

Dr Carolyn Lam:

Welcome to Circulation on the Run, your weekly podcast summary and backstage pass to the journal and its editors. I'm Dr. Carolyn Lam, associate editor from the National Heart Centre and Duke-National University of Singapore. In just a moment, we're going to be discussing new results of the pioneer trial, and the patient with atrial fibrillation who undergoes intracoronary stenting, a familiar conundrum. What's the role of NOACs? Is there still a role for full-dose triple therapy with warfarin? First, here's your summary of this week's journal.

The first paper tells us about the clinical impact of left atrial appendage closure. Dr. Melduni and colleagues from the Mayo Clinic in Rochester, Minnesota, studied 9,792 patients undergoing bypass or valve surgery between 2000 and 2005. They used propensity score matching to estimate the association of left atrial appendage closure with early post-operative atrial fibrillation- defined as atrial fibrillation within 30 days of surgery- ischemic stroke, and mortality. They found that after adjustment for treatment allocation bias, left atrial appendage closure during routine cardiac surgery was significantly associated with an increased risk of early post-operative atrial fibrillation, and did not influence the risk of stroke or mortality.

They therefore concluded that it remains uncertain whether prophylactic exclusion of the left atrial appendage is warranted for stroke prevention during non-atrial-fibrillation-related cardiac surgery.

The next study provides pre-clinical evidence that genes on sex chromosomes may contribute to the sexual dimorphism of abdominal aortic aneurysms. That is, we well know that abdominal aortic aneurysm is a male-predominant disease. Now, in this paper, by first author Dr. Alsiraj, corresponding author Dr. Cassis and colleagues from the University of Kentucky, female LDL-receptor-deficient mice, with an XX or XY sex chromosome complement, were infused with angiotensin II for 28 days to induce abdominal aortic aneurysms. DNA microarrays were performed on the abdominal aortas, and to mimic the males, the female mice were administered a single dose of testosterone.

They found that an XY sex chromosome complement, in phenotypic females, profoundly influenced aortic gene expression profiles and promoted abdominal aortic aneurysm severity. When XY females were exposed to testosterone, aneurysm rupture rates were striking. The mechanisms for augmented abdominal aortic aneurysm severity in XY females included increased inflammation, augmented matrix metalloproteinases, and oxidative stress. These results, therefore, demonstrate that genes on the sex chromosomes regulate aortic vascular biology and contribute to sexual dimorphism of aortic abdominal aneurysms. Sex chromosome genes may therefore serve as novel targets for sex-specific abdominal aortic aneurysm therapeutics.

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The next two studies shed light on the mechanism of action of PCSK9 monoclonal antibodies on lipoprotein metabolism. In the first study, Dr. Watts and colleagues from University of Western Australia carried out a two-by-two factorial trial, of high-dose atorvastatin versus evolocumab on stable isotope tracer kinetics in 81 healthy, normal lipidemic, non-obese men.

They found that both atorvastatin and evolocumab independently accelerated the fractional catabolism of VLDL apoB, IDL apoB, and LDL apoB. On the other hand, evolocumab, but not atorvastatin, also decreased the production rate of IDL apoB and LDL apoB. The reduction of LDL apoB and LDL cholesterol was significantly greater with a combination versus either mono-therapy. In summary, they found that in healthy, normal lipidemic men, evolocumab decreased the concentration of atherogenic lipoproteins, particularly LDL, by accelerating their catabolism, and by reducing IDL and LDL production. The latter effects are incremental to statins.

The second paper to deal with this topic comes from Dr. Ginsberg and colleagues from Columbia University in New York, who studied 18 participants, this time 10 of whom were women, who completed a placebo-controlled two-period study, receiving two doses of placebo followed by five doses of alirocumab. These authors found that alirocumab decreased LDL cholesterol and LDL apoB by increasing IDL and LDL apoB fractional clearance rates, and by decreasing LDL apoB production rates. These results were consistent with increases in LDL receptors available to clear IDL and LDL from the blood during PCSK9 inhibition. These two papers are discussed in a beautiful accompanying editorial by Dr. Chris Packard from University of Glasgow. In his editorial entitled "Unpacking and Understanding the Impact of PCSK9 Inhibitors on Apolipoprotein B Metabolism." Those were your highlights! Now for our feature discussion.

