Rethinking targets of blood pressure and guidelines for hypertension clinical management

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Introduction

Arterial hypertension is a widely diffuse clinical condition characterized by epidemic proportions, marked impact on national health care systems and a major role in the global burden of cardiovascular (CV) and renal diseases [1]. Hypertension is, in fact, significantly related to an increased risk of developing myocardial infarction, stroke, congestive heart failure, chronic kidney failure and mortality [2]. Effective treatment of hypertension is, in turn, consistently paralleled by a significant reduction of CV and renal morbidity and mortality, independently of age, gender, CV risk profile or concomitant diseases [3]. Despite solid evidence supporting the benefits obtained in hypertensive patients, when an effective antihypertensive strategy achieves the blood pressure (BP) targets currently recommended (i.e. BP levels below 140/90 mmHg in the general population and below 130/80 mmHg in high-risk hypertensive patients, such as those with diabetes mellitus or proteinuria), BP control is poorly achieved in clinical practice [4].

Beyond the concomitant presence of additional CV risk factors and associated clinical conditions, several causes have been advocated for explaining the worldwide poor rates of BP control [5]. Among these factors, poor adherence of patients to therapeutic (pharmacological or non-pharmacological) prescriptions, insufficient physician–patient communications, clinical inertia, lack of knowledge or poor implementation of recommendations proposed by guidelines, sub-optimal antihypertensive drug dosages or insufficient use of combination therapies are those most commonly reported, as they may explain, at least in part, the gap between recommended and achieved rates of BP control at a global level.

Among these factors, however, references to ineffectiveness of hypertension guidelines or objective difficulties to transfer guidelines’ recommendations to daily clinical practice are not usually quoted. On the other hand, in a complex and widespread condition, as arterial hypertension, concise and effective guidelines are definitely needed. In this regard, the rapid innovations of diagnostic options, the availability of newer drugs and novel therapeutic strategies and, most of all, the continuous new scientific findings on the pathophysiology of arterial hypertension, which have been reported over the last 30 years indeed represent a good reason to periodically review the field and provide doctors with a synthetic appraisal of the advances with the consequent recommendations. As an example of the continuous changes, Table 1 reports a number of concepts, statements and treatment options, largely accepted in the 1970s or even in the early 1980s. Today, these concepts look obsolete and have been substantially overwhelmed by new and more solid scientific evidence and substituted by different statements and clinical behaviours.

For these reasons, guidelines remain extremely important for all physicians aware or not of the new scientific achievements and of the suggested modifications in the clinical management and treatment of arterial hypertension. Nonetheless, rethinking the ways to develop guidelines and to translate them to achieve a more effective
application of evidence-based standards and algorithms to clinical practice should be seriously considered, as it could potentially have high beneficial impact on BP control and outcomes in hypertension.

Guidelines for hypertension management: have they fulfilled their mission?

Over the last two decades, various scientific groups or different international and national societies have issued several sets of guidelines for the clinical management of arterial hypertension. The most popular, widely diffused and extensively applied examples are those represented by the guidelines issued by the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, whose latest edition has been issued in 2007 in the USA [6], and by those realized by the European Society of Hypertension (ESH) and European Society of Cardiology (ESC), whose latest edition appeared in 2007 [7]. This latter document was recently reviewed by a group of authors to identify the potential changes in the light of the numerous large, randomized, controlled clinical trials completed over the last 2 years [8]. Also, practical guidelines for the clinical management of hypertension are issued in many other countries, for instance, UK [9], Canada [10,11] and Japan [12], where they are currently available and routinely applied for the clinical practice by resident physicians. Differences among these sets of guidelines are in some cases substantial, while in other cases they are less evident; sometimes, they are based on the peculiarities linked to the different health care systems in their own countries or to different strategic approaches to be used in the context of specific resident populations or subsets of patients.

