Cyberseminar Transcript

Date: October 18, 2017

Series: HERC Health Economics Seminar

Session: Comparative Effectiveness of Warfarin versus Direct Oral Anticoagulants in Nonvalvular Atrial Fibrillation Using Quasi-Experimental Methods

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Dr. Wei Yu: This is Wei Yu, a health economist at HERC. We are very happy to have Dr. Nicolae Done to have a presentation today. Dr. Done is the health economist at the AcademyHealth Delivery System Science Fellow at the Center for Access Policy Evaluation and Research in the VHA and also at the Boston University School of Medicine. He leads studies on innovative programs aimed at interesting increasing access to primary and specialist service for US Veterans. He also conduct the comparative effectiveness analysis of prescription medication using real world evidences in order to improve the evidence base for clinical practice. He received his PhD in health economics and policy at the John Hopkins Bloomberg School of Public Health where his [unintelligible 00:01:06.13] project evaluated early evidence of the hospital's global budget programs in Maryland. Prior to his doctoral program, Dr. Done is the, is the research analyst in the Program in Health Care Financing at the Harvard TH Chan School of Public Health where he helped model the impact of proposed single payer system in the state of Vermont. He has also been involved in international projects involving comparative healthcare, financing and health system reform. Dr. Done now you can start your presentation.

Dr. Nicolae Done: Okay, great. Thank you so much Wei. So hello everyone, I am going to talk today about my work on comparative effectiveness of direct oral anticoagulants verses warfarin in patients with Atrial Fibrillation. Just to set the talk in context, so basically why do we care about this? Atrial fibrillation is the second most common cardiovascular condition. It leads to a 3- to 5- fold increase in the risk of stroke in the patients that are afflicted. And the main line of treatments are oral anticoagulants or OACs as we call them. These drugs, also known as blood thinners, drastically reduce the risk of stroke and are recommended by clinical guidelines in all Atrial Fibrillation patients that are at high risk of stroke.

Up until recently the only option available as an oral anticoagulant was warfarin. It’s been available for several decades now and it’s actually very effective. It reduces the risk of stroke by about 60 to 70 percent according to some estimates and the way it acts is actually on an enzyme that recycles vitamin K in the human body. Because of that it has numerous food and drug interactions. So anything that affects the supply of vitamin K in the blood can basically interact with this drug. And therefore, the patients that are treated with warfarin require that vitamin K levels be frequently monitored and the dose be adjusted. So there’s a whole infrastructure, particularly in the VA for this where patients come into these outpatient anticoagulation clinics to have their blood monitoring performed. Warfarin also, as you may expect, increases the risk of bleeding because it’s a blood thinner and it prevents some of the blood clotting that is responsible for stroke. There is reversible agent. For warfarin it is actually very effective because it binds more tightly to warfarin than to the direct oral anticoagulant. So a few years ago the first direct oral anticoagulants or DOACs came on the market. These are dabigatran, which is a thrombin inhibitor in case you’re interested and rivaroxaban, apixaban and edoxaban, which all three of them are Factor Xa inhibitors. So they affect the specific blood clotting factor. They are, therefore non-vitamin K antagonists, and they’ve been shown to be at least non-inferior to warfarin in large phase III clinical trials. They are, however, more expensive. They are still on patents since they been recently approved and they’re more expensive to use. An interesting fact about some of the studies that have been done it showed the reductions in stroke compared to warfarin are concentrated in hemorrhagic strokes. So there’s sort of an interesting interaction between hemorrhage and stroke there.

The object of our study then to evaluate the comparative effectiveness and safety of the DOACs using evidence from the VA large administrative database. And a bit more of a why we think this is important. So even though DOACs have been shown to be at least non-inferior to warfarin in clinical trials, these results may not necessarily translate to medical practice. There’s many reasons for this. First of all differences in the patient population. So, as you maybe be aware the Veteran population is very different from the general population. They have higher morbidity in general. Their adherence to drugs has been shown to be substantially lower due to a whole host of mental health conditions, substance abuse problems and so on. Also because the VA is an integrated delivery system that’s run by the federal government there are also differences in clinical practice. So in the VA there may be differences in the intensity of follow-up, the dosing that the patients receive or other variations in revision of care that may affect the outcomes of patient fibrillation.

