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While Antiplatelets Are Good…They Aren't for Everyone

Announcer:
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Dr. Caso:
Thank you very much for inviting me. So, you heard about the general problem. And you heard about recurrence. And I think it's, I always said, this is for me the worst defeat that I can have when I have a patient where I did all the diagnostic workup, and then she or he is coming back. But still, we have to make peace with this on the current knowledge, because as you saw, the risk is still very high. So, especially 12% during the first week after a TIA. It's clear the better you do the workup, the earlier you find the cause of the stroke, you will have a lower risk of recurrence. And we know, as on the other side, we know that 80% of strokes can be prevented. Stroke is a preventable, treatable, beatable disease. This is always we repeat to our patients. We repeat when we have - with our colleagues, something that we can do. But still, we are not there, where we want to be.

So, just to put you in the context of a typical patient that we see every day in our clinic, Mr. Roberto, he is 75 years old. He came to us with the onset of transient mild aphasia, NIHSS 2. He didn't realize that he was not speaking well, you know, men tend to speak less, so probably nobody noticed that he was not speaking at a certain point. At a certain point, wife said maybe it's a little bit too low of the changes. So, he came after 12 hours, and we performed the CT, which was negative. His clinical history was hypertension, diabetes mellitus. His BMI was more than 25. He was on treatment with ramipril 5 mg, and he took metformin.

So, you can imagine, minor stroke. So, we looked, we had the CT negative, and during the night DAPT was started. And you see the lesion is not so big, but it looks a little bit like embolic stroke, no, it's it works – it looks really, it could have been embolic. And we looked also at the intravessel - intracerebral circulation, but you can see nothing special, maybe a little bit even more on the other side not such a good flow, but not really something special.

So, what did we do? Based on the current guideline, and you heard this already, there's a full indication, minor stroke, NIH of 2, not disabling stroke. We started DAPT with the loading dose of 300 mg of clopidogrel and did all the workup and then we said after 21 days, you have to switch to single antiplatelet.

We also, you know, you have to get the full package because NIH of 0, you started antiplatelets, but we give also advice about statins, to start statins, because he didn't do. We told him please stop smoking and start to lose weight. And then we said you have to do healthy lifestyle and so on and so on. So, everything seems quite clear, more clear in this talk, we were happy because we thought that we did a good job. And we give him all the tools to not to come back.

But this happens after 10 days, and he told me, he confessed to me that he stopped clopidogrel already after 10 days because he had some nose bleeding. So, I said okay, but I told you 21 days. And he said, 'Yes but you know this nose bleeding so - I felt so uncomfortable eating with my family and always have this disturbance,' and so he stopped it without consulting the general physician. And interestingly, you see that lesion is really strange because it's near the old lesion, yet again some minor aphasia, but this time

everybody noticed because probably due to the fact that he already went through this.

So, now he also has to think about now the load, the lesion load that he has. It was - we started with a small lesion and now we have a big lesion. And you know that every stroke, what it means for the brain on long-term, because stroke is also a major cause of depression, dementia, so losing your brain capacity, it's something that absolutely you need to be aware of when you're treating any kind of recurrence.

So, we were like, what did we do wrong? So, we advised him, we told him, and he told me, he was so proud, 'You know, Doctor, I lost some weight,' he goes, 'I start walking,' and so on. He was, but then we really, again, went through all what we did. We looked at the blood pressure, he told me that he started to measure every day, and we know the effect of good medical treatment of hypertension. And I asked him, 'Were you compliant with the statins?' He said, 'Yes, I was completely compliant with the statin.' And he told me, 'I started losing weight, I started walking,' and so on. So probably, we have to look for the antithrombotic.

And then what did we do? So, as I said, we did everything what we had to do. Then I asked my students and my residents, 'So, what else can it be?' So, we have a kind of flowchart in our - we have our briefing after our clinical round, and then we discussed maybe we missed something, vasculitis or all these unusual causes, or whatsoever, a cardiac source. So, we put on the Holter many times again; plaques, but the carotid were completely clear; neoplasms which it could be because one of the reasons when you have a recurrence, it can be paraneoplastic; or we looked again for the hypertension and cholesterol, but we did, I asked him also maybe you do not sleep well. Now, we are searching more and more for sleep apnea, inactivity, overweight, nutrition. So, you have to check all this additional, let's say, less branded risk factors in order to think about the cause of recurrence.

So again, what can we do? We can intensify the preventive drugs and lifestyle treatment, that's something that we can do at the long run. But here, we had a very, let's say, immediate, early acute recurrence. Change anti thrombotics; sometimes there's the so-called aspirin resistance, or what we hope if there are new drugs on the horizon.

