Editorial
The new European Society of Hypertension/European Society of Cardiology (ESH/ESC) Guidelines

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The 2007 guidelines on hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) [Mancia *et al.* 2007] differ for several aspects from the previous hypertension guidelines issued by the two Societies in 2003 [Guidelines Committee ESH/ESC, 2003]. In some instances the difference mainly consists in a reinforcement or extension of what was only suggested by the previous guidelines, based on the increased amount of data obtained in the last four years. In other instances, however, it consists in an actual change from what was recommended in 2003 because of the new data provided by trials and other types of studies. In this paper we will report on some of these differences and discuss their rationale.

Cardiovascular risk factors and total cardiovascular risk

In the 2007 ESH/ESC guidelines there are several changes in the listed cardiovascular risk factors [Mancia *et al.* 2007]. One, the thresholds indicating abnormal values of total serum cholesterol, LDL cholesterol and blood glucose have been lowered, with, in addition, the inclusion of threshold values also of the remaining components of lipid profile such as serum HDL-cholesterol and triglycerides. Two, attention has been paid to the need of measuring waist circumference as a means to determine visceral obesity, which is the type of obesity related to an increased cardiovascular risk [Bergman *et al.* 2007]. Three, specific mention has been made of the metabolic syndrome as a condition in which the combination of only slight alterations (above the previously mentioned lower threshold values) in plasma lipids, blood glucose, waist circumference and blood pressure nevertheless determine a high total cardiovascular risk, i.e. a chance of having a morbid or fatal cardiovascular event within 10 years equal or greater than 20%. Four, while making a step backward on the need to collect information on inflammatory markers (the recommendation does no more refer to C reactive protein measurements), emphasis has been given to the importance of assessing target organ damage, because target organ damage has a high prevalence in hypertension [Mancia *et al.* 1998] and may make the prognosis substantially worse [Mancia *et al.* 1998], thus being responsible *per se* for the high cardiovascular risk level of an individual even when blood pressure is only modestly elevated or in the high-normal range.

As shown in Figure 1, compared to the 2003 guidelines, in the 2007 guidelines more measurements aimed at detecting target organ damage are advised for routine, based on their undisputable predictive value for cardiovascular morbidity and mortality, large availability and low cost (EKG, estimated creatinine clearance or glomerular filtration rate through standardized formulae, serum creatinine and microalbuminuria).

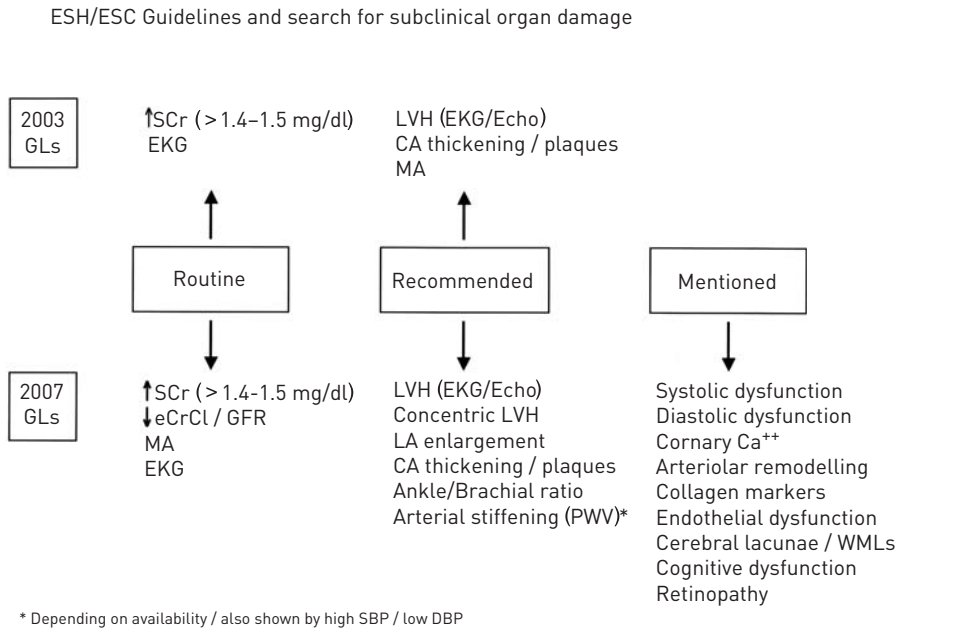

Figure 1. Assessment of target organ damage hypertension-related according to the 2003 and 2007 ESH/ESC Guidelines.