So here I will take a little break and just to understand who the audience is, so I would like to ask you to answer the question [inaudible 0:07:09.6] what is your professional role? Are you a VA researcher? Are you a project manager, coordinator or assistant? Are you from the VA Program Office or operations staff? Are a clinician; a non-VA researcher; or anything other non-VA attendee? So I will let you answer this question and we’ll pick up shortly after that.

Heidi: Great, responses are coming in, I’m just giving everyone a few more moments. Unfortunately I was limited in my response choices so I had to combine the last two. So for any non-VA, we have just one non-VA option. I apologize, I wish I could break them up further but they like to limit my poll options here. Okay, it looks like we’ve slowed down so I’m going to close that out and we’ll take a look at the results. And we have 35% of the audience saying that they are VA research investigator, data manager or analyst; 4% VA project manager, coordinator or assistant; 0 program office or operations staff; 43% VA clinicians and 17% non-VA. Thank you everyone.

Dr. Nicolae Done: Okay, great. So let’s move on. So, we have looked at some of the studies that have been done using real world evidence. And these are all recent as you can imagine. The most recent one was done last year by Yao and collaborator on a population of privately insured patients. There’s four studies done in 2015. Most of them in the US on various populations, however there’s also a study on French patients by Maura and collaborator. Most of the studies have looked at dabigatran only because this was the first drug to be approved. However, the Yao study looked at three DOACs, dabigatran, rivaroxaban and apixaban and the French study looked at dabigatran and rivaroxaban. Most of these studies have used propensity-score matching as a way to balance the groups of patients receiving warfarin verses DOACs and their results tend to show that DOACs are favored compared to warfarin, but there are certain differences and specifics based on what outcomes they looked at, what drugs they examined and study design. So the interest results I would say come from Yao and collaborators, here they found that apixaban is superior to warfarin in terms of reducing stroke and embolism. However, dabigatran and rivaroxaban were found to be similar to warfarin. For major hemorrhage apixaban and dabigatran were superior but rivaroxaban was similar to warfarin. Two studies have looked at death, so mortality. The Graham, Villines and Maura studies. And two of them favor DOACs, the Maura study has found no difference, however, the Maura study tends to be a little bit underpowered for the size of the effect that they wanted to detect. So, in general we can kind of draw the conclusion that DOACs would have tended to be favored compared to warfarin.

And before we go more deeply into, into the study, I want to motivate this by saying that any real world efficacy study faces a problem of selection bias. So what does that mean? Basically it boils down to the fact that patients who are prescribed warfarin tend to be different from patients who are prescribed DOACs. And if these differences are unobserved by a researcher and they researcher fails to control for these unobserved characteristics they may bias the estimates of the effects that we see. Particularly if these characteristics are associated with the treatment and also affect the outcome that we’re looking at. So in order to address this concern, we proposal to use an instrumental variable approach. These methods, what they basically do is they rely on a plausibly exogenous source of variation in treatment and use it as an instrument to kind of compare apples to apples. So to compare similar patients and also then compare their outcomes. This is actually what is done in a typically randomized experiment. So the most obvious instrument here is sort of a coin flip. It randomly allocates the treatment and control groups, usually with a 50 percent probability in each group. In our case, because we want to do this in the real world, we don’t have access to this experimental design, so therefore we want to use a quasi-experimental design. So we’re using for this study the variation in the provider prescribing pattern. Which we are argue, and this is obviously an assumption, but an assumption that we find quite plausible that the provider prescribing patterns have a very large quasi-random component. This sort of depends a lot on local practices, on the specific provider preferences and so on. You know, and I cite here a study done by Dr. Prentice and collaborators in 2014, who’s also the senior author on this study that had used a similar method for comparing diabetic drugs. So we propose to use the same method here.

