



SPEAKER ORIENTATION

presented by

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Hello everyone, this is Sandeep Nathan from the University of Chicago recording the audio commentary to accompany the Optimizing Protection For Non-ST Elevation Acute Coronary Syndrome Patients with Antiplatelet Therapy, A Visiting Professor CME Program. This is the program sponsored by PCME and supported by a generous grant from Daiichi-Sankyo and Eli Lilly. For the purposes of this audio recording, I will refer to each one of the slides by title to minimize any confusion that may arise if the slides get shuffled in the future.

Okay, so let us begin. The first slide is the Table of Contents covering all of the major sections. You will notice that in the back-up slides there is also an additional section on antiplatelet testing that you may wish to use some of the slides from. So, the first slide is a sort of setup slide looking at the importance of the platelet in acute coronary syndromes, and there is a lot of build on the slide, so each one of the rectangles detects boxes up here as you click. While this is sort of represented as a wheel, I think it is important to recognize that there is considerable inter-relatedness between all of these issues, as well as considerable overlaps, so that is probably how I would present this: that high platelet reactivity is perhaps a quantifiable and modifiable risk factor and all of these other issues kind of get at that central scene.

Alright, so the first section is pathophysiology of atherothrombosis and the first content slide is atherothrombosis and its clinical manifestations. We all recognize that atherothrombosis represents a generalized disorder of vascular structure and function. And in white are all of the major manifestations of atherothrombosis in the various vascular beds. Accompanying it in yellow is a list of

many of the therapeutic modalities that we employ in these different vascular territories. The next slide is the role of platelet activation and aggregation. Platelet activation and aggregation, of course, represent a central event both in physiologic hemostasis, as well as pathologic thrombosis. This is a very complex slide that looks at many of the mechanisms by which platelets are activated and aggregated. Some of the key adhesive cells that were proteins and receptors are highlighted, as well. There is also mention of some of the pharmacologic compounds, which we will get into in greater detail in subsequent illustrations. So, I think one of the key issues to hit on this is that, while the glycoprotein IIb/IIIa receptor serves as the final common pathway for platelet aggregation via cross-linking of soluble fibrinogen, there are a number of adhesive receptors on the cell surface that bind various ligands and may be therapeutically modulated by the different compounds shown here.

The next slide is the central role of platelets and the interaction with coagulation in the genesis of thrombosis and thrombin (which is shown at the top of the slide) and its central role in this and binding with PAR-1. It is also the cross-over between the coagulation cascade and the platelet cascade; but very importantly, there is also the thromboxane prostanoid receptor, labeled as TP, and the ADP P2Y₁₂ receptor, both enormously important in terms of pharmacologic modulation with aspirin and the P2Y₁₂ inhibitors, respectively.

The next slide introduces the section on pharmacology of antiplatelet agents and the first illustration site of action of antiplatelet agents picks up where the prior illustration left off. The various receptors and the pharmacologic agents that bind these receptors are shown here. P2Y₁₂ inhibitors bind to pyridines like ticlopidine, clopidogrel, and prasugrel; and non-thienopyridines P2Y₁₂ inhibitors, like ticagrelor, bind the ADP P2Y₁₂ receptor. The PRT-128 compound may also bind this receptor. Thrombin, of course, binds the PAR-1 and PAR-4 receptors and the thrombin receptor antagonist, the first of which is SCH-530348, blocks this process. Aspirin interferes with generation of thromboxane A₂ via the COX-1 pathway and arachidonic acid precursors. And finally the glycoprotein inhibitors subset abciximab, eptifibatide, and tirofiban, block interaction of soluble fibrinogen with the glycoprotein IIb/IIIa receptor complex.

The next slide is a summary of some of the oral antiplatelet agents that are available now, as well as future agents. Aspirin, of course, is at the top of the list as a compound, as mentioned earlier, that blocks the generation of thromboxane A₂ by interference with COX-1 pathway in the platelet. Ticlopidine and clopidogrel represent compounds that have been around a while as P2Y₁₂ inhibitors that irreversibly bind this receptor and thereby reduce confirmation and activation of the glycoprotein IIb/IIIa receptor complex, as well as down-regulating the sensitivity of various other receptors. Prasugrel is the newest entry into this arena; also, an irreversible thienopyridines P2Y₁₂ inhibitor. Ticagrelor, representing a novel compound that we recently learned about in the PLATO study and a reversible agent, is the first oral entry into the CPTP class of agents, the cyclopentyltriazolopyrimidines. PRT-128 or elinogrel is another reversible agent that is available both as an oral and IV formulation, and SCH-530348, at the bottom of the slide, is the first in class of a thrombin receptor antagonist that binds PAR-1.