GLS: guidelines, LVH: left ventricular hypertrophy; SCr: serum creatinine, MA: microalbuminuria, eCrCl: estimated creatinine clearance, PWV: pulse wave velocity, WML: white matter lesions.

Several additional measurements, however, are recommended, because, although less easily available and more complex and expensive, they also have an important prognostic value that allow to more accurately stratify patients' total risk. This is the case for measurements derived from (1) echocardiography, which allows to determine the presence of left ventricular hypertrophy whose association with an increased incidence of cardiovascular morbidity and mortality has been repeatedly documented both in hypertensive individuals and in the general population [Levy *et al.* 1990], particularly when the hypertrophy is of concentric type [Muiesan *et al.* 2004] and even when only atrial dilatation is present [Gerdts *et al.* 2007], (2) carotid ultrasonography, its related detection of arterial plaques or arterial wall thickening also being associated with an increased incidence of cardiac and cerebrovascular events [O'Leary *et al.* 1999; Hodis *et al.* 1998], (3) the ratio between arm and ankle blood pressure, the low value of which indicates advanced large artery damage [McKenna *et al.* 1991] and (4) pulse wave velocity across the arterial tree, an accurate reflection of arterial distensibility which, when increased, indicates poor prognosis also in presence of modest blood pressure elevations [Willum-Hansen *et al.* 2006].

Several other elements of novelty provided by the 2007 ESH/ESC guidelines on organ damage and more in general total cardiovascular risk deserve to be mentioned. The 2007 ESH/ESC guidelines recommend organ damage to be searched in different organs because of the evidence that multiple organ damage (e.g. in the kidney and the heart) carries a worse prognosis than damage limited to a single organ [Mancia, 2006]. They also recommend organ damage to be assessed before and during treatment because data are now available that treatment-induced improvement of left ventricular hypertrophy and increased urinary protein excretion are associated with a reduced incidence of cardiovascular events [Verdecchia *et al.* 2003], thereby offering physician and patients an insight on whether the treatment adopted is providing protection. Finally, they critically address the markers of organ damage that, although not included in the recommendations, are the object of a large fraction of current

Table 1. Availability, prognostic value and cost of some markers of organ damage according to ESH/ESC 2007 Guidelines.

Markers	CV predictive value	Availability	Cost
Electrocardiography	++	++++	+
Echocardiography	+++	+++	++
Carotid Intima-Media Thickness	+++	+++	++
Arterial stiffness (Pulse wave velocity)	+++	+	++
Ankle-Brachial index	++	++	+
Coronary calcium content	+	+	++++
Cardiac/Vascular tissue composition	?	+	++
Circulatory collagen markers	?	+	++
Endothelial dysfunction	++	+	+++
Cerebral lacunae/White matter lesions	?	++	++++
Est. Glomerular Filtration Rate or Creatinine Clearance	+++	++++	+
Microalbuminuria	+++	++++	+

The weight of each marker is expressed by the number of pluses (from 0 to 4).

research, possibly becoming of practical use in a not too far future. A cross comparison of all organ damage markers for key features such as prognostic value, availability and cost, is given a table format (Table 1).

Blood pressure threshold and target for treatment

The 2007 ESH/ESC guidelines support the view that the beneficial effects of antihypertensive drug administration is largely due to blood pressure lowering *per se*, regardless how it is obtained. By critically examining old and more recent trial data they recommend treatment of the general hypertensive population (including the elderly) to start, whenever the blood pressure values are consistently equal or above 140 mmHg systolic or 90 mmHg diastolic, the goal being to go below these values and even lower if this is tolerated by the patient. This is justified by the (1) epidemiological data that the incidence of cardiovascular morbid and fatal events is related to blood pressure down to values of about 110 mmHg systolic and 70 mmHg diastolic [Prospective Studies Collaboration, 2002], (2) absence of any substantial evidence of a reduction in vital organ perfusion and an increase in cardiovascular morbidity and mortality (i.e. a J curve) by active treatment within this blood pressure range [Prospective Studies Collaboration, 2002], (3) data that reducing blood pressure to values well below 140/90 mmHg does not increase side effects [Mancia, 2006] and (4) consideration that setting a more ambitious blood pressure goal may be strategically important to at least more frequently achieve the less ambitious one [Mancia, 2006].

