Strategies for Prevention of Stroke Associated with Atrial Fibrillation

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The Relationship between AFib and Stroke

DR. SUNNY KAPUR: Hello everyone, my name is Sunny Kapur. I'm a cardiac electrophysiologist at the Brigham Woman's Hospital, and I'll be talking in this session about strategies for the prevention of stroke associated with atrial fibrillation.

There are a few disclosures that I have related to this talk that are shown here. The outline of what we'll be talking about goes into four sections. The first will be outlining the relationship between atrial fibrillation and stroke. The second will be talking about pharmacologic prevention of cerebrovascular accident (CVA) in atrial fibrillation. The third will be non-pharmacologic prevention of CVA in atrial fibrillation, and the fourth will be the concept of trying to prevent recurrent strokes associated with atrial fibrillation.

The first section goes over the relationship with atrial fibrillation and stroke. So, as we note, atrial fibrillation is associated with significant morbidity and mortality. One of most common associated morbidities is symptoms; many patients can have severe or even disabling symptoms associated with the arrythmia, although around 25% of patients with atrial fibrillation are asymptomatic. There's also a known increase in mortality associated with atrial fibrillation, potentially related to the comorbidities that lead to both cardiovascular death as well as the arrythmia.

However, what's shown on the right is a cartoon that depicts probably the most talked about and potentially the most important morbidity associated with atrial fibrillation, which is cardioembolism. As we know, in the arrythmia of atrial fibrillation there's an increased risk of thrombus forming within the atrium and subsequently embolizing through the systemic vasculature to any vascular bed. Most notably, if this were to embolize into the brain, it could result in a cerebrovascular accident or stroke.

Now, it's important to note that atrial fibrillation is not only related to strokes, but related to the most debilitating strokes. Atrial fibrillation-related strokes are one and half times more disabling, two times more increased mortality, and have a 70% likelihood of resulting in death or permanent disability. This is significantly more morbid than strokes not associated with atrial fibrillation. And so, it's important to note that strokes related with atrial fibrillation are among the most devasting of CVAs that can occur.

Now, exactly why does AFib lead to a stroke? Why does thrombus form within the atrium? And in fact, that relationship is not completely clear. In older days we used to think that arrythmia itself would result in stasis, which would subsequently result in thrombus formation; however, it's become increasingly clear that it's a much more complex relationship. We know that vascular risk factors can lead to abnormal atrial substrate, which can lead to a stroke. And the arrythmia itself is probably more of a modulating factor that potentially could increase the risk, but in and of itself is not the sole cause of thrombus formation.

One of the major studies that kind of supported this, is shown here. This diagram shows--in the middle-centered line for multiple different patients -- the event and time of a cerebrovascular event. And what's shown is recording from implanted monitors of their burden of the arrythmia. And what you can see for some patients -- for example, on the top -- that there is relatively low burden of atrial fibrillation preceding the event. The second from top patient shows no significant atrial fibrillation in the weeks preceding the cerebrovascular event. There are some patients, as shown in the middle, patient number 10, where the vast majority of the atrial fibrillation is seen after the cerebrovascular event. Suffice to say, the

relationship in time -- the temporal relationship between the arrythmia and cerebrovascular events in atrial fibrillation -- is not directly causative, and supports the notion that the arrythmia itself is important but not the sole reason why strokes can occur in atrial fibrillation.

Other studies have supported the suggestion that atrial substrate remodeling -- abnormal atrial substrate -- may be the direct cause of thrombus formation in the atrium. What's shown here are studies that have suggested that atrial remodeling, as measured either by electrocardiographic parameters or as measured by echocardiographic parameters, both are related to an increased risk of stroke, even adjusted for atrial fibrillation. Again, the relationship between atrial fibrillation and stroke is not completely understood and not completely linear; however, it is likely a complex relationship between atrial remodeling, the arrythmia itself, vascular risk factors and potentially even hematologic risk factors.

Now, despite the fact that we don't know all about why thrombus forms, one of the things that has been clinically observed is that the vast majority of thrombi, somewhere upwards of 90%, accumulate in one specific corner of the atrium known as the left atrial appendage. This is an area of the atrium which, based on fluid mechanic studies, potentially has the most stagnation of blood; and therefore, is likely to be the reason why thrombi are predisposed to this area. We'll circle back to this point as we go through the talk.

Pharmacologic Prevention of CVA in AFib

Now let's talk a little bit about pharmacologic prevention of CVAs in atrial fibrillation. While we don't completely understand the relationship, numerous epidemiologic data have shown that a relationship exists between atrial fibrillation and stroke.

