Hitting the Mark: Blood Pressure Targets and Agents in Those With Prevalent Cardiovascular Disease and Heart Failure

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Blood pressure (BP) is one of the key modifiable risk factors for cardiovascular disease (CVD) both in primary and secondary prevention of disease. In this review, we discuss BP treatment in prevalent CVD and heart failure. Evidence for specific agents based on their neurohormonal effects and evidence for target values for systolic or diastolic BP are covered. The potential adverse effects of overtreatment of BP are also discussed. BP targets for those with CVD should generally be less than 140/90 mm Hg but require individualization of therapy for any further reduction based on the clinical setting.

Key Words: Blood pressure, Blood pressure medications, Heart failure, Atherosclerosis

Introduction

The debate after the release of the recommendations of the committee members of the Eighth Joint National Committee has renewed interest in blood pressure (BP) targets not only in the general population but also in those presumably at highest risk of the cardiovascular complications of hypertension (HTN)—those with known cardiovascular disease (CVD). Intuitively, it would seem that these individuals would have the highest absolute risk of future disease related to HTN and that lower BP targets would be of greatest benefit in these groups. We review here the available observational and clinical trial data on BP targets in those with a history of myocardial infarction (MI), stroke, and heart failure (HF), discuss BP agents of choice in these same conditions, and then briefly discuss the potential side effects of too stringent BP control.

BP Control After MI

Hypertension has been recognized for decades as a risk factor for incident MI and remains, worldwide, the most prevalent modifiable risk factor for coronary artery disease (CAD).[1] Treatment of HTN after an MI is a quality metric in many hospitals and clinics as are smoking cessation and use of aspirin, beta-blockade, angiotensin-converting enzyme inhibitors (ACEIs), and statins. Most data specific to MI focuses on individual BP agents rather than targets. Although a heterogeneous set of studies of secondary prevention of CVD provide some insights into target BP in this population (Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial and Studio Italiano Sugli Effetti CARDIOvascolari del Controllo della Pressione Arteriosa SIStolica), to our knowledge, randomized controlled trials (RCTs) have not targeted different BP goals after MI. Observational data suggest that BP targets may be limited by adverse effects of diastolic hypotension (see "J shape" later).

In terms of BP agents, the duration of benefit of beta-blockade in the post-MI period is unclear and benefit is likely accrued through slowing of heart rate and BP lowering. A 1999 meta-analysis combined results from 31 long-term trials of beta-blockade and showed a robust benefit for all-cause mortality (relative risk [RR], 0.77; 95% confidence interval [CI], 0.69-0.85).[2] Because of this substantial body of data, beta-blockade is generally continued indefinitely for those with past MI, albeit with a paucity of evidence in those post-MI patients without HF.[3]

There is strong evidence for use of ACEIs in patients with stable ischemic heart disease and preserved ventricular function, which has been summarized in a systematic review by Baker and colleagues.[4] In the large RCTs of ACEIs, there was a significant benefit in terms of total mortality (RR, 0.87; 95% CI, 0.81-0.94) and recurrent MI (RR, 0.83; 95% CI, 0.73-0.94) but with more limited data on angiotensin receptor blockers (ARBs). A benefit of ACEI treatment was seen even in those with prevalent CAD or diabetes who did not have clinically defined HTN, in another meta-analysis of similar primary data, emphasizing the notion that its action is both neurohormonal and antihypertensive.[5] The combination of ACEIs and ARBs has not shown benefit in various populations and, in fact, may be associated with increased risk of acute kidney injury,[6,7] hypotension,[6] and hyperkalemia.[7]

Guideline Recommendations

The report[8] from the committee members of the Eighth Joint National Committee did not specifically address the question of BP targets in prevalent CAD. The 2011 American Heart Association/American College of Cardiology Foundation Secondary Prevention Guidelines[9] recommended no change to their 2006 recommendation, which noted strong RCT evidence for treating those with BP more than 140/90 mm Hg with beta-blockers or ACEIs as first-line therapies. Based on current level of evidence, we believe these recommendations are reasonable.

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BP Control After Stroke

Stroke comprises a clinically heterogeneous set of events, with most strokes being ischemic (~80%) and a smaller percentage because of intracerebral or subarachnoid hemorrhage. Most data related to BP control after stroke are, therefore, primarily applicable to ischemic stroke. Within that category, identification of discrete risk factors (atrial fibrillation, carotid stenosis, hypercoagulable disease, etc.) should occur in tandem with decisions regarding BP targets.[10] Discussion of management of BP in acute stroke is beyond the scope of our review; we instead address the issue of BP control beyond the acute care setting, during which there may be significant risk associated with aggressive lowering of BP.

