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Strengthening and Updating European Guidelines for the Management of Arterial Hypertension

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The joint European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines for the management of hypertension were published in 2003,^[1] and have since become the most frequently cited publication in the medical literature. Since 2003, however, a range of new evidence has emerged from clinical trials and other studies about the treatment of hypertension, and the guidelines are currently being updated by a working group co-chaired by Prof. Mancia, on behalf of the ESH, and Prof. Guy G. de Backer, MD, PhD (University Hospital, Ghent, Belgium), on behalf of the ESC. They hope that the new guidelines will be available sometime in 2007.

Speaking at a session on hypertension guidelines held jointly with the American Society of Hypertension on June 13,^[2] Prof. Mancia stressed that the European guidelines will not just be updated but will also be strengthened by new evidence supporting recommendations already in the previous edition. Since final decisions about the new guidelines have yet to be made, Prof. Mancia outlined the areas that he believes should be discussed and what, in his personal opinion, should be confirmed or modified for the next publication based on new data published since 2003. These cover 4 main areas: 2 that should be reinforced because what was originally in the guidelines was correct and 2 that may lead to changes.

Strengthening by Additional Evidence

Blood Pressure Control (< 140/90 mm Hg)

Prof. Mancia believes that there is increasing evidence that the benefit associated with antihypertensive therapy is in large part due to blood pressure lowering per se and that lowering the blood pressure to < 140/90 mm Hg is protective for the patient, regardless of the type of antihypertensive agent given. Evidence for the correlation between the magnitude of blood pressure reduction and the rate of cardiovascular morbidity and mortality and stroke comes from the 2003 report from the Blood Pressure Lowering Treatment Trialists' Collaboration,^[3] which showed that when blood pressure was reduced to < 140/90 mm Hg, cardiovascular disease and events were also reduced. The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial showed that patients whose blood pressure was controlled to < 140/90 mm Hg had much less cardiovascular disease and fewer events than patients whose blood pressure remained uncontrolled.^[4]

Lower Blood Pressure Target in High-Risk Patients

Increasing evidence shows that in high-risk patients, the blood pressure target should be lower, maybe even lower than 130/80 mm Hg, Prof. Mancia believes. Recent evidence comes from a retrospective analysis of the incidence of congestive heart failure (CHF) in the patients in the Irbesartan Diabetic Nephropathy Trial (IDNT), in which the incidence of CHF in high-risk hypertensive patients was at a minimum in patients with blood pressure < 130/90 mm Hg.^[5] Prof.

Mancia anticipates that the recommendation that target blood pressure should be < 140/90 mm Hg, or < 130 mm Hg systolic blood pressure (SBP) in high-risk patients, will be reinforced in the new guidelines.

Combination Treatment as First Choice

Another thing the guidelines will confirm is the importance of combination treatment, Prof. Mancia predicted. Further evidence in support of this approach has come from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), in which about 90% of patients, all high-risk, had to be on combination treatment to achieve the specified blood pressure control targets.^[6] The 2003 recommendation to consider combination treatment as an alternative to monotherapy as an initial treatment strategy in patients with high untreated blood pressure or who are at high risk will be reinforced. Additional evidence has come from the VALUE study,^[7] in which patients randomized to amlodipine achieved 4 mm Hg lower blood pressure levels than patients on valsartan during the first 6 months of the study -- and as a result had fewer cardiovascular events, Prof. Mancia pointed out.

Total Cardiovascular Risk

The 2003 guidelines contained a "strong element of novelty," ie, the need to look at total cardiovascular risk and modulate treatment strategies accordingly, Prof. Mancia recalled. In order to assess cardiovascular risk properly, it is necessary to consider subclinical organ damage, which has prognostic significance, although it is not always obvious, he advised. New evidence has shown the importance for prognosis of changes in organ damage induced by treatment. Several studies, including the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study,^[8] have shown that regression of left ventricular hypertrophy (LVH) and reduction of urinary protein excretion with antihypertensive treatment are associated with decreased cardiovascular morbidity and mortality. So it is important to measure changes in organ damage induced by treatment, and physicians "can have faith that when this happens there is a greater chance of patients being protected in the long term."

A lot of ongoing research is looking at improving assessment of cardiovascular risk based on new measures of risk factors/markers, Prof. Mancia said. Some additional measures of organ damage have prognostic significance, but whether they can be practically used in the clinic is still open to question. Some are expensive to do and some, such as liver function tests, are both difficult and time consuming. However, there are 2 areas for which evidence is growing: the importance of home and ambulatory blood pressure measurements as a marker of cardiovascular risk, and the importance of multiple measures of organ damage. The new guidelines will be quite clear that we should not be satisfied at looking at damage in one organ, Prof. Mancia predicted.