The first step is trying to estimate the stroke risk, determine exactly how to risk stratify patients who have atrial fibrillation for their predisposition to stroke. Now, while this doesn't apply to every single patient with atrial fibrillation, a number of clinical observational studies have shown that clinical risk scores can be used to stratify patients' risk for cerebrovascular accidents within atrial fibrillation.

On the left is one of the more commonly used scores that has been used in the past known as the $CHADS_2$ Score, which the risk factors shown below, and on the right is the CHA_2DS_2-VASc Score, a more recent updated version of the score that provides some more granular data on the risk of stroke. The CHA_2DS_2-VASc Score has more components associated with it, as you can see, which more accurately identifies truly low-risk patients and it also reclassifies some patients to a potentially higher or lower risk score.

What's seen on the bottom left is a table which estimates, based on the clinical risk score either by $CHADS_2$ or CHA_2DS_2-VASc, what the annual risk of stroke might be. And as you can see, as clinical risk factors accumulate, the estimated annual risk of stroke begins to increase. Now, it's important to note this is annual risk, and so just like interest in the bank, this can accumulate rapidly over years or over decades. But certainly, it gives us an estimate of what the perceived stroke rate might be.

Now, the way that we influence this, the way we try and mitigate this risk, as we all know, is by -- as a frontline -- systemic anticoagulation. That, of course, has its own risks, and so a concept has been developed that if patients are at a higher risk for a stroke, then they potentially would be benefit from anticoagulation. If they're at very low risk for a stroke, then perhaps the risk of anticoagulation outweigh the benefits; and therefore, anticoagulation is not necessarily recommended, although maybe

considered. Fundamentally what we think is that there's a balance between the benefit versus bleeding risk associated with anticoagulation versus no anticoagulation. And so, the fundamental guidelines, which is shown here, is from the 2014 guidelines, suggest that if there's a high enough risk anticoagulation should be prescribed. If there is not a high enough risk, then it is a discussion of whether anticoagulation may be of benefit or may be of harm.

Now, it's a little bit more granular, a little bit more complex than just adding up numbers and saying are you above a threshold. Different societies have interpreted the data differently. What's shown here is a European flow chart, a European guideline set, which tries to help clinicians work through whether or not anticoagulation might be of benefit. What's important to note here is that there is a subset of patients with prosthetic mechanical heart valves, or moderate to severe mitral stenosis that are felt to benefit from anticoagulation, and specifically benefit from vitamin K antagonists, or warfarin, or coumadin. It's important to note that these previously used to be known as valvular atrial fibrillation; although, that term has largely fallen out of favor due to the fact that many other patients with valvular heart disease don't have the same unique risk associated with their atrial fibrillation.

As you work through the flow chart here, you see that the cardioembolic risk scores, the $CHA2DS_2$-VASc score, are an important part. But it also makes the point that single points are not all created equal. Points associated with gender may be interpreted differently. It also makes the point that oral anticoagulation is an important component, but the type of oral anticoagulation is also worth considering. We'll talk about this more in a minute.

This looks at the Canadian Guidelines, which again, use some of the similar concepts; assessing cardioembolic risk based on clinical risk scores; although, it gives somewhat of a different end result and a different flow chart. It's interesting to note that aspirin has commonly been used for patients who are at low risk that do not reach the level of needing other oral anticoagulants. The evidence is a little bit fuzzy on whether or not aspirin monotherapy is of any benefit or of any harm for those low-risk patients, and so various guidelines either support or do not support the use of aspirin in that context.

What's important to note is that over the past 10 to 15 years there's been a dramatic alteration in the landscape of systemic oral anticoagulation, as opposed to 15-20 years ago where oral vitamin K antagonists were the sole anticoagulant. As we're all aware, there have been a number of other oral anticoagulants that have been developed, as shown here, over the past 15 years. These have a very significant amount of data showing them to be both safe and effective in comparison with vitamin K antagonists. As such, current guidelines -- this is the 2019 American Guidelines -- suggest that one of these novel oral anticoagulants are recommended over warfarin in patients eligible for it who have atrial fibrillation as a first-line therapy. Again, excluding those patients with moderate to severe mitral stenosis or mechanical heart valves.

In prior guidelines all anticoagulation, including vitamin K, were considered reasonable as first-line, but that's changed in recent years given the overwhelming data suggesting the safety of DOACs (direct oral anticoagulants). So, while there is a wealth of data to show that there is a benefit of systemic anticoagulation, what's important to note is that not every patient can tolerate it.

