Unresolved Issues in the Management of Hypertension

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Elevated blood pressure (BP), along with tobacco use and dyslipidemia, is one of the 3 most important modifiable risk factors for cardiovascular disease (CVD). Over the last 4 decades there have been a series of epidemiological studies, clinical trials, and pathophysiologic investigations that have substantially enhanced our knowledge of the relationship of elevated BP to outcomes. In brief, the risk associated with elevated BP and coronary heart disease or stroke is continuous starting at ≈110 mm Hg systolic in individuals with no previous CVD. BP lowering, per se, reduces CVD events, especially in those with systolic BP (SBP) >160 mm Hg. A reduction in SBP by 10 mm Hg can lead to an ≈25% relative risk reduction in coronary heart disease and a 35% to 40% relative risk reduction in stroke in trials of 5 years (which generally translates into ≈2.5 years of intervention before an event).

Reducing dietary sodium, increasing potassium, and reducing weight and alcohol intake each lower SBP by 2 to 3 mm Hg depending on the degree of change in the above factors. The effects of these interventions on BP lowering appear to be more marked in those with elevated BP than in those with “average” BP levels. Collectively, the dual approach of lowering BP using antihypertensive drugs in those with elevated BP combined with a population-based approach to lifestyle modification, which shifts the BP distribution in a population, can lead to the greatest clinical and public health benefits. Yet, despite the widespread availability of inexpensive and safe antihypertensive agents and knowledge of nonpharmacological approaches to lowering, the burden of CVD from elevated BP in most countries remains high, and the rates of BP “control” are low. The reasons are summarized below.

Areas of Scientific Uncertainty

Most trials of hypertension that have reported clear reductions in major vascular events have included individuals with initial SBP >160 mm Hg. By contrast, trials involving lower initial BP levels have produced contradictory results, as reviewed by Staessen et al. In particular, we do not have any trial of BP lowering, per se, in the elderly (ie, >65 years of age), in those with SBP between 140 and 160 mm Hg, where clear reductions in mortality or morbidity are evident. The reasons for the inconsistent results may be several and include modest degrees of BP lowering (<5 mm Hg systolic compared with larger reductions in BP in trials with SBP >160 mm Hg) and relatively short duration of interventions. In early trials of BP lowering, clear results were obtained within 1 to 2 years in those with initial BP >200 mm Hg. By comparison, trials in those with SBP >160 mm Hg took ≈3 to 5 years to provide clear evidence of benefit. Among patients entering recent trials, other risk factors (eg, smoking or lipids) were better controlled, which may have resulted in slower progression of vascular disease and the need for longer durations of treatment to modify outcomes.

Guidelines: Balancing Advocacy and Evidence

Guidelines for the management of hypertension have been based on the randomized trials, as well as extrapolations from observational studies. Although such an approach may be “wise,” it should not impede the conduct of trials in populations for which the evidence for BP lowering is not clear. For example, guidelines have recommended that individuals with BP in the range of 140 to 159 mm Hg systolic should be treated with antihypertensive therapy. A careful analysis of these studies is provided by Zanchetti et al, and the uncertainties caused by extrapolations on the basis of “wisdom” (a euphemism for opinion) are being challenged by the 2009 modification of the European guidelines. Indeed, these revised guidelines call for randomized trials in a number of areas to provide firmer data as to the benefits of treating individuals with stage 1 hypertension (especially the elderly), a group that constitutes a large proportion of individuals classified as being hypertensive. Similarly, the guidelines regarding how aggressively individuals with diabetes mellitus need to be treated (ie, to a target of ≤130 mm Hg) are on the basis of retrospective and post hoc observational analyses within selected randomized trials rather than direct comparisons where patients are randomized to achieve different BP levels. Although diabetes increases the risk of CVD in individuals, the studies appear contradictory as to whether the risk is similar to having previous coronary disease. In addition, although lowering BP with a blocker of the renin-angiotensin system prevents progression to end-stage renal disease in diabetes mellitus with overt proteinuria, similar data in those with microalbuminuria, per se, are lacking. In some specific types of patients (eg, those with vascular disease, left ventricular dysfunction, or heart failure), angiotensin-converting enzyme inhibitors (and perhaps angiotensin receptor blockers) reduce major vascular events, independent of the initial BP level and despite modest BP lowering. Similarly, β-blockers prevent death and myocardial infarction after a recent infarct. However, similar benefits in these types of patients have not been shown with diuretics or calcium channel blockers, suggesting that, in specific circumstances, drugs such angiotensin-converting enzyme inhibitors or β-blockers may be of value independent of their ability to lower BP. However, in the majority of individuals without...
vascular disease or heart failure and who have hypertension, no clear benefit of one class of BP-lowering agent over another class is apparent (although in 2 recent trials the combination of amlodipine plus an angiotensin-converting enzyme inhibitor was superior to other alternatives in high-risk patients).\textsuperscript{14,15}

**Challenges in Preventing Hypertension**

Although the “prevention” of hypertension using nonpharmacological approaches is attractive, it has not been widely implemented. This may be because of inconsistencies in the observational data relating sodium intake to mortality. For instance, some studies demonstrate a U-shaped relationship between estimates of sodium intake and CVD.\textsuperscript{16} By contrast, the relationship between Na\textsuperscript{+} intake and BP is clear and consistent, so that the lack of a clear relationship with CVD events is puzzling. The reduction in BP by Na\textsuperscript{+} restriction, per se, is modest in magnitude in randomized trials, unless entire diets are replaced (something that may not be practical as a public health policy). In addition, Na\textsuperscript{+} content of food in many countries is largely determined by the processing of food rather than its preparation or the addition of salt at the table, which makes it difficult for individuals to lower the Na\textsuperscript{+} intake substantially. Interestingly, higher levels of K\textsuperscript{+} intake in the diet may prevent strokes, but this hypothesis requires more systematic evaluation.