The next slide on pharmacokinetic and pharmacodynamic properties of antiplatelet therapies summarizes some of the key features of clopidogrel and

prasugrel with respect to metabolism and binding, onset of action, etc. I think the key point to mention in the slide is that both of these compounds are inactive oral pro-drugs that must be metabolized to their active state via the first-pass hepatic pathways. Clopidogrel unfortunately has a remarkably inefficient conversion multi-step sequential pathway that requires a number of enzyme sets. There is significant protein binding and delayed onset of action and significant interaction with the cytochrome P450 2C19 allele polymorphisms. Prasugrel, on the other hand, offers much more complete bioavailability with limited protein binding, very rapid onset of action, and, while it is a pro-drug that must be metabolized to its active state, the metabolic pathway is more efficient yielding a more active metabolite and higher levels of inhibition of platelet aggregation.

The next slide is sort of a summary of well over a decade of data. The evolution of antiplatelet therapy in acute coronary artery syndrome shows what we have accomplished as we have gone from placebo to aspirin, from aspirin to dual antiplatelet therapy with clopidogrel, and then to dual antiplatelet therapy with prasugrel. We see a stair-step reduction in ischemic events in high-risk patients. Accompanying that, however, is an uptake in major bleeding as we get to higher and higher levels of platelet inhibition.

The next section is effective antiplatelet agents on platelet reactivity, and the first slide is a summary of a number of studies that link high ex-vivo platelet reactivity and ischemic events. Now, preceding many of these studies there was considerable debate as to whether platelet reactivity or platelet aggregation was a metric that was a value in predicting future ischemic events and, more importantly, was this something that was modifiable with the goal of reducing ischemic events. I think we can say with conviction that, based on the abundance of retrospective data and prospective observational data, that the residual platelet reactivity or high levels of aggregation post-treatment really do constitute a very significant and independent risk for future ischemic events in patients with high-risk acute coronary syndrome who are undergoing PCI. The key set still evolving, of course, is whether this could be modified in a very deliberate and sort of logical fashion to reduce the future risk of ischemic events.

The next slide on platelet inhibition with antiplatelet therapies plots how platelet inhibition in patients treated with 300 of clopidogrel loading and 75 maintenance; 600 of clopidogrel loading and 75 maintenance in prasugrel, 60-mg loading 10-mg maintenance, and what we find is that compared to either dose of clopidogrel, prasugrel offers greater potency, more rapid onset of platelet inhibition, and more consistent inhibition of platelet aggregation with only a very narrow wedge of the population manifesting poor platelet inhibitory response.

The next slide is work from Samer Kabbani and colleagues from some years ago in an era that pre-dated drug-eluting stents and, even in the BMS era, there was a clear demonstration of baseline platelet reactivity pre-PCI seeming to determine one-year outcomes following coronary stenting. In patients with high platelet reactivity, at pretty much every time point, there was an excess of major adverse cardiovascular events.

The next slide on platelet reactivity in clinical outcomes is a more contemporary analysis. This is a subset of the EXCELSIOR data from Germany that looks at residual platelet reactivity. Now, the main thrust of this study was looking at

the cytochrome P450 CYP2C19 allelic variance and residual platelet aggregation, but this data very clearly shows that higher residual platelet aggregation is associated with an excess of MACE events.

The next slide shows three cumulative frequency distribution curves which essentially get at the same issue. Higher levels of residual platelet aggregation in patients who are treated with thienopyridines are associated with higher rates of stent thrombosis periprocedural myocardial infarction, as well as long-term post-PCI ischemic events. You may wish to present only a portion of this or none of it at all, depending on your time constraints and your audience.

The next slide is inhibition of ADP-induced platelet aggregation using various loading and maintenance doses of clopidogrel and prasugrel. So, if you look across the top you have clopidogrel and prasugrel, and across the side you have got loading doses and maintenance doses and so, certainly, 600-mg of clopidogrel yields more platelet inhibition than 300-mg at least in the short-term, and 150 of maintenance dose clopidogrel is more effective than 75-mg, at least with respect to platelet aggregation parameters. But, compared to any dose of clopidogrel, prasugrel is associated with greater levels of platelet inhibition, both in terms of the acute load, as well as the maintenance.

And in the next slide, impact of prasugrel versus clopidogrel on platelet inhibition, we see the data from PRINCIPLE TIMI 44, which is a relatively small, but very important crossover study that looked at the various permutations of clopidogrel and prasugrel loading and maintenance doses. The first set of graphs shows 6 hours post load of platelet inhibition in patients receiving 600 of clopidogrel versus 60 of prasugrel, and there is more than double the effect with respect to inhibition of platelet aggregation to 20-micromolar ADP stimulation. And the same is true with a 10-mg maintenance dose of prasugrel versus a 150-mg maintenance dose of clopidogrel, again more sustained and robust platelet inhibition as seen with prasugrel at both time points.

