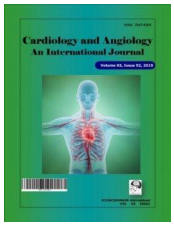

Cardiology and Angiology: An International Journal
3(4): 181-191, 2015, Article no.CA.2015.018
ISSN: 2347-520X

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What's New and What Gaps in 2013 European Guidelines for the Management of Arterial Hypertension: A Reappraisal

Pietro Scicchitano[1], Michele Gesualdo[1], Santa Carbonara[1], Pasquale Palmiero[2], Pietro Nazzaro[3], Annapaola Zito[1], Gabriella Ricci[1], Luisa de Gennaro[4], Pasquale Caldarola[4], Francesca Cortese[1] and Marco Matteo Ciccone[1*]

[1]Department of Emergency and Organ Transplantation (DETO), Cardiovascular Diseases Section, University of Bari, Piazza G. Cesare 11–70124, Bari, Italy.
[2]Department of Cardiology, Local Health Service-Brindisi, Italy.
[3]Department of Basic Medical Sciences, Neurosciences and Sense Organs, Division of Neurology-Stroke Unit, Hypertension, University of Bari, Bari, Italy.
[4]Department of Cardiovascular Disease, "San Paolo" Hospital, Bari, Italy.

Authors' contributions

This work was carried out in collaboration between all authors. Authors MMC, PS, MG, PP, PC and PN designed the study and wrote the first draft of the manuscript, contributed in answering the comments of the reviewers. Authors SC, AZ, GR, LDG and FC managed the literature searches and revised the draft of the paper. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/CA/2015/17967
Editor(s):
(1) Anonymous.
Reviewers:
(1) Anonymous, King George's Medical University, India.
(2) Xing Li, Division of Biomedical Statistics and Informatics and Department of Health Sciences Research, Mayo Clinic College of Medicine, USA.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=843&id=26&aid=9171

Mini-review Article

Received 31st March 2015
Accepted 16th April 2015
Published 8th May 2015

ABSTRACT

Arterial hypertension is the most common cardiovascular risk factor causing over 9 million deaths worldwide. Its treatment is crucial in preventing adverse outcomes, in reducing morbidity and mortality and related socio-economic impact of cardiovascular diseases. The European Society of Cardiology and the European Society of Hypertension recently published the new guidelines for the management of hypertension in order to provide physicians diagnostic and therapeutic tools and indications for improving health outcomes. Despite the new advances proposed by the authors,

**Corresponding author: E-mail: marcomatteo.ciccone@uniba.it;*

gaps in evidences still persist. The aim of our paper is to give an overview about the new aspects proposed in the arterial hypertension management and the dark side of the knowledge still persisting about such a matter.

Keywords: Arterial hypertension; hypertension management; gaps in evidence; guidelines.

1. INTRODUCTION

Hypertension is a well-known risk factor for cardiovascular disease (CVD) [1]. Increased values of arterial pressure lead to organ damages and clinical adverse events such as ischemic heart disease, stroke, heart and kidney failure. Due to its asymptomatic features, hypertension is considered as a "silent killer" responsible for about nine million deaths each year all over the world [1].

The European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) recently developed an update of the Guidelines on the Management of Hypertension [2] to be followed by cardiologists, family practitioners, nephrologists, internists and endocrinologists. These new guidelines were determined from a drafting panel composed by eminent scientists and academics from European Society of Hypertension and European Society of Cardiology in order to give a frank overview and methods in the general management of hypertensive condition.

These new guidelines point out new advances as compared to previous position papers [3,4], although many gaps still persist in the general management of hypertensive patients.

The 2013 manuscript [2] tries to summarize the specific recommendations in order to fast the consultation processes. This is a novelty for guidelines presentation which is linked to the high level of evidence reached for each point of the recommendations. Only 29% of the recommendations presents level of evidence C (i.e. derived from a consensus of opinions of experts and/or small studies, retrospective studies or registries) and this is due to an increased availability of data from randomized clinical trials. This increases the value of the document and suggests that treatments based on evidence medicine are now available in the general management of arterial hypertension [5]. Despite such positive aspects, the presence of several gaps still persists and deserves much more attention from the international scientific community.

