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REVIEW ARTICLE

2013 ESH/ESC Guidelines for the Management of Arterial Hypertension: What Has Changed in Daily Clinical Practice?

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Abstract This is a review article aiming to make focus on the changes made in the European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines for the management of arterial hypertension with some criticism for each element discussed in the text. Given that in the real world clinical practice physicians would hardly spend the time needed for studying the 77 pages manuscript of the recently released 2013 ESH/ESC hypertension guidelines, the present review summarizes all the significant updates (along with their clinical implications) compared to the 2007 ESH/ESC hypertension guidelines and the 2009 reappraisal document.

Keywords Hypertensive patients · Position statement · Update

Over the 4-year period after the reappraisal of the 2007 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines for the management of arterial hypertension [1] made in 2009 [2], new evidence on several diagnostic and therapeutic aspects of hypertension necessitated the edition of a new version of these guidelines. Publication of a new document, 6 years after the previous one, was felt to be timely. Thereby, the ESH/ESC Task Force released the new 2013 guidelines on hypertension [3] in the ESH annual Meeting.

It is a lengthy document (77 pages), extremely comprehensive where all issues on the diagnostic evaluation, treatment approach and follow-up of hypertensive patients are thoroughly discussed. Thus, it is worthy to be studied by any physician dealing with hypertensive patients. However, in the real world clinical practice, for the majority of medical practitioners, it is at least doubtful if there is available time for the study of such a detailed manuscript. Given that the present guidelines [3] differ in many aspects from the previous ones [1, 2] and that the available pocket edition of the present guidelines is just a brief summary of the guidelines, a document making focus on the most important changes made in daily clinical practice would be of wide utility saving valuable time for physicians. The present review summarizes the updates made on the ESH/ESC hypertension guidelines with some critical comments or/and suggestions to improve implementation of these guidelines. The most significant novelties are listed below:

1 Classes of Recommendations—Levels of Evidence

While not done in previous editions, the 2013 guidelines [3] grade the strength of recommendations (I, IIa, IIb or C) and the level of scientific evidence (A, B or C) on major diagnostic and treatment issues. This is common practice in every guidelines document nowadays giving doctors the opportunity to evaluate the necessity and urgency of any specific recommendation.

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2 Assessment of Total Cardiovascular (CV) Risk

Re-emphasis on integration of BP levels, CV risk factors (RFs), asymptomatic organ damage (OD) and clinical complications for total 10-year CV risk assessment has been given in the new 2013 guidelines [3]. The traditional Table stratifying the CV risk in categories of low, moderate, high, and very high risk according to the BP levels and the presence of RFs, OD, diabetes, chronic kidney disease (CKD) or symptomatic CV disease (CVD) has substantially been revised (5 lines and 4 columns instead of 4 lines and 5 columns). The removal of the column referring to subjects with normal BP (120–129/80–84 mmHg) seems reasonable since the aim of this Table is to guide physicians evaluate the CV risk in hypertensives (or even in individuals with borderline BP—high normal category) and not in normotensives.

In asymptomatic subjects with hypertension but free of CVD, CKD, and diabetes, total CV risk stratification using the Systematic COronary Risk Evaluation (SCORE) model is now recommended as a minimal requirement (Class I, Level B).

As there is evidence that OD predicts CV death independently of SCORE, a search for OD should be considered, particularly in individuals at moderate risk (Class IIa, Level B).

It is reconfirmed that decisions on treatment strategies depend on the initial level of total CV risk (Class I, Level B).

The document would benefit from a clearer definition of which of the two strategies for stratifying total risk should be used or specification of which is more important (BP values and associated RFs/OD or the SCORE model).

3 Factors—Other Than BP—Influencing Prognosis; Used for Stratification of Total CV Risk

New RFs have been added in the Table of clinical variables that should be used to evaluate the CV risk. Male sex, which was absent from the Table in the previous guidelines, is highlighted in the new revised Table. Both obesity [defined as body mass index (BMI) $\geq$30 kg/m^2] and abdominal obesity (defined as waist circumference $\geq$102 cm for men and $\geq$88 cm for women, in Caucasians), and not just the latter one, are now considered to influence prognosis. Moreover, it is stated that risk may be higher in individuals with increased fibrinogen, apolipoprotein B, lipoprotein (a), and high sensitivity C-reactive protein levels. The incorporation of these "new" factors was almost inevitable since they were already used for risk stratification from most physicians.

