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Session: Blood Pressure Measurements in the Application of Outcomes Research

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DeAndre: Welcome to Virus Database of Memphis cyberseminar entitled *Blood Pressure Measurements in the Application for Outcomes Research in the CVW*. Thank you to Cyber for providing technical and promotional support for this series.

Today’s speaker, Dr. Csaba Kovesdy, is Nephrology Section Chief at the Memphis VA Medical Center and Fred Hatch Professor of Medicine and Nephrology at the University of Tennessee Health Science Center. He is an outcomes researcher whose main research interests are predictors and therapeutic interventions for cardiovascular and other clinical outcomes in patients with non-dialysis chronic kidney disease. Questions will be monitored during the talk and will be extended to Dr. Kovesdy at the end of the session.

A brief evaluation questionnaire will pop up when we close the session. If possible, please stay until the very end and take a few moments to complete it. I am pleased to welcome today’s speaker, Dr. Kovesdy.

Dr. Csaba Kovesdy: Thank you DeAndre and welcome everybody. Welcome to today’s seminar series. Thank you for the introduction. As you heard, my name is Dr. Csaba Kovesdy; I am a Nephrologist at the Memphis VA, and today’s topic is blood pressure measurements, and their application for outcome research using the CVW.

The objective of the discussion will be to review blood pressure measurements as a variable in the National VA Research Databases, where it is located, what the file structures, what ancillary variables you can expect, and what is availability is. Then examine practical aspects of how to analyze blood pressure in this database.

Finally, and this will be the bulk of the talk, will be about recent studies that we have published about examining blood pressure in the database and how it could be used in upcoming research.

Now before we get started, we have some poll questions, the first one is about your primary role in the VA.

Heidi: The options here are:

* Primary care specialty provider
* Mental health provider
* Nurse
* Researcher
* Administrator

We will give you all just a few more moments. Responses are coming in, but I will give you just a few more moments before I close this pole out. I am just waiting for things to slow down a little bit, and I am going to close it out here.

So we see about:

5% Primary care or specialty provider

0% Mental health provider

15% Nurse

63% Researcher

17% Administrator

Thank you everyone for participating.

Dr. Csaba Kovesdy: Thank you, and we have a second pole question about your experience using blood pressure in your research.

Heidi: And the options here are:

* Heard of it, but no experience using it
* I have experience using it
* Not heard of it/no experience using it

We will give you all just a few more moments to respond before I close things out here. It looks like responses are slowing down, so I am going to close.

We are seeing:

 31% Heard of it, but no experience using it

 62% I have experience using it

 7% Not heard of it/no experience using it

Thank you everyone for participating.

Dr. Csaba Kovesdy: Thank you. So it is not surprising I suppose that those of you who are researchers have used it because it is really a commonly used variable. So a little bit of background, as you know, blood pressure is measured on virtually all veterans who receive clinical care. That is for all inpatient encounters, outpatient encounters; it is actually part of the check-in process often times. Hypertension is usually defined as an elevated blood pressure. We will discuss this in a little bit more detail later, but blood pressure higher than 140/90 is in general considered hypertension and it is considered the number one risk factor for cardiovascular morbidity and mortality worldwide.

In the VA system, there are a very large number of blood pressure measurements, which really offers a unique opportunity for an outcomes researcher like myself. No blood pressure measurements can be found in the vital signs domain. The CVW contains vital signs from all sites starting October 1, 1999. So that is just about 17 or 16 ½ years or so.

Overall, there are about 2-billion records considering all different vital signs, but this is a few years old, so we will probably pass that number. The data is refreshed every night, so it is really up-to-date, and there are many link tables in the vital signs domain. This is basically a summary of what you find. You have the link there on the internet if you want to check it out yourself, and they are just pointing out that on this list you have the systolic and diastolic blood pressure as separate variables. They are not under the results or the results from the [\_\_\_\_\_ 00:05:40], which contain all other ones. In fact, blood pressure is included under those too, but you can have them at separate variables in this table. Then one of the ones that obviously is of interest is the time and date when the measurement was taken.

Now in terms of method data, you have two tables. The vital sign table and the vital type table, and you can see the vista files that they are extracted from for those of you who are interested in these very fine details. On the bottom, you can see the link to the table descriptions on the share point and the data reports.

So a few details about the data profile that is available. You see on the left side, a list of the various vital signs that are recorded, and you will see that they vary in frequency. For example, pain and what is underlined, blood pressure are measured very, very frequently. This data is from April 2011, and at that point, there were about 369-million blood pressure measurements. For others, these occur much less often, and depending on which one you want to use, you have to decide if that is sufficient for you or not.

We see the same numbers by year. Again, as of April 2011, you can see that the measurements were recorded the first time in 1999, and there was an upshift in the number of measurements every year. Again, probably reflecting the changing demographics in the VA with the increasing number of patients being enrolled, and 2011 is a partial year. So it is not because of fewer measurements really.

What are the limitations of the database—and these are inherent in the database itself. There is no unit of measurement that you will find, so you will have to go back to your documentation to determine, for example, that height is measured in inches, weight in pounds, respirations in breaths per minute, pain has its own scale, pulse and temperature you can see. Obviously, blood pressure is measured in millimeter mercury—probably not a problem; most of us know that.

