SPECIAL ARTICLE

2003 Update of the Guidelines of the Spanish Society of Cardiology on High Blood Pressure

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Since publication of the Spanish Society of Cardiology Clinical Practice Guidelines on High Blood Pressure in January 2000, a new body of scientific evidence has been obtained that needs to be taken into account in clinical practice. A complete clinical evaluation by assessment of the global cardiovascular risk score should be done in patients with hypertension. In this connection, ECG findings and urine albumin excretion are of particular value. Up to now, the results of most important clinical trials indicate that the aim should be to normalize blood pressure, with stricter control in patients at higher risk (diabetes, target organ damage or left ventricular hypertrophy). Antihypertensive therapy should be selected on an individual basis, taking in account that patients with certain associated pathologies will benefit more from particular groups of drugs. Those with diabetes or left ventricular hypertrophy seem to benefit from pharmacological block of the renin-angiotensin system, and patients with heart failure from combined therapy with ACE inhibitors plus beta-blockers.

Key words: *High Blood Pressure. Cardiovascular risk. Treatment update.*

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Actualización (2003) de las Guías de Práctica Clínica de la Sociedad Española de Cardiología en hipertensión arterial

Desde la elaboración de las guías de práctica clínica en hipertensión arterial en enero del año 2000 se han producido nuevas evidencias científicas que hay que tener en cuenta en el ámbito de la práctica clínica. Es necesario realizar la evaluación clínica del hipertenso mediante la estratificación de su riesgo cardiovascular global, en la que los datos aportados por el electrocardiograma (ECG) y el análisis de orina (detección de excreción urinaria de albúmina) son de especial relevancia. Hasta la actualidad, los resultados de múltiples estudios disponibles indican que en la hipertensión arterial lo más importante es normalizar los valores de la presión arterial, con un control más estricto en los hipertensos de mayor riesgo (diabéticos, lesión de órgano diana y enfermedad cardiovascular asociada). La individualización del tratamiento constituye la base de la elección de fármacos antihipertensivos. Sin embargo, debe tenerse en cuenta que los hipertensos con ciertas enfermedades asociadas obtienen un mayor beneficio de determinados grupos farmacológicos. Los hipertensos diabéticos o con hipertrofia ventricular izquierda parecen beneficiarse del bloqueo farmacológico del sistema renina-angiotensina y los pacientes con insuficiencia cardíaca deben recibir tratamiento combinado con inhibidores de la enzima de conversión de la angiotensina (IECA) y bloqueadores beta.

Palabras clave: *Hipertensión arterial. Riesgo cardiovascular. Actualización del tratamiento.*

INTRODUCTION

Control of hypertension represents a mainstay of cardiovascular disease prevention. Nevertheless, it is still not adequate in either primary or secondary prevention, as shown by the results of the CARDIOTENS study, in which fewer than 20% of patients with hypertension and associated coronary heart disease actually complied with blood pressure control measures.[1]

This update incorporates those recommendations for patients with hypertension and associated cardiovascular disease published since the last guidelines appeared in REVISTA ESPAÑOLA DE CARDIOLOGÍA in January 2000.[2] Some sections have been enhanced, in which case the relevant page is indicated, and new sections have been included discussing aspects which were not then envisaged. Although none of the original para-