The cut-off values or/and definitions for some of the concomitant RFs have been changed. High pulse pressure in the elderly is now defined as $\geq$60 mmHg. Sokolow-Lyon index (SV1 + RV5) >3.5 mV (and not >3.8 mV, as reported in the 2007 document [1]) is henceforward diagnostic of electrocardiographic left ventricular hypertrophy (LVH). Modified Sokolow-Lyon index (largest S-wave + largest R-wave) >3.5 mV and R wave amplitude in lead aVL (RaVL) >1.1 mV are now included at the diagnostic criteria of electrocardiographic LVH. The cut-off value for LV mass index as diagnostic criterion of echocardiographic LVH has been lowered to >115 g/m^2 for men and >95 g/m^2 for women (instead of >125 and 110 g/m^2, respectively) in line with the American Society of Echocardiography recommendations [4]. Indexation of LV mass for body height, in which height's exponentiation to the allometric power of 1.7 is deemed optimal (g/m$^{1.7}$), can be considered in overweight and obese patients in order to scale LV mass to body size and avoid under-diagnosis of LVH. An intima-media thickness (IMT) >1.5 mm (instead of >1.3 or 1.5 mm, reported in the 2007 document [1]) is now considered diagnostic for the presence of a carotid plaque. Carotid-femoral pulse wave velocity (PWV) is clearly recognized as the "gold standard" for measuring aortic stiffness. A carotid-femoral PWV >10 m/s (and not >12 m/s, as reported in the previous version [1]), by using the direct carotid-to-femoral distance, is now considered to independently influence prognosis. It is recognized that automated devices can be an alternative to the use of a continuous-wave Doppler unit and a BP sphygmomanometer for ankle-brachial index (ABI) measurement. Glycated haemoglobin (HbA_1c) >7 % (53 mmol/mol) is included at the diagnostic criteria of diabetes mellitus. Serum creatinine levels and creatinine clearance (calculated with the Cockroft-Gault formula) are no more suggested as prognostic factors in the new guidelines [1]. CKD is now defined based only on the estimated glomerular filtration rate (eGFR) and is classified as asymptomatic OD if eGFR is 30–60 ml/min/1.73 m^2 or as established renal disease if eGFR is <30 ml/min/1.73 m^2. The abbreviated Modification of Diet in Renal Disease (MDRD) formula is currently recommended for the calculation of eGFR but new methods such as the Chronic Kidney Disease EPIdemiology Collaboration (CKD-EPI) formula aim to improve the accuracy of the measurement. A value for albumin-to-creatinine ratio (ACR) $\geq$30 mg/g, uniform for both genders (instead of $\geq$22 for men and $\geq$31 mg/g for women, reported in the 2007 document [1]) is considered significant prognostic factor. Finally, the previously reported "peripheral artery disease" is now more specifically defined as "symptomatic lower extremities peripheral artery disease". All the aforementioned changes are in the direction of a more clear or/and simple definition of these variables in line with other scientific societies or/and documents.

4 Markers of OD

The traditional Table scoring (from + to ++++) the CV predictive value, availability, reproducibility and cost-effectiveness of the most significant markers of OD has substantially been revised. Specific recommendations, graded in strength (I, IIa, IIb or C) and level of evidence (A, B or C), on the search for asymptomatic OD, CVD, and CKD are now provided in the 2013 guidelines [3]. There is a Class I, Level B recommendation for the performance of an electrocardiogram (ECG), the measurement of serum creatinine and estimation of GFR, the assessment of urinary protein by dipstick and the assessment of microalbuminuria in spot urine in relation to urinary creatinine excretion in all hypertensive patients. Echocardiogram, ultrasound scanning of carotid arteries, carotid-femoral PWV and ABI should be considered (Class IIa, Level B) in all hypertensive patients. When myocardial ischaemia is suspected, a stress ECG test, and, if positive or ambiguous, an imaging stress test are recommended (Class I, Level C). In case of suspected major or exercise-induced arrhythmias, a long-term ECG and a stress ECG should be respectively considered (Class IIa, Level C). Examination of the retina should be considered in difficult to control or resistant hypertensive patients (Class IIa, Level C) while it is not recommended in mild-to-moderate hypertensive patients without diabetes, except in young patients (Class III, Level C). In hypertensive patients with cognitive decline, brain magnetic resonance imaging (MRI) or computed tomography may be considered (Class IIb, Level C). These recommendations on diagnostic evaluation of heart, arteries, kidney, retina and brain offer physicians a clear distinction between routine tests, additional tests (based on history, physical examination and findings from routine tests) and tests for extended evaluation (mostly domain of the specialist).

Increased attention to OD-guided therapy during the follow-up of the patients has been paid in the 2013 guidelines [3]. A figure presenting the sensitivity to detect treatment-induced changes, the time to change and the prognostic value of change of the several markers of asymptomatic OD is now available in the new guidelines [3]. In general, it is advisable to assess RFs and asymptomatic OD at least every 2 years (but not earlier than 3–6 months). This is a very important knowledge regarding the appropriate patients' follow-up.

5 Office or Clinic BP Measurement

At present, BP can no longer be estimated using a mercury sphygmomanometer in many—although not all—European countries because of the progressive banning of the medical use of mercury for environmental purposes. Auscultatory or oscillometric semiautomatic sphygmomanometers are used instead. This policy is potentially against the accuracy of the measurements since the use of mercury sphygmomanometers was the "gold standard" method up till now, however the use of automatic manometers is simpler both for doctors and patients.

It is now clear that the time needed with the patient seated before beginning BP measurements is 3–5 min.

When checking for orthostatic hypotension, BP should be measured 1 and 3 min (and not 1 and 5 min, as reported in the 2007 document [1]) after assumption of the standing position. Orthostatic hypotension is now specifically defined as a reduction in systolic BP (SBP) of >20 mmHg or in diastolic BP (DBP) of >10 mmHg within 3 min of standing and has been shown to carry a worse prognosis for mortality and CV events. The definition of another variable in this version of guidelines is for sure useful in terms of using common criteria whereas the shortening of the time interval needed before BP measurement in the standing position means saving of valuable time for physicians.