It is important to know that there are not qualifiers in the database so you will not know, for example, details such as which arm the blood pressure was taken from or whether there were any circumstances that might warrant special considerations. All you have is a number, time, and date.

Here is your summary of links if you want to obtain more information. Again, these will be available for you for download if you want to check it out yourself.

Now, what are some of the practical aspects? I want to point some of these out because I have learned them in the course of using the variable. Obviously, the first time you start using blood pressure you have to clean your data, and you will consider systolic and diastolic blood pressure as two separate numeric continuous variables.

There are some rules that you can use when determining which measurements may be erroneous or may be typos. Biologic plausibility obviously helps although I have to tell you that there is no unit form or rule for what numbers are acceptable. So it is more of a common sense type of approach. For example, for systolic blood pressure measurements, above 300 are fairly unlikely. Although, if you have a measurement of 310, you could argue that it is possible but fairly unlikely. Obviously, if you have a measurement of 1,000, that is completely unlikely. So you will have to draw an arbitrary line at some level that seems reasonable. The same could be said for a diastolic blood pressure of 200—I have used myself these two cutoffs for higher limits of blood pressure.

There is really no plausibility of the rule for what could be considered the lowest value. Obviously, zero values are not possible, so those you could exclude. Then I have used diastolic blood pressure of less than ten and systolic of less than 40 as arbitrary cutoffs for potentially unreliable measurements. It is important to note that systolic and diastolic blood pressure go hand-in-hand so that measurements yield both. There are a very small number of measurements where systolic blood pressure is not accompanied by diastolic blood pressure and I usually exclude those. Again, they are so small that they do not have a significant bearing on the overall results when you analyze them.

Obviously, systolic blood pressure has to always be higher than diastolic blood pressure, and I usually exclude those. Again, they are so small that they do not have a significant bearing on the overall results when you analyze them. Obviously, systolic blood pressure has to always be higher than diastolic blood pressure. Again, there are a very small number of measurements where your diastolic blood pressure is higher than systolic. Maybe they recorded their own systolic and diastolic and vice-versa. It is probably safest to exclude those.

A few words about the date and time of blood pressure measurements. It is important to note that the format used in recording it is year, month, day, hour, minute and second. That is important because, as you know, blood pressure could be measured several times a day, so you cannot just record the day. When you use these for your analysis, you will have to consider how you want to include it. Again, you include all the measurements, you could average them, you could use an individual value as long as you date variable is coded appropriately.

A few interesting points here in patients who are hospitalized, routinely their blood pressure is measured several times a day, and you may want to consider each one of them separately in this context. On the other hand, if you have outpatients that come to clinics, you may see multiple measurements the same day because the patient had multiple visits on the same day, in which case they may all be valid single measurements.

However, you may see the same blood pressure measurement repeated within the same outpatient clinic visit. That to me may be a red flag because often times, blood pressure is not measured under standard circumstances, and the patient might have just rushed up the stairs, or be upset, in which case blood pressure may be artificially elevated; the technician may decide to repeat the blood pressure after 10 or 15 minutes. In cases like this, I tend only to consider the last blood pressure measurement related to that particular clinic visit.

So now that we are delving more into the research side of it, we would like to have some poll questions, just as a segway into the research part. This question asks you about what the ideal target blood pressure is in patients with essential hypertension.

Heidi: I feel bad here. I am not a subject expert, so I am not exactly sure how to read these. Dr. Kovesdy I am not sure—if you could read these that would be wonderful.

Dr. Csaba Kovesdy:

* Less than 130/80
* Less than 140/90
* Between 130-140/80-90
* Less than 120/80

Heidi: Wonderful and the responses are all coming in, and we will give you all just a few more moments to respond here, and then I will close it out. It looks like things are slowing down. We are seeing:

8% Less than 130/80

 50% Less than 140/90

 18% Between 130-140/80-90

 25% Less than 120/80

Thank you everyone.

Dr. Csaba Kovesdy: Thank you and very interesting results. Again, this is a controversial topic. I am not sure that there really is a single correct answer. That is my prerogative to put up questions like this, and I apologize if that upsets you, but I just wanted to illustrate that this is really not an easy question. It really depends on what kind of patients we discuss. Aside from having potential hypertension, they may have poor comorbidities, which may push you to choose one or the other blood pressure target. Maybe the data that I am showing you may make this easier to understand.

So here is another one. Again, this may not be totally straightforward. Elevated blood pressure is associated with adverse outcomes in which population?

* + All populations
	+ In those with no comorbidities
	+ In advanced chronic heart-failure
	+ In patients on hemodialysis

Heidi: And responses are coming in. We will give you all just a few more moments to fill that out before I close it out here. Okay, it looks like things are starting to slow down. So we are seeing:

82% All populations

 0% In those with no comorbidities

 16% In advanced chronic heart failure

 2% In patients on hemodialysis

Thank you everyone.

Dr. Csaba Kovesdy: All right, thank you, very interesting results, and again, probably all populations are true, but you might ask what does elevated blood pressure mean. So we will delve a little bit into that.