What's shown here is some older data which looks at a real-world database of nearly half a million patients who have increasing risk of cardioembolic events who actually are prescribed oral anticoagulation. And while this is a little older data, it does hold true that somewhere around 50% of patients actually receive

the indicated oral anticoagulation. And the reason is what's shown on the right, that oral anticoagulation has some significant side effects and limitations. Both warfarin as well as novel oral anticoagulants can result in increased bleeding and for certain patients be harmful. As such, some non-pharmacologic prevention strategies have been developed for patients who might not be able to tolerate long-term anticoagulation.

Non-Pharmacologic Prevention of CVA in AFib

As we talked about before, high-risk patients with atrial fibrillation are often times prescribed anticoagulation, but somewhere around 50% to 60%, as seen on the bottom right, can actually tolerate this without issue. The other 40% or so are either contraindicated or relatively intolerant of anticoagulation. These are patients who with anticoagulation have important bleeding issues that would make it relatively contraindicated for them to be on it for a life-long prescription.

Now, there are ways to try and estimate bleeding risk, just like there are ways to estimate cardioembolic risks, and clinical risk scores have been developed. One of the more commonly used one is the HAS-BLED Score. As points in the HAS-BLED clinical risk factors accumulate, the annual bleeding risk estimate also increases. The components of the HAS-BLED Score are shown on the right of the screen, and the components of the CHA_2DS_2-VASc Score, which talked about before, are also listed. And what's important to note is that many of these risk factors overlap between the two scores. As such, as patients have a higher risk of cardioembolic events, they also potentially carry a higher risk of bleeding, and this explains why many patients with atrial fibrillation, while we certainly find it to be an important indication to anticoagulate them systemically, will have problems associated with that as they have an increased bleeding risk.

In terms of the types of bleeding that might occur, as you can imagine, the contraindications for either relative or absolute for systemic anticoagulation is varied. Bleeding to the brain, of course, is a very important one that we are often worried about. GI bleeding is a very common one. Patients with multiple falls is one that's very important to note. Urologic bleeding in the bladder is also important. There are also some lifestyle contraindications for long-term anticoagulation based on patients' professions.

So, what do we do about this? Well certainly, we can use some of the information that we talked about before. As we mentioned earlier on, an observation has been known for many years, which is that around 90% of the thrombi that develop occur in the left atrial appendage. Now while we use systemic anticoagulation to "thin the blood" throughout the blood stream, predominately the source of action with regards to reduction of cardioembolic events occurs at the left atrial appendage.

And so, a strategy has been developed over 70 years ago to simply remove the left atrial appendage. Reports of doing this during open-heart surgery dates back to 1949 and has over the years largely been proven successful in reducing cardioembolic events. Removing the left atrial appendage can be helpful even in patients who cannot tolerate long-term anticoagulation.

Now of course, open-heart surgery is a relatively invasive procedure, and as such over the last 20-25 years there has been an increased interest in developing minimally—or--non-invasive ways to achieving that same goal, which is to say removing, excluding, or occluding the left atrial appendage. Shown here are some cartoons of various strategies that have been developed by the medical industry.

The one that is most prominently used in the United States; although now two are approved, is the WATCHMAN device, which dates back to 2002. Over the course of the last nearly 20 years, a number of datasets and trials have been conducted which have shown the efficacy of this WATCHMAN device as a non-pharmacologic way to reduce cardio embolism in patients who have a relative contraindication to long-term anticoagulation.

A meta-analysis of two of the largest trials that looked at WATCHMAN implantation versus warfarin are shown here. And on the top line you can see that overall efficacy -- which looked at all strokes, as well as cardiovascular and unexplained death -- show that there is essentially equipoise between a WATCHMAN and warfarin. Put another way, if you were to look at the risk of stroke in patients who received a WATCHMAN device, which is shown as the point estimates on the bottom right of the screen, and compare it to what you would expect for patients treated with warfarin, you see that these point estimates essentially overlap the solid line of those patients treated with warfarin -- meaning that if a patient can't tolerate warfarin, this is a very reasonable alternative.

Now, it is important to note that the solid line is what patients would be expected to have for their ischemic stroke risk if they were treated with warfarin. What's shown in the dotted line is what patients would have if they were not treated. And unfortunately, no real randomized control trials exist comparing no anticoagulation to WATCHMAN or to left atrial appendage occlusion; however, looking at this imputed risk we can see that there might be a dramatic reduction.

