Moderator: Welcome to the VA HSR&D Investigator Insights Podcast series. In this episode Dr. Christopher Rentsch of the London School of Hygiene and Tropical Medicine, and Yale University discusses using large-scale VA data sets to understand, and evaluate the effectiveness of prophylactic anticoagulant therapy for treating COVID-19.

Maria: My first question is, what drew you to Health Services Research, given that you have a pharmacoepidemiology background? It's an interesting combination, and I'm very curious to learn how you came to study HSR-related things.

Christopher Rentsch: First of all, thank you, Maria, for the introduction and for inviting me to share our exciting work. I think I start answering your questions by defining what I think Health Services Research is. My understanding is that this type of research encompasses all aspects of healthcare with a specific focus on patient care, cost, and quality. And at the VA, I understand that Health Services Research is often done to identify, evaluate, and rapidly implement the evidence-based strategies that improve the quality, and safety of care delivered to Veterans.

Which brings me on to pharmacoepidemiology, which is simply research that evaluates the safety, and effectiveness of medications with the ultimate goal of creating real-world evidence to support treatment guidelines that improve the quality, and safety of care delivered to Veterans. I think Health Services Research and pharmacoepidemiology go hand in hand, which is exactly what is demonstrated in our paper.

Maria: When you first began to hear about the COVID-19, and the SARS-CoV-2 emergence, what were your immediate concerns as a health professional, as an investigator?

Christopher Rentsch: I can remember being initially cautious but alarmed when I first heard of the COVID-19 outbreak in Wuhan, China. Then, as it spread west into Europe, the level of caution, and frankly, unbelievability of the situation started to increase within me. I mean, existing in the time of a pandemic was not on my list of things I thought 2020 would bring.

And because I live in London, UK, I think the first time I felt any sort of panic was when the outbreak in Northern Italy began being covered in the news, which was just too close to home. When the pandemic eventually arrived in the U.K., there were still relatively few cases in the U.S. My immediate concerns were how we were going to monitor and track COVID-19 patients on a national scale here in the U.K. But it wasn't long before I reminded myself of the wealth of the VA electronic health record data, and the system within the VA which houses national de-identified data in a secure way on all Veteran patient care. And that this wealth of data would be a solution to answer many of the world's questions being asked early in the pandemic, and continues to be that today.

Maria: That's great. And thank you for pointing out the solution-oriented nature of the data because it is something I think that VA has been rather proud, I think, of both its response from rapid responding research as well as our vaccination programs. Early on in the pandemic, treatments as opposed to preventive measures were rather scarce. When did you first begin to hear that anticoagulant therapy might be efficacious?

Christopher Rentsch: From very early stages of the pandemic we knew that deaths from COVID-19 have been partially attributed to the formation of blood clots that have led to more serious \_\_\_\_\_ [00:03:49] violent events like lung failure, heart attack, and stroke. And that these events are quite common in patients with severe cases of COVID-19. Anticoagulants, commonly known as blood thinners, prevent the formation of these blood clots. And therefore, several expert organizations recommended the use of low-doses of anticoagulation, otherwise called prophylactic anticoagulation, for patients admitted to the hospital with COVID-19, and who are eligible to receive it.

However, before our study there was limited data-driven evidence that directly addresses whether there is benefits from this therapy in patients with COVID-19. Our study, which has been published in the BMJ, is the largest nationwide analysis of patients admitted to hospital with COVID-19 in the U.S. looking to address this very question about the role of prophylactic anticoagulation in patients hospitalized with COVID-19.

Now, we designed our study to emulate a clinical trial, which is just to say we used high-quality observational data in our rigorous advanced methodologies, and found in the VA electronic health records, we were able to comprehensively account for reasons why people were given or were not given prophylactic anticoagulation. Using those methods, we found that patients given low-dose blood thinning drugs within the first 24 hours of being hospitalized with COVID-19 are 19% to 34% less likely to die compared to those not put on any anticoagulant.

