Aim and Scope
Heart and Metabolism is a journal published three times a year, focusing on the management of cardiovascular diseases. Its aim is to inform cardiologists and other specialists about the newest findings on the role of metabolism in cardiac disease and to explore their potential clinical implications. Each issue includes an editorial, followed by articles on a key topic. Experts in the field explain the metabolic consequences of cardiac disease and the multiple potential targets for pharmacotherapy in ischemic and nonischemic heart disease.

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As we bury our heads deeper and deeper in our subspecialties, it is easy to lose sight of the fundamentals. One of these fundamentals, which has a dramatic impact on risk reduction, is the effective treatment of hypertension.

Hypertension is often likened to Cinderella; a treasure ignored, belittled, and unrecognized until highlighted by the attention of a Prince. The last year has seen such Princely attention in the form of updated ESC/ESH, and AHA/ACC, hypertension guidelines. These guidelines, which have grabbed the attention of the lay and professional press, are the focus for most of the articles in this issue of our journal.

Although much has been made of transatlantic differences in hypertension guidance, in truth they have very much in common. These threads of commonality are emphasized in this issue. Reading through the articles the key areas of focus are: (i) the blood pressure threshold at which treatments should be started and titrated to achieve; (ii) increased reliance on home and ambulatory blood pressure (BP) measurement; (iii) the emphasis on single pill combination therapy; (iv) restricting the use of β-blockers to those patients with indicative comorbidities. These points are dealt with logically and serially in this issue.

As always, it is best to start at the beginning. The article by Giuseppe Mancia addresses the issues of what level of BP merits initiation of treatment and how low to go. This an area where the US and European BP guidelines give different recommendations. In terms of starting medication, the level of hypertension is: 130/80 mm Hg in the United States and 140/90 mm Hg in Europe. As Prof Mancia points out, descriptive epidemiological studies show that cardiovascular risk starts to increase above a systolic blood pressure of 110 mm Hg. However, that does not necessarily equate to the BP threshold at which treatment will have more benefit than harm. Indeed, the surety of benefit exceeding harm only becomes convincing at untreated systolic blood pressures above 140, based on randomized controlled trials. The difficulty is that many individuals with a systolic BP of 130 to 139 exceed the conventional cardiovascular (CV) risk threshold of a 10% chance of a CV event over the next 10 years, where we become comfortable with primary prevention. The gray zone between 130 to 140 systolic and 80 to 90 diastolic is therefore one of the few areas of disagreement between the European and American guidelines. The general consensus amongst the authors in this issue is that patients in this gray zone should only be treated if they are at very high risk or there is evidence of hypertension-mediated organ damage (HMOD). Obviously, lifestyle advice can be still be given in the absence of these additional markers of risk. What about the opposite problem—younger patients with BP>140/90 but overall CV risk below the 10% risk threshold? This is the low-to-medium risk group in Figure 3 in Prof Mancia’s review (see p 8) and as he points out it is difficult to know what to do, but the temptation is
to reduce the blood pressure to preserve the future, even though the 5-year absolute risk reduction is vanishingly small.

So, we know the threshold at which to start treatment, but how do we make the diagnosis? The article by Hobbs charts the progressive move in guidelines from office to home/ambulatory measurement of BP to diagnose hypertension. The obvious advantages are the recognition of white-coat or masked hypertension, an increased number of measurements on which to assess treatment response and make treatment decisions, the recognition of nocturnal hypertension (nondippers) and the removal of biases due to rounding BP readings up or down. However, despite the move to out-of-office BP measurement, a mixed economy of measurements is still recommended, as is the calibration of home monitors. The accepted compromise is the use of out-of-office measurement to confirm the diagnosis of hypertension, before committing to what is usually a lifelong therapy. Table III (p 12) is also a very useful aide-memoire of the out-of-office equivalents to an in-office BP reading at the 140/90 treatment threshold.

On the basis of the articles so far we know the threshold at which to consider treatment and we know how to measure BP accurately to determine if this threshold has been breached; what do we do now? The original article by Krzysztof Narkiewicz and the refresher corner by Chris Arden deal with the interrelated issues of lifestyle intervention, choice of antihypertensive medications, and maximizing their effect by capitalizing on compliance. The lifestyle interventions that have an evidence base in prevention or treatment of hypertension are summarized in Table II of a recent review. As Dr Arden explains, compliance requires adherence to the prescribed medication and persistence, taking the prescribed medication for the recommended duration. There is strong evidence that both these components of compliance are improved by using single-pill combination (SPC) therapies. The use of SPC formulations in the initial treatment of hypertension features strongly in both the European and American guidelines. The article by Prof Narkiewicz deals with the ideal individual components of the SPC and whether this should be with two, or three, agents; chosen from angiotensin-converting enzyme inhibitor/angiotensin receptor blocker with a calcium channel blocker and/or a diuretic (see Figure 1 on p 17). All these combinations have a very strong evidence base and a wide variety of formulations that offer the opportunity to personalize treatment.

Whilst most patients will, hopefully, have their blood pressure controlled by an SPC formulation there are specific groups where treatments need to be better tailored. The use of β-adrenoceptor blockers and mineralocorticoid antagonists in specific hypertensive patients is also covered in the article by Prof Narkiewicz, whilst the treatment of other risk factors that cluster with, and magnify, the damage caused by hypertension is discussed in the article by Borghi et al.

All in all, this issue provides a comprehensive guide to managing the patient with hypertension. In addition, the case report by Prof Ferro details the state-of-the-art investigation of a rare case where the underlying cause of hypertension was identified. Finally, I discuss the advantages of the ultimate SPC, the polypill. In combination, I believe these articles address a critically important topic in a practical and pragmatic way. I sincerely hope they help keep the hypertension Cinderella in the limelight!

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REFERENCES

Blood pressure classification and values to treat

Giuseppe Mancia, MD, PhD
University of Milano-Bicocca, Milan, Italy

Correspondence: Prof Giuseppe Mancia, piazza dei Daini, 4 - 20126 Milano, Italy
E-mail: giuseppe.mancia@unimib.it

Abstract: Blood pressure (BP) values can be classified in two ways, i.e., either based on the relationship between BP and cardiovascular risk, or on threshold values at which antihypertensive drugs are indicated for blood-pressure lowering, as shown by randomized outcome trials. As there are substantial differences between the two classifications, this can be confusing, especially for the patient. Current hypertension guidelines do not entirely clarify this.

Heart Metab. 2019;79:5-9

Keywords: antihypertensive drug; blood pressure; cardiovascular risk; hypertension

Introduction

Classification of blood pressure (BP) values relies on two different criteria, one based on the relationship between BP and cardiovascular (CV) risk and the other on the values at which BP lowering with antihypertensive drugs is indicated, based on evidence from randomized outcome trials. Because the two classifications differ substantially, this not infrequently generates confusion, especially for the patient, which is not entirely resolved by current hypertension guidelines.1,2

Classification based on the relationship between BP and CV risk

Epidemiological data agree that in the general population BP correlates positively with the incidence and risk of CV outcomes, a relationship which is progressive for systolic and diastolic values above 110 to 115 mm Hg and 70-75 mm Hg, respectively.3,5 This holds true for all major CV outcomes (myocardial infarction, stroke, heart failure)6,7 as well as for fatal and nonfatal CV events; the increased risk of fatal events even extends to all-cause mortality.3,6 A similar relationship also holds for BP and major renal outcomes, such as renal insufficiency, need for dialysis, and kidney transplantation.5 Thus, from an epidemiological perspective, the lower the BP, the lower the individual’s risk; which at the population level justifies the adoption of lifestyle changes that favor BP reduction, such as restriction of salt intake, encouraging exercise, more vegetable-based diets, antismoking campaigns, etc. Widespread implementation of these measures, however, has so far almost invariably turned out to be difficult. Indeed, compared with historical data, no substantial BP reduction has been reported in the worldwide population. On the contrary, BP values have been shown to have increased in the largely represented medium or low-income countries,9 leading to the prediction that in 10 to 20 years hypertension will be noticeably more prevalent than it is today, affecting perhaps more than half of the elderly population.10

Despite its continuous nature, the relationship between BP values and CV risk is customarily subdivided into different categories, the aim being to make doctors’ perception of subjects’ risk easier and more
immediate. The most popular BP classification is the one generated by the 7th US Joint National Committee Guidelines in 2003,\textsuperscript{1,11} which has been adopted by European guidelines, including the recent ones published in 2018 (Table I).\textsuperscript{1,11} Paradoxically, a major departure from this classification has been proposed by the US in their recent guidelines, which have: i) reduced the BP threshold at which a BP increase can be termed “hypertension” from 140/90 mm Hg to 130/80 mm Hg; and ii) lowered the value at which BP can be defined as elevated to >120/80 mm Hg, regardless of the subject’s age (Table I, right section).\textsuperscript{2} This has generated widespread disagreement and debate, particularly because in older subjects defining a systolic BP ≥120 mm Hg as elevated, means that virtually the whole elderly population is affected.