The next section is efficacy of antiplatelet agents and the first slide is the effect of aspirin dose on secondary risk reduction in patients with known vascular disease. This is a slide that I think is familiar to everybody. It is from the Antithrombotic Trialists' Collaboration analysis of about 65 trials of various doses of aspirin in patients with known vascular disease and the upshot of this trial or this analysis is that any dose of aspirin above 75 yields comparable risk reduction in the secondary prevention population. At less than 75, there is, in broad terms, directional consistency with all of the other groups of aspirin doses. However, the confidence interval is really quite wide and starts to overlap the line of unity, so any dose above 75 in Europe and any dose above 81 in the United States is associated with comparable protection secondary MACE events in patients with known vascular disease.

The next slide is also familiar, I am sure, to everybody. This is a top line analysis of CURE. CURE was a comparison of aspirin and placebo versus aspirin and clopidogrel. Clopidogrel administered as a 300-mg loading dose and 75-mg daily thereafter in 12,562 patients with acute coronary syndromes presenting within 24 hours of onset of ischemic tight chest pain. There was a 20-percent risk reduction in favor of dual antiplatelet therapy and that benefit does start early and it persisted for the duration of the 12-month follow-up period. In the next slide, we see the CURE PCI

sub-study, which again showed that there was benefit of early use of dual antiplatelet therapy. Now, remember that only about a third of these patients in the overall population underwent PCI in CURE. The majority of them (two thirds or so) were medically managed. Whereas a 20-percent relative risk reduction event was seen in the overall population, perhaps a more robust 31-percent relative risk reduction was seen in the PCI population of CURE.

The next slide looks at the CHARISMA data. CHARISMA was a large study looking at the value of extended dual antiplatelet therapy in sort of a mixed population, both primary and secondary prevention populations were included in CHARISMA. The primary prevention population was enriched on the basis of multiple risk factors and the secondary risk reduction population had qualifying coronary artery disease, cerebrovascular disease, or peripheral arterial disease events in their past. The overall population did not benefit in a statistically significant fashion. However, if you look at the pre-specified subgroups, at the top of this pictogram is the secondary prevention population posting at 12-percent relative risk reduction in ischemic events with dual antiplatelet therapy with a narrowly significant P-value. The primary prevention population, of course, did not evidence any benefit whatsoever with dual antiplatelet therapy.

The next two slides looked at post-hoc analysis from CHARISMA. The next slide is the CHARISMA post-hoc analysis of patients with prior myocardial infarction showing that if you had a prior MI you certainly did have significant benefit from dual antiplatelet therapy. Again, all of these post-hoc slides are only useful for hypothesis generation, but I think it bears mention that in this slide and the following slide, which looks at patients without prior myocardial infarction, there does appear to be a beneficial benefit on the basis of the type and amount of vascular disease you had in your past history.

The next slide is the design of TRITON TIMI 38, which is published recently in the *New England Journal*. In TRITON, 13,600 or so patients with high-risk acute coronary syndrome, either non-ST elevation acute coronary syndrome or ST elevation MI, scheduled to undergo PCI were randomized in a double-blind fashion to clopidogrel administered as a 300-mg load and 75-mg daily thereafter versus prasugrel 60-mg as a load and 10-mg daily thereafter. They were followed for median duration of 12 months. The primary and co-primary endpoints were shown on the slide.

The next slide shows the balance of safety and efficacy in TRITON TIMI-38 and it puts on the same scale the occurrence of the ischemic events, as well as the TIMI major non-CABG bleeds. There was a 19-percent relative risk reduction in ischemic events in patients treated with prasugrel versus clopidogrel following percutaneous coronary intervention, but this is balanced, if you will, with a modest increase in bleeding. I think it is important to mention in the interest of fair-balance that, while the absolute increase in bleeding is relatively small, there were a number of life-threatening bleeds that were seen in the prasugrel-treated patients including a small, but statistically significant, uptake in fatal bleeding, which rose from 0.1-percent in the clopidogrel-treated patients to 0.4-percent in the prasugrel treated patients.

The next slide shows the stent thrombosis analysis from TRITON, which demonstrates that prasugrel certainly did decrease, in a very substantial and clinically

meaningful fashion, the incidence of stent thrombosis compared with clopidogrel.

The next slide, TRITON TIMI-38 net clinical benefit, breaks out some of the high-risk subgroups of interest. So, in the post-hoc analysis of TRITON, three key subgroups were identified that perhaps merit greater caution when considering dual antiplatelet therapy. Those are patients with prior stroke or TIA, patients greater than the age of 75, and patients of low body weight, less than 60-kg. The key group of interest, I think, among these are the patients with prior stroke and TIA who did not derive any significant clinical benefit, but certainly did have a higher risk of bleeding, including intracranial hemorrhage, when treated with prasugrel versus clopidogrel. In the other two groups, the elderly patients and the patients below 60-kg body weight, there was neither clinical benefit nor net clinical harm, and so caution needs to be exercised when considering TAPT in these groups.

