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Hypertension Guidelines: What is Expected to Change in 2006

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INTRODUCTION

Evidence-based medicine suggests that practice hypertension guidelines should be primarily based on the evidence from large outcome trials [1-5]. However, new data appear in the literature every day. In 2005 a total of 63,286 publications that included the keyword "hypertension" appeared in the MedLine, of which 2,484 were reports of clinical trials. Only few of these trials are expected to change current recommendations for the management of hypertension in clinical practice. This document presents several issues in the current hypertension guidelines that the author believes need to be modified mainly because of new information from recent clinical trials.

FIRST LINE ANTIHYPERTENSIVE DRUGS

There is general agreement between European and American guidelines regarding the choice of first line drugs in hypertension [1-2]. Diuretics, β -blockers, angiotensin converting enzyme (ACE) inhibitors, calcium antagonists and angiotensin receptor blockers are recommended as first line treatment in hypertension. The only difference between guidelines is that the US JNC-7 placed diuretics a small step ahead (to be administered in most of patients) [5]. In 2005, a metaanalysis of 13 randomized controlled outcome trials that included 105,951 patients, questioned the efficacy of β -blockers in preventing cardiovascular events and suggested that these drugs should be regarded as second line antihypertensive treatment [6]. This metaanalysis showed significantly lower efficacy of β -blockers compared to other drugs in preventing stroke. A previous metaanalysis also showed reduced cardiovascular protection with β -blockers in the elderly [7] and in the Canadian Hypertension Guidelines 2005 these drugs are not recommended as first line treatment in the elderly [3]. These data do not diminish the usefulness of β -blockers in their compelling indications, such as post myocardial infarction, in heart failure, angina, tachyarrhythmia, etc.

CHOICE OF ANTIHYPERTENSIVE DRUG TREATMENT AND NEW ONSET DIABETES

A series of outcome trials designed to compare the efficacy of several antihypertensive drug classes consistently showed that the incidence of new onset diabetes within 2-5 years is by 20-30% less common in subjects on treatment based on renin-angiotensin system blockers (ACE inhibitors or angiotensin receptor blockers) compared to other drugs [8-10]. The available evidence suggests that this difference is due to a

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protective effect of renin-angiotensin system blockers as well as a detrimental effect of the other drugs (β -blockers and diuretics). It should be taken into account that, in the majority of the trials, the protective effect of renin-angiotensin system blockers was evident even when these drugs were co-administered with low-dose diuretics [11].

These data suggest that in subjects at increased risk of diabetes development (pre-diabetics or with metabolic syndrome), treatment should be based on renin-angiotensin system blockers and other drugs might be added if needed to achieve optimal blood pressure control. In these subjects, the β -blocker-diuretic combination should be regarded as second line treatment, unless there is a compelling indication for the administration of these drugs.

COMBINATION THERAPY IN HYPERTENSION

Combination pharmacotherapy is essential for the optimal blood pressure control in most hypertensive patients. Scientific societies should develop clear guidelines regarding the use of two-drug and three-drug combinations, which are widely used in clinical practice. The role of the β -blocker-diuretic combination as first line combination therapy should be reconsidered (see “First line antihypertensive drugs” and “Choice of antihypertensive drug treatment and new onset diabetes”). Detailed recommendations are also needed for the role of fixed-dose combinations and for treatment initiation with drug combination. The American guidelines recommend treatment initiation with two drugs in subjects with stage-2 hypertension (blood pressure $\geq 160/100$ mmHg) and in those with blood pressure $>200/100$ mmHg above the recommended goal (e.g. subjects with diabetes and/or renal disease and blood pressure $\geq 150/90$ mmHg) [2]. The European guidelines also endorsed treatment initiation with combination, but gave a rather unclear indication, that is to be applied on the basis of the blood pressure level and total cardiovascular risk [1]. Treatment initiation with combination is being widely used in clinical practice well before it was recommended by Hypertension Societies. The European guidelines should provide a detailed proposal regarding this issue, as well as for the preference of low doses and the avoidance of overestimation of the blood pressure level that can lead to overtreatment.

FAST BLOOD PRESSURE CONTROL IN HIGH-RISK PATIENTS

The recent outcome trial VALUE [9], which was designed to compare the efficacy of an angiotensin receptor blocker (valsartan) with a calcium antagonist (amlodipine) in hypertensive patients with high total cardiovascular risk, showed

that the cardiovascular risk was significantly lower in subjects in whom blood pressure was effectively controlled within the first 6 months, compared to those not controlled. Interestingly, this benefit was independent of the drug class (valsartan or amlodipine). It should be noted, however, that the majority of patients in the VALUE trial were treated before the study, and treatment was withdrawn for study entry. Therefore, this study does not directly address the issue of the significance of fast blood pressure control, but rather the importance of retaining steady and effective control.

These data suggest that, specifically in hypertensive patients at high cardiovascular risk, blood pressure control should be achieved without delay and blood pressure should remain at optimal levels. Treatment initiation with two drugs should be considered in these patients, particularly if blood pressure is $>200/100$ mmHg above the recommended goal (see “Combination therapy in hypertension”). However, when blood pressure is close to the target, treatment should be carefully titrated to prevent symptomatic overtreatment.

