An Updated Meta-Analysis With a Few Surprises

Norman M. Kaplan

The meta-regression analysis by Verdecchia et al in this issue of Hypertension updates the 2003 analyses of Staessen et al and the Blood Pressure Lowering Treatment Trialists’ Collaboration (BPLTTC). It includes the 5 trials published after those 2003 manuscripts were composed.

All 5 of the additional studies were secondary prevention trials, all on patients with known coronary heart disease (CHD). In 4 of the 5, either an angiotensin-converting enzyme inhibitor (ACEI) or a calcium channel blocker (CCB) was compared with a placebo, providing an additional 3.0 to 6.1 mm Hg further reduction in the mean systolic blood pressure. In all of these 4 trials of ACEI or CCB versus placebo, patients were also receiving other antihypertensive drugs, mainly directly toward their coronary disease.

The new analysis confirms and strengthens the conclusion of the previous analyses: when compared against placebo, ACEIs and CCBs protect against myocardial infarction (MI) and stroke; when compared against older drugs (diuretics and β-blockers), neither ACEIs nor CCBs add much more protection against either stroke or MI. However, as shown previously, ACEIs provide better coronary protection than CCBs, whereas CCBs provide better stroke protection than ACEIs.

Unlike the 2003 analyses, this one does not examine the effects of these drugs on congestive heart failure, in which ACEIs (and angiotensin II receptor blockers) have been shown to be particularly effective.

One of the new trials, the International Verapamil-Trandolapril Study (INVEST), examined CCB-based therapy against β-blocker–based therapy. Many more such comparative trials are in process, one having been completed but as of now not published.

In the face of the conclusive evidence that lowering of blood pressure is beneficial, truly placebo-controlled trials are now unethical, and there is little to be learned from additional comparisons of one drug against placebo in the background of multiple other drugs. In addition, the lower blood pressure goals now mandated by expert committees will require >1 drug in at least two thirds of all hypertensives, so attention has obviously turned to trials that are designed to compare different combinations against one another.

As this analysis shows again, the lower the blood pressure as provided by any drug, the greater the protection against CHD and stroke. However, Figures 3 and 4 in this article nicely portray the differential benefits of ACEI-based therapy against CHD and CCB-based therapy against stroke. It should be noted that among 5888 people >65 years of age followed for 10 years in the Cardiovascular Health Study, the incidence of CHD was >2-fold greater than was the incidence of stroke. Thus, although hypertension in the elderly is usually listed as a “compelling” indication for the use of CCBs, the greater danger of CHD in the elderly and the greater protection against CHD provided by ACEI-based therapy suggest that ACEIs should be given more precedence in the treatment of the elderly.

After reviewing all of the evidence available from these analyses, the following conclusions seem appropriate.

- More meta-analyses of currently completed trials are not needed (but the blood pressure trialists are rumored to be preparing another).
- The primary clinical need is to more effectively lower blood pressure, systolic more than diastolic. Current practice is woefully inadequate so that more intensive therapy is clearly needed, with the possible exception of patients >80 years of age who are not yet well studied.
- Most patients will need ≥2 drugs, preferably with a diuretic as the first choice. Although there is legitimate concern about the potentiation of diabetes with high doses of diuretic, most of the trouble likely has come from β-blockers.
- The future of drug therapy belongs to prevention, which is just now being addressed, and to intensive management of all cardiovascular risk factors, in particular, dyslipidemia. As others have said, it is “time to move on.”

References


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