Let us discuss our first topic, blood pressure and mortality. High blood pressure is regarded as a causative factor when we discuss adverse outcomes such as mortality or cardiovascular events. In general, everybody agrees that treating elevated blood pressure is beneficial. However, when we see what the blood pressure guidelines, in general, tell us, these guidelines seem to focus on the highest of the two blood pressure components. Remember that we have the systolic and the diastolic components, as if we define elevated blood pressure or hypertension as more than 140/90 than either component, if it is higher than the particular threshold, whether it is systolic or diastolic, that patient is considered to have hypertension.

However, often times we have a discrepancy. So for example, a patient with a blood pressure of 160/70 would have systolic hypertension, the diastolic component is 70; it is in normal range really. In this case, the guidelines tell us to lower systolic blood pressure to less than 140. Conversely a patient who has a blood pressure of 140/100 had diastolic blood pressure; 140 is right around the frequent target that you would want to use, but, in this case, your primary target, according to the guidelines, would be the diastolic blood pressure. You want to lower it to below 90.

The problem that arises is that in certain studies and in certain populations, there is a so-called J-shape or U-shape phenomenon in which case we can assume that in some patient’s lower systolic and diastolic blood pressure could also be associated with higher mortality. Also, when you treat systolic and diastolic blood pressure, you lower them concomitantly. So if your goal is to lower systolic blood pressure you willingly or inadvertently concomitantly lower diastolic blood pressure as well. If we assume that there is a J-shape phenomenon, this may mean that while you are lowering, let us say, your diastolic toward the desirable range, you may be inadvertently pushing your diastolic into an undesirable range. The current guidelines and the current knowledge does not address this conundrum sufficiently.

The other point here is that the treatment targets are much less well defined for patients with chronic kidney disease—now I am a Nephrologist, so it is my main area of interest. The main reason for that is most hypertension treatment trials have excluded patients with chronic kidney disease or end stage renal disease as a priority. So most of the guidelines regarding CKD patients are based on extrapolations from clinical trials that were performed in non-CKD patients.

So the first group that we will be discussing is the one where we study blood pressure and mortality in U.S. Veterans. This was published a couple of years ago, and we started with about 4.3-million patients who have available serum creatinine and EG for our measurements over a two-year time period and of these, we used an algorithm to define prevalent chronic kidney disease, and we had about 650,000 of these patients. These were non-dialysis dependent CKD patients.

We obtained outpatients blood pressure measurements over a seven-year period from enrollment until the end of our follow-up at that point. We obtained ancillary co-variants—you see them listed there from various sources in the VA database—and information about all-cause mortality from the vital status files.

First, we studied systolic and diastolic blood pressures separately as continuous variables as we expected non-linear associations; we used splines to examine this. Then we also took a look at the actual blood pressure, meaning the combination of the systolic and diastolic blood pressure at an individual level. First, we used categorizations according to JNC 7, hypertension definitions using normal pre-hypertension stage one and stage two hypertension, again, using usually the higher of the two components to categorize patients in any of these four mutually exclusive stages.

Then to take a more granular look at blood pressure, we examined mutually exclusive combinations of systolic and diastolic blood pressures where we took very granular categories of 15 categories for systolic and ten categories for diastolic blood pressure. This way, for example, we could examine a blood pressure of 150/60 and its changes in an individual patient or maybe a blood pressure of 80/40. We first examined associations with all-cause mortality in crude analysis, and then adjusted for potential confounders and time-dependent Cox models.

Some general data, as you can see here not surprisingly, this was an older cohort. These were CKD patients, which are typical of older individuals, the median age being around 73-years. Our mean estimated GFR was right around 50, so CKD stage 3A with quite a few patients with more advanced stages though. Our mean blood pressure levels are baseline 135/72. Again, probably a testament of a good job that the Nephrologist with the VA—this is actually not a bad blood pressure control for patients with CKD.

Just very briefly—I am sorry about the complicated slide. I just wanted to point out a few things here and the baseline characteristics according to the JNC 7 blood pressure categories. On the left, you have patients with “normal” blood pressure, and then pre-hypertension stage one and stage two. Not surprisingly, African-Americans were more represented in the higher blood pressure categories. Comorbidities were, in general, more common in those who had higher blood pressure except for CHF, a notable exception that was much more common in patients with the lower blood pressures. I am not really sure that we can call this normal blood pressure in fact.

Medication used usually tracked blood pressure levels in that and the hypertensives were used more often in those with the highest blood pressure levels, except for loop diuretics which were more common in the low blood pressure group tracking the CHF diagnosis. Cholesterol was in general higher in those with higher blood pressure levels.

Of these 650,000 plus patients, 238,000 or so of them died. It was a pretty high mortality rate, but again something that we have seen in other CKD cohorts. A medium follow up with five point seven years, and when we looked at the association between systolic and diastolic blood pressure, we saw a U-shaped association, which was our hypothesis from the get, go, and you see the actual associations shown here.

