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Highlights from ACC.20/WCC Virtual Late-Breaker Session

Dr. Gibson:
The COVID-19 pandemic represents a significant and unique challenge for the cardiology community. For the first time in history, The American College of Cardiology had to cancel their scientific sessions due to the pandemic and instead organized a three-day virtual meeting, during which practice change in clinical trials were featured. And today, we'll be discussing highlights from six of those trials. Welcome to ReachMD, I'm Dr. Michael Gibson, a Professor of Medicine at Harvard Medical School and joining me today are Dr. Deepak Bhatt and Carolyn Lam. Dr. Bhatt is the Executive Director of Interventional Cardiovascular Programs and Professor of Medicine at Harvard Medical School, and Dr. Carolyn Lam is the Senior Consultant of The National Heart Center in Singapore and Professor of Duke-NUS Cardiovascular Academic Clinical Programs. Dr. Bhatt, Dr. Lam, it's great to have you both on.

Dr. Bhatt:
It's really great to be here with you, Mike, especially at this time.

Dr. Lam:
Likewise.

Dr. Gibson:
Thanks Deepak. Thanks Carolyn. Well, let's jump right in. Uh, Carolyn, you're a heart failure expert. Talk to us about some of the findings from the VICTORIA Study.

Dr. Lam:
I'd love to tell you about VICTORIA. So, as you said, it was presented virtually as a late-breaking trial. It randomized 5,050 patients with worsening, chronic HFrEF to receive vericiguat or placebo. Vericiguat being a soluble guanylate cyclase stimulator and with the primary outcome being a composite of cardiovascular death of first heart failure hospitalization. So, I think the first thing I really want to point out about VICTORIA is – it was a high-risk heart failure population, which few prior trials have really addressed. Two-thirds were enrolled within three months of a heart failure hospitalization, 60% were on triple therapy, 90% on dual therapy, 15% what – already had an ARNI, 30% had the device. So, this is a really well treated, high-risk, uh, heart failure population with a median NT-proBNP of 2,800. So, over immediate follow up of only about 10.5 months, the targeted number of events was already achieved with a primary event occurring in 35.5% in the vericiguat group and 38.5 in the placebo group, and that was a significant reduction with a hazards ratio of 0.90. In other words, a relative risk reduction of 10%. Now here's where it's important to remember that the population we're talking about because the annualized primary event rate that I just mentioned, are three times higher than that of, for example, PARADIGM heart failure or DAPA-HF and the NT-proBNP, but - was almost two times higher than in those prior trials. Thus, even though the relative risk reduction may seem moderate of 10%, it actually translates into a clinically meaningful, absolute risk reduction and that was 4.2% per year, meaning an annual number needed to treat of only 24 to prevent this composite of cardiovascular death or heart failure hospitalization. And remember, this is on top of excellent therapy. And the final point was vericiguat was generally safe and well tolerated. There was a little bit more tendency for symptomatic hypotension and syncope and more anemia with vericiguat, but the serious adverse events were similar to placebo. Importantly, no adverse effects, electrolytes, or renal function. Remembering that this included patients all the way down to a GFR of 15, lower than we've before and yet at 12 months, that 10 mg target dose of vericiguat was achieved in – in 90% of patients, similar to placebo. So, I really think Clyde Yancy who was the commenter at the ACC late-breaker said it best. He said we've got another win for HFrEF. And – and, you know, I agree. It's a new pathway. It's stimulating a good thing. It's stimulating cyclic GNP rather than blocking the bad stuff with all our renin-angiotensin blockers so on. It's a high-risk patient group with significant unmeant needs and vericiguat - you know – once daily, easy to titrate, safe, well tolerated. No need to monitor renal function. So, I think it – it is an important novel addition to our guideline-based treatments for HFrEF.

Dr. Gibson:
Yeah, and a number needed to treat of only 24; quite impressive. Carolyn, talk to us a little bit about PARAGON HF.

