Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document

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Abbreviations: ACE, angiotensin-converting enzyme; BP, blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; ESH, European Society of Hypertension; ET, endothelin; IMT, carotid intima-media thickness; JNC, Joint National Committee; LVH, left ventricular hypertrophy; LVM, left ventricular mass; PDE-5, phosphodiesterase-5; PPAR-γ, peroxisome proliferators-activated receptor-γ; PWV, pulse wave velocity; SBP, systolic blood pressure; WHO, World Health Organization

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Introduction

In the 2 years since the publication of the 2007 guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) [1], research on hypertension has actively been pursued and the results of new important studies (including several large randomized trials of antihypertensive therapy) have been published. Some of these studies have reinforced the evidence on which the recommendations of the 2007 ESH/ESC guidelines were based. However, other studies have widened the information available in 2007, modifying some of the previous concepts, and suggesting that new evidence-based recommendations could be appropriate.

The aim of this document of the ESH is to address a number of studies on hypertension published in the last 2 years in order to assess their contribution to our expanding knowledge of hypertension. Furthermore, some critical appraisal of the current recommendations of the ESH/ESC, as well as of other guidelines, might be a useful step toward the preparation of a third version of the European guidelines in the future.

The most important conclusions are summarized in boxes. The points that will be discussed are reported in Box 1.

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Box 1. Issues

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Assessment of subclinical organ damage for stratification of total cardiovascular risk

The 2007 ESH/ESC guidelines recommend total cardiovascular risk be evaluated in each patient to decide about important aspects of treatment: the blood pressure (BP) threshold at which to commence drug administration, the target BP to be reached by treatment, the use of two-drug combinations as the initial treatment step, and the possible addition to the antihypertensive treatment regimen of lipid-lowering and antiplatelet agents [1]. Among the criteria to assess total cardiovascular risk, the European guidelines consider subclinical organ damage to be a very important component, because asymptomatic alterations of the cardiovascular system and the kidney are crucial intermediate stages in the disease continuum that links risk factors such as hypertension to cardiovascular events and death. On the basis of a number of criteria (prognostic importance, prevalence in the population,

availability and cost of the assessment procedures, etc.), the 2007 European guidelines considered detection of organ damage as important for the diagnostic and prognostic evaluation of hypertensive patients. They further subdivided the different types of organ damage into (1) those that can be identified by relatively simple and cheap procedures [electrocardiogram, serum creatinine, estimated glomerular filtration rate (eGFR), and measurement of urinary protein excretion in order to detect microalbuminuria or proteinuria], which were thus regarded as suitable for routine search in the whole hypertensive population, and (2) those that require more complex procedures or instrumentations (echocardiogram, carotid ultrasonography, pulse wave velocity), which were for this reason only recommended for a more in-depth characterization of the hypertensive patient. Since then, other studies have added useful information on the importance of detecting subclinical organ damage in the hypertensive population, strengthening the recommendation to use the most easily available and the least costly procedures in the routine examination of individuals with hypertension.

Heart

A few recent papers have revived interest in the power of the electrocardiogram to predict the risk of cardiovascular events. In a prospective survey including 7495 American adults, a new indicator of left ventricular hypertrophy (LVH), the Novacode estimate of left ventricular mass index that is based on both voltage and strain pattern criteria, has been reported to be significantly related to 10-year cardiovascular mortality [2]. The relation remained significant after adjusting for age, SBP, smoking, cholesterol, and diabetes. Furthermore, in the LIFE trial, the investigators have reported that in hypertensive patients with electrocardiographic LVH, left bundle branch block identifies individuals at increased risk of cardiovascular mortality (hazard ratio 1.6), sudden cardiovascular death (hazard ratio 3.5), and hospitalization for heart failure (hazard ratio 1.7) [3]. Finally, a very recent prospective study [4] focused on the R-wave voltage in lead aVL as being rather closely associated with left ventricular mass (LVM), and additionally predictive of incident cardiovascular events even when hypertension is not accompanied by electrocardiographic LVH (9% higher risk for each 0.1 mV higher R-wave).

Additional evidence is also available on the predictive power of cardiac abnormalities, as detected by echocardiography, an approach of continuing interest because of its ability to more directly and precisely quantify LVM and geometric LVH patterns. A retrospective study has recently updated information from more than 35 000 normotensive and hypertensive participants with normal left ventricular ejection fraction [5]. Despite normal left ventricular function, an abnormal left ventricular geometric pattern was found in 46% of the patients (35% left ventricular concentric remodeling and 11% LVH), and the associated risk of all-cause mortality was twice as large as that of patients with normal left ventricular geometry. Although in another study on an African–American population, the relationship between left ventricular geometric patterns and all-cause mortality was markedly attenuated after adjusting for baseline variables, and remained significant only in men [6], the increased risk associated with LVH has been confirmed by other observations. In a prospective study on a cohort of 1652 Greek hypertensive patients followed up for 6 years, echocardiographic LVH was significantly associated with either a composite of all-cause mortality and cardiovascular events (hazard ratio 1.53) and with stroke (hazard ratio 2.01), after adjustment for major cardiovascular risk factors [7]. Furthermore, a retrospective analysis of 1447 Japanese hypertensive patients who participated in the CASE-J trial showed that cardiovascular events occurred about 2.6 times more frequently in patients with a LVM index 125 g/m^2 or more compared with those with a LVM index below this value [8]. Finally, in the PAMELA population, echocardiographic LVH was associated with a four-fold to five-fold significant increase in cardiovascular morbidity and mortality when data were adjusted for a large number of potential confounders, including office, home, and ambulatory BP values. A 10% increase in LVM increased the risk more markedly when baseline LVM was already abnormal, but an increasing risk was evident also when calculated from LVM values within the normal range [9].

Blood vessels

The relationship of carotid intima–media thickness (IMT) and plaques with subsequent cardiovascular events, already discussed in the 2007 guidelines, has been further strengthened by data from ELSA [10], which have shown that baseline carotid IMT predicts cardiovascular events independent of BP (clinic and ambulatory) and this occurs both for the IMT value at the carotid bifurcations and for the IMT value at the level of the common carotid artery. This suggests that both atherosclerosis (reflected by the IMT value at the bifurcations) and vascular hypertrophy (reflected by the common carotid IMT) exert an adverse prognostic effect in addition to that of high BP. An adverse prognostic significance of carotid plaques (hazard ratio 2.3) has also been reported in a sample of residents of the Copenhagen County free of overt cardiovascular disease, which was prospectively followed for about 13 years [11]. Evidence has also accrued on the adverse prognostic value of arterial stiffening. In the Copenhagen County population, an increased pulse wave velocity (PWV >12 m/s) was associated with a 50% increase in the risk of a cardiovascular event [11]. Furthermore, an independent predictive value of PWV for cardiovascular events has been shown in Japanese men followed for 8.2 years [12]. Finally, indirect indices of aortic stiffness and wave reflection, such as central BP and augmentation index, have been confirmed as independent predictors of cardiovascular events in two recent studies [13,14]. In particular, in one of these

studies of 1272 normotensive and untreated hypertensive patients, only central SBP consistently and independently predicted cardiovascular mortality after adjustment for various cardiovascular risk factors, including LVM and carotid IMT [14]. However, it should be emphasized that in most available studies, the additive predictive value of central BP beyond brachial pressure appears limited, which leaves the question whether central BP measurements should be regularly considered in the clinical profiling of hypertensive patients in need of further investigation.

Kidney

Several new data [15] reinforce the already solid evidence on the prognostic value of eGFR that was available at the time of the 2007 guidelines [1]. In the population of Gubbio (Italy), an eGFR in the lowest decile was associated with a significantly higher incidence of cardiovascular events (hazard ratio 2.14) [16], and in the abovementioned Greek study [7], an eGFR between 15 and 59 ml/min per 1.73 m^2 was associated with a 66% increase in the composite endpoint of all cause mortality and cardiovascular events after adjustment for baseline cardiovascular risk and independent of LVH [7]. Likewise, in a *post hoc* analysis of data from the VALUE trial [17], eGFR according to the MDRD formula was significantly predictive of all outcomes except stroke (with hazard ratios between 1.23 and 1.70 according to the different outcomes) and was more sensitive than calculation of the creatinine clearance value according to the Cockroft–Gault formula, which was only predictive of all-cause mortality.

The baseline eGFR by the MDRD formula turned out to be importantly predictive of both renal and cardiovascular events also in the large number ($n = 11\,140$) of type 2 diabetic patients included in the ADVANCE trial, even when data were adjusted for many potential confounders, including the concomitant urinary protein excretion value. For every 50% reduction of baseline eGFR the risk of cardiovascular events significantly increased 2.2-fold, the concomitant increase in the risk of cardiovascular death and renal events being 3.6-fold and 63.6-fold, respectively [18].

New evidence is also available to support the already large amount of data in favor of the prognostic value of the moderate increase in urinary protein excretion, defined as microalbuminuria [19,20]. In two population studies, the Gubbio study [16] and the Copenhagen County study [11], microalbuminuria was confirmed as an important predictor of cardiovascular outcome, the adjusted hazard ratio being, respectively, 2.15-fold and 3.10-fold greater in patients with microalbuminuria compared with those without. In the Gubbio study, the association of microalbuminuria with low eGFR had a multiplicative effect (hazard ratio 5.93). In the ADVANCE trial [18], a change from one clinical stage of albuminuria to the next was associated with a 1.6-fold, 2.0-fold, and 3.3-fold increase in the multivariate-adjusted risk of cardiovascular events, cardiovascular death, and renal events, respectively, this being the case also when the change from normoalbuminuria to microalbuminuria was involved. The effects of higher baseline urinary protein excretion and reduced eGFR were independent of each other and the association of microalbuminuria and an eGFR value less than 60 ml/min per 1.73 m^2 brought about an additional increase in risk: 3.2-fold for cardiovascular events, 5.9-fold for cardiovascular mortality, and 22.2-fold for renal events.

Additional measures of organ damage

The 2007 European guidelines mention a number of additional measures of organ damage for which evidence of prognostic relevance was available, but no use in the clinical practice could be foreseen because of drawbacks of practical relevance, such as the high cost and low availability of the devices involved, the complexity and time consumption inherent in the procedures, and in several instances the lack of standardization of the values obtained between laboratories and across countries. Based on the evidence available in the last 2 years, no addition to the measures of organ damage included in the 2007 guidelines can be supported, although the growing availability of more sophisticated techniques and the reduced cost of their use brought about by technological progress, makes future additions likely.

In this context, the use of nuclear magnetic resonance deserves special mention. Although not prospective in nature, a very recent study systematically employing nuclear magnetic resonance imaging in a group of 142 hypertensive patients without overt cardiovascular disease has provided the interesting information that silent cerebrovascular lesions are even more prevalent (44%) than cardiac (21%) and renal (26%) subclinical damage, and do frequently occur in the absence of other signs of organ damage [21]. Increasing evidence also relates these lesions to cognitive dysfunction [22,23], a problem of primary importance because of the senescence of the population [24]. With magnetic resonance imaging becoming more and more frequently employed in diagnostic procedures, silent cerebrovascular disease is likely to become more frequently investigated in prognostic and therapeutic studies in hypertension.

The prognostic value of structural alterations in small subcutaneous arteries has recently been confirmed by two independent studies [25,26]. However, the invasive nature of this measurement prevents larger scale application of this method. A new noninvasive method for assessing the media–lumen ratio of small retinal arteries seems promising for large-scale evaluation [27], although its predictive value remains to be investigated.

Evidence remains inconclusive on a marker of a vascular alteration that has been actively investigated in the past decade, namely endothelial dysfunction. In a population sample of individuals without overt cardiovascular disease (67% with hypertension and 22% with diabetes mellitus) from the Northern Manhattan study, measures of flow-mediated vasodilatation predicted the incidence of cardiovascular events, but this effect was not independent of traditional cardiovascular risk factors [28]. Likewise, in the large cohort of elderly patients of the Cardiovascular Health Study, flow-mediated vasodilatation added very little to the prognostic accuracy of traditional risk factors [29]. On the contrary, Muiesan *et al.* [30] have recently reported that in a small cohort ($n = 172$) of uncomplicated hypertensive persons followed for about 8 years, flow-mediated vasodilatation of the brachial artery below the median value was significantly associated with a 2.7-fold increase in incident cardiovascular events even after adjusting for all major cardiovascular risk factors. However, the same group of investigators also have reported that endothelial dysfunction in the subcutaneous vessels of hypertensive patients was not predictive of cardiovascular events [31], possibly because endothelial dysfunction in different vascular beds may have a different prognostic significance. Clearly, the prognostic value of endothelial dysfunction in hypertension remains to be further elucidated.

It should be emphasized that the addition of new measures of organ damage to the assessment of total cardiovascular risk requires not only the demonstration of their prognostic importance, but it has to improve the power to predict the incidence of cardiovascular events. This is by no means easy to be documented, and indeed data are available that in some instances new risk factors of individual prognostic significance do not improve, when added to the others, the accuracy by which cardiovascular risk can be quantified, thus only making the diagnostic procedures more complex, time consuming, and costly. This is exemplified by the recent results of the Framingham study, which showed that inclusion of inflammatory markers did not lead to any substantial improvement in the accuracy (sensitivity and specificity) by which total cardiovascular risk was assessed [32].

Subclinical organ damage as a marker of high cardiovascular risk

Although subclinical organ damage undoubtedly increases the level of cardiovascular risk, the question arises whether it always brings the patient into the high-risk category, that is, an absolute risk of at least 20 cardiovascular events in 10 years per 100 patients. The 2007 European guidelines classify hypertensive patients with subclinical organ damage among those with a high total cardiovascular risk. This is further supported by more recent evidence on the contribution of subclinical cardiac, vascular, and renal damage to the total cardiovascular risk. As regards to subclinical cardiac damage, analysis of the data provided by some of the major prospective studies indicates that in hypertensive patients, echocardiographic LVH, particularly if of the concentric variety, is associated with an incidence of cardiovascular events equal to or above 20% in 10 years [5,7,33]. An incidence greater than 20% in 10 years has also been reported for men, but not for women, with echocardiographic LVH in the Framingham population study [34]. Finally, in the hypertensive patients of the CASE-J trial, echocardiographic LVH was associated with a 10-year incidence of cardiovascular events of 24% compared with the 10% incidence seen in patients without LVH [8].

Similar evidence exists for vascular damage. In the elderly patients of the Cardiovascular Health Study [35], the 10-year incidence of major cardiovascular events was higher than 20% when the common carotid IMT was 1.06 mm or more (fourth and fifth quintiles) and below 10% in those with an IMT in the first quintile (<0.87 mm). In the hypertensive patients of the ELSA study [10], the incidence of all (major and minor) cardiovascular events was greater than 20% in 10 years when IMT (common carotid plus bifurcation) was in the third and fourth quartiles (≥ 1.16 mm) or when at least one plaque had been detected. In contrast, patients with IMT in the first or the smallest IMT quartile (<0.98 mm) had incident cardiovascular events below 10% in 10 years. In hypertensive patients, the 10-year incidence of major cardiovascular events was higher than 20% when carotid-femoral PWV (aortic stiffness) was 16.3 m/s or more (fifth quintile) and below 10% in those with an aortic stiffness in the first and second quintiles [36]. Furthermore, even asymptomatic peripheral vascular disease as detected by a positive ankle-brachial index has prospectively been found to be associated in men with an incidence of cardiovascular events approaching 20% in 10 years [37,38].

Finally, old and recent evidence leaves little doubt that in hypertensive individuals, renal subclinical organ damage is associated with a 10-year risk of cardiovascular events of 20% or more. It has already been reported some years ago that reduced renal function, defined by a serum creatinine more than 1.5 mg/dl is associated with a 10-year incidence of cardiovascular events 20% or more [39,40]. In the recent prospective cohort of Greek hypertensive patients [7], a low eGFR was associated with incident cardiovascular events of about 20% in 10 years, an even higher incidence being observed when low eGFR occurred together with LVH. Furthermore, in the hypertensive patients prospectively studied by Jensen *et al.* [41], the incidence of ischemic heart disease was 20% in 10 years in the presence of microalbuminuria and of only 5% in its absence. Also, in the Gubbio population study, the incidence of cardiovascular events

was greater than 20% in 10 years, but only in those individuals in whom microalbuminuria in the highest decile was associated with eGFR in the lowest decile [16]. Over 78% of these patients had hypertension.