When we consider treating these blood pressures, consider these hypothetical scenarios. You have a patient who may have a systolic blood pressure of 180 and the diastolic of 80. In this case, you would want to treat him accordingly to all of the guidelines. You have to lower the systolic blood pressure and based on our associations here, you can hypothesize that you are doing a good thing because you are moving in a favorable direction down to the sweet spot of around 140 millimeter mercury in this particular patient. The problem is that giving him the hypertension medications will also lower the patient’s diastolic blood pressure and as you can see, hypothetically at least, you may be moving the patient in the wrong direction on the diastolic blood pressure mortality association curve.

So the question is, which one is dominant? Is it beneficial to lower systolic in a beneficial direction or is it bad because diastolic is moving in the wrong direction? In order to examine this, we created this complicated table where you can see on top diastolic blood pressure categories and here on the left side, the diastolic blood pressure category. For each individual combination of systolic and diastolic blood pressure, you will see a heather ratio compared to this referum point here, the referum point being a blood pressure of 140-150/80-90. So the heather ratios are all compared to this point. The reason you have empty cells here is because we just did not have enough patients to have meaningful results in these extreme groups, and, of course, systolic had to be higher so you cannot have patients with blood pressures of 80/110.

So let us take again a hypothetical patient here. This patient may have a blood pressure anywhere between 160-170/70-80 and then you see the relative mortality hazard for this patient would be one point zero seven, meaning that this patient compared to this particular patient with a blood pressure of 140-150/80-90 has a seven percent increased risk of mortality. Now again, hypothetically, and I have to stress that this is observational, and we are not actually treating patients, but let us say that we lower this patient’s blood pressure to these groups. So we want the patient to have an ideal blood pressure—or close to ideal—of 140 or so, and this would also lead to a decrease in diastolic blood pressure to let us say 50-60. When we examine the risk of mortality associated with this particular combination, what we see is that the risk is, in fact, ten percent higher than what it was in the original group. So based upon this, we may have some concerns about the diastolic blood pressure driving the overall mortality in the wrong direction in spite of the systolic blood pressure moving in the right direction.

When we examine this to many potential pair-wise combinations, in general, what we saw is that when the diastolic blood pressure was pushed diagonally below a level of around 70, in general, we saw an increase in the hazard ratios associated with that move. Again, I have to emphasize that we did not actually move patients from one cell to another. These were all separate individual measurements. So this is all hypothesis generating and is not in any way proving that by taking blood pressures to these levels would harm patients.

So in conclusion, we saw a J-shape or U-shape association for both systolic and diastolic blood pressure in this study. Our ideal systolic blood pressure was somewhere in the 130-150 range, and an ideal diastolic blood pressure was somewhere between 70-90 depending upon which models we looked at, and again…

[No audio 00:25:55-00:26:11]

Dr. Csaba Kovesdy: The interesting finding here was when we considered the pair-wise combinations of systolic and diastolic under circumstances where treatments of systolic would result in lowering of diastolic below 70, we saw an association with higher mortality. Hence, what we would suggest is to approach these patients carefully; look at individual characteristics, symptoms, more than hypoperfusion. Finds such as increasing creatinine, decreased kidney function in the face of lowering blood pressure or maybe angina, cardiovascular symptoms or dizziness indicating brain hypoperfusion; in which case, we should consider that pushing blood pressure to arbitrarily define targets in a particular individual may actually be hazardous.

So the next question would be actual blood pressure control. Again, the previous study was purely observational. We did not invoke treatment at any level. As we mentioned before, the ideal blood pressure level in hypertensive patients with chronic kidney disease is unclear. Some guidelines, especially years ago JNC 7, for example, advocated stricter control in chronic kidney disease hypothesizes that this is a high-risk group, and if we assume that high blood pressure is bad, then lower blood pressure has to be better. This however did not consider the possibility of the J-curve and the potential harm from pushing blood pressure too low. Now this hypothesis that lower blood pressure is better in patients with CKD has not been rigorously tested in clinical trials yet.

So we performed an observational modeling of a hypothetical clinical trial, which was published last year. Our objective was to compare outcomes associated with treated systolic blood pressure of less than 120 versus those associated with the currently recommended blood pressure target of less than 140 in this national prevalent cohort of CKD patients. This was an observational study in patients who had prevalent CKD, and uncontrolled hypertension. They subsequently received additional prescriptions for antihypertensive medications and experienced a decrease in outpatient systolic blood pressure. So this is again somewhat complicated but we can walk through it fairly quickly.

We started with 650 plus patients, the same cohort that we examined in the previous study. The first step was to define uncontrolled hypertension. For this, we used most of the criteria employed by this print file, which is a large [\_\_\_\_\_ 00:28:47] file testing exactly this hypothesis. This was based on blood pressure measurements and usage of antihypertensive medications and the number of antihypertensive medications. Based upon this, we identified 300,000 patients who had a baseline EG far left of 60 and had uncontrolled hypertension.

Of these, 100,000 patients or so have no change in their blood pressure or an increase in systolic blood pressure during the follow-up period. The rest—about 18,000 or so—had systolic blood pressure of less than 120 on more than fifty percent of their follow-up visits and 176,00 had systolic blood pressure between 120 to 140 at more than fifty percent of their follow-up visits. So we went from uncontrolled hypertension to this “ideal” or maybe predefined target for what you might want to do in the clinical trial aiming for these two targets.

