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COMMENTARY

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Blood pressure lowering treatment and the Framingham score: Do not fear risk

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An important consideration for starting blood pressure lowering treatment is one's cardiovascular risk. The widely used Framingham risk score uses age, sex, total and HDL-cholesterol, smoking, and systolic blood pressure to estimate the 10-year risk of coronary heart disease, cerebrovascular disease, peripheral artery disease, and heart failure.[1] Patients with a higher Framingham score have a higher cardiovascular risk and a more profound absolute risk reduction with treatment, leading to a lower number needed to treat. In general, the decrease in patients that receive treatment compared with those who do not receive treatment (ie, the relative risk reduction) is relatively constant, but in the case of anti-hypertensive treatment, there is a limit to the level of blood pressure lowering is beneficial. Meta-analyses have shown that the relative risk reduction achieved with anti-hypertensive treatment is similar across the blood pressure spectrum.[2,3] However, uncertainties arise at the extremes, where the relation between blood pressure and cardiovascular events becomes non-linear. Indeed, multiple studies have shown a paradoxical increase in cardiovascular events in patients with the lowest on-treatment blood pressure suggesting that at lower blood pressure levels a more cautious approach is warranted.

In this post hoc analysis of the Systolic Blood Pressure Intervention Trial (SPRINT), Ling Zhang and colleagues explored the effects of intensive and standard blood pressure lowering treatment according to baseline cardiovascular risk using the Framingham risk score.[4] They stratified the patients in both treatment arms in three strata of the Framingham risk score: <10%, 10%-20%, and >20% risk of cardiovascular disease. They demonstrate that there is no interaction between the effects of intensive blood pressure lowering treatment and cardiovascular outcomes, suggesting that the positive effects of intensive treatment are not dependent on baseline cardiovascular risk. However, hypotension, syncope, bradycardia, and acute renal failure were twice as common in patients with a Framingham risk score 10%-20% and >20% who were randomized to intensive treatment compared with those receiving standard therapy.

The finding that the benefit of intensive treatment is independent of the Framingham risk score is consistent with a meta-analysis of individual patient data from the Blood Pressure Trialists Collaboration showing that lowering blood pressure provides similar relative protection at all levels of baseline cardiovascular risk.[5] The present post hoc analysis further supports recent studies that have shown that the increased risk of cardiovascular events at the lower end of the blood pressure spectrum may be attributable to reversed causality. In this case, the association between lower blood pressure and increased cardiovascular risk is caused by other factors than blood pressure lowering treatment. The hypertension J-curve points to the observation from population studies and randomized trials, including SPRINT, that with low systolic and diastolic blood pressure values the risk of cardiovascular events does not decrease further and, at lower blood pressure values, even increases.[6-8] However, the causality of this association has been disputed as these studies also show that in the lower systolic and diastolic blood pressure strata, participants had a higher cardiovascular risk and more cardiovascular events at baseline. Moreover, recent studies have revealed that the association between low blood pressure and cardiovascular outcomes is the same regardless of blood pressure lowering treatment and is independent of the attained absolute blood pressure level.[9,10]

Because individuals with the highest Framingham risk score have the highest absolute risk, they will benefit most if the relative risk reduction is similar compared to those with lower risk scores. The finding that there was no significant interaction in treatment effect according to baseline Framingham risk score suggests exactly that. The authors also performed a Cox regression analysis to assess the association between low, medium, and high Framingham

risk and cardiovascular outcomes. Here, individuals with the highest risk score had a clear benefit of intensive blood pressure lowering treatment, while in those at low cardiovascular risk there was no significant advantage. The problem is that blood pressure is both incorporated in the Framingham risk score and a pivotal determinant of the effects of anti-hypertensive treatment. Unsurprisingly, patients with the highest risk score also had the highest blood pressure level. Likely, they benefited most from blood pressure lowering treatment just because their blood pressure was significantly higher. The much higher blood pressure levels may also have accounted for the higher rate of serious adverse events in the medium and high risk stratum. Hypotension, syncope, bradycardia, and renal failure were all more frequently reported in those with a higher Framingham risk score. However, as with the interaction between the Framingham risk score and the cardiovascular events, the interaction between baseline cardiovascular risk and the serious adverse events was not significant. This suggests that the occurrence of serious adverse events was not dependent on the Framingham risk score, but that other factors associated with Framingham risk (ie, blood pressure) accounted for these differences.

Finally, it should be noted that "serious" adverse events in SPRINT ranged from a fatal or life-threatening event to a condition that entailed "a clinically significant hazard or harm to the participant that might require medical or surgical intervention." This rather liberal definition is also represented by the high prevalence of serious adverse events: 38.3% in the intensive treatment group and 37.1% in the standard treatment group.[11] Hypotension, bradycardia, and syncope were more frequent in those receiving intensive treatment, yet the prevalence of injurious falls was similar. Renal failure, defined as a >0.3 mg/dL (26.5 μmol/L) rise or >1.5-fold increase in serum creatinine,[12] was significantly more frequent in the intensive treatment group, but may have been caused by a more profound decrease in renal perfusion pressure as there was no increased risk of adverse cardiorenal outcomes.[13,14]

In conclusion, the present post hoc analysis of SPRINT shows that the benefits of anti-hypertensive therapy also apply to individuals at high cardiovascular risk. The higher risk of adverse events associated with intensive blood pressure lowering therapy in patients with a high Framingham risk score is likely a direct result of the more profound blood pressure decrease in this group. As with every clinical decision, the authors correctly state that the adverse events and benefits of intensive treatment require to be carefully weighed against each other. It is, however, important to stress that the long-term benefits of intensive blood pressure lowering treatment in SPRINT outweighed the reversible adverse events in the short term. The authors therefore rightfully conclude that intensive blood pressure treatment in SPRINT was beneficial regardless of the Framingham risk score.

DISCLOSURES

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