[MUSIC PLAYING]

PETER NOSEWORTHY: Hi, I'm Peter Noseworthy, cardiac electrophysiologist at Mayo Clinic in Rochester, Minnesota. I am involved in the care of patients with atrial fibrillation, and I also have an appointment in the Center for the Science of Health Care Delivery where I perform a number of comparative effectiveness studies.

Today, I'm going to be talking about the use of observational data to close the gap between what we've learned in clinical trials and what we do everyday in clinical practice. And in particular, I'm going to talk about the use of a new class of drugs, the non-vitamin K, oral, anticoagulants for the prevention of cardioembolic stroke and atrial fibrillation.

Let's start with the case. If you imagine an 81-year-old woman with a history of hypertension and persistent atrial fibrillation who was admitted with a TIA, she's had a major GI bleed in the past, which was associated with a supra-therapeutic INR. At the time of the stroke, or TIA, she was off warfarin. She has a creatinine of 1.1 and a weight of 70 kilograms, which yields a creatinine clearance of 52 mL per minute. Her echocardiogram demonstrates moderate aortic stenosis and moderate mitral regurgitation.

What is the best drug to treat this patient with? She is not somebody who, perhaps, would have been well-represented in the clinical trials. But what would you do in your daily practice? No anti-thrombotic therapy, aspirin at low dose, 81. Would you restart warfarin and, perhaps, take efforts to control her INR? Initiate a reduced dose apixaban, or a full dose apixaban, or perhaps full dose rivaroxaban?

Cases like this raise many considerations. We saw in her echocardiogram that she had some valvular heart disease, but is this enough valvular heart disease to preclude the use of one of the novel agents? She also has mild renal insufficiency. And in this case, would she required dose reduction, even though, based on the labeling, she may not necessarily require a reduction of the dose of apixaban?

Her prior high INR may indicate poor adherence. And perhaps, she may not be a good candidate for warfarin in the long run. Or perhaps, her prior GI bleeding mark her at somebody who's at exceedingly high risk of bleeding and should avoid future anticoagulation

altogether, even having had a stroke. Let's see what observational data can help us to understand how to treat patients like this.

Well, for many years, the only agent available for anticoagulation was warfarin. This was first discovered in the 1940s when researchers at the Wisconsin Alumni Research Foundation identified a source of bleeding in cattle who were eating spoiled clover. This was initially marketed as a rat poison, but within 10 years, it was approved for oral anticoagulation. It received widespread recognition when Dwight D Eisenhower was treated for a coronary event while in office with warfarin.

And for about five decades, this was our only option. Patients became used to adjusting their dose and monitoring their blood and their blood INR levels. And there were really no other options. In 2006, Ximelagatran neared approval, but was ultimately pulled due to hepatotoxicity.

And it was not until 2010 when the first direct oral direct anticoagulant became available. This was dabigatran. It was followed quickly by rivaroxaban, apixaban, and edoxaban, most recently in 2015. And patients now have a number of choices for anticoagulation for the prevention of cardioembolic stroke and atrial fibrillation.

The efficacy and safety of these drugs has been well-established in a series of large, pivotal clinical trials, each of which was published in *The* New *England Journal of Medicine.* And meta analyzing these data, we can see that we expect these drugs to be at least as effective as warfarin in preventing stroke or systemic embolism. It may be that there's a slight superiority of dabigatran and apixaban, in comparison to warfarin. But as a class, these fair very well.

Similarly, for major bleeding, we anticipate similar bleeding rates that we would observe with warfarin. Perhaps most striking is there appears to be quite a dramatic reduction in the risk of intracranial bleeding, about 50% of the risk that's observed with warfarin. I should make the caveat, however, that the intracranial bleeding is a relatively rare event. So in absolute terms, these numbers are quite small. Nonetheless, as a class, these drugs perform better, in terms of intracranial bleeding.

These studies represent an excellent example of the generation of clinical knowledge, moving from a basic observation to translation to clinical practice with the development of a new drug, which is rigorously tested in randomized, controlled trials. We now move, however, from the

trial phase of evaluation of these medications into implementation. And we have tens of thousands, or hundreds of thousands, of patients taking these medications. And we can start to learn things about how they perform in everyday practice.