The 2007 European guidelines classify patients with subclinical organ damage as being at high risk also when BP is in the high normal range, but admittedly evidence that this is invariably the case is less clear. In the general population of the Framingham study, no information was made available on the prognostic value of echographic LVH, separately in the normotensive and hypertensive population [34]. Furthermore, in the same population, the association of renal dysfunction with cardiovascular events was lost after adjustment for cardiovascular risk factors, including BP [42]. In the PREVEND population study [43], microalbuminuria (20–200 mg/l) was associated with only a 4.7% cardiovascular mortality in 10 years, that is, a moderate absolute risk according to the SCORE classification [44], and in the nonhypertensive, nondiabetic individuals of the Framingham study, a microalbuminuria above the median value was associated with a rate of incident cardiovascular events of only 8.8% in 10 years compared with a 2.9% rate in individuals with microalbuminuria below the median value [45].

Prognostic value of treatment-induced modifications of subclinical organ damage

The 2007 European guidelines have emphasized that treatment-induced changes of organ damage affect the incidence of cardiovascular events, thereby recommending that organ damage be measured also during treatment. Reference was made to the data obtained in the LIFE study [46], in which hypertensive patients in whom treatment was accompanied by regression of echocardiographic LVH or a delayed increase in LVM had less incident cardiovascular events, including sudden death, than those in whom no regression from or earlier progression to LVH occurred. It was also mentioned that both in LIFE [47] and in other studies [48], a similar relationship was found between treatment-induced changes in proteinuria and renal or cardiovascular events. This means that, compared with patients in whom treatment had little or no antiproteinuric effect, reduction in proteinuria was associated with a reduced incidence of cardiovascular events and less progression to end-stage renal disease.

Since 2007, data on the relationship between treatment-induced changes in cardiac damage and cardiovascular protection have been enriched by further analyses of the LIFE study, which have shown that also treatment-induced changes in left atrial dimension [49], left ventricular geometry [50], and in electrocardiographic signs of LVH correlate with incident cardiovascular event rate [51]. Furthermore, there have been reports that in hypertension, inappropriate changes in LVM during treatment adversely affect cardiovascular prognosis [52]. Finally, the predictive power of treatment-induced IMT changes in the carotid arteries has for the first time been investigated in a recent analysis of ELSA trial data. This analysis failed to show a predictive role of treatment-dependent IMT changes, but the smallness of these changes compared with the large individual differences in baseline IMT makes it difficult to draw definitive conclusions [10].

The correlation of treatment-induced changes in proteinuria with cardiovascular event incidence has been challenged by some findings of the ONTARGET trial. In this trial on a large number of high or very high cardiovascular risk patients, the group treated with a combination of an angiotensin-converting enzyme (ACE) inhibitor and an angiotensin receptor antagonist showed, throughout the study duration, less increase in proteinuria than the group on monotherapy with one or the other drug, but this relative antiproteinuric effect was not accompanied by a reduction in cardiovascular events and was even associated with an increase in renal events [53]. However, these results do not necessarily undermine the important concept that treatment-induced changes in proteinuria can be a marker of the more or less pronounced beneficial effects of treatment because alternative explanations for the ONTARGET results are possible. For example, in ONTARGET, most patients had a normal renal function and few (4%) exhibited overt proteinuria, which resulted in a very limited number of the endpoint that matters for renal protection, that is, chronic renal failure. Furthermore, in the very high cardiovascular risk population studied, the powerful blockade of the renin–angiotensin system provided by the ACE inhibitor and angiotensin receptor antagonist combination might have exhibited an adverse effect of its own that superseded and masked the beneficial influence associated with a reduction in proteinuria. In favor of this beneficial influence are some recent analyses of the ADVANCE study in patients with type 2 diabetes. In these patients, on-treatment values of proteinuria showed a close independent association with both renal and cardiovascular events, the contribution of proteinuria being unrelated to the concomitant values of eGFR [18].

Conclusion

Evidence on the important prognostic role of subclinical organ damage continues to grow. In both hypertensive patients and the general population, the presence of electrocardiographic and echocardiographic LVH, a carotid plaque or thickening, an increased arterial stiffness, a reduced eGFR (assessed by the MDRD formula), or microalbuminuria or proteinuria substantially increases the total cardiovascular risk, usually moving hypertensive patients into the high absolute risk range. The changes in electrocardiographically or echocardiographically detected LVH induced by treatment reflect the effects on

Box 2. Subclinical organ damage in total cardiovascular risk stratification

(1) In hypertension, assessment of total cardiovascular risk is important to optimize the decision about treatment initiation, intensity and goals.
(2) Quantification of total cardiovascular risk must include a search for subclinical organ damage, which is common in hypertension and has independent prognostic significance.
(3) In patients with hypertension, the presence of subclinical organ damage usually brings cardiovascular risk into the high range. Subclinical organ damage alone may not be sufficient to bring normotensive individuals into the high-risk category, although this may occur with multiple organ damage and the metabolic syndrome.
(4) As detailed in the 2007 ESH/ESC guidelines, several measures of renal, cardiac and vascular damage can be considered for total cardiovascular risk quantification. Because of their simplicity, wide availability and limited cost measures based on urinary protein excretion (including microalbuminuria), eGFR (MDRD formula), and ECG are suitable for routine use. Cardiac and vascular ultrasounds are more and more easily available in Europe, and their use in the evaluation of the hypertensive patient can be encouraged.
(5) Subclinical organ damage should be assessed both at screening and during treatment because a number of treatment-induced changes in organ damage relate to cardiovascular and renal outcomes, thereby offering information on whether the selected treatment is protecting patients from progressing organ damage and potentially from cardiovascular events.
(6) Several other measures of subclinical organ damage have been shown to have prognostic significance, but their complexity, low availability, and high cost prevent their routine clinical use. It is likely that technological progress will make use of some of these measurements more common in the future. Any measure, however, should be considered only if it adds to the overall precision of cardiovascular risk quantification.

cardiovascular events, thereby offering valuable information on whether patients are more or less effectively protected by the adopted treatment strategy. Despite some recent inconsistent results [53], solid evidence suggests that this is the case also for treatment-induced changes in urinary protein excretion, although the problem remains open for treatment-induced vascular changes. Thus, assessing the presence of subclinical organ damage is of crucial importance in the hypertensive population. This assessment can make use of simple and cheap procedures that can provide routine information before and at various times during treatment. It can also rely on more sophisticated approaches that can further characterize patients' cardiac and vascular status. In all instances, multiple organ damage assessment is useful because of the evidence that in the presence of two signs of organ damage (even when inherent to the same organ), cardiovascular risk may be more markedly increased, with an almost inevitable upgrading to the high cardiovascular risk category [7,16].

It is not clear from published data whether subclinical organ damage can bring total cardiovascular risk to the high range also in patients with high normal BP. However, organ damage when it is particularly pronounced, or affects multiple organs, or is accompanied by metabolic risk factors, is associated with a two-fold or three-fold increase in relative risk also in normotensive individuals [11,54–56], and the 2007 guidelines recommend considering relative risk as a guide for the need of treatment in young and middle-aged patients. In this context, it is also important to emphasize that the occurrence of undetected organ damage in patients that doctors decide to treat probably explains the apparently paradoxical findings of several observational studies that the incidence of cardiovascular events is higher in treated than in untreated hypertensive patients even after adjustment for usual cardiovascular risk factors and past clinical history [57–62]. This is consistent with the concept that antihypertensive treatment even if beneficial cannot usually take a high total risk back to a low-risk category [63]. These findings presumably reflect the fact that in medical practice, BP-lowering treatment is often deferred until organ damage occurs, when complete reversibility is not achievable [63,64]. More extensive use of organ damage assessment may thus help to reach a more timely decision about the initiation of treatment and thus favor its greater success.

Some of the issues discussed in Assessment of subclinical organ damage for stratification of total cardiovascular risk section are summarized in Box 2.

Treatment approach

Major guidelines [1,65–70] on the management of hypertension recommend the initiation of antihypertensive drugs in all patients with a SBP 140 mmHg or more and/or a DBP 90 mmHg or more, and to adjust the treatment strategy in order for the patients to be below these values. They further recommend drug treatment to be initiated within a lower BP range, that is, a SBP between 130 and 139 mmHg and a DBP between 85 and 89 mmHg in patients with diabetes or a history of cardiovascular or renal disease, aiming at achieving SBP/DBP values <130/80 mmHg.

The 2007 ESH/ESC guidelines [1] have accompanied these recommendations with information on the evidence they are based upon, and a critical reappraisal of this issue has recently been undertaken by members of the present Task Force [71], in the light of further

information provided by recent trials. The purpose of the present ESH document is to clarify the size and the type of evidence on which these recommendations are based, and thus help the planning and conduction of future studies which may fill possible evidence gaps.

When to initiate antihypertensive treatment

Guidelines recommend use of antihypertensive drugs in patients with grade 1 hypertension at low or moderate cardiovascular risk, that is, when BP is between 140 and 159 mmHg SBP and/or 90 and 99 mmHg DBP, provided nonpharmacological treatment has proved unsuccessful. However, it should be recognized that the evidence in favor of this recommendation is scant because older trials of 'mild hypertension' focused on patients whose BP could be higher than those defining grade 1 hypertension [72,73], or included high-risk patients [74]. Even the recent FEVER trial [75], which was mentioned in the 2007 guidelines to support intervention in grade 1 hypertensives with low/moderate cardiovascular risk, does not provide conclusive evidence because mean entry BP was just below 160 mmHg (159 mmHg), there was a large proportion (89%) of patients receiving antihypertensive therapy at baseline, and a noticeable number of patients had evidence of organ damage or a history of cardiovascular disease, thereby not belonging to the low-risk or moderate-risk category [71].

Guidelines also point out that the BP threshold for drug treatment is not related to age and recommend starting antihypertensive drugs at SBP at least 140 mmHg or DBP at least 90 mmHg in the elderly as well. However, as shown in Table 1, there is no single trial on elderly hypertensive patients [76–85] that recruited patients with a SBP in the grade 1 hypertension range (i.e., <160 mmHg) [71]. Therefore, it can be concluded that current guidelines recommendations on BP values at which to initiate drug treatment in the elderly are not based on results from trials, but derived from other findings (see below) and perhaps encouraged by the large benefits of antihypertensive therapy in all available trials in the elderly, admittedly at higher initial blood pressures.

Table 1 SBP and DBP at randomization in antihypertensive treatment trials in the elderly

	Recruitment BP criteria			Mean BP at randomization	
Trial	SBP (mmHg)		DBP (mmHg)	SBP (mmHg)	DBP (mmHg)
EWPHE	160–239	Or	90–119	183	101
Coope/Warrender	>170	Or	>105	196	99
SHEP	≥160	And	<90	170	77
STOP-1	≥180	Or	≥105	195	94
MRC-elderly	160–209	And	<115	185	91
Syst-Eur	160–219	And	<95	174	85
Syst-China	160–219	And	<95	171	86
SCOPE[a]	160–179	Or	90–99	166	90
HYVET	160–179	And	<110	173	91
JATOS	≥160	And	<120	171	89

BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure. Modified with permission from [71]. [a]In SCOPE, 50% of patients pretreated with low-dose thiazide.

Evidence is also scant for the guidelines recommendation to initiate drug treatment in the high normal BP range when patients have diabetes. Recommendations are substantially based on the results of the 'normotensive' component of the ABCD trial [86], which has important limitations, however: 'normotension' was defined as a SBP less than 160 mmHg, the trial size was small ($n = 480$), the primary endpoint was the change in creatinine clearance (with no statistically significant difference between treatments), and a statistically significant reduction of cardiovascular events in the group randomized to more intensive treatment was limited to the incidence of stroke but did not extend to other cardiovascular events. Recommendations also derive from subgroup analyses of two large trials, MICROHOPE [87] and ADVANCE [88]. However, in MICROHOPE, normotension was defined by history, entry BP values were not mentioned, and the statistical significance of cardiovascular event reduction in the 'normotensive group' was not reported; in ADVANCE, the benefit of antihypertensive treatment was significant in patients with an entry SBP 140 mmHg or more, but not in those in whom it was below this value. Similar findings were obtained when stratification was based on the presence or absence of a history of hypertension.

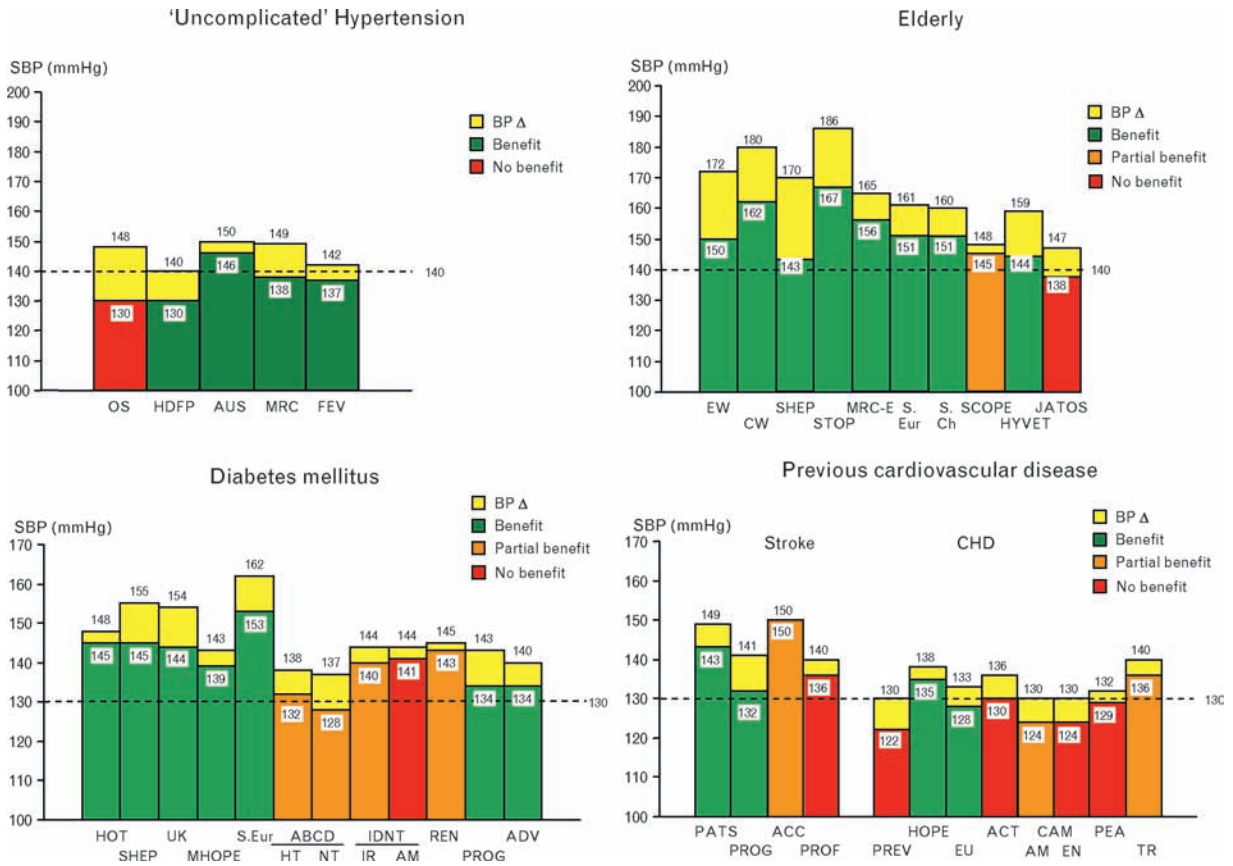
There have been strong recommendations to start antihypertensive treatment at high normal BP values also in patients with previous cerebrovascular disease. These have been based on the report from the PROGRESS trial [89] that in patients with a previous stroke or transient ischemic attack BP lowering was accompanied by a marked reduction in the incidence of recurrent stroke and cardiovascular events in both hypertensive and normotensive patients. However, in this study, hypertension was defined by SBP values of 160 mmHg or more, and in a subsequent analysis, a significant reduction in recurrent stroke with treatment was only observed when entry SBP was 140 mmHg or more [90]. Furthermore, entry BP values in PROGRESS were reported irrespective of background treatment (present in 50% of the patients [89,90]), and therefore they cannot be used to take decisions on initiation of treatment in untreated patients. Finally, the weight of evidence of PROGRESS has not been helped by the substantially negative results of a more recent large placebo-controlled trial of antihypertensive treatment in patients with cerebrovascular disease, the PROFESS study [91]. Although these negative results may be subject to various interpretations [71,92], they remain a disturbing finding requiring more straightforward investigation in a more simply designed trial.