The next several slides address the persisting concern of duration of dual antiplatelet therapies in patients undergoing drug-eluting stent implantation. Slides 32 and 33 in this deck are derived from the Duke LANDMARK analysis and essentially illustrate that the lowest rates of events in patients in the Duke data bank analyzed in the context of a LANDMARK analysis were in the groups of patients who received a drug-eluting stent and were able to complete an extended period of dual antiplatelet therapy. In the interest of fair-balance, again, I think it is important to mention that numerous biases are built into any LANDMARK analysis, and this is no different.

And indeed, if we go to the next slide, we see sort of a counterpoint to that. This is the data from a very large DES registry experience, inclusive of 3,000 patients and 5,400 treated lesions. This is a slide titled “DES thrombosis and duration of thienopyridine therapy.” And what the investigators found was that although stent thrombosis did certainly happen with some frequency in the first year (about 1.9-percent), the majority of this was loaded within the first six months. From the 6-month time point until the conclusion of this study at 18 months follow-up, only an additional 4.5-percent stent thrombosis actually happened. So, within the first 180 days, 1.4-percent stent thrombosis; from 180 days all the way out to 18 months, an additional 0.5-percent stent thrombosis. And so this slide, as well as the following slide titled “Cumulative hazard for stent thrombosis,” illustrate that within the first 6 months, dual antiplatelet therapy was extraordinarily important, at least on the basis of this analysis. It is arguable how much dual antiplatelet therapy from the 6- to 18-month time frame is needed to prevent stent thrombosis.

The next slide on early discontinuation of antiplatelet therapy shows an important risk factor for stent thrombosis. It reflects the findings from Lakovou and colleagues published in *JAMA* a couple of years ago. And this is a finding that has been echoed by a number of other investigators. Premature discontinuation of dual antiplatelet therapies is associated with an extraordinarily high risk of stent thrombosis, compared to all of the other risk factors that have been identified. It appears to be the number one reason for stent thrombosis, at least early after DES implantation.

However, if you look at the next slide, which is “Percent of stent thrombosis not attributable to clopidogrel discontinuation,” a significant number of them also you have been unrelated to the consideration of DAPT discontinuation. So, DAPT continuation, at least in the early time frame and perhaps for an extended

period of time, is certainly important post-DES implantation. But, there are other factors at play here as well.

The next slide on mortality following PCI for ACS by clopidogrel use suggests that population mortality and nonfatal morbid events seem to rise quite significantly once clopidogrel is discontinued.

The next series of slides introduces this issue of interaction with the proton pump inhibitors in patients treated with dual antiplatelet therapy. These data are very much in evolution, and there is really an extensive list of studies that have looked at this and I think in fairness it should be mentioned that there are a lot of conflicting data. It is well beyond the scope of this program to parcel all of that data and try to figure out where the agreement and disagreement is.

The next two slides, starting with impact to PPI and platelet response to clopidogrel, and then the following slide on PPI and clopidogrel, summarize where we were until very recently with this issue. The first slide looks at platelet aggregation with various PPIs, and the upshot of this is that omeprazole is most likely to interfere with the therapeutic platelet inhibition that we are striving for with dual antiplatelet therapy. Pantoprazole and esomeprazole do not interfere with platelet inhibition in this analysis.

The next slide is from the Canadian Medical Association Journal published earlier this year and looks at PPIs, clopidogrel, and MACE. All of the key interactions are highlighted in yellow with boxes around them. Current use of PPIs did seem to increase the risk of major adverse cardiovascular events in this analysis. Although, pantoprazole seems to be the only "safe" PPI. The other PPIs that were evaluated, omeprazole, lansoprazole, and rabeprazole, all seem to increase major adverse cardiovascular events. More recently, however, we have learned from TRITON TIMI 38, PRINCIPLE-TIMI 44, and from the COGENT study, that perhaps the hazard associated with PPI use in DAPT patients was overstated.

The next slide on the influence of PPI use on antiplatelet drugs shows the data from PRINCIPLE-TIMI 44 and TRITON TIMI 38. Whether on clopidogrel or prasugrel, there appears to be no interaction with respect to major adverse cardiovascular events (at least clinical events). The PRINCIPLE-TIMI 44 data would suggest that perhaps there is an impact on platelet aggregation, but it does not seem to translate in the larger TRITON analysis.

And so, the next slide on the TRITON TIMI 38 PPI sub-study talks in a little bit more detail of hazard ratios and confidence intervals and again demonstrates that there appears to be no significant difference with respect to clinical events in patients on PPI and DAPT.