The aim of this paper is to give an overview about both advances and gaps in the general management of arterial hypertension, in relation to the new ESC/ESH guidelines (see also Table 1).

2. CARDIOVASCULAR RISK PROFILE ASSESSMENT

The introduction section focused on the cardiovascular risk profile assessment of patients suffering from arterial hypertension, pointing out the definitions of the terms adopted in order to make a uniform evaluation of such patients all over the European nations whoever may be the physician involved [2].

Although the proposed definitions are equal to those written in the previous guidelines [4,5], some novelties can be outlined.

The first one is represented by the introduction of the SCORE (Systematic Coronary Risk Evaluation) risk charts in order to assess cardiovascular risk, in line with the ESC guidelines on CVD prevention [6] and dyslipidemia management [7]. This model expresses the estimated 10-year risk of cardiovascular mortality by including parameters such as age, gender, smoking status, total cholesterol and systolic blood pressure [8].

Nevertheless, SCORE "underscores" the estimation of the global cardiovascular risk of the patients because it did not consider additional risk-modifying factors such as sedentary lifestyle, obesity, impaired metabolism of carbohydrates, high serum levels of triglycerides or low concentrations of high-density lipoprotein cholesterol, a family history of cardiovascular disease at early age (before 55 years for men and 65 years for women). Furthermore, asymptomatic organ damage can be considered as a potential, new risk-modifier: the presence of left ventricular hypertrophy, carotid intima-media thickening (≥0.9 mm) or atherosclerotic plaques, carotid/femoral pulse wave velocity (PWV), which utility was emphasized lowering the normal values from >12 m/s (ESC-ESH 2007) to actual >10 m/s [3] and urine albumin/creatinine ratio $\geq 90^{th}$ percentile predict cardiovascular mortality independently of SCORE model [9-11].

Table 1. New advances and still persisting gaps in guidelines for the management of arterial hypertension

What's new?
• Unique systolic blood pressure target:
• Less than 140 mmHg for all healthy subjects (140-150 mmHg for patients older than 80 years if their mental and physical heath allow it).
• Diastolic blood pressure target:
• <90 mmHg, with the exception of diabetic patients whose target is <85 mmHg.
• Adjunct value of Home and Ambulatory blood pressure monitoring in accurate risk assessment.
• Reduction in salt intake to 5-6g/day to reduce blood pressure.
• Individualized approach to drug therapy based on global cardiovascular risk and comorbidities of patient.
• No treatment for subjects with high normal blood pressure.
• Catheter-based renal denervation seems to be a promising approach for resistant hypertension.
What gaps?
• In the global risk-assessment algorithm, elderly people per se should be considered a category at moderate to high cardiovascular risk.
• Emerging cardiovascular risk factors should be considered in total risk stratification
• Home blood pressure monitoring could cause discomfort or concern in some patients

Aware of such limitations of the SCORE charts, the 2013 ESC guidelines [2] proposed a second chart for the assessment of the cardiovascular risk which includes the evaluation of asymptomatic cardiovascular diseases expressions as able to further increase the patients' risk profile. Despite this implementation, the new guidelines did not provide any indication about the predictive value of each chart nor the incremental value of each organ damage markers in the context of hypertensive patient risk stratification. This generates confusion above all among general practitioners who, unaware of the main and specialized tools and parameters showed by guidelines, remain unable to advice patients for the best tool to study and evaluate their disease state.

One more novelty of 2013 ESC-ESH guidelines is that no mention is for patients showing normal pressure but risk factors or even organ damages. In contrast to the previous 2007 recommendations, the authors did not consider lifestyle changes or at least drug therapy when considering patients at normal pressure values. This seems quite unusual in relation to the great weight that 2013 ESC-ESH paper gives to organ damages and cardiovascular risk factors when considering a hypertensive patient.

