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HYPERTENSION: SYSTEMATIC APPROACH TO TREATMENT

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Annotation: Hypertension, also known as high blood pressure, is a long-term medical condition in which the blood pressure in the arteries is persistently elevated. High blood pressure usually does not cause symptoms. It is, however, a major risk factor for stroke, coronary artery disease, heart failure, atrial fibrillation, peripheral arterial disease, vision loss, chronic kidney disease, and dementia. Hypertension is a major cause of premature death worldwide.

Key words: Hypertension, isolated hypertension, antihypertensive drugs, chlorthalidone, doxazosin, ACE inhibitors, ARBs, beta blockers, CCBs.

Isolated hypertension

ISH has often been defined as a systolic blood pressure above 160 mmHg, with a diastolic blood pressure below 90 mmHg [6-8]. However, using definitions from the 2017 American College of Cardiology/American Heart Association Blood Pressure Guideline [2], a systolic pressure of 130 mmHg is the upper limit of normal at all ages.

ISH mostly occurs in older patients. Data from the Framingham Heart Study and the National Health and Nutrition Examination Survey (NHANES) have shown that the systolic pressure rises and the diastolic pressure falls after age 60 years in both normotensive and untreated hypertensive subjects [5] and that ISH accounts for 60 to 80 percent of cases of hypertension in older adults [3]. Furthermore, the systolic and pulse pressures appear to be the major predictors of coronary disease in older adults; in contrast, diastolic pressure is the major predictor under age 50 years, and all three indices were equal predictors between the ages of 50 and 59 years [2].

Meta-analysis — A 2000 meta-analysis included eight outcome trials of 15,693 patients ≥60 years of age with ISH (including SHEP, Syst-Eur, and MRC described below) [6]. At a median follow-up of 3.8 years, the number of patients who needed to be treated for five years to prevent one major cardiovascular event was 26. The number needed to be treated was lower in males (18 versus 38 in females [percent of patients benefitting 5.6 and 2.6 percent, respectively]), patients aged 70 or more years (19 versus 39 in patients under age 70 years [percent of patients benefitting 5.3 and 2.6 percent, respectively]), and those with previous cardiovascular events (16 versus 37 without such a history [percent of patients benefitting 6.3 and 2.6 percent, respectively]).

Total mortality correlated directly with systolic blood pressure at study entry, but inversely with diastolic blood pressure. However, the diastolic blood pressure was not significantly associated with outcome for combined fatal and nonfatal events.

These results underestimate the true benefit of effectively treating versus not treating ISH, as illustrated by findings in the SHEP trial described in the next section [5]. Only approximately 70 percent of treated patients reached goal blood pressure during the study, yet the outcomes of the nonresponders were included in the analysis. In addition, increases in blood pressure necessitated the institution of antihypertensive medications in 13 percent of placebo-treated patients at one year and 44 percent at five years.

The trials in the meta-analysis all had baseline mean systolic pressures of 160 mmHg or more [6]. In addition, these trials failed to achieve a systolic pressure less than 140 mmHg, although two trials with favorable outcomes attained a mean systolic pressure between 140 and 145 mmHg. No trials have been performed in patients with ISH with baseline systolic pressures of 140 to 159 mmHg [17].

Choice of antihypertensive drugs — The 2015 American Heart Association statement on the treatment of blood pressure in ischemic heart disease, the 2013 European Society of Hypertension/European Society of Cardiology guidelines on the management of hypertension, and meta-analyses from 2008 and 2009 concluded that the amount of blood pressure reduction is the major determinant of reduction in cardiovascular risk in both younger and older patients with hypertension, not the choice of antihypertensive drug [16,17,18]. When differences in outcomes have been noted, as in the ALLHAT trial, the drug producing better outcomes had better blood pressure control.

ALLHAT trial — The ALLHAT trial of over 41,000 patients with mild hypertension and at least one other risk factor for coronary heart disease found that low-to-moderate-dose chlorthalidone(12.5 to 25 mg/day) was associated with fewer cardiovascular complications than amlodipine and lisinopril [9]. A doxazosin arm was discontinued early because of a higher rate of adverse outcomes.