From my point of view, I never believed so much in aspirin resistance, because now we did a study, an Italian study, it's still not published. But what we realized, that all the values that you use when you evaluate aspirin resistance, then when you put them again on aspirin, they disappear. So, more than aspirin resistance, maybe they didn't take the drug as they said. So, and also we have a lot of labs, but the interpretation of these tests are quite complicated. So, as I said before, this resistance is partially reversible, and we have no randomized trials. We will see what we find out with our trial. Very difficult to perform the trial because you have to do every like hour and we are getting crazy, and people refuse to do it. So, hopefully, we are trying to enroll many centers, but I'm not sure if we will have good data about this. So, as I said, there is no evidence on testing, so we have to improve compliance and treat all risk factors.

So, regarding the guidelines, we know that absolutely for every subtype, we need a special treatment. When we have AF, we need a anticoagulation. If there is an extracranial stenosis, it must be managed. Intracranial, so it should - intracranial stenosis should be managed medically. But still, we do not - regarding our treatment in our, let's say, cryptogenic, maybe atherosclerotic, maybe there is no real - if you don't have a cause like carotid stenosis, it's very difficult to find the right medical treatment for these patients.

So, this is what we knew from the literature, aspirin works. We know so that we reduce the number of recurrence, but it works not good enough. So, probably also clopidogrel works, but we need a loading dose of at least 300 mg. And we know that aspirin works. And this is something that when I started to do stroke treatment, we had the stroke unit and we didn't have thrombolysis, we didn't have thrombectomy, and then we this patient came, we did everything, CT, Doppler, and so on, to do what? They look at me now and say, 'I give you aspirin.' So, they look at me, 'Okay, doctor, it's fine.' But I told them the literature we have, and we know that we are doing something good for you, but still.

So, we know, and you heard this already, that double is better, but you have a risk reduction by DAPT. But you have - everything in life, you pay a price. If it's working better, then you have more moderate and severe extracranial bleeding. And how should we do DAPT? How long? For how long? Who benefits? And who is harmed? Because for long, we know there was this ancient MATCH trial done many years ago, where we continued for more than 3 months DAPT, and there was a huge increase in major bleeding. Who benefit and who is harmed are very important questions.

And you see that you have a reduction of stroke in the first 10 to 14 days, you have a risk reduction of ischemic stroke, but it's for a very tiny population. In patients who have minor stroke or a high-risk TIA, you can use it for 3 weeks. So again, what shall we do with our patient who had not such a small lesion? A very early recurrence? So, can I give him or her again DAPT?

So, we have no data about moderate stroke, and we don't have data about major stroke. And I can tell you one of my experience. One night I was on call, I was called, and a colleague, a nonvascular neurologist was there. And I had COVID, I realized when he was calling me, I said, 'Oh, I cannot come I think I have COVID.' So he gave me the - he said, 'Okay, it's a minor stroke, he has only some dysarthria.' I said, 'Are you sure?' 'Yes, yes, I proceed with DAPT.' Then I realized it was not only dysarthria, it was anarthria, and this

man was going to coma. And it was a huge posterior stroke. And you cannot imagine how this patient bled. So, it was a really terrible situation, because I was not - I could not go because, as a specialist, I could not go. But this is what happened.

And what shall we do? Are there other categories like where we can have a benefit from double antiplatelets? So, we know that a patient to have an intracranial atherosclerosis, the DAPT works better than single antiplatelets. And we have good results from the trials that early aggressive antiplatelet, ticagrelor versus aspirin, works better. And clearly there is a higher benefit in case for the protection of high early recurrence.

But then this year, we had this interesting paper. It's a Chinese paper, the INSPIRES paper. And you see that the combination of aspirin plus clopidogrel in patients having a stroke or high-risk TIA, an atherosclerotic cause, had a higher risk of bleeding. So, it was a better risk reduction, but with a higher risk of bleeding.

So, regarding ticagrelor, so we know to ticagrelor has, there are no data about ticagrelor resistance. And we know from the SOCRATES trials that there is no benefit from ticagrelor compared to aspirin. And we have the THALES trial, and I will show you now the results.

As you see SOCRATES trial showed no or significant reduction, and there were no more bleed, but it was single versus single. When you had the combination, you had, again, a better reduction. But again, you had the situation of more severe bleeds, and also intracranial hemorrhage. Something, again, good treatment, but be careful, be aware of the bleeding risk.

But what we do not know is which of the two combination is more effective: aspirin plus clopidogrel, versus aspirin plus ticagrelor. So, we have good data we know, but what of the two should we choose? Probably when you go to France, you will get the ticagrelor. In other, based on where is, let's say, who did the trial, who was more involved in the trial, will advise you to one or the other. So, clopidogrel is a good alternative for aspirin, in a clopidogrel for short term. It could be an alternative for aspirin plus clopidogrel after stenting, especially when we have a resistant or we have a documented allergy to clopidogrel.

So, this is the ESO guidelines. In high-risk TIA or stroke was an NIHSS less than 5, aspirin and ticagrelor can be an option for 30 days. So again, we are between Sheila and Caridi, you know, we have to, on one side prevent ischemia, on the other side we have to avoid hemorrhage. So, very difficult decision that we have to take. So, we will find the answer together, what is the right treatment at the right moment for our patient.

Thank you very much for your attention.

Announcer:
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