

**EDITORIAL**

## Current Guidelines for Hypertension: Important Highlights for Clinical Practice

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inhibitor; angiotensin receptor blocker;  
 $\beta$ -blockers; calcium channel blockers*

**LIST OF ABBREVIATIONS:**

ACEI = angiotensin-converting enzyme  
inhibitors

ADA = American Diabetes Association

AHA = American Heart Association

ARB = angiotensin receptor blockers

CCB = calcium channel blockers

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**ABSTRACT**

In 2007 the European Society of Hypertension, the American Heart Association and the International Society of Hypertension-World Health Organization published new guidelines for the management of hypertension. According to these new guidelines, drug treatment is recommended in all subjects with consistent elevation of blood pressure above 140 mmHg systolic and/or 90 mmHg diastolic. In high-risk subjects, treatment initiation is indicated in lower blood pressure levels (systolic above 130 mmHg and/or diastolic above 85 mmHg). The higher the blood pressure level the sooner the treatment is commenced, with emphasis being placed on the critical role of combination pharmacotherapy in order to achieve optimal blood pressure control. The implementation of the new guidelines is expected to achieve more effective cardiovascular protection in hypertensive patients.

**INTRODUCTION**

In 2007 the European Society of Hypertension, the American Heart Association and the International Society of Hypertension-World Health Organization published new guidelines for the management of hypertension.<sup>1-3</sup> The need of developing new guidelines for hypertension is due to recently published research data suggesting important modifications in the diagnostic and therapeutic strategies in clinical practice. The implementation of the new guidelines is expected to achieve more effective cardiovascular protection in hypertensive patients.

**TOTAL CARDIOVASCULAR RISK ASSESSMENT IN DECISION  
MAKING**

The European as well as the American guidelines of 2007 in general proposed more aggressive approaches compared to previous guidelines, regarding treatment initiation and also blood pressure goals.<sup>1-3</sup> In both guidelines the intervention strategy is decided on the basis of total cardiovascular risk assessment. High risk hypertensive patients are regarded as those with (a) stage III hypertension, (b) asymptomatic target organ damage (left ventricular hypertrophy, microalbuminuria, atherosclerosis of carotid arteries), (c) diabetes mellitus, (d) at least three additional cardiovascular risk factors (e.g. metabolic syndrome), or (e) established cardiovascular disease (coronary heart

disease, stroke or transient ischemic attack, renal insufficiency or proteinuria, intermittent claudication, aortic aneurysm).

#### TREATMENT INITIATION

According to the new guidelines, drug treatment is recommended in all subjects with consistent elevation of blood pressure above 140 mmHg systolic and/or 90 mmHg diastolic. In all subjects with high total cardiovascular risk, treatment initiation is indicated in lower blood pressure levels (systolic above 130 mmHg and/or diastolic above 85 mmHg). The higher the blood pressure level the shorter should be the duration of observation before treatment initiation. In high-risk hypertensives prompt drug treatment initiation is recommended, whereas in those at low risk a period of observation by applying non-pharmacological measures (lifestyle modification) for up to 1-12 months (according to the level of total risk) might be allowed.

#### BLOOD PRESSURE GOAL

In hypertensive subjects with low total cardiovascular risk, the goal of treatment is to reduce office blood pressure below 140 mmHg systolic and 90 mmHg diastolic and even lower if treatment is well tolerated (as it is the case in most patients). In all high-risk hypertensives the goal of treatment is lower (systolic below 130 mmHg and diastolic 80 mmHg). Reaching optimal blood pressure control is essential in order to achieve effective protection from cardiovascular events. Inadequate blood pressure control is associated with lesser cardiovascular protection.

#### FIRST LINE ANTIHYPERTENSIVE DRUGS

The primary criterion for choosing antihypertensive drugs is their proven ability to prevent cardiovascular morbidity and mortality in large outcome trials. In the recent American, International and British hypertension guidelines four classes of drugs are recommended as first line treatment of hypertension: thiazide diuretics, angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs).<sup>2-4</sup>

Traditional cardiovascular drugs such as beta-blockers are no longer recommended as first line treatment in hypertension, unless there is a specific indication (e.g. myocardial infarction or heart failure). The European guidelines made a more conservative statement for beta-blockers focusing on the negative metabolic effects of these drugs.<sup>1</sup> According to the European guidelines beta-blockers remain a first line choice for the treatment of hypertension. However, these drugs, and particularly their combination with diuretics, should be avoided in hypertensive patients with metabolic syndrome or with high risk of developing diabetes mellitus, unless there is a specific indication for their use.

#### COMBINATION ANTIHYPERTENSIVE PHARMACOTHERAPY

Using antihypertensive drug monotherapy the recommended blood pressure goals can be reached in fewer than 50% of hypertensive patients. In most cases combination of 2-3 and often more drugs is needed. This is particularly true in high-risk hypertensives, who have more difficulty to control hypertension and also lower treatment target.

