0:05
Hi. My name is doctor Dr. Shaun Goodman. I'm a cardiologist at St. Michael's Hospital and it's my pleasure to spend a little bit of time with you talking about the optimization of oral anti thrombolytic strategies in patients with stable atherosclerotic cardiovascular disease. Does the COMPASS guide us in the context of the insights into anticoagulation strategies in Canadian patients with CAD (INTENT CAD) the program.

0:32
As you are very familiar, there are major clinical manifestations of patients with atherosclerotic cardiovascular disease. And while as a cardiologist I typically focus on the management of patients with coronary artery disease such as stable angina and myocardial infarction. Indeed, many patients have other forms of atherosclerotic cardiovascular disease and often polio-vascular disease involving the cerebrovascular and peripheral arterial systems.

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Now, we know from recent clinical trials trying to mitigate the residual risk of atherosclerotic cardiovascular disease that we continue to have high event rates in our patients.

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This is an example from the FOURIER trial that took over 27,500 high risk, stable patients with established atherosclerotic cardiovascular disease including prior myocardial infarction, prior non hemorrhagic stroke, and symptomatic peripheral arterial disease. And of course, this was the addition of evolocumab a PCSK9 inhibitor on top of statin therapy compared to placebo on top of statin therapy. But what we can see is that even with the best treated patients with PCSK9 inhibition there is a high residual risk in the patient population.

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despite high rates of use of secondary prevention therapies, like anti platelets, like aspirin and other medical therapies.

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The COMPASS trial, of course, included patients with coronary or peripheral arterial disease, such as those who are 65 years of age or older. And those who are younger, who had documented atherosclerosis involving, for example, multiple vascular beds and or had multiple risk factors.

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Key exclusion criteria from COMPASS were: individuals who needed, dual anti-platelet therapy, non aspirin or anti-platelet therapy, or, for example, in atrial fibrillation settings, oral anticoagulation therapy. COMPASS also excluded very recent stroke or a hemorrhagic or lacunar stroke and also excluded patients with severe heart failure as the final bullet on this slide notes. They also excluded patients from the COMPASS trial who had a particularly low levels of EGFR less than 15 milliliters per minute.

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But this is a good opportunity to remind folks that in Canada, the product monograph for rivaroxaban has changed in the last couple of years, and we are now able to give it to patients with moderate to severe renal impairment. For example, rivaroxaban may be given all the way down to a creatinine clearance of 15 milliliters per minute.

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Now, the COMPASS trial results are very familiar to you. Of course, the primary outcome was a composite of time to first cardiovascular death, stroke or myocardial infarction, and we can see that the patients were randomized to receive aspirin alone.

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The dotted red line on this slide had the highest event rate over the course of approximately 2 to 3 years time. In contrast, those individuals who receive 2.5 milligrams, twice daily of rivaroxaban added to aspirin, had a significant and substantial risk reduction with this combination therapy.

4:02
The rivaroxaban, alone arm. The dotted a light blue line: intermediate, in terms of events, between aspirin and the riva, 2.5 milligrams, twice daily, plus aspirin, did seem to confer some modest numeric benefit. But it was not statistically significantly different than aspirin alone. And so this is not a strategy that we would utilize on a go-forward basis. But in contrast rivaroxaban 2.5 milligrams twice daily added to aspirin is a game changing therapy.

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I'll again point out that these high risk atherosclerotic cardiovascular disease patients were well managed with good background therapy in addition to aspirin. Over 90% receive lipid modifying therapy and there's other secondary prevention therapies. So this benefit that we see with rivaroxaban 2.5 milligrams twice daily added to aspirin, is on top of well established, secondary prevention therapy.