6 Out-of-Office BP Thresholds for Definition of Hypertension

SBP thresholds for the diagnosis of hypertension according to ambulatory BP monitoring (ABPM) have more precisely been defined to 130 mmHg over 24-h (instead of 125–130 mmHg) and 135 mmHg for the day-time (instead of 130–135 mmHg) while according to home BP monitoring (HBPM) have more accurately been defined to 135 mmHg (instead of 130–135 mmHg).

7 Definition of the "Dipping" Status

The normal BP decrease during the night, known as dipping status, is now specifically defined using the night-to-day BP ratio (the ratio between average night-time and day-time BP) from ABPM. According to this ratio more dipping categories are currently proposed [3]: absence of dipping (ratio >1.0); mild dipping (ratio >0.9 and ≤1.0); dipping (ratio >0.8 and ≤0.9); and extreme dipping (ratio ≤0.8).

Once again, the use of common specific criteria (for both out-of-office BP classification and the dipping status) from all health care providers is undoubtfully desirable.

8 Clinical Indications for Out-of-Office BP Measurement

Office BP remains the "gold standard" for screening, diagnosis and management of hypertension while out-of-office

BP is considered an important adjunct to office BP. ABPM and HBPM provide somewhat different information on the subject's BP status and risk and the two methods should thus be regarded as complementary, rather than competitive or alternative. A revised Table summarizing the basic indications for the use of ABPM or/and HBPM for diagnostic purposes is now available in the 2013 document (major indications are suspicion of white-coat, masked or nocturnal hypertension, suspected hypotension, considerable variability of office BP and treatment-resistant hypertension).

9 Prognostic Value of Out-of-Office BP, White-Coat Hypertension and Masked Hypertension

Strengthening of the prognostic value of HBPM and of its role for diagnosis and management of hypertension, alongside ABPM (which remains the reference for out-of-office BP), is a fact in the new guidelines. Meta-analyses of prospective studies in the general population, in primary care and in hypertensive patients have shown that the prediction of CV events is significantly better with out-of-office BP than with office BP and that the prognostic significance of HBPM is similar to that of ABPM after adjustment for gender and age. The prognostic significance of night-time BP and its superiority versus day-time BP is confirmed in the 2013 document [3].

An update of the prognostic significance of white-coat hypertension and masked hypertension has also been made in the new guidelines [3]. Prognosis is better in white-coat hypertension than in sustained hypertension and appears to be similar to that in true normotension. The incidence of CV events is about two times higher in masked hypertension than in true normotension and similar to the incidence in sustained hypertension.

Given the high visit-to-visit, circumstantial, daily and seasonable BP variability, the recommendation for performing out-of-office BP measurements ensures a more valid patient classification.

10 BP During Exercise

An "exaggerated BP response to exercise" or "exercise hypertension" is, for the first time in guidelines, defined as a SBP of >210 mmHg for men and >190 mmHg for women although it is mentioned that there is currently no consensus on the normal BP response during dynamic exercise testing and that other definitions of "exaggerated BP response to exercise" have also been used in studies.

Another interesting new statement is that in the case of normal resting BP, exercise-induced hypertension can be considered an indication for ABPM because of its association with masked hypertension. This acknowledgement highlights a new significant prognostic aspect of exercise testing in daily medical practice.

11 Central BP

Although the current guidelines [3], like the previous ones [1], consider that the measurement of central BP and augmentation index should not be recommended at present for routine clinical use, at the same time they now focus at the fact that isolated systolic hypertension in the young may be the only exception: in some of these individuals increased SBP at the brachial level may be due to high amplification of the central pressure wave, while central BP is normal.

Hopefully, this version of guidelines favors a more detailed examination of young patients.

12 Causes of Secondary Hypertension

Thyroid diseases are recognized as potent cause of secondary hypertension while it is now recommended that symptoms suggestive of thyroid disease should be sought when obtaining patient's medical history.

Obstructive sleep apnoea (OSA), another cause of secondary hypertension, has recently been the subject of a consensus document from the ESH and the European Respiratory Society [5]. A few prospective studies have linked severe OSA to fatal and nonfatal CV events and all-cause mortality with this association appearing to be closer for stroke than coronary heart disease (CHD) and to be weak with OSA of mild-to-moderate severity [5]. On the basis of four available meta-analyses, the effect of prolonged, continuous positive airway pressure (CPAP) therapy on ambulatory BP is very small (1–2 mmHg reduction). The risk of new-onset hypertension in normotensive subjects with OSA is lower if they are treated with CPAP, although the benefit seems restricted to those with daytime sleepiness. However, it is clearly stated in the 2013 guidelines [3] that well designed therapeutic studies are too few and the aforementioned issues should be further investigated.

The incidence of renal artery stenosis has lately been found to be increased in patients with peripheral artery disease (PAD). Thus, this diagnosis must be kept in mind when resistant hypertension is encountered in these patients.

All three disorders previously reported are common causes of secondary hypertension and this more detailed discussion is welcomed.

13 Left-Right Arm BP Difference

It is clearly defined that differences between the two arms in SBP >20 mmHg and/or in DBP >10 mmHg, if confirmed in more than one occasions, should trigger further investigations of vascular abnormalities (aortic coarctation, subclavian artery stenosis).