Dr. Lam:
Ah, Mike, you'll remember discussing PARAGON with me when – when it just came out at the ESC. And as I reminded everyone, PARAGON randomized a bit more than 4,800 patients who had HFpEF to receive sacubitril-valsartan or valsartan and it narrowly missed its primary composite outcome, which was cardiovascular death and total heart failure hospitalizations. With that infamous p-value of 0.059. And I think you'll remember what was really talked about was that significant heterogeneity with possible benefit of sacubitril-valsartan in patients with a lower ejection fraction and in women in particular. So at the ACC, there was some follow up to this that I think are clinically relevant. So, one of them presented as an, oh, an oral session that was streamed online, focused on NT-proBNP and basically showed that baseline NT-proBNP, as you may expect, predicted events in HFpEF, and sacubitril-valsartan reduced NT-proBNP by 90% versus valsartan. But importantly, NT-proBNP did not appear to identify the patient most likely to benefit from sacubitril-valsartan. In other words, it didn't modify the relationship, or the treatment that – and it did not explain the differences between men and women or higher or lower EF. Uh, there was another, presentation that was a moderated poster that focused on systolic blood pressure. Really asking, is there a sweet spot, systolic blood pressure and HFpEF, and, were the potential benefits of sacubitril-valsartan mediated by blood pressure reduction. Well, the short answer is, a mean, baseline and mean achieved systolic blood pressure of 120 to 129 mmMg appear to identify that no-risk risk patients with HFpEF, so that may be the sweet spot. But baseline, blood pressure did not modify the treatment effect and blood pressure lowering did not account, uh, for the effect of sacubitril-valsartan either.
One more, is focusing on age. This was a poster on demand and – and it really points out that we may need to watch out for blood pressure in some patients, particularly the elderly. So, it – it basically looked at the influence of age and showed that the efficacy of sacubitril-valsartan relative to valsartan was not modified by age, but, um, hyperkalemia and renal dysfunction were actually lower with sacubitril-valsartan regardless of age, and hypotension, though, was more frequent among the older patients. So, we may need to watch that with our older patients. And then finally, because heart failure is becoming, such a condition that we need polypharmacy for. There was another poster that looked at, um, outcomes with concurrent mineralocorticoid receptor antagonist MRA use in PARAGON-HF. So, um, you know, MRA use was – was in more than a quarter of patients at baseline. Uh, an increase over the course of the study and that the short, uh, message is the clinical efficacy of sacubitril-valsartan was consistent regardless of background MRA use. Sacubitril-valsartan, in fact, attenuated the decline in GFR over time relative to valsartan with a larger effect size in patients on concomitant MRAs. So, clinically, this means addition of sacubitril-valsartan to MRA is safe, uh, without an increased risk of hyperkalemia or worsening renal function. So, those are some important messages from ACC.

Dr. Gibson:
Carolyn, thanks so much. Alright, well another hot topic has been the use anticoagulants in the setting of chronic and acute coronary syndromes. Deepak, you presented data from the diabetic subgroup from COMPASS. Tell us what you found.

Dr. Bhatt:
Yeah, absolutely. Well, this was really referring to dual pathway inhibition. Maybe it's a term people aren't so familiar with. Everyone knows about DAPT or dual antiplatelet therapy, but this is a concept of combining an antiplatelet and a low dose of an anticoagulant, dual pathway inhibition, and really it was you, Mike, that brought this strategy into the light with the ATLAS-2 trial showing that a combination of aspirin and what I'll call a vascular dose of rivaroxaban 2.5 mg twice a day reduced ischemic events quite significantly in patients presenting with an acute coronary syndrome. That study included a significant reduction in all-cause mortality, as well as cardiovascular mortality. That led to the COMPASS trial. That and – and some observations from prior trials like COMPASS. Taking that strategy of dual pathway, uh, inhibition to study patients with either CAD or PAD. So, that's the broad COMPASS trial and those patients were randomized either aspirin alone, aspirin plus placebo, but aspirin alone versus aspirin plus that same dose of rivaroxaban. Now there's another, um, rivaroxaban alone at a lower dose that I won't discuss because that didn't really shine. It didn't look awful, but it didn't – meet statistical significance, but the winning arm in that three-arm trial was the aspirin and the vascular dose of rivaroxaban. So, that's - the overall COMPASS trial positive study led to the FDA approval of rivaroxaban at that dose in that COMPASS-like population. What was presented at ACC virtually, as a late breaker and published simultaneously in Circulation was COMPASS-Diabetes. Well, we looked specifically at that subgroup of patients with diabetes at enrollment into their study, to see how that regimen of dual pathway inhibition compared with aspirin alone. And what we found, first of all, is that the results in both those patients, with and without diabetes, were "positive" for the primary endpoint. That is, there was a significant reduction in MACE or Major Adverse Cardiovascular Events in both those subpopulations. So, it is with diabetes and COMPASS, those without diabetes, and again, everyone had coronary artery disease or peripheral artery disease or both. But what was interesting, was even though their relative risk reductions were similar and statistically significant, the absolute risk reduction was larger, numerically speaking, in those with diabetes because of their higher baseline risk by virtue of having diabetes. And what I've been talking about here is the primary endpoint of cardiovascular death,

