Resistant Hypertension and Susceptible Outcomes: Exploring the Benefits of Aggressive Blood Pressure Control

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> "The degree to which cardiovascular risk is reduced with treatment of resistant hypertension is unknown." American Heart Association Scientific Statement on resistant hypertension, 2008.[1]

Mounting evidence demonstrates that resistant hypertension—defined even as simply as requiring four or more antihypertensive drugs to achieve office blood pressure (BP) control—is associated with impaired health-related quality of life[2] and a substantially greater risk of adverse cardiovascular outcomes and death relative to nonresistant hypertension.[3–9] This evidence is concerning given that an estimated one in five treated hypertensive patients in the United States meets this definition of resistant hypertension and, of these, most have uncontrolled BP.[10] BP control, insofar as it is achievable, continues to be recommended as a means to reduce cardiovascular risk in patients with resistant hypertension. Such recommendations certainly seem reasonable based on the known and substantial benefits of BP reduction in the general hypertensive population and in patients with more severe hypertension requiring aggressive therapy.[11]

On the other hand, some data suggest that more aggressive therapy is associated with worse outcomes in patients with resistant hypertension. For example, use of more antihypertensive drugs has been linked with a progressive worsening of health-related quality of life[2,12] and a greater risk of adverse cardiovascular events,[7] such that patients taking the greatest number of antihypertensive agents have the worst outcomes on average. What is not known is whether more aggressive treatment regimens somehow *cause* these adverse outcomes or simply reflect worse underlying pathology. Given these seemingly conflicting data, clinicians are faced with challenging questions: to what extent does (more aggressive) treatment, to achieve a goal BP, benefit a particular patient with resistant hypertension? And, are there diminishing returns, or even harms, associated with increasingly aggressive antihypertensive therapy?

In this issue of the *Journal*, Fatemi and colleagues[13] provide another piece to this puzzle with their report from a retrospective evaluation of the association between BP control and all-cause mortality among US veterans with resistant hypertension. This study included 628 veterans with resistant hypertension, defined as having uncontrolled office BP while taking three or more antihypertensive drugs (including a diuretic), who were receiving routine hypertension care at the Washington DC VA Medical Center. The investigators divided this cohort to facilitate a comparison between patients who had achieved BP control (n=234; 37%) and patients who had not (n=394; 63%) after 3 years of subsequent routine care. Baseline characteristics were generally similar between the groups, including similar proportions of patients using each of the major classes of antihypertensive agents with the exception of β-blockers, which were employed slightly more frequently in patients who achieved BP control at year 3. Clinic BP at time of inclusion in the cohort appears to have been modestly different between the groups, perhaps ~7/2 mm Hg lower in the group that achieved BP control at year 3, although these data were not explicitly reported. By year 3 of follow-up (the year in which BP was used to define the controlled and uncontrolled comparison groups), BP differences were considerably greater, by design, with mean BP approximately 22/8 mm Hg lower in the controlled BP group.

During 6 years of total follow-up, all-cause death occurred significantly more often in the group defined as having uncontrolled resistant hypertension than in the group with controlled resistant hypertension. This association between uncontrolled BP and greater risk of all-cause death persisted in multivariate analyses that adjusted for several other known cardiovascular risk factors (adjusted hazard ratio for uncontrolled vs controlled BP, 2.48; 95% confidence interval, 1.64–3.76). The authors concluded that these data "strongly suggest a robust mortality benefit probably derived from BP control in this high-risk population."

Before delving into the study details, it's worth noting that similar analyses have been performed before—at least twice, in fact—in much larger populations and with different conclusions. Using data from the International Verapamil-Trandolapril Study (INVEST), we compared risk of all-cause mortality and cardiovascular mortality among approximately 17,000 patients with coronary artery disease and either nonresistant or resistant hypertension.[3] Not surprisingly, patients with resistant hypertension, regardless of BP control, had a greater risk of all-cause and cardiovascular mortality than patients with controlled nonresistant hypertension. Yet, we observed no difference in outcomes between patients with controlled and uncontrolled resistant hypertension, despite a mean BP difference of

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approximately 28/10 mm Hg between these groups at the visit prior to death or censoring. Similarly, Irvin and colleagues[5] recently observed no difference in mortality or stroke risk in patients with uncontrolled resistant hypertension vs those with controlled resistant hypertension over a median follow-up of 6 years in a population-based cohort of about 14,000 US patients.