Now, I should say, of course, the gold standard method to derive evidence for the safety or effectiveness of medications are randomized clinical trials. However, trials investigating this question are still underway, and have not yet been fully reported. As we await full reporting of these ongoing clinical trials, we believe our findings using VA data provide strong, real-world evidence to support guidelines recommending the prophylactic use of blood thinning drugs as initial therapy upon hospital admission for COVID-19 patients.

Maria: Since you brought up that you're still waiting for the randomized controlled trial data to come in, are you hoping for consistency with your findings?

Christopher Rentsch: As an individual, you, it uses observational, real-world data, otherwise not interventional data. I don't work in trials. I'm always hoping that anything that I estimate in real-world data using good data, good methods will be replicated in clinical trials or vice versa. There's also a field within pharmacoepidemiology who take published clinical trials, and a test, and often are able to replicate those trials in real-world data.

We are eagerly awaiting the full reporting of trials, ongoing trials looking at anticoagulants in the context of COVID-19. There have been some early findings from some press releases that we, our results may be replicated, but nothing has yet to be fully reported.

Maria: Some of your key findings indicate that they were consistent with and potentially generalizable from the VA population to the non-VA population. Just as the general question, given your background was working with VA data for quite some time, how often have you seen this happen with other studies that the VA data is generalizable to the non-VA population?

Christopher Rentsch: That is an interesting question that any VA research or researcher can tell you that they are commonly asked this question. And I think, unfortunately, there is no simple answer. And I think the answer does differ from study to study. I think, if a study was trying to estimate the absolute rate of some outcome, let's say cardiovascular disease, then I think it would be difficult to assume that the rate of cardiovascular disease among Veterans is similar to the rate in the general population.

This is simply because Veterans, as we know, are on average older, and have a higher prevalence of chronic health conditions, and risk behaviors than the general U.S. population. However, let's say a study was trying to estimate the relative rate of some exposure on an outcome; for example, comparing the rate of cardiovascular disease between smokers and non-smokers in the VA. I think this relative rate would be more plausibly generalizable to non-VA populations than any absolute rates could be. But, of course, any claims of generalizability need to include careful consideration, and may not be appropriate for all studies.

In the context of COVID-19 we developed a predictive index based off VA data, and have since shown that the risk of COVID-19 mortality associated with age, sex, and comorbid disease diagnoses that we observed in VA data was consistent across other academic, and non-VA national healthcare samples in the U.S., which is reassuring for us regarding the generalizability of our VA COVID-19 research.

I should admit that the generalizability between VA and non-VA populations is a key area of research in our group. And we have much more plans to further shed light on this important question.

Maria: Your results of initiating prophylactic anticoagulation within 24 hours of hospital admission, the relative risk reduction of mortality was as high as 34%. Thirty-four percent seemed really high in a really good way. Did it surprise you?

Christopher Rentsch: We had hypothesized that we would see some sort of benefit from initiating prophylactic anticoagulation as opposed to no anticoagulation therapy. And we \_\_\_\_\_ [00:10:18] found several reasons. But, first, we were aware of the high rates of blood clots leading to serious complications in COVID-19 patients. And of course, we know that anticoagulants are known to prevent the formation of these blood clots. Second, certain anticoagulants have antiviral, and potentially anti-inflammatory properties, and might be particularly effective in patients with COVID-19.

And third, recent experimental studies have shown that certain anticoagulants have been shown to block the SARS-CoV-2 viral spike protein from binding. Which essentially means anticoagulants may reduce viral and its activity. But I can share with you, we were, what we were most surprised about, which is how robust our results were to the large number of sensitivity analyses we performed.

In the end, I think we performed a tool of around ten sensitivity analyses to see if our estimates from the primary analysis changed under various sets of assumptions. Our primary conclusion, though, did not change in any one of those additional analyses undertaken.

Maria: Are you aware whether these findings have been taken up in clinical use by VA?