To go a little more in detail in this approach we’re going to use a specific type of instrumental variable method. It’s called two stage residual inclusion or 2SRI and it’s been pioneered and developed by Terza and collaborators. So I have this paper in case you want to read more. Briefly the way this works is in the first stage regression, that you see here, we regress the indicator of which drug the patient was prescribed. So one if it’s a DOAC and zero if it’s warfarin. And we regress this in a logistic regression on the instrument which is the facility prescribing history. So the proportion of DOACs that were prescribed by that particular facility in the year prior to the patient’s actual prescription. We also include a set of demographic characteristics, risk adjustments, measures, provider quality measures and also station and near fixed effects to kind of control for other factors that may, may affect the treatment assignment. After this stage, what we do is predict this epsilon. So this becomes epsilon hat. Which means that it’s predicted from this equation and we call this the residual, hence the name of the method: two-stage residual inclusion.

So we use then this residual in a second stage regression where ewe regress the outcome in a Cox proportional hazards model, we regress it on the drug that the patient was prescribed, either DOAC or warfarin. The same set of patient characteristics that may affect outcomes as well, and also station and near fixed effects and then this, this residual here has the specific role of controlling for unobserved confounders during treatment section which is exactly what our goal is. The individuals are censored at the end of the study or at the occurrence of first outcome which is a fairly standard way of running a Cox proportional hazards model in this type of study.

And to give you an example of how this works for given patients. This is just kind of an example of a patient that had their first warfarin or a DOAC prescription on June 1, 2014. This is called their index date. Then we look backwards one year in their so called baseline period and using the data that we have available from the VA and Medicare we construct the set of patient risk adjusters, we construct the instrument which is the facility prescribing pattern that I mentioned and also a set of facility quality measures, which again, may affect the treatment assignment which I’ll talk about in a couple of slides. Then we also look in the outcome period, or after the index date and we construct measures of adverse outcomes that we’re interested in. So, first one is death from any cause, acute myocardial infarction or stroke, hemorrhage, hospitalization, and cost of care. So these are the outcomes that we propose to look at by the end of this study. We are still in the preliminary stages of our study so today I’m only going to show the effect on death and a combined outcome of heart attack or stroke. And I’ll explain why we chose to do that.

So the data that we use, as I mentioned, comes from the VA Corporate Data Warehouse or CDW as well as from Medicare claims. So we have access to 100% [unintelligible 00:18:15.4] service claims, both inpatient and outpatient as well as the Part D prescription claims. And we take the information on patient’s death from the Vital Statistics File, which is very, tends to be very reliable. We use Medicare claims because as you probably noticed, most of the outcomes that we look at are very acute. So they, and our population is old. So we only focus on Medicare beneficiaries which also are Veterans and most of these outcomes tend to actually be observed in acute care settings like hospitals and emergency rooms including, stroke, acute myocardial infarction and so on. And also because we want to capture their prescription for oral anticoagulants. We need the Part D information.

So here is just a brief table showing how we selected our sample. We started with a cohort of patients who were over the age of 60 and who were diagnosed with Atrial Fibrillation between 2012 and 2014. About 200,000 patients. Then we restricted this sample to the patients who were prescribed an oral anticoagulant during the same period. This got our sample down to about 60,000. We then excluded patients who were enrolled in Medicare Advantage. This is because Medicare Advantage plans, which are managed care plans don’t actually report their claims to the federal government so therefore we cannot be sure that we are observing all their outcomes. We also excluded patients who had post-acute care styles in, between 2011 and ’15. And also patients that were under the age of 66 at the date of their index prescription. This is because we wanted to only capture the beneficiaries that were in Medicare due to age and not necessarily ones that are due to being disabled. So our final sample size for now about 35,000. As I mentioned, we are still in the middle of the study so we are expecting to get another year of Medicare data in 2018 which will allow us to increase our sample size.

This is just kind of a histogram of the time and follow-ups. As I mentioned we censor our patients either when the study ends, therefore we get to about 1400 total days in the study, about three years or when the first outcome occurs. So some of the patients are in the study for much shorter periods of time, this period of time also depends on when their first index prescription has occurred. So therefore here you see this very interesting distribution in follow-up time.

Here is a table of the baseline characteristics for these patients. As you can see our average age is about 76, most of the patients are male, also most of them are white, which is representative of the Veteran population in general. We also have the distance from the patient’s zip code of residence to the nearest VA facility which obviously tends to affect treatment and we have an average of about 13 miles of distance to the VA. Some patients obviously live very close, there’s also some patients, for example, in Alaska where they live very far from the VA.