Despite the large number of guidelines proposed over the last few years, however, the results achieved in the worldwide control of high BP and of the hypertension-related CV and renal consequences are still extremely poor. In a recent analysis derived from a large global survey on BP control in a setting of specialist care, the International Survey Evaluating Microalbuminuria Routinely by Cardiologists in Patients with Hypertension (I-SEARCH) study [13], which included ~22 000 hypertensive patients followed up in specialist clinical settings, a relatively poor control of BP was evident in almost all countries, and the rate of control of hypertension was 25% on average (Figure 1). Similarly, in Italy, a survey performed in ~52 000 hypertensive individuals, included in observational studies and population surveys published between the year 2000 and 2007, demonstrated that only 22% of hypertensive patients were at BP targets, whereas 39% did show Stage 1 hypertension, almost one patient out of three had Stage 2 hypertension, and only 3.7% were at Stage 3 hypertension.

Fig. 1. A global perspective on BP control in a referred cohort of hypertensive patients, included in the I-SEARCH study (N = 22 282) [13]. Modified from Bramlage et al., J Clin Hypertens (Greenwich), 2010 (in press).

Table 1. Hypertension in the early 1970s: when I was a medical student

<table>
<thead>
<tr>
<th>Feature</th>
<th>Details</th>
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<tr>
<td>Higher BP thresholds than currently adopted (BP levels more than 150/95 mmHg).</td>
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<tr>
<td>Normal levels for systolic blood pressure: 100 mmHg plus individual age.</td>
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<tr>
<td>Higher possibility to have a stroke (mostly haemorrhagic) than other cardiovascular or non-cardiovascular events.</td>
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<td>No availability of guidelines for hypertension diagnosis and treatment.</td>
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<td>Availability of antihypertensive drugs with more side effects than benefits.</td>
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<tr>
<td>No scientific support for the use of combination strategies (‘stepped’ or ‘one-by-one’ therapeutic approaches).</td>
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<tr>
<td>No evidence of cardiovascular benefits by reducing BP levels.</td>
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<tr>
<td>Target of therapy was to reduce BP to a level that produced more benefit (i.e. BP-lowering effect) than harm (i.e. side effects).</td>
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<td>Abnormal activation of sympathetic nervous system and volume repletion represented the prevalent pathophysiological mechanisms.</td>
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<tr>
<td>Pathophysiological role of renin–angiotensin system was confined only to renovascular forms of arterial hypertension.</td>
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Everything is changed!
hypertension and 5% had isolated systolic hypertension (Figure 2) [14]. Another failure of the hypertension treatment, highlighted in this Italian meta-survey, was that the prevalence of hypertension-related CV risk factors among patients followed up by specialists (internal medicine, cardiology, nephrology or diabetology), hypertension units or general practitioners was very high [14]. In particular, hypercholesterolaemia was described in 56% of the individuals, diabetes mellitus in 15% and obesity in 36%, so that, when the global CV risk was calculated in this hypertensive population, more than half of the patients showed a high or very high global CV risk profile [14].

The most promising data in terms of improved control of hypertension have been recently reported by the National Health and Nutrition Examination Survey (NHANES) survey, which showed that, in the USA, ~35% of the individuals achieved the recommended control of hypertension, i.e. BP levels below 140/90 mmHg [15]. As shown in Figure 3 [16], however, when one focuses on the percentage of patients with controlled hypertension as related to treated patients, it is evident that, over the last 30 years, while significant increases of the awareness and of the number of patients receiving antihypertensive treatment were recorded, this virtuous trend in the increased treatment rate was not paralleled by proportional improvements in the control of hypertension in the population. Consequently, the gap between the number of patients treated and the number of patients controlled was

![Fig. 2. BP stratification in Italian hypertensive patients included in clinical studies and population surveys (N = 52 715). Modified from Volpe et al. [14].](image)

![Fig. 3. Rates of awareness, treatment and control of high BP in the USA (1976–2004). As indicated by bold characters, the percentage of patients with uncontrolled BP did not change over the years. Modified from Chobanian [16].](image)
not modified and constantly remained at ~26% over the last 30 years. Accordingly, when one looks at the absolute data, the number of patients with uncontrolled hypertension in the USA actually increased over the last 30 years (from 37 to 42 millions of hypertensive patients) [16]. A very recent analysis of the NHANES survey, performed by Egan and colleagues [17], has described more promising trends in the USA, with an estimated control rate of ~50% in the period between 2007 and 2008, as the result of BP-focused actions.