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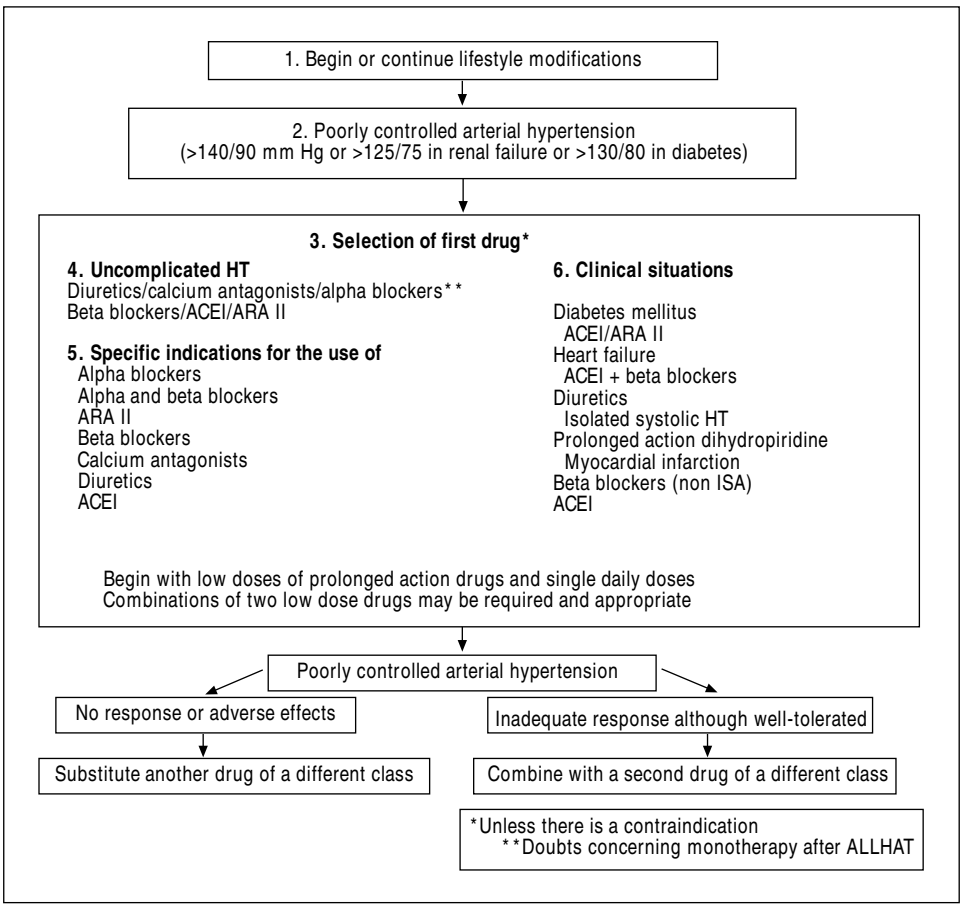

Fig. 1b. Treatment scheme for hypertension based on the recommendations of the VI JNC Report.
HT indicates hypertension; ACE, angiotensin converting enzyme; ARA II, angiotensin receptor antagonists; ISA: intrinsic sympathomimetic activity.

graphs have been withdrawn, the new text can sometimes be understood to replace the old. Finally, Tables 5 and 7 have been modified; the latter now includes the original Table 14 which has been deleted, and a Table (2b) and a Figure (1b) have been added.

DEFINITION AND CLASSIFICATION OF HYPERTENSION

Diagnosis of hypertension (page 67) (new text)

It should be remembered that many people have a transitory increase in blood pressure. This phenomenon, referred to as "alerting reaction" or "white coat syndrome", is less common when blood pressure measurements are taken by nursing staff, and values tend to become less pronounced in successive measurements.[3] The clinical and therapeutic implications of this phenomenon are important, as 20%-25% of patients with apparent hypertension in the office are estimated to have an alerting reaction. Therefore, it is necessary to reduce this proportion by using the correct methodology to measure blood pressure.[4]

It has recently been proposed that a home blood pressure of 125/80 mm Hg is equivalent to an office pressure of 130/85 mm Hg (upper limit of normal) and a home measurement of 115/75 mm Hg corresponds to 120/80 mm Hg in the office (optimal blood pressure level).[5] The last International Consensus Conference on ambulatory blood pressure monitoring proposed a lower value than normal for daytime measurements (<130/80 mm Hg).[6]

Complementary tests (page 68) (new text)

Measurements

Whenever feasible microalbuminuria should be measured in any patient with hypertension, especially if the patient has diabetes mellitus.

An electrocardiogram (ECG) should be included in the strategy for clinical evaluation of a patient with hypertension. The information it provides is important for both clinical follow-up and for risk stratification: presence of criteria suggestive of left ventricular hypertrophy, rhythm disorders (atrial fibrillation) and conduction (atrioventricular block, left bundle branch block) and signs suggestive of ischemic cardiopathy (changes in the ST-T segment). Patients with hypertension who experience a QRS voltage reduction during follow up, or in whom baseline signs of left ventricu-

TABLE 2b. **Criteria for left ventricular hypertrophy**

Criteria	ECG findings
Sokolow-Lyon	S (V1)+R(V5-6)>3.5 mV
Wilson	S (V1)≥2.4 mV
Romhilt-Estes	≥5 points
Gubner	R(I)+S(III)≥2.5 mV
Cornell	R (aVL)+S (V3)>2.8 mV (V) or 2.0 (M)
Perugia	Romhilt≥5 or overload VI or Cornell≥2.4 mV (V) or 2.0 (M)

Modified by Schillaci et al.[58] M indicates male, F, female; LV, left ventricle.

lar hypertrophy are either not present or disappear, have a better prognosis.[7,8] Table 2b shows the most common electrocardiographic criteria for left ventricular hypertrophy in daily clinical practice.

Consideration of all these factors will determine the individual prognosis for each patient, as well as the risk stratification and the therapeutic attitude, as specified in Table 5 (modified).