As already discussed in the 2007 European guidelines [1] and further analyzed in a recent review [71], although no less than five trials are available [93–97], the information whether drug treatment should be initiated at high normal BP values in patients with coronary disease is inconclusive. First, in most trials, attention was directed to the putative-specific effects of the drugs studied rather than to the BP-related ones, which were sometimes incompletely quantified. Second, in these trials, patients were subdivided for their higher or lower entry BP value on a background of antihypertensive drug administration, and thus the so-called 'normotensive' patients probably belonged to a higher BP category when untreated. Third, the results show considerable discrepancies between and even within trials [71].

Blood pressure goals

The evidence available on the BP targets of antihypertensive treatment has recently been reviewed by some members of this committee and is summarized in Fig. 1 [71]. As illustrated in the upper-left panel, in four out of five trials in uncomplicated hypertensive patients [72–75,98], SBP was reduced to less than 140 mmHg in the actively treated group while remaining at or above this value in the placebo or control group. In three out of four trials, the BP difference was associated with a difference in outcome, and in FEVER [75] this occurred for on-treatment values that were just slightly below and slightly above 140 mmHg. With the limitation mentioned in a previous section (that patients were not invariably at low or moderate cardiovascular risk and

Fig. 1



Achieved SBP in patients randomized to a more active (lower part of histograms) or less active (upper part of histograms) treatment in trials on uncomplicated hypertension (left upper panel), elderly hypertensive patients (right upper panel), patients with diabetes mellitus (left lower panel) and patients with previous cardiovascular disease (CVD; right lower panel). The yellow part of the histogram indicates the between-group difference (Δ) in achieved SBP. The green, red and orange rectangles indicate, respectively, trials with significant benefits of more active treatment, trials without significant benefits, and trials with significant benefits of more active treatment limited to some secondary endpoints. CHD, coronary heart disease. Abbreviations at the bottom of the rectangles indicate trials as follows: OS, OSLO study; HDFP, HDFP-stratum I; AUS, Australian; MRC, MRC-mild; FEV, FEVER; EW, EWPHE; CW, Coope and Warrander; SHEP, SHEP; STOP, STOP; MRC-E; MRC-elderly; S.Eur; Syst-Eur; S.Ch; Syst-China; SCOPE, SCOPE; HYVET, HYVET; JATOS, JATOS; HOT, HOT; UKPDS, UKPDS; M.HOPE; MICROHOPE; ABCD, ABCD (HT, hypertensives; NT, normotensives); IDNT, IDNT (IR, irbesartan; AM, amlodipine); REN, RENAAL; PROG, PROGRESS; ADV, ADVANCE; PATS, PATS; ACC, ACCESS; PROF, PROFESS; PREV, PREVENT; HOPE, HOPE; EU, EUROPA; ACT, ACTION; CAM, CAMELOT (AM, amlodipine; EN, enalapril); PEA, PEACE; TR, TRANSCEND. For trial acronyms see Acronym List section. Modified with permission from [71].

with grade 1 hypertension), this evidence supports the recommendation of guidelines to reduce SBP to less than 140 mmHg in the general population of patients with grade 1 or 2 hypertension and low or moderate total cardiovascular risk.

Whether this recommendation should also apply to elderly hypertensive patients is unproved by outcome trials, however. As shown in the upper-right panel of Fig. 1, although in all trials [76–84], but one [85], the groups of elderly hypertensive patients randomized to more active treatment had a significantly lower incidence of cardiovascular outcomes, in no trial (except the only one with negative results [85]) the on-treatment SBP values were lowered to less than 140 mmHg. Thus, there is no trial evidence in support of the guidelines recommendation to adopt the less than 140 mmHg SBP target in elderly patients.

The lower panels of Fig. 1 show that the guidelines recommendation to lower BP less than 130/80 mmHg in patients with diabetes [86–88,99–106] or a history of cardiovascular disease [89,91,93–97,107,108] is also not supported by incontrovertible trial evidence. For diabetes, the recommendation in favor of intense treatment was probably due to the enthusiasm generated by some trials, such as HOT [99] and Syst-Eur [102], showing a greater absolute reduction of cardiovascular outcomes for a small BP difference in diabetic patients than in nondiabetic hypertensive patients. As shown in the lower-left panel of Fig. 1, only in one small trial were SBP values less than 130 mmHg actually achieved, and they were associated with a doubtful reduction in cardiovascular outcomes [86]. Similar results characterize trials in patients with a history of cerebrovascular or coronary disease with the additional confusing feature that in some trials in which SBP was lowered to less than 130 mmHg, no benefit was observed compared with the group with higher on-treatment values (lower-right panel of Fig. 1).

Information derived from *post hoc* analysis of trials and trials on organ damage

Information on BP thresholds and targets for drug treatment has also been derived from *post hoc* analyses of event-based trials and from studies on the effects of treatment on organ damage of prognostic importance, though, admittedly, this is weaker evidence.

Post hoc analyses of the incidence of cardiovascular events in relation to the BP achieved by treatment have been performed in the large group of hypertensive patients of the HOT study [99], in the high cardiovascular risk patients recruited for the VALUE trial [109,110], the INVEST trial [111–114], and the ONTARGET trial [115,116], and in the patients with diabetic nephropathy of the IDNT trial [117,118]. In the HOT study, the lowest incidence of cardiovascular events occurred at a SBP of 138 mmHg and a DBP of 82 mmHg [99]. In the VALUE trial, hypertensive patients in whom the achieved BP was below 140/90 mmHg showed a clear-cut reduction in the incidence of cardiovascular events (stroke, myocardial infarction, and hospitalized heart failure) with respect to the patients in whom on-treatment BP remained above these values, independent of the type of treatment employed [109]. In the INVEST trial, the incidence of cardiovascular events was progressively smaller as the proportion of visits in which BP was found to be controlled (<140/90 mmHg) increased even when data were adjusted for patients' demography, clinical conditions, and treatments [112]. The greater cardiovascular protection associated with on-treatment SBPs less than 140/90 mmHg showed a trend for cardiovascular events to become even less common as the achieved SBP decreased to about 130 mmHg [113]. On the contrary, in the ONTARGET, clear-cut beneficial effects of BP reductions were seen when initial SBPs were above 140 mmHg, even when adjustments for potential confounders were made, and at each initial BP, a greater BP reduction was usually accompanied by a greater cardiovascular protection. However, in patients in whom initial SBP was in the 130 mmHg range, the benefit was less pronounced and mainly evident for stroke [115]. Similar findings have recently been reported for the subgroup of diabetic patients recruited in ONTARGET [116]. Finally, in the patients with diabetic nephropathy of the IDNT reduction of SBP to less than 120 mmHg was related to lower cardiovascular mortality [117] and to progressive reduction of proteinuria as well as in end-stage renal disease [118].

As to the relationship between BP and subclinical organ damage, data from the LIFE trial have shown that the frequency of LVH regression is linearly related to the BP changes induced by treatment, the maximal efficacy being found for large BP reductions from the entry values [119]. A recently published study has also shown that presence of ECG-LVH is reduced by tighter as compared with less tight BP control (131.9/77.4 and 135.6/78.7 mmHg, respectively) in nondiabetic hypertensive patients [120]. Furthermore, several studies have provided evidence that antihypertensive treatment is accompanied by a reduction or a delayed progression in urinary protein excretion, be it in the proteinuric or microalbuminuric range, even when initial BP is below 140/90 mmHg [121,122]. The most recent evidence has been provided by the ADVANCE trial, which has shown that in diabetic patients, most of them under antihypertensive treatment, further BP lowering by the addition of an ACE inhibitor–diuretic combination significantly and markedly reduced the incidence of renal endpoints. These mainly consisted of the appearance, the progression, or the regression of urinary protein excretion, within a range of initial systolic or diastolic BP values from above 160/100 to below 120/70 mmHg [123]. The

hazard ratio for a renal endpoint was 0.81, 0.75, 0.85, and 0.70 in the actively treated as compared with the control group, at initial SBP values equal or above 160, 159–140, 139–120, and less than 120 mmHg, respectively. Furthermore, this *post hoc* analysis of the ADVANCE data has shown the adjusted risk of a renal endpoint to decrease progressively as the SBP achieved during treatment decreased to values of about 110 mmHg [123].

The J-curve phenomenon

Recently, there has been some withdrawal from a perhaps excessive enthusiasm for aggressive lowering of BP, based on the data of some trials [91,108] as well as *post hoc* analyses of the results of other trials on high-risk patients [113,115,124]. These data have raised the doubt that in patients at high cardiovascular risk, antihypertensive treatment regimens that reduce SBP to values close or below 120–125 mmHg and DBP below 70–75 mmHg may be accompanied by an increase (rather than a further reduction) in the incidence of coronary events, that is, by a J-curve phenomenon. This has led to readdressing the question as to whether BP is sometimes lowered too far, and in doing so, underperfusion of vital organs increases cardiovascular risk. The issue is open to the following considerations. First, although a BP value below which organ perfusion is compromised must exist, observational studies in patients initially free of cardiovascular disease [125] show that the relationship between BP and cardiovascular event rate is substantially linear down to very low BP values (about 110/70 mmHg), which are only exceptionally attained by antihypertensive treatment. Second, it is possible that in high cardiovascular risk patients, an impairment of the mechanisms that guarantee blood flow autoregulation elevates the BP threshold below which organ perfusion is reduced [92,126]. However, the extent of this elevation (which may be different between patients in relation to the degree of organ damage and age) has never been unequivocally established by trials specifically designed to explore the advantages of more versus less intense BP lowering. Third, despite adjustment for between-group initial demographics and clinical differences, *post hoc* analysis of trial results cannot escape the problem that in the group in which on-treatment BP was lowest, there could have been a greatest initial cardiovascular risk that caused both the excessive BP reduction and the increased incidence of cardiovascular events. Indeed, this is supported by the evidence of a similar J-curve phenomenon in placebo-treated groups of several trials [127]. Fourth, all these *post hoc* analyses consistently showed that, the nadir of cardiovascular outcome incidence was represented by a rather wide range of BP values, that is between 120 and 140 mmHg SBP and 70–80 mmHg DBP, suggesting that within this low BP range, the differences in achieved cardiovascular protection are small [71]. This is in line with the results of observational studies that the relationship between BP and cardiovascular events is linear when cardiovascular events are quantified on a logarithmic scale [125], which implies smaller absolute differences at lower BP values.

Are the 2007 recommendations still applicable?

Although the trial evidence is scant, it appears reasonable to reconfirm that, in grade 1 hypertensive patients at low and moderate risk, drug therapy should be started, if BP remains equal to or above 140/90 mmHg, after a suitable time period with appropriate lifestyle changes with the goal to bring BP below this cutoff value. Initiation of antihypertensive treatment in grade 1 hypertension (without waiting for BP to increase to grade 2 range or organ damage to develop) is also suggested by a recent analysis of all major trials with antihypertensive agents [63]. This analysis has revealed that in trials on high cardiovascular risk patients, the 'residual risk', that is, the risk level attained by intense therapy (often including lipid-lowering and antiplatelet agents), can very rarely decrease below the cutoff defining a high-risk condition (i.e., 20% cardiovascular events in 10 years). This means that, although reduced by therapy, a high initial risk remains high. On the contrary, in trials involving hypertensive patients at initial low or moderate risk, the 'residual risk' could often be brought to less than 10% in 10 years, which implies that earlier initiation of antihypertensive therapy may be beneficial. These arguments favor similar threshold and target BPs for drug treatment in the elderly. With the current availability of well tolerated drugs, BP lowering does not appear to be associated with any substantial increase in adverse effects or in cardiovascular or noncardiovascular risk.

Initiation of antihypertensive drug therapy in diabetic patients with high normal BP is presently unsupported by prospective trial evidence. This is the case also for the lower BP goals (<130/80 mmHg) recommended for diabetics but never really achieved in any single large trial and are even more rarely attained in medical practice. For the time being, monitoring subclinical organ damage, and particularly microalbuminuria and proteinuria, appears to be the best guidance to decide the BP values for treatment initiation as well as treatment goals in diabetic patients. Perhaps, and at least until the completion of studies such as ACCORD (in which the beneficial effects of targeting BP below either 140 or 120 mmHg are prospectively examined [128]), it may be useful to recommend that in diabetes, SBP be reduced well below 140 mmHg, without mentioning specific targets that are unproven. This would be in line with the results of the ADVANCE trial in which the macrovascular and microvascular benefits of antihypertensive treatment were seen in diabetic patients in whom SBP was brought down to less than 135 mmHg compared with patients on placebo in whom SBP remained at approximately 140 mmHg [88]. Similar cautious recommendations can be given to patients with previous cardiovascular events, for whom current trial evidence is controversial concerning both initiation of

Box 3. Treatment initiation

(1) Although trial evidence is scanty, it appears reasonable to recommend that, in grade 1 hypertensives (SBP 140–159 mmHg or DPB 90–99 mmHg) at low and moderate risk, drug therapy should be started after a suitable period with lifestyle changes. Prompter initiation of treatment is advisable if grade 1 hypertension is associated with a high level of risk, or if hypertension is grade 2 or 3.

(2) In patients with high normal BP (SBP 130–139 mmHg or DPB 85–89 mmHg) uncomplicated by diabetes or previous cardiovascular events, no trial evidence is available of treatment benefits, except for a delayed onset of hypertension (crossing the 140/90 mmHg cutoff).

(3) Initiation of antihypertensive drug therapy in diabetic patients with high normal BP is presently unsupported by prospective trial evidence. For the time being, it appears prudent to recommend treatment initiation in high normal BP diabetic patients if subclinical organ damage (particularly microalbuminuria or proteinuria) is present.

(4) Trial evidence concerning antihypertensive drug treatment in patients with previous cardiovascular events in absence of hypertension is controversial, and further trials must be completed before firm recommendations can be given.

(5) In general, early BP-lowering treatment, before organ damage develops or becomes irreversible or cardiovascular events occur, appears a prudent recommendation, because in high-risk hypertensive patients, even intense cardiovascular drug therapy, though beneficial, is nonetheless unable to lower total cardiovascular risk below the high-risk threshold.

antihypertensive drug treatment when BP is in the high normal range, and the benefit of aiming at a BP target of less than 130/80 mmHg.

No prospective outcome trial has ever been performed in those patients with a high normal BP that the 2007 ESH/ESC guidelines [1] tentatively classified as being at high cardiovascular risk because of the presence of multiple risk factors, metabolic syndrome, or subclinical organ damage. It has previously been mentioned that within this BP range, subclinical organ damage may not invariably lead to a high cardiovascular risk, and it is unclear how often this may occur. The evidence in favor of BP-lowering interventions in these patients is limited to that reported by the TROPHY [129] and the PHARAO studies [130], in which administration of an antihypertensive drug delayed the onset of hypertension (i.e., the crossing of the 140/90 mmHg cut-off). Whether this goal should be pursued mainly with lifestyle modifications or with addition of antihypertensive agents remains undetermined, however.

One last point deserves greater attention when making recommendations for medical practice. For a number of reasons (cost, progressively greater incidence of patient dropout, long-term management difficulties) randomized trials can only run for a few years and therefore extrapolation of the results to the frequently much longer life expectancy of patients is not without limitations. The extrapolation may fail to take into account that the benefit of antihypertensive treatment may become progressively more evident with time, possibly because regression of organ damage has a slow time course, in parallel with the long-term remodeling of large arteries,

Box 4. Blood pressure goals of treatment

(1) On the whole, there is sufficient evidence to recommend that SBP be lowered below 140 mmHg (and DBP below 90 mmHg) in all hypertensive patients, both those at low moderate risk and those at high risk. Evidence is only missing in the elderly hypertensive patients, in whom the benefit of lowering SBP below 140 mmHg has never been tested in randomized trials.