From this data, we did not know for sure whether these decreases in blood pressure happened as a result of therapeutic intervention. We next invoked antihypertensive medication prescriptions and excluded those patients who had an unchanged or decreased number of antihypertensive medications during follow-up. In these cases, you could hypothesize that the decrease in blood pressure could have happened because of illness, for example.

So we were left with 5760 patients who had a systolic blood pressure of less than 120 and an increase in the number of their blood pressure medications, and 72,000 or so patients who had a systolic blood pressure of 120-130 millimeter mercury.

Next what we did was a propensity score matching where we matched patients according to the propensity of having one or the other blood pressure target in order to account for the effect of confounders. This is kind of an observational study equivalent of maybe a randomization procedure. It is not perfect, but as long as we know what the predictors are and they are available to us, it does a good job of matching patients with similar characteristics. Therefore, we ended up with two groups of 5760 patients each.

What you see here is a complicated table that I will not dwell on very long, but here you see the characteristics of the overall cohorts, again seeing the larger number in the conventional study. What you see is that most of your clinical characteristics were different, which may explain, for example, differences in survival. However, after propensity matching, what we saw here was that they were fairly well matched for the most important characteristics, which were their comorbidities. You can see that they are virtually identical in the prevalence of cardiovascular disease, the prevalence of heart failure, the comorbidity index, and their estimated GFR level. Not surprisingly, their follow-ups of systolic and diastolic blood pressure were different because this was the aim of creating these two groups. Then there were some differences, small, but that we said there is significance for the actual types of antihypertensive medications that were are using as baseline.

What you see here is the actual measurements of systolic and diastolic blood pressure throughout follow-up. On the X axis, you see calendar quarters so four of these will make up a whole year. What you see here is there was a difference in systolic and diastolic blood pressure that persisted throughout the entire follow-up. Again, both were systolic and diastolic blood pressure.

[No audio 00:32:26-00:32:37]

…cause mortality. The top line is the conventional arm of the systolic blood pressure of 120-139 and the bottom one is the systolic blood pressure of less than 120. So in this group with chronic kidney disease, patients who had the systolic blood pressure of less than 120 experienced high mortality during follow-up here.

The results were fairly consistent for various sub-groups whether it was younger or older patients, males, females—even though the females were a small number of the overall cohort—sick or less sick patients, patients with more or less advanced kidney disease, diabetics, known diabetics, and pre-existing CHF or CAD.

So in conclusion, blood pressure had declined to levels corresponding to strict control whether associated with significantly higher mortality compared to blood pressure that declined to levels corresponding to usual controls. Again, I have to emphasize that working that we used here, the blood pressure declines, it does not necessarily mean that it was a treated blood pressure where the blood pressure was a result of actual treatments. This is again observational and hypothesis generating. The good news is that the strength trial is in fact testing the same hypothesis in a traditional clinical trial setting. It is enrolling significant proportions of patients with chronic kidney disease so we will have exactly the same patient population to be examined. Hopefully, we will have results in a few years.

Now finally I will show you some preliminary data, which has not been published yet but it is in the process of being published. This is about the systolic blood pressure levels and outcomes in elderly patients with chronic kidney disease. The chronic kidney disease affects about ten percent of the general population. It is more common in the elderly, and it is associated with increased mortality and increased cardiovascular disease risk. It is unclear if age modifies the association of traditional risk factors with outcomes in chronic kidney disease.

So we set out to assess to association between systolic blood pressure levels and mortality incidents, coronary heart disease incidents, [\_\_\_\_\_ 00:34:54] strokes, and end-stage renal disease in a group of non-dialysis dependent chronic kidney disease patients of different age. This was an observational study, again in the National VA cohort. This was a different cohort. This time we examined an incidence cohort, so we captured patients at the first time that they had a measured eGFR was deemed to be chronic kidney disease. We examined associations between outpatients in systolic blood pressure categories and different outcomes in subgroups categorized by age, again, adjusted for multiple confounders.

I will fairly quickly show you the main results of the study. This was mortality. Again, you see here on the axis, there are different age categories, a total of five of them. What you see here with the different colors they show the different systolic blood pressure levels from less than 100 to more than 170 in millimeter mercury increments. What you see here is that mortality indeed has a U-shaped or J-shaped curve type of association, which was fairly consistent in all age groups, although some flattening was seen in more advanced ages, but the same phenomenon that we saw in the previous study was present here, again with an ideal blood pressure of 130-40 showing the lowest mortality.

What were more interesting were the results that we saw in the vascular and renal endpoints. This was for coronary heart disease. Again, this was defined as the incidence of coronary artery bypass grafting, PCIs, or acute myocardial infarctions in patients who had no such diagnosis over at least two years prior to these events. What you see here is a linear association, as opposed to the J-shape, we saw in the previous slide. You saw the lower, the better type of phenomenon in which the highest blood pressures are associated with the highest incidence of these events.