For instance, we can perform comparative effectiveness work, comparing the drugs to each other, something that was not done in the trials. We can get a sense of realized outcomes in terms of how well the trial findings are generalizable to clinical practice. And we can observe utilization patterns and sometimes gain insights about how these drugs perform by examining these.

We can go one step forward to look at risk stratification, individualized treatment choices, niche indications that may not have been included in the trials. We can look at patterns of adherence and compliance and how that impacts outcomes and, ultimately, make decisions to identify the best drug for the right patient.

Now, instead of using randomized trial data, we will be using observational data. And these two data sources have complementary strengths and weaknesses. The strength of a randomized trial, of course, is random treatment allocation, which minimizes bias. In observational data, we are inherently confounded by indication. There may be a reason a practicing physician chooses one medication over another. And even with the sophisticated statistical methods, it's hard to fully overcome this limitation.

In contrast, randomized trial data is limited by generalizability. The patients, including clinical trials, are highly selected. And there can be a form of the Hawthorne effect, during which patients treated in a randomized controlled trial receive idealized therapy. In comparison, those treated in observational data sets are relatively unselected and we think are generally representative of real world practice.

So in this talk, I'm going to discuss five studies that examine the use of observational data to try to fill some of these gaps. The first is what I would call the real world clinical trial, essentially recapitulating what was done in the randomized trials in clinical practice. This helps us understand the generalizability of the clinical trial findings to everyday practice.

I will then look at the improbable trials, things like head-to-head comparisons that may be too expensive to do in practice. I can look at dosing deviations and differences in adherence because no trial will ever randomize patients to either under or overdosing or to on-and-off therapy if they have an indication.

We can also look at niche indications that may have been under-represented in the clinical trial. And in this situation, I'll talk about hypertrophic cardiomyopathy. Patients with atrial fibrillation and hypertrophic cardiomyopathy require anticoagulation, but it's unlikely we'll have a large enough clinical trial to answer the question about whether NOACs are reasonable in this situation.

I will look at the individualized clinical trial and look at examination of outcomes, in particular patient subgroups by age and renal function. And I will give an example of when observational data allows us to generate new hypotheses that may motivate future clinical trials.

First, the real world trial-- do the findings of the clinical trials translate to clinical practice? The data source I used in these studies was the Optum Labs data warehouse, which includes over 100 million patients. At its back bone, it's an administrative claims data set, but it is enriched with clinical data from the electronic health record, which allows us to do a deep dive and to validate some of the findings that we need to use claims to identify. Although it is not necessarily an exactly representative sample, because it is an insurance claims data set, it does pull broadly from all regions of the US and is broadly representative of current clinical practice.

When we create a cohort within the Optum Labs data warehouse, we start by identifying all users of the anticoagulants-- apixaban, dabigatran, rivaroxaban, and warfarin-- 1.8 million patients. We then require a 12-month run in period, during which time we can characterize patient demographics and baseline characteristics that will be important when we match.

We required, in these studies, patients to have atrial fibrillation and then applied clinical trial exclusion, valvular heart disease, or end-stage renal disease requiring dialysis. We then match on various clinical variables and end up with three pairwise comparisons, comparing each of these drugs to warfarin.

When we look at the Rocket-AF trial, we anticipate that rivaroxaban will be similar to warfarin, in terms of stroke or systemic embolism, and major bleeding, but will be associated with a reduction in intracranial bleeding. In Optum Labs data warehouse, it's remarkable how well we can recapitulate these data. In fact, if you look at the point estimate for major bleeding to two decimal points, our relative rates are equal, even the confidence intervals. And the trend for intracranial bleeding holds true.

This was also the case when we compared the Aristotle trial, which randomized apixaban to warfarin. And we were able to demonstrate that there was a reduction of stroke or systemic embolism with apixaban in comparison to warfarin, that there's a reduction in major bleeding, and most strikingly, in intracranial bleeding.