Even in randomized, controlled clinical trials, the proportion of patients who achieved a satisfactory BP control is low. In an analysis of a large number of randomized, controlled, international clinical trials performed in the last two decades, the percentage of patients who achieved thresholds of BP normalization (i.e. BP below 140/90 mmHg) was only a minority [18]. In addition, normalization of BP (i.e. BP below 130/80 mmHg) was never achieved in hypertensive patients with diabetes mellitus, with or without renal disease [18]. This was confirmed in a more recent analysis of clinical trials, including only trials performed in the last two decades (the majority of which have been carried out according to the principles of the evidence-based medicine) [19]. Of note, the few clinical trials in which the involved patients reached the recommended targets have been mostly conducted in high-risk patients who were not always hypertensive or in patients already on antihypertensive treatment with baseline BP values which were already close to normal limits [19].

As an unavoidable reflection of this unsatisfactory control of BP, hypertension remains one of the main causes of ischaemic heart disease, stroke, congestive heart failure and renal failure, as all of these conditions continue to grow year after year and to impose an increasing disease burden to health care systems around the world [1].

Therefore, we have to admit that, in spite of their unquestionable scientific and cultural value, nowadays, hypertension guidelines have not fulfilled the premises, as there are probably limits in the translation from these guidelines to clinical practice, so that the strategies to achieve a more effective BP control either in the USA (where recommendations were mostly based on the achievement of BP control) [6] or in Europe (where guidelines are mostly focused on the control of global CV risk in patients with hypertension) [7] have not been able to modify the poor trends of control of high BP and its CV and renal consequences. Thus, a critical analysis of this aspect should be required and new models for guidelines should be designed.

Rethinking guidelines to improve blood pressure control

There are clearly a number of aspects that could be improved to attain more effective control of high BP in hypertensive patients. Table 2 summarizes some of the factors that seem to play an important role in the persistently poor control of hypertension and that may actually represent specific issues to be addressed in future guidelines. Among these factors, some of them may be ascribed to physicians’ behaviours, some to insufficient physician–patient communication and some others to patients’ poor compliance to the prescribed antihypertensive therapy. On the other hand, according to the format of the various sets of guidelines, which have been issued so far, two aspects need to be highlighted.

The first aspect is that we definitely need more practical and simple guidelines for the clinical management of hypertension that can be widely applied and easily translated to individual cases by doctors, especially general practitioners, operating in different clinical settings or countries. The current format of hypertension guidelines appears too long and often complicated. As a consequence, the individual physician may exceed in a free interpretation and application of the recommendations. As an example, even normal levels and targets of BP to be achieved are not so immediate to be identified; for instance, there are many qualifications for clinical BP (optimal, normal, pre-hypertension, three grades of hypertension, isolated systolic hypertension, etc.) and too many ‘normal’ values, according to the techniques (24-h ambulatory, clinic, home BP measurements) or the type of hypertension (office, isolated clinical and masked hypertension) [6,7]. Indeed, general practitioners have to deal everyday with different common diseases and they are required to apply different guidelines (e.g. chronic pulmonary disease, diabetes mellitus, dyslipidaemia, ischaemic heart disease, heart failure, etc.). Therefore, the main messages should be as simple as possible and clearly highlighted. For instance, a general threshold of BP below 140/90 mmHg in all patients, if tolerated, could be a good starting point. As a corollary to this approach, the thresholds recommended in specific groups of hypertensive patients (i.e. elderly, diabetic, proteinuric, etc.) could be outlined. In light of this, guidelines need to commit each physician to achieve at least the general BP targets. In order to reach this purpose, guidelines should be less complex and must provide clues for written recommendations on lifestyle changes and to optimize treatment by pursuing up-titration and combination therapies, if needed. An encouraging example of the efficacy of simplified treatment algorithms is provided by the experience of the Simplified Treatment Intervention to Control Hypertension study [20], a cluster, randomized, controlled clinical trial performed in south-western Ontario, Canada. The approach used in this study showed that patients allocated in the intervention group achieved ~65% of BP tar-

Table 2. Potential explanation behind poor BP control in hypertension

| Poor motivation of physicians to get BP levels to targets. |
| Poor control of additional risk factors (e.g. obesity, physical inactivity, cigarette smoking, sedentary life). |
| Physicians’ clinical inertia in the presence of unsatisfactory BP control. |
| Poor physician–patient communication. |
| Insufficient use of combination strategies based on rational, effective and synergistic antihypertensive drug classes. |
gets compared with 53% of patients allocated in the guideline-based group [20].