Christopher Rentsch: Yes, of course, important to always think through. We found something of the data, how do we implement this and share this with the people who can make change? First off, a good thing to note about our study was that we estimated around 85% of the patients in our nationwide cohort had received prophylactic anticoagulation within 24 hours of being admitted to hospital with COVID-19. The vast majority of patients who were eligible to receive this therapy were already doing so, even when we conducted this study which used data through the end of July 2020.

But as soon as we were confident in our findings, we reported that directly to the VA Central Office and joined calls with the chief medical officers around the country, many of whom took immediate steps to implement our findings in the VA treatment guidelines, and clinical care. Indeed, after one of the presentations I gave on a chief medical officer presentation, many started contacting me and my team directly to see, what was the level of use of anticoagulation at their specific site?

We developed a big infographic that we shared with chief medical officers that showed by station which were performing at average, already having 85% of the patients or more being prescribed this therapy, and the few patients that were good to have some areas for improvement. We shared all of that information immediately as we were confident in our findings, and very happy to say that they were implemented around the country.

Maria: In an ideal world, if you could, what would the body of your research work result in? What would be the end result? Would it be changes in policy, adoption of new clinical standards, all of those things?

Christopher Rentsch: Well, the short answer is yes. My ultimate goal is to provide high-quality evidence that impacts treatment guidelines, and clinical standards to the benefit of VA patients, and beyond. And I mentioned earlier, the gold standard method to derive evidence is through high-quality randomized clinical trials. But I think what our paper demonstrates is the value of VA data as we said earlier, particularly during outbreaks like COVID-19, whereby we were able to respond to the urgent need for evidence on the safety, and effectiveness of potential therapies to treat or prevent COVID-19.

The VA is one of the few sources of electronic health record data globally of its size with the necessary outpatient, inpatient linked SARS-CoV-2 testing data to perform high-quality studies in COVID-19. We thank the VA HSR&D who managed to organize several studies investigating different potential therapies very early on in this pandemic, including ours on anticoagulants. And we eagerly await the results of ongoing clinical trials on anticoagulants, particularly those investigating whether this therapy should be given to non-hospitalized patients who are newly diagnosed with COVID-19.

Maria: My next question is with regard to VA, how did you come to VA, and to do work within VA Health Services Research?

Christopher Rentsch: I started my VA research career in Atlanta in 2011. I actually began as a clinical research coordinator, which had me enrolling patients into survey studies, performing phlebotomy, extracting plasma in a lab, and shipping those samples off to the CDC, and other things like that. However, I had a knack for analyzing large, complex datasets. And this opened up doors for me to perform research using the wealth of electronic health record data in the VA.

I have now been wrangling and analyzing VA data for a decade in a variety of different clinical areas. When the COVID-19 pandemic hit the U.S. in early 2020, I, along with an expansive team of VA researchers around the country, began analyzing the data daily. And it was natural that we worked with the VA Health Services Research and Development Service to answer key questions left unanswered in the pandemic.

Maria: It's really great to hear that you understand and appreciate the uniqueness of the VA's wealth of data. I'd like to know, does serving the U.S. Veteran population through your work, does it, what does it bring to you, either personally or professionally?

Christopher Rentsch: I thank you for this question. Like many of us, I have family members who have served and are currently serving in the military. When I finished my master's degree at Emory University in Atlanta, an excellent job opportunity became available at the Atlanta VA. And I took it. For the first three years of my time as a VA researcher, I was very fortunate to meet, and develop relationships with Veterans in, and around Atlanta. These relationships are, in my mind even when I look at numbers on the computer screen, and any findings from my analyses that in any way promotes healthier living among Veterans, is always a huge win for me.

Moderator: The views and opinions expressed in the preceding podcast are concerned with the scope of recently concluded or ongoing VA HSR&D funded research, and do not necessarily reflect current or to be implemented VA policy. To learn more about this research visit the VA HSR&D website at www dot hsrd dot research dot VA dot gov.

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