However, what you will see is that the shape of this elevation flattens considerably as patients age. Whereas, we saw a very marked increase in risk in patients who are in the youngest, and the oldest age group was hardly any association and effect when you look at the confidence interval. Most were not significantly different from the middle category here, which was again 130-140. Again, the ideal blood pressure seemed to be widening a little bit. In those older than 70, it was more like 130-150 and then with an increase in risk in those who had higher blood pressure levels.

Stroke probably showed the same phenomenon and maybe even more marked increase in risk from the highest to the lowest category in the youngest age group. Again, [\_\_\_\_\_ 00:37:41] very tightly packed confidence in troubles in those who were 50 to 60 higher number of patients obviously the same as the age is still present in those who are 70 to 80, although again, the ideal here is widening a little bit. But then the association kind of dissipates and goes away in the group that is more than 80-years-old.

Perhaps the most marked effect that was noted was with end-stage renal disease, where the lowest levels were below 120-130 and were about the same in the younger age groups—a huge increase in risk seen with the high blood pressure categories with a six-fold higher risk of end-stage renal disease in those who had systolic blood pressures of more than 70. Again, the flattening most markedly seen in the more than 80-year-old age group where there were not significant differences except for the group that had a systolic blood pressure of more than 170.

In conclusion, it seems that age modifies the association between systolic blood pressure and various outcomes in these patients with chronic kidney disease. The low blood pressure was associated with higher mortality in all age groups. High blood pressure was associated with mortality somewhat blunted in the elderly, and then the most marked associations were seen for high blood pressure for these cardiovascular end point and ESRD. These associations were linear. However, I have to point out that interpreting the associations with the lowest blood pressure categories have to consider competing risk for the higher mortalities seen in these groups. Simply put, somebody may have a low risk for a stroke if that person dies before the stroke occurs. So it is a little harder to claim that lowest blood pressures are protective against these without doing specialized analysis or clinical trials.

In general, what we saw was that the association of systolic blood pressure with all outcomes were blunted in the elderly and were almost absent when age went above 80. Again, this is a fairly significant proportion of our patient populations with CKD nowadays.

In summary, we discussed that blood pressure is an important risk factor and treatment target. Blood pressure is measured ubiquitously and essentially all veterans that come to see us, and combined with the rich clinical data that is available in the various databases, blood pressure offers a unique opportunity to perform comparative effectiveness research. Perhaps the future will be the linking of this data with the genetic material and the genetic analysis that are being conducted in the Million Veteran Program, which will offer even more exciting opportunities for research.

Here is my contact information if you desire to get in touch with me, feel free to do so. Thank you very much.

DeAndre: Thank you so much Dr. Csaba Kovesdy. We will give everyone a few moments to formulate any questions that they may have for you at this time.

Dr. Csaba Kovesdy: Okay.

Heidi: For questions, you can use that “Questions” pane that is on the dashboard on the right-hand side of your screen. If that collapsed against the side of your monitor, just click on that orange arrow at the upper right-hand corner of your screen to open that back up. We have a good amount of time left for questions here, so this is a great opportunity to submit those questions. We will have time to get through a good number of them today.

[No Audio 00:41:07-00:41:24]

Heidi: Maybe you answered all of the questions during your presentation, and everyone is fully comfortable and knows there—oh, here we go. DeAndre, did you see that one come in there?

DeAndre: No, I do not have it.

Dr. Csaba Kovesdy: I hope we did not answer all the questions, otherwise what would we be doing research on.

Heidi: Did you find it DeAndre?

DeAndre: No, it is not showing up on my screen.

Heidi: Okay, the questions that we have here: Given that even with propensity scoring that there was a significant difference among different antihypertensives, how do you interpret that? And thank you for a great presentation.

Dr. Csaba Kovesdy: Well, it is hard to interpret because we did not set out to balance them on those medications. When we did the matching, we used the variables that seemed to be most important as confounders. One could argue to what extent using a calcium channel blocker versus a non-dihydropyridine could have a major impact on mortality in this group, and there is some research in this respect—not very good research, I have to tell you; not at the clinical trial level. So we did not consider this a fatal flaw.

Obviously, the problem is that if you start matching on a very high number of variables, you will restrict the number of patients that will be eligible. So the nice aspect of having the group of 650,000 patients to start with, is that it allows us to do this virtual screening and virtual randomization. Bear in mind that we went from 650,000 down to 5,000 when we just followed the procedures that one might follow in the SPRINT’s Trial to find suitable patients.

So it is not easy to find both a substantial number of patients and make them completely identical—and, by the way, if we adjusted just for those differences that remained, the result still were significant. So one thing that one could do obviously in the propensity [\_\_\_\_\_ 00:43:42] study is to include the variable that still show differences between the groups in an adjusted analysis.

DeAndre: Okay Heidi thanks, I have it up now; it did pop up.

The next question is—Some national databases typically ignore the first VP measurement. You said something similar today, but you implied something may be taken only the last one. Isn’t averaging together multiple BPs best for maximizing reliability? And if you average, do you literally take the average systolic or diastolic or use some other summarizing rules?