Here are some of the clinical characteristics that we have calculated for this, for these patients. So we rely on the Elixhauser Comorbidity Index which is a very standard measure of risk. So our mean in the sample is six. Which pretty much means that about, on average patients have six comorbidities in addition to Atrial Fibrillation. Here I also show some of the, I would say maybe some of the interesting measures. So congestive heart failure, about 42% have that. Renal failure, liver disease also, as I mentioned, I think it’s important to have measures of depression and alcohol abuse which would be about a quarter of our sample suffers from depression. Because, as I mentioned, these are determinants of, for example, patient adherence. We also calculated the Body Mass Index, or BMI, the CHA2DS2-VASc score which is an indicator of the risk of stroke, HAS-BLED score which is also an indicator of the risk of bleeding and we also look at blood pressure control and LDL cholesterol control in these patients. The measures of provider quality that we use are the level of blood pressure control at the facility level, also the level of LDL cholesterol control and HbA1c for control rates.

On average in this sample 80% of patients were prescribed warfarin, as we started, obviously this was much higher proportion, but then as the drugs came on the market overall the rate of DOACs increased. So overall 20% about 20% of patients were prescribed DOACs, dabigatran was the most commonly prescribed DOAC with 11%. The instrument, which as I said is the facility level percent of DOACs prescribed the facility in baseline ranged from about 0% at the beginning of the study to about 64% in certain facilities. The average was about 6.6%.

So here I will stop again we want to ask you another question. Which is: what is your experience with Instrumental Variable methods? So, you can answer: either that you haven’t heard about them; that you’ve learned about them in a class or seminar but have never used them; you have used them in your research but only sort of the linear models or you have used them extensively, including the 2-Stage Residual Inclusion method. And this is just to kind of give us an idea about your familiarity with these methods.

Heidi: And responses are coming in. I’ll give everyone a few more moments to respond before we close it out and go through the results. It looks like we’ve slowed down so I’m going to close that out. And what we’re seeing is 43% of the audience saying they have not heard about instrumental variables at all. 43% have learned about them but have not used them; 10% have used them in their research but only linear models; and 5% have used them including the 2-Stage Residual Inclusion. Thank you everyone.

Dr. Nicolae Done: Okay, great thanks Heidi. So that’s very interesting, so hopefully this presentation will sort of show you can example of a 2-stage residual study that you can maybe then use in your own research. First thing that we want to do when we kind of, before showing the result is to really show the properties of our instrument. So as I mentioned, our instrument is the proportion of DOACs prescribed in the facility, in the baseline year. So, the first thing we wanted to do is to show some variation. Because if there’s no variation we cannot use it as an instrument. So here you can that it very low in the first month of 2012, and then tends to increase and also the variations across patients depending on which facility they get their treatment at tends to also increase. So this variation is quite substantial around 2015. There are still facilities that have prescribed, you know, very low rates of DOACs verses the ones the prescribed already quite a lot.

Another thing that we want our instrument to do is to effectively, sort of randomize the patients that receive a certain treatment, right? So conditional on all of the variables that we include in our, in our regression we want the instrument to kind of use that variation and just let us compare apples to apples. So here I show the covariates so that the characteristics of the patient at baseline, based on which drug they received. Right? So you can see that there are some differences. If you look here in this third column, this is standardized difference, so the standardized difference basically the difference in the mean divided by the standard deviation and it’s a pretty standard way of showing how similar the groups are. Ideally, we want this to be lower than point one but there are other rules of thumb that they, you know, lower than point two is also fine and so on. Here we can see that the groups are actually quite similar. So they’re not that, it’s not that big of a difference. However, I want to caution you that we not only care about these observed characteristics, but we also care about potentially unobserved characteristics. So, because they’re unobserved we cannot look at them and we cannot measure them. So in general, you know, as I said, the samples are pretty, pretty similar, maybe there’s a little bit of a difference in age, so patients with warfarin tend to be slightly younger. Patients that are prescribed warfarin also tend to have higher rate of renal failure and so on.