In this latter regard, guidelines have been somehow shy in promoting high dosages of the newer classes of antihypertensive drug classes, such as angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, as they have been used in clinical trials. In addition, the use of combination therapies is recommended only for patients with initial BP or with high or very high CV risk [6,7]. It is quite likely that a larger use of higher dosages or combination therapies may achieve a better health care target that has not been achieved yet over the last 30 years. At the same time, a clear schedule of controls (for instance of renal function) should accompany the suggested therapeutic approach.

Another important aspect to be highlighted is the relevance of the first visit in each hypertensive patient, particularly in terms of physician–patient communications (e.g. clearly explaining the risk associated to hypertension and providing written recommendations for lifestyle changes), as well as in terms of rational choice of the appropriate therapeutic approach, based on the specific characteristics of the patient. In this latter regard, it is important to keep in mind that both the JNC7 [6] and ESH/ESC [7] guidelines identify specific clinical conditions, which may favour the use of a specific class of drug in large subgroups of patients, which broadly cover the general hypertensive population. At the same time, it is important to more clearly define and highlight the importance of the use of combination therapies in patients who have markedly BP levels. Also, patients with high CV risk profile, such as those with diabetes mellitus or renal disease, may require an early approach with combination therapy at low or high dosages to achieve the recommended treatment goals. In fact, safe achievement of the recommended treatment goals is extremely important to motivate both the patient and the physician and to reach persistent and effective control of hypertension. Furthermore, an early successful control of BP may help to prevent the well-known phenomenon of clinical inertia.

In this regard, it should be also reminded that, in several recent studies based on a prompt use of combination therapy, such as the Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension trial [21], the use of combination therapy in patients already treated, but not controlled, showed that the relatively poor baseline control of BP of 37% was improved to almost 90% with both combination therapy strategies. This has been observed also in other international, randomized, controlled clinical trials performed with other antihypertensive drugs able to counteract the renin–angiotensin system [22,23]. This means that the achievement of BP control is feasible and achievable in the setting of clinical studies [24,25], and it may also be successfully attempted within the context of clinical practice.

Another important aspect, which is somehow neglected in the current hypertension guidelines, is the importance of follow-up. The frequency of the subsequent visits of the patients according to the severity of arterial hypertension and to the presence of hypertension-related organ disease should be more clearly described. This is of particular relevance in order to verify the safety and the efficacy of a given antihypertensive treatment, both in terms of BP control and in terms of organ damage protection. Available evidence demonstrate that the reduced incidence, the delayed progression or even the regression of markers of hypertension-related organ damage, such as left ventricular hypertrophy, microalbuminuria or renal damage, are paralleled by a significantly reduced risk of developing major CV events in hypertensive patients at different degrees of CV risk [26]. Therefore, indications on the frequency of examinations (visits, electrocardiogram, creatinine clearance, microalbuminuria, echocardiogram, vascular ultrasound, etc.) should be suggested on the basis of the patient’s risk profile. A clear-cut minimal data set should be attained in each individual patient and preferred to a long list of advanced, specialistic tests, following criteria of appropriateness and economy.

With regard to the target BP levels in patients at very high risk due to previous CV event, available recommendations in guidelines need probably to be deeply revised. In fact, achievement of BP levels below 130/80 mmHg in patients with high CV risk profile, including diabetes mellitus, previous myocardial infarction or stroke, needs to be reconsidered in view of recent clinical trials, which have shown that, in these subgroups of hypertensive patients, lower BP levels may be associated with an increased risk of major CV events [23,27–29].