Today we are going to be discussing one of the most common conundrums in all of cardiovascular medicine, and that is the care of patients with atrial fibrillation who also need percutaneous coronary intervention. Of course, both dual antiplatelet therapy and oral anticoagulation therapy would be indicated to reduce the risk of stent thrombosis and thromboembolism in atrial fibrillation, respectively. However, with the intensification of the anti-thrombotic regimen, there is the inevitable trade-off with more bleeding. Now, to discuss this, we have the first and corresponding author on a very novel study of the pioneer trial, and that is Dr. Michael Gibson, from Harvard Medical School and Beth Israel Deaconess Medical Center. We also have the editorialist for this very exciting paper, Dr. Deepak Bhatt from Brigham and Women's Hospital, and finally, we have Dr. Dharam Kumbhani, associate editor from UT Southwestern. Welcome, gentlemen!

Dr Deepak Bhatt: Thank you.

Dr Michael Gibson: Thanks.

Dr Dharam Kumbhani: Thank you.

Dr Carolyn Lam: So, Michael, could I start with you? This is a sub-study of the pioneer study. Could you tell us how this is different from the primary results, what were you looking for, and what you found?

Dr Michael Gibson: As you know, as [inaudible 00:07:40] said, we have a lot of bleeding with conventional triple therapy, and we used two regimens to try and reduce that bleeding. One was a reduced dose of rivaroxaban, 15 milligrams, plus thienopyridine. The other strategy was baby dose rivaroxaban, 2.5 milligrams twice a day, plus DAPT. What we found in the overall study was a significant reduction in bleeding- from, say, 26.7% down to 18% for riva plus DAPT- that's the baby dose plus DAPT- and down to 16.8% for the 15 milligrams of riva plus the thienopyridine.

You'd have to treat about 11 to 12 patients to prevent one significant bleeding event. That's the mainstay. What we found in this very, very important sub-study is that that was associated with reduction in hospitalization. All-cause hospitalization was reduced, and cardiovascular hospitalization went down from 28.4% to about 20% for the two regimens. Bleeding with hospitalization went down, from 10.5% to about 6%. At the end of the day, you'd only have to treat 10 to 15 people to prevent one hospitalization, so from a health economic perspective, and from a patient viewpoint and hassle perspective, this was very important.

Dr Carolyn Lam: In fact, Michael, I would say from a clinician-cardiologist perspective, these results are really very applicable. In fact, I really like, in the accompanying editorial, what Deepak wrote, that it may be one of those rare occasions where a sub-study provides very clinically meaningful information compared to the primary study. Deepak, would you like to elaborate a little bit more about that?

Dr Deepak Bhatt: Sure. A really great point that you've raised. It wasn't, in fact, a sub-study we're talking about in Circulation. It was an analysis from the overall trial, looking at a different endpoint than the primary endpoint, the hospitalization, and the composite of hospitalization and mortality. I think that's a very important endpoint. If it were a heart failure trial, for example, that's the endpoint everyone would hone in on- mortality and hospitalization. The fact that that was significantly reduced, I think, is very clinically meaningful. Mike mentioned the economic implications, which for sure are there, by reducing hospitalizations and re-hospitalizations.

The impact on cardiovascular hospitalizations- the reduction there- I find particularly remarkable. The reduction in bleeding, of course, is good, and in its own right has a great deal of value, but the additional reduction in cardiovascular hospitalizations, I think, is quite reassuring for those that are worried about the efficacy of the two experimental regimens that he and his colleagues studied. Sure, the trial's not powered in each individual sub-group for

rare events like stroke, but the fact that CV hospitalizations are not increased, and in fact reduced, tells me that this is a winning strategy or strategies.

Dr Carolyn Lam: Right. Michael, another issue, though- this is open label, and I suppose one of the criticisms could be that there is a bias for clinicians managing patients on the traditional Vitamin K antagonist to maybe hospitalize patients more for some reason. What is your response to that?

Dr Michael Gibson: That is always the criticism of an open label trial, but again, the events were adjudicated, and for the heart events, that's done in a blinded fashion, so it's reassuring that there was a blinded assessment of the heart events.

Dr Carolyn Lam: True. How about comments on generalizability? I mean, what do you think? Trial setting, real world ...