PHARMACOLOGICAL TREATMENT OF HYPERTENSION

Choice of initial treatment (page 72) (new text)

Several studies have demonstrated the benefit of treating hypertension, in terms of reduced cardiovascular and renal disease and mortality. However, new evidence has recently come to light which may in some cases necessitate modification of the therapeutic strategy. A meta-analysis of 17 studies examining treatment of hypertension in a total of 47 653 patients illustrated the benefit of reducing blood pressure. A mean reduction in systolic blood pressure of 10-12 mm Hg and in diastolic blood pressure of 5-6 mm Hg, compared to controls, reduced the incidence of cerebrovascular accidents by 38%, myocardial infarction by 16% and cardiovascular mortality by 21%. The reduction in the risk of stroke was apparent after only a few years´ therapy, whereas the reduction in the risk of coronary heart disease required more prolonged treatment.[9] It is of note that this benefit was independent of initial blood pressure levels and of the type of anti-hypertensive agent used. Moreover, the true benefit of treatment might have been underestimated due to the short follow-up period, which in no study was longer than 5 years.

Another very recent meta-analysis of 61 prospective observational studies, which included a million subjects with no prior cardiovascular disease at baseline, confirmed that in persons more than 40 years of age blood pressure figures, both systolic and diastolic, are directly related to vascular and overall mortality, with no evidence of a lower limit, at least to 115/75 mm Hg. This indicates that increases in blood pressure levels, even if they are within the normal range, may increase the risk of cardiovascular death in middle-aged and older patients, with no evidence of a safety threshold, at least to very low blood pressure figures.[10]

The benefit of treating hypertension can be seen in patients of all ages. The STOP study demonstrated that a therapeutic strategy based on diuretics and beta blockers for 25 months in patients 70-84 years of age was accompanied by a 38% reduction in risk of fatal and non-fatal stroke and myocardial infarction and, specifically, a 45% reduction in morbidity and mortality due to stroke. The reduction in mortality was 43%, thus highlighting the importance of adequate blood pressure control in the elderly. In absolute terms, treatment of elderly patients with hypertension prevents more cardiovascular complications than similar treatment in younger patients.[11]

TABLE 5. **Stratification of the risk and treatment** (modified)

	A	B	C	D
Blood pressure, mmHg	No RF/No TOI no CVD	1-2 RF/no TOI no CVD	3 RF/DM with TOI	With CVD
BP normal-high (130-139/85-89)	Low risk/Lifestyle modification	Low risk/Lifestyle modification	High risk/ Drug therapy	Very high risk/ Drug therapy
HT slight (140-159/90-99) grade 1	Low risk/Lifestyle modification	Medium risk/Lifestyle modification	High risk/ Drug therapy	Very high risk/ Drug therapy
HT moderate (160-179/100-109) grade 2	Medium risk/ Drug therapy	High risk/ Drug therapy	Very high risk/ Drug therapy	Very high risk/ Drug therapy
HT severe (≥180 or ≥110) grade 3	High risk/ Drug therapy	High risk/ Drug therapy	Very high risk/ Drug therapy	Very high risk/ Drug therapy

RF indicates risk factor; TOI, target organ involvement (left ventricular hypertrophy, microalbuminuria, hypertensive retinopathy); DM, diabetes mellitus; CVD, cardiovascular disease (ischemic heart disease, cardiac insufficiency, chronic atrial fibrillation, cerebrovascular disease and aortic and peripheral vessel disease); BP, blood pressure; HT, hypertension. Low risk: <15% severe cardiovascular episodes in 10 years. Medium risk: 15%-20% severe cardiovascular episodes in 10 years. High risk: 20%-30% severe cardiovascular episodes in 10 years. Very high risk: >30% severe cardiovascular episodes in 10 years.

TABLE 7. **Indications for specific treatment** (modified)

	Indication I Evidence efficacy	Indication IIa In favor of efficacy	Indication IIb Relative contraindication	Indication III Contraindication inefficacy
Diuretics	Heart failure Isolated systolic HT Elderly	Diabetes Osteoporosis	Dyslipidemia Sexually active male Renal insufficiency	Gout
Beta blockers	Ischemic heart disease Heart failure Tachyarrhythmia Essential tremor	Migraine Hyperthyroidism Atrial fibrillation	Peripheral arteriopathy Sports Physical activity Dyslipidemia	Bronchial asthma COPD Atrioventricular block 2nd, 3rd Depression
Calcium antagonists	Isolated systolic HT Elderly Ischemic heart disease	Peripheral arteriopathy heart failure Atrial fibrillation HT×cyclosporine HT×tacrolimus		Atrioventricular block 2nd-3rd
ACE inhibitors	Heart failure Post-AMI Nephropathy DM Type 1 Type 2 Stroke (P. secondary)	Prev. secondary cv Proteinuria Renal insufficiency no DM		Pregnant Bilateral renal artery stenosis Hyperpotassemia
ARA-II	Nephropathy DM2 LVH Intolerance to ACE inhibitors	Heart failure Renal insufficiency	Angioneurotic edema due to ACE inhibitors Proteinuria	Pregnant Bilateral renal artery stenosis Hyperpotassemia
Alpha blockers	BH Prostate	Dyslipidemia	Orthostatic arterial hypotension	