So, what should we discern from the present report?[13] On the surface, these results suggest that BP control is associated with a reduced risk of death among persons with resistant hypertension, and that typical BP goals for the general hypertension population (eg, <140/90 mm Hg) may be applicable to patients with resistant hypertension. Moreover, these associations are biologically plausible and qualitatively consistent with a wealth of epidemiologic data linking lower BP to lower risk and with randomized controlled trial data demonstrating that reducing BP prevents major adverse events in the general hypertensive population. Nevertheless, this study has limitations that may warrant a more cautious interpretation. Most importantly, findings from registry-type studies of this sort must not be inferred as proof that lowering BP in patients with resistant hypertension causes a reduction in occurrence of death. Indeed, many other factors may explain the association observed between controlled resistant hypertension and reduced risk of death. For example, both groups reportedly used a similar number of antihypertensive agents throughout the study period, which begs the question: what differences existed between the two groups that allowed one to achieve much better BP control than the other when, presumably, both groups received similar care? Patients who achieved BP control may have had significantly greater adherence to their antihypertensive regimens than those who did not, as has been demonstrated elsewhere.[14,15] Patients who are adherent, in general, are known to have lower all-cause mortality rates than patients who are consistently nonadherent to therapy, even when comparing adherent and nonadherent placebo users—a phenomenon known as the healthy adherer effect.[16] Presumably, adherence data were unavailable to Fatemi and colleagues, but it is conceivable that patients who achieved BP control were generally healthier individuals who take their medications regularly and thus would have had a lower mortality rate anyway. Even if adherence was high in both groups, the inability to achieve BP control among some patients may have reflected, for example, greater unmeasured underlying vascular disease or excess renin-angiotensin-aldosterone system activity that increased their risk for death independent of BP control.

Neither the present work by Fatemi and colleagues,[13] nor previous studies[3,5] definitively answer the question of whether greater BP control or more aggressive therapy leads to a reduction in mortality in patients with resistant hypertension. However, taken at face value, these studies suggest a nuanced picture of the influence of BP control on mortality, which may be partially dependent on underlying risk. In relatively lower-risk populations, such as those studied here, more aggressive BP reduction may substantially reduce all-cause mortality because such patients have comparatively fewer competing risks. In contrast, for patients with more significant underlying coronary disease who are already at a higher risk for death (ie, patients with underlying coronary artery disease), more aggressive BP reduction may offer comparatively less benefit.[17] Further evaluation of these data might offer important additional clues to guide treatment and future research, such as who should be targeted for more aggressive therapy—and with what antihypertensive agents—to optimally reduce risk across a resistant hypertension population.

Related to this issue of competing risks, high BP is not the only prevalent major cardiovascular risk factor that exists in patients with resistant hypertension. However, almost nothing is known of the benefits of nonantihypertensive cardiovascular risk reduction strategies in this population. One recent post hoc analysis from the Treating to New Targets (TNT) trial[18] demonstrated that, compared with the addition of a low-potency statin dose, addition of a high-potency statin (ie, atorvastatin 80 mg daily) was associated with substantially reduced mortality and cardiovascular morbidity in patients with resistant hypertension. Importantly, this benefit was observed independent of BP control, suggesting that strategies targeting global risk—that is, beyond BP reduction—may be important in the management of patients with resistant hypertension. Unfortunately, few other similar analyses have been performed and substantial gaps exist in our understanding of optimal comprehensive approaches to improving prognosis in this common high-risk phenotype.

The work by Fatemi and colleagues generates interesting questions and is a timely and useful addition to the literature. However, 7 years after the publication of the American Heart Association resistant hypertension Scientific Statement, the degree to which risk is reduced with treatment of resistant hypertension remains largely unknown. To answer this question, adequately powered randomized clinical trials are urgently needed. Until such definitive studies have been performed, it seems prudent to individualize treatment goals through shared decision-making with patients, recognizing that for some patients with resistant hypertension, a standard <140/90 mm Hg (or <150/90 mm Hg) goal may not optimally lower the risk of adverse events or maximize quality of life.

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