Furthermore, while patients with three risk factors were previously compared to those with established organ damage, chronic kidney disease or diabetes, the current guidelines, strangely separate these categories by considering the former at favorable prognosis than the latter.

3. METHODS FOR BLOOD PRESSURE ASSESSMENT

The 2013 ESC/ESH guidelines pointed out the new approach to methods for blood pressure assessment in relation to the continental nationwide laws. In particular, they pointed out the out-of-order use of mercury sphygmomanometer due to its dangerousness although the use of the semiautomatic instrument deserves a tight attention in daily and home monitoring of blood pressure. No other great variations in the methodology for the blood pressure monitoring and measurement can be outlined from standard international guidelines.

In opposition to previous recommendations, the 2013 ESC guidelines emphasized "out of office" blood pressure (BP) monitoring in form of home blood pressure monitoring (HBPM) and ambulatory blood pressure monitoring (ABPM), by favoring the former rather than the latter, in agreement with recent evidences showing that blood pressure values detected with these two methods predict organ damage and risk of cardiovascular outcomes better than BP assessed in the office (office pressure measurement) [12-14]. Although office pressure measurement, i.e. the blood pressure evaluation in the medical environment, represents the gold standard for the diagnosis of arterial hypertension, the guidelines underline the

complementary role of HBPM and ABPM in the general assessment of BP. This is the reason why the 2013 paper contains more accurate definitions about the cut-off values for diagnosis of the office, home and ambulatory blood pressure measurements, paying more attention to technical procedures or their evaluations.

Furthermore, 2013 guidelines offer a sort of simplification of ABPM interpretation which makes the guidelines more useful and practical than previous one. The paper considered as main prognostic factor the mean BP value recorded over 24 hours (cut-off values ≥130 mmHg for systolic and/or ≥80 mmHg for diastolic blood pressure). This is really important because enhances the relevance of the masked hypertension outlined by 24 h BP monitoring and defined as normal BP at the office measurement with increased BP levels at ABPM or HBPM. This condition is considered equivalent to sustained hypertension in term of predictor of major cardiovascular events [15]. Although the ESC 2013 guidelines did not advise to perform ABPM in all subjects with normal blood pressure values and other cardiovascular risk factors, the relevance of ABPM is particularly sustained.

4. ORGAN DAMAGE ASSESSMENT

The section devoted to organ damage assessment repeats the directions of previous guidelines, in relation to the effectiveness and low cost of the available techniques used for early detection of vascular injuries (i.e. PWV and ankle-brachial index). More importance has now been assigned to the role of magnetic resonance imaging (MRI) for cerebral microbleeds evaluation (observed in 5% of individuals) and for the study of silent brain lesions in hypertensive patients. Although the guidelines do not recommend the routine use of MRI due to lack of data [16], they promote the management of more trials evaluating the predictive value of MRI in hypertensive patients. Furthermore, retinopathy grades III and IV are actually considered to be more predictive of cardiovascular mortality than mild lesions of fundus oculi.

5. TARGET BLOOD PRESSURE VALUES

The 2013 guidelines simplify the goals for antihypertensive treatment: in opposition to the 2007 version which indicated different blood pressure targets in relation to age, gender and co-morbidities. Not only the actual guidelines did not consider anymore the cardiovascular risk in normotensives but, focusing more on high blood pressure values, the new document only recommends a systolic BP target <140 mmHg as the best target to be reached in hypertensive patients. This cut-off is strongly recommended (Class I) for patients with low-to-moderate cardiovascular risk and with diabetes [2], while it shows a class IIa recommendation for patients with history of stroke and transient ischemic attack, coronary artery disease and chronic kidney disease [2]. In patients older than 80 years the systolic BP target should be maintained between 140-150 mmHg if their mental and physical health allow it. According to the diastolic blood pressure, it is recommended a target value <90 mmHg, with the exception of patients with diabetes mellitus whose target should be <85 mmHg [2].