To put it another way, if you were to look at three of the largest trials or registries for the left atrial appendage occlusion device and calculated an imputed risk score based on their cardioembolic risk, and then see what was the observed risk score based on the left atrial appendage occlusion device, you see that there is around a 60% to 80% reduction in cardioembolic risk.

As such, in the United States and throughout the world, left atrial appendage devices are used for patients who have a relative contraindication for long-term anticoagulation. The phrasing of this is different based on different guidelines. The FDA indication is for having an appropriate rationale to seek a non-pharmacologic alternative to warfarin. The Centers for Medicare and Medicaid Services (CMS) coverage phrasing says, “deemed unable to take long-term oral anticoagulation”. But suffice it to say that this a very reasonable alternative for patients who cannot tolerate long-term oral or systemic anticoagulation; although, the exact meaning of that is a little bit nebulous.

To summarize, left atrial appendage occlusion is an option to reduce risk of stroke in patients with atrial fibrillation, but right now it's reserved for patients who cannot take anticoagulation. I wanted to mention that WATCHMAN is the device that’s been used and clinically approved for years in the United States. Recently a new device known as the Amulet has also been approved and is becoming commercially available.

Prevent Recurrent AFib Strokes

For the final topic we’ll talk about preventing recurrent strokes with atrial fibrillation. And I just wanted to catalyze this part of the conversation by a case.

This is a case of a 68-year-old man, diabetes, hypertension, prior transient ischemic attack (TIA) who was admitted with a stroke. His MRI shows imaging consistent with a left middle cerebral artery (MCA) distribution stroke. There's no stenoses seen in the major arteries of his head or neck. His echocardiogram shows no obvious source. His EKG and telemetry are normal, and he receives an implantable loop recorder. So why is that, why would someone get an implantable loop recorder?

Well, as we know, one of the main problems with strokes is that around 25% are cryptogenic. We don't have a clear idea of why the patient developed their stroke. Now, of course, based on the topic of this talk, you might wonder whether or not occult or undiagnosed atrial fibrillation is related. As we know, the relationship in time, the temporal relationship between the arrythmia and the stroke may not be directly related. And as such, occult paroxysmal atrial fibrillation is always considered to be a concern.

Now, over the years people have looked for atrial fibrillation with EKGs or even wearable monitors, but recent studies have shown that by actually implanting a loop recorder for long-term rhythm monitoring, upwards of two to three years, we can increase the ability to detect atrial fibrillation. The CRYSTAL-AF study looked at the diagnosis of atrial fibrillation from the index event to the cryptogenic stroke in patients who received an implantable loop recorder versus those who were in the control arm and did not.

And as you can see, there is six, seven, even eight times increased risk, increased ability to detect atrial fibrillation. For these patients it's important, because if you were to implant loop recorder and get something of a result consistent with this, as in the diagnosis of atrial fibrillation, then you could change the management by prescribing oral anticoagulation, and that would hopefully prevent recurrent strokes associated with atrial fibrillation.

The data for this has been relatively convincing, and so in the 2019 American Guidelines, updating from the 2014 guidelines, in patients with cryptogenic stroke in whom other external ambulatory monitoring is inconclusive, implantation of a cardiac monitor is reasonable to optimize detection of atrial fibrillation.

Now, this is, of course, to detect atrial fibrillation in patients with a prior stroke. One might think, is there an extension of that where we could use some technology, some wearable monitoring in order to detect atrial fibrillation before strokes occur and potentially allow for the utilization of anticoagulation or other strategies to prevent strokes even before the index stroke occurs. And that’s an area of great research and great promise. Currently screening strategies for atrial fibrillation have some barriers, and unfortunately, have not been largely positive; however, in the future with the evolution of technology hopefully this will change.

So, just in summary, atrial fibrillation is a heterogenous disorder that requires the tailoring of clinical therapy. But one of the most important morbidities is the relationship between atrial fibrillation and cardio embolism, or stroke. Although the exact mechanisms are not clearly understood, the arrythmia is important, but possibly not the sole cause of the cardioembolic event.

There are both pharmacologic and non-pharmacologic approaches to cardioembolic protect in patients with atrial fibrillation, and important patient-specific considerations are required in order to make the correct choice in how to treat patients and prevent cardioembolic events. And identifying patients with atrial fibrillation and instituting appropriate therapy prior to a stroke or after a primary stroke is an important goal.

Thank you very much for your time.