The next slide again is on impact of antiplatelet agents and PPIs on outcomes from TRITON-TIMI 38. The slide breaks out the MACE composite with respect to all of its components, showing that most of the point estimates straddled the line of unity with wide confidence intervals.

And the final slide of the section is data from COGENT, recently presented by Deepak Bhatt at TCT. It again shows the prospective assessment of omeprazole and clopidogrel. Not only did PPI (represented here by omeprazole) not increase cardiovascular events, they substantially reduced gastrointestinal events.

So, to summarize this section, there is remarkable similarity in this area with an earlier concern about a statin DAPT interaction, which ultimately was laid to rest.

The next section on dosing of antiplatelet agents begins with the slide from ALBION, higher levels of inhibition of platelet aggregation suggesting a dose-effect relationship. This compares 300, 600, and 900-mg of clopidogrel administered as a loading dose. The upshot of this is that either 600 or 900-mg yields more rapid and higher levels of immediate platelet inhibition than 300-mg. If a higher maintenance dose of clopidogrel is not instituted, however, presumably all these curves will eventually re-converge on 75-mg maintenance therapy. But, at least in the immediate peri-PCI period, there appears to be value in a higher loading dose of clopidogrel.

The next slide is data from the PREPAIR randomized study looking at 600-mg as a double loading strategy. 600-mg seems to drive down non-response, defined variably in the first graph as less than 10-percent response, less than 20-percent, less than 40-percent suppression of 20-micromolar ADP induced aggregation. Late aggregation also seems to be enhanced in patients treated with a conventional strategy of 300-mg the day before PCI or 600-mg greater than 2 hours before PCI vs the 600-mg double-load group represented by orange. So, to be clear about this, patients in this study who received either of the two conventional strategies that are widely implemented really had comparable levels of platelet aggregation at the time of PCI vs those who received 600-mg the day before PCI, as well as on the morning of PCI at least 2 hours prior to assessment of platelet aggregation.

The next slide is work from Bonello and colleagues that was also published last year. It looks at a vast guided strategy for reducing a hypo-response or resistance to clopidogrel. In this study, everyone received 600-mg of clopidogrel 24 hours prior to testing. Then, they were randomized to a control group vs a VASP-guided therapy group, if they were deemed nonresponsive to their first load of 600-mg. Non-responsive in the study was a VASP ratio of greater than 50-percent. Patients in the guided arm could receive up to three more loading dose of clopidogrel to make a total of 2.4-gm of clopidogrel, after which they were continued on standard therapy. At 30-day follow-up, as you can see in the second half of this slide, there were significantly fewer major adverse cardiovascular events in patients who underwent VASP-guided loading of clopidogrel, or rather reloading of clopidogrel. Very interestingly, in this admittedly small study, in a total of 162 patients there was no increase in major or minor bleeding. For a more detailed explanation of VASP phosphorylation or vasodilator-stimulated phosphoprotein phosphorylation, there are slides in the backup deck, as there are for light-transmission aggregometry and VerifyNow.

The next slide is the primary endpoint of OPTIMUS. OPTIMUS was a study that looked at the value of a higher maintenance dose of clopidogrel, 150-mg vs the standard 75-mg in diabetic patients who had responded in suboptimal fashion to a standard loading dose. In this study, patients who were non-responders or hypo-responders to clopidogrel, about 64 type 2 diabetic patients, were screened to get the 40 patients that were actually randomized in the study. The standard dose group continued for two months on 75-mg with assessment of platelet inhibition at time 0.1, 30 days later at time 0.2, and then 30 days later at time 0.3. The high-dose group received 150-mg of maintenance dose clopidogrel. As you can here, platelet inhibition

was driven off in those patients who received 150, but as soon as they were crossed back over between time 0.2 and 0.3 to standard dose platelet inhibition, they went right back to normal or right back to their baseline. Despite the improved response in the 150-arm of the non-responders, approximately 60-percent of these patients on 150-mg maintenance therapy still manifested suboptimal response.

The next slide shows the study design for the recently presented OASIS-7 trial. This is a very large multinational study looking at patients with high-risk unstable angina, non-ST elevation acute coronary syndromes, as well as stent implant for an early invasive strategy. These patients were randomized in a two-by-two factorial randomization to high-dose clopidogrel, 600-mg as a load, 150-mg on days 2 through 7, and 75-mg daily thereafter for the duration of the 30-day period vs the standard dose clopidogrel, a second factorial randomization to a full strength vs a low-dose aspirin after at least one dose of 300-mg or more of aspirin. The primary efficacy and safety outcomes are shown on the slide.

In the next slide, "Comparison of clopidogrel dosing: Primary outcome and components," the overall cohort did not do any better with high-dose clopidogrel. However, the pre-specified PCI cohort (comprised of the majority of the patients – 17,200 of the 25,000 who underwent PCI – clearly did do better with respect to myocardial infarction, as well as the overall composite, and this is driven, not surprisingly, in part by a reduction in stent thrombosis. The non-PCI cohort did just as well with the standard dose of clopidogrel as the high-dose clopidogrel.