In observational studies, high BP is a well-recognized risk factor for both incident and recurrent stroke or transient ischemic attack (TIA).[11] Numerous studies have addressed the question of whether BP control in the months after the event can decrease the risk of future events. A group of these studies were assessed in meta-analysis and meta-regression in 2003.[12] Seven randomized trials were included, and the use of BP lowering agents across a range of classes was associated with a decreased risk of recurrent stroke, with the degree of benefit varying based on the extent of BP lowering. Treatment with antihypertensive drugs vs placebo resulted in substantial reductions in stroke (RR, 0.76; 95% CI, 0.63-0.92). This benefit was seen in those with and without diagnosed HTN. Notably, there was substantial heterogeneity in the effects related to different drug classes, with no evidence for benefit using beta-blockers; the beta-blocker studies included in this analysis, however, also had a lesser effect on BP, making both direct comparison, and assessment of whether the effects seen are related to medication or achieved BP, more difficult.

CLINICAL SUMMARY

- Antihypertensive therapy is of benefit in those with atherosclerotic cardiovascular disease.
- The benefit of antihypertensive therapy in atherosclerotic cardiovascular disease may be due to both a blood pressure lowering effect as well neurohormonal effects.
- Blood pressure targets for those with prevalent cardiovascular disease should be less than 140/90 mm Hg.
- In patients with systolic heart failure, blood pressure agents are used primarily for their neurohormonal benefits rather than for targeting specific blood pressure levels.

Although most studies were defined by the agent or agents used, the Secondary Prevention of Small Subcortical Strokes group addressed the issue of target BP after symptomatic lacunar stroke, randomizing patients to either a target systolic blood pressure (SBP) less than 130 mm Hg or a target SBP of 130 to 149 mm Hg.[13] In this study, medication use was at the discretion of the treating physician. An SBP difference of 11 mm Hg, on average, was achieved between the 2 groups. There was a nonsignificant lower rate of recurrent stroke (hazard ratio, 0.81; 95% CI, 0.64-1.03) and of MI or vascular death (hazard ratio, 0.84; 95% CI, 0.68-1.04) with the lower target BP. Although these results did not meet statistical significance, it was hypothesized that inadequate power rather than the absence of an effect may have contributed.[14] The other potential possibilities to explain the lack of benefit included the fact that beta-blockers were the primary BP agents used rather than diuretics or ACEIs, which in theory may be more effective in poststroke patients.[15]

An important study included in the 2003 meta-analysis was the Perindopril Protection Against Recurrent Stroke Study trial,[15] which randomized more than 6000 adults with a first stroke or TIA to perindopril or placebo, with optional addition of indapamide to the perindopril arm. Those who received both drugs had a 43% decrease in the risk of recurrent stroke (Fig 1), whereas those only receiving perindopril in the active treatment arm did not have a statistically significant benefit. The benefit of the intervention was seen in those with or without HTN and with or without CKD (defined by estimated glomerular filtration rate <60 mL/min/1.73 m^2) at the baseline visit.[16] The trialists concluded that combination therapy (with its associated effect on reduction in SBP and diastolic blood pressure [DBP]—12/5 mm Hg in this trial) should be considered in all stroke survivors.

Several important major studies have been published since the 2003 meta-analysis. A study of ARB vs a calcium channel blocker[17] (the Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention trial) showed a benefit of ARB vs CCB in secondary prevention of recurrent CVD events and mortality post-stroke, independent of BP control (BP was lowered by 13.2/3.2 mm Hg with eprosartan and 16/7 mm Hg with nitrendipine). A larger study, the Prevention Regimen for Effectively Avoiding Second Strokes study,[18] examined the role of telmisartan in prevention of recurrent stroke and cardiovascular events. This study randomized 20,000 patients with ischemic stroke to telmisartan vs placebo at a median of 15 days after their stroke. The primary outcome was recurrent stroke. SBP and DBP were 3.8/2.0 mm Hg lower in the intervention group, but there was no difference in the primary outcome after 2.5 years. There has been debate over whether the lack of benefit was because of the modest BP difference, the use of other BP-lowering agents in the placebo arm including ACEIs, or the shorter follow-up time relative to other studies.

Guideline Recommendations

The 2011 American Heart Association/American Stroke Association society guidelines[19] recommend, based on the meta-analysis and the 2 trials discussed earlier, that all patients receive a BP-lowering agent after a stroke regardless of whether they have a documented history of HTN; they do not suggest individualized targets because no study before the Secondary Prevention of Small Subcortical Strokes group specifically addressed target BP, but note that reductions in SBP and DBP of up to 10 to 12/5 mm Hg were associated with benefit. The guidelines