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If we now look at these bar graphs and the individual components, in addition to the primary outcome, we can see that cardiovascular mortality was significantly reduced. Stroke was statistically significantly reduced. And myocardial infarction while not significantly reduced, the hazard ratio of 0.86 suggests a benefit of the combination of rivaroxaban and aspirin compared to aspirin alone. Probably why we didn't see a statistically significant reduction in myocardial infarction reduction is you'll recall that the COMPASS trial was stopped prematurely on the recommendation of the Data and Safety Monitoring Committee because of overwhelming benefits of rivaroxaban 2.5 milligrams twice daily on top of aspirin compared to aspirin alone for the primary outcome. And I have no doubt that if the trial had gone on for a longer time period, we would have seen a statistically significant reduction also in myocardial infarction.

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Importantly, there was also, in a relatively short timeframe, numeric reduction in all cause mortality with the addition of rivaroxaban to aspirin compared to aspirin alone.

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Now, this is a busy slide taken right from the New England Journal of Medicine Publication, with the main trial results by John Eikelboom and colleagues from COMPASS but the purpose of showing this is the subgroup analyses are very consistent across a variety of pre-specified subgroups. So, really, regardless of a patient's age and their sex, what part of the world they came from, their body weight, their estimated eGFR, whether they did or didn't have diabetes, etc. there is a consistent reduction with rivaroxaban 2.5 milligrams twice daily added to aspirin compared to aspirin alone.

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Now, we can look at some subgroups and look at absolute event rates. And this is just a blow up of those individuals who had an estimated eGFR far below 60 milliliters per minute. These are patients with moderate to more significant chronic kidney dysfunction compared to those who had apparently normal renal function with eGFR 60 and above. And the point of this slide is really, or this blow up on the slide is to show that not surprisingly, those with renal dysfunction moderate to severe renal dysfunction have a higher

absolute event rate. And they derive a similar relative risk reduction compared to those who have normal renal function. And so the absolute risk reduction is even greater in those who have a modest to significant kidney disease, and, therefore, the absolute risk reduction translates into a lower number needed to treat.

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And so, consistent benefit means that we pick out the highest risk subgroups. They will derive the biggest bang for the buck. And I'm not just talking from a financial perspective or a cost effectiveness perspective, but from a clinical perspective, from a patient perspective.

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Now, COMPASS included not only coronary artery disease patients, but also those with peripheral arterial disease. And importantly, in the COMPASS trial, peripheral arterial disease was defined not only as those with lower extremity disease, symptomatic, lower limb claudication, for example, and low ankle brachial index measurements. But also those individuals who had arterial disease in the cerebral vascular system for example, carotid artery disease. Again here, peripheral arterial disease is defined as anything peripheral to the heart. So, not only lower extremity but also cerebrovascular disease.

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So 27% of the population, over 7000 patients, had some form of peripheral arterial disease with or without concomitant coronary artery disease. The subgroup analysis suggests that whether one qualified for COMPASS on the basis of coronary disease or peripheral artery disease, the benefit was similar.

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In fact, as I showed earlier, there was a fairly dramatic reduction with rivaroxaban added to aspirin compared to aspirin alone in terms of those patients who had cerebrovascular disease.

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Now, of course, if one had peripheral arterial disease and was enrolled in the COMPASS trial, there was, in addition to overall cardiovascular outcome benefit, important significant reductions in MALE--major adverse limb events--and major amputation risk.

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What's the downside? Of course, any additional anti-thrombolytic therapy added to aspirin, compared to aspirin alone, will increase modestly the risk of bleeding. And so major bleeding unsurprisingly was statistically significantly higher, about a 1.5 to 2-fold increase with the addition of rivaroxaban 2.5 milligrams twice daily to aspirin, compared to aspirin by itself.

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However, there was no statistically significant increase in fatal or nonfatal intracranial hemorrhage or non-fatal bleeding into other critical organs. And so while there is a small price to pay from a patient perspective, there was no significant increase in catastrophic bleeding related events.

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Now, often, major bleeding manifested, particularly in the first year after randomization as major gastrointestinal bleeding. And this was broken down into the sort of traditional about a third that were upper gastric or duodenal, about a third colonic or rectal. And then another third, from an unknown non-identified gastrointestinal site.