Dr Michael Gibson: Yeah, I think that's one of the advantages. This was very much a real-world kind of study. It was truly done throughout the world. We had a very broad entry criteria. Anyone who was getting a stent put in- you didn't have to have ACS, although about half the patients did. The only real exclusive criteria was you couldn't have any bleeding or be profoundly anemic. You couldn't have a stroke or [TIA 00:11:58] in the past. Other than that, it made real-world practice in a lot of ways.

Dr Dharam Kumbhani: This is Dharam. If I may ask both the other people on the call, is ... Rivaroxaban is not FDA approved, in these doses, for use. I'm wondering if they might provide some comment, given the benefit that we see in this trial, overall, what their thoughts are and what the next steps might be.

Dr Carolyn Lam: Sure. Maybe Michael, then Deepak?

Dr Michael Gibson: Yeah, that's a good point. It is important to point out that you'd need to check the prescribing information in your country. In some countries- I think it's about 54 countries- the 2.5 milligram dose is available. It is approved for ACS, but is not approved for a-fib. Then, you have a dose of 20 milligrams that's approved worldwide for a-fib, but there are some countries- it's important to note, in some countries, 15 milligrams is the full dose that's approved- say, in Japan and Taiwan. There are Japanese studies showing that 15 milligrams was not only safer than warfarin, but more efficacious than warfarin in a trial like J-ROCKET. You're right, the 15 milligram dose is available in the US- it's approved for renal insufficiency, but at this time, it's not labelled for the ACS or stented patient.

But again, physicians are at liberty to look at this data, which is the first real data that we have to guide decision-making in this setting, and they're at liberty to make their own choices.

Dr Deepak Bhatt: Yeah, I would agree with that assessment, and emphasize ... Like Mike said, it's an international audience for Circulation, so I would say, look in your own

country, and in many parts of Europe, the 2.5 milligram rivaroxaban dose is available and approved for ACS, and could therefore be used for this purpose, though not strictly falling within the label indications. In the US, there's the 15.

I think, if I just answer the previous question, the results are very generalizable, and for doctors that critique that point, I'd say, "Why didn't you enroll your patients in the trial?" There's the RE-DUAL as well, that's ongoing, with dabigatran, AUGUSTUS with apixaban, and I'm missing one that's also ongoing as well, I think, but there are four different trials that are out there. The Pioneer was the first to report ...

Dr Carolyn Lam: I think you're thinking of the Entrust AF-PCI with Edoxaban.

Dr Deepak Bhatt: The most recent one, yes. I forgot the acronym, there. If people are really thinking that the results don't apply to their patients, well, there are trials that are ongoing. Enroll your patients. But to say, "Oh, my patients, I'm not going to enroll them in the trial," and then say, "The results aren't generalizable," I always find that an odd thing. I think the results are very generalizable. The one word of caution I would say, though, is to make sure to renally dose, as was done in the trial. That is, there was a downward adjustment in dose from the 15 milligrams to the 10. In real life, we've seen in registries with NOAC use, whether it's rivaroxaban or any of the others, a lot of times, the renal function is not carefully monitored in those patients that are on the fringe in terms of their renal function, and that's the one situation NOACs can backfire, where the dose isn't corrected for their degree of renal dysfunction. Other than that one caveat, I think the results are quite generalizable.

Dr Carolyn Lam: Excellent comments. We should wrap up soon, but not before I want to ask Dharam. Thank you for managing this beautiful paper. What, to you, is the take-home message for clinicians out there?

Dr Dharam Kumbhani: Yeah, it was an absolute honor and delight to manage this, and I think the paper's great. The editorial's great. It's gotten a great response. I think the take-home message is that this is a very clinically relevant question, and a very clinically relevant trial, and it shows that the needle will be moving towards using non-VKA-based agents, especially in patients such as this, who have both a-fib and PCI. I think this is very exciting space, a very important space. This trial suggests that if you use the strategy rivaroxaban low dose, with or without a DAPT, that it is safer, both in terms of mortality and bleeding, compared with what is traditionally being used with warfarin plus DAPT. I think this was a very, very exciting trial.

Dr Carolyn Lam: Indeed, and congratulations to all three of you. Thank you so much for joining me on Circulation On The Run. Thank you, listeners, for joining us too, and don't forget to tune in next week.