Table I Classification of blood pressure (BP) values in the US hypertension (HT) guidelines issued in 2003 and 2017.\textsuperscript{2,11}

<table>
<thead>
<tr>
<th>BP (mm Hg)</th>
<th>2003</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120/80</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>120-129/80-84</td>
<td>Prehypertension</td>
<td>Elevated</td>
</tr>
<tr>
<td>130-139/85-89</td>
<td>Grade 1 HT</td>
<td>Grade 1 HT</td>
</tr>
<tr>
<td>140-159/90-99</td>
<td>Grade 2 HT</td>
<td></td>
</tr>
<tr>
<td>160-179/100-110</td>
<td>Grade 3 HT</td>
<td></td>
</tr>
<tr>
<td>&gt;180/110</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Classification based on randomized outcome-based trials

The decision to start antihypertensive drug treatment cannot be based on the above-mentioned epidemiological data because of the need to additionally prove that, at any given BP value, a BP-lowering intervention is associated with a reduction of CV outcomes or that, in the words of the famous epidemiologist J. Rose, the therapeutic intervention “does more good than harm.” Over the last 50 years this has been demonstrated for progressively lower initial BP values, which have led to the recommendation that antihypertensive drugs be used at progressively lower pressures: historically this was a systolic BP greater than 180, later 160 mm Hg (grade 2 and 3 hypertension) and then for patients with grade 1 hypertension, ie, with a BP in the 140 to 159 mm Hg systolic and 90 to 99 mm Hg diastolic BP range, if accompanied by a high CV risk.\textsuperscript{1,15} In the latest 2018 European guidelines antihypertensive drug treatment is recommended in patients with grade 1 hypertension even when their CV risk is only low to moderate because: i) the HOPE-3 trial has shown that in these patients a two-drug antihypertensive regime significantly lowers the risk of CV outcomes;\textsuperscript{15} and ii) this has been confirmed by a meta-analysis of randomized trials, which has shown that in low-risk grade 1 hypertension, treatment capable of reducing systolic and diastolic BP by approximately 7/5 mm Hg significantly reduces all hypertension-related CV morbidity or fatal events (Figure 1).\textsuperscript{14} Most importantly, the recommendation to reduce BP by antihypertensive drug

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trials (n)</th>
<th>Baseline SBP/DBP (mm Hg)</th>
<th>Difference SBP/DBP (mm Hg)</th>
<th>Standardized RR (95% CI)</th>
<th>Absolute risk reduction 1000 pts/5 years (95% CI)</th>
<th>NNT 5 years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>4</td>
<td>146/91</td>
<td>-7.1/-4.5</td>
<td>0.33 (0.11-0.98)</td>
<td>-21 (-26, -1)</td>
<td>47 (39, 1301)</td>
</tr>
<tr>
<td>CHD</td>
<td>5</td>
<td>145/91</td>
<td>-6.5/-4.2</td>
<td>0.68 (0.48-0.95)</td>
<td>-12 (-18, -2)</td>
<td>86 (55, 531)</td>
</tr>
<tr>
<td>Stroke + CHD</td>
<td>4</td>
<td>146/91</td>
<td>-7.1/-4.5</td>
<td>0.51 (0.36-0.75)</td>
<td>-34 (-43, -19)</td>
<td>29 (23, 54)</td>
</tr>
<tr>
<td>CV death</td>
<td>4</td>
<td>146/91</td>
<td>-7.1/-4.5</td>
<td>0.57 (0.32-1.02)</td>
<td>-9 (-14, -1)</td>
<td>110 (72, -2223)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>4</td>
<td>146/91</td>
<td>-7.1/-4.5</td>
<td>0.53 (0.35-0.80)</td>
<td>-19 (-25, -8)</td>
<td>54 (40, 119)</td>
</tr>
</tbody>
</table>

Figure 1 Effect of systolic and diastolic blood pressure (SBP and DBP) reduction by drug treatment in trials involving patients with grade 1 hypertension and a low-to-moderate cardiovascular (CV) risk. RR, relative risk; CHD, coronary heart disease; CI, confidence interval; NNT, number of events saved by treating 1000 patients for 5 years. Effects of treatment were calculated for a BP reduction of 10/5 mm Hg. Reproduced from ref 14: Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 2. Effects at different baseline and achieved blood pressure levels—overview and meta-analyses of randomized trials. J Hypertens. 2014;32(12):2296-2304. Copyright © ISH/ESH 2014.
treatment has been extended to grade 1 elderly hypertensive patients; based on the evidence from three pooled trials (HDFP, HOPE, PATS = 6389) that in grade 1 hypertensive patients aged >60 years, BP reduction was accompanied by clear-cut and marked reductions in outcomes: CV death by 45%; all-cause death by 21%; and CV events by 42%. At present, in the very elderly (patients aged ≥80 years) the BP threshold for drug treatment remains higher, ie, a systolic BP ≥160 mm Hg, since at this more advanced age the only available evidence remains that provided by the HYVET trial in which patients were recruited only if their systolic BP was ≥160 mm Hg.1

Whether antihypertensive drug treatment should be extended to patients with a BP <140/90 mm Hg has received a different answer in different guidelines, as well as by the same guidelines in different years! There is a general agreement that subjects with high normal BP values, ie 130 to 139/85 to 89 mm Hg (Table I) have a noticeable increase of CV risk compared with subjects with a lower BP value,16 with in addition a much greater risk of later developing frank hypertension.17 Evidence is limited and inconsistent, however, on whether under these circumstances a BP-lowering intervention is beneficial. In 2007, for example, the European guidelines advised lowering BP by antihypertensive drugs if the CV risk of patients with a high normal BP was high, such as when hypertension coexists with diabetes.18

In contrast, in 2013, the same guidelines have excluded any use of antihypertensive drugs in patients with a BP within this range.12 While in 2018 they have restricted drug treatment to patients with a very high CV risk (Figure 2) because of evidence from a meta-analysis of randomized trials that, in patients with a high normal BP, a BP reduction was accompanied by a reduction of stroke only if there was a history of CV events.19 US guidelines agree with the European guidelines that only some patients in this BP range need drug treatment.2 Based on the results of the SPRINT trial as well as on a large network meta-analysis,21 the US guidelines identify these patients as those with a CV risk >10% (chance of an event within 10 years). This is a much larger fraction of the population than that considered in the European guidelines, since a CV risk ≥10% is common in both elderly males and females in whom a BP between 130 to 139/85 to 89 mm Hg is highly prevalent. The European guidelines consider the evidence behind this recommendation as questionable, also because in the SPRINT trial baseline BP values were in the high normal BP range as a result of antihypertensive treatment at enrolment (in most instances with two drugs), which suggests that the majority of patients originally had frank hypertension, rather than high normal pressures. Furthermore, network meta-analyses are based on nonrandomized comparisons,1 which reduces the scientific strength of their results.