Dr. Csaba Kovesdy: Well, those are great questions, and it really depends on the circumstances. One problem we obviously have when we work with a very large data set is that we do not have the luxury of checking the individual charts. You will be able to do that if you have a smaller study like a clinical trial, but here we are trying to come up with universal rules because it is not feasible to check the individual charts. So when I said that I would use the last one, that was born out of the observation that within a single clinic visit repeated blood pressure measurements usually occur only or mostly when the measurer—the person recording the blood pressure—thinks that there might have been a problem with the previous one.

For example, if I am checking a patient today in the Nephrology Clinic and the patient comes in, has a blood pressure measured under standard circumstances,—sits there for ten minutes and nothing is wrong, then the blood pressure is 135/75, that will be the single number entered into the system.

However, the next patient might run up to the clinic huffing and puffing and say I am late for my appointment, and I could not find parking—and that happens more often than we would like. Then the technician measures the blood pressure and finds that it is 180/100 and says this may be high because the patient just rushed up the stairs—it is not considered standard circumstance. So then, they ask the patient to wait around for 10 or 15 minutes and then repeat the blood pressure and that blood pressure would be 140/80 for example. In this case, I would argue that we should not average the blood pressure because it may give us the sense that this patient has uncontrolled hypertension whereas, the 140/80 should be considered. So within the same clinic visit, I tend to favor the last available measurement.

Now if the circumstances are different, for example, a patient is an inpatient where blood pressure is measured routinely several times a day, irrespective of the circumstances and not repeatedly for a specific cause. Then indeed some kind of an averaging may give us a better sense of incorporating all of the information that we get from repeat measurements.

Whether you want to consider a plain averaging or use more sophisticated methods such as time averaging where you weigh the blood pressure measurement according to the length of time that that particular measurement was associated with, that really depends on your analysis. When they are happening during the same day, I think you could just use a plain mathematical average. When you average measurements over a longer period of time, you could consider time averaging, and there are formulas to do that.

DeAndre: Thank you. Our next question is—Can you distinguish patient position for BP measure, sitting, standing, lying in the data in NCW?

Dr. Csaba Kovesdy: Yes, unfortunately, that is not available. As I mentioned on that slide, there are not qualifiers in the database, so the only thing you have was a blood pressure level and the time and date when it was measured. You also have information on things like the clinic that is associated with the provider and so on, and so forth. But not the circumstances of the measurement, which include things like which arm it is measured in, whether it was sitting or standing.

Again, this poses interesting questions, which I did not mention; sometimes the blood pressure is repeated when orthostatic changes are being checked. So as you can see, you have to be extra careful when you see these blood pressures being repeated in quick succession because currently there is no way to know whether this is done for reason to correct an error or for reason to test some physiological response.

DeAndre: Thank you, and to follow-up with that question, can you just distinguish a BP during a procedure, dialysis or associated with a clinic visit?

Dr. Csaba Kovesdy: Well, that depends on the code that is associated with the particular visit. So if the blood pressure measurement is linked to a dialysis treatment code—a dialysis clinic visit code. I think it is 601 if my memory is serving me right, maybe not—then you could consider those.

If you want to go into that much detail, you will look at the time difference between the individual measurements. For example, in an inpatient dialysis setting, you may see blood pressure measured every 15 or 30 minutes, and if you see several measurements strictly checked every 15 minutes linked to a clinic code or a procedure code that signal dialysis then indeed you can probably identify with fairly good certainty the circumstances where the blood pressure was measured.

DeAndre: Do you have any advice to try to discern the best BP values to use in a different context?

Dr. Csaba Kovesdy: Well, again it takes some contemplation because it very much depends on knowledge of how the system works, where blood pressure is measured, and what triggers certain measurements. This is why it helps to—I find it very difficult to do this research for people who do not practice and do not work at the VA. You have to have the knowledge of what really a blood pressure measurement means in dialysis, how that is done, with what frequency, how the clinics are coded, and why certain things are done under the circumstances.

Remember, everything will basically be assumptions, which is not the best way, but dealing with millions, and millions of measurements, you just have to do your best to identify the circumstances based on your knowledge and experience of the systems and biology. Then you come up with a rule that is probably sensible.

DeAndre: Do you include ICU and nighttime reading in your studies?

Dr. Csaba Kovesdy: The ones that I have shown you are based purely on outpatient blood pressure measurements. You are posing a very interesting question, something that we are actually studying actively in so far as what inpatient blood pressures mean. That is a very interesting and valid scientific question because, on the one hand, we round on inpatient, and we see their blood pressures. Often times they are high, and we make adjustments, so you could consider this an ideal environment where you have the luxury of checking blood pressures several times a day, every day, and then you can initiate medications that are administered to the patient for sure—assuming that they do not refuse taking them.

So you know that the patient is taking the medication, and then you can check the blood pressure measurements and laboratory measurements to make sure there are no adverse effects and make sure that the medication is effective. So in that respect, the inpatient setting is considered by some to be a perfect environment where anti-hypertensive medication can be initiated or titrated.

On the flip side of it, of course, patients are not inpatients for reasons of treating blood pressure for most of these patients. They are there for some other illness, and that illness may have an independent effect on blood pressures. So if the patient has an infection, the blood pressure may be lower than what it is at home, or if they are in there for a painful condition, for example, the blood pressures may be higher than when they go home, and they do not experience pain.