What is only a suggestion in the general hypertensive population becomes, however, a strong recommendation in individuals with a history of renal disease, coronary disease, cerebrovascular disease or diabetes in which evidence is now available (Figure 2) [Messerli *et al.* 2006] that lower blood pressure targets increase the size of cardiovascular protection and that under these circumstances a cardiovascular protective effect is observed when treatment is implemented at initial blood pressures below 140/90 mmHg, i.e. in the high – normal or even the normal range. This means that the blood pressure threshold for treatment should be flexible in relation to the level of total cardiovascular risk, with a corresponding flexibility in the target blood pressure values to be reduced by treatment. In the ESH/ESC guidelines this is visualized by a dashed line which indicates the approximate blood pressure threshold for active intervention at each risk level (Figure 3) [Mancia *et al.* 2007].

Two further questions addressed by the ESH/ESC guidelines are whether (1) treatment of individuals at high or very high risk differ from that of the lower risk ones only as regards the blood pressure threshold and target values for treatment and (2) similar treatment recommendations pertain to individuals in whom an elevated cardiovascular risk is due to conditions different from diabetes or a history of cardiovascular or renal disease. The former question is given a clear answer because evidence exists that additional treatment peculiarities distinguish high or very high risk from lower risk individuals. For example, in high and very high risk individuals

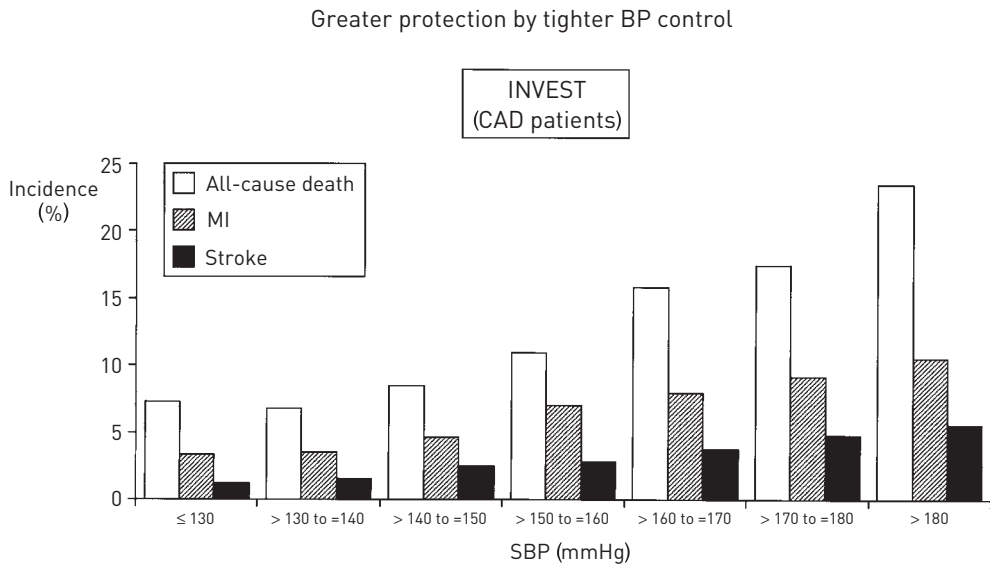

Figure 2. Relationship between low blood pressure values and reduction of events in the International Verapamil SR/Trandolapril (INVEST) Study. CAD: coronary artery disease, MI: myocardial infarction, SBP: systolic blood pressure. Figure modified from Messerli *et al.* 2006.

