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Preventing Ischemic Stroke in Today's World

Announcer:
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Dr. Sharma:
I'm going to start off with the first talk, which really just lays the background for what we're going to talk about today, which is preventing ischemic stroke. Now, we're going to talk about a lot of statistics. I'll tell you about how common this disease is, and I think most people in this room would agree that it's very common.

One of the things to remember is this quote, which is one of my favorite epidemiology quotes. This is Austin Bradford Hill, and he wrote one of the first papers tying cigarette smoking to lung cancer. And he really established how we go about establishing causality when we cannot do randomized trials as we can't with cigarette cancer. And that's one of the seminal publications of Richard Doll and Austin Bradford Hill. And what he said was health statistics represent people with the tears wiped off. So, as we go through the numbers, all of the things we as healthcare practitioners deal with on a daily basis, the human loss and grief that stroke engenders, just remember that, and that's really what all of this is about.

So, you know, it is a common and increasing disease. In 2019, over 12 million strokes worldwide, over 100 million survivors. And as you'll see, as the population ages, we're going to expect more and more people experiencing this and living with it. In the U.S., almost 800,000 people experience a stroke every year, about a quarter of those are recurrent strokes. So, ones where we already know that person is at higher risk. And on average, in this country, every 40 seconds, someone has a stroke.

The incidence of stroke is strongly age dependent. So, it starts to take off at about the age of 55, and roughly doubles for each decade thereafter. And men and women are different. So, if you look at the incidence of men, the incidence of stroke and MI is very close; MI is perhaps a little more common. In women, that's not the case; in women, the incidence of stroke, especially as women get older, is higher than the incidence of MI. So, this is data from Oxfordshire.

This is data from the U.S. and it's a bit of a complicated graph, so I'll just explain it briefly. What each of those lines represents is a 10-year age span. So, on the left-hand side of the slide at the bottom, those people are 25 to 35 years of age, and 10 years after that. And on the right-hand side, it continues, beginning at people who are 65 to 74, and going all the way up to 85 plus. And on the X axis, you have years from 2007 to 2017. So, two things to notice. This graph had to be split in two, because the scale is so high on the right side. So, stroke mortality increases markedly as you get lower. Now, mortality isn't zero anywhere even for 25-year-olds, but significantly higher, almost two orders of magnitude as you get to be 85.

The other thing is, in spite of all of the things we've done, there was a decline in mortality in 2007, it started to level off, so we're not experiencing those declines in mortality. And in some populations, young people are experiencing more mortality, higher incidence as we accumulate risk factors in the young that we did not have before.

The other thing just to add to one of the themes of this talk is stroke is very much a disease of women. This is stroke mortality in the U.S., and two separate things there. That solid line is for men and women, the proportion of deaths at each age. And what you see is for women, stroke is a more important cause of death than for men at all ages. And it increases as they get older, so that separation is higher as you get into the higher age groups. The bar graphs represent the absolute number of deaths in men and women; women in red, men in blue. And what you see again, as women get older, the absolute number of deaths gets higher. Stroke is very much a disease of women, more likely to experience it, more likely to experience caregiver burden, looking after someone with a stroke.

The other thing that significantly affects occurrence and recurrence of stroke is race. So, this demonstrates the risk of recurrence in white and black Americans, and black Americans right from the incident event have an increased risk of recurrent stroke. There probably are a number of factors that influence this social determinants of health, access to healthcare, a number of issues, but this significant difference exists throughout the age span.

This graph I think gives you an idea of the impact of stroke on the healthcare system. What they did was they looked at hospital visits, so ED visits and admissions, the light blue bars are prestroke. So, you match people with the same characteristics, and you get a sense of what the frequency is of hospital visits. The dark blue bar is after a stroke. On the extreme left is all strokes and the middle is disabling strokes, and on the right, strokes without disability. And this is the long-term course, so they're looking at what happens 6 months afterwards. So, soon after a stroke, you have an increased number of visits due to complications, all the rest of the things. If you survive 6 months, throughout that entire process, on average, what you have is a 0.37% increase in the rate of hospital visits. Now, that's hard to get your head around, but think of it this way, every 3 people that have a stroke, there's another person with those same health problems visiting and using the ED and getting admitted. If they are disabled, for every 2 people that have a disabling stroke, you add another person to your system, in terms of hospital resources. So, huge consumption of hospital resources.

Now, in terms of costs, these are global numbers from the U.S. 2014 $45.5 billion, and about half of it is direct medical costs, the are other indirect costs. By the way, this is almost certainly an underestimate in terms of the financial impact. In 2009, we did a micro-costing study. So, we gave people diaries who had had stroke and we asked them a bunch of questions about how it impacted their life, what extra things they needed to have. And one of the very startling things that we found was, even if you had an MRS of 0, so no symptoms, no disability, it impacted your life, 20% of people with an MRS of 0 said they needed help of a caregiver. And what you have to remember is even if you're walking, talking, returning to activities, that changes your perception of yourself, and you do rely on other people. So, there is a lot of resource utilizations not measured here.