COPD indicates chronic obstructive pulmonary disease; HT, hypertension; ACE, angiotensin converting enzyme; AMI, acute myocardial infarction; DM, diabetes mellitus; DM2, diabetes mellitus type 2; LVH, left ventricular hypertrophy; BH: benign hyperplasia.

DO THE NEW ANTIHYPERTENSIVE AGENTS PROVIDE GREATER CARDIOVASCULAR PROTECTION THAN STANDARD DRUGS? (NEW SECTION)

The JNC VI guide indicates that the initial treatment of choice in non-complicated hypertension is diuretics or betablockers. This recommendation was derived from the large number of studies demonstrating a reduction in cardiovascular morbidity and mortality with these compounds[12] (Figure 1b). Nevertheless, the WHO-ISH guidelines establish no preference for this pharmacological therapy, and indicate that fixed dose combinations are more appropriate than excessive increases of doses of either compound.[13]

It is therefore of great clinical relevance to know whether the new drugs (calcium antagonists, angiotensin converting enzyme [ACE] inhibitors and angiotensin receptor antagonists [ARA II]) are able to improve prognosis in patients with hypertension, to a greater extent than diuretics and beta blockers. We might also consider whether the new antihypertensive agents confer protection over and above that derived from their hypotensive effect. Different studies have recently compared the effect of anti-hypertensive therapy with diuretics and/or beta blockers versus a management strategy based on calcium antagonists and ACE inhibitors. CAPPP (ACE inhibitors versus beta blockers/diuretics),[14] INSIGHT (nifedipine GITS versus hydrochlorothiazide plus amiloride),[15] NORDIL (diltiazem versus beta blockers/diuretics)[16] and STOP-2 (ACE inhibitors versus dihydropyridine calcium antagonists versus beta blockers/diuretics)[11] are the main trials which have studied the prognostic influence of these different therapeutic interventions. In general, no significant differences were noted in the main endpoints of the studies (mortality and important cardiovascular complications) and it is suggested that in high blood pressure what is important is the reduction in blood pressure rather than the actual agent used.

In all these studies a significant proportion of patients treated for hypertension still had high blood pressure during follow-up. It could therefore be suggested that when blood pressure is raised the most important action is to lower it. With blood pressure figures near normal or in high risk patients with hypertension (diabetic patients or patients with target organ damage) a particular therapeutic group may confer greater cardiovascular protection, particularly those pharmacological groups which block the renin-angiotensin system, as suggested by the results of the HOPE,[18] MICRO-HOPE,[18] IDNT[19] IRMA II, [20] RENAL[21] and LIFE[22] studies. Which, although not all addressed the issue of hypertension, these studies provide a solid base for recommendations in daily clinical practice.

The possibility that blood-pressure-lowering drugs may confer cardiovascular protection beyond their antihypertensive role has been examined in various meta-analyses.[9,23] No significant overall differences were detected between the newer antihypertensive drugs (ACE inhibitors and calcium antagonists) versus classic agents (diuretics and beta blockers). Of note, however, was the importance of adequate blood pressure control; intensive blood pressure reduction was associated with greater reduction in cardiovascular events. One of these meta-analyses compared the results of different randomized studies, and included 62 605 patients with hypertension. All the drugs used conferred similar cardiovascular protection and, compared with diuretics and beta blockers, calcium antagonists were accompanied by a greater reduction in the risk of stroke (13.5%; 95% CI, 1.3-24.2; *P*=.03) and a lower reduction in the risk of myocardial infarction (19.2%; 95% CI, 3.5-37.3, *P*=.01), thereby providing a similar overall cardiovascular benefit.[24] The differences in systolic blood pressure control (2-3 mm Hg) could account for the high risk of cardiovascular complications (especially heart failure) in one study with doxazosin[25] and the high risk of stroke in patients treated with captopril in another study.[17]

In clinical practice therefore, normalization of blood pressure figures should take precedence over therapeutic strategy for treatment of patients with hypertension, with the drug used initially being of lesser importance. Notwithstanding these observations, this is of relative consequence because most patients with hypertension require a combination of drugs.

The indications for specific treatment in Table 7 have been modified.

