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First Choice of Antihypertensive Therapy

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It is now well established that a high blood pressure (BP) that can not be normalized by nonpharmacologic means (low salt diet, weight loss, exercise, smoking cessation), should be treated pharmacologically. The therapeutic target BP is still a moving target, as in the past it used to be 160/95 mmHg. However, nowadays most guidelines accept the epidemiologic target of 140/90 for the general population, whereas a lower target of ≤130/80 is desirable for high risk populations, such as diabetics or patients with chronic renal insufficiency. However, a really "normal" BP is now believed to be ≤120/80 mmHg, because evidence from numerous observational studies (such as the Framingham Heart Study) and interventional long-term outcome trials indicates that even small increases in BP above this level are associated with a linear increase in risk of cardiovascular and cerebrovascular complications.

Whereas there is general agreement that lowering BP to target is the first and most important consideration, there is still ongoing debate as to what should be the first choice approach. There are six broad classes of antihypertensive drugs available today. The older agents are diuretics (including distal and loop diuretics), sympatholytic agents (including β-adrenergic blockers, α-adrenergic blockers and central sympathetic suppressants) and direct vasodilators (such as hydralazine and minoxidil); the newer classes are calcium channel blockers (CCB's), angiotensin-converting enzyme inhibitors (ACEI's) and angiotensin receptor blockers (ARB's).

The earlier clinical trials that produced incontrovertible evidence of benefit in terms of end organ protection from antihypertensive therapy, used mostly combinations of thiazide diuretics with sympatholytics—mostly β-blockers. Interestingly, the results revealed significant decreases in rates of strokes, renal failure and heart failure, but only marginal and inconsistent decreases in coronary artery disease. A possible explanation for this was suggested by subsequent clinical studies that described the side-effects of these classes: the most important seems to be aggravation of insulin resistance (which is already a characteristic of untreated essential hypertension and normal aging), resulting in hyperinsulinemia, hyperglycemia, dyslipidemia, i.e. components of what is now called the "cardiometabolic syndrome." Each one of these components, along with other metabolic disturbances that accompany diuretic therapy, such as hypokalemia, hyperuricemia and, not least, stimulation of the renin-angiotensin system, represent additional coronary risk factors that tend to partly offset the benefits of BP lowering.

By contrast, the newer classes of antihypertensive drugs are devoid of such adverse effects: The CCB's are metabolically neutral, whereas the ACEI's and ARB's are metabolically beneficial, as they tend to restore insulin sensitivity and minimize metabolic aberrations. Indeed, in most comparative trials, the relative risk of new onset type 2 diabetes is diminished by about 18-20% with CCB's and 35-40% by ACEI's compared to thiazides.

So why is there still a debate regarding what should be the drug(s) of first choice?

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Two reasons: One is that the largest NIH-supported trial, the Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT), showed that patients on diuretic therapy had a significantly better BP control, lesser incidence of strokes and no difference in incidence of coronary events compared to patients on ACEI. Critics counteract that the study was poorly designed as it had a large proportion of black patients who respond to diuretics, but not to ACEI's, hence the ACEI group had significantly higher BP's throughout, hence more strokes and yet, not more coronary events, hinting at cardioprotection by the ACEI.

The second is the theory that drug-induced diabetes is somehow "benign" and should not be a deterrent, since patients who became diabetics during drug trials suffered a lot fewer cardiovascular events that patients who were already diabetics upon entering the trial. Critics counteract that these differences are quantitative, as they reflect a shorter duration of newly diabetic patients' follow-up rather than qualitative differences in diabetic status; indeed new onset diabetes would be expected to produce complications at a later stage, beyond the specific trials' follow-up period.

So common sense dictates that the first choice antihypertensive should be one that offers the best metabolic profile (usually an ACEI or ARB), but additional agents should be used as needed to attain optimal BP control (usually a diuretic or CCB or both), whereas β-blockers should be used only if specially indicated for co-morbidities, such as in cases of coexisting coronary disease or chronic heart failure.

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