(2) The recommendation of previous guidelines to aim at a lower goal SBP (<130 mmHg) in diabetic patients and in patients at very high cardiovascular risk (previous cardiovascular events) may be wise, but it is not consistently supported by trial evidence. In no randomized trial in diabetic patients has SBP been brought down to below 130 mmHg with proven benefits, and trials in which SBP was lowered to below 130 mmHg in patients with previous cardiovascular events have given controversial results.

(3) Despite their obvious limitations and a lower strength of evidence, *post hoc* analyses of trial data indicate a progressive reduction of cardiovascular events incidence with progressive lowering of SBP down to about 120 mmHg and DBP down to about 75 mmHg, although the additional benefit at low BP values becomes rather small. At these low BP values also beneficial effects on organ damage have sometimes been observed. A J-curve phenomenon is unlikely to occur until lower values are reached, except perhaps in patients with advanced atherosclerotic artery diseases.

(4) On the basis of current data, it may be prudent to recommend lowering SBP/DBP to values within the range 130–139/80–85 mmHg, and possibly close to lower values in this range, in all hypertensive patients. More critical evidence from specific randomized trials is desirable, however.

Box 5. Choice of antihypertensive drugs

(1) Large-scale meta-analyses of available data confirm that major antihypertensive drug classes, that is, diuretics, ACE inhibitors, calcium antagonists, angiotensin receptor antagonists, and β-blockers do not differ significantly for their overall ability to reduce BP in hypertension.

(2) There is also no undisputable evidence that major drug classes differ in their ability to protect against overall cardiovascular risk or cause-specific cardiovascular events, such as stroke and myocardial infarction. The 2007 ESH/ESC guidelines conclusion that diuretics, ACE inhibitors, calcium antagonists, angiotensin receptor antagonists, and β-blockers can all be considered suitable for initiation of antihypertensive treatment, as well as for its maintenance, can thus be confirmed.

(3) Because the percentage of patients responsive to any drug class is limited and patients responsive to one drug are often not those responsive to another drug, keeping the number of drug options large increases the chance of BP control in a larger fraction of hypertensives. This is of crucial importance because cardiovascular protection by antihypertensive treatment substantially depends on BP lowering *per se*, regardless of how it is obtained.

(4) Each drug class has contraindications as well favorable effects in specific clinical settings. The choice of drug(s) should be made according to this evidence. The traditional ranking of drugs into first, second, third, and subsequent choice, with an average patient as reference, has now little scientific and practical justification and should be avoided.

(5) Drugs acting via direct renin inhibition are the only new classes of antihypertensive agents that have recently become available for clinical use. Several additional new classes are under an early investigational phase. Selective antagonism of endothelin receptors holds some promise to improve rate of BP control in hypertensive patients resistant to multiple drug treatment.

small arteries, and cardiac structure associated with a BP elevation [131]. This appears to be supported by the results of the few trials in which patients were followed for a number of years after termination of randomized treatment. In the SYST-EUR and SHEP trials, for example, the beneficial effects of antihypertensive treatment on the incidence of cardiovascular events remained evident years after termination of the double-blind phase of the trial, despite the fact that antihypertensive treatment was started also in the placebo group [132,133]. A similar phenomenon, which is referred to as the 'legacy effect', has also been reported for the Steno 2 trial [134], which reported a postinterventional benefit on the microvascular and macrovascular complications of type 2 diabetes after 13.3 years of follow-up with an intensive multifactorial therapy that included antihypertensive drugs and in the UKPDS trial [135] during a 10-year follow-up of the effect of a previous 10-year intensive blood glucose control in diabetes.

The most important points related to threshold and target BP values for treatment are summarized in Boxes 3 and 4.

Treatment strategies

Choice of antihypertensive drugs

In their 2003 [136] and 2007 versions [1], the European guidelines reviewed the large number of randomized trials of antihypertensive therapy, both those comparing active treatment versus placebo and those comparing treatment regimens based on different compounds (Box 5). They concluded that the main benefits of antihypertensive treatment are due to lowering of BP *per se*, and are largely independent of the drugs employed. Therefore, thiazide diuretics (as well as chlorthalidone and indapamide), β-blockers, calcium antagonists, ACE inhibitors, and angiotensin receptor antagonists can adequately lower BP and significantly and importantly reduce cardiovascular outcomes. All these drugs are suitable for the initiation and maintenance of antihypertensive treatment either as monotherapy or in some combinations with each other.

The issue of the equivalence of the various classes of antihypertensive agents, and of various agents within a given class, has been a long debated one, heralded in the 1970s by the incautious suspicion of a role played by reserpine in breast cancer [137], and continuing in the 1990s with the campaign against calcium antagonists as responsible for coronary events, bleeding, and cancer [138,139]. After the acquittal of calcium antagonists, even by their prosecutors, attention has been recently focused by different groups of investigators on a possible inferiority of β-blockers and diuretics as well as on the possible inferiority of ACE inhibitors for stroke prevention and of angiotensin receptor antagonists for coronary disease prevention. Obviously, paying careful attention to possible adverse effects or limitations of both new and old drugs is an obligation of physicians and clinical epidemiologists and must be taken seriously by members of guidelines committees. On the contrary, unfounded suspicion should not be used to deprive patients of the benefits of drugs.

β-*Blockers*

The evidence upon which β-blockers have been questioned as first choice antihypertensive drugs [140] and actually downgraded in the British recommendations [141] was discussed in the 2007 European guidelines.

New arguments on the place of β-blockers in antihypertensive therapy have been added since then [142–144]. In a meta-analysis of nine of 22 randomized controlled trials of β-blockers [145], a significant inverse correlation has been reported between the heart rate achieved by β-blocker therapy and cardiovascular outcomes (i.e., the lower the achieved heart rate, the higher the incidence of outcomes), including myocardial infarction and heart failure, known to be favorably influenced by β-blockade [146,147]. On the contrary, a recent meta-analysis of 147 randomized trials (the largest meta-analysis so far available) reports only a slight inferiority of β-blockers in preventing stroke (17% reduction rather than 29% reduction with other agents), but a similar effect as other agents on preventing coronary events and heart failure, and a higher efficacy than other drugs in patients with a recent coronary event [148]. Furthermore, the recent publication of a 20-year follow-up of the UKPDS trial [149] comparing atenolol and captopril in diabetes has found the incidence of cardiovascular outcomes to be similar in patients on the β-blocker or the ACE inhibitor, with a reduction in all-cause mortality favoring the β-blocker. This is consistent with retrospective observational data of large numbers of patients on different antihypertensive treatment regimens for longer periods than in randomized trials, showing that the incidence of cardiovascular outcomes was not higher on atenolol-based treatment than on other antihypertensive agents [150].

Finally, no systematic analysis has been made of the possible role of a smaller BP reduction by β-blocker-based treatment in those trials in which β-blockers appeared to have a smaller effect on stroke. For instance, interpolation of ASCOT data on stroke in the meta-regression analysis of the Blood Pressure Lowering Treatment Trialists' Collaboration [151] makes it clear that the odd ratio falls very close to the place expected because of the 2.7 mmHg difference in SBP between β-blocker/diuretic and calcium antagonist/ACE inhibitor treatments [152]. On the whole, however, β-blockers do not appear to be systematically inferior to other antihypertensive agents in their ability to reduce BP. A recent pooling analysis from more than 40 000 hypertensive patients under different monotherapies has shown no inferiority (and, possibly, a numerical superiority) of β-blocker monotherapy [153] in lowering brachial BP. However, studies like CAFÉ [154] suggest that, for the same brachial SBP, central SBP may be higher with β-blockers than with other antihypertensive agents because of a greater wave reflection due to bradycardia and/or peripheral vasoconstriction. This interesting observation deserves to be confirmed, although its real impact on antihypertensive management may be small because the difference between peripheral and central BPs is known to become attenuated at an older age [155,156], when hypertension and antihypertensive treatment are most common.

There is no doubt that β-blockers as well as diuretics (especially when combined together) have adverse metabolic effects and facilitate new-onset diabetes [157,158] in predisposed patients such as those with the metabolic syndrome or impaired glucose tolerance [55,159,160]. The importance of this phenomenon, however, may have been exaggerated by the way results of most prospective studies and trials have been analyzed; that is, by limiting analyses of changes in plasma glucose or in antidiabetic prescriptions to patients initially free of diabetes or with a blood glucose below 7.0 mmol/l (126 mg/dl). Indeed, a recent analysis of data from the 3.8-year long ELSA trial has shown that new diagnoses of diabetes at the end of this study in patients without diabetes at baseline are accompanied by a number of cases in which diagnosis of diabetes at baseline was no longer confirmed at the end of the study. However, the overall balance remains positive for new-onset diabetes [160]. Furthermore, it is still unclear whether drug-induced diabetes carries the same negative prognosis as naturally occurring diabetes, with some authors emphasizing studies showing that trial patients with new-onset diabetes do not have a higher incidence of cardiovascular outcomes during the trial and several years thereafter [133,161], whereas others underline the opposite conclusions in other studies [143,162–164].

It is also true that, when compared with other agents in trials using subclinical organ damage as an endpoint, β-blockers have been shown to be less powerful than ACE inhibitors, angiotensin receptor antagonists, and calcium antagonists in reducing an increased left ventricular mass [165], carotid IMT thickening [166], aortic stiffness [131], and increased small artery wall-to-lumen ratio [167–169], and this may be supposed to result in less cardiovascular protection in the long run. When discussing β-blockers, however, it should not be ignored that they are not a homogeneous class, and that vasodilating β-blockers, such as celiprolol, carvedilol, and nebivolol, appear not to share some of the negative properties described for other compounds. For instance, celiprolol lowers aortic stiffness and central pulse pressure [170], whereas atenolol does not [131]. Nebivolol, at doses producing the same BP reduction, lowers heart rate significantly less than atenolol [171], and because of the lesser bradycardia combined with peripheral vasodilatation, it has better effects on central BP than atenolol [172]. In the GEMINI study [173], carvedilol had less adverse effects on glycosylated hemoglobin, total cholesterol, and triglycerides than metoprolol; and nebivolol, at variance from metoprolol, has been found to improve insulin sensitivity [174] and to have the same metabolic effects as an ACE inhibitor [175]. Both carvedilol and nebivolol have been used in outcome trials in chronic heart failure (admittedly not in hypertension) and found capable of reducing the primary endpoint of mortality and hospitalization [176]: in COMET, carvedilol

treatment was accompanied by less new-onset diabetes than metoprolol [177], and in the SENIORS trial, new-onset diabetes had the same incidence on nebivolol or placebo [178]. When compared with metoprolol, carvedilol resulted in significantly less cases of microalbuminuria and progression to proteinuria in hypertensive diabetic patients [173], and nebivolol has recently been shown to improve coronary flow reserve and left ventricular filling pressure in the hypertensive heart [179]. Whether the protective cardiovascular action shown by carvedilol and nebivolol in patients with heart failure is also displayed in hypertension remains to be determined in a controlled trial.

Thiazide diuretics

A prominent role for thiazide-like diuretics in antihypertensive therapy, such as that given to these compounds in the JNC-7 report [66], is an object of continuing debate [143,161]. The evidence that a BP lowering induced by diuretics can reduce all types of cardiovascular events is robust [161], but it cannot be denied that most of the trials, the meta-analysis of which has been the basis for raising doubts on β-blockers, have also used thiazides. This makes it difficult to distinguish the separate role of these two drug classes. Likewise, the diabetogenic role of β-blockers and diuretics is difficult to discriminate, and when it has been dissociated diuretics appear worse than β-blockers [157]. Diuretics have rarely been studied in depth for their capacity to regress organ damage, and when tested have often been found inferior to calcium antagonists or ACE inhibitors [165,180,181]. Furthermore, all large studies that have explored the tolerability of various classes of antihypertensive agents on persistence to therapy have found diuretics to be, together with β-blockers, the least tolerated compounds [153] or those accompanied by the least persistence on treatment [182,183]. Finally, a recent meta-analysis has reported outcome benefit for low-dose but not for high-dose diuretics [184]. In addition, the results of the ACCOMPLISH trial (to be discussed in the preferred drug combinations section) have raised doubts as to whether thiazides are always the best protective component of combination therapy [185].

Angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists

The concept that ACE inhibitors may be somewhat inferior to other antihypertensive agents in preventing stroke has repeatedly been raised on the basis of some meta-analyses [148,186] and meta-regression analyses [187]. A pathophysiological hypothesis to support the claim that ACE inhibitors may be inferior to angiotensin receptor antagonists in preventing stroke has also been elaborated [188]. On the contrary, it has been suggested that angiotensin receptor antagonists would be inferior to ACE inhibitors in preventing myocardial infarction [189,190].

All these concepts, as well as their pathophysiological interpretations, have been undermined by the results of the very large ONTARGET, directly comparing cardiovascular outcomes under treatment with an ACE inhibitor (ramipril) or an angiotensin receptor antagonist (telmisartan) [191]. ONTARGET has shown telmisartan not to be statistically inferior to ramipril as far as the incidence of a composite endpoint including major cardiac outcomes are concerned. A similar incidence of strokes was also observed on both treatments. Recent meta-analyses including older and more recent trials confirm the conclusion that ACE inhibitors and angiotensin receptor antagonists have the same preventive effect on myocardial infarction [192,193].

The absolute benefit induced by the relatively small BP reduction produced by either treatment is more difficult to calculate, because ONTARGET was deliberately conducted in high-risk patients and for obvious ethical reasons could not include a placebo comparison arm. Therefore, it is difficult to decide whether the benefit has to be gauged from historical comparison with the placebo arm of the HOPE trial [93], carried out several years earlier, or with the placebo arm of the simultaneously run TRANSCEND, on patients intolerant to ACE inhibitors [108]. The patients of TRANSCEND treated with placebo had a slightly lower incidence of cardiovascular events than placebo-treated patients in HOPE, either because higher prevalence of concomitant therapies than in HOPE (but similar to that in ONTARGET) or because of a higher proportion of women.

ONTARGET [191] and TRANSCEND [108] have also provided some additional information on the respective role of an ACE inhibitor and an angiotensin receptor antagonist on the appearance of new diabetes in high-risk patients. Despite the fact that telmisartan has repeatedly been shown to possess PPAR-γ-activity [194], incidence of new diabetes was nonsignificantly different between telmisartan and ramipril in ONTARGET [191] and only slightly and nonsignificantly lower incidences were observed in TRANSCEND [108] and in PROFESS [91] with respect to the placebo group. However, most patients were also receiving other antihypertensive agents that may have obscured the specific antidiabetogenic effects of the drugs being tested. Despite these considerations, the claim that PPAR-γ-activity may give telmisartan a greater antidiabetogenic action remains unproven.

Calcium antagonists

Calcium antagonists have been cleared from the suspicion of causing a relative excess of coronary events by the same authors who had raised the suspicion [195]. On the contrary, some recent meta-analyses [148,186,187,196] suggest that these agents may have some additional advantage in preventing stroke, although it is not clear

whether this can be ascribed to a specific protective effect or to a slightly better BP control, often achieved in the calcium-antagonist-treated patients. It is still unclear whether calcium antagonists are less effective in protecting against new-onset heart failure, as is apparent in several studies and large meta-analyses [148,186]. The recent meta-analysis by Law *et al.* [148], however, shows that trials in which a BP difference was sought between an antihypertensive agent and control, the efficacy of calcium antagonists in preventing heart failure was only slightly lower than that of other antihypertensive agents (19 versus 24%). The question revolves around how much of this apparent inferiority of calcium antagonists is a real limitation in their cardiovascular protection, the result of a difficulty in diagnosing a clinically relevant but soft outcome such as an incipient heart failure, or a consequence of trial designs preventing the use of diuretics and ACE inhibitors (agents essential in heart failure therapy) in patients randomized to calcium antagonists. It is relevant that in trials in which a calcium antagonist was always or commonly administered in combination with a diuretic (FEVER [75]) or an ACE inhibitor (ASCOT [197]), there was no statistically significant excess of heart failure in the calcium antagonist arm. Incipient heart failure has also been found to be markedly reduced (−39%) in hypertensive patients on calcium antagonist treatment compared with those on placebo in the ACTION trial [96,198–200].