14 Waist Circumference Measurement

It is made clear that this measurement should be performed in the standing position, at a level midway between the lower border of the costal margin and the uppermost border of the iliac crest.

15 Laboratory Investigations

Serum sodium is now included in the routine tests. HBA_1c (instead of oral glucose tolerance test) is now recommended as additional test if fasting plasma glucose is >5.6 mmol/l (102 mg/dl).

It was high time for elucidating the three issues previously reported since the adoption of these recommendations was already common practice for most physicians.

16 Assessment of LV diastolic function

According to recent echocardiographical recommendations [6], the Doppler transmitral inflow pattern should be combined with pulsed tissue Doppler of the mitral annulus. A tissue Doppler-derived early diastolic (e′) septal velocity <8 cm/s, lateral velocity <10 cm/s, a ratio between early transmitral (E) blood flow velocity and e′ (E/e′ averaged ratio) ≥13 and a left atrium volume index (LAVi) ≥34 ml/m^2 are considered abnormal. This is in line with echocardiographic societies recommendations.

17 Cardiac MRI

This technique should be considered for the assessment of LV size and mass when echocardiography is technically not feasible and when imaging of delayed enhancement would have therapeutic consequences.

18 Assessment of Myocardial Ischaemia in Hypertensive Patients with LVH

In the 2013 guidelines [3] a special section is devoted in the algorithm followed to diagnose myocardial ischaemia in hypertensive patients with LVH which is a procedure particularly challenging. The role of exercise electrocardiography, perfusion scintigraphy, stress echocardiography and stress cardiac MRI is discussed. A normal exercise test has an acceptable negative predictive value in patients without strong symptoms indicative of obstructive CHD. When the exercise ECG is positive or uninterpretable/ambiguous, an imaging test of inducible ischaemia is warranted for a reliable identification of myocardial ischaemia. The use of dual echocardiographic imaging of regional wall motion and transthoracic, Doppler-derived coronary flow reserve on the left anterior descending artery has recently been suggested to distinguish obstructive CHD (reduced coronary reserve plus inducible wall motion abnormalities) from isolated coronary microcirculatory damage (reduced coronary reserve without wall motion abnormalities). A coronary flow reserve <1.91 has an independent prognostic value in hypertension. This algorithm is valuable for guiding physicians.

19 Initiation of Antihypertensive Drug Treatment

The traditional Table of the recommended intervention (lifestyle changes, drug treatment or nothing) guided by the underlying CV risk (low, moderate, high and very high risk based on the office BP levels and the presence of RFs, OD, diabetes, CKD or symptomatic CVD) has substantially been revised (5 lines and 4 columns instead of 5 lines and 5 columns). The removal of the column referring to normotensives made the use and interpretation of the Table simpler, as previously discussed.

Major changes compared to the 2007 guidelines [1] have been made regarding the treatment approach of (i) the individuals with high normal BP, (ii) the young patients with isolated systolic hypertension and (iii) the elderly. These are probably the most significant changes made in hypertension guidelines since they refer to a large proportion of the population. Specifically, with the possible exception of masked hypertension, initiation of BP-lowering treatment is now not recommended at normal or high normal BP (Class III, Level A) even in high/very high risk patients (with diabetes, CVD or CKD). Drug treatment is also not recommended in young patients with isolated systolic hypertension (Class III, Level A). In elderly hypertensive patients drug treatment is now recommended when SBP is ≥160 mmHg (Class I, Level A) and may be considered when SBP is in the 140–159 mmHg range, provided that antihypertensive treatment is well tolerated (Class IIb, Level C). Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes octogenarian (Class IIa, Level C). Given the available data from large studies, the previously

reported alterations in the therapeutic strategy of these groups of individuals seeking for medical guidance emerge as more realistic.

Prompt initiation of drug treatment is recommended in individuals with grade 2 and 3 hypertension with any level of CV risk, a few weeks after or simultaneously with initiation of lifestyle changes (Class I, Level A), as already proposed in the 2007 guidelines [1]. In grade 1 hypertensive patients lowering BP with drugs is recommended when total CV risk is high/very high (Class I, Level B) and should be considered at low to moderate risk, when BP is within grade 1 range at several repeated visits or elevated by ambulatory BP criteria, and remains within this range despite a reasonable period of time with lifestyle measures (Class IIa, Level B); this is more or less in accordance with the previous guidelines [1].

In white-coat hypertensives without additional RFs, therapeutic intervention should be considered to be limited to lifestyle changes only, but this decision should be accompanied by a close follow-up (Class IIa, Level C). In white-coat hypertensives with a higher CV risk because of metabolic derangements or asymptomatic OD, drug treatment may be considered in addition to lifestyle changes (Class IIb, Level C). These recommendations are in agreement with the 2007 guidelines [1]. However, according to the 2013 guidelines [3], both lifestyle changes and drug treatment may be considered also when normal ambulatory BP values are accompanied by abnormal home BP values (or vice versa) because this condition is also characterized by increased CV risk. This detail should be carefully kept in mind by busy physicians.