Figure 2 Blood pressure (BP) values at which to initiate antihypertensive drug treatment in the 2018 European guidelines.1
Initial antihypertensive drug treatment – BP or CV risk criteria?

In patients with grade 2 or 3 hypertension CV risk is almost invariably close to or in the high range, this being the case also in most hypertensive patients with an advanced age. In contrast, in younger patients with grade 1 hypertension CV risk may range from a low/moderate to high/very high, which has for years raised the question whether a decision on treatment implementation should be based on their risk level or just on their mild BP elevation. As mentioned above, recent evidence has shown that in grade 1 hypertension BP-lowering treatment leads to patient protection regardless of the CV risk, making BP criteria the main decision factor. Evidence has also been obtained against the argument that, because it saves more events, treatment of a high CV risk condition can be more cost-effective than treatment of a low risk condition.22 In a meta-analysis of trials on hypertensive patients with different risk levels, the number of events saved by BP-lowering interventions was progressively greater as the patient’s risk increased. This was more than counterbalanced, however, by a disproportionally greater increase of the residual risk (Figure 3), indicating that limiting treatment of high- or very high-risk hypertensive individuals denies effective CV protection to a large number of patients, with a strong negative impact on overall costs.23 This offers strong support to early antihypertensive treatment, ie, when risk is still low to moderate and the phase of risk irreversibility has not yet been reached.

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Figure 3 Absolute cardiovascular (CV) risk reduction by a BP reduction of 10/5 mm Hg (systolic/diastolic). Data for CV events, CV death and all-cause death. Concomitant effects on residual CV risk are also shown. Reproduced from ref 23: Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 3. Effects in patients at different levels of cardiovascular risk—overview and meta-analyses of randomized trials. J Hypertens. 2014;32(12):2305-2314. Copyright © ISH/ESH 2014


Diagnosing hypertension

F. D. Richard Hobbs, CBE, FMedSci
Nuffield Professor and Head, Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

Correspondence: Radcliffe Primary Care Building, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG, UK
E-mail: richard.hobbs@phc.ox.ac.uk

Abstract: As the most common long-term condition in most developed health-care systems and a major risk factor for premature death and major cardiovascular disease events, hypertension remains one of the world’s most important risk factors for preventable disease. Its early and accurate diagnosis is therefore important. Recent guideline updates have reinforced the importance of repeated blood pressure readings to accurately diagnose hypertension, upgrading recommendations that ambulatory or repeated home-based blood pressure assessments are more reliable in diagnosing hypertension (and correlate better with clinical outcomes). European guidelines have maintained the diagnostic threshold for Stage 1 hypertension at levels above 140 systolic and 100 diastolic, but this differs from US guidelines that consider this threshold as Stage 2 hypertension. There is no reliable evidence, however, that patients would benefit from current therapies with these lower US thresholds. ■ Heart Metab. 2019;79:10-14

Keywords: ABPM; blood pressure threshold; diagnosis; HBP; hypertension

Background

Hypertension is the commonest long-term condition in most global adult populations, affecting up to 13% of the population,\(^1\) and is a major preventable cause of cardiovascular disease (CVD), all-cause death, and premature death. According to WHO Global Burden of disease estimates, hypertension is far and away the most important of all known global disease risk factors in terms of death and morbidity secondary to vascular events such as stroke and heart attack.\(^2\) Hypertension is therefore a major preventable cause of cardiovascular disease (CVD) and premature death on a global scale.

There is a long-standing and considerable evidence base showing that lowering blood pressure (BP) can substantially reduce premature morbidity and mortality.\(^3,4\) However, despite these important outcome data, BP control rates are poor worldwide. Only about 40% of patients with hypertension are treated, and of these only about 35% achieve BP <140/90 mm Hg.\(^5\) This poor treatment rate may be partly related to inadequate or delayed recognition of hypertension. Accurate and early diagnosis of hypertension is therefore a priority for health care internationally.

Specialist guideline recommendations for the diagnosis of hypertension

International hypertension guidelines, such as the joint ones from the European Society of Hypertension and European Society of Cardiology (ESH/ESC), have in the past advised that screening and diagnosis of hypertension was predominantly based on office blood pressure (BP), measured at least twice and on at least two visits. The process for conducting office BP measurement is shown in Table I. The recommendations are more conservative than the main US Hypertension Guidelines,\(^6\) which use lower BP thresholds to diagnose hypertension and recommend more intensive treatment regimes.

Since 2013,\(^7\) the ESC guidelines have added that out-of-office BP measurement is also considered useful, to confirm diagnosis or identify the type of
Diagnosing hypertension

Importantly, some types of elevated blood pressure, such as white-coat hypertension, can only be identified if out-of-office BP is measured. In the 2018 ESH/ESC hypertension guideline, whilst diagnosis for many health settings can remain based on office BP, recommendations include a wider use of out-of-office BP measurement, performed with ambulatory blood pressure measurement (ABPM) or repeated home blood pressure measurement (HBPM) to confirm the diagnosis, detect white-coat or masked hypertension, and monitor BP control.

Challenges in accurate BP measurement

The upgraded guideline recommendations regarding out-of-office measurements has stemmed from better recognition that routine BP measurement is often unreliable. BP varies throughout the day and between seasons. Other factors affecting BP measurement are common and include: talking, which can increase SBP by 17 mm Hg and DBP by 6 mm Hg; exposure to acute cold, which can induce increases of about 11 and 8 mm Hg, respectively; and acute ingestion of alcohol, which can result in 8 and 7 mm Hg higher SBP and DBP, respectively, lasting for about 3 hours.

Using the wrong cuff size has a similar magnitude of effect, and other suboptimal techniques affect the BP readout to a lesser extent. An expectation bias of the measurer has also been documented, where BP values are rounded to the nearest 5 or 10 mm Hg value. Blood pressure is also lower when a nurse measures it, as opposed to a doctor. While this difference has been described to be 7 mm Hg on average, there aren’t different BP targets depending on who performs the BP measurement.

BP measurement methods also vary substantially in clinical practice. A UK-based study, testing how BP was measured in routine practice via an online survey among UK charities and patient groups, showed that initial BP was significantly lower in respondents in whom BP was measured once, as compared with two or three measurements. This may suggest that where the BP is measured as normal on the first reading, GPs may accept this without remeasurement and record the initial reading in the health record. When more measurements are done, BP tends to come down with subsequent readings. It is probable that the last or lowest reading is recorded. It may be that routinely collected BP data that are used for development of risk calculators are on the low side.

White-coat and masked hypertension

White-coat hypertension is diagnosed when BP is normal on ABPM and high on clinic measurements. Cardiovascular risk in individuals with white-coat hypertension is similar to that of normotensive patients, even though those with white-coat hypertension may have between 5 and 10 mm Hg higher SBP on office readings than a normotensive population. While individuals with white-coat hypertension may still be in the normal range, they should be followed up, because they are more likely to develop hypertension over time. When a person with previous white-coat hypertension goes on to develop hypertension, it is important to treat them based on home readings to avoid overtreatment.

When BP is normal in the clinic but elevated on ABPM, people are considered to have masked hypertension. Masked hypertension is associated with a doubled CV risk compared with normotensive patients.

Table I Processes for office BP measurement.

| AF | atrial fibrillation | BP | blood pressure | DBP | diastolic blood pressure |

Patients should be seated comfortably in a quiet environment for 5 minutes before beginning BP measurements. Take at least three BP measurements, 1–2 minutes apart, and take additional measurements if the first two readings differ by >10 mm Hg. BP is recorded as the average of the last two BP readings.

Measurements of BP should be repeated in patients with arrhythmias, such as AF. Use a standard bladder cuff (12–13 cm wide and 35 cm long) for most patients, but have larger and smaller cuffs available for larger (arm circumference >32 cm) and thinner arms, respectively.