Changes to be Considered

Diuretics and Beta-blockers

There is no longer any room for considering diuretics as a main first-choice treatment for hypertension, according to Prof. Mancia. However, the position of beta-blockers remains open to discussion -- certainly they have not lost their status, he said. Meta-analyses and some studies such as ASCOT have shown that beta-blockers may do worse than other drugs in protecting hypertensive patients, and a number of people consider this as evidence that beta-blockers are less effective than other antihypertensive drugs. Prof. Mancia voiced caution about this, however; in other studies, beta-blockers "did not do so badly," he pointed out. For example, in the International Verapamil SR-Trandolapril Study (INVEST) study in patients with hypertension and coronary artery disease (CAD), the outcome was the same, regardless of which drug the patients started treatment on.^[9] So there may be patients and conditions such as CAD where beta-blockers maintain their importance.

Calcium Channel Blockers

There have also been selective reports expressing both encouraging and discouraging views about certain drugs, according to Prof. Mancia. Calcium channel blocker (CCBs) have been reported to be ineffective in hypertension, in CAD patients, and for prevention of CAD/coronary heart disease -- but based on recent evidence, Prof. Mancia does not agree with this. A meta-analysis of blood pressure trials in diabetic and nondiabetic patients^[10] showed no difference in outcomes with

different antihypertensive drug classes, he said. The VALUE results suggested that the CCB was slightly better than the angiotensin receptor blocker (ARB) against the incidence of fatal and nonfatal myocardial infarction (MI),^[7] and although Prof. Mancia does not believe this is true, "it certainly rules out the fact that these drugs cannot be given in hypertension," he concluded. "Given the importance of combination treatment, this is good news," he stated.

There has also been some evidence that CCBs may be less effective for prevention of CHF, Prof. Mancia noted, but again there is evidence from a clinical trial -- A Coronary disease Trial investigating Outcome with Nifedipine GITS (ACTION) study^[11] -- in which patients, many of whom had angina, had a 38% reduction in new-onset heart failure with the CCB. "So at least we know that when blood pressure is reduced, even by a CCB, this is a good measure to prevent CHF," said Prof. Mancia.

ACE Inhibitors and ARBs

Some of the new evidence about angiotensin converting enzyme (ACE) inhibitors and ARBs is anecdotal and need not be considered, Prof. Mancia stressed. For example, "it is simply not true" that ARBs are associated with increased risk of MI, he said. Other positive, scientifically based evidence is available on other conditions, however. Thus, ARBs may have specific protective properties as both primary and secondary prevention against stroke. Four studies have been published about this since the 2003 guidelines, 2 (LIFE^[12,13] and MOSES^[14]) positive, and 2 (SCOPE^[15] and ACCESS^[16]) not positive. "We will have to balance the evidence," said Prof. Mancia, adding that it is extremely important that both aspects should be considered.

Evidence mainly from IDNT and VALUE showed the advantage of ARBs in the prevention of CHF. IDNT also showed both primary and secondary prevention of atrial fibrillation with an ARB.^[17] A recent meta-analysis showed a 28% reduction in risk of atrial fibrillation with both ACE inhibitors and ARBs,^[18] and with the growing incidence of using drugs acting against the renin-angiotensin system in this setting, it will be extremely important in the future to identify the mechanisms for this apparently clear effect, Prof. Mancia noted.

Metabolic Syndrome

The new guidelines will feature greater consideration for metabolic changes associated with antihypertensive treatment, Prof. Mancia predicted. There is no question that patients with the metabolic syndrome do much worse than patients who do not have it, Prof. Mancia stressed. Current ESH/ESC and other guidelines recommend that patients considered at high risk are candidates for treatment, even patients with blood pressure in the high normal range.

The metabolic syndrome is a high risk condition, involving ≥ 3 risk factors, very often end organ damage, and diabetes. An analysis of the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study cohort after 10 years by Prof. Mancia and colleagues showed that patients with the metabolic syndrome had a 5.5-fold higher risk of diabetes, 2-fold higher risk of new hypertension, and a 2.5-fold higher risk of echocardiographically confirmed LVH compared with patients who did not have the metabolic syndrome.^[19] If antihypertensive drug treatment in these patients is supposed to treat all these conditions, then diuretics and beta-blockers are not good candidates in these patients, Prof. Mancia noted.

New-onset diabetes is less common when patients are treated with ACE inhibitors, ARBs, or CCBs, compared with diuretics or beta-blockers, he noted. There is also a wide body of evidence that CCBs, ACE inhibitors, and ARBs are better than diuretics or beta-blockers at preventing and causing regression of various types of end organ damage. Prof. Mancia suggested that one option may be to be more interventionist and recommend avoidance of diuretics and beta-blockers in patients with the metabolic syndrome.

Beyond Guidelines

Guidelines should go beyond scientific evidence, he stressed. Blood pressure control to $< 140/90$ mm Hg are still poor in common clinical practice, and in addition, recent data have shown that, even on treatment, blood pressure remains high ($> 180/100$ mm Hg) for 22% to 44% of hypertensive patients. To address this problem, a new international initiative, the Hypertension Task Force, has been launched with the aim of devising the best possible strategies to increase the number of patients who achieve blood pressure control. The task force had its first meeting in May 2006 in New York, with many international, American, Asian, and European hypertension and nephrology

societies participating. It will target clinicians, nurses, and other healthcare professionals and call for partnerships between healthcare providers, national and international societies, foundations, and governments. A statement is in development.

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