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And about three quarters of the major bleeding episodes, whether they were GI related or not, were generally, ultimately, clinically, either mild or only moderate intensity. And so this is what we need to

counter-balance against the dramatic reductions that we see in cardiovascular outcomes and an all cause mortality reduction with the addition of rivaroxaban.

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This is captured nicely in this comparison over the course of time where you can see that there's an absolute risk difference in favor of the use of rivaroxaban added to aspirin compared to aspirin alone in reducing cardiovascular deaths stroke myocardial infraction, whereas the risk of fatal bleeding or symptomatic bleeding into a critical organ was very modest and relatively similar over the course of the approximate three year timeframe of follow-up.

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Now a bunch of investigators in Copenhagen looked at their patient population and they were independent of the COMPASS trial. They looked at not only the application of COMPASS to the Copenhagen heart study patient population but also a number of different contemporary trials that have looked at other evidence based treatments like antiplatelets, like lipid lowering therapies, like antihyperglycemic, therapies. And what we can see in the secondary prevention management of patients at least in Copenhagen in Denmark is that there's a substantial number of people that are eligible with ischemic heart disease for a COMPASS like regimen, including those with prior myocardial infarction.

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They estimated the number of events that could be prevented in this patient population. If they had been able to apply the COMPASS like trial regimen with rivaroxaban over the course of about five years and looking at the risk of cardiovascular death, myocardial infarction, or stroke. In an accompanying editorial by Nana and Peterson, they pointed out that the findings suggested that the antithrombotic strategy from the COMPASS trial rivaroxaban 2.5 mg twice daily added to aspirin compared to aspirin alone, appear to have the greatest potential to improve population health specifically in those patients with established atherosclerotic cardiovascular disease. So not that this is a competition, and that one therapy should necessarily trump another therapy; but indeed, if we're looking at newer evidence-based secondary prevention therapies on top of our usual treatments, like aspirin, and statin, and beta blockers

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and ACE inhibitors or ARBs, we should be thinking preferentially, at least initially, of using rivaroxoban; we will get the biggest bang for our buck by using that strategy in secondary prevention.

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Now, in Canada, in 2018, you're aware that Health Canada approved the use of rivaroxaban 2.5 milligrams twice daily, in combination with low dose ASA for the prevention of stroke, MI, cardiovascular death, and for the prevention of acute limb ischemia and mortality in patients with both coronary artery disease and or those who have peripheral arterial disease. And we were lucky, we got an early Christmas present at the end of December 2019; I say, lucky as clinical practitioners looking after these types of patients in Ontario, that those who are 65 years of age or older and/or on social assistance, those who are eligible for coverage from Ontario Ministry of Health and long-term Care. There is now a limited use code that we can prescribe for our patients and they get covered with rivaroxaban

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2.5 milligrams twice daily in combination with aspirin for the prevention of cardiovascular events, and those who have concomitant coronary artery disease and peripheral artery disease.

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So I think that the important clinical implications, if I can summarize from COMPASS, are patients with so-called stable atherosclerotic cardiovascular disease. They probably aren't as stable as we think.

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They are at risk for recurrent cardiovascular events, particularly those with coronary artery disease and concomitant peripheral arterial disease; we can look at those who have other risk factors or features like those with diabetes. Those with moderate renal dysfunction. For example, in eGFR between 15 and 59 milliliters per minute, those with moderate heart failure currently or in the past. Those who are current smokers; these are all patients who are particularly high event rate risk for recurrent events. And if we can identify those at lower bleeding risk, these are the individuals who derive the greatest absolute and net clinical benefit from a regimen like rivaroxaban 2.5 milligrams twice daily added to aspirin compared to aspirin alone. And so I think we can take this important information from the COMPASS trial and we can apply it in our routine clinical practice.

16:00
I encourage you to think about these patients in your own practice as part of the INTENT CAD program and to look online in the INTENT CAD Program for web based tools and the next steps for you to potentially identify these patients who will be receiving, hopefully down the road, in your hands, will reap the benefits of adding rivaroxaban about 2.5 milligrams twice daily to aspirin. Thanks very much.