The cuff should be positioned level with the heart. When using auscultatory methods, use phase I and V (disappearance) Korotkoff sounds to identify systolic and DBP, respectively.

Measure BP in both arms at the first visit to detect possible between-arm differences. Use the arm with the higher value as the reference.

Measure BP 1 minute and 3 minutes after standing in all patients at the first measurement, and in all subsequent visits in the elderly, patients with diabetes, and in those with other conditions in which orthostatic hypotension may frequently occur.

Record heart rate and use pulse palpation to exclude arrhythmia.
Diagnosing hypertension

Blood pressure thresholds for diagnosing hypertension

When using office measurement (Table I), the blood pressures that determine whether hypertension is present, and its staging, are shown in Table II.

ABPM is usually programmed to record BP at 20- to 30-minute intervals, and average BP values are usually provided for daytime, night-time, and 24 hours. ABPM offers additional information over HPBM, for instance night vs daytime blood pressure (to detect “nondipping” blood pressure at night, which has a particularly poor prognosis), and it correlates best with long-term outcomes such as end-organ damage and stroke, compared with other methods.

ABPM also allows identification of white-coat hypertension and masked hypertension. ABPM BP values are usually lower than office BP values, and the diagnostic threshold for hypertension is ≥130/80 mm Hg over 24 hours, or 135/85 mm Hg for the daytime average (both equivalent to office BP ≥140/90 mm Hg), Table III.

A systematic review and meta-analysis that compared the relative accuracy of clinic measurements and HBPM, with ABPM as a reference standard, concluded that neither clinic nor home measurement had sufficient sensitivity or specificity to be recommended as a single diagnostic test. About 25% of patients are misdiagnosed if only clinic measurement is used. Treatment decisions based on clinic or home BP alone might result in substantial overdiagnosis, if ABPM is considered a reference standard.

Performing ABPM before the start of lifelong drug treatment might therefore lead to more appropriate targeting of treatment. A modeling study, assessing cost-effectiveness of further measurement in the clinic, HBPM and ABPM after an initial raised reading in the clinic in a primary care population aged 40 years or older, showed that ABPM is the most cost-effective diagnostic strategy for hypertension in men and women of all ages. Savings from better-targeted therapy counterbalanced the additional costs associated with ABPM.

Finally, in relation to diagnosis, there is a strong argument that health systems need to screen populations for hypertension since it is common, important, and usually asymptomatic. Indeed, when structured population screening programmes have been undertaken, a majority of people (>50%) were unaware of their hypertension. However, the best method of screening is not determined, and when to start and repeat case-finding varies by country. Most guidelines therefore simply recommend opportunistic case-finding or screening from age 35 or 40 onwards.

Clinical evaluation after diagnosing hypertension and assessment of target-organ damage

Once hypertension is diagnosed a number of tests and examinations should be performed to: establish hypertension grading; screen for potential secondary causes of hypertension; identify contributing factors to the development of hypertension (lifestyle, concomitant medications, or family history); identify additional cardiovascular risk factors (including lifestyle and family history); identify comorbidities; and establish target end-organ damage (TOD) and any existing cardiovascular, cerebrovascular, or renal disease.
Medical history

A medical history should address in particular: time of the first diagnosis of hypertension, including records of any previous medical screening; hospitalization; records of current and past BP values; records of anti-hypertensive and other medications; family history of hypertension, cardiovascular disease, stroke, or renal disease; a lifestyle evaluation, including exercise levels, body weight changes, diet history, smoking history, alcohol; and history of any other cardiovascular risk factors.

Clinical examination

Physical examination may establish potential secondary causes of hypertension, signs of comorbidities, and TOD. Patients should undergo auscultation of the heart, carotid and renal arteries, and vascular system to detect murmurs or bruits which need further investigation. Peripheral arteries should be palpated. Height and body weight should be measured and body mass index (BMI) calculated. Funduscopy should be performed to detect hypertensive retinopathy. Urine should be tested for hematuria and proteinuria. The routine blood tests and clinical investigations are listed in Table IV. The main investigation is the electrocardiograph, particularly to exclude left ventricular hypertrophy, past myocardial infarction or arrhythmias.

Summary

Hypertension is the world’s most common long-term condition and one of the most important risk factors for coronary heart disease, stroke, and renal failure. There is a huge evidence base to guide therapy but early and accurate diagnosis of hypertension is needed first. Guidelines are now more consistent on the blood pressure cutoff criteria to determine hypertension and principally recommend out-of-office measurement before confirming a diagnosis.

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The 2018 European guidelines: tailoring treatment to new hypertension goals

Krzysztof Narkiewicz, MD, PhD
Department of Hypertension and Diabetology, Medical University of Gdansk, Gdansk, Poland

Correspondence: Prof Krzysztof Narkiewicz, Department of Hypertension and Diabetology, Medical University of Gdansk, Debinki 7c, 80-952 Gdansk, Poland
E-mail: knark@gumed.edu.pl

Abstract: The 2018 European hypertension guidelines recognize poor patient adherence, physician inertia, and secondary hypertension as main causes of unsatisfactory blood pressure (BP) control. While the definition and classification of hypertension remained unchanged, the blood pressure targets are more stringent. The guidelines recommend preferred use of two-drug combination therapy for the initial treatment of most patients and the preferred use of single-pill combination (SPC) therapy in hypertension management. The new strategy is based on simplified drug treatment algorithms, with the preferred use of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) combined with a calcium channel blocker (CCB) or/and diuretic as the core treatment strategy for most patients, with β-blockers used for specific indications. Despite the increased efficacy provided by combining agents from two different classes, more than 20% of patients do not achieve BP goals even with two-agent SPCs, and require the use of a three-drug SPC comprising an RAS blocker + CCB + diuretic. Ideal core components of the SPC should be tailored to both the clinical condition and the patient’s age, necessitating combinations of several drugs as double and triple SPCs. Furthermore, these combinations need to be supported by randomized clinical trials. The perindopril-based family of SPCs (dual combinations with indapamide, amlodipine, or bisoprolol, and triple combinations of perindopril, amlodipine, and indapamide) offer a wide range of opportunities to individualize treatment and control blood pressure with one tablet in the vast majority of our patients.

Keywords: guideline; hypertension; treatment

Introduction

Despite enormous progress in cardiovascular pharmacotherapy and well-documented benefits of blood-pressure lowering,1,2 the management of hypertension remains challenging and blood pressure control is far from satisfactory.3,4 After the publication of the 2013 European guidelines,5 several important clinical studies gave us new insights into critical aspects of hypertension management, including blood pressure goals and the benefits of combination treatment. These issues were addressed in the 2018 guidelines,6 which identified key barriers in hypertension management, lowered BP targets, and proposed novel treatment strategies.
Key barriers to success

The 2018 guidelines recognize poor patient adherence, physician inertia, and secondary hypertension as main causes of unsatisfactory BP control.

Patient adherence

Low adherence to the prescribed medications can concern up to 50% of patients with apparently resistant hypertension, and has been consistently linked to higher risk of cardiovascular events. Early recognition of poor adherence to treatment might reduce the number of costly investigations and procedures, including interventional treatment. Nonadherence is related to several factors including the fact that hypertension is chronic and generally symptom-free, the side effects associated with certain drugs, pill burden, and the complexity of some treatment regimens. There is a close inverse relationship between compliance and pill burden; compliance decreases as the number of daily doses increases. Importantly, patient adherence can be improved by an appropriate therapeutic and follow-up regimen.

Physician inertia

There is overwhelming evidence that failure to diagnose hypertension or to reveal uncontrolled treated hypertension (diagnostic inertia) and failure to initiate or escalate treatment (therapeutic inertia) contribute to poor BP control. An important factor that plays a role in the suboptimal rate of BP control is the frequent utilization of monotherapy. It has been well demonstrated that combination of two drugs from different classes with complementary mechanisms of action provides greater BP-lowering efficacy, compared with increasing the dose of monotherapy. Combination therapy has been estimated to have an additional BP-lowering efficacy, approximately five times greater than that obtained by doubling the dose of monotherapy.