New antihypertensive drugs

The new drug that has substantially increased its database in the last 2 years is aliskiren, a direct inhibitor of renin at the site of its activation, which is now available for treating patients both in United States and Europe. The new data on aliskiren can be summarized as follows. First, although the specific advantages of interfering with the activation of renin are not yet clear [201,202], aliskiren has been shown to be effective in lowering SBP and DBP in hypertensive patients when given in monotherapy at a single daily dose. Second, the drug is effective also in combination with a thiazide diuretic, a calcium antagonist and an ACE inhibitor or an angiotensin receptor antagonist [203–205]. Third, data have recently emerged on the ability of aliskiren to protect against subclinical organ damage when combined with an angiotensin receptor antagonist. In one study in diabetic hypertensive patients with proteinuria, this drug combination led to a greater reduction in urinary protein excretion than the administration of an angiotensin receptor antagonist alone [206], but in another study on hypertensive patients with LVH, the combination did not cause a LVM reduction significantly greater than that obtained by administration of an angiotensin receptor antagonist alone [207]. In a third study in heart failure patients, this combination was significantly superior to angiotensin receptor antagonist administration in causing a reduction in the plasma concentration of brain natriuretic peptide [208], a recognized prognostic marker for heart failure [209]. It remains to be seen whether greater effects on organ damage may also be obtained by increasing the dose of traditional blockers of the renin–angiotensin system. The completion of ongoing hard endpoints trials with aliskiren in mono and combination therapies is expected with interest. Meanwhile the available evidence justifies its use in hypertension, particularly in combination with other agents. This is also supported by the favorable tolerance profile of aliskiren. The main side-effect appears to be an increased incidence of diarrhea, but only at doses higher than the recommended dose [203].

New antihypertensive agents that are currently under investigation include nitric oxide donors, vasopressin antagonists, neutral endopeptidase inhibitors, AT_2 angiotensin receptor agonists, and antagonists of endothelin receptors. Although their mechanisms of action hold promise of BP-lowering effectiveness and possibly of specific organ protection, their investigational phase is still far away from use in the clinical setting, and thus assessment of their pros and cons compared with current drug options is impossible. An exception is represented by endothelin receptor antagonists, because a compound of this class that selectively blocks ET_A receptors, darusentan, has been recently tested in patients defined as resistant, because of lack of BP control on treatment with at least three drugs, including a diuretic. Administration of darusentan on the top of the existing treatment significantly reduced office and 24 h mean BP over a 14-week period, with a doubling of the percentage of patients achieving BP control and only a moderate increase in the rate of side-effects (mainly edema and sodium retention) compared with placebo [210]. These results are potentially important because resistant hypertension is not a phenomenon of marginal proportion, the number of patients unable to achieve BP control despite multiple drug treatment being around 15–20% [211].

Is ranking antihypertensive agents in order of choice useful or deceiving in practice?

The 2007 European guidelines avoided ranking antihypertensive agents in order of choice. Ranking started with the first Joint National Committee report [212] and the 1978 WHO report [213], and was justified by the fact that the few available agents widely differed in tolerability and some of them could only be used in combination. With the development of several well tolerated classes of antihypertensive agents, the habit of ranking has continued for good reasons (such as the need to wait for the evidence of benefit by new agents) but also for less good reasons, such as the interest of pharmaceutical companies in having their drugs classified as 'first choice', or the pleasure of investigators to see their studies capable of awarding 'first rank' to a drug [152].

Box 6. Combination therapy

(1) Evidence has continued to grow that in the vast majority of hypertensive patients, effective BP control can only be achieved by combination of at least two antihypertensive drugs.
(2) Addition of a drug from another class to the initially prescribed one should thus be regarded as a recommendable treatment strategy, unless the initial drug needs to be withdrawn because of the appearance of side-effects or the absence of any BP-lowering effect.
(3) The combination of two antihypertensive drugs may offer advantages also for treatment initiation, particularly in patients at high cardiovascular risk in which early BP control may be desirable.
(4) Whenever possible, use of fixed dose (or single pill) combinations should be preferred, because simplification of treatment carries advantages for compliance to treatment.
(5) As mentioned in the 2007 ESH/ESC guidelines, several two-drug combinations are suitable for clinical use. However, trial evidence of outcome reduction has been obtained particularly for the combination of a diuretic with an ACE inhibitor or an angiotensin receptor antagonist or a calcium antagonist, and in recent large-scale trials for the ACE inhibitor/calcium antagonist combination. The angiotensin receptor antagonist/calcium antagonist combination also appears to be rational and effective. These combinations can thus be recommended for priority use.
(6) Despite trial evidence of outcome reduction, the β-blocker/diuretic combination favors the development of diabetes and should thus be avoided, unless required for other reasons, in predisposed patients. Use of an ACE inhibitor–angiotensin receptor antagonist combination presents a dubious potentiation of benefits with a consistent increase of serious side-effects. Specific benefits in nephropathic patients with proteinuria (because of a superior antiproteinuric effect) expect confirmation in event-based trials.
(7) In no less than 15–20% of hypertensive patients, BP control cannot be achieved by a two-drug combination. When three drugs are required, the most rational combination appears to be a blocker of the renin–angiotensin system, a calcium antagonist, and a diuretic at effective doses.

However, once it is agreed that (1) the major mechanism of the benefits of antihypertensive therapy is BP lowering *per se*, (2) the effects on cause-specific outcomes of the various agents are similar or differ by a minor degree, (3) the type of outcome to occur in a given patient is unpredictable, and (4) all classes of antihypertensive agents have their pros and cons (well summarized in Tables 7 and 8 of the 2007 ESH/ESC guidelines), it is obvious that any all-purpose ranking of drugs for general antihypertensive usage is unnecessary and probably deceiving [152]. It is on the basis of this striving for ranking that at different times investigators have been warning the media that millions of people may be dying every year because of the use of calcium antagonists, the use of β-blockers, or the use of angiotensin receptor antagonists. These campaigns cause lay people to wonder whether antihypertensive therapy is beneficial or dangerous. This behavior should be discouraged. Even reasons based on costs, often used to justify ranking, have recently been weakened by the advent of generic compounds within every class of antihypertensive agents.

The 2007 European guidelines [1], rather than indulging in an all-purpose ranking, decided to prepare a table with drugs to be preferred in specific conditions, on the basis of the concept that different classes and sometimes different agents within the same class have some properties that can make them more or less suitable in given conditions. This fits well the general purpose of European guidelines, that of being 'educational and not prescriptive or coercive for the management of individual patients who may differ widely in their personal, medical, and cultural characteristics' [1], thus requiring decisions different from the average ones recommended in several other guidelines.

Preferred drugs

Box 11 in the 2007 European guidelines [1] is the core for the ranking of agents for specific conditions rather than for general usage. No single agent is generally proscribed, but each agent can be preferentially prescribed in specific conditions [152]. Only minor differences from what indicated in the 2007 guidelines should be considered now, as discussed in specific sections below.

Monotherapy and combination therapy

Blood pressure lowering with the two approaches

The 2007 ESH/ESC guidelines underline that, no matter which drug is employed, monotherapy can effectively reduce BP in only a limited number of hypertensive patients, most of whom require the combination of at least two drugs to achieve BP control [1] (Box 6). A recent meta-analysis of 42 studies has shown that combining two agents from any two classes of antihypertensive drugs increases the BP reduction much more than doubling the dose of one agent [153]. Admittedly, the advantage of combination therapy over monotherapy may partly be due to the fact that any agent used in monotherapy is ineffective or scarcely effective in a number of patients, so that its combination with an agent effective in these patients must induce a greater response than doubling the dose of an ineffective agent. However, although it is possible that the use of two drugs together implies the administration of a futile one, searching for the most

effective monotherapy in every given patient is painstaking, and may discourage compliance (although pharmacogenetics may in future provide predictive clues). Furthermore, there are physiological and pharmacological synergies that justify the greater effectiveness of drug combinations, and this strategy appears to be that on which the selection of antihypertensive medication may be increasingly based. In a public health perspective, it seems desirable to foresee a substantial increase in the use of combination treatment in clinical practice from the relatively low prevalence of today [214]. This could help attain the goal of substantially improving BP control in the hypertensive population from its present low rate worldwide [215].

Two-drug combinations as first step treatment

The 2007 ESH/ESC guidelines [1] recommend the combination of two drugs to be considered as initial treatment whenever hypertensive patients have a high initial BP or are classified as being at high/very high cardiovascular risk because of the presence of organ damage, diabetes, renal disease, or a history of cardiovascular disease. This recommendation was not based on evidence from morbidity/mortality trials because in no study has the advantage of this approach been prospectively assessed. It was based on the arguments that (1) combination therapy can reduce BP to a greater extent and achieve the BP goal more promptly, (2) when a high-risk condition exists, an event may occur within a relatively short time interval, requiring protective interventions to be implemented without an excessive delay, (3) in several trials, the protective effect of BP reduction became manifest shortly after initiation of the BP-lowering treatment, and (4) initial combination treatment may be associated with a lower degree of treatment discontinuation, possibly because treatment discontinuation (an extremely common phenomenon [182,183,216]) depends also on the frustration that originates from the patient's perception of the inability to reach BP control [217]. In a *post hoc* analysis of the VALUE trial [109], the cardiovascular event rate was less regardless of the type of treatment in patients in whom BP control (<140/90 mmHg) was achieved within 1 month. Although suggestive, the VALUE data obviously do not provide indisputable evidence for the advantage of early BP control (and thus initiation of treatment with a two-drug combination), as it is possible, and even likely, that the immediate responders might have been at lower cardiovascular risk, which could also be the reason for the more prompt BP reduction obtained with treatment. In order to validate combination therapy as a first step strategy at least in high-risk hypertensive patients, an appropriate trial could be conducted comparing earlier BP control by a combination of two drugs to later control achieved by initial monotherapy followed by the two-drug combination in those patients requiring it. However, it appears doubtful that the issue really deserves trial evidence, and probably the choice between initiating with monotherapy or combination may better be based on the wisdom of the previously mentioned arguments.

Preferred drug combinations

Some of the large-scale trials published in the last 2 years importantly expanded information on the advantages and disadvantages of several two-drug combinations in hypertension. The new evidence available and its implications for guidelines recommendations are discussed below.

Angiotensin-converting enzyme inhibitor–diuretic combinations The combination of an ACE inhibitor, perindopril, and the diuretic indapamide had already been shown in the PROGRESS study to have a greater BP-lowering effect than the ACE inhibitor alone and, in parallel, a much greater preventive effect on recurrent stroke [89]. In ADVANCE [88], the same combination of indapamide and perindopril given to patients with type 2 diabetes (on top of continuation of preexisting therapy) for more than 4 years was followed by a significantly greater antihypertensive effect than administration of placebo (SBP and DBP difference −5.6 and −2.2 mmHg, respectively). This was associated with a reduced incidence (−9%) of diabetes-related complications (composite endpoint of macrovascular and microvascular outcomes). In addition, the perindopril–indapamide combination was well tolerated with an overall rate of adverse effects only slightly greater than that observed in the placebo group, and a high number of patients (>80%) remaining on active drug treatment throughout the trial. Similarly, in the large majority of the very elderly patient of HYVET [84], the administration of the indapamide–perindopril combination resulted in a greater BP reduction as well as a lower rate of cardiovascular outcomes and serious side-effects compared with placebo.

Angiotensin-converting enzyme inhibitor–calcium antagonist combinations A combination of an ACE inhibitor and a dihydropyridine calcium antagonist was the most widely used combination therapy in Syst-Eur and Syst-China [81,82], as well as in the HOT study [99] in order to achieve lower BP goals. INVEST used the combination of a nondihydropyridine calcium antagonist, verapamil, and the ACE inhibitor trandolapril with comparable beneficial effects as the combination of a β-blocker and a diuretic [111]. The combination amlodipine–perindopril was widely used in the ASCOT study, being more effective in lowering BP and cardiovascular events than the combination of a β-blocker with a thiazide [197].

In the ACCOMPLISH trial [185], more than 11 000 hypertensive patients with a relatively elevated cardiovascular risk were randomized, after stopping previous treatment, to receive an ACE inhibitor, benazepril, plus either the calcium antagonist amlodipine or hydrochlorothiazide. Over the 3 years of follow-up, both treatments

reduced BP very effectively, the average on-treatment values being 132.5/74.4 mmHg in the hydrochlorothiazide group and about 1 mmHg lower (131.6/73.3 mmHg) in the calcium antagonist group. The rate of serious side-effects was limited and similar between the two groups. In the group receiving the benazepril–amlodipine combination, however, the incidence of the primary endpoint (a composite of several cardiovascular fatal and nonfatal events) was 20% less than in the group receiving the benazepril–hydrochlorothiazide combination, with a significant reduction also in cause-specific events such as myocardial infarction, although not heart failure. This provides outcome evidence in favor of the concomitant administration of an ACE inhibitor and a calcium antagonist that was hitherto unavailable. However, it would be premature to conclude from this trial that an ACE inhibitor–calcium antagonist combination is inherently and invariably superior to the combination of an ACE inhibitor and a diuretic. In ACCOMPLISH, the rate of cardiovascular outcomes was lower than expected in high-risk patients, possibly because of the extensive use of statins (68%), antiplatelet agents (65%), and revascularization procedures (18–20%). The ACCOMPLISH findings may also depend on the large proportion of diabetic patients included (60%): indeed, in the STAR study [218], hypertensive patients with an impaired fasting glucose exhibited a worse metabolic response to the glucose load test (as well as a greater rate of new-onset diabetes) if treated with a combination of a blocker of the renin–angiotensin system and a diuretic than if treated with the combination of a renin–angiotensin system blocker and a calcium antagonist.

Combination of an angiotensin receptor antagonist with a calcium antagonist or a diuretic An angiotensin receptor antagonist has been frequently combined with a diuretic in a number of trials, such as LIFE [219] and SCOPE [83,220], which have documented the protective effects of this treatment strategy. Until now, no outcome study has been conducted using the combination of an angiotensin receptor antagonist with a calcium antagonist. An exception is the RENAAL trial, in which the benefit of losartan (versus placebo) in delaying progression to end-stage renal disease was seen on the top of preexisting antihypertensive therapy frequently including calcium antagonists [105]. Furthermore, a large body of evidence exists that combining an angiotensin receptor antagonist with a calcium antagonist or a diuretic provides an effective reduction of BP and a high rate of BP control in a variety of hypertension categories, has a tolerability profile even more favorable than that seen when an ACE inhibitor is used instead (because cough and angioedema are much less frequently seen) and protects against subclinical organ damage [221–223]. Evidence has grown in particular on the combination of an angiotensin receptor antagonist with a calcium antagonist (usually amlodipine), which has been proved capable of most effectively reducing even severe hypertension [223,224].

Combinations of calcium antagonists with diuretics or β-blockers Despite the fact that small pharmacologic studies have raised doubts on the synergistic effects of adding a diuretic to a calcium antagonist, this combination was included in the recent meta-analysis by Wald *et al.* [153] without detracting from the demonstration of a greater BP-lowering effect of combining calcium antagonists with other drugs compared with doubling the calcium antagonist dose in monotherapy. Even more importantly, the association of a calcium antagonist with a diuretic has been used in the FEVER, ELSA, and VALUE trials [75,166,225] with greater benefits. No outcome trial has explored the combination of a calcium antagonist with a β-blocker, but this has been the second used association in the HOT study [99].