DIURETICS (PAGE 76) (NEW TEXT)

Indications

The JNC VI report, in the absence of an elective indication for the use of other agents, recommends diuretics as the first choice of drug for the treatment of hypertension, as their efficacy has been amply demonstrated in prevention of cardiovascular complications.

Their antihypertensive efficacy in control of high systolic blood pressure in elderly patients is superior to that of other agents (together with calcium antagonists), although they probably only control no more than 25%-35% of cases, with the other patients requiring combination therapy.

The best option for use in second place is diuretics in combination with ACE inhibitors, ARA II, and beta and alpha blockers. When the diuretic itself forms the basis of treatment in monotherapy, the preferred combinations are with beta blockers, ACE inhibitors and ARA II.

The results of the ALLHAT study revitalized the role of diuretics as one of the basic compounds for treatment of hypertension, both in monotherapy and in combination therapy.

Recent data from the ARIC study demonstrated no significant increase in the risk of new onset diabetes due to diuretic agents (RR=0.95; *P*=ns), unlike beta blockers (RR=1.26; *P*<.05).[26]

ALPHA BLOCKERS (PAGE 78) (NEW TEXT)

The current most common alpha blockers are terazosin and, especially, doxazosin.

Up until publication of the ALLHAT study (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) it was assumed that doxazosin was a valid drug for use in monotherapy. Its blood pressure lowering effect is comparable to other hypotensive agents. However, use of alpha blockers as first-line treatment of hypertension is now controversial after the premature termination of the doxazosin arm in the ALLHAT study. These patients had a greater risk of heart failure than control patients treated with clortalidon.[25]

Despite these observations, alpha blockers remain a drug available for use in multiple combinations, since, as stated above, blood pressure figures should be lowered to normal values and combinations of 3, 4 or more drugs are frequently required.

BETA BLOCKERS (PAGE 78) (NEW TEXT)

Maximum evidence for use of beta blockers comes from patients with hypertension associated with ischemic heart disease (angina and myocardial infarction), heart failure, tachyarrhythmias, resting tachycardia and excessive tachycardia in situations of physical or emotional stress.

The combination of beta blockers and ACE inhibitors has been shown to improve quality and quantity of life in patients with symptomatic left ventricular dysfunction (CAPRICORN[27]), in different forms of clinical presentation of heart failure (MERIT-HF,[28] CIBIS II[29] and COPERNICUS[30]) and in patients with ischemic heart disease (especially in post-myocardial infarction), patients with heart failure, asymptomatic ventricular dysfunction or anterior infarction. The results of the HOPE study[18] suggest that this combination should be extended to all patients with ischemic heart disease. The results of the ELITE II study and the Val-Heft trial indicate that patients with heart failure who are unable to tolerate ACE inhibitors should be treated with an ARA II. Patients with hypertension and heart failure who cannot tolerate beta blockers should probably be given a combination of an ACE inhibitor and an ARA II.[31,32] The results of the recently

published OPTIMAAL study33 in patients with postinfarction ventricular dysfunction and anterior myocardial infarction or reinfarction indicate that treatment with losartan (50 mg/d) is no superior to captopril (150 mg/d), although the use of both in combination with beta blockers is possible with no evidence of a negative interaction between them.

The probability of the onset of diabetes mellitus is increased 25% when initiating long-term therapy with a beta blocker. This effect, however, is not seen with diuretics, calcium antagonists or ACE inhibitors.[26]

CALCIUM ANTAGONISTS (PAGE 80) (NEW TEXT)

The efficacy of these compounds is notable in elderly patients with high systolic blood pressure, either alone or in association with diabetes mellitus. Several meta-analyses have questioned the safety of dihydropyridine calcium antagonists for treatment of patients with coronary heart disease. However, an important number of these studies incorporated methodological defects (most were case-control studies), used short acting calcium antagonists, or included very heterogeneous groups of patients. Recent studies undertaken in patients with hypertension have demonstrated that sustained release dihydropyridine calcium antagonists (nifedipine in the INSIGHT study), but not dihydropyridine calcium antagonists (diltiazem in the NORDIL study), are as effective as diuretics and beta blockers for the prevention of cardiovascular complications in patients with hypertension.[15,16] Recent data from the ALLHAT study, which compared the efficacy of a therapeutic strategy based on amlodipine with others based on chlorthalidone and lisinopril, again showed the clinical importance of achieving adequate blood pressure reduction in high risk patients. This study suggests important advantages of classical treatment with diuretics (chlorthalidone) versus treatment with ACE inhibitors or dihydropyridine calcium antagonists for the prevention of congestive heart failure (CHF) or stroke reduction.[34]