Now what I’m going to show is the results sort of just in comparison, so the same variables but split by whether the patient was above the median or below the median in terms of the values of their instruments. So the value, the proportion that their facility prescribed DOACs in the previous year. So here what we expect to see as I mentioned is that we want these to be even smaller. We want these two groups to be as similar as possible. And based on this, based on these results, we are pretty confidence that our instrument sort of, in effect, randomizes the patients quite well. You can see for example the difference in age now is much smaller, the difference in renal failure, also now is a lot smaller and so on. There’s still some differences, obviously just by chance, even in a randomized control trial there’s bound to be some differences between the two groups but overall we can say that covariate balance has improved. Another property that our instruments should have is that it should strongly affect the treatment assignment. So if you have, if you are part, if you are receiving treatment from a facility that has a high rate of proportion of DOACs, obviously you should be also more likely to receive a DOAC. So we can see here a summary of the rates the patients get DOACs by the quartile of the instrument. So this is quartile one, two, three, and four. We can see that the rate increase for about, from about 4.5% to about 38% in the highest quartile. So this again, shows us that the instrument tends to be quite strong. So it has a large effect on the treatment assigned. However, this has to also happen in a multivariate context.

So here, we actually show the results from the first stage regression which I’ve showed you. Where we regress the treatment that the patient got on the instrument and all of these other covariates. So here you can see that this coefficient, the odds ratio is about six and it’s highly statistically significant which is exactly what we would expect for a strong instrument. So how do we interpret this? By unit, one unit increase in the instrument, increase the odds of receiving a DOAC by six fold. So this is the first stage. Now we can sort of take a look at some of the outcomes again, in kind of a univariate context. So without looking at the regression results. Here are the Kaplan-Meier survival curves for patients who receive warfarin verses patients who are prescribed a DOAC. So the red curves are for DOAC patients and the blue are for warfarin patients. So here, basically what this tells us is that, at least in terms of mortality DOAC patients tend to do better. So they tend to survive longer compared to DOAC, compared to warfarin patients.

We can also run something that’s called log-rank test. So log-rank tests are also sort of simple tests that, essentially what they do is they try to allocate the events that we expect. So in this case the event is death under the null hypothesis that the two drugs are the same. So they don’t have any differential effect on the patient population. So here, on the right hand column you can see that under this null hypothesis, in the warfarin group we expect to see about 6274 deaths and then for DOACs 1373. However, what we observe for warfarin is a significantly higher rate of death in our actual sample. And for DOACs we see lower rate of death. The test statistic which is a chi square statistic is highly statistically significant as shown by the P value which is very close to zero.

So now we can turn to the multivariate results. As I mentioned, we’re showing the two stage residual inclusion results, I’m showing the equations here just to remind you what the models look like. I’m also going to show you the results from the so called naïve model, I’m showing these two, the second stage and also the naïve model and the naïve model we basically don’t include this epsilon hat term. And we basically are kind of naïve in a sense, in the sense that we pretend that the DOACs and warfarin and prescribed to similar patients and pretend that this data comes from a randomized clinical trial.

So here are the results. The one that you should first focus on is this hazard ratio. So what this tells us is that patients who are prescribed DOACs after accounting for their unobserved confounders are 66 percent less likely to die compared to warfarin patients. So there’s quite a dramatic decrease in risk of death. We can also see that this is almost twice as large of an effect compared to the naïve estimate. So if anything, adjusting for the confounders tends to make DOACs look even more favorable than warfarin. And if you remember this is kind of consistent with what we saw in the summary tables which is that warfarin tends to be prescribed to patients that are younger and have, at least in some cases, a lower risk of death. So this sort of makes sense. Another thing that we can look at here is the effect of stage one residuals, so the epsilon hat that we’ve included in this regression. Again, this effect is highly statistically significant which does tell us, it sort of confirms to us that this unobserved confounding exists and that we should control for it which is exactly what we do.

