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Blood pressure related outcomes in a diabetic population

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There has been significant controversy over the past decade regarding what is appropriate blood pressure control to optimally reduce cardiovascular disease (CVD) and kidney disease related events in patients with diabetes. The recent discussion on blood pressure targets in diabetes set the stage for a thought provoking contribution by Wu et al (1) who report in individuals with diabetes with persistently low pressures <120/80 mmHg or pressures that drop below 120/80 mmHg have an increase in CVD events and mortality over time.

Based on data derived from larger clinical trials in those with diabetes, the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC)7 advised a 130/80 mmHg target (2). However, “achieved” systolic blood pressures in those trials were rarely below 130/80 mmHg and limited to only a few studies (3, 4). The Action of Control Cardiovascular Risk in Diabetes (ACCORD) trial was then designed to investigate whether targeting pressures in diabetic patients down to 120/80 mmHg would improve CVD outcomes to a greater extent than a goal of less than 140/90 mmHg. At trial end, the overall CVD results were null, but stroke was reduced in those with achieved pressures of <120/80 mmHg (5). Another recent trial, the Systolic Blood Pressure Intervention Trial (SPRINT), was designed to investigate whether pressures <120/80 mmHg would improve outcomes in patients with kidney disease compared to 140/90 mmHg. The SPRINT investigators reported an improvement in fatal and nonfatal major CVD events in the intensive arm <120/80 mmHg (6). While this trial excluded diabetic patients, a recent post hoc analysis of ACCORD and a meta-analysis suggest a systolic target of <130 mmHg may be more appropriate in the diabetic population (7, 8) rather than the more conservative

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JNC8 recommendation of <140 mmHg (9). Nevertheless, the discrepancy in the extant trial data have left many confused as to an appropriate blood pressure control for those with diabetes.

The authors performed a passive secondary analysis of an existing prospective Chinese cohort to examine whether blood pressures <120/80 mmHg followed longitudinally, increased mortality in a normotensive, diabetic population. Perhaps the single greatest strength of the current contribution is the population size from which the investigators were able to draw. The cohort is derived from a population located in Kailuan, China wherein 101,510 individuals were enrolled across 11 hospital settings starting in 2006 with three follow up examinations in 2008, 2010, and 2012 with study termination in 2014. As part of the cohort individual demographics, medical histories, and lifestyle questionnaires were administered. The authors included all with established diabetes and excluded those with established hypertension; e.g. those with diagnosed hypertension, blood pressure >140/90 mmHg, or taking anti-hypertensives. In an attempt to reduce confounding for mortality outcomes, the authors further excluded baseline CVD and cancer. This left 2,311 individuals to follow longitudinal blood pressure measurements and risk for CVD events and mortality. While this may appear to be a modest number, this final sample was uniform, obviating the need to adjust their modeling for clinical confounders.

The collective data from Wu et al suggest an increase in CVD outcomes in diabetics with pressures <120/80 mmHg. In contrast to the observation that CVD outcomes increased at this 120 mmHg threshold, these data are reminiscent of the signal of increased adverse events observed in ACCORD and SPRINT. Despite this signal, it should also be noted that data from a follow up analysis of the blood pressure component of ACCORD support intensive treatment improved the primary outcome as well as the secondary outcome for stroke (7). We should then weigh these discrepant observations in the context of a meta-analysis of all randomized clinical trials through 2015 that included diabetics (8). Data from this study suggested improvement in outcomes with systolic pressures <130 mmHg, and that CVD risk reductions were proportional to the magnitude of the blood pressure reduction. The collective data from these trials, including that of Wu et al, suggest there may be a “sweet spot” somewhere between a target systolic pressure of 120 mmHg and 135 mmHg. Despite this study being limited to a secondary analysis of a prospective observational cohort, these data, combined with the prior randomized clinical trial and meta-analysis observations (5–9), do provide additional information suggesting caution in targeting pressure of <120/80 mmHg except perhaps in select groups of the diabetic population at high risk for stroke.

Another important observation made by the authors is that using baseline or final blood pressure readings limits inferences to blood pressure control over time. The authors use 2006 and 2008 blood pressure data to determine a trajectory and then relate to CVD events (MI and stroke) and mortality from 2008 through 2014. The authors’ use of blood pressure trajectory is reminiscent of attempts to use time averaged blood pressures in order to relate to outcomes (10). While the concept of using time averaged readings is not new, applying this concept to analysis of population studies is new and should be considered more widely. The authors refer to the potential change in blood pressure over time as an important concept

to apply to study and analytic design in the context of participant safety. The reliance on a single blood pressure to predict risk is problematic. This may be best illustrated by both the ACCORD and SPRINT studies wherein achieved pressures were less than 120/80 mmHg and yielded somewhat disparate results on CVD outcomes, yet the intensively treated arms in both trials had increased adverse events and a signal for harm.

By utilizing trajectory blood pressure patterns the authors have uncovered rather novel findings. While it is no surprise the authors observed an increased mortality and CVD events in those whom develop hypertension (>140/90 mmHg) between 2006 and 2008, it is of interest that there was an increase in events in those with stable blood pressures <120/80 mmHg and those whose blood pressures dropped from 120–139/80–89 mmHg to that <120/80 mmHg over two years. When considering the 120 mmHg as a threshold, there are some fundamental differences in this current analysis and previous work in this area. ACCORD and SPRINT were by design randomized clinical trials incorporating high risk hypertensive populations treated over time to a blood pressure goal in contrast to the current contribution which included a normotensive population with diabetes and without advanced complications. This is a limitation to comparisons of blood pressure goals. Another notable difference is the composition of the cohort which is Chinese, predominantly male, and with early stage diabetes without complications (e.g. eGFR ~86 ml/min/1.73 m^2 and CVD excluded at baseline). The inferences derived from this study to the general hypertensive population are rather limited.

The current study does add to the discussion regarding what is appropriate blood pressure control in diabetics. The report from Wu et al provide important information in a very specific population that blood pressures <120/80 mmHg may be associated with an increase in events. These data coupled with the signal for adverse event from a number of studies in those <130/80 mmHg, suggest that target pressures below 120/80 mmHg should be reserved for select diabetic individuals at highest risk for stroke. The signal for adverse events in these trials and the heterogeneity in outcomes is a concern at these lower pressures is concerning. The authors further extend our understanding of the importance in assessing blood pressure change over time rather than reliance on initial or achieved blood pressures in study design to better understand risk at this level of blood pressure control in high risk populations.

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