New dihydropyridine calcium antagonists have recently appeared which afford notable advantages for the treatment of patients with hypertension. Their efficacy is similar to other antihypertensive agents, but they are much better tolerated, thereby avoiding the appearance of adverse side effects, which are one of the main limitations of calcium antagonists.[35]

BLOCKING THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (PAGE 81) (NEW TEXT)

Results from several different studies indicate that ACE inhibitors exert a cardiovascular protective effect in patients with hypertension, at least to the same extent as diuretics, beta blockers and calcium antagonists. Furthermore, unless expressly contraindicated, they should be included in the therapeutic strategy for treating patients with hypertension and heart failure or ischemic cardiopathy (especially in post-myocardial infarction patients with heart failure, ventricular dysfunction and anterior infarction). Angiotensin converting enzyme inhibitors, together with ARA II, constitute the first-line therapy in diabetic patients with hypertension. The results of the MICRO-HOPE study[18] provided strong support for their use in patients with hypertension and type 2 diabetes mellitus. In patients with asymptomatic ventricular dysfunction and in the different degrees of severity of heart failure their combination with beta blockers reduces the risk of complications and prolongs life. Unless otherwise indicated, they should thus be included in the therapeutic strategy of these patients.

AT1 RECEPTOR ANTAGONISTS (PAGE 82) (NEW TEXT)

Results of recent studies suggest that ARA II have gained ground in the algorithm for treating hypertension. As well as the almost automatic use of an ARA II in cases of intolerance to ACE inhibitors other further indications have appeared. Their renoprotective efficacy has been demonstrated in patients with type 2 diabetes mellitus. Indeed, the American Diabetes Association (ADA) has included these compounds as first-line therapy in patients with type 2 diabetes mellitus with proteinuria or microalbuminuria.[19-21]

The recent publication of the LIFE study has shown that for patients with hypertension and left ventricular hypertrophy a regimen based on an ARA II (losartan) conferred greater cardiovascular protection than that conferred by treatment with the beta blocker atenolol. The reduced risk of stroke was the main factor influencing the improved prognosis in the group of patients treated with ARA II.[22] This study holds special clinical relevance because it is so far the only randomized clinical trial to demonstrate the superiority of a drug (losartan) from the ARA II family, compared with classic antihypertensive therapy (beta blockers or diuretics), in reducing the rate of cardiovascular morbidity and mortality in patients with hypertension. Prior to the publication of the ALLHAT[34] study this effect had not been seen with other drugs such as calcium antagonists or ACE inhibitors. Nevertheless, confirmation of the benefits of ARA II in patients with hypertension must await the results of other ongoing studies, such as VALUE, which compares valsartan with amlodipine in high risk patients with hypertension, or yet other studies which, though finished, are pending definitive publication, such as SCOPE, which compared candesartan with placebo in older patients

with slight or moderate hypertension.[16,36]

Available data for patients with heart failure suggest a similar efficacy to ACE inhibitors, and the results of the Val-Heft trial indicate that the combination of ACE inhibitors and ARA II might be of benefit, at least in patients not treated with beta blockers.[32] Subgroup analysis of patients in the ELITE II and Val-Heft studies had suggested a possible negative interaction between ARA II and beta blockers; however, the results of the OPTIMAAL study indicate that the combination of both compounds in postmyocardial infarction patients is accompanied by a similar benefit to that obtained with ACE inhibitors and beta blockers.[31,33]

OTHER ANTIHYPERTENSIVE DRUGS (NEW SECTION)

Omapatrilate is the first of the vasopeptidase inhibitors, a new family of drugs not yet on the market. Vasopeptidase inhibition is a new concept in cardiovascular therapy; it involves the simultaneous inhibition of two enzyme pathways which participate in the regulation of cardiovascular function, neutral endopeptidase (NEP) and angiotensin-converting enzyme (ACE). This mixed action of NEP and (ACE) entails increased production of natriuretic and vasodilator peptides, such as the atrial natriuretic peptide, the cerebral natriuretic peptide of cardiac origin, and the type C natriuretic peptide of endothelial origin, as well as an increase in the half-life of other vasodilator peptides, such as bradykinine and adrenomedulin. Although omapatrilate has been shown to possess superior antihypertensive efficacy to other drugs, including ACE inhibitors, the recent OCTAVE study suggests that the incidence of adverse side effects with omapatrilate, mainly angioedema, seems to be higher than that with ACE inhibitors, which might limit its generalized use in patients with hypertension.[37]

OTHER PHARMACOLOGICAL TREATMENT (NEW SECTION)

A decrease in blood pressure figures should be included in the overall cardiovascular risk management strategy in patients with hypertension. This requires a combined approach to the different risk factors with lifestyle modification, platelet antiaggregating agents, lipid lowering drugs and hypoglycemic agents.

