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While DOACs are Good for Some Things, They Are Not for Everyone

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

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Dr. Bahit:
It's great to be here with such a great group of friends. So, over the next couple of minutes, I will be talking about three different clinical settings, atrial fibrillation, stroke, and post MI.

Chris and Elaine have been talking about atrial fibrillation, but I would like to summarize key aspects. We know that atrial fibrillation is associated with a five-fold increased risk of stroke. We know that patients who have a stroke related to atrial fibrillation have larger strokes, they're at greater risk of mortality, and also greater risk of disability long-term. But we also know that the risk is largely modifiable with oral anticoagulation.

We know that the guidelines recommend that treatment for stroke prevention in patients with atrial fibrillation who are eligible for oral anticoagulants, direct oral anticoagulants are the preferred options. It was discussed before that there are different groups of patients in whom we don't have enough data. And one of these groups are the patients who have renal impairment. As Chris mentioned, we know from data from ARISTOTLE and our other studies that as the renal function decreases, there is an increased risk of stroke, bleeding, and mortality.

Chris also showed something similar to these. We know that the elimination of the direct oral anticoagulants is different, 80% renal for dabigatran, and 25% renal for apixaban. We know that Chris also mentioned that we don't have data when the patients have creatinine clearance below 25. And we don't have the data on patients in dialysis. Chris also alluded to this, and we know that patients who have increased age also have increased risk for stroke, but also have increased risk for bleeding. They are more frail and they have increased risk for falls or risk of falls. But we also know that these are the patients who receive, less commonly, you know, oral anticoagulants.

So, what are the unmet needs in patients with atrial fibrillation? As I said, you know, there's data lacking for patients who have creatinine clearance of 25 or lower, we know that patients who have increased risk of bleeding, elderly patients, patients with falls, who are frail, these are patients in whom there's an unmet need. There's also another group of patients, and these are patients who are required to receive antiplatelet therapy because maybe they have CAD associated with atrial fibrillation.

Then there's another group that we haven't discussed, and these are the patients that are considered unsuitable for oral anticoagulation. And as Elaine alluded, there's also this perceived risk of high risk for bleeding. And we know that of the patients who have atrial fibrillation, only less than 50% of them receive DOACs. And when we look at those patients, 1 out of 4 received off-label doses of the DOACs. And we also know that when we look at long-term, at 1 year, the persistence on oral anticoagulation is less than optimal.

So, what happened in patients with stroke? We know that according to the 2019 statistics, the stroke prevalence is around 77 million people around the world. We know that stroke is the second leading cause of death globally, and it's associated with a high risk for

disability worldwide. But we also know that in patients who have a stroke, there's a higher risk for recurrent events early after the initial one.

So, what do the guidelines say in terms of treatment for non-cardioembolic stroke? Current guidelines recommend early initiation of antiplatelet therapy short-term between 25 and 90 days. And the use of aspirin plus clopidogrel or ticagrelor depends on the risk for ischemic stroke or risk for TIA. And then the patient continues with single antiplatelet therapy.

In terms of long-term secondary prevention, the recommendation is to continue single antiplatelet therapy, but in patients who have a history of CAD or PAD, there's the recommendation to consider low-dose rivaroxaban plus the antiplatelet therapy.

So, despite the treatment with antiplatelet therapy, either single or dual, there's an increased risk of events. And this slide summarizes, you know, the residual risk of recurrent stroke in contemporary studies. As you can see, this slide show four different trials using different antiplatelet therapies, and the risk of ischemic stroke at 90 days rises from 4.6 to 11.4, despite the treatment. When we look at long-term, we also see that when we look at follow-up of 5 years, this data from the TIA registry, there's increased risk for stroke and TIA, it's around 8 to 9%.

So, the question of recurrent risk of recurrent events led us to look at other options in terms of the decrease in this risk. Dual antiplatelet inhibition plus anticoagulant therapy was considered as a strategy to decrease the risk of stroke. And this is data from a subgroup analysis of the COMPASS trial, looking at patients who have prior stroke. This was around 1,000 patients in the three different arms. And the results of this analysis showed that compared with aspirin alone, rivaroxaban plus aspirin was associated with a 58% decrease in the risk of ischemic stroke. There was also a decrease in MACE, cardiovascular death, stroke, and MI. However, there was an increased risk for bleeding, major bleeding in this patient population. It's important to mention that in this trial, you know, the drug was not initiated early after a stroke.