myocardial infarction, or stroke, but if one looks at the endpoint of all caused death, there too, there was a consistent relative risk reduction in both those patients with and without diabetes and COMPASS. However, the absolute risk reduction for mortality was three-fold higher in those with diabetes versus those without diabetes. So, I think this really illustrates, first of all, the high rate of death in these people with diabetes and concomitant to their atherosclerosis, but the potential benefits of going beyond just aspirin alone is a concept that, you know, other trials, such as CHARISMA with aspirin and clopidogrel or PEGASUS, with aspirin and ticagrelor also gotten, that is, if you got lots of atherosclerosis, even if you're stable, there is a benefit of doing more than aspirin alone, but here I think we've shown nicely with – in a regimen that is approved broadly in the U.S. and in many regions of the world for this large population of folks with stable atherosclerosis again, CAD or PAD or both. Uh, hopefully at low bleeding risk, otherwise, the strategy can backfire. That adding to just aspirin alone in that stable outpatient, you might, otherwise, say well they're doing okay, I'm not going to mess with them, is often the right thing to do.

Dr. Gibson:
Great, Deepak. One of the most exciting things, I thought, at the meeting was what you showed about EPA levels and outcomes in the REDUCE-IT study. Tell us about that.

Dr. Bhatt:
Sure, so just a really quick recap of REDUCE-IT, that was an 8,000+ patient trial, patients had either established atherosclerosis could be in there in their coronary or cerebral vasculature, their peripheral arteries, or had to have diabetes and, at least, one cardiovascular risk factor. So a hybrid secondary prevention, high-risk primary prevention trial, and in addition to those clinical criteria, patients had to have triglycerides that ended up being over 100 mg/dl or so – so the range of, high normal to mildly elevated to moderately elevated triglycerides, the intent was to enroll about a population of, let's say, triglycerides between 135 or 500 that had ended up with about 10% with normal triglycerides. So, atherosclerosis or high-risk primary prevention plus elevated triglycerides, those patients were randomized icosapent ethyl versus placebo. Icosapent ethyl being a highly purified ethyl ester of eicosapentaenoic acid or EPA, which is an omega-3 fatty acid, but this is a prescription medicine, very tightly sort of manufactured, regulated, a composition that is very pure with respect to its EPA. So, very distinct unlike say, fish oil supplements, which have never been shown to provide any cardiovascular benefit. So, that's the overall trial – overall trial. Very positive significant reductions in ischemic events – ischemic events including things like cardiovascular, death where there was a 20% reduction that was significant – significant reductions in MI, stroke, hospitalizations for unstable angina, revascularizations, sudden cardiac deaths, cardiac arrests. So, very positive overall trial. What we've done most recently, what I presented just about a week ago as a late breaker at ACC Virtual, was the EPA or icosapentaenoic acid levels from the overall REDUCE-IT trial. The first part looked at baseline levels and showed that the benefits of icosapent ethyl versus placebo were consistent across the fuller range of baseline EPA levels. Why does that matter? Well, some people have said, what if I eat a lot of fish and seafood and – and "naturally" getting higher EPA levels. Well, that's true. If you do eat a lot of fish and seafood, your EPA levels will be higher than someone that doesn't. However, even in the highest, say, tertile of EPA levels in our study, at baseline, there was still significant and substantial benefit from having been randomized to icosapent ethyl versus placebo. So, it's not the case at all. You can just eat a lot of fish and get the benefits that we observed in REDUCE-IT or there's still incremental benefits even in people that have high baseline EPA levels because of diet or because of other factors we don't really even know of, genetics and other things that might contribute to variability and baseline EPA. So that was part one. Pretty interesting I think just in terms of applicability of the trial results to populations that might have higher baseline EPA levels. The second part, which I think is scientifically really quite provocative is that we looked at on-treatment levels of EPA and what we found were highly statistically significant correlations between on-treatment EPA levels and lower risks of endpoints, such as cardiovascular death, MI, stroke, revascularization, hospitalization for unstable angina, sudden cardiac death, and cardiac arrest. So, all those endpoints where we saw clinically significant reductions, now we're seeing very strong correlations with attained EPA levels and benefit. Now going beyond just that, what we also saw was – was in the overall trial, there was a trend towards lower all-cause mortality, which I think would have been significant probably if we just could have kept the trial going a bit longer, and in the large USA subgroup has published in Circulation a couple of months ago, we did, in fact, see a 30% lower all-cause mortality that was significant, but, nonetheless, in the overall trial was a trend with our analysis looking at EPA levels again, a very strong statistically significant correlation with on-treatment EPA and lower all-cause mortality. And as far as the endpoint of heart failure in the overall trial was numerically lower with icosapent ethyl versus placebo, but that wasn't a statistically significant finding. What we found in this EPA level analysis, was again a very strong and tight correlation between on-treatment EPA levels and lower rates of hospitalization for heart failure and no heart failure. And just to remind the audience, this is a double-blind placebo-controlled trial. All the events were blindly and independently adjudicated by your group, Mike, that you were chairing. So, uh, these sorts of endpoints I – I think you can take to the bank. They are objectively defined, and we're seeing statistically significant associations here with EPA levels. So, I think what we've done is take the results from REDUCE-IT, which really, I think, were quite remarkable in terms of clinical endpoint reduction, but now provided the mechanistic underpinning of why we might have seen such large risk reductions both in relative and absolute terms across a variety of different endpoints, now extending that to heart failure.