Stratification of CV risk in four categories

Blood pressure (mm Hg)					
Other risk factors, OD or disease	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥ 180 or DBP ≥ 110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors, MS, OD or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Established CV or renal disease	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

Figure 3. Stratification of cardiovascular risk in four categories according to 2007 ESH/ESC Guidelines. SBP: systolic blood pressure, DBP: diastolic blood pressure, CV: cardiovascular, HT: hypertension. Low, moderate, high, very high risk refer to 10 year risk of a CV fatal or non-fatal event. The term "added" indicates that in all categories risk is greater than average. OD: subclinical organ damage, MS: metabolic syndrome. Figure modified from Mancia *et al.* 2007.

treatment with a combination of two or more antihypertensive drugs is almost always necessary, given that the size of blood pressure reduction to achieve is greater and the chance to obtain it with monotherapy small [Hansson *et al.* 1998]. Also, starting treatment with a two antihypertensive drug combination is advisable because delaying blood pressure control may lead to an event even within a few month time interval. Finally, evidence exists that a high or very high risk hypertensive patients can have an additional benefit by adding to an effective antihypertensive drug

regimen antiplatelet treatment and a statin, the latter independently on whether serum cholesterol values are or are not elevated [Sever *et al.* 2003; Hayden *et al.* 2002]. Assessing total cardiovascular risk thus has key implications for the overall treatment strategy to be adopted.

Whether the above treatment strategy (lower blood pressure thresholds and targets for treatment, antihypertensive drug combination as initial treatment and administration of antiplatelet and lipid lowering drugs) should be recommended also in subjects in whom the high risk condition is due to factors other than renal disease, cardiovascular disease or diabetes is uncertain. However, treating with antihypertensive drugs individuals in whom the high risk is due to an organ damage such as proteinuria or microalbuminuria has been shown to have a nephroprotective effect even at initial blood pressures lower than 140/90 mmHg [Jafar *et al.* 2003]. Furthermore, treating normotensive patients with ace-inhibitors or angiotensin receptor antagonists may have a favourable effect on the incidence of new onset diabetes or hypertension [Mancia *et al.* 2006]. Thus guidelines do not oppose this treatment attitude, although leaving its implementation to the judgment of the physician.

General antihypertensive treatment strategies: lifestyle changes and drug treatment

The lifestyle changes to be adopted in the hypertensive patient are similar in the 2003 and 2007 ESH/ESC Guidelines, although the more recent Guidelines place more emphasis on the need to implement this treatment step in all individuals with a blood pressure in the hypertensive or high-normal range, via the help of specific professional figures and the adoption of periodical reinforcement that may reduce the extremely low chronic compliance rate to this intervention. There is also no substantial change in the new guidelines as regards the drug classes suitable for initiation and maintenance of antihypertensive treatment, which thus remain thiazide diuretics, ace-inhibitors, calcium antagonists, angiotensin receptor antagonists but also beta-blockers. This is in contrast with the recommendations of some other guidelines [NICE/BHS, 2006] which have only considered beta-blockers for 4th line treatment based on the unfavourable results obtained in large scale trials [Lindholm *et al.* 2005; Dahlof *et al.* 2002, 2005].

The decision to keep beta-blockers on board as useful general drugs has been based on the following considerations. One, in most trials beta-blockers have been used together with thiazide diuretics, so that it is difficult to discriminate between the favourable or unfavourable role of one vs the other drug class. Two, data from several trials do not support the conclusion that compared to other drug classes beta-blockers have lesser antihypertensive and cardiovascular protective effects, similar discrepancies characterizing available meta-analyses of trial data [Bradley *et al.* 2006; Pepine *et al.* 2003]. Three, it is futile to pay too much attention to which drug should be initially preferred because administration of two or more drugs is necessary to control blood pressure in the majority of hypertensive patients, limiting the monotherapy period to few weeks only. Finally, rather than having a prescribing attitude guidelines should advice which drugs may have specific advantages and should thus be preferred in the various clinical conditions that physicians are confronted with in their daily practice. In this context, beta-blockers remain the drugs of choice in conditions frequently associated with or originated from hypertension such as heart failure, a previous myocardial infarction or angina pectoris. However, because they favour an increase in body weight, have dyslipidemic effects and adversely affect glucose metabolism so as to enhance the risk of developing diabetes [Mancia *et al.* 2006; Sharma, 2001], they should not be preferred, particularly in combination with a diuretic, in individuals in which the risk of incident diabetes is high, such as when there is a metabolic syndrome, a condition which is adversely affected by these drugs in a multiple fashion. Even in this instance, however, banning the whole beta-blocker category may be unjustified because the newer class of vasodilator beta-blockers has been found to be largely devoid of dysmetabolic effects, with a reduced incidence of new onset diabetes compared to traditional beta-blockers [Torp-Pedersen *et al.* 2007].