Secondary hypertension

If inadequate control of BP is confirmed by the out-of-the-office measurement, and nonadherence is ruled out, patients should be screened for a secondary cause of hypertension, especially primary aldosteronism and renal artery stenosis. The new guidelines stress that early detection of secondary causes of hypertension is important because interventions may be curative or at least improve blood pressure control.

2018 guidelines: unchanged definition, but lower blood pressure targets

The 2018 guidelines reaffirmed the validity of the previous hypertension definition and classification. Hypertension is defined as office SBP values ≥140 mm Hg, and/or diastolic BP (DBP) values ≥90 mm Hg. The same definition and three-grade classification are used in younger, middle-aged, and older subjects.

The 2013 hypertension guidelines recommended an office BP treatment target of <140/90 mm Hg, regardless of the number of risk factors, comorbidities and level of CV risk. The 2018 Task Force recommends that when BP-lowering drugs are initiated, the first objective should be to lower BP to <140/90 mm Hg in all patients. However, if the treatment is well tolerated, treated BP values should be targeted to 130/80 mm Hg or—in subjects younger than 65—lower to values between 120 and 130 mm Hg. The optimal treated DBP range is between 70 and 80 mm Hg. Importantly, the new recommendations stress that BP control should be achieved within 3 months.

New strategy – central place of SPCs

More stringent BP targets make achievement of BP control more challenging. Consequently, our approach to hypertension management had to be changed. The 2018 ESH/ESC guidelines presented a new SPC treatment strategy (Figure 1) to improve BP control including: (i) preferred use of two-drug combination therapy for the initial treatment of most people with hypertension; (ii) the preferred use SPC therapy for most patients; (iii) simplified drug-treatment algorithms with the preferred use of an ACE inhibitor or ARB combined with a CCB or diuretic as the core treatment strategy for most patients, with β-blockers used for specific indications.

The major differences between the 2013 and 2018 guidelines are summarized in Table I. The 2013 guidelines recommended that low-dose combination therapy be used as a first-line treatment only in patients with marked BP elevation (grades 2 and 3) and high/very high CV risk, but not in grade 1 hyperten-
sion. Furthermore, the level of recommendation for SPC use was weak (class IIb “might be considered”).

The new guidelines recommend (class I) the initiation of treatment with a SPC comprising two drugs in most patients in order to improve the speed, efficiency, and predictability of BP control. While the preferred two-drug combinations are an RAS blocker with a CCB or a diuretic, a β-blocker in combination is an alternative when there is a specific indication for its use, such as angina, in the first year post-myocardial infarction, heart failure with an ejection fraction <40%, or heart-rate control.

Thus, initial therapy for most patients with hypertension should be with a combination of two drugs, not a single drug. The only exception would be in a limited number of low-risk patients with stage 1 hypertension whose SBP is <150 mm Hg or older, especially frail, patients, in whom more gentle reduction of BP may be desirable.

Despite the increased efficacy provided by combining agents from two different classes, more than 20% of patients do not achieve BP goals with two-agent SPCs and require the use of a three-drug SPC comprising an RAS blocker + CCB + diuretic (Figure 1–step 2).

RAS blockade is a cornerstone of combination therapy. Importantly, increasing the dosages of ACEIs and ARBs appears to have a less marked effect on adverse events in comparison to CCBs, diuretics and β-blockers. Therefore, the use of RAS blocker combinations is logical because these agents can be used at higher doses in combination therapy without increasing treatment-related adverse events.

As outlined above, there are several reasons explaining the dominant position of SPCs in management of hypertension such as faster and better BP control, less variability in response, safety, and better tolerability and better adherence to therapy. In other words, SPCs in hypertension management meet the challenge, takes into account the human factors, and minimizes the risk of treatment failure.

Looking for optimal SPCs

Ideal core components of SPCs should be useful in various clinical conditions and in different age groups, available in combination with several drugs in double and triple SPCs, and supported by randomized clinical trials (evidence-based medicine).

The perindopril-based family of SPCs (dual combinations with amiodipine, indapamide or bisoprolol, and triple combination of perindopril, amiodipine, and β-blocker) is an example of SPCs that meet these criteria. In addition, the use of SPCs is logical because these agents can be used at higher doses in combination therapy without increasing treatment-related adverse events.

Table 1 Positioning of combination therapy in 2013 and 2018 European hypertension guidelines.

<table>
<thead>
<tr>
<th>2013 guidelines⁵</th>
<th>2018 guidelines⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial combination therapy in stage 1 Not recommended</td>
<td>Strong recommendation (class I)</td>
</tr>
<tr>
<td>Initial combination therapy in stages 2 and 3 Weak recommendation (class IIb)</td>
<td>Strong recommendation (class I)</td>
</tr>
<tr>
<td>SPC preferential use Weak recommendation (class IIb)</td>
<td>Strong recommendation (class I)</td>
</tr>
</tbody>
</table>

Figure 1 Core drug treatment strategy for uncomplicated hypertension according to the 2018 ESC/ESH hypertension guidelines.³

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; HMOD, hypertension-mediated organ damage; MI, myocardial infarction; o.d., once daily; PAD, peripheral artery disease

β-Blocker

Consider β-blockers at any treatment step, when there is a specific indication for their use, eg, heart failure, angina, post-MI, atrial fibrillation, or younger woman with, or planning, pregnancy.
and indapamide) offer opportunities to individualize treatment and control blood pressure with one tablet in the vast majority of our patients.

Among ACE inhibitors, perindopril (used as monotherapy or in combination) has strong evidence of cardiovascular protection in different clinical high-risk conditions including hypertension (ASCOT-BPLA study), diabetes (ADVANCE trial), coronary artery disease (EUROPA trial), post-stroke patients (PROGRESS) and hypertension in the very elderly (HYVET). Importantly, treatment with perindopril, in contrast to the ARBs, results in a significant further reduction in all-cause mortality.

The new guidelines stress that most randomized clinical trials demonstrating the benefits of CCBs in outcomes have used dihydropyridines (especially amlodipine). Finally, there is growing evidence that the long-term risk:benefit ratio of thiazide-like diuretics, such as indapamide, is more favorable than that of thiazides.

Putting guidelines into practice

There is a clear-cut gap between the potential of modern antihypertensive therapy and actual blood pressure control in real life. Therefore, the guidelines identify interventions that may facilitate drug adherence and consequently improve prevention of hypertension-mediated cardiovascular events. Key interventions include counselling and empowerment of the patient, motivational strategies, self-monitoring of BP, and accessibility to drugs including reimbursement of SPC pills.

For many years SPCs were considered an option in hypertension treatment. In 2019, routine SPC use, including initiation of treatment, is becoming a new standard of hypertension management replacing the previous strategy. In accordance with the new European guidelines, SPCs based upon RAS blockers have the greatest potential to deliver strong antihypertensive efficacy with excellent tolerability, improve compliance through reduced pill burden, and provide optimal cardiovascular protection.