Approximately 57 percent of the patients were greater than 65 years of age. With respect to clinical outcomes at follow-up at nearly five years, the following results were reported in the patients 65 years and older:

The incidence of fatal coronary heart disease and nonfatal myocardial infarction (ie, the primary outcome) and all-cause mortality was the same for all three agents.

●A higher rate of heart failure was observed with amlodipine, compared with chlorthalidone (RR 1.33, 95% CI 1.18-1.49); the relative risk was similar to that in the entire ALLHAT population.

●Compared with chlorthalidone, lisinopril had significantly higher rates of combined cardiovascular disease outcomes (RR 1.13) ,combined coronary heart disease (RR 1.11), and heart failure (RR 1.20) . There was also a nonsignificant trend for a higher rate of stroke with lisinopril (RR 1.13, with a 95% CI 0.98-1.30). Each of these values was similar to those in the entire ALLHAT population.

Thus, all three antihypertensive agents were associated with the same cardiovascular and overall mortality and incidence of nonfatal myocardial infarction, a finding consistent with smaller comparative trials in older adults, such as STOP-Hypertension-2 [2]. The lower rates of some secondary outcomes with chlorthalidone in ALLHAT may have reflected at least in part lower attained blood pressures, rather than a specific drug benefit [2]. In addition, the superiority of chlorthalidone as compared with lisinopril in preventing certain secondary endpoints may have been due to the presence of a substantial number of Black participants who experienced inferior antihypertensive responses to lisinopril compared with chlorthalidone; chlorthalidone and lisinopril produced similar results in White participants [2].

Long-acting calcium channel blockers — Long-acting calcium channel blockers have proven efficacy and safety in older adult patients with hypertension, particularly those with ISH. This

has been demonstrated in a variety of clinical trials in older adult patients with hypertension, including ALLHAT [9], Syst-Eur trial [4], STOP Hypertension-2 [2], the Syst-China trial [3], and the ACCOMPLISH trial [6].

Angiotensin inhibition — In ALLHAT, the angiotensin-converting enzyme (ACE) inhibitor lisinopril produced, for certain cardiovascular endpoints, inferior outcomes compared with chlorthalidone at 12.5 to 25 mg daily, an effect that may have been due at least in part to greater blood pressure reduction with chlorthalidone [6]. In contrast, ACE inhibitors were associated with a lower rate of adverse cardiovascular events than thiazide diuretics at the same degree of blood pressure control in the Second Australian National Blood Pressure (ANBP2) trial of older adult patients with hypertension [8]. However, there are potentially important concerns about the design of this trial [9].

Many older adult hypertensive patients have a specific indication for an ACE inhibitor or angiotensin II receptor blocker (ARB), including heart failure, prior myocardial infarction, and proteinuric chronic kidney disease. (See appropriate topic reviews.)

Beta blockers — There is evidence that, in the absence of a specific indication for their use (eg, heart failure, myocardial infarction), beta blockers should not be considered for primary therapy of hypertension, particularly in older adult patients [9]. They may be worse than other agents for the prevention of stroke (particularly among smokers) and, perhaps with atenolol, death.

Summary of antihypertensive drug choice

For the treatment of hypertension with monotherapy, there is agreement from a 2008 meta-analysis and major society guidelines that, in the absence of a specific indication for use of a particular class of antihypertensive drugs (eg, ACE inhibitors and beta blockers for heart failure), it is the attained blood pressure, not the particular drug, that is the primary determinant of outcome with single-agent antihypertensive therapy [9,10].

In general, three classes of drugs are considered first-line therapy for the treatment of hypertension in older adult patients: low-to-moderate-dose thiazide diuretics (eg, 12.5 to 25 mg/day of chlorthalidone), long-acting calcium channel blockers (most often dihydropyridines), and ACE inhibitors or ARBs [10].

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