In masked hypertension, both lifestyle measures and antihypertensive drug treatment should be considered, because this type of hypertension has been consistently found to have a CV risk very close to that of in- and out-of-office hypertension (Class IIa, Level C). Efficacy of antihypertensive treatment should be assessed by ambulatory and/or home BP measurements. These recommendations are for the first time clearly stated in the ESH/ESC guidelines. However, the optimal out-of-office BP values to be reached with treatment remain unclear as well as whether targets should be lower in high risk hypertensives.

During the first week after acute stroke it is reconfirmed that it is not recommended to intervene with BP-lowering therapy irrespective of BP level, although clinical judgement should be used in the face of very high SBP values (Class III, Level B).

It is now explicitly recommended that all patients with LVH receive antihypertensive agents (Class I, Level B). It is not clear whether this suggestion includes individuals in the high normal BP category. Moreover, some questions regarding the strength of recommendation for echocardiographic examination (Class IIa, Level B) are raised.

20 BP Treatment Goals

Significant changes in the target BP have been made and the new guidelines now recommend a unified target SBP in both higher and lower CV risk patients.

A SBP goal of <140 mmHg is now recommended in all hypertensive patients (Class I or IIa, Level A or B for specific group of patients e.g. with diabetes, CKD etc), with the exception of the elderly and the potent exception of the patients with overt proteinuria: In elderly hypertensive patients less than 80 years old there is solid evidence to reduce SBP to between 150 and 140 mmHg (Class I, Level A), but a goal of <140 mmHg may be considered in fit elderly (Class IIb, Level C), whereas in the fragile elderly population SBP goals should be adapted to individual tolerability (Class IIb, Level C). In individuals older than 80 years it is recommended to reduce SBP to between 150 and 140 mmHg if they are in good physical and mental condition (Class I, Level B). In patients with overt proteinuria, SBP values <130 mmHg may be pursued, provided that changes in eGFR are monitored (Class IIb, Level B).

A DBP of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended (Class I, Level A).

Given the luck of solid evidence for stricter BP control, the new recommended targets are simpler in their implementation in daily practice.

21 Lifestyle Changes

The recommended lifestyle change measures are more precisely described in the new guidelines [3]. There is a Class I, Level A or B (based on the effect on BP and/or CV risk profile or based on outcome studies, respectively) recommendation for: (i) salt restriction to 5–6 g per day, (ii) moderation of alcohol consumption to ≤20–30 g of ethanol per day (140 g per week) in men and to ≤10–20 g of ethanol per day (80 g per week) in women, (iii) increased consumption of vegetables, fruits, and low-fat dairy products (Mediterranean diet), (iv) reduction and maintenance of weight to BMI of about 25 kg/m^2 (the optimal BMI is unclear) and of waist circumference to <102 cm in men and <88 cm in women (unless contraindicated) (weight loss can also be promoted by anti-obesity drugs, such as orlistat and, to a greater degree, by bariatric surgery, which appears to decrease CV risk in severely obese patients), (v) regular physical exercise, i.e. ≥30 min of moderate dynamic aerobic exercise (walking, jogging, cycling or swimming) on 5–7 days per week and (vi) smoking cessation with assistance (varenicline though effective has recently raised concerns regarding its safety profile).

The benefit of the adoption of lifestyle measures is more precisely weighted in the 2013 document [3]: clinical studies show that the BP-lowering effects of targeted lifestyle modifications can be equivalent to drug monotherapy. This piece of information is very important since it practically means avoidance of drug therapy for high normal/grade 1 hypertension individuals and less drugs for grade 2 and 3 hypertensives.

22 Treatment Strategies and Choice of Drugs

The new guidelines [3] recommend that individuals with high normal BP or white-coat hypertension should be scheduled for regular follow-up (at least annual visits) to measure office and out-of-office BP, to check the CV risk profile and to reinforce recommendations on lifestyle changes, which represent the appropriate treatment in many of these patients.

It is reconfirmed that diuretics (thiazides, chlorthalidone and indapamide), beta-blockers, calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) are all still suitable and recommended for the initiation and maintenance of antihypertensive treatment (even in the elderly), either as monotherapy or in some combinations with each other (Class I, Level A).

As suggested in previous guidelines [1] as well, some agents should be considered as the preferential choice in specific conditions because used in trials in those conditions or because of greater effectiveness in specific types of OD (Class IIa, Level C). Other drug combinations should be considered and probably are beneficial in proportion to the extent of BP reduction. However, combinations that have been successfully used in trials may be preferable (Class IIa, Level C). Diuretics and calcium antagonists may be preferred in isolated systolic hypertension of the elderly (Class I, Level A).

The new guidelines [3] also reconfirm that initiation of antihypertensive therapy with a two-drug combination may be considered in patients with markedly high baseline BP or at high CV risk (Class IIb, Level C).

In contrast to the 2007 document [1], the 2013 guidelines [3] report that the combination of two antagonists of the renin-angiotensin system (RAS) is not recommended and should be discouraged (Class III, Level C). This is a very important issue since a modification of the therapeutic scheme in a large proportion of patients is now necessary.

In line with what is reported in the 2007 guidelines [1], the new guidelines [3] reconfirm that combinations of two antihypertensive drugs at fixed doses in a single tablet may be recommended and favoured, because reducing the number of daily pills improves adherence, which is low in patients with hypertension (Class IIb, Level B).