Now I’m going to show the results for the combined outcome of stroke or heart attack. And the reason why we combine these, at least for now is that we are a bit underpowered with this sort of data that still has to come in. So we want to kind of observe these events jointly. You can see from these Kaplan-Meier survival curves, again, DOACs tend to do better in terms of these outcomes but it’s kind of hard to tell. So they’re very, the curves are very close. Log-Rank test, just like in the other case, still tells us that there is a difference, so the P value is very close to zero. The number of events expected in warfarin group is higher, is lower than the one that we actually observed. So we observed 1855 strokes and heart attacks whereas we actually observe 1900 in our sample.

So here are the multivariates, regression estimates, as you can see this effect is actually quite large as well but it is imprecisely estimated so after adjusting for confounders, having prescribed a DOAC reduces the risk by about 43% of a stroke or heart attack. The P value here tells us that, you know, we don’t have much confidence in this particular estimate because our sample size is quite small. And, but this effect is still a lot, a lot larger than what we see in the naïve estimate.

Another thing that we want to, to test, is whether our instrument is actually valid. And, you know, to a certain extent this is not fully testable but there are ways in which we can further increase our confidence in our instrument. So, if this instrument is valid it should only affect the risk of an outcome, like death or stroke by effecting the treatment assignment. So whether or not you get a DOAC or warfarin, right? So what we try to do, is we do a falsification test in the spirit of this paper by Pizer in 2016. Where we take a separate cohort of patients that are diagnosed with Coronary Artery Disease or (CAD). These patients are at a high risk of stroke but clinically they're not prescribed oral anticoagulants. So there is no treatment assigned, right? So sort of the mechanism by which we hypothesize that the instrument affects our Atrial Fibrillation cohort, this should not exist. Therefore when we run a Cox proportional hazards model, the same as we did in our AFib cohort. If we only use the instrument as an explanatory variable, it should not be predicative of the outcome.

Let me show you these, these results. First, again, the univariate result. So the log-rank as you can see now this test statistic is not statistically significant as a conventional level. And also other, sort of the, the two curves very much overlapping. Seen for the stroke and AMI so the curves are very, very close and we can see also that the chi square test tells us that there's no difference between the two. From the multivariate regression estimate we also get statistically insignificant coefficients. so even though we have a larger sample size of CAD patients, about 130,000, the hazard ratios that we estimate has a 95% confidence interval that includes one and P-values are quite large, about point five in both cases. Which, as I said, further increases our confidence in the instrument.

So, in conclusion what we find here is that even after adjusting for unobserved confounding direct oral anticoagulants reduce the risk of death by about 66% compared to warfarin. These comparatively are larger than in others, but ones that looked at death by Graham and Villines found much smaller effects compared to what we found. We've also found reductions in the risk of stroke or heart attack by about 43% but this effect right not is not significant, because again, we don't have quite the sample size that we set out to achieve.

So the next steps in this project, as I mentioned, we will incorporate another year of Medicare claims data which should both increase the sample size and also allow us to follow up the patients that we already have for longer which means we're going to observe more outcomes. We also want to compare the DOACs to warfarin individuals, so apixaban, rivaroxaban, dabigatran tends to have sort of different, different effects that we saw in previous studies. We are now constructing measure of patient drug adherence so we want to see how much these affects are due to patient adherence as opposed to the fundamental properties of DOACs themselves. We plan to look at other outcomes as well. So the incidents of hospital stay, hemorrhage, and also to perform a cost effectiveness analysis. So to see whether the improvements we see in DOACs are actually worth the cost and what the tradeoffs there might be. And, lastly, we want to compare this method with propensity score matching just to kind of see how we compare to previous studies that have done this kind of analysis.

There are obviously plenty of limitations. First of all Medicare data lag which leaves us a bit underpowered. There are some significant rates of missing data for some measures, particularly BMI, ZIP code of residence. This is also, as of now, an intent-to-treat analysis which means that once you're assigned to a drug based on your index prescription we assume that you stay on that drug but we found that about 10% of the patients tend to switch drugs later on after their initial assignment. So we will run additional analyses where we account for this. There is obviously this whole idea that there may be unobserved quality measures that we don't see that affect both treatment and are subjugated with the outcome. However, we're less concerned about this because what we know is that for these quality measures to make a difference they would have to be very highly correlated with DOAC prescribing but at the same time uncorrelated with the measures that we do include and we think that's quite unlikely. A more technical term here relates to generalizability as many of you probably know, instrumental variable estimates are still Local Average Treatment Effects, they don't necessarily generalize to the whole population and I include here just for reference a paper by Chapman and Brooks that shows that in certain conditions this method can lead to an effect that is significantly different from the effect in the general population. And the more obvious limitation on generalizability, as I mentioned this is a sample of Veterans so it may not generalize to other populations.

