REVIEW

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Misconceptions and Facts About Treating Hypertension

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ABSTRACT

Hypertension is a powerful risk factor strongly linked to adverse cardiovascular outcomes. Because of its high prevalence, health care providers at many levels are involved in treating hypertension. Distinct progress has been made in improving the rates of hypertension awareness and treatment over years, but the overall control of hypertension remains inadequate. Several recent guidelines from different sources have been put forward in an attempt to bridge the gap between existing evidence and clinical practice. Despite this effort, several misconceptions about treating hypertensive cardiovascular disease continue to persist among clinicians. This review highlights some of the misconceptions regarding antihypertensive therapy.
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It is difficult to overestimate the benefits of widespread adequate hypertension control on cardiovascular morbidity and mortality at the population level.[1] The overall prevalence of hypertension is high and likely to increase with the aging population and increasing prevalence of obesity and other risk factors.[2,3] Despite this, the benefits of antihypertensive therapy have been established by a solid bulk of evidence.[3] The rates of hypertension awareness, treatment, and control have been improving over recent decades but are still far from adequate.[2] Moreover, several misconceptions persist among practicing clinicians, commonly in the areas in which evidence is scarce or misinterpreted.

MISCONCEPTION #1: HYDROCHLOROTHIAZIDE IS THE MOST USEFUL AND VERSATILE THIAZIDE DIURETIC

Facts

Hydrochlorothiazide remains by far the most commonly prescribed antihypertensive agent in the United States and worldwide.[4] This is not surprising since starting with Joint National Committee (JNC) I, every subsequent JNC advocated "thiazides" for the first-line therapy for hypertension by stating that thiazides should be preferred over other drugs because they had been shown to reduce morbidity and mortality.[3] The authors of the various JNCs thereby tacitly implied that thiazides were synonymous with hydrochlorothiazide. Before we continue to subscribe to such wisdom, we should consider the following simple facts:

1. Hydrochlorothiazide is one of the weakest antihypertensive agents available. In head-to-head comparison by 24-hour ambulatory monitoring, the antihypertensive efficacy was shown to be inferior to other drug classes, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and calcium channel blockers.[5] Moreover, hydrochlorothiazide's antihypertensive effect does not last 24 hours, thereby leaving the critical early morning hours unprotected.[5-7]
2. Hydrochlorothiazide in its usual dose of 12.5 to 25 mg per day has never been shown to reduce the risk of myocardial infarction, stroke, or death.[4] In fact, higher doses have been shown to increase the risk of sudden cardiac death in a dose-dependent fashion.[8]
3. Even in combination with an angiotensin-converting enzyme inhibitor, hydrochlorothiazide has been shown to be inferior to a calcium channel blocker, such as amlodipine. In the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension

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trial, despite identical blood pressure reduction, the amlodipine-based combination reduced cardiovascular events by 20% better than the hydrochlorothiazide combination, a fact that led to a premature termination of the study.[9]

4. All efficacy and outcome data for thiazides are solely derived from chlorthalidone and indapamide. Antihypertensive therapy based on both of these drugs have been shown repeatedly to decrease the risk of heart attack, stroke, heart failure, and even death in several prospective randomized trials, such as Systolic Hypertension in the Elderly Program, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), Hypertension in the Very Elderly Trial, and Perin-dopril Protection against Recurrent Stroke Study.[10-13] However, both of these drugs, chlorthalidone and indapamide, are distinctly different from hydrochlorothiazide and have been documented to exert pleiotropic effects that may account for their superior efficacy.[4,14]

CLINICAL SIGNIFICANCE

- Hydrochlorothiazide should be avoided, particularly as the first-line therapy for hypertension. When diuretics are used in hypertension, chlorthalidone or indapamide should be preferred.
- There is little if any evidence that blood pressure lowering by decreasing sympathetic activity translates into reduction of meaningful clinical outcomes in uncomplicated hypertension.
- Combination therapy with angiotensin-converting inhibitors has been demonstrated to reduce calcium channel blocker-induced peripheral edema.
- The optimal blood pressure targets for a wide range of hypertensive patients are still debated.

It is clear that hydrochlorothiazide should be avoided as the first-line therapy for hypertension. If a thiazide is deemed to be appropriate, our choice should be chlorthalidone or indapamide, as is stated in the British National Institute for Health and Clinical Excellence guidelines.[15]

MISCONCEPTION #2: THIAZIDES ARE NOT EFFECTIVE FOR HYPERTENSION IN ADVANCED RENAL DISEASE

Facts

Hypertension commonly begets chronic kidney disease and becomes increasingly difficult to treat as renal disease progresses. It is a common notion of many nephrologists that thiazide diuretics are ineffective antihypertensive agents in moderate to advanced renal disease.[16] Of note, the evidence base for this recommendation that was made into several guidelines is unknown. On the contrary, observational data and small randomized studies suggest that thiazide diuretics can result in meaningful blood pressure reduction in these patients (for review, see Agarwal and Sinha[16]). Most recently, in a small study of patients with chronic kidney disease (estimated glomerular filtration rate of 20-45 mL/min/1.73 m^2), Agarwal et al[17] added chlorthalidone to existing medications in a dose of 25 mg/day and doubled the dose every 4 weeks if the blood pressure remained elevated.[17] Twelve subjects completed the 12-week treatment period, and the 24-hour ambulatory blood pressure, which was 143.1/75.1 mm Hg at baseline, was reduced by 10.5/3.1 mm Hg ($P = .01/P = .17$). Adverse events, such as hypokalemia, hyperuricemia, hyponatremia, and transient creatinine elevations, were surprisingly common; clearly, patients should be closely monitored for these.[17]

MISCONCEPTION #3: ADRENERGIC ACTIVITY IS A MAJOR TARGET IN TREATING PRIMARY HYPERTENSION

Facts

This seemingly attractive statement is supported by the current understanding of basic physiology. Adrenergic activity has a major influence on both cardiac and vascular mechanisms of the blood pressure control.[18] Also, it is intimately related to other important hormonal and metabolic regulatory mechanisms, such as renin-angiotensin system, insulin resistance, glucose, and fat metabolism. Understandably, modulation of adrenergic activity was considered a seminal target for hypertension research for decades. Unfortunately, this resulted in rounds of frustration. Selective alpha1-adrenergic blocker doxazosin was studied in a large ALLHAT trial; the doxazosin arm was terminated prematurely because of a higher risk of heart failure.[19] No outcome data are available for centrally acting agents suppressing sympathetic activity, such as clonidine, and these drugs have significant adverse effects that make them unsuitable for common use. Beta-blockers were once considered a first-line therapy for primary hypertension, but their cardiovascular protective effect failed when used in uncomplicated hypertension.[20] Several meta-analyses showed that beta-blockers (atenolol being most commonly studied) confer lower protection against stroke and may be associated with higher all-cause mortality compared with other antihypertensive agents.[21] In addition, beta-blockers are associated with an increased risk of new-onset diabetes mellitus and may worsen glycemic control in patients with established diabetes.[22] Vasodilating beta-blockers, such as carvedilol and nebivolol, do not seem to carry adverse metabolic or hemodynamic effects, but so far no outcome data have been put forward in hypertension. Therefore, beta-blockers as a class should not be considered for initial therapy of hypertension unless another indication for their use is present. Finally, catheter-based radiofrequency