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Introduction

Cardiovascular disease (CVD) is the leading cause of death across the most developed countries and its prevalence is rapidly increasing in the developing countries as well. The pathogenesis of CVD involves the interaction of several risk factors that contribute to the development and progression of cardiovascular disease. Among them, a primary role is played by hypertension, diabetes, obesity and being overweight, abnormalities of lipid control, and poor lifestyle. High blood pressure is certainly the most important risk factor, affecting over 30% of the overall population, and is responsible for a significant increase in the risk of major cardiovascular complications including myocardial infarction, stroke, renal disease, and peripheral artery disease. Hypertension is frequently associated with one or more additional risk factors for cardiovascular disease, as clearly evident from the hypertensive population of the Framingham Study and the Brisighella Heart Study, where about 80% of subjects were affected by at least one additional risk factor with a large prevalence of lipid disorders (high total cholesterol and/or triglycerides). An additional portion of cardiovascular risk in hypertension is the result of the presence of target-organ damage that primarily involves the heart (left ventricular hypertrophy—LVH), the kidney (various

Claudio Borghi, MD; Crescenzio Bentivenga, MD; Eugenio Cosentino, MD; Matteo Landolfo, MD

Internal Medicine - Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

Correspondence: Claudio Borghi, UOC di Medicina Interna, Ospedale Policlinico S.Orsola Malpighi, 40138 Bologna, Italy E-mail: claudio.borghi@unibo.it

Abstract: Cardiovascular disease is the leading cause of death in many countries across the world, and is the final step in the interaction among several risk factors, including hypertension. The presence of additional cardiovascular risk factors is a common feature in more than 80% of hypertensive patients, and must be considered in the choice of blood pressure-lowering treatment. According to ESC-ESH guidelines, the combination of a renin-angiotensin system (RAS) inhibitor and a calcium-channel blocker and/or a diuretic can cover the large majority of therapeutic needs in patients with hypertension complicated by additional metabolic risk factors and target-organ damage. In particular, the results of the ASCOT and ADVANCE trials and their long-term follow-up have demonstrated the supremacy of angiotensin-converting enzyme ACE inhibitors (perindopril) combined with amlodipine and/or indapamide in high-risk and diabetic patients in comparison with other classes of first-line treatments. Furthermore, the results of the ASCOT-LLA study have demonstrated a favorable synergistic interaction between statins (atorvastatin) and blood pressure-lowering treatment with a larger benefit in terms of major cardiovascular events in patients treated with the combination of an ACE inhibitor and a calcium channel blocker. The differences in the individual response to separate treatment strategies are reasonably supported by distinct pathophysiological profiles, with a different level of involvement of the renin-angiotensin and calcium transport systems in patients with a higher probability of cardiovascular complications. The available evidence clearly supports the importance of an individualized choice of antihypertensive drugs in the treatment of patients with hypertension complicated by comorbidities contributing to the overall cardiovascular risk profile.

Keywords: ACE inhibitor; hypertension; lipid; risk factor
degrees of renal impairment and proteinuria) and the arterial vessels (reduced distensibility and increased vascular stiffness) and is responsible for an excess in the risk of cardiovascular complications beyond blood pressure control alone.\textsuperscript{6,7} Finally, many recent studies have clearly demonstrated that the prevalence of hypertension is increased in several patient groups with non-cardiovascular diseases including chronic inflammatory diseases (eg, rheumatoid arthritis, psoriatic arthritis), psychiatric illness, headache, and hyperuricemia/gout.\textsuperscript{8,9} In particular, elevated levels of serum uric acid have been demonstrated to increase the relative risk of new-onset hypertension as well as the rate of major cardiovascular complications (myocardial infarction, stroke, and heart failure) in patients with hypertensive disease, regardless of the presence of additional CV risk factors. Most of these additional risk factors coexist in the same hypertensive patients\textsuperscript{5} and are responsible for a significant increase in the residual risk of major CV events\textsuperscript{10} in patients with a satisfactory blood pressure control in response to treatment.\textsuperscript{10}

All this evidence clearly suggests the importance of an integrated treatment of hypertension in patients with multiple risk factors and/or target-organ damage and/or additional non-cardiovascular disease. The choice of the antihypertensive strategy should be adapted to the characteristics of the patient and the concomitant disease according to the results of randomized clinical trials and additional evidence from observational studies and daily practice.

Hypercholesterolemia

In practical terms the most common comorbidity in the hypertensive population is a lipid disorder, in particular an increase in the plasma LDL-cholesterol.\textsuperscript{3} The treatment of these patients is based on the concomitant use of antihypertensive drugs and statins with or without additional lipid-lowering drugs. The 2018 ESC-ESH Guidelines for hypertension\textsuperscript{7} clearly support the use of drug combinations since most of these patients have a medium-to-high risk profile that can be managed by the use of RAS blockers, diuretics, and calcium channel blockers. On the other hand, the results of the Cholesterol Collaborative Trialist Group have reported the efficacy of statin treatment in hypertensive patients with a relative risk reduction of major CV events comparable to those observed in the normotensive population.\textsuperscript{11} The results of the CCT meta-analysis have been confirmed by the results of the ASCOT-LLA study, where treatment with 20 mg of atorvastatin in patients with hypertension has reduced the rate of major cardiovascular events.\textsuperscript{12} Recently, the benefit of statin treatment was confirmed over 15 years of follow-up, despite a massive uptake of statin therapy in the group of patients originally allocated to placebo control.\textsuperscript{13} Regarding the best antihypertensive treatment in patients with hypercholesterolemia, the results of the ASCOT-LLA\textsuperscript{14} (Figure 1) clearly suggest the supremacy of concomitant administration of an ACE inhibitor (perindopril) with a dihydropyridine calcium channel blocker (CC—amlodipine) over the treatment with a β-blocker (atenolol) and a diuretic (hydrochlorothiazide). The combination of ACEI and CCB was responsible for a great proportion of the benefit observed in the study in terms of prevention of coronary artery disease and stroke as a probable consequence of some favorable interaction between the drugs and the mechanisms responsible for the progression of atherosclerosis. According to the results of the ASCOT BPLA study,\textsuperscript{12} the same combination of ACE inhibitor and CCB should be recommended in patients with metabolic syndrome that affects a high proportion of the hypertensive population and is associated with an increase in serum TG in over 30% of the patients.\textsuperscript{3} In particular, the condition of insulin resistance, which is usually observed in these patients, can promote an overactivation of the tissue renin-angiotensin system that can contribute to explaining both the higher rate of cardiovascular events and the favorable response to renin-angiotensin and calcium channel blockade. The same mechanism is prob-

\begin{figure}
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\includegraphics[width=\textwidth]{figure1.png}
\caption{Effects of treatment with perindopril/amlodipine vs atenolol/thiazide in different subgroups of comorbid hypertensive patients in the ASCOT BPLA study.}
\end{figure}
ably involved in the favorable effect of perindopril and amlodipine in patients with elevated LDL-cholesterol with a large involvement of a common pathophysiological pathway in the excess of cardiovascular risk observed in patients where hypertension is complicated by lipid disorders.