6. METABOLIC ASSESSMENT

The metabolic syndrome is not recognized anymore as independent risk factor but all its components are considered as single factors. There is no mention in the current guidelines about the metabolic syndrome as a whole. The authors of the new guidelines considered only the single features of metabolic syndrome in the general assessment of the patient suffering from hypertension. This is a point of criticism when considering the new guidelines: the metabolic syndrome gathers features and conditions that increase too much the cardiovascular risk profile of hypertensive patients. Thus, much more attention should be paid to the patient suffering from metabolic syndrome.

7. THERAPEUTIC APPROACH

The section dealing with the treatment strategies presents the major novelties of this document, mainly arising from randomized controlled trials performed in recent years, but also from the need to reform the previous organization. First of all, pharmacological treatment should be based on patient's overall risk, determined by clinic blood pressure values and other cardiovascular risk factors, such as subclinical organ damage, diabetes mellitus, symptomatic cardiovascular disease or chronic kidney disease [2], outlining not to give (Class IIIA) any drugs in case of high normal blood pressure (systolic values between 130 and 139 mmHg) but recommending to encourage life style changes.

According to pharmacological treatment, the new guidelines substantially reconfirm the 5 major

classes of antihypertensive drugs (thiazide diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor blockers, [ARBs]) for the initiation and maintenance of treatment, either as monotherapy or in association (Class IA) [2]. Nevertheless, for the first time the paper contraindicated the combination therapy between ACE inhibitors and ARBs in relation to the results of ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) [17].

Furthermore, the 2013 version updated the recommendations about the starting of combined therapy in high cardiovascular risk patients or with high blood pressure values (Class IIb) in relation to the findings coming from three large-scale clinical trials published after 2007 (Avoiding Cardiovascular events through combination therapy in Patients Living with Systolic Hypertension [ACCOMPLISH], Action in Diabetes and Vascular disease: Preterax and diamicron Controlled Evaluation [ADVANCE] and (ONTARGET). The current hypertension guidelines dedicate a whole subsection to aliskiren, the first selective inhibitor of plasma renin activity. This drug, alone or in combination, reduces systolic and diastolic BP in all age hypertensive patients [18], increases its effectiveness in association with a thiazide diuretic, a renin-angiotensin system blocker on a different site [19] or a calcium channel blocker [20] and finally improves asymptomatic organ damage indices [21]. Despite the large initial expectations, this drug was not included in the recommendations of new guidelines due to the poor results coming from literature [22,23]. The altitude study, for example, randomized diabetic patients to receive aliskiren in addition to an ace inhibitor or an ARB. it was discontinued due to the onset of renal complications, hyperkalemia and hypotension [22]. In subjects with reduced left ventricular ejection fraction, aliskiren did not reduce cardiovascular mortality or readmission rate at 6 months, nor showed any clinical benefit within one year [23].

8. DRUG-RESISTANT HYPERTENSION

Unlike the previous version, the 2013 ESC guidelines on arterial hypertension management amply dealt with the problem of resistant hypertension, defined as blood pressure that remains high despite treatment with at least three antihypertensive agents at the maximum tolerated dose [2]. Its diagnosis requires a careful assessment of blood pressure values through ABPM and an evaluation of patient's compliance to drug therapy, after a prudent exclusion of all the causes which can sustain high blood pressure. The true resistant hypertension is a relevant public health problem due to its role in increasing the risk of developing complications such as myocardial infarction, stroke, heart or kidney failure, death regardless of age, gender and/or other associated diseases [24-26]. Therefore, high costs for the national health system are related to resistant hypertension. The current guidelines underlined that resistant hypertensive patients should be evaluated by an appropriate and thoroughly trained team in order to optimize anti-hypertensive drugs administration or consider minimally invasive treatments [2].

