

Large swings in systolic blood pressure over a series of physician visits are a sign that patients may face higher risks of all-cause mortality, coronary heart disease, stroke, and end-stage renal disease, according to a large study of US veterans.

In a fully adjusted model, higher systolic blood pressure variability—measured as a standard deviation from the baseline systolic blood pressure—was associated with an increase in all-cause mortality ranging from 10% to 80% depending on the extent of visit-to-visit variability. Similarly, the risk of coronary heart disease ranged anywhere from two- to nearly six-fold higher among individuals with variations in their measured systolic blood pressure.

“The association with risk is strikingly strong and consistent,” said senior investigator Csaba Kovesdy (University of Tennessee Health Science Center, Memphis). “There was a very nice graded association, which was consistent for deaths, stroke, coronary heart events, and end-stage renal disease, even after adjusting for confounders. What we know about [variability] thus far is this type of association exists. There have been previous studies showing similar results, but ours was probably the largest. This is not an entirely a new phenomenon.”

The study, published in the September 27, 2016, issue of the Journal of the American College of Cardiology, analyzes 3,285,684 individuals with and without hypertension within the US Veterans Affairs healthcare system. The patients were 60 years old, on average, and had a mean baseline systolic blood pressure of 133 mm Hg.

To assess variability, the subjects were divided into four quartiles based on the standard deviation of systolic blood pressure across eight outpatient measurements. In quartiles 1, 2, 3, and 4, the visit-to-visit variability in systolic blood pressure was

For the pregnant women, treatment with a vitamin K antagonist (VKA) offers the lowest risk of adverse outcomes, researchers found. But for the fetus, the lowest risk is seen with low-molecular-weight heparin (LMWH). Yet dose appears to matter: fetal risk is similar between LMWH and warfarin, provided that the VKA's dose is no greater than 5 mg daily.

During a median follow-up of 8 years, there were 484,887 deaths, 67,227 coronary heart disease events, and 62,523 strokes. Compared with patients in quartile 1, those in quartiles 2, 3, and 4 had a 10%, 32%, and 80% higher risk of death. For coronary heart disease, the respective hazard ratios for quartiles 2, 3, 4 were 2.11, 3.59, and 5.92, all of which were statistically significant compared with quartile 1. For stroke, the hazard ratios for quartiles 2, 3, and 4 were 2.05, 3.63, and 6.60, respectively. Similar trends were observed for end-stage renal disease.

### Could Variability Be Added to EMRs?

To TCTMD, Kovesdy said visit-to-visit variability in blood pressure is not used in clinical practice, but added that the variable is potentially easy to obtain with electronic health records. He said physicians are always on the lookout for “red flags” in their patients, and variation in systolic blood pressure is potentially something that could be used to identify higher-risk patients if incorporated into computerized records.

“Most patients have longitudinal blood pressures recorded, and it would take a fairly simple and rudimentary algorithm to calculate variability,” said Kovesdy. “All it would take to factor it in would be the longitudinal blood pressure measurements the patient has had and to compute any number of markers of variability. We used a simple standard deviation, but there are potentially more sophisticated, more accurate measures.”

The real question, Kovesdy told TCTMD, is what the results “really mean.” It’s possible visit-to-visit variability in systolic blood pressure is simply a marker of inherent patient risk and not the cause of adverse outcomes per se. While such variability might not be the target for an intervention, it could serve as a means to identify patients in need of closer monitoring, he suggested.

This inconsistency might also be a marker of poor medication adherence. “For somebody who is on antihypertensive medication, if they take the medication on and off, they might have these large swings in high and low blood pressure,” he said. “In this case, we don’t know if the swings in blood pressure are directly related to adherence, but if they were, improved adherence could potentially lead to better outcomes.”

Kovesdy noted, however, that their study included patients without hypertension (37.1%). If the association between visit-to-visit variability and outcomes was the result of medication adherence, it would be limited to patients with hypertension, which it was not, he said. It’s also

possible the variation in systolic blood pressure is causal, with wide variations in blood pressure resulting in intermittent ischemia leading to MIs and strokes, he suggested.

The bottom line is that the reasons for blood-pressure variation still need to be better studied, said Kovesdy. If the causes could be identified, future steps would entail attempting to reduce the wide swings in blood pressure to improve clinical outcomes. “This is a whole lot of stuff,” he said. “It’s not for one person or one group. Our findings will hopefully stimulate more research in this direction.”

In an editorial accompanying the study, Lawrence Krakoff, MD (Icahn School of Medicine at Mount Sinai, New York, NY), and Robert Phillips, MD (Weill Cornell Medical College, New York, NY), state that the size of the present study “dwarfs previous surveys and provides robust support for the importance of systolic blood pressure in predicting risk of future mortality and cardiovascular and renal disease.”

Like Kovesdy, the editorialists state that the association between variability needs further study. Varying adherence in two clinical trials—ALLHAT and AASK—was associated with variations in systolic blood pressure, they note, but the connection to clinical outcomes was less clear. “Systolic blood pressure variability needs to be understood as to causes and reversibility,” they write, adding that studies are also needed to determine if the “prevention or diminution” of visit-to-visit variability is beneficial in disease prevention.