STATINS IN HYPERTENSIVE SUBJECTS WITH MULTIPLE CARDIOVASCULAR RISK FACTORS

In the ASCOT-LLA outcome trial [12] 10,305 hypertensive subjects with no history of coronary heart disease, total cholesterol ≤ 250 mg/dl, triglycerides ≤ 400 mg/dl and 3 additional cardiovascular risk factors (age ≥ 55 years, male sex, type 2 diabetes, family history of premature coronary heart disease, left ventricular hypertrophy, peripheral artery disease, microalbuminuria or proteinuria, history of stroke or transient ischemic attack) were randomized to treatment with a statin (atorvastatin 10 mg) or placebo. The study was discontinued after 3.5 years of follow-up (before its prescheduled end) because of a statistically significant and clinically important benefit in the atorvastatin arm (reduction in coronary as well as stroke events by about 30%) [12]. Interestingly, this benefit appeared early and was independent of cholesterol levels at baseline. In addition, there was a positive interaction of atorvastatin, regarding the cardiovascular protection, with amlodipine but not atenolol (patients were also randomized to antihypertensive treatment based on amlodipine or atenolol) [10].

In 2005 the Canadian Society of Hypertension translated the ASCOT-LLA study findings into practice guidelines [3]. In the strategy for global vascular protection, recommendations are given for the use of (a) aspirin in hypertensive subjects with controlled blood pressure and (b) statin in certain non-hyperlipidemic hypertensive subjects with established atherosclerotic disease or with 3 additional cardiovascular risk factors as mentioned above.

MASKED HYPERTENSION

The term “masked hypertension” has been recently introduced to describe subjects with normal blood pressure in the clinic but elevated home or ambulatory blood pressure, namely hypertension that is hidden until out-of-office blood pressure is assessed [14]. Studies have shown that subjects with masked hypertension have similar left ventricular mass and carotid wall thickness as the untreated hypertensives [15]. The recent outcome study SHEAF in 4,939 treated elderly hypertensives in France showed that masked hypertensives (diagnosed on the basis of office and home blood pressure measurements) have the same risk for cardiovascular disease as the untreated hypertensives [16].

These data suggest that in subjects with masked hypertension the decision to treat and the achievement of blood pressure control should be primarily based on out-of-office blood pressure measurements (at home or with ambulatory monitoring). As is the case for the phenomenon of “isolated office” or “white coat” hypertension, where again management decisions are based primarily on out-of-office blood pressure measurement, necessary prerequisites are (a) reliable assessment of out-of-office blood pressure (accurate device, appropriate measurement conditions, correct measurement technique) and (b) confirmation of elevated out-of-office blood pressure after a few weeks or months by using the same or the alternative measurement technique (home or ambulatory blood pressure monitoring).

HOME BLOOD PRESSURE MONITORING

The phenomena of “masked hypertension” and “isolated office” or “white coat” hypertension are observed in about 30% of subjects attending an outpatient clinic or office for elevated blood pressure [14]. For the evaluation of these cases the assessment of out-of-office blood pressure is essential. Home blood pressure monitoring is widely available, cheap and well accepted by patients [17]. Therefore, it is a valuable and cost-effective technique for the evaluation of both “white coat” and “masked hypertension” [17].

The European Society of Hypertension Guidelines endorse the application of home blood pressure monitoring in clinical practice and recommend the use of reliable electronic devices that measure blood pressure at the arm (not the wrist) [14]. Given the need for complementary assessment of blood pressure with out-of-office measurements in many patients, hypertension guidelines should provide clear and detailed recommendations regarding the few accurate devices for home blood pressure monitoring available on the market (for list see www.dableducational.org [18] and www.hypertension.gr), as well as the optimal home blood pressure monitoring schedule

for decision making (duplicate morning and evening measurements for 7 work days) and for long-term follow up (one measurement per week) [14,17].

BLOOD PRESSURE GOAL

The recent hypertension guidelines recommend a blood pressure goal of <140/90 mmHg to be reached in all hypertensive subjects irrespective of their age, and <130/80 mmHg in those with diabetes and/or renal damage [1-5]. Recent studies in patients with established coronary heart disease treated with calcium antagonists [19] or ACE inhibitors [20] and in subjects with a history of stroke treated with an ACE inhibitor and a diuretic [21] showed that aggressive blood pressure reduction at levels well below the conventional 140/90 mmHg goal is associated with significant additional cardiovascular protection.

Although the abovementioned studies were not designed to define the optimal blood pressure goal in these patients, they suggest that, when the total cardiovascular risk is high, the blood pressure goal should be <130/80 mmHg or lower, and it does not really matter whether the high risk is due to diabetes, renal damage, cardiovascular disease, or coexistence of multiple cardiovascular risk factors. The 2003 European Society of Hypertension guidelines recommend in high risk subjects early initiation of antihypertensive drug treatment at blood pressure levels >130/85 mmHg. Blood pressure goal in all high risk hypertensives should be <130/80 mmHg.

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