The non-pharmacological approaches to resistant hypertension are another novelty in 2013 guidelines. Although the paper outlined the lack of large cohort studies and long-term efficacy, safety, morbidity and mortality data, non-pharmacological, invasive approaches to hypertension is considered the future of hypertensive patients' treatment. Implantable device stimulating the carotid baroreceptors can be an optimal treatment option with few side effects [27,28], as well as renal artery sympathetic denervation by radiofrequency [29-31]. The ESH believes that, although the conclusion of Simplicity HTN-3 depicts the renal denervation as an ineffective technique [32], more trials are needed in order to better validate these pathophysiological concepts, the efficacy in specific subgroups of patients and the clinical outputs obtained through different devices employed.

9. GAPS

The 2013 guidelines confirm a therapeutic approach to hypertensive patients according to total cardiovascular risk highlighting the need for a tailored treatment. In elderly patients, the document recommends a systolic BP target between 140-150 mmHg (class IA) in subjects younger than 80 years or <140 mmHg if case of healthy patient (class IIb C); in individuals older than 80 years the systolic BP target still continues to be set at 140-150 mmHg if mental and physical heath allow it (class IB). Thus, in the global risk-assessment algorithm the age is considered as a risk factor when overcome 55 years in men and 65 years in women.

Nevertheless, old adults, especially the frail elderly, should be *per se* considered as a category at moderate to high cardiovascular risk due to their co-morbidities. Older adults often suffer from isolated systolic hypertension which decreases vascular compliance and increases pulse pressure, which are powerful predictor of cardiovascular events even more than the single values of systolic or diastolic blood pressure [33]. Furthermore, the impact of cardiovascular risk factors on vascular outcomes is greater in very elderly subjects and this should be taken into account [34,35]. Other medical conditions such as urinary incontinence, falls and fractures, depression, cognitive dysfunction, functional impairment with lack of moderate or vigorous exercise and delirium can negatively influence the outcome of the elderly patients. For this reason geriatricians use the term "geriatric syndromes" to gather the condition of the elder with his/her co-morbidities [36,37]. The novel targets proposed for hypertensive old persons are really interesting above all because point out that antihypertensive therapy should be carefully tailored in such category of patients in order to avoid a steeper decrease in diastolic pressure which could compromise the blood perfusion of important organs, such as heart and brain. Although such particular attention to elderly people, the 2013 guidelines did not consider the evaluation of their physical and mental performance and, therefore, no indicators were provided for optimization of the treatments in relation to subject's health state while, for the first time, cerebral microvascular lesions are considered as target organ damage.

The new guidelines on hypertension management are particularly endowed with stratification of cardiovascular risk profile of individuals. Nevertheless, they did not consider nontraditional risk factors which contribute to atherosclerosis development and to increase cardiovascular risk. Hyperuricemia is currently recognized as an independent risk factor for cardiovascular disease: Baseline serum uric acid (SUA) levels can effectively predict cardiovascular mortality [38-40]. The association between SUA and increased risk for cardiovascular events/all-cause mortality was demonstrated in untreated subjects with essential hypertension [41]. Elevated plasma levels of homocysteine (HCY is deemed a powerful marker of cardiovascular diseases [42,43]. Elevated HCY plasma values ameliorate risk prediction in subjects considered at "intermediate risk" according to Framingham risk score [44]. In patient with established coronary artery disease, increased HCY levels are strong predictors of cardiovascular mortality. HCY concentrations are slightly associated with angiographic extent of coronary atherosclerosis and strongly related to history of myocardial infarction, impaired left ventricular ejection fraction and death due to cardiac causes [45]. Moreover, high HCY levels have an important value in predicting re-stenosis and major adverse cardiac events after successful coronary angioplasty [46]. The evaluation of such a molecule is not fully considered in the overall text of the guidelines and this limits the complete evaluation of cardiovascular risk score of hypertensive patients.

Furthermore, the guidelines briefly refer to lipoprotein(a) and C-reactive protein, declaring that risk may be higher than indicated in the charts in patients with increased levels of such compounds [47,48]. Additional assessment of the serum levels of these molecules should be taken into account in order to fully predict cardiovascular events [49].

Our opinion is that guidelines should win the reticence in recommending screening for nontraditional risk factors, in relation to the wide evidences supporting their prognostic power and the amelioration of cardiovascular risk when a reduction in their serum levels is reached [50-53].

