discussion today.

Slide 63 – Thank you

Great, well, I'd like to thank everyone for joining us for this review of some of the more recent data. Please go ahead and take the participant CME post-survey and evaluation. Your participation will help shape future CME activities.

Hopefully, this was an enjoyable hour or so and, hopefully, something that you can take back, that's useful to your practices.

Thank you so much for joining us.

Dr. Cannon: Thank you.