So this it. I would like to acknowledge my co-authors and funding from the department of Veteran’s affairs and if you have any questions about this or other studies please feel free to mail me. I have my email address here and I’ve included all the references for anyone who wants to read more on these topics. So thank you very much and I open it up for questions now.

Dr. Wei Yu: Dr. Done, there's one question from the audience. Let me read the question for you. It’s about the 2-stage model and the question is so why does the 2-stage model adjust for other covariates in both stages and wouldn't this be the OAC variable from stage one include an adjustment about this?

Dr. Nicolae Done: Right, so that is a good question. So, actually the reason why we include these variables in both stages, so there is no, so I think, I think, where this is going, you know, is there at some point sort of a problem of like multicollinearity or you know, if we include them in the first stage why do we include them in the second stage, is there not a problem there? So no. The short answer is no, these should be included in both equations. The idea is that these factors affect both the treatment assignment, so they should be included in this equation, but they also affect outcome, so they should also be included in the second. And then there's, there's going to be no, you know, no issues with this. In fact, this is how is recommended to be done. There is sort of a, what's called an exclusion restriction but these variables do not sort of take part in that restriction. So it is perfectly okay to include them. And, as to the point of why does the, this residual control for unobserved confounders, I would say, you know, if you go and look at the paper that I’ve cited by Terza it is actually mathematically demonstrated so, you know, I don't have time here to kind of go through that but on an intuitive level, you know, we can argue that whatever we don't include in this equation is pretty much unobserved factors and it's basically sort of the effect of these unobserved, this epsilon represents the effect of these unobserved factors on the treatment assignment. So therefore by including this epsilon hat we, in a sense, kind of mechanically control for those unobserved characteristics. So I hope that makes sense. It’s a great question.

Dr. Wei Yu: Okay, there's another question about the variable you obtained and the, your slides [unintelligible 00:48:54.00] and you used the distance to VA in CDW data in the question is, where to find that information. The CDW has a file?

Dr. Nicolae Done: Yeah, so I forget exactly, I think it's taken from the PSSG, the PSSG is a VA center and it's a PSSG distance file. I believe what we do is, we match that to the zip code of residence for each patient. So we have a file on the one hand, that has the distance between the nearest VA Medical Center or community based outpatient clinic and the centroid of the zip code, of every zip code in the United States, right? So we basically have these distance files. Then we merge these distance files to our sample using the particular zip code that each patient resides in. So therefore, for each patient we then get kind of an average distance in miles. But I don't know exactly right now. I’d have to go back and look at how these measures were determined but I’m sure there is a source of data. I think, if you look again, PSSG file. I forgot what PSSG stands for.

Heidi: Planning System and Support Group.

Dr. Nicolae Done: The Planning System and Support Group. So for anyone who's interested they can search for that.

Dr. Wei Yu: Okay, now another question is what was the reference TTR for the included into study patients, and any difference in events read for patients with low TTR compared to those with TTR greater than 70 percent.

Dr. Nicolae Done: Yes, that's a great question, so we have not gotten to that yet, that's why I don't have results. We are in the process of calculating those measures and we will include them in our future analyses, in the final analyses for this study. So that's a great question, these are sort of, what we consider this is kind of a measure of, in a sense adherence right? It’s not quite adherence but it's sort of shows whether the warfarin the patient received actually leads to correct therapeutic range for that oral anticoagulant. So that is a great question. We do expect this to affect the outcomes but right now we just have not calculated that, these measures yet.

Dr. Wei Yu: Okay, I don't have any more questions.

Dr. Nicolae Done: Okay, we can wait if there are any more.

Dr. Wei Yu: [unintelligible 00:52:08.11]

Dr. Nicolae Done: Yeah, okay, sure. Great, thank you so much everyone.

[ END OF AUDIO ]