**Diabetes**

Among the different conditions complicating hypertensive disease, the presence of diabetes, and in particular type 2 diabetes, is very common. Glucose abnormalities significantly increase the risk of major cardiovascular complications associated with hypertension with a probability of coronary artery disease that is as much as twice that in patients with normoglycemia and the same level of blood pressure control.\(^\text{15}\) In patients with hypertension and diabetes, the guidelines emphasize the importance of blood pressure control and the achievement of appropriate targets of treatment with the extensive use of drug combinations as first-line strategy. Renin-angiotensin inhibitors are certainly the drugs of choice according to their cardiovascular and renal protective effect and should be combined with diuretics and/or calcium channel blockers. The effectiveness of the double combination of ACE inhibitors and CCBs in diabetic patients has been demonstrated by the prespecified subgroup analysis of the ASCOT-BPLA study, where the administration of perindopril and amlodipine resulted in a significant decrease in the rate of the primary end point (-13%, \(P=0.02\)). Similar results have not been obtained with the use of angiotensin receptor blockers (ARBs) despite a comparable reduction in blood pressure, and the outcome results of clinical trials involving angiotensin II receptor blockers and CCBs are still awaited. As far as the clinical efficacy of the combination of an RAS blocker with a diuretic in the diabetic population is concerned, the results of the ADVANCE trial\(^\text{16}\) have clearly demonstrated that perindopril with indapamide favorably affects the primary end point (Hazard Ratio=0.91; 95% CI: 0.83-1.00, \(P=0.041\)) when compared with placebo despite the inclusion of an open-label ACE inhibitor in the control group. Similar results have been obtained with the use of ARBs (Losartan, Valsartan)\(^\text{17,18}\) in combination with hydrochlorothiazide despite very different study designs that involved nondiabetic patients and were actually based on a comparison between single drugs instead of combinations. The clinical benefit observed in the ADVANCE trial with the combination of perindopril and indapamide was increased in patients adding calcium channel blockers,\(^\text{19}\) thus confirming the importance of combination treatment and the reliability of the guideline assumptions in terms of recommended drugs. The results of the ADVANCE study have been extended by the long-term observation of the population in the ADVANCE-ON study\(^\text{20}\) where the benefit of randomized treatment was maintained after the withdrawal of double-blind therapy. Reasonably, the further step of personalized treatment in patients with diabetes at risk of cardiovascular disease will be the extensive use of the most recent antidiabetic drugs (GLP-1 agonists, DPP-4 inhibitors) and in particular SGLT-2 inhibitors, that have been shown to improve blood pressure control and cardiovascular outcome.\(^\text{21}\) Among the first-line glucose-lowering drugs only metformin and gliclazide have been proven to exert some degree of cardiovascular protection in patients with diabetes and impaired metabolic control. In particular the factorial analysis of the ADVANCE study\(^\text{22}\) has confirmed some favorable interaction in patients treated with the combination of ACE inhibitor, diuretic, and gliclazide suggesting the importance of an integrated control of concomitant risk factors in patients with hypertension and metabolic diseases.

**Conclusion**

Hypertension is typically accompanied by comorbidities that act as additional risk factors in over 80% of patients. The treatment of arterial hypertension is largely based on blood pressure control but the choice of the antihypertensive strategy should be individualized according to patient characteristics, available evidence from randomized clinical trials, hypertension guidelines, and pathophysiological background, with an almost universal support for first-line combinations of drugs inhibiting the renin-angiotensin system, vascular calcium handling, and the salt and water axis. \(^\text{19}\)

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Global interventions in hypertension

Charalambos Vlachopoulos, MD; Dimitrios Terentes-Printzios, MD
Hypertension and Cardiometabolic Syndrome Unit, 1st Department of Cardiology, Athens Medical School, Hippokration Hospital, Athens, Greece

Correspondence: Charalambos Vlachopoulos, MD, 24 Profiti Elia str, Athens 14575, Greece
E-mail: cvlachop@otenet.gr

Abstract: It has been well established that among numerous traditional, as well as emerging, risk factors and biomarkers, hypertension still remains the most potent modifiable risk factor for cardiovascular disease. Although major diagnostic and pharmacological advances have been implemented in clinical practice, they have not been associated with a reduction in hypertension-related complications and adverse events. This highlights the major effort needed to achieve optimal prevention, detection, and management of hypertension worldwide. Several societies and regulatory authorities have suggested actions and means to overcome the current problems and obstacles. The main goals of these endeavors are expected to be achieved through the use of generalized worldwide approaches and better education of both physicians and patients. This strategy is further underlined by the disappointing results so far of actions that were either inappropriately directed at specific populations or were hampered by erroneous or complicated methods of addressing hypertension-related consequences. In addition, the essential clustering of other risk factors with hypertension, in conjunction with the crucial effect of subclinical target-organ damage on the prognosis, creates the need for a holistic approach to diagnosis and cardiovascular prevention. This review summarizes current global intervention strategies and also proposes additional ways to further improve the management of hypertension worldwide. ■ Heart Metab. 2019;79:25-29

Keywords: arterial stiffness; global; hypertension; intervention; organ damage; vascular aging

Introduction

Hypertension affects more than 1 billion people around the world, and that number keeps on rising every year. High blood pressure that remains either uncontrolled, or even untreated, is the sole most important cause of stroke, coronary artery disease, and heart failure. These crucial consequences of hypertension have alarmed scientists, who have focused their research on the unraveling of potential pathophysiological mechanisms of hypertension. Based on these pathophysiological pathways, various antihypertensive agents have been discovered, with a clear impact on cardiovascular risk. However, despite this impressive progress in the last few decades, the global epidemic of hypertension keeps growing. This highlights the need for well-articulated changes in the way we diagnose, evaluate, and treat high blood pressure. The traditional health care model for control of blood pressure through office visits, as well as the “one-size-fits-all” approach, have been tested and proven to be insufficient. In this review, we refer to current global strategies aimed at reducing the ill effects of hypertension, and we also suggest alternative ways to improve the management of hypertension worldwide.

How big is the problem?

A substantial number of prehypertensive subjects are now considered as patients, who must be treated accordingly. This is a result of the introduction
of lower and stricter cutoff points for the definition of hypertension based on the Systolic Blood Pressure Intervention (SPRINT) trial and several relevant meta-analyses. No matter how hypertension is defined, its prevalence is increasing worldwide as the net result of two counteracting components. On the one hand, there is a constant reduction of mean blood pressure levels by age, primarily in high-income countries, and to a lesser extent, in middle-income countries. This reflects progress in detection and management of hypertension, but it also reflects improvements in lifestyle, especially in early life. However, on the other hand, this beneficial effect is counteracted by aging of the global population, which results in a rise in the number of hypertensive patients, especially in low- and middle-income countries where increasing longevity is most marked.

The increased global prevalence of hypertension translates into a larger worldwide economic burden. The worldwide economic cost, due to both loss of productivity and the direct health care costs from noncommunicable diseases, is projected to reach 50 trillion US dollars between 2010 and 2030, with approximately 50 percent of this cost attributed to CVD. In fact, 1 out of 5 deaths worldwide have inadequate blood pressure control as the culprit. Even more disturbing is the increase in related events in low-income countries. Therefore, it comes as no surprise that the Global Burden of Disease Study currently recognizes hypertension as the principal risk factor for disability and disease worldwide. In fact, the World Health Organization Global Plan of Action for the prevention of noncommunicable diseases provides policy guidance to achieve nine voluntary goals by 2025, including a reduction by one quarter in the prevalence of hypertension. On a national and international level, medical groups and authorities prioritize and firmly support research and clinical actions to achieve blood pressure targets.

### Abbreviations

CVD: Cardiovascular disease; DASH: Dietary Approaches to Stop Hypertension; PWV: Pulse-wave velocity; SAGE: Systolic blood pressure, Age, fasting Glucose and Estimated glomerular filtration rate; SPRINT: Systolic Blood Pressure Intervention Trial; SUPERNova: Supernormal vascular aging

### Issues on blood pressure prevention, diagnosis and evaluation

People cannot be protected from a health hazard that they are not aware of. It is crucial for them to be aware of the repercussions of hypertension on their health and to know how they can access blood pressure measurement. Unfortunately, even in our contemporary era, exact and valid measurements of blood pressure are difficult. Many efforts have been made by government and nongovernment organizations to implement proper validation of monitors with stringent protocols. This becomes extremely difficult when taking into consideration the need for simpler and more cost-effective devices. However, while lower prices might increase the accessibility for patients of blood pressure monitors, they do not guarantee the quality of measurements. Given the rising preference for ambulatory and home blood pressure measurements, where these are not performed by medical personnel during office visits, the need for reliable and accurate devices is further highlighted.

There is strong evidence that a team-based care strategy for hypertension that includes physicians, nurses, pharmacists, and community health workers is more effective for attaining blood pressure control than the “one-person” approach. This team must communicate to patients the devastating consequences of clustering of risk factors that translates into a heightened global cardiovascular risk, as was initially attempted a few decades ago with the description of the metabolic syndrome. Therefore, both the care team and the patients must be aware that targeting only one risk factor is insufficient to provide overall cardiovascular protection, and only if the patient is shielded from all risk factors can prevention be maximized.