The next slide is also from CURRENT OASIS-7 and breaks out the bleeding outcomes in the PCI population. While TIMI major bleeding was not significantly different in the high-dose clopidogrel vs standard-dose clopidogrel population, if you look at the second parameter, CURRENT major bleeding, and the second-to-last parameter, RBC transfusions greater than 2-units, both of those were increased in patients receiving the high-dose clopidogrel strategy.

The next slide is on the impact of maintenance and loading doses of antiplatelet agents on a residual platelet aggregation. This is a very small case series, but a fascinating one nonetheless, published in *Circulation* this year. It looks at platelet inhibition in 7 patients presenting with stent thrombosis. Response to platelet therapy was characterized both with point-of-care assays, as well as with light-transmission aggregometry. Genotyping for CYP2C19 alleles was performed and the upshot is that, as patients were increased on their maintenance dose of clopidogrel after a 900-mg reload, a stair-step reduction in the platelet inhibition or residual platelet aggregation was seen as you went all the way up to a maintenance dose of 300-mg daily. Unfortunately, the patients that actually did get to 300-mg daily had to be taken off of it due to arthralgias and GI toxicity, but I think it proves a point that higher doses of clopidogrel, at least in maintenance, do reduce platelet inhibition, although probably not in a tolerable fashion. On the other hand, prasugrel 10-mg, both numerically and statistically, is associated with a much higher reduction in platelet aggregation or residual platelet aggregation as compared with any of the other maintenance doses of clopidogrel.

The next slide is the design of the GRAVITAS trial. The GRAVITAS trial is one of the number of trials that is investigating the value of tailored antiplatelet therapy. I think this is a particularly important trial since it will be the first one to hopefully evaluate with point-of-care aggregometry in a relatively large population

(about 2,800 patients). Patients are going to be stratified on the basis of high residual platelet reactivity using the acoustic VerifyNow whole blood assay, and then randomized to standard-dose clopidogrel 75-mg daily for 6 months vs high-dose clopidogrel 150-mg maintenance dose for 6 months following for the occurrence of major adverse cardiovascular events. At the end of this, hopefully we will have some sense of whether there is value in prospectively characterizing platelet reactivity and altering antiplatelet therapy on the basis of residual platelet aggregation.

The next slide is TRILOGY. This is a study looking at the value of prasugrel vs clopidogrel in medically managed unstable angina and non-ST elevation MI patients. The primary efficacy endpoint is the composite cardiovascular death, myocardial infarction, and stroke.

The next section is on understanding antiplatelet response variability, and this is a one-hour talk in and of itself. I think that the challenge here is going to be picking out some of the key pieces of information and conveying it relatively quickly. The first slide in this section on mechanism of clopidogrel response variability is a very nice summary of the numerous considerations related to this issue of clopidogrel response variability. I touched upon some of the considerations in one of the earlier slides. Clopidogrel is an oral pro-drug that is absolutely inactive in its ingested form and requires first-pass hepatic transformation. It does so through the sequential pattern shown here. A number of cytochrome P450 enzyme sets are involved, 3A4, 3A5, CYP2C19, 1A2, 2B6, and so on before the active thiol metabolite is yielded. Meanwhile, 85-percent of the ingested compound is degraded by esterases and is not available for biotransformation. Once the active thiol metabolite is actually generated, there are a number of receptor-level issues that may impede antiplatelet response, including P2Y₁₂ receptor polymorphism. Very importantly, there has been a lot of focus on genetic polymorphism of the hepatic enzymes. We will touch upon that in some of the subsequent slides.

The next slide is a summary of pharmacogenomics consideration. It is fairly self-explanatory. Various receptors and enzymes may impact the biotransformation, efficacy, and pharmacodynamics of various antiplatelet agents. This is a body of data that is very rapidly evolving.

The next slide, the first clopidogrel responsiveness study, looks at the response variability phenomenon at various timeframes within the first two hours after a 300-mg loading dose of clopidogrel. The majority of patients, 63-percent, are “resistant” or significantly hypo-responsive. That decreases to about 30-percent at 24 hours. And at 5 days and 30 days only about 15-percent of patients are significantly hypo-responsive to a 300-mg loading dose of clopidogrel.

The next slide, “Does more clopidogrel alter responsiveness?”, introduces issues with 600-mg clopidogrel. It not only elicits a more rapid response, but also drives down the incidence of hyper-responsiveness. Certainly, both of the graphs represent calcium distribution, with the distribution shifted overall to the right with 600-mg of clopidogrel vs 300 in resistance, driven down from 28-percent with 300 in this analysis to 8-percent with 600. So, 600-mg certainly does seem to do a few things that are perhaps of therapeutic value. It more rapidly achieves plateau platelet inhibition. The absolute degree of platelet inhibition vs 300 appears to be higher, at least in the immediate timeframe, which may be of relevance if patients are being loaded immediately pre-PCI. It also seems to drive down relative hypo-response or

non-response.