Significant weight loss in individuals, although clearly effective in lowering BP, has not been sustainable in the long term, but weight loss as a strategy to reduce BP (and diabetes mellitus and dyslipidemia) is more likely to be successful if individual efforts are complemented by societal efforts at modifying the environment (Figure). Therefore, prevention of hypertension or reduction of BP levels of an entire community requires policy level interventions (which influence Na\textsuperscript{+}, K and fat content of processed food).

**Special Considerations for Future Trials**

Trials are needed in individuals with a range of BP starting from “normal” or “high normal” up to levels of SBP <160 mm Hg, except in those special circumstances where specific agents have been shown to be effective in reducing major vascular events (eg, the use of angiotensin-converting enzyme inhibitors or β-blocker after myocardial infarction). Trials are also needed in individuals at moderate risk, especially those over the age of 65 years or those with some specific complications (eg, atrial fibrillation) that puts them at risk of stroke, coronary heart disease, or heart failure, all of which should be theoretically reduced by BP lowering. Trials should be designed to obtain a difference in SBP of ≥8 to 10 mm Hg between the groups being compared to clearly test the hypothesis that BP lowering is beneficial in such individuals. This generally requires a combination of 2 or 3 antihypertensive agents used together, in those with a BP <160 mm Hg. Such a concept has been proposed in the context of the polypill, and the tolerability of using 3 antihypertensive agents in a single capsule appears well documented.\textsuperscript{18} Large trials are needed to assess whether such an approach will lead to clinically worthwhile benefits in those at moderate risk, prehypertension on stage 1 hypertension (ie, <160 systolic BP), especially in the elderly. Second, given that patients in future trials will likely be on multiple effective therapies, the event rates in the control group may be lower than expected and disease progression relatively slow; consequently, there may be a lag of 1 to 2 years before differences in events between the active and control groups emerge. Therefore, future trials need to be of longer duration (5 to 10 years) compared with the previous trials. Such prolonged trials raise issues of cost and feasibility, and, for a commercial sponsor, the length of patent life left after the study results become available. However, given that antihypertensive therapy is usually life long and that the “lifetime” risk of CVD in a 50-year–old subject is ≈40% to 50%, such prolonged trials are crucial to public health. Innovative trials using low-cost approaches, factorial designs (where ≥2 interventions can be jointly tested, thereby providing more value for a given investment), “passive” post-trial follow-up, simple trials with minimal monitoring and few data collection, and joint funding by governmental agencies may make such studies feasible. Such low-cost trials are only practical if regulators agree to substantial simplification of many of the wasteful practices in clinical trials.
which drive up cost but are peripheral to the main questions, sponsoring companies are less defensive, the studies are designed using ultra simple approaches, and investigators are willing to collaborate at modest or little reimbursements. Perhaps governments (at least in the wealthiest countries) may also agree to provide modest extensions of the patent life for drugs by 1 or 2 years for agents that are clearly shown to prevent mortality or major morbidity. Such innovations and efficiencies in trial design and conduct; partnerships among commercial entities, governmental bodies, and academies; and new incentives may be required to make large trials of important questions with 8 to 10 years of follow-up feasible.

Use of Non-BP-Lowering Approaches to Lower Risk in the Hypertensive Population

Elevated BP clusters with other risk factors for CVD and, thus, reducing the risk of CVD require a multidimensional approach. The value of simultaneously lowering BP and lipids in those with elevated levels of both risk factors is well documented in the Anglo Scandinavian Cardiac Outcomes Trial.14 Trials simultaneously evaluating both BP and low-density lipoprotein lowering in those at moderate risk and stage 1 hypertension or “prehypertension” are underway, and, if positive, combinations of BP-lowering drugs with a statin (eg, in a combination pill) will become justified. Such approaches may have the potential to reduce CVD by two thirds to three fourths.18

Summary

Although much progress has been made in the prevention of the cardiovascular and renal complications of elevated BP in those with stage 2 and higher hypertension, clear evidence supporting the role of BP lowering in those with moderately elevated or high-normal BP levels is urgently required. Given that this represents a very large population, there is urgency in obtaining reliable information on how best to manage these moderate risk individuals. Approaches using combination therapies of multiple BP-lowering drugs, lipid-lowering agents, lifestyle modification, and policy changes (which affect diet, activity, and weight) collectively have the potential to reduce CVD to a large extent (Figure). This goal can be achieved through systematic research, which generates clear evidence that can persuade governments, physicians, and patients to implement findings into clinical practice.

Disclosures

S.Y. has received research funding and honoraria for speaking for a number of pharmaceutical companies that manufacture blood pressure–lowering medication, including Sanofi-Aventis, Boehringer Ingelheim, Bristol Myers Squib, Astra Zeneca, Servier, and Merck Frost as well as organizations that support the concept of blood pressure lowering as a prevention strategy, such as the Heart and Stroke Foundation of Ontario and the National Heart, Lung, and Blood Institute.

References


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