Now, you know, we treat patients, we take care of people, so we think about costs in an individual. These are costs in a managed care system in 2010. And what I did was I took the mean, so in 2010, the mean for the first stroke was about $40,000, and then added two times a standard deviations, so the distribution is skewed towards the right, more disabling strokes cost a lot more. So, in 2010 went up to $203,000. Now, I don't know what it's like for you, but my dollars in 2010 were worth a lot more than they are now. So, these are 2024 costs, and I've just adjusted them with the CPI, the consumer price index, in the U.S. And healthcare, by the way, doesn't follow the CPI, it's actually more expensive than that. So, you can assume that this is an underestimate. So, if you want to take a few numbers home, the first stroke on average is about $57,000. And toward the high end, it's at $285,000, so close to $300,000. Recurrent strokes are always more expensive than the first stroke, more likely to be disabled, more likely to have other comorbidities. So, in today's dollars, about $72,000 for a recurrent stroke all the way up to $500,000. This is for the first year alone. Remember that the case-specific mortality is relatively low, so 15-18%, somewhere in there, the remainder survived mostly with some disability for years.

So, preventing stroke is going to be very cost effective. And what do we do about that? So, these are a schematic of the current guidelines, and you're not meant to read the boxes. But really what's happened over the last 20 years or so, certainly back to 2013, is a number of trials which have established dual antiplatelet therapy for minor stroke, TIA, in the short term. It has been beneficial, but we really haven't touched, for the most part, long-term risk. There is one difference, however. These are from the European guidelines where for patients who have coronary disease or peripheral artery disease – and by the way, for this purpose peripheral artery disease included the carotid arteries – for those people, there's the option of using a combination of an antiplatelet aspirin with low-dose rivaroxaban 2.5 mg BID.

And that's based on data from the COMPASS trial which randomized 27,395 patients into three arms. And we did look at people who have a history of prior stroke. So, in COMPASS, if you'd had a prior stroke, there were a couple of things that surprised us. First off, your annual risk of another stroke was 3.4%, even though the prior stroke had been, on average, 4 years prior to trial entry. So, a person who survived 4 years, we usually think of as being pretty low risk. Right? But these people all have atherosclerotic disease, 3.4% per year means that in 3 years, you get the double-digit absolute risks, which is pretty significant, more than 10% risk. With the combination of rivaroxaban and aspirin, that was cut almost in 60%, right, so it went from 3.4% to 1.1%. We decreased the risk of cardiovascular death, stroke, and MI as well, that composite, and MI was reduced. The cost of doing it was an increase in major bleeding. So, major

bleeding went from 0.5% to 1.9%. And the other gap we have in this data was because we were concerned about the risk of bleeding, we didn't allow anybody to be randomized shortly after stroke. So, you weren't allowed in a month before. So, strong benefit using this combination with a cause to bleeding and no data early after stroke.

We've looked as well at anticoagulants in other populations. For embolic stroke of uncertain source, the ESUS trials, and there were two of them: NAVIGATE and RE-SPECT ESUS. In NAVIGATE, we compared rivaroxaban to aspirin, and RE-SPECT, dabigatran to aspirin, and unfortunately, none of these worked. So, a stroke that looks embolic that really makes you concerned about the recurrence risk, makes you consider anticoagulation, unfortunately, we didn't get benefit here. And more recently in ARCADIA, in patients with markers of left atrial cardiopathy, we didn't get benefit either.

And in spite of the advances with dual antiplatelets, the absolute risk of stroke, even within the short-term, 90 days, remains high. So, it has had a meaningful impact on recurrence rates. But those recurrence rates are still fairly high in the first 90 days. And over the long-term, that risk accumulates. You know, one of the things we often think about when we look at these curves is that all of the risk is upfront, and we're targeted to treating that upfront risk. And there's no question that the curves rise very steeply in the first week, in the first 90 days. But if you look at this, that X axis is in years, and it just keeps on going up and up and up year after year.

We do have some ideas of the types of stroke and the markers which confer increased risk. And one of these is stroke that's associated with large-artery atherosclerosis. So, not just surgical stenosis, but atherosclerosis that's present there, present elsewhere. And that really was very similar to the group we studied in COMPASS. So, with TOAST categorizations, large-artery athero, very steep early curve, but then the curve continues to climb. This is over the first year.

The other groups that do have increased risk are the ones that were ideologically have markers of an embolic stroke, so multiple infarcts in the brain, those ones have, again, a very steep early rise, and then they continue to go. And less risky, but also riskier is a single infarct, and least is when you have no infarct at all.

So, when we think about where we are currently, in spite of the antithrombotic treatment options we currently have, there's still a high early and a long-term ongoing risk. And what do we have over the long-term? It's really aspirin, which has a relative risk reduction of about 20%. And that's what we've had for the past 50 years. COMPASS gave us the idea, this notion of combining an anticoagulant with an antiplatelet at the right dose but resulted in bleeding. So, really, we're looking for a strategy that has the impact of COMPASS without the risk of bleeding.

Thanks very much. I will pass it on to Dr. Caso to continue the story.

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