Angiotensin-converting enzyme inhibitor–angiotensin receptor antagonist combinations The 2007 ESH/ESC guidelines [1] did not regard the combination of an ACE inhibitor and an angiotensin receptor antagonist among those best suited for widespread use because they act, though at a different level, on the same BP control mechanism, that is, the renin–angiotensin system. The 2007 European guidelines, however, reported some results in chronic kidney disease or diabetic patients [226], mostly with proteinuria, claiming a greater antiproteinuric effect than with administration of an ACE inhibitor or an angiotensin receptor antagonist alone. The widespread use of this combination has now been questioned by the results of ONTARGET [53,191], in which the combination of full doses of telmisartan and ramipril reduced the initial BP values slightly more than the reduction seen with the administration of one or the other drug alone, without, however, any further reduction in cardiovascular or renal endpoints (except proteinuria), and indeed with a greater number of renal side effects and a more frequent discontinuation of the initial treatment. As mentioned in a previous section, a *post hoc* analysis of the BP changes in ONTARGET [115] has elaborated the hypothesis that excessive lowering of BP in patients whose baseline BP was less than 130 mmHg (either spontaneously or as effect of previous therapy) may have been responsible for an excess rather than a reduction of cardiovascular events. An alternative explanation that has been advanced [63] is that in ONTARGET, the multiple therapies used had already brought these high-risk patients to the bottom level of cardiovascular risk achievable, and that combination of the full doses of two blockers of the renin–angiotensin system could not further reduce the risk. However, the adverse effects of the administered drugs were free to manifest themselves. Furthermore, the reasons have been discussed that make it difficult to extrapolate the

ONTARGET findings to the general population of hypertensive patients.

Nonetheless, the results of ONTARGET do not support large-scale use of this combination of drugs in hypertension and suggest that its use in proteinuric renal patients should be studied further and more critically. A recent meta-analysis of 49 studies, albeit small and mostly short term, has confirmed that the combination of the two blockers of the renin–angiotensin system has significantly greater antiproteinuric effect than either component [227]. However, although reduction of proteinuria is often considered to lead to and/or reflect renoprotection (i.e., delayed occurrence of end-stage renal disease) [228], proteinuria reduction, particularly in short-term studies, should not be taken as necessarily equivalent to renal function preservation and prevention of cardiovascular outcomes. An example of this are some findings of the ONTARGET study [53] already discussed.

In this context, it should be remembered that the results of the only study (the COOPERATE study) that reported a superior protective effect of double blockade of the renin–angiotensin system on renal outcomes [229] have been questioned [230,231]. Also, the widely quoted favorable results of concomitant ACE inhibitor and angiotensin receptor antagonist administration reported in trials on patients with left ventricular dysfunction or heart failure should be considered cautiously, as the benefits were not seen in all trials (absent in VALIANT [232]), or they were small (Val-HeFT [233]) or evident only if hospitalization was added to mortality (CHARM [234]). Finally, in all these trials, the combination markedly increased the incidence of side-effects such as hyperkalemia and an elevation in serum creatinine.

Fixed dose (or single pill) combinations

Guidelines have long favored the use of combination of two antihypertensive drugs at fixed doses in a single tablet, because reducing the number of pills that have to be taken daily has been shown to improve compliance [235], which is low in hypertension. Use of fixed dose combinations of two drugs can directly follow initial monotherapy when addition of a second drug is required to control BP, or be the first treatment step when a high cardiovascular risk makes early BP control desirable. This approach is now facilitated by the availability of different fixed dose combinations of the same two drugs, which minimizes one of its inconveniences, that is, the inability to only increase the dose of one drug but not that of the other.

Conclusion

New and old evidence strongly supports combination treatment as the most effective strategy to control BP, and therefore recommends treatment strategies largely based on the addition of a drug from another class to the initially prescribed agent, whenever BP control is not achieved, unless the starting drug needs to be changed because of side-effects or the absence of any BP reduction. It suggests that the combination of two antihypertensive drugs may offer advantages also as first step treatment, particularly in patients at high cardiovascular risk, in whom early BP control may be desirable. It favors, whenever possible, the use of fixed dose combinations of two drugs in a single tablet because of the advantage brought about by simplification of the treatment regimen. Finally, it warns against the use of a combination of an ACE inhibitor and an angiotensin receptor antagonist at least in very high cardiovascular risk patients such as those in ONTARGET. It remains to be established whether the latter combination may have a beneficial role in patients with chronic renal disease and proteinuria, or even in some lower risk hypertensives.

Because the 2007 European guidelines did not include the ACE inhibitor–angiotensin receptor antagonist combination between the preferred combinations, the scheme they presented does not appear to require substantial modification at present. It should be underlined, however, that outcome reduction has been documented in trials using the following combinations: ACE inhibitor and diuretic, angiotensin receptor antagonist and diuretic, calcium antagonist and diuretic, and ACE inhibitor and calcium antagonist. Successful trials have also used β-blocker and diuretic in association, but this is the combination more easily inducing new diabetes in predisposed patients [158].

Finally, it is important to remember that no less than 15–20% of the patients need more than two antihypertensive drugs to achieve an effective BP reduction. The combination of a blocker of the renin–angiotensin system, a calcium antagonist and a thiazide diuretic may be a rational three-drug combination, although other drugs, such as a β-blocker or an α-blocker, may be included in a multiple approach, depending on the clinical circumstances.

Therapeutic approach in special conditions

Elderly

Both the 2003 [136] and 2007 ESH/ESC guidelines [1] regretted that, although there was overwhelming evidence of the benefits (outcome reduction) of pharmacological lowering of BP in the elderly, this evidence was inconclusive for patients aged 80 years or above, in whom only a meta-analysis of a limited number of patients from various trials [236] and the pilot HYVET [237] were available, suggesting beneficial effects for morbidity but not for mortality.

Now this gap in the evidence has been filled with the much expected publication of the results of the HYVET [84]. In HYVET, 3845 patients aged 80 years or more in whom entry SBP was 160 mmHg or more (average 173 mmHg) were randomized to receive either placebo or

active treatment, consisting of indapamide (1.5 mg daily) and the eventual addition of the ACE inhibitor perindopril (2 and 4 mg daily) with the target to attain a SBP value below 150 mmHg. Drug administration (with the indapamide–perindopril combination given in about three-quarters of the patients) reduced BP to a value much lower than placebo, that is, 144/78 versus 161/84 mmHg. This was accompanied by clear-cut beneficial effects, and, according to advice from the safety board, the trial was stopped after an average treatment duration of less than 2 years. The beneficial effects consisted of a 30% reduction in stroke (just short of statistical significance) and statistically significant reductions in congestive heart failure (64%), major cardiovascular events, and all-cause death (21%). These results indicate that even in the very elderly stratum of the population, antihypertensive treatment does not only prevent cardiovascular morbid events but also translates into prolongation of life.

On the basis of the important evidence provided by HYVET [84], guidelines can now more positively recommend that antihypertensive treatment be extended to hypertensive patients aged 80 years and above. However, in consideration of the very old age of the patients to which recommendations are directed, the characteristics of the population included in HYVET and the nature of the study should be given some attention, in order not to extend treatment recommendations to individuals or contexts different from those of HYVET. HYVET deliberately recruited patients without cardiovascular disease, and in good physical and mental conditions, and excluded ill and frail individuals who are so frequent among octogenarians. Although alterations of baroceptor control often occur in the very elderly [238], HYVET patients had similar BP values in the sitting and standing positions even on treatment, confirming the interpretation that particularly healthy individuals were enrolled. The report that incidence of adverse effects was lower in the active treatment arm than in the placebo arm, underlines the excellent tolerability of drugs used and the fact that the adverse effects were more likely to be due to the hypertension *per se* than to the treatment. Nonetheless, this supports once more the highly selected nature of the octogenarians enrolled. Finally, the premature interruption of the trial made its duration so short (1.8 years) as to leave unanswered the question whether the benefit of antihypertensive treatment persists for several years.

In conclusion, an evidence-based general recommendation can now be given to prescribe antihypertensive treatment to octogenarians with SBP above 160 mmHg with the target to lower it below 150 mmHg, but because of differences in the general health of very elderly patients, the decision to treat should be taken on an individual basis, and BP lowering should be in any case gradual and carefully monitored by the doctor.

Since the publication of the 2007 ESH-ESC guidelines, some additional useful information on the treatment of hypertension in the elderly has been added. A large prospective meta-analysis of major antihypertensive therapy trials has been published, showing that patients aged less or more than 65 years achieve the same proportional benefit from a given lowering of BP and there is no hint that different classes of antihypertensive drugs are more efficacious in reducing outcomes in younger or older patients [239]. The latter information confirms what was already pointed out in the 2007 ESH/ESC guidelines, that in the elderly drug treatment can be initiated with thiazide diuretics, calcium antagonists, angiotensin receptor antagonists, ACE inhibitors, and β-blockers, which is in line with general guidelines. The HYVET adds further evidence to the role of diuretics and ACE inhibitors. For isolated systolic hypertension of the elderly, there are three trials [78,81,82] that have used a diuretic [78] and a calcium antagonist [81,82], respectively, as first-line treatment.

As mentioned previously, a recent reappraisal of trials [71] has underlined that no single trial on hypertension in the elderly [76–85] has enrolled patients with grade 1 hypertension (i.e., SBP 140–159 mmHg). Furthermore, in no placebo-controlled trial of antihypertensive treatment in the elderly [76–84], on-treatment SBP values have been lowered to less than 140 mmHg, and the only trial comparing achieved SBP values below and above 140 mmHg [85] is also the only one unable to demonstrate a benefit of more intense therapy, although the trial was underpowered because of a limited number of events. Although clearly not evidence based, the recommendations of the 2007 ESH/ESC guidelines to initiate antihypertensive therapy in the elderly according to the same criteria used for younger individuals (i.e., for SBP $\geq$140 mmHg) and to use the same SBP goal as in younger patients can still be considered as prudent recommendations, particularly when treatment is well tolerated. However, firm evidence on these two clinically important issues should be obtained through appropriately designed new trials.

A reassessment of recommendations on treatment of the elderly with hypertension is given in Box 7.

Diabetes mellitus

Reappraisal of antihypertensive treatment trials on diabetic patients [71] has strengthened the information provided in the 2007 ESH/ESC guidelines, by clearly showing that the evidence in favor of initiating BP-lowering therapy in diabetic patients with high normal BP is quite scanty, and that favoring a SBP target below 130 mmHg is almost nonexistent. Added to the recognized difficulty of achieving SBP values less than 130 mmHg in diabetic patients [240], the critical reappraisal of trial data suggests that the recommendation commonly given to all hypertensives, to

Box 7. Antihypertensive treatment in the elderly

(1) Since the publication of the last guidelines, evidence from large meta-analyses of published trials confirms that in the elderly antihypertensive treatment is highly beneficial. The proportional benefit in patients aged more than 65 years is no less than that in younger patients.

(2) Data from meta-analyses do not support the claim that antihypertensive drug classes significantly differ in their ability to lower BP and to exert cardiovascular protection, both in younger and in elderly patients. The choice of the drugs to employ should thus not be guided by age. Thiazide diuretics, ACE inhibitors, calcium antagonists, angiotensin receptor antagonists, and β-blockers can be considered for initiation and maintenance of treatment also in the elderly.

(3) In the elderly, outcome trials have only addressed patients with an entry SBP at least 160 mmHg, and in no trial in which a benefit was shown achieved SBP averaged less than 140 mmHg. Evidence from outcome trials addressing lower entry and achieving lower on-treatment values are thus needed, but common sense considerations suggest that also in the elderly drug treatment can be initiated when SBP is higher than 140 mmHg, and that SBP can be brought to below 140 mmHg, provided treatment is conducted with particular attention to adverse responses, potentially more frequent in the elderly.

(4) At variance from previous guidelines, evidence is now available from an outcome trial (HYVET) that antihypertensive treatment has benefits also in patients aged 80 years or more. BP-lowering drugs should thus be continued or initiated when patients turn 80, starting with monotherapy and adding a second drug if needed. Because HYVET patients were generally in good conditions, the extent to which HYVET data can be extrapolated to more fragile octogenarians is uncertain. The decision to treat should thus be taken on an individual basis, and patients should always be carefully monitored during and beyond the treatment titration phase.

lower systolic BP as much as possible below 140 mmHg, appears realistic and prudent for diabetic patients too. More complicated is a decision about initiation of pharmacological therapy when BP values are still in the high normal range. If deferring treatment due to the lack of solid evidence appears legitimate, it also seems reasonable to give due consideration to data showing prevention of progression or enhancement of regression of organ damage, particularly microalbuminuria, which is especially ominous in diabetic patients because it reflects a greater risk of end-stage renal disease and cardiovascular events [241]. In this context, the results of ADVANCE are interesting because a beneficial effect of treatment on microalbuminuria and proteinuria was seen at normotensive BP levels, although normotension was often achieved by the previous use of antihypertensive drugs, with a clear-cut reduction in the appearance of new microalbuminuria (−21%) [123]. This expands the evidence on the ability of antihypertensive drug treatment to exert a primary preventive influence against diabetic nephropathy [86,242,243]. However, the crucial issues of whether to initiate antihypertensive treatment in diabetic patients with high normal BP and whether goal BP should be lower than that recommended in the general hypertensive population should be explored through suitably designed intervention trials.

As to antihypertensive drugs to be preferred in diabetes, the 2007 ESH/ESC guidelines based their recommendation to use any agent capable of effectively lowering BP on the evidence of a large meta-analysis showing substantial equivalence of antihypertensive agents belonging to various classes in preventing cardiovascular outcomes in diabetes [186]. This recommendation was coupled to that of using combinations of drugs that include an agent blocking the renin–angiotensin system, because of the particular effectiveness of this type of agent on renal protein excretion and long-term preservation of renal function. The only large study exclusively devoted to diabetics completed after the 2007 guidelines, the ADVANCE trial [88], used the combination of a diuretic, indapamide, and an ACE inhibitor, perindopril, often on top of preexisting antihypertensive agents to produce some further BP decrease associated with a significant albeit modest reduction (9%) in the combined endpoint of macrovascular and microvascular complications, a significant 14% reduction of all cause mortality, and a significant 21% reduction of renal outcomes, such as proteinuria, microalbuminuria, doubling of serum creatinine, dialysis and renal transplantation. ACCOMPLISH, though not entirely devoted to diabetes, included 60% of diabetic patients among the more than 11 000 individuals enrolled. The study compared the use of an ACE inhibitor, benazepril, in association with either the calcium antagonist amlodipine or the diuretic hydrochlorothiazide and reported superiority of the ACE inhibitor–calcium antagonist combination [185].

Although diabetic-dependent microvascular complications are all related to BP within a wide range of values [244], antihypertensive treatment appears to affect them in a different fashion. BP reduction has a pronounced protective effect on renal complications (see Renal disease section). However, it does not appear to substantially affect neuropathy [245], whereas data on the ability of BP-lowering strategies to protect against eye complications are not consistent. Several years ago, the UKPDS study [246] reported a reduced incidence of various eye

Box 8. Antihypertensive treatment in diabetic patients

(1) In diabetic patients, antihypertensive treatment should be always initiated when BP is 140/90 mmHg or more. Initiation of treatment in the high normal BP range is at present not sufficiently supported by outcome evidence from trials. It can, nevertheless, be recommended, particularly when microalbuminuria is present, based on the evidence of its favorable effect on regression and progression of this sign of organ damage.
(2) The BP goal traditionally recommended in diabetes, that is, less than 130/80 mmHg is also not supported by outcome evidence from trials, and has also been very difficult to achieve in the majority of the patients. Thus, it appears realistic to only recommend to pursue a sizeable BP reduction without indicating a goal which is unproven.
(3) Meta-analyses of available trials show that in diabetes all major antihypertensive drug classes protect against cardiovascular complications, probably because of the protective effect of BP lowering *per se*. They can thus all be considered for treatment.
(4) In diabetes, combination treatment is commonly needed to effectively lower BP. A renin–angiotensin receptor blocker should always be included because of the evidence of its superior protective effect against initiation or progression of nephropathy.
(5) In hypertensive diabetic patients, tight blood glucose control (HbA_{1c} to 6.5%) is beneficial, particularly on microvascular complications. Recent evidence suggests that combining effective blood glucose and BP control increases protection, particularly of the kidney.
(6) Tight blood glucose control should not be pursued abruptly and patients should be monitored closely because of the increased risk of severe hypoglycemic episodes.
(7) Microvascular complications of diabetes in different organs are differently affected by treatment. Antihypertensive treatment exerts a major protective effect against renal complications, whereas evidence of a similar effect on eye and neural complications is less consistent.

lesions (and of eye interventions) in hypertensive type 2 diabetic patients under tight versus those under standard BP control, strengthening the favorable conclusion drawn from previous smaller or less controlled studies [86,247,248]. However, no significant beneficial effects of BP reduction by an ACE inhibitor–diuretic combination on eye complications has recently been reported in the hypertensive type 2 diabetic patients of ADVANCE [88,249], and substantially negative data have also resulted from the DIRECT trial in normotensive type 1 diabetic patients in whom BP was reduced by an angiotensin receptor antagonist [250]. Interestingly, the inconsistency between older and more recent studies extends to the effect of tight blood glucose control on eye complications, with favorable reports from UKPDS [251] and negative ones from ADVANCE [249]. Whether a protective effect of BP and glucose control on diabetic retinopathy may only be observed in early phases of the disease and on appearance rather than progression of retinopathy remains to be tested by specific trials.