The next slide shows the response variability of antiplatelet agents, prasugrel vs clopidogrel, and it breaks it out with respect to the various individual issues: absorption, metabolite formation, polymorphism of the cytochrome P450 enzyme sets, the impact of allelic variance of CYP2C19, and various other proposed mechanisms that may impact antiplatelet responsiveness.

The next slide is clopidogrel non-responsiveness and its correlation with 3A4 enzyme activity. As shown on one of the prior slides, there is a sequential enzymatic pathway for metabolism of clopidogrel to its active thiol metabolite in 3A4 and 3A5 in the sequence. This is data that was presented a few years ago and subsequently published looking at the level of cytochrome P450 3A4 enzymatic activity and responsiveness or generation of active metabolite and reduction in platelet aggregation 4 hours post clopidogrel. It certainly does seem to track the activity of the CYP3A4 enzyme set.

The next slide is data I think everyone is familiar with. Prasugrel appears to be effective even in clopidogrel non-responders. So, in patients who are responsive to clopidogrel, there is a further increment in platelet inhibition. But, in patients who are non-responsive to clopidogrel (represented by the blue line), all of these patients were also converted to a fairly tight range of platelet response, all above 50-percent inhibition of platelet aggregation at 24 hours following the loading dose.

The next slide again looks at the rate of non-responders to P2Y12 inhibitors in aspirin-treated patients, whereas a significant proportion of patients receiving 300-mg of clopidogrel immediately after the loading dose are hypo-responsive or non-responsive. Only about 3-percent of patients receiving 60-mg of prasugrel are hypo-responsive, and that drops further to 0-percent with prasugrel at day 28, vs 45-percent of clopidogrel-treated patients who are still non-responsive. Now, in presenting all these slides, I think it is very important to emphasize that we really have not defined what the biologic cutoff is for non-responsiveness, and so all of these are relatively “arti-factual” cutoffs. In this study, non-responsiveness was defined as inhibition of platelet aggregation less than 25-percent in response to 20-micromolar per liter ADP stimulation. In other studies, the cutoff is less than 10-percent. These are all nice round numbers that are implemented in the studies, but it remains to be seen what the most valuable or clinically relevant cutoff for platelet inhibition is. There are a number of studies underway that will hopefully shed some light on that. We already have some data, of course, both with light transmittance aggregometry from Paul Gurbel’s group, as well as with point-of-care aggregometry using VerifyNow from the Scripts Group. But, I think it is important to recognize that these cutoffs are somewhat artificial.

The next series of slides get into cytochrome P450 2C19 allelic variance and the occurrence of MACE in clopidogrel-treated patients. The first slide is from the Triton-TIMI 38 analysis, published in the *New England Journal*, looking specifically at clopidogrel and splitting things up by the CYP2C19 to allelic start to 2 allelic variance. Carriers certainly seem to have a higher rate of MACE. The primary efficacy outcome is on the first slide, and definite or probable stent thrombosis is shown on the second slide. I think for all of these slides, it really merits a very close read through the source data – this was a fairly involved study – as well as the accompanying study in *Circulation* earlier this year, looking at allelic variance and MACE following treatment

with prasugrel, again taken from the Triton-TIMI 38 experience. The *New England Journal* paper was two studies in one that looked at the prevalence of various allelic variants in normal individuals receiving clopidogrel, and then carrying that forward to look at major adverse events in patients taken out of the Triton-TIMI 38 data set. The theme, however, in all of these slides is that clopidogrel seems to be impacted quite significantly by CYP2C19 allelic variance representing poor metabolizers of clopidogrel, whereas prasugrel does not.

The next slide shows how carriers vs non-carriers of the reduced function CYP2C19 allele are impacted when treated with clopidogrel vs prasugrel, and there appears to be no interaction.

Another analysis is presented in the next slide on allelic CYP2C19 star 2 variant associated with increased MACE events post PCI. Once again, patients who are carriers seem to suffer with respect to the primary composite of ischemic morbidity and mortality, as well as definite stent thrombosis, when treated with clopidogrel.

The next slide, "Pharmacogenomics of prasugrel," is sort of the companion analysis of the paper from the *New England Journal* presented a few slides ago. It is now looking specifically at the pharmacokinetics and pharmacodynamics of prasugrel, which do not appear to be impacted significantly by all of the different allelic variants that are presented. Very importantly, the CYP2C19 resulted in a 32-percent reduction in the area under the curve of active metabolite with clopidogrel and a 9-percent absolute reduction in platelet inhibition with clopidogrel.