You could also argue that these blood pressure measurements should not be considered as indicative of the patient’s true blood pressure and should not be used to direct therapy because we do not know for sure whether they represent the same target that the patient will be exposed to most of the time when they leave the hospital.

There are plenty of [\_\_\_\_\_ 00:52:24] reports that warrants for the research. Then obviously, on these screens when you talk about ICU, for example, where patients are in with serious illnesses, and often times the blood pressures are affected in the way that they are causing hypertension, this poses totally different questions. In fact, we looked at this—it is unpublished data—but you see exactly the opposite association so not surprisingly it is a straight inverse association meaning that the higher blood pressure are associated with the best survival in the inpatient setting, and especially in the ICU.

Again, this is not surprising, and I do not think that anybody would want to initiate chronic hypertensive management in an ICU patient.

DeAndre: Okay, thank you, and I have another comment here—In a recent investigation that I did, there were a number of entries with the same date and time taken, but the SBP and/or DBP were different. I also found what you were just mentioning where there were BPs taken within 15 minutes of each other. We only kept the second reading.

Dr. Csaba Kovesdy: Yes, so I can see that we have others that use this a face the same problem. I know, I have seen the same with the blood pressure measurements done at the same time, down to the second, and I am not really sure what to do with those. I ended up averaging them I think, but there is really no right or wrong answer there. I am not sure really why those have occurred. It is not a huge number of them, so it may be just chance, a typo, somebody not recording the exact time, or entering the wrong time for the same date.

Then for the 15 minutes intervals, be careful about it. I guess taking the same measurement gives you some information, and I suppose that you skip the first one for a reason similar to why I would have skipped them. Again, if they are measured at these equal intervals, you have to think about something like a dialysis environment, and you might want to check on the clinic code or the encounter code associated with that date and time and see if you really want to consider blood pressure measurements during dialysis.

That in itself can be studied, but dialysis patients are a whole different category. They have very different associations. I have not shown you any data about that, but blood pressure is a very interesting question, to put it mildly, in dialysis patients.

DeAndre: Thank you. We have one question left. This question is—How did you restrict just to outpatients? I have not seen a variable that indicates outpatient versus inpatient readings. Have I missed this?

Dr. Csaba Kovesdy: No, you have not, and I am sorry that I did not make this clear. So basically what you do is you find the inpatient/outpatient indicator from different files. So they are available in the set and probably some other ones where you have data about inpatient and hospitalizations with admission date, discharge date and a lot of other things. You would basically have to merge the data from those data sets with you vital sign databases and basically combine the blood pressure measurement dates with the admission/discharge dates. That way you would be able to identify the inpatient/outpatient measurements.

DeAndre: Okay, thank you. I believe that is all the questions.

Heidi: We actually have one other question here DeAndre. We got a question—What was the answer to the two poll questions?

Dr. Csaba Kovesdy: Yeah, well the answer is, it depends. So, let me just quickly pull up these questions to see—so the first one was the ideal target blood pressure in patients with essential hypertension? So assuming nothing else, it would be 140/90. That is the latest JNC 8 recommendation although JMC 8 also says that in patients older than 60, you can go with 150/90. So that just relaxes the requirement there.

The other ones, you know the 130/80 used to be the CKD and some other comorbidity, diabetes-related target blood pressure but the agencies have backtracked from that. It is now 140/90; 120/80 is the normal blood pressure but it is not a treatment target per say, and then the 130-140 is something that is really dear to my heart because it takes into account the J-shape.

So there are not recommendations like that, although some agencies like the Europeans and some others also caution about over-treating blood pressure, but most guidelines use the less than 130. My problem with that is obviously that 80/40 is a perfect blood pressure according to those guidelines, and no sensible physician would want their patient to be treated to that low a blood pressure.

Then the fourth question would be in which population is higher blood pressure associated with adverse outcomes? Most of you said all populations and I cannot fault you for that. I mean if you say elevated blood pressure, let us say a high blood pressure of 180/100, yes, as I showed you in most populations, even CLD patients, this is associated with poor outcomes.

Then again, if you say that elevated blood pressure means a higher blood pressure no matter of the blood pressure level. In other words, is a blood pressure of 120 better than a blood pressure of 130? There it is less clear, so that kind of an association is not true for patients with comorbidities, for example, and those with CKD or CHF we have a marked J-shape.

So again, on purpose I worded these questions equivocally so I would be able to point out some of the controversies that we are facing nowadays.

DeAndre: Thank you. I want to thank you once again Dr. Csaba Kovesdy for a wonderful presentation today. Our next session is scheduled for Monday, May 4th from 1:00 to 2:00 p.m. Eastern. It is entitled *Improving Mortality in Ascertainment*. We hope that you can join us for the session. Heidi…

Heidi: Yes, if you could all just wait a few more moments, I am going to close the session out here. When I do that, you will be prompted for a feedback form. We really do read through all of your feedback; if you could take a few moments to fill that out, we would very much appreciate it. Thank you, everyone for joining us today, and we hope to see you at a future HSR&D Seminar. Thank you.