Lipid lowering therapy

The use of lipid lowering drugs, especially statins, in patients with hypertension should be adjusted to their cardiovascular risk. The association of hypertension and dyslipidemia increases the risk, so that lipid lowering pharmacological therapy should take into account this risk. Hypertensive patients with type 2 diabetes mellitus and prior cardiovascular disease (especially ischemic heart disease) should maintain their LDL cholesterol below 100 mg/dL. In hypertensive patients with no other associated risk factors LDL cholesterol should be kept below 160 mg/dL, and in the presence of other associated risk factors the aim of treatment is to achieve LDL cholesterol values below 130 mg/dL.

Platelet antiaggregating agents

These compounds, especially low dose aspirin, have proved their worth in secondary prevention in patients with ischemic heart disease and cerebrovascular disease. In the absence of contraindications or intolerance, patients with hypertension and type 2 diabetes mellitus should receive a low dose (75-100 mg/d) of aspirin. Patients with hypertension and a high or very high cardiovascular risk profile should probably also receive aspirin, provided their blood pressure is well controlled.[35,38,39]

HIGH BLOOD PRESSURE AND COEXISITING CARDIOVASCULAR DISEASE (PAGE 83) (NEW TEXT)

Patients with cerebrovascular disease

The results of the HOPE and PROGRESS studies suggested that ACE inhibitors should be included in the therapeutic regimen for patients who have had a stroke.[18,40] A group of stroke patients was included in the HOPE study and although the design did not permit definitive conclusions in this group, results suggest that ramipril could be useful in patients with cerebrovascular disease. Results of the PROGRESS study indicated that the combination of an ACE inhibitor (perindopril) and a diuretic (indapamide) reduced the risk of cardiovascular complications in patients with stroke. This benefit seems very dependent on the antihypertensive effect of the combination.

Patients with coronary heart disease

The results of the HOPE study suggested that patients with hypertension and ischemic heart disease treated with beta blockers whose blood pressure remains high should receive ACE inhibitors, although this type of compound would probably benefit most patients with coronary heart disease. Thus, unless contraindicated, a beta blocker and ACE inhibitor should constitute the basis of antihypertensive therapy in patients with ischemic heart disease (especially postmyocardial infarction). Nevertheless, recently published data extracted from the database of the GISSI-3 study regarding the use of lisinopril in acute myocardial infarction (AMI) suggest that ACE inhibitors should be used with caution during the acute stage of the infarction in

patients with a history of hypertension but with a low diastolic blood pressure during the AMI.[41]

Patients with left ventricular hypertrophy

The greater ability of ACE inhibitors to reduce left ventricular hypertrophy in patients with hypertension is based on results of several meta-analyses, although recent comparative studies indicate that dihydropyridine calcium antagonists and even diuretics achieve regression of the hypertrophy as much as ACE inhibitors.[42] As mentioned previously, the results of the LIFE (Losartan For Endpoint reduction) study indicate that in patients with hypertension and left ventricular hypertrophy a therapeutic strategy based on losartan is associated with greater cardiovascular protection than atenolol, with no differences in blood pressure control. The main endpoint was the reduction in the risk of stroke, and a special benefit of treatment with ARA II was noted in the subgroups of patients with diabetes mellitus and with systolic hypertension.[22,43,44]

Patients with heart failure

In the absence of formal contraindications to their use, ACE inhibitors should be included in the management of patients with left ventricular dysfunction and with varying degrees of severity of heart failure. Results of the ELITE II and Val-Heft studies suggested that patients with contraindications or adverse side effects to ACE inhibitors (especially dry cough) should be treated with ARA II; the combination of hydralazine and isosorbide dinitrate should be reserved for those patients unable to tolerate either ACE inhibitors or ARA II.[31,32] Results of the CAPRICORN, CIBIS II, MERIT-HF and COPERNICUS studies indicate that beta blockers should be combined with ACE inhibitors in patients with left ventricular dysfunction and heart failure.[27-30] The Val-Heft trial suggested that patients treated with ACE inhibitors but unable to tolerate beta blockers should receive ARA II.[32] Results of the RALES study, however, indicated that patients with severe heart failure treated with ACE inhibitors should receive low dose spironolactone (25-50 mg/d).[45]

Patients treated with ACE inhibitors and beta blockers whose blood pressure can still not be adequately controlled (<130/85 mm Hg) may also receive amlodipine or felodipine, which have no effect on mortality.