Recommendations on antihypertensive management of diabetes are summarized in Box 8.

Renal disease

As mentioned in previous sections, in the last 2 years, further evidence has accumulated in favor of targeting reduction of microalbuminuria and proteinuria, mostly through blockers of the renin–angiotensin system, in order to reduce end-stage renal disease and cardiovascular events. A *post hoc* analysis of RENAAL data indicates that the incidence of end-stage renal disease showed an independent relationship with SBP and albuminuria reduction, suggesting that improving renal outcomes in patients with diabetic nephropathy may require a dual strategy, targeting both BP and albuminuria [228]. Also, in the type 2 diabetic patients of ADVANCE, urinary protein excretion (both baseline and on-treatment values) has been reported to be closely correlated with the primary outcome of the study (macrovascular and microvascular events) [18]. On the contrary, ONTARGET has recently reported that the combination of full doses of the ACE inhibitor ramipril and the angiotensin receptor antagonist, telmisartan, though reducing BP a few mmHg more than therapy with either ramipril or telmisartan and influencing progress of proteinuria to a slightly but significantly greater extent, was accompanied by a greater incidence of renal outcomes (mostly acute dialysis and doubling of serum creatinine) and by no further reduction of cardiovascular outcomes [53,191]. As mentioned in a previous section, only a minority (about 4%) of ONTARGET patients had overt proteinuria at baseline, whereas worsening of renal outcomes mostly occurred in the patients without baseline microproteinuria or macroproteinuria, in whom changes in urinary protein excretion could only differ to a minor degree [53]. Finally, the changes in urinary protein excretion were small and so the between-treatment differences in renal outcomes were quite infrequent (2.03, 2.21, and 2.49% with ramipril, telmisartan, and the combination, respectively). Therefore, ONTARGET patients can hardly be compared to the more severe nephropathy cohorts in whom the role of urinary protein excretion in predicting end-stage renal disease was mostly investigated. When the effects of telmisartan versus placebo on renal outcomes were studied in the TRANSCEND trial [108], no significant differences were found as far

as rate of GFR decline and end-stage renal disease is concerned [252]. No data on renal outcomes are available from PROFESS [91], also comparing telmisartan with placebo.

The 2007 ESH/ESC guidelines [1] shared with other guidelines [66,253] the recommendation to lower BP below 130/80 mmHg in renal patients, but it recognized that evidence from trials having renal patients randomized to more versus less intense BP lowering was scanty. Little additional evidence, either pro or con this lower BP target, has been accumulated since. No large trial completed in the last 2 years focused on patients with renal dysfunction, and in no instance SBP was brought below the target of 130 mmHg. A meta-analysis, from randomized controlled trials of BP lowering in patients on dialysis, is of interest: BP-lowering treatment was associated with a significant reduction in cardiovascular events (29%), all-cause mortality (20%) and cardiovascular mortality (29%), for a SBP/DBP difference versus control of −4.5/−2.3 mmHg [254]. Regretfully, no information was provided about the absolute BP values achieved with treatment, although the finding that the protective effects were significant only in the subgroup of hypertensive patients may suggest that on-treatment BP values were not particularly low. The matter is further complicated by the extensive use of blockers of the renin–angiotensin system in renal patients. These drugs are thought to possess specific renal protective properties, which make the effect attributable to BP reduction more difficult to unravel.

Cerebrovascular disease

Stroke and transient ischemic attacks

It has been pointed out that the results of the PROGRESS trial, though clearly showing the benefits of lowering BP in patients with previous cerebrovascular events [89], cannot be taken to support a recommendation to initiate BP-lowering treatment in cardiovascular patients with BP in the high normal range, as in this trial the benefits of treatment were seen only in individuals with a baseline SBP of 140 mmHg and above, who often were on antihypertensive drugs already [90]. Nor can the PROGRESS data be taken to support a SBP target below 130 mmHg, as the average SBP achieved on more intense treatment was 132 mmHg. However, the trial did show that an on-treatment SBP of 132 mmHg was better than an on-treatment SBP of 141 mmHg, that is, the average SBP of the placebo patients. In the other trial that first showed the benefits of BP lowering in patients with cerebrovascular disease, the PATS study [255], SBP values remained too high (143 and 149 mmHg in the active and placebo arms of the trial, respectively) to help clarify when to initiate treatment and to what level should BP be lowered in cerebrovascular patients. The same is the case for ACCESS [256]. Finally, it cannot be denied that the matter has been further confused by the recent publication of the negative results of the PROFESS study [91]. In this very large trial, in patients with previous stroke or transient ischemic attack, bringing SBP to 136 mmHg by adding telmisartan, rather than to 140 mmHg by adding placebo, was not accompanied by any significant reduction in recurrent strokes or major cardiovascular events. Various interpretations have been given for these unexpected negative findings: the small BP difference, in line with the evidence from the PROGRESS that the small BP difference in patients on monotherapy also failed to significantly reduce outcomes, the short duration of the follow-up (only 2.5 years), the frequent use of concomitant therapy (all patients were on antiplatelet agents and half of them were on lipid-lowering agents), the large dropout of patients during treatment, and the initiation of treatment very close to the qualifying cerebrovascular event. The fact remains that PROFESS has not really helped to clarify the remaining issues about antihypertensive treatment of the cerebrovascular patient.

A matter of continuing concern is the optimal BP management during the acute phase of stroke. The results of a small trial, the Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS), suggest a beneficial impact of administering lisinopril or atenolol in patients with acute stroke and a SBP more than 160 mmHg [257], but many of the current uncertainties remain to be clarified.

Cognitive dysfunction and dementia

The 2007 ESH/ESC guidelines stressed the importance of better clarifying the role of high BP and BP-lowering treatment on the development of cognitive dysfunction and dementia but acknowledged that the available evidence was scanty and confusing [1]. Little further evidence has been added in the past 2 years, except for the results of the HYVET on hypertensive octogenarians. All patients included in this trial were tested at baseline and yearly during treatment for cognitive function with the Mini-Mental State Exam (MMSE), and patients whose score fell to less than 24 or by more than three points in any one year, were assessed with further tests in order to investigate possible incident dementia. The results showed only a nonsignificant trend for reduction of both cognitive decline and dementia with active treatment (hazard ratio 0.86 with 95% confidence intervals of 0.67–1.09) [258]. Thus, the results of HYVET cannot help to clarify the matter, but the characteristics of the study have not been well suited for investigating dementia: indeed, at baseline, all individuals were rather healthy and with a good cognitive function and, in particular, the short duration of the follow-up (only 2 years) was unlikely to allow precise assessment of a slowly developing condition such as cognitive decline. The relationship between high BP, antihypertensive therapy, and cognitive loss is an important issue that deserves further studies, although it should be recognized these studies are difficult to design and conduct. In this

context, it is promising, but by no means conclusive, that a meta-analysis that included HYVET and other placebo-controlled trials showed a small and statistically significant reduction in the incidence of dementia (−13%) in the actively treated patients [258].

Coronary heart disease and heart failure

It has already been extensively discussed whether the current recommendation to lower SBP below 130 mmHg in patients with concomitant coronary heart disease is well founded. It has been pointed out that some of the analyses of recent trials raising the possibility that low achieved BP values are associated with increased rather than decreased risk of cardiovascular outcomes [113,115] are *post hoc* with well known limitations. It has also been recognized that a reappraisal of all trials of antihypertensive agents in patients with coronary heart disease has provided contradictory evidence on the presence or absence of benefits of lowering SBP below 130 mmHg [71]. Until firmer evidence is provided by new trials, it appears reasonable to lower SBP down to the 130–139 mmHg range in patients with concomitant coronary heart disease.

The failure to significantly reduce heart failure with preserved systolic function in the I-PRESERVE study [259] has to be pointed out. Although this type of heart failure is most often related to hypertension, in I-PRESERVE randomization to the angiotensin receptor antagonist, irbesartan, or to placebo, in more than 4000 patients with chronic heart failure and a left ventricular ejection fraction more than 0.45 (88% of whom had a history of hypertension) did not show any difference in the primary endpoint of death from any cause or hospitalization for a cardiovascular cause as well as in the secondary outcome of a composite of heart failure events. This occurred despite a 3.5/2.0 mmHg SBP/DBP difference in favor of irbesartan. The negative results of I-PRESERVE, however, should be seen in the context of the complex design of the trial, in which a background of intense antihypertensive therapy, including 25% of ACE inhibitors (39% during the trial), was maintained, and initial BP was only 136/79 mmHg, thus further strengthening the question as to whether lowering SBP much below 140 mmHg is of any further benefit. It should be noted that 59% of I-PRESERVE patients were on antiplatelet agents, 19% on oral anticoagulant therapy, and 30% on lipid-lowering agents.

The efficacy of angiotensin receptor antagonists in the prevention of heart failure has come under some discussion also as a result of the TRANSCEND [108] and PROFESS [91] studies. In both these placebo-controlled trials, randomization to telmisartan did not reduce the incidence of hospitalization for heart failure below that occurring on placebo. In ONTARGET [191], the number of hospitalizations for heart failure was lower (though not significantly) with ramipril than with telmisartan. However, the risk of heart failure in all these trials was rather low, and definitive conclusions cannot be reached at present.

Atrial fibrillation

The 2007 ESH/ESC guidelines summarize evidence from *post hoc* analyses of heart failure [233,260,261] and hypertension trials [262,263] showing a lower evidence of new atrial fibrillation in patients receiving an angiotensin receptor antagonist (in one trial [260] an ACE inhibitor). While warning against the possible bias of *post hoc* analyses, nonetheless the guidelines suggested angiotensin receptor antagonists and ACE inhibitors as preferred drugs in hypertensive patients at risk of developing atrial fibrillation. A plausible explanation for this was the association between atrial enlargement and LVH, the favorable effects of blockers of the renin–angiotensin system on both cardiac alterations, and the relationship between LVH regression and reduction in new-onset atrial fibrillation [49,264]. However, data accumulated since then do not consistently support this recommendation. Although in ONTARGET [191] new atrial fibrillation was slightly less frequent with telmisartan than with ramipril, placebo-comparisons in TRANSCEND [108] and PROFESS [91] could not confirm a protective effect of this angiotensin receptor antagonist against new onset of atrial fibrillation. In TRANSCEND [108] the hazard ratio was 1.02, and in PROFESS [91] treatment discontinuation for atrial fibrillation occurred in 81 patients on telmisartan and in 50 patients on placebo. In I-PRESERVE [259], atrial arrhythmia is reported in 77 patients on irbesartan and 68 patients on placebo.

The 2007 ESH/ESC guidelines also reported the results of small studies suggesting that the angiotensin receptor antagonists may exert favorable effects on recurrent atrial fibrillation in patients with previous episodes of this arrhythmia [265,266]. Along the same lines, enalapril has been reported to facilitate maintenance of sinus rhythm after conversion treatment [267]. However, the guidelines stressed the small number of patients in these studies and concluded that more information was expected from ongoing specific trials with sufficient statistical power. Two specific trials have been completed quite recently (CAPRAF [268], GISSI-AF [269]) and their results are not supportive of protective effects from angiotensin receptor antagonists against recurrence of atrial fibrillation. In GISSI-AF 1442 patients (85% with a history of hypertension) having had at least two episodes of atrial fibrillation in the previous 6 months, need for DC conversion and frequently treated with ACE inhibitors and class I and III antiarrythmic drugs were randomized to either valsartan (up to 320 mg/day) or placebo and followed up for a mean period of 223 days. Incidence of at least one episode of atrial fibrillation was 51.4% on valsartan and 52.1% on placebo (hazard ratio

0.99, $P = 0.84$). A recent meta-analysis of all studies of secondary prevention of atrial fibrillation with blockers of the renin–angiotensin–aldosterone system appears to indicate an overall benefits of these agents, however (R. Schmieder *et al.*, personal communication).

One further point deserves mention. In a recent meta-analysis [270] including almost 12 000 patients with systolic heart failure, and therefore at high risk of atrial fibrillation, β-blockers were found to significantly reduce (by about 27%) the incidence of atrial fibrillation. A history of atrial fibrillation and systolic heart failure may be a specific indication for using β-blockers.

Hypertension in women

This aspect deserves a brief comment because of the recent publication of a new meta-analysis from the Blood Pressure Lowering Treatment Trialists' Collaboration, investigating benefit of antihypertensive treatment in men and women [271]: both BP lowering and reduction in outcomes were similar in the two sexes and no sex-related differences in response to various classes of antihypertensive agents could be detected.

Hypertension and erectile dysfunction

Erectile dysfunction is a prevalent condition in hypertensive patients and a predictor of future cardiovascular events. Screening and treatment of erectile dysfunction improves management of cardiovascular risk factors. After initiating therapy with phosphodiesterase (PDE) 5 inhibitors, patients are more likely to take antihypertensive medication and BP control is improved [272]. Older antihypertensive drugs (diuretics, β-blockers, centrally acting drugs) exert negative effects, whereas newer drugs have neutral or beneficial effects (calcium antagonists, ACE inhibitors, angiotensin receptor antagonists, nebivolol) [273].

Treatment of associated risk factors

Lipid-lowering agents

The benefit of combining a statin with antihypertensive treatment in hypertensive patients was well established by the ASCOT-LLA study [274], as summarized in the 2007 ESH/ESC guidelines [1]. The negative results obtained with another statin in the ALLHAT study [275] can be attributed to insufficient lowering of total cholesterol (11% in ALLHAT as compared with 20% in ASCOT). Further analyses of ASCOT have shown the addition of a statin to the amlodipine-based antihypertensive therapy can reduce the primary cardiovascular outcome even more markedly than addition of a statin to the atenolol-based antihypertensive therapy [276,277]. The beneficial effect of statin administration to patients without previous cardiovascular events has been strengthened by the findings of the JUPITER study [278], showing that lowering LDL-cholesterol by 50% in patients with baseline values less than 130 mg/dl (3.4 mmol/l), but elevated C-reactive protein (CRP), reduced cardiovascular events by 44%.

In conclusion, the recommendation given in the 2007 guidelines to consider statin therapy in hypertensive patients who have an estimated 10-year risk of cardiovascular events more than 20% can be reconfirmed, but the JUPITER study [278] suggests that statin benefits can be observed also in patients with elevated CRP and at moderate cardiovascular risk (about 15% cardiovascular events in 10 years).

Antiplatelet therapy

A large meta-analysis has just been published of serious cardiovascular outcomes and major bleeds in six primary prevention trials (95 000 individuals at low cardiovascular risk, 660 000 person-years) and 16 secondary prevention trials (17 000 individuals at high cardiovascular risk, 43 000 person-years) that compared long-term aspirin versus control [279]. In the primary prevention trials, aspirin allocation led to a significant 12% reduction in serious cardiovascular events (mostly nonfatal myocardial infarction). However, as a consequence of the overall low risk of the individuals, absolute event reduction amounted to only 0.06 events per 100 patient-years, which was counterbalanced by an absolute increase in major gastrointestinal and extracranial bleeds of 0.03 bleeds per 100 patient-years. In the secondary prevention trials, aspirin allocation yielded a greater absolute reduction in serious cardiovascular events (1.5 event per 100 patient-years). Although only few secondary prevention trials carefully reported bleed incidence, data from trials reporting bleeds suggest an extracranial bleed excess of no more than 0.2 event per 100 patient-years. It can, therefore, be concluded that, although administration of aspirin has a clear benefit/harm ratio in patients with cardiovascular disease, there is only a very tiny excess of benefit over harm in the low-risk patients included in primary prevention trials.