In particular, quite recently, in the Action to Control Cardiovascular Risk in Diabetes trial [29], as well as in a post-hoc analysis of the ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial BP cohort [30], the old mantra ‘the lower, the better’ has been seriously challenged. In fact, in these studies [29,30], as well as in previous analyses of mega-trials [31,32], it has been repeatedly shown that, in high CV risk individuals, lower BP levels can be associated with a higher risk of CV events, mostly fatal and non-fatal myocardial infarction. These very ambitious BP targets are anyway very difficult to attain in the daily clinical practice. It could be more reliable to try to achieve BP control below 140/90 mmHg, ensuring at the same time a strict control of concomitant CV risk factors and markers of organ damage, so that global CV risk profile is reduced, as schematically illustrated in Figure 4 [33]. This figure provides a simplified and integrated approach to cut CV risk down to the average risk of the general population even in high-risk patients.

Finally, special attention should be dedicated to the elderly patients. Also, in this case, however, the importance of BP reduction remains a priority to reduce the incidence of CV events, especially stroke and myocardial infarction. With regard to elderly or very elderly patients, on the basis of the currently available clinical evidence, the target BP should be cautiously and slowly achieved. In this specific population, a target BP below 150/90 mmHg may be considered acceptable, also on the basis of the most updated evidence [34].
Hypertension guidelines and physicians: tips for a new alliance

While the educational and cultural value of evidence-based guidelines remains a cornerstone of modern medicine, it is important to make an effort to render guidelines more simple, straightforward, friendly and accessible by physicians. For this purpose, in future guideline sets, some key aspects should be highlighted. A non-inclusive list of potentially important actions follows: (i) to prompt every doctor to achieve the best possible control of BP levels in each individual patient; in this view, given the universally recognized high clinical impact of high BP, implementation of lifestyle measures and/or optimization of dosages of drugs (or combination of drugs) to achieve target BP levels below 140/90 mmHg in the clinical practice should be mandatory in adult hypertensive management; in this regard, the use of electronic supports for hypertensive outpatients’ follow-up should be mentioned and implemented on the basis of several positive experiences in USA [35] or in Europe [36,37]; (ii) to dedicate enough time to estimate global CV risk of any individual patient; in this view, given the universally recognized high clinical impact of high BP, implementation of lifestyle measures and/or optimization of dosages of drugs (or combination of drugs) to achieve target BP levels below 140/90 mmHg in the clinical practice should be mandatory in adult hypertensive management; in this regard, the use of electronic supports for hypertensive outpatients’ follow-up should be mentioned and implemented on the basis of several positive experiences in USA [35] or in Europe [36,37]; (ii) to dedicate enough time to estimate global CV risk of any individual patient; also in this case, the use of electronic support may result in better outcome [36]; (iii) to recommend periodic assessment of the presence of organ damage during the follow-up through simple markers (e.g. microalbuminuria, electrocardiogram, serum creatinine, creatinine clearance, etc.), which may make physicians more confident and committed to achieve the BP goals; (iv) to ensure a good metabolic control, in order to control global CV risk particularly in hypertensive patients with glucose metabolism abnormalities, obesity, metabolic syndrome or borderline values of serum cholesterol or triglycerides; (v) to perform a screening for ischaemic heart disease in high-risk hypertensive patients for whom there is indication to achieve target BP levels below 130/80 mmHg. A careful diagnostic approach could be applied to patients with family history of coronary artery disease or at least three risk factors for coronary artery disease, positive provocative tests, electrocardiographic evidence of left ventricular hypertrophy or echocardiographic left ventricular dysfunction (even in this case, this recommendation may help physicians to identify safe treatment goals); (vi) to attain BP levels below 150/90 mmHg as the preferred target in patients aged more than 65 years; (vii) to consider BP below 130/90 mmHg in patients with diabetes and/or renal disease, although caution should be used in patients with history of coronary or cerebrovascular diseases; (viii) to diagnose resistant hypertension only when appropriate; this label, in fact, is given to patients often and inappropriately by physicians in the presence of difficult to treat or challenging hypertension, and any reasonable attempt to rule out potential causes of persistently high hypertension should be done; (ix) to improve patient–physician communication and to implement an informative ancillary use of home BP measurement as a fundamental step in the management of hypertension. Finally, more importance (and time) to the first visit should be recommended.

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