In the new guidelines emphasis has been placed in the critical role of combination pharmacotherapy in order to achieve optimal blood pressure control. The rationale for combining drugs is to achieve larger reduction in blood pressure. The additional antihypertensive effect is larger for some drug combinations and weaker for others. Combination of drugs with different and complementary mechanisms of action provide strong synergistic blood pressure lowering effect (e.g. renin angiotensin system blockers combined with diuretics or CCBs). On the other hand, drugs sharing common mechanisms of action provide smaller additional blood pressure lowering effect (e.g. ACEIs combined with ARBs or beta-blockers). However, the primary criterion for choosing drug combinations should be their proven ability to provide long-term cardiovascular protection.

An additional benefit obtained by the appropriate selection of antihypertensive drug combinations is the potential to reduce the incidence of adverse effects of the drugs. In other words, the addition of a second drug might reduce the adverse effects of the first one, or the reverse. For example, ACEIs and ARBs reduced the incidence of hypokalemia induced by diuretics and also the ankle edema induced by CCBs. In addition, beta-blockers attenuate the tachycardia induced by dihydropyridine CCBs and diuretics attenuate the counterregulatory sodium retention induced by all vasodilatory drugs.

In most cases treatment initiation with monotherapy is indicated. According to the American and the European hypertension guidelines, treatment initiation with a combination of two drugs should be considered when there is a consistent rise in blood pressure of more than 20 mmHg systolic and/or 10 mmHg diastolic above the recommended goal, particularly in subjects with high total cardiovascular risk.

The use of fixed-dose combinations is a very popular therapy in hypertension. Many fixed-dose combinations of ACEIs or ARBs with thiazide diuretics (mostly hydrochlorothiazide) are available and widely used. Apart from the strong additive antihypertensive effect provided by these combinations, it should be remembered that the vast majority of the outcome trials that assessed the efficacy of ACEIs and ARBs in improving prognosis have used these drugs in combination with thiazide diuretics. The combination of CCBs with thiazide diuretics also gives strong additional antihypertensive effect and is an evidence-based choice on the basis of an outcome study data (VALUE).<sup>5</sup> On the other hand, the combination of a beta-blocker with a thiazide diuretic should be avoided if

possible, particularly in subjects at increased risk of diabetes development.

In the 2007 guidelines of the American Heart Association (AHA) - American Diabetes Association (ADA) for the management of hypertension in diabetic patients and the 2007 guidelines of the US National Kidney Foundation KDOQI Clinical Practice Guidelines for the management of diabetic hypertensives with renal damage, it is recommended that antihypertensive drug treatment should be initiated with ACEIs or ARBs with the addition of a diuretic as a second drug in most cases.<sup>6-8</sup>

The first fixed-dose combination of an ARB with a CCB has recently become available on the market and several similar combinations are expected to follow in the future. This combination also offers strong additional antihypertensive effect and has a potential metabolic advantage compared to diuretic based combinations, particularly in subjects with pre-diabetes or metabolic syndrome.<sup>9,10</sup> An outcome study (ACCOMPLISH) providing a direct comparison of a combination of an ACEI with a dihydropyridine CCB versus an ACEI-diuretic combination in high risk hypertensives is expected to report its final results in 2008.<sup>11</sup>

The combination of an ACEI with an ARB remains controversial. This combination provides substantial additional antihypertensive effect, but lower than that obtained when each of these drugs is combined with a thiazide diuretic or a CCB. The long-term cardiovascular effects of this combination are still under investigation. There is evidence that this combination provides significant additional antiproteinuric effect in patients with diabetic or non-diabetic nephropathy and proteinuria. Furthermore, outcome studies in heart failure showed additional cardiovascular protection with this combination compared with ACEIs alone. On the other hand, one large outcome study in subjects post-myocardial infarction with heart failure showed no additional benefit with the ACEI-ARB combination compared to each of the monotherapies. The use of this combination in patients with heart failure requires close monitoring of blood pressure, serum creatinine and potassium. A large outcome study (ONTARGET) comparing an ACEI (ramipril) (n= 8576) with an ARB (telmisartan) (n=8542) and their combination (n=8502) in the prevention of cardiovascular events in high risk patients was just published.<sup>12,13</sup> It reported that the ARB was equivalent to the ACEI in patients with vascular disease or high risk diabetes and was associated with less angioedema. The combination of the two drugs was associated with more adverse events without an increase in benefit.

In a substantial proportion of hypertensive patients, the recommended blood pressure goal is not achieved despite the use of two drugs. The most popular triple combination is a renin-angiotensin blocker with a thiazide diuretic and a CCB.<sup>14</sup> In most cases triple antihypertensive drug therapy can be administered altogether in the morning, provided that long-

acting drugs with full 24-hour coverage are used. If needed, more drugs might be added, with preference in first line drugs, often at higher than usual dosing and some of the drugs might be administered before night-time sleep. Patients with resistant hypertension should be referred to a special hypertension clinic for further investigation and management.

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