Now, we could also use these data to form the improbable clinical trial. And the best example of this would be the head-to-head comparison. It's unlikely that we will ever have large scale, randomized trials comparing each of the NOACs to each other. This would be too costly and it's unlikely to be funded by drug companies. We can also evaluate the effective dosing deviations, which is an impossible randomization. We cannot randomize patients to over- or under-dosing. And we can look at the effective adherence because, in the current era, we cannot randomized patient to no therapy if they have an ongoing indication.

Comparing these drugs to each other, we demonstrate that rivaroxaban, dabigatran, and apixaban have similar effectiveness. There was no statistical difference in the effectiveness between these drugs. The difference we see, however, is in major bleeding, and apixaban fares better than either dabigatran or rivaroxaban with a rate of major bleeding that is about half of either of those drugs. It appears that rivaroxaban is associated with the highest re-bleeding rate and is, in fact, statistically significantly higher rate than even dabigatran.

Let's look now at dosing deviations and adherence. The hope with these medications is that adherence would be better. We know that it's hard to take warfarin. It's cumbersome to have blood drawn periodically. And the dietary interactions are very cumbersome to patients. So the hope was that the direct anticoagulants would have much better adherence.

However, we do not necessarily see that that is the case in practice. And one year out, about half of patients have discontinued the use of these medications. And that's true for low-risk patients, who may not have a firm indication in the long run, but it's even true for patients who are at high risk of stroke or systemic embolism and have firm, ongoing indication for anticoagulation.

When we evaluate the relationship between adherence and the risk of stroke, you can see that, for patients at high risk of stroke, there's a graded relationship between time off anticoagulation and their risk of stroke. In lower-risk patients-- those with CHA2DS2Vasc scores of zero or one-- we were unable to identify that relationship. This is important because one of the challenges in our field is whether or not we should be anticoagulating patients on

the low end of the risk spectrum. And here we identified that, on or off therapy, that rates are low, perhaps favoring no anticoagulation relation in the lowest end of the risk spectrum.

What about bleeding risk? Well, here we show that there is a graded relationship between adherence and bleeding risk in low-risk patients, but this is not observed in higher-risk patients, suggesting that adherence increases bleeding risk in these low-risk patients, again underscoring the potential harm of anticoagulation in this patient group.

Now, dosing of these medications is complex. Although we don't require ongoing dose adjustment, renal function has to be considered. Because of this, there are often errors in dosing in clinical practice. And we wanted to examine how these deviations from the labeling impact outcomes.

This is an overview of the approach to dosing and renal disease. Dabigatran, rivaroxaban, and edoxaban are dose-based on creatinine clearance, whereas apixaban is dosed based on a combination of age, weight, and the baseline creatinine. In patients who had no indication for dose reduction, but who did receive a reduced dose, there's a potential for under-dosing.

Well, who are these patients? You can see here that they tend to be elderly, many of them are over the age of 80. They're more likely to be female than male, and they tend to be on the high end of the risk spectrum, often with CHA2DS2Vasc scores of four or greater. When we look at the impact of under-dosing, we can see that, for patients treated with apixaban, there did not appear to be a benefit in terms of reduced bleeding, but there was a sizable increase in the risk of stroke, suggesting that under-dosing in these elderly, high-risk patients may have potentially deleterious consequences.

Now, I stress here that the risk of stroke was very low in the patients treated with full dose apixaban, which contributes to the high relative difference in these drugs. We did not, however, identify a statistically significant difference in under-dosing with either dabigatran or with rivaroxaban. Why is that finding? And is it unique to apixaban?

Well, it could be that we were better powered to detect a difference in apixaban-treated patients. These patients were at the high end of the risk spectrum with high CHA2DS2Vasc scores. They were older. They were more often female. It's also true that reducing the dose of apixaban reduces the dose by 50%, whereas reducing the dose of rivaroxaban is a 25% reduction. It's also maybe the case that because apixaban is the least renally-cleared of these medications, that renal dosing is less important for apixaban. And thus, a dose reduction may

have accentuated consequences.