Of course, the division between primary and secondary prevention is artificial and arbitrary, and individuals who have not yet experienced a cardiovascular event can be at very different levels of total risk. Attention has been directed to the possible benefits of aspirin in patients with diabetes but still free of overt cardiovascular disease. In the hypertensive patients with diabetes in the HOT study, cardiovascular outcome reduction by aspirin did not achieve statistical significance [280,281], nor was a clear benefit seen in diabetic patients included in other trials [281]. Furthermore, the recent findings of a large primary prevention study carried out on diabetic patients in Japan could only show that low-dose aspirin was associated with a nonsignificant reduction in cardiovascular outcomes [282]. Therefore, the benefits of antiplatelet therapy in diabetes remain to be established.

The finding that in the HOT study, the greatest benefit of low-dose aspirin and the best benefit/harm ratio occurred in patients with serum creatinine more than 1.3 mg/l [280] has been further elaborated by estimating GFR and calculating the effects of aspirin versus placebo in three groups with eGFR 60 ml/min per 1.73 m^2 or more, 45–59 ml/min per 1.73 m^2, and less than 45 ml/min per 1.73 m^2. There was a significant trend for increasing reduction in major cardiovascular events and death with progressive decline in eGRF, the reduction being particularly marked in hypertensive patients with eGFR less than 45 ml/min per 1.73 m^2. In this group of patients, the risk of bleeding was modest as compared with the cardiovascular benefit [283].

In conclusion, the prudent recommendations of the 2007 ESH/ESC guidelines can be reconfirmed: antiplatelet therapy, in particular low-dose aspirin, should be prescribed to hypertensive patients with previous cardiovascular events; it can also be considered in hypertensive patients without a history of cardiovascular disease with reduced renal function or with a high cardiovascular risk. In patients receiving aspirin, careful attention should always be given to the increased possibility of bleeding, particularly gastrointestinal.

Glycemic control

The 2007 European guidelines reviewed the data on the target blood glucose and HbA_{1c} values to be reached in diabetic patients, an issue of practical importance because of the highly prevalent association of type 2 diabetes with hypertension [1]. They indicated a tight blood glucose control, that is, a glycemic value less than 6.0 mmol/l (108 mg/dl) and an HbA_{1c} less than 6.5%, to be desirable as a means to minimize the blood glucose-related macrovascular and microvascular complications, as shown in observational studies [1,284]. Since then, two major large-scale randomized trials, ADVANCE and ACCORD, focused on the effects of tight versus standard blood glucose control in type 2 diabetes, have been published with inconsistent results [285,286]. In ADVANCE, the factorial design included assessment of the effects of tight blood glucose control (goal $HbA_{1c} < 6.5\%$) via administration of gliclazide-MR as well as other available pharmacological means versus standard blood glucose control in patients with or without the additional administration of the indapamide/perindopril combination, as mentioned in the previous sections. In patients with tight blood glucose control, the average on-treatment HbA_{1c} was 6.5%, a value definitely lower than that seen in the standard treated group (7.3%). This was accompanied by a significant, although modest, reduction (−10%) in the composite primary endpoint (microvascular and macrovascular events) of the trial, which was entirely due to reductions of the microvascular component, as macrovascular endpoints did not show any significant between-group difference. In ACCORD, the goal was to lower HbA_{1c} to less than 6.0%, which led to a 6.5% average on-treatment HbA_{1c} value reached by patients on tight blood glucose control (versus 7.5% of the comparison group). This was associated with a reduction in the incidence of myocardial infarction, which was accompanied, however, by a significant and marked increase (+35%) in all-cause mortality, leading the tight blood glucose control arm to a premature termination. The reasons for the different results of the two trials are unclear, although the most likely hypothesis seems to be that, compared with ADVANCE, tight blood glucose control in ACCORD was obtained much more abruptly (less than 6 months versus 2 years) by a much larger use of antidiabetic drugs (thiazolinediones 91.7 versus 16.8%, insulin 77.3 versus 40.5%, and metformin 86.6 versus 73.8%), which might have favored hypoglycemic-related events as indirectly shown by the exceedingly high number of hypoglycemic episodes reported in the tight blood glucose as compared to the control group.

The blood glucose goals recommended in the 2007 guidelines [1] can thus remain unchanged, although with the caveat that tight blood glucose control should probably be pursued gently and values well below 6.5% HbA_{1c} should be avoided. Further support to this unchanged recommendation comes from the ADVANCE findings that in the group in which tight blood glucose control was combined with more intense antihypertensive treatment, the magnitude of the beneficial effects was significantly greater because of a reduced rate of all-cause mortality as well as of new-onset microalbuminuria [287]. It should be emphasized that in a recent meta-analysis that pooled data from the four randomized trials so far available on tight blood glucose control (ADVANCE, ACCORD, UKPDS, and VADT) [285,286,288,289], this group showed a risk of severe hypoglycemic episodes that was about 2.5 times greater than that of the group under standard glucose control strategy [290]. This calls for the tight blood glucose control strategy to be applied with close monitoring of the patients.

The issue of the polypill

A recent study [291] has tested the effects on various cardiovascular risk factors of a pill containing three antihypertensive drugs (an ACE inhibitor, a β-blocker, and a diuretic), a statin, and aspirin at low dose in individuals free of cardiovascular disease but just with one cardiovascular risk factor. At the end of the 12-week treatment, there was a reduction in BP, serum cholesterol, and urinary thromboxane 2 (as an index of antiplatelet action), as expected from the effects of the single polypill components. There was also no increment of the side-effects due to the individual components when given together in the single pill. It should be emphasized, however, that the rationale upon which the polypill has been developed is not the reasonable one of assembling together several drugs in order to facilitate treatment in those very high risk patients requiring multiple therapies [292]. The

rationale for the polypill, as heralded by Wald and Law (who have even patented the concept), is that the polypill, containing all types of agents shown capable of reducing cardiovascular risk, may reduce cardiovascular risk by more than 80% in all individuals and should be given to all individuals 55 years and older, irrespective of previous cardiovascular disease [293]. This can be criticized due to various aspects: as reported previously, aspirin in low-risk individuals has only small cardiovascular benefits counterbalanced by excess bleeding [279]; antihypertensive agents lower BP only very moderately in normotensive individuals (as also found in the recent polypill trial [291]), statins are generally well tolerated but sometimes accompanied by serious adverse events; and furthermore, the extent of their benefit in individuals without any risk factors in unproven. Furthermore, the concept of treating 'cardiovascular risk' as an entity without targeting and monitoring the individual risk factors appears unsound.

New trials needed

In the past 10–15 years, several trials of antihypertensive therapy have been completed, but these have mostly centered on comparisons between different agents or focused on high cardiovascular risk patients, and have used so complex designs and so numerous concomitant therapies as to often make interpretation of their results difficult and controversial (Box 9). Although these trials have nevertheless added further useful information, some major issues have not been explored or have been insufficiently clarified. As a consequence, many important decisions on hypertension management are currently taken only on the basis of *post hoc* analyses of trial data relating cardiovascular events to achieved BP values, which have notorious limitations because of loss of randomized design and potential differences in baseline risk of patients achieving different BP values. Therefore, it appears highly desirable that recommendations on the BP threshold for initiation of drug treatment and on BP targets in different groups of patients are supported by information from prospective randomized trials designed to address persisting gaps in current knowledge.

The following issues appear in urgent need to be approached by simply designed trials:

(1) Should antihypertensive drugs be prescribed to all individuals with grade 1 hypertension (SBP 140–159 mmHg or DBP 90–99 mmHg), even when total cardiovascular risk is relatively low or moderate? It is obvious that a randomized trial of active versus placebo treatment based on hard cardiovascular outcomes would be very difficult to perform in truly low cardiovascular risk patients with grade 1 hypertension, because in such patients, the very low rate of cardiovascular events would make it necessary to plan a study of a size and/or duration of unrealistic proportions. However, a placebo-controlled trial using intermediate endpoints such as LVH, microalbuminuria, or other signs of organ damage of recognized prognostic importance would be feasible, ethical, and clinically relevant.
(2) Should antihypertensive drugs be prescribed to the elderly with grade 1 hypertension and should antihypertensive treatment achieve a goal of below 140/90 mmHg also in the elderly? All successful trials on elderly hypertensive patients have recruited patients with SBP 160 mmHg or above, and in most

Box 9. New trials needed

Many important decisions on hypertension management must currently be taken without the support of evidence from large randomized controlled trials. The following issues appear in urgent need to be approached by simply designed trials.

(1) Should antihypertensive drugs be prescribed to all patients with grade 1 hypertension, even when total cardiovascular risk is relatively low or moderate? Because of the very low rate of cardiovascular events expected in these patients, a placebo-controlled trial using intermediate endpoints such as signs of organ damage of recognized prognostic importance would be feasible, ethical, and clinically relevant.
(2) Should antihypertensive drugs be prescribed to the elderly with grade 1 hypertension, and should antihypertensive treatment achieve a goal of below 140/90 mmHg also in the elderly? These trials could make use of hard cardiovascular outcomes and could be placebo-controlled.
(3) Should antihypertensive drug treatment be started in diabetic patients or in patients with previous cerebrovascular or cardiovascular disease when BP is still in the high normal level, and should BP goal be below 130/80 mmHg in these patients? These issues can be approached by placebo-controlled trials because no trial evidence is still available on the benefit of lowering high normal BP or of achieving BP goals below 130/80 mmHg.
(4) What are the lowest safe BP values to achieve by treatment in different clinical conditions? This issue should be approached by trials comparing more or less intense BP-lowering treatment strategies in patients with different cardiovascular risk levels.
(5) Are lifestyle measures known to reduce BP also capable of reducing morbidity and mortality in hypertension? A controlled randomized trial using intermediate endpoints (organ damage) would be feasible and desirable in patients with high normal BP or grade 1 hypertension.

of them, the mean entry value has been above 170 mmHg. Likewise, in all trials conducted so far, the achieved SBP has always been above 140 mmHg. Because elderly hypertensive patients are characterized by a greater cardiovascular risk (and thus by a greater number of events within the few years of a trial duration), these trials could make use of hard cardiovascular outcomes and could be placebo controlled.

(3) All guidelines suggest to initiate antihypertensive treatment in diabetic patients or in those with previous cerebrovascular or cardiovascular disease when BP is in the high normal level (SBP 130–139 mmHg or DBP 85–89 mmHg) and recommend to achieve a goal SBP below 130 mmHg. Although these recommendations may be wise, they are not founded on trial evidence. For instance, in no successful trial of antihypertensive treatment in diabetic patients has SBP values less than 130 mmHg been achieved. In most trials on high cardiovascular risk patients, the randomized treatment was started on the background of heavy preexisting antihypertensive drug regimens, because the wrong assumption was made that all these patients anyway required very aggressive BP lowering (the results of taking wisdom for evidence [71]). In other trials, a large proportion of patients was concomitantly treated with agents that may have interfered with the agents to be tested. For example, in the I-PRESERVE trial [259] on chronic heart failure with preserved systolic function, 39% of the patients in whom the effect of an angiotensin receptor antagonist was tested were also concurrently treated with an ACE inhibitor, although no evidence is available that an ACE inhibitor is beneficial in this type of heart failure. Here again, a relatively simple trial design specifically aimed at answering these questions in patients with previous stroke or coronary event or with diastolic heart failure would be needed.

(4) Identification of the lowest safe BP values on treatment under different clinical conditions is of obvious clinical importance, deserving to be addressed by an 'ad hoc' prospective trial that compares more versus less intense BP-lowering treatment strategies in patients with different cardiovascular risk levels.

(5) Several types of lifestyle changes have been shown to be capable of reducing BP, but they are unproven to reduce mortality and morbidity in hypertension. Although a morbidity/mortality study with lifestyle changes in grade 1 hypertensive patients may not be a feasible task, a controlled randomized trial using intermediate endpoints (organ damage) would be feasible and desirable.

Acronym list of trials and studies

ABCD: Appropriate Blood Pressure Control in Diabetes.
ACCESS: Acute Candesartan Cilexetil Therapy in Stroke Survivals.
ACCOMPLISH: Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension.
ACCORD: Action to Control Cardiovascular Risk in Diabetes.
ACTION: A Coronary Disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system.
ADVANCE: Action in Diabetes and Vascular disease; Preterax and Diamicron-MR Controlled Evaluation.
ALLHAT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.
ASCOT: Anglo-Scandinavian Cardiac Outcomes Trial.
AUSTRALIAN: Australian Therapeutic Trial in Mild Hypertension.
BENEDICT: Bergamo Nephrologic Diabetic Complications Trial.
CAFE: Conduit Artery Function Evaluation.
CAMELOT: Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis.
CAPRAF: Candesartan in the Prevention of Relapsing Atrial Fibrillation.
CASE-J: Candesartan Antihypertensive Survival Evaluation in Japan.
CHARM: Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity.
CHHIPS: Controlling Hypertension and Hypothension Immediately Poststroke.
COMET: Carvedilol or Metoprolol European Trial.
COOPER and WARRENDER: Treatment of Hypertension in Elderly Patients in Primary Care.
COOPERATE: Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-Converting-Enzyme Inhibitor in Non-Diabetic Renal Disease.
DIRECT: Diabetic Retinopathy Candesartan Trials.
ELSA: European Lacidipine Study on Atherosclerosis.
EUROPA: European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease.
EWPHE: European Working Party on High Blood Pressure in the Elderly.
FEVER: Felodipine Event Reduction.
GEMINI: Glycemic Effect in Diabetes Mellitus: Carvedilol–Metoprolol Comparison in Hypertensives.
GISSI-AF: Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Atrial Fibrillation.
HDFP: Hypertension Detection and Follow-up Program.
HOPE: Heart Outcomes Prevention Evaluation.
HOT: Hypertension Optimal Treatment Study.
HYVET: Hypertension in the Very Elderly Trial.
IDNT: Irbesartan Diabetic Nephrophaty Trial.
INSIGHT: International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment.
INVEST: International Verapamil SR/Trandolapril study.

I-PRESERVE: Irbesartan in Heart Failure with Preserved Systolic Function.
JATOS: Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients.
JUPITER: Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin.
LIFE: Losartan Intervention For Endpoint Reduction in Hypertension.
MDRD: Modification of Diet in Renal Disease.
MICROHOPE: Microalbuminuria, Cardiovascular and Renal Outcomes in the Heart Outcomes Prevention Evaluation.
MRC: Medical Research Council Trial of Treatment of Mild Hypertension.
MRC elderly: Medical Research Council Trial of Treatment of Hypertension in Older Adults.
ONTARGET: Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial.
OSLO: Oslo Study of Treatment of Mild Hypertension.
PAMELA: Pressioni Arteriose Monitorate E Loro Associazioni.
PATS: Post-stroke Antihypertensive Treatment Study.
PEACE: Prevention of Events with Angiotensin Converting Enzyme Inhibition.
PHARAO: Prevention of Hypertension with the Angiotensin-converting enzyme inhibitor Ramipril in Patients with High-Normal Blood Pressure.
PHYLLIS: Plaque Hypertension Lipid Lowering Italian Study.
PREVEND: Prevention of Renal and Vascular End Stage Disease.
PREVENT: Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial.
PROFESS: Prevention Regimen for Effectively Avoiding Second Strokes.
PROGRESS: Perindopril Protection against Recurrent Stroke Study.
RENAAL: Reduction of Endpoints in Noninsulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan.
SCOPE: Study on Congnition and Prognosis in the Elderly.
SCORE: Systematic Coronary Risk Evaluation.
SENIORS: Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure.
SHEP: Systolic Hypertension in the Elderly Program.
STOP: Swedish Trial in Old Patients with Hypertension.
Syst-China: Systolic Hypertension in China.
Syst-Eur: Systolic Hypertension in Europe.
TNT: Treating to New Targets.
TRANSCEND: Telmisartan Randomized Assessment Study in ACE-I Intolerant Subjects with Cardiovascular Disease.
TROPHY: Trial of Preventing Hypertension.
UKPDS: United Kingdom Prospective Diabetes Study.
VADT: Veterans Affairs Diabetes Trial.
Val-HeFT: Valsartan Heart Failure Trial.
VALIANT: Valsartan In Acute Myocardial Infarction Trial.
VALUE: Valsartan Antihypertensive Long-term Use Evaluation.

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