The final section is on investigational antiplatelet agents. Ticagrelor, I think, is a compound that has gained a lot of visibility and interest with the presentation and simultaneous publication of the PLATO data. Ticagrelor represents, as I mentioned earlier, the first oral entry into the new class of agents known as the cyclopentyltriazolopyrimidine (or CPTPs for short). Ticagrelor is an orally active drug that does not require metabolic transformation to exert its inhibitory effects. There is no active metabolite. It is a very rapid onset of action and it is a reversible agent which is gone within about 24 hours after the last dose. Compared to clopidogrel, this also is associated with greater and more consistent platelet inhibition.

The primary endpoints, major efficacy endpoints at 12 months of PLATO, are shown on the next slide. They show that there is a substantial reduction in ischemic morbidity and mortality in patients treated with ticagrelor vs clopidogrel, when they present with high-risk acute coronary syndromes. I think one of the major distinctions of PLATO vs Triton-TIMI 38 was that, in PLATO, patients were treated before the decision to intervene was undertaken. Whereas, in Triton-TIMI 38, all of the patients that were included were scheduled to undergo PCI, either primary PCI for STEMI or scheduled PCI for high-risk non-STEMI or unstable angina. And so, the primary endpoint death for vascular cause is myocardial infarction. Stroke was reduced, but I think the really interesting, intriguing finding here is that death from any cause was also significantly reduced in patients randomized to receive ticagrelor vs clopidogrel.

Very interestingly, while the primary ischemic endpoint was suppressed in patients receiving ticagrelor, and all of the Phase I and Phase II data would indicate that ticagrelor yields superior levels of platelet inhibition to clopidogrel, there

was no increase, no statistically significant increase, in major bleeding in patients treated with ticagrelor. The breakout of some of these endpoints are also available in the backup slides.

The next slide introduces the thrombin receptor antagonist, SCH530348, which is a PAR-1 inhibitor that does not require metabolic activation. Again, it is active in its orally ingested form, has a very rapid onset of action, and potentially may not increase bleeding. TRA-PCI is the phase II study that was recently published in *Lancet*. It was presented a couple of years ago and this was a study of patients undergoing non-urgent PCI or cath with possible PCI. A total of 1,000 or so patients were enrolled. Ultimately, about 573 patients underwent PCI and were randomized in an equal ratio to receive one of three doses of SCH530348 vs placebo; they then underwent a second randomization for the maintenance dose of the thrombin receptor antagonist.

The next slide shows the primary endpoint, which is a safety endpoint of TIMI major and minor bleeding. While it is tempting to say that there was a stair-step progression, at least a numeric progression in major bleeding with increasing loading doses of TRA, if you look at all TRA patients together vs placebo, there was no significant difference at all.

The next slide shows myocardial infarction, the PCI Cohort, and I think it is important to mention that this study was in no way powered to look at efficacy endpoints. However, again, there is sort of a numeric trend in favor of lower rates of myocardial infarction in patients treated with any dose of TRA.

The next slide sets up the investigational compound elinogrel, which is a reversible inhibitor of P2Y12 also available as an intravenous compound, in addition to the oral formulation. It is currently in development for both acute and chronic ischemic management. Additional slides, looking at Elinogrel in ERASE-MI, as well as Innovate-PCI, are included in the backup slide set.

So, that brings us to the conclusion slides. Platelets are the principal effectors of cellular hemostasis, a very key component of pathologic thrombosis, and we at least touched upon the numerous receptors that are involved in platelet activation and aggregation, as well as some of the potential targets for current and future antiplatelet compounds. The thrust of this, of course, is that there is a significant response variability that is seen with clopidogrel, and that does seem to translate to an excess of ischemic events in high-risk patients. The relationship between non-responsiveness or high platelet reactivity on treatment and adverse clinical events has been clearly demonstrated, with antiplatelet non-responsiveness emerging as a very important and potentially modifiable clinical entity.

The next slide summarizes some of the key bottlenecks in clopidogrel response from intestinal absorption to genetic variations and the cytochrome P450 isoenzyme sets, as well as polymorphisms at the level of the P2Y12 receptor. Antiplatelet therapy with higher doses of clopidogrel may yield some benefit in certain individuals; however, the newer compounds, prasugrel and perhaps in the future some of the pipeline agents, will more definitively address this issue of non-response or hyporesponse in patients at high risk for future atherothrombotic events. I think the final caveat to all of this is that while the newer data suggests that perhaps there is a disassociation between therapeutic efficacy and the risk of bleeding, the majority of

the data would suggest that higher levels of platelet inhibition are in large part associated with at least a modest increase in major and minor bleeding, particularly in the peri-PCA period.

I think that concludes the speaker's notes for the slide set. Thanks so much for your attention.