Hypertensive patients with heart failure and preserved systolic function represent an important group among those with heart failure. Although no prognostic studies are available regarding treatment of these patients, the basis of therapy should be to optimize diuretic treatment avoiding over-diuresis, achieve adequate blood pressure control (<130/85 mm Hg), maintain sinus rhythm, "bradycardize" the patient with beta blockers or "bradycardizing" calcium antagonists (verapamil or diltiazem) and achieve regression of the myocardial hypertrophy-fibrosis with ACE inhibitors or ARA II. Studies currently in progress will help to provide important information regarding the correct treatment of these patients.[46-49]

Patients with peripheral arterial disease

Calcium antagonists, ACE inhibitors and beta blockers could be a good alternative to control blood pressure in these patients, in whom certain changes in lifestyle such as smoking cessation and regular physical exercise form the basis of treatment.

Patients with atrial fibrillation

The incidence and prevalence of atrial fibrillation are increasingly associated with hypertension. Data from a recent Spanish study (CARDIOTENS) indicate that nearly 70% of patients with atrial fibrillation have a history of hypertension.[1] The main aim of treatment in these patients is to restore sinus rhythm and control the ventricular response in patients with chronic atrial fibrillation. Beta blockers or "bradycardizing" calcium antagonists are the best option to limit ventricular response in patients with tachycardia. The combination of low dose diuretics, ACE inhibitors or ARA II are good alternatives for blood pressure control. Interesting results recently reported from a study with ARA II (irbesartan) showed that this drug is useful for preserving sinus rhythm in patients with atrial fibrillation who have undergone cardioversion.[50] Chronic anticoagulation should be considered in any patient with hypertension and atrial fibrillation, though good blood pressure control is preferable prior to initiating anticoagulating therapy.

HYPERTENSION WITH RENAL INVOLVEMENT (PAGE 84) (NEW TEXT)

Results from the MICRO-HOPE study with ramipril and other studies with ARA II (RENAAL, IDNT and IRMA II) provide strong evidence for inclusion of ACE inhibitors or ARA II in the treatment plan of diabetic patients with nephropathy (microalbuminuria and proteinuria).[18-21] Some data also exist demonstrating the usefulness of ACE inhibitor-ARA II combinations in renal protection.[51,52] The efficacy of the combination of both drugs to reduce cardiovascular morbidity and mortality in different clinical situations is currently being analyzed in several studies, some like ONTARGET still in progress, and others like VALIANT which have only recently finished. Diuretics, calcium antagonists and even beta blockers can all be considered good alternatives for combination therapy.[53]

HYPERTENSION AND DIABETES (PAGE 85) (NEW TEXT)

The results of the INSIGHT study indicated that treatment with a sustained release dihydropyridine calcium antagonist (nifedipine GITS) was accompanied by fewer new cases of diabetes mellitus than treatment with diuretics.[15] Angiotensin converting enzyme inhibitors (HOPE study)[54] and ARA II (LIFE study)[54] have also been shown to prevent the onset of newly diagnosed diabetes mellitus.

The ADA has recently recommended maintaining blood pressure levels <130/80 mm Hg for patients with diabetes mellitus.

As already mentioned, results of the MICRO-HOPE study with ramipril and the ARA II studies (RENAAL with losartan in diabetics with nephropathy and IDNT and IRMA II with irbesartan in diabetic patients with nephropathy and microalbuminuria, respectively) have provided a set of data which suggest that treatment with one of these compounds should take precedence in the overall management plan for diabetic patients in general and those with hypertension in particular.[18-21] The studies with ARA II demonstrated conclusively that these compounds delay the onset of kidney deterioration independently of their antihypertensive effect. In fact, the recent ADA recommendations establish that ARA II should be considered the first-line therapy for patients with type 2 diabetes mellitus, hypertension, and kidney disease (microalbuminuria and proteinuria). This treatment should be given within the multifactorial context of therapy in diabetic patients, in which control of glycemia and plasma lipids are the main therapeutic aims.

HYPERTENSION IN THE ELDERLY (PAGE 86) (NEW TEXT)

The recent publication of the results of an extension to the follow-up of the SYST-EUR study indicate that treatment with calcium antagonists in elderly patients with high systolic blood pressure is accompanied by a very significant reduction in cognitive deterioration and risk of dementia.[55]

HYPERTENSION IN WOMEN (PAGE 87) (NEW TEXT)

Hormone replacement therapy

Menopause is associated with an increased cardiovascular risk due to age and the accumulation of risk factors associated with both processes. The prevalence of hypertension, dyslipidemia, diabetes mellitus and obesity all increase, together with the development of endothelial and hemostatic dysfunction, which increases the risk of cardiovascular complications. Although modern hormone replacement therapy in menopausal women is not associated with any significant increase in blood pressure, and the drugs even have a favorable effect on some of the components of cardiovascular risk, information currently available, in particular from the results of the HERS study, contraindicate their routine use for cardiovascular risk reduction in this population.[56,57]

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