Finally, although the vast majority of patients do not have a specific cause for their increased blood pressure, there are those few that have secondary hypertension and often can be cured. Thus, an important chapter in the initial evaluation of newly diagnosed hypertension is the investigation for possible secondary causes. This investigation requires multidisciplinary teams with the proper expertise, access to relevant tests, even in low-income countries, and finally, simple and evidenced-based algorithms for detection of the secondary causes.
The role of arterial aging and stiffness

Vascular function and early structural alteration are biomarkers of CVD and independent predictors of the corresponding risk.13 Vascular age, as assessed by arterial biomarkers, such as aortic stiffness, is a promising concept. Furthermore, it meets the criteria for the ideal biomarker of cardiovascular risk that can integrate diverse known, and unknown, cardiovascular risk factors and their cumulative effect over time.14 In fact, a provocative idea was recently introduced regarding individuals who have supernormal vascular aging (SUPERNova). SUPERNOVA can be diagnosed in subjects who present an exceptionally low arterial stiffness for their age and sex.15 By choosing the word SUPERNOVA, the authors refer to the life of a supernova—a large explosion that takes place at the end of a star’s life cycle. The relationship between black holes and supernovae is not established, but the theory of physics suggests that time slows down in a black hole, just like the aging of arteries in SUPERNOVA subjects. While the ability to age slowly is predetermined by genes, lifestyle and pharmaceutical interventions can also decelerate vascular senescence and improve prognosis.5

Aortic pulse wave velocity (PWV), is the “gold standard” measure of aortic stiffness. Blood pressure and age are the principal determinants of aortic stiffness. The connection between hypertension and aortic stiffness is bidirectional. Evidence from the Framingham Heart Study suggests that higher blood pressure levels can accelerate the degree of aortic stiffness, giving rise to a vicious cycle of accelerated hypertension and further stiffening of large arteries.16 Moreover, the annual increment in PWV is greater in hypertensive subjects, suggesting of a “premature” stiffening in these patients.17 However, the other direction of the aortic stiffness-hypertension relationship is more intriguing and important. Indeed, important data show that aortic stiffening in young normotensive individuals is a predictor of increased systolic blood pressure and the development of hypertension in later life.16 In a meta-analysis of 17 published studies, aortic PWV data from 15 877 subjects followed up for a mean of 7.7 years were compiled.18 Aortic stiffness was found to be a strong predictor of future cardiovascular events and all-cause mortality; an increase in aortic PWV by 1 m/s was associated with an increase in the risk of 14%, 15%, and 15% in CVD events, CVD death, and all-cause death, respectively. The results of this meta-analysis were confirmed recently19,20 with individual data from 17 635 subjects where the addition of PWV improved risk prediction by 13% (Figure 1).

While reimbursement from health care authorities5 and improvement of the cost-effectiveness of dedicated devices can lead to further utilization of PWV measurement, additional approaches that could aid integration into clinical practice have been offered. The most promising approach is a strategy that employs a simple clinical score (the SAGE score) that predicts high aortic PWV values based on widely available clinical variables (systolic blood pressure, age, glycemia, and estimated glomerular filtration rate) and can prioritize measurement of aortic PWV.21

Treatment and health care issues

Pharmacological treatment is not easily available worldwide due to its high cost. Single-pill combinations that could also include statins or antiplatelets might provide a viable alternative as shown by recent studies in low-income countries to manage both high blood pressure and dyslipidemia.22 However, it is not only the lack of resources but also the limited number of physicians who are available to deal with the problem. An option to tackle this matter is the involvement of other specialists in the management of hypertensive patients, such as pharmacists or nurses. Extreme caution and care must be provided to ensure their proper training and education prior to dealing with patients to ensure best practice.

Another essential issue is the need for personalized medicine based on age, gender, and race; this has regrettably not been addressed in recent large randomized studies, leading to doubts on the exact treatment targets and the ideal treatment regimens. On the other hand, specific strategies must be implemented to identify risk factors for nonadherence. Nonadherence is the leading cause of uncontrolled blood pressure worldwide. Several solutions have been proposed, such as alternative treatment regimens (eg, single-pill combinations)23 or technological advancements (eg, mobile-based applications)9 to monitor and reduce nonadherence. Nevertheless,
none of these have been successful so far, stressing the need for additional means to overcome this problem.

Apart from pharmacological treatment, lifestyle modification is crucial in the management of hypertension. However, the ways to achieve a healthy lifestyle must be clearly defined. For example, the use of several different diets, like the DASH or the Mediterranean, must be integrated into one simple message regarding nutrition after validation in randomized studies. Similarly, clear strategies for weight reduction, as well as exercise prescription, must be advocated.

Finally, motivational incentives directed either to the patient or even to the physician are needed to counterbalance inertia related to the management of hypertensive patients. All these actions must be orchestrated by a well-organized and efficient health care system that is responsible for the dissemination of knowledge and provision of means to prevent, diagnose, and ultimately treat hypertension.

Conclusion

Hypertension is the number one cause of disability and death worldwide. Thus, it is necessary to implement several worldwide actions on prevention, diagnosis, evaluation, and treatment of increased blood pressure so as to tackle its grave repercussions on organs and prognosis. The concept of vascular aging might be a useful tool regarding initial evaluation, as well as therapeutic targets; however, further research is warranted. The idea of personalized medicine through technological advancements and mobile or tablet applications seems to be the future of hypertension management. Moreover, single-pill combinations have shown encouraging results, especially in...

![The prognostic role of aortic pulse wave velocity in studies in Europe.](image)

**Figure 1** Number of subjects included in studies investigating the predictive role of aortic pulse wave velocity in Europe until 2018. The countries are colored based on the number of participants included in relevant studies.
low-income countries where the prevalence of hypertension is rising. Finally, it is clear that, the earlier these preventive efforts take place, the larger the gain will be regarding disease progression and disease-related outcomes.

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Primary hyperaldosteronism—seek and you may find

Abstract: Primary hyperaldosteronism (PHA), also referred to as primary aldosteronism (PA), remains a largely under-recognized and suboptimally managed secondary cause of hypertension, associated with significant cardiovascular morbidity and mortality. When caused by a classical unilateral Conn’s adenoma, it is potentially curable with adrenalectomy. However, identifying this remains problematic and acts as a barrier to best management. The gold-standard investigation to determine lateralization is adrenal vein sampling (AVS). This procedure is invasive and technically challenging, and results can be inconclusive. Hence, there has been much interest in finding a noninvasive yet reliable alternative to this, and the most promising candidate at present is $^{11}$C-metomidate positron emission tomography-computed tomography (PET-CT) scanning. We present the case of a patient with PHA in whom initial imaging revealed bilateral adrenal pathologies: however, after having both AVS and $^{11}$C-metomidate PET-CT which showed unilateral overproduction of aldosterone, the patient had an adrenalectomy with improvement of blood pressure. We discuss the benefits of this investigation and the potential impact it could have on managing PHA.

Keywords: metomidate; PET-CT; primary hyperaldosteronism

Case report

A 66-year-old retired quality surveyor was referred to the Guy’s Hospital (London, UK) hypertension clinic in 2011. His general practitioner had been struggling to control his high blood pressure (BP), which was not causing symptoms. He was diagnosed with hypertension in his early 20s during a routine medical check for work. He had a background history of hypercholesterolemia, and had been diagnosed with colonic adenocarcinoma in 2011, which was managed by surgery followed by radiotherapy and chemotherapy.

At his first clinic visit, he was taking four antihypertensive medications, namely bumetanide 1 mg od, lisinopril 20 mg od, diltiazem modified-release 120 mg od, and doxazosin 4 mg od. His lowest clinic BP was 156/88 mm Hg. He was investigated for secondary causes of hypertension. Renin was 7.4 mU/L and aldosterone 277 pmol/L, giving an aldosterone:renin ratio (ARR) of 37.4, all of which were in the normal ranges. He had mild renal impairment with creatinine 99