Dr. Gibson:
Fascinating Deepak, and it makes you wonder if, uh, you know, EPA levels themselves are biologic target. I think it's just absolutely fascinating. Thanks for sharing that with us. I am going to share the results of a couple of, uh, trials. One was TAILOR-PCI. I think everyone knows that there's a substantial number of people out there who are resistant to clopidogrel. They don't metabolize it well. And, in the past, we had tried to identify those patients with platelet testing functions to see, well maybe if we increase the dose or maybe if we switched them to another drug, we can improve outcome. And most studies were not successful, but TAILOR-PCI tried an entirely different approach. Rather than testing the platelet, this trial tested the genome – they did genetic testing, and they randomized people to either just clopidogrel as you ordinarily would or they said we're going to do genotype. And if you are clopidogrel-resistant or poor metabolizer, we're going to give you ticagrelor. And then they looked at the outcomes at a year. Now, what they found was that in those people who were poor metabolizers, they're focusing just on poor metabolizers in the primary analysis, there was a - a significant or trend towards significant reduction in outcomes, a 1.8% reduction in outcomes, a P of 0.056 at the year, a – a 2.1% absolute reduction at 30 days was highly significant. This is very provocative, and it's the very first genome-guided way of, treating ACS in a cardiovascular patient. A little bit of a limitation here. A lot of us would have been excited to see the comparison of the conventional strategy with a comparison of those who underwent genotyping. That's not what was done at the analysis. It was the nonresponders treated with ticagrelor versus the nonresponders treated with clopidogrel in some ways that recapitulates what we know with PLATO. I do look forward to some more in-depth analyses of the strategy – of the strategy of genotyping versus not. The other trial I wanted to mention, was the VOYAGER-PAD trial and, Deepak – you said that – done a nice job of summarizing COMPASS for us. This is not focusing on CAD but on PAD, and this was about 6,500 patients. Everyone got aspirin, and they had had a recent, lower extremity revasc, so post revasc for PAD, and they either got the vascular dose of rivaroxaban at 2.5 mg twice a day or placebo. And they looked at acute limits in major amputation, death, MI, stroke, and at three years, there was a significant reduction in that endpoint down from 19.9 to 17.3; a number needed to treat of only 39. Now the question that always comes up, is what's the price. Uh, was there excess bleeding. And I have to say this was one of the first trials where there was a little bit of a three-punch. There was no excess TIMI major bleeding of the primary safety endpoint. A P value was .06. So, we always are concerned about the net benefit in these kinds of trials. Here we saw a clear reduction in ischemic endpoints, what I call major adverse vascular events, and a modest numeric, but not statistically significant increase in bleeding, which on the whole, I think makes this a viable strategy. Well thanks to all of you for joining us in the audience today. It's been great having you. I thought this was a very informative wrap up. I hope you enjoyed it as well.

Dr. Bhatt:
Terrific doing this with you. Thanks so much.

Dr. Lam:
Thank you.