Thus, in clinical practice and management of hypertensive patients, the screening of emerging risk factors should be encouraged to complete and enhance the global risk assessment of cardiovascular disease.

By considering the instrumental approach to hypertensive patients, the guidelines support the HBPM approach for a more accurate cardiovascular risk assessment to obtain a careful picture of blood pressure profile, evaluate the efficacy of pressure-lowering therapy and increase the adherence of patients to treatments. Nevertheless, BP presents short-term fluctuations over the 24-hour cycle [54]. At the moment, it is not establish whether antihypertensive treatment should aim at reducing absolute BP values or shall counteract BP variability. Furthermore, the HBPM could cause discomfort or worry to the patients during the performance. Thus, such a monitoring might be lived with concern by patients and this emotional stress might cause increasing blood pressure by itself.

Finally, the cardiovascular risk algorithm is also based on organ damage assessment that requests several laboratory and instrumental examinations. This struggles with long waiting lists in public hospitals and high costs of private healthcare that not allows all patients to bear the fees due to of the great economic difficulties of these times.

10. 2013 ESH/ESC GUIDELINES vs. EIGHTH JOINT NATIONAL COMMITTEE GUIDELINES

The 8th JNC guidelines on hypertension [55] are the expression of general and worldwide guidelines for the management of hypertension and they are the evolution of the previous 7th JNC guidelines [56]. The 2013 ESC/ESH guidelines [2] also differ from the extra-continental one [55] as some points and cut-offs are not equal from each other. One of the major differences that can be pointed out regards the evaluation of the role of age per se in the general management of hypertensive condition. JNC 8th effectively gave a great importance to age by considering it as a fundamental characteristics able to make the physician changed his/her pharmacological or interventional management of the hypertensive patient [55]. While 2013 European guidelines considered "age" as a common cardiovascular risk parameter in the SCORE model for cardiovascular risk stratification, preferring cardiovascular risk stratification as the leading factors for maneuvers in hypertension condition [2], the JNC 8th underlined the need for an "age-based therapy" [55]. Nevertheless, a great positive advantage of the JNC 8 report was the consideration of "race" as a condition able to induce a change in pharmacological treatment of the patients. The black population, in particular, deserved different approaches as compared to non-black one in relation to the different characteristics of their hypertensive state [55]. Such a consideration is not pointed out in the 2013 ESC guidelines and even the SCORE model for cardiovascular risk stratification did not contemplate any remind to race as able to influence the treatment of hypertension. This is a great limitation of the European guidelines above all in relation to the great immigration flows in the continental lands [57]. Nevertheless, despite such a positive aspect, the JNC 8th did not offer a full representation of the cardiovascular risk profile of individuals. In contrast to 2013 ESC/ESH guidelines, the JNC 8th did not provide any reference about a model for cardiovascular risk evaluation of patients and a different pharmacological strategy for hypertension management in relation to the different total cardiovascular risk profile of the patients.

11. CONCLUSION

In conclusion, the 2013 guidelines on hypertension management offer new diagnostic and therapeutic possibilities on the basis of numerous clinical trials and updates performed during the last years. Many points, however, remain to be clarified such as: Blood pressure values at treatment starts and target BP values in elderly patients; the quantification of the eventual reduction in cardiovascular morbidity and mortality by adopting the new therapeutic approaches for resistant hypertension; the benefits of the drug treatment in subjects at high cardiovascular risk and with high-normal blood pressure. Therefore, we think that new randomized controlled trials will resolve all the issues pointed out in this overview in order to improve the management of that part of hypertensive patients still not on perfect BP control. Furthermore, we think that more attention should be paid to age and patients' frailty: the general practitioners will be able to really help specialists in reaching a full evaluation of all the aspects related to hypertension and finally overcome the gaps in evidence. Practically, a tight collaboration among researchers and medical doctors is the basis for the reduction of the great number of limitations of the current perspective on hypertension, in order to obtain a full control of this cardiovascular risk factor.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=843&id=26&aid=9171