So, in another subgroup of strokes, these are ESUS patients, embolic stroke of undetermined source, you know, direct oral anticoagulation had been tested. There was the NAVIGATE trial that tested rivaroxaban versus aspirin. And the trial showed that rivaroxaban was not superior to aspirin to prevent recurrence of stroke, and it was associated with an increased risk of bleeding.

The RE-SPECT ESUS, that tested dabigatran versus aspirin also showed that dabigatran was not superior to aspirin. There were similar rates of major bleeding; however, dabigatran was associated with an increased risk of clinically relevant non-major bleeding.

So, what are the unmet needs in patients with non-cardioembolic stroke? You know, as I've mentioned, you know, we see an increased risk of recurrent events early on. And you know, for long in term, we know from data from COMPASS, that the addition of low-dose rivaroxaban decreased the risk of MACE but increased the risk for bleeding. And there's clearly a need for a secondary prevention medication that prevent events without an increased risk of bleeding.

So, now we're going to look at patients post MI. And this is similar to what happened basically with non-cardioembolic stroke. We know that despite treatment, current treatment, medical treatment, and new devices, there are high rates of events after a myocardial infarction. We know that half of the events occurred early on within 90 days of the event. And we know that patients who present with recurrent myocardial infraction, they have increased mortality.

This is data that showed that the increased risk of a recurring cardiovascular event after acute coronary syndrome, we know that approximately 12% of patients have a recurrent cardiovascular event at 1 year after a myocardial infarction.

When we look at the timing of the events of this recurrent event, we know that half of them occur within 90 days. The graph shows a meta-analysis of seven clinical trials looking at early or late recurrence of MACE. And as you can see, half of the events occur early on within 90 days. And in the Kaplan-Meier curve is data from PLATO, as you can see also that half of the events occur within 90 days.

Similar data is shown here in this slide, looking at the Swedish registry data that included 97,000 patients. These were all patients who had a myocardial infraction and were followed up throughout a year. As you can see that almost half of the events occurred early on.

So, in trying to understand or to better treat the patients in order to reduce the recurrence of cardiovascular events post myocardial infarction, the addition of oral anticoagulation to antiplatelet therapy was tested. Three different trials assessed this, ATLAS ACS 1: TIMI 46, TIMI 51, and COMPASS trial. We know from these trials that rivaroxaban was associated with reduced myocardial infarction. The mechanism and the hypothesis behind this is that we know that thrombin is elevated in acute coronary syndromes and persists elevated, in particular, in patients who have recurrent events. So ideally, if we target thrombin, we could reduce the events.

And this is what was seen when we look at the trial as they used rivaroxaban. When we look at the pooled analysis of the ATLAS TIMI 46 and 51, we see that combined rivaroxaban doses was associated with a 46% decrease in the risk of myocardial infarction. When we look at data from COMPASS, there was a 14% reduction in recurrence of MI when we looked at rivaroxaban plus aspirin, compared to

aspirin, and 11% reduction in myocardial infarction when we look at rivaroxaban versus aspirin.

However, there was an increased risk of bleeding. In the ATLAS TIMI 46, there was a dose-dependent increase in clinically relevant bleeding that was two-fold for riva 5 mg, that increases to five-fold with riva 20 mg. In the ATLAS TIMI 51, there was a four-fold increased risk of TIMI major bleeding with rivaroxaban versus placebo. And in the COMPASS trial, there was also an increased risk for major bleeding with the two different arms of rivaroxaban.

So, as I explained, there's an increased risk of recurrent event post MI. Low-dose rivaroxaban was able to reduce the thrombin generation to reduce cardiovascular events; however, there was an increased risk of bleeding. So, there's again here a need for a better secondary prevention therapy that reduces events without the risk of bleeding.

So, in summary, in three settings that I described, atrial fibrillation, non-cardioembolic stroke, and patients in the post MI setting, there's a need for treatment that reduces cardiovascular events without increasing the risk of bleeding.

Announcer:
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