Let's move on to a potential niche indication for anticoagulation. In this case, I'll talk about hypertrophic cardiomyopathy. Now, we know that patients with atrial fibrillation and hypertrophic cardiomyopathy require anticoagulation. They're on, on average, of about a 4% annual risk of stroke. However, this can also be associated with some valvulopathy, which is acquired. And the US and European guidelines are relatively vague about the use of NOACs as an option for hypertrophic cardiomyopathy, and there are currently no data to guide our decisions.

When we identify patients with hypertrophic cardiomyopathy within the Optum Labs data warehouse, we can then compare those who were treated with NOACs to those who were treated with warfarin. And we identified no difference in the effectiveness for the reduction of stroke or systemic embolism and similar safety, in terms of major bleeding, intracranial bleeding, and GI bleeding.

Also, importantly, if we stratify by baseline risk as gauged by the CHA2DS2Vasc score, we can see that there's no trend for difference across the range of baseline risk. This underscores the fact that even patients with a CHA2DS2Vasc score of zero or one should be anticoagulated in the context of hypertrophic cardiomyopathy. And indeed, we should not be applying the CHA2DS2Vasc score to patients with hypertrophic cardiomyopathy.

What about the individualized clinical trial? Let's look at some individual patient subgroups and characteristics and see how that impacts the relative effectiveness of the medications in comparison to warfarin. Here's a comparison of dabigatran to warfarin across a range of baseline renal function with GFR on the x-axis. And what you can see is that these lines cross both for stroke and for major bleeding.

So in this case, baseline real function has an impact on both the effectiveness and the safety of these medications. At the low end of the GFR spectrum, these patients are at high risk of major bleeding with dabigatran. But the protective effects of dabigatran for the prevention of stroke are most powerful.

Shown another way, we can see, based on the outcome of interest and the GFR range, which of these medications would be favored for the prevention of these endpoints. The red boxes favor dabigatran, whereas the blue favor warfarin. And on the right column, you can see, overall, dabigatran fairs better for each of these outcomes. However, for thromboembolism

warfarin appears to do better at the high end of the GFR for the prevention of thromboembolism and at the low end of the spectrum for the prevention of bleeding on anticoagulation.

Lastly, I'd like to talk about the use of these kind of data for hypothesis generation. Soon, we can see unexpected patterns in practice that can motivate further investigation with a randomized trial. I'll talk specifically about the effect of anticoagulation discontinuation after ablation.

This is, in a sense, looking at utilization patterns to motivate future clinical trials. So after a apparently successful catheter ablation for atrial fibrillation, many patients may wish to discontinue anticoagulation, assuming that their risk of cardioembolic stroke is reduced by the procedure. Even though current guidelines do not suggest this, what we can see here is that about 2/3 of patients have discontinued anticoagulation within a year of catheter ablation. And again, this is true for both low-risk patients, in whom it may be reasonable to stop the medication, but even more importantly for high-risk patients who likely have an indication for ongoing anticoagulation.

If we look at the impact of anticoagulation discontinuation after ablation, we can see that, in high-risk patients, those with CHA2DS2Vasc scores of two or greater, or at more than two-fold increased risk of cardioembolic stroke. Now, of course, these kind of data are inherently confounded by indication. And to rigorously test this, we would need a randomized trial. And this is currently enrolling.

In summary, these data have been useful in performing the real world clinical trial, which generally demonstrate that NOACs perform well in clinical practice. We're also able to perform the improbable clinical trial, comparing these drugs to each other and examining the effects of adherence and dosing on the outcome, again demonstrating that apixaban appears to be associated with the lowest bleeding risk of those medications, that are equally effective, and that adherence is particularly important in high-risk patients and that under-dosing is a potential problem in apixaban-treated patients.

We've identified that patients with hypertrophic cardiomyopathy may be reasonable candidates for treatment with direct anticoagulants. And we have been able to identify important interactions between renal function and age and the relative safety and effectiveness of drugs like dabigatran. And we are able to identify practice patterns that may inform future clinical

trials. I thank you very much for your attention.