Conditions favouring use of specific drugs or drug combinations

A qualifying aspect of the 2007 ESH/ESC guidelines is the adoption of an expanded view on what the goal of antypertensive treatment is. According to the 2007 ESH/ESC guidelines the treatment of the hypertensive patient should aim at achieving the maximum possible reduction in total cardiovascular risk. This means to achieve an optimal blood pressure control but also to

Table 2. Preferred drugs according different clinical conditions in the 2007 ESH/ESC Guidelines.

Condition	ISH (elderly)	→ D / CA
	MS	→ ACEI / ARB / CA
	DM	→ ACEI / ARB
	Pregnancy	→ CA / MD / BB
	Blacks	→ D / CA
Subclinical OD	LVH	→ ACEI / CA / ARB
	Asympt. atherosclerosis	→ CA / ACEI
	MA	→ ACEI / ARB
	Renal dysfunction	→ ACEI / ARB
Clinical event	Previous stroke	→ any BP lowering agent
	Previous MI	→ BB / ACEI / ARB
	Angina pectoris	→ BB / CA
	CHF	→ D / BB / ACEI / ARB / antialdo agents
	AF (recurrent)	→ ARB / ACEI
	AF (permanent)	→ BB / nonDHCA
	ESRF/proteinuria	→ ACEI / ARB / loop D
	PAD	→ CA

OD: organ damage, ISH: isolated hypertension, MS: metabolic syndrome, DM: diabetes mellitus, LVH: left ventricular hypertrophy, MA: microalbuminuria, MI: Myocardial infarction, AF: atrial fibrillation, ESRF: end stage renal failure, PAD: peripheral artery disease, D: diuretics, CA: calcium antagonists, ACEI: angiotensin converting enzyme inhibitors, ARB: angiotensin receptors blockers, BB: Beta-blockers.

modify other correctable components of total cardiovascular risk, such as dysmetabolic risk factors and target organ damage. It also means to prevent the appearance of clinical conditions that once present markedly increase cardiovascular risk and thus the incidence of cardiovascular events and death. A large body of evidence collected in recent years indicates that for a similar reduction in blood pressure the above goals are often more effectively reached by some drugs as compared to others, which explains why in the 2007 guidelines the list of which drugs should be preferred in which clinical conditions has grown considerably (Table 2). The need to delay progression or favour regression of renal, cardiac and carotid artery damages, for example, also calls for a strategy that pursues blood pressure control through the preferential use of some drugs. This is the case, for example, when specific clinical conditions make the risk of atrial fibrillation, new onset diabetes, diabetic nephropathy or, in subjects with a high-normal blood pressure, hypertension particularly high and thus the need to avoid and delay this priority.

The list of conditions in which some drugs may be preferred to others does not include prevention of stroke, although two trials have shown that for a similar reduction in blood pressure hypertensive patients treated with an angiotensin receptor antagonist had less chance of having a first or recurrent cerebrovascular event than patients treated with other drugs [Schrader *et al.* 2003 and 2005]. Demonstrating that some drugs are more effective than others in preventing stroke could be of importance because (1) stroke is the third cause of death worldwide as well as a major cause of patients' disability, dependence and health care cost [Grassi *et al.* 2007], (2) optimal blood pressure is often difficult to achieve, particularly in the elderly [Mancia, 2006] and (3) the possibility exists to identify patients at greater risk of cerebrovascular complications (history of stroke, paroxymal atrial fibrillation, asian ethnicity), in whom the possibility would thus exist to preselect the most protective drugs. However, the data provided by a meta-regression analysis of all available trials indicate that, regardless the treatment type, progression of stroke is linearly and strongly related to the degree of blood pressure reduction induced by treatment with little or no effect when no blood pressure reduction occurs [Staessen *et al.* 2003]. This was responsible for the emphasis given in the guidelines to the paramount importance of blood pressure lowering strategies for cerebrovascular prevention. It should nevertheless be recognized that the large dispersion of the results of single trials around the line correlating blood pressure changes with cerebrovascular events makes a specific contribution

of antihypertensive drugs possible. This contribution would be valuable also because, despite large use of combination treatment, achieving optimal blood pressure control is, in daily clinical practice, rare.

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