Contra-indications to the use of antihypertensive drugs have been partially reappraised in the new guidelines [3]. Hypercalcaemia and hypokalaemia have been added to the possible contra-indications for the use of thiazides. PAD is not any more considered possible contra-indication to the use of beta-blockers while chronic obstructive pulmonary disease is not considered contra-indication to the use of vasodilating beta-blockers. RAS blockers are now contra-indicated in women with child bearing potential (Class III, Level C).

Some of the limitations of traditional beta-blockers do not appear to be shared by some of the vasodilating beta-blockers, such as celiprolol, carvedilol and nebivolol—more widely used today—which reduce central pulse pressure and aortic stiffness better than atenolol or metoprolol and affect insulin sensitivity less than metoprolol. Nebivolol has recently shown not to worsen glucose tolerance compared with placebo and when added to hydrochlorothiazide.

Drugs to be preferred in specific conditions have somehow been reconsidered, as well. Beta-blockers are now recognized as the preferred treatment in the case of aortic aneurysm. Beta-blockers and mineralocorticoid receptor antagonist (if heart failure coexists) have been added in the drugs to be preferred for the prevention of new or recurrent atrial fibrillation while ACE inhibitors in the preferred treatment in case of PAD. Loop diuretics are no more included in the drugs of choice in hypertensive patients with end-stage renal disease or/and proteinuria.

No recommendation is given to favour a particular diuretic agent (between thiazides, chlorthalidone and indapamide) in the new [3] or the previous [1] versions of guidelines. Spironolactone has been found to have beneficial effects in heart failure and, although never tested in randomized controlled trials on hypertension, can be used as a third- or fourth-line drug and helps in effectively treating undetected cases of primary aldosteronism. Eplerenone has also shown a protective effect in heart failure and can be used as an alternative to spironolactone.

Calcium antagonists have been cleared from the suspicion of causing a relative excess of coronary events and ARBs from concerns for potent association with cancer onset.

Drugs acting via direct renin inhibition at the site of its activation are the only new classes of antihypertensive agents that have recently become available for clinical use. Aliskiren, the only agent of this class available at present, is suitable for treating hypertensive patients, both as monotherapy and when combined with other antihypertensive agents (i.e. a thiazide diuretic, a calcium antagonist, another blocker of the RAS though the last combination is

not recommended). Prolonged administration in combination treatment can have a favourable effect (i) on asymptomatic OD, such as urinary protein excretion or (ii) on prognostic biomarkers for heart failure, such as B-type natriuretic peptides. No trial is available on the effect of aliskiren on CV or renal morbid and fatal events in hypertension.

All the aforementioned details about the specific properties or/and limitations of the BP-lowering classes and agents should be kept in mind by all physicians.

The algorithm of moving from a less to a more intensive therapeutic strategy whenever BP target is not achieved has only minor changes from the previous guidelines [1], i.e. (i) we can move from a single agent at low dose to a two-drug combination without using the single agent at full dose or switching to a different single agent, (ii) we can switch a two-drug combination at full doses to a different two-drug combination before adding a third drug and (iii) in patients with resistant hypertension, adding drugs to drugs should be done with attention to results and any compound overtly ineffective or minimally effective should be replaced, rather than retained in an automatic step-up multiple-drug approach (Class I, Level C). These new suggestions aim to a quicker achievement of BP target which is valuable in terms of better patients' compliance.

A revised colored schema for priorital two-drug combination is now available in the 2013 guidelines [3]. "Other antihypertensive drugs" have replaced α-blockers in one of the six vertices of the known hexagon showing the possible combinations between classes of antihypertensive drugs. Moreover, (i) the ARBs/ACE inhibitors combination is now not recommended (red continuous line instead of black dashed line), (ii) the beta-blockers/thiazides combination is now considered useful—with some limitations—(green dashed line) instead of possible but less well tested (black dashed line) while (iii) the beta-blockers/calcium antagonists combination is now considered possible but less well tested (black dashed line) instead of preferred (continuous line). It is made clear that although verapamil and diltiazem are sometimes used with a beta-blocker to improve ventricular rate control in permanent atrial fibrillation, only dihydropyridine calcium antagonists should normally be combined with beta-blockers.

As also reported in the 2009 reappraisal of guidelines [2], the treatment simplification associated with the use of the so-called polypill (i.e. a fixed-dose combination of several antihypertensive drugs with a statin and a low-dose aspirin) may only be considered if the need for each polypill component has been previously established.

In the 2013 guidelines [3], it is clear that decisions on antihypertensive therapy of frail elderly patients should be left to the treating physician and based on monitoring of the clinical effects of treatment (Class I, Level C). This is truly a realistic approach.

Elevated BP at control visits during the follow-up of the patients should always lead physicians to search for the cause(s), such as poor adherence, persistent white-coat effect or use of BP-raising substances. If ineffective treatment is regarded as the reason for inadequate BP control, the treatment regimen should be modified without delay to avoid clinical inertia—major contribution to poor BP control worldwide.

Consideration should be given to the evidence that CV protection may be greater in patients with consistent BP control throughout visits. The clinical importance of visit-to-visit BP variability within treated individuals, vis-a-vis the achieved long-term average BP level, is not yet indisputably proven. Visit-to-visit BP variability may be lower with the combination of a calcium antagonist and an ACE inhibitor, than with the combination of a beta-blocker and a diuretic but this should not be used at present as a criterion for antihypertensive drug choice until further investigation.

23 Treatment Strategies in Hypertensive Women

23.1 Oral Contraceptives (OCs)

A more specific position regarding the use of OCs is adopted in the 2013 guidelines [3]. Current recommendations indicate that OCs should be selected and initiated by weighing risks and benefits for the individual patient. BP should be evaluated using properly taken measurements and a single BP reading is not sufficient to diagnose hypertension. Women aged ≥35 years should be assessed for CV RFs, including hypertension. It is not recommended that OCs be used in women with uncontrolled hypertension. Discontinuation of combined OCs in women with hypertension may improve their BP control. In women who smoke and are ≥35 years old, OCs should be prescribed with caution.

23.2 Hormone Replacement Therapy (HRT)

As previously recommended by the ESH/ESC guidelines, HRT and selective oestrogen receptor modulators are not recommended and should not be used for primary or secondary prevention of CVD (Class III, Level A). If treatment of younger perimenopausal women is considered for severe menopausal symptoms, the benefits should be weighed against potential risks.

All current knowledge about OCs and HRT should be clearly communicated to women with child bearing potential and (peri)menopausal women, respectively.

23.3 Pregnancy

Drug treatment of severe hypertension in pregnancy (SBP >160 mmHg or DBP >110 mmHg) is recommended (Class I, Level A). The approach in this issue is different from the previous guidelines [1] where severe hypertension was defined as SBP ≥170 mmHg or DBP ≥110 mmHg and was considered an emergency requiring hospitalization.

In agreement with previous versions of guidelines, drug treatment may also be considered in pregnant women with persistent elevation of BP ≥150/95 mmHg, and in those with BP ≥140/90 mmHg in the presence of gestational hypertension, subclinical OD or symptoms (Class IIb, Level C). Moreover, in women at high risk of pre-eclampsia, provided they are at low risk of gastrointestinal haemorrhage, treatment with low dose aspirin from 12 weeks until delivery may be considered (Class IIb, Level B). Methyldopa, labetolol and nifedipine remain the preferential antihypertensive drugs in pregnancy. Intravenous labetolol or infusion of nitroprusside should be considered in case of emergency (pre-eclampsia) (Class IIa, Level B).

Obstetricians and gynecologists should be cautiously alert since they are the main doctors dealing with pregnant females.

24 Treatment Strategies in Haemodialysis Hypertensive Patients

Some general considerations on how to manage high BP in patients on haemodialysis are for the first time available in ESH/ESC guidelines. Firstly, accurate measurement of BP is essential for the management of haemodialysis patients. However, a pre-haemodialysis BP may not reflect the average BP experienced by the patient. Thus, the question of how and where the measurements should be made is of particular importance, with clear evidence for the superiority of self-measured BP at home over pre-haemodialysis BP values. Secondly, the BP to be pursued by treatment in patients on haemodialysis has not been clearly established in this context. Thirdly, all antihypertensive drugs except diuretics can be used in the haemodialysis patients, with doses determined by the haemodynamic instability and the ability of the drug to be dialysed. Drugs interfering with homeostatic adjustments to volume depletion should be avoided to minimize hypotension during the fast and intensive reduction of blood volume associated with the dialytic manoeuvres.

Close collaboration with nephrologists is obviously important for better patients' prognosis.

25 Treatment Strategies in Hypertensive Patients with Erectile Dysfunction

This issue was for the first time discussed in the 2009 reappraisal of guidelines [2]. In the new guidelines [3], it is reconfirmed that compared with older antihypertensive drugs (diuretics, beta-blockers, centrally acting), newer agents (ARBs, ACE inhibitors, calcium antagonists and vasodilating beta-blockers) have neutral or even beneficial effects on erectile function. Phospho-diesterase-5 inhibitors may be safely administered to hypertensives, even those on multiple drug regimens (with the possible exception of alpha-blockers and in absence of nitrate administration) and may improve adherence to antihypertensive therapy.

When vasodilating beta-blockers are prescribed to males they should be reassured about the safety of this treatment since they are usually highly suspicious affecting their compliance to treatment.

26 Treatment Strategies in Patients with Resistant Hypertension

Special attention to new (pharmaceutical or/and invasive) treatment approaches has been paid in the 2013 guidelines [3]. Specific recommendations include the following:

Mineralocorticoid receptor antagonists, amiloride, and the alpha-1-blocker doxazosin should be considered, if no contraindication exists (Class IIa, Level B). At variance from an earlier report, endothelin antagonists have not been found to effectively reduce clinic BP in resistant hypertension and their use has also been associated with a considerable rate of side-effects. New BP-lowering drugs (nitric oxide donors, vasopressin antagonists, neutral endopeptidase inhibitors, aldosterone synthase inhibitors, etc.) are all undergoing early stages of investigation. No other novel approach to drug treatment of resistant hypertensive patients is currently available.

In case of ineffectiveness of drug treatment, invasive procedures such as renal denervation and baroreceptor stimulation may be considered (Class IIb, Level C). The invasive approaches are considered only for truly resistant hypertensive patients, with clinic SBP ≥160 mmHg or DBP ≥110 mmHg and with BP elevation confirmed by ABPM (Class I, Level C). It is also recommended that these procedures remain in the hands of experienced operators and diagnosis and follow-up restricted to hypertension centers (Class I, Level C). The updated position paper of the ESH on interventional therapy of resistant hypertension should be consulted for more details [7]. Moreover, newer studies (SYMPLICITY HTN-3) [8] have recently downgraded the efficacy of renal denervation in

terms of BP reduction and highlighted the need for careful patients' selection. Its long-term efficacy in terms of CV and renal protection is under investigation, as well. Research in this area is ongoing and new invasive procedures (e.g. creation of a venous-arterial fistula, neurovascular decompression) are under study.

Patients with resistant hypertension should be monitored closely. Office BP should be measured at frequent intervals and ambulatory BP at least once a year. Frequent home BP measures can also be considered and measures of organ structure and function (particularly of the kidney) instituted on a yearly basis. The use of mineralocorticoid receptor antagonists, should prompt frequent assessment of serum potassium and serum creatinine concentrations, especially if there is concomitant treatment with a RAS blocker. Whether BP reduction substantially lowers CV risk in patients with resistant hypertension is still unclear.

27 Treatment Strategies in Hypertensive Emergencies (Including Malignant Hypertension)

Hypertensive emergencies (large elevations in BP associated with OD) are clearly distinguished from hypertensive urgencies (isolated large BP elevations without acute OD). In most cases of hypertensive emergencies, it is suggested that physicians aim at a <25 % BP reduction during the first hours, and proceed cautiously thereafter. Current treatment is founded on agents that can be administered by intravenous infusion and titrated, and so can act promptly but gradually in order to avoid excessive hypotension and further ischaemic OD. Labetalol, sodium nitroprusside, nicardipine, nitrates and furosemide are among the intravenous agents most usually employed but treatment should be individualized by the physician. Drugs should subsequently be switched to orally. When diuretics are insufficient to correct volume retention, ultrafiltration and temporary dialysis may help. A brief comment regarding the asymptomatic patients with isolated mild/intermediate BP elevations without acute OD that use to flock in the emergency departments would be useful in the guidelines document. These patients should be at first reassured about their low acute risk and they should be referred to their attending physician.

28 Perioperative Management of Hypertension

Suggestions concerning the perioperative management of hypertension are for the first time provided in the ESH/ESC guidelines based on experience only (Class IIb, Level C). Sudden withdrawal of clonidine or beta-blockers immediately before surgery should be avoided because of potential BP or heart rate rebounds. Both types of agent can be continued over surgery and, when patients are unable to take oral medications, beta-blockers can be given parenterally and clonidine transdermally. Diuretics should be avoided on the day of surgery because of potential adverse interaction with surgery-dependent fluid depletion. ACE inhibitors and ARBs may also be potentiated by surgery-dependent fluid depletion and it has been suggested that they should not be taken on the day of surgery and restarted after fluid repletion has been assured. Post-surgery BP elevation, when it occurs, is frequently caused by anxiety and pain after awakening, and disappears after treating anxiety and pain. A correct informing of surgeons could save many of the resultant problems.

29 Treatment of Primary Aldosteronism

The suggested treatment of this entity in the 2013 guidelines [3], at variance from the previous version [1], depends on the unilateral or bilateral localization of the disease: in documented unilateral primary aldosteronism, caused either by aldosterone-producing adenoma or unilateral adrenal hyperplasia, the treatment of choice is unilateral laparoscopic adrenalectomy, whereas treatment with mineralocorticoid receptor antagonists is indicated in patients with bilateral adrenal disease (idiopathic adrenal hyperplasia and bilateral adenoma). Glucocorticoid-remediable aldosteronism is treated with a low dose of a long-acting glucocorticoid, e.g. dexamethasone.

30 Treatment of Associated RFs (Lipid and Glycaemic Control)

Recommendations regarding the lipid and glycaemic control in hypertensive patients have essentially been revised compared to the previous guidelines [1]. Specifically:

It is now recommended to use statin therapy in hypertensive patients when at moderate to high CV risk, targeting a low-density lipoprotein cholesterol value <3.0 mmol/l (115 mg/dl) or when overt CHD is present, to achieve low-density lipoprotein cholesterol levels <1.8 mmol/l (70 mg/dl) (Class I, Level A).

In hypertensive patients with diabetes, a HbA_1c target of <7.0 % is now recommended with antidiabetic treatment (Class I, Level B) while a less tight HbA_1c target of <7.5–8.0 % should be considered in more fragile elderly patients with a longer diabetes duration, more comorbidities and at high risk (Class IIa, Level C). The recent guidelines for the treatment of diabetes released by the ESC and the European Association for the Study of Diabetes (EASD) [9] should be consulted for more details.

Given that dyslipidaemia and diabetes are frequent comorbidities in hypertensives, all physicians should be aware about the relevant guidelines, as well.

31 Conclusions

Several significant changes have been adopted in the European hypertension guidelines affecting, at least in part, daily clinical practice. In general the new guidelines, compared to previous ones, is a more comprehensive document with adequate discussion of most of the important aspects of arterial hypertension, giving answers in many current debates and providing physicians with more specific recommendations in several practical issues. However, they should be more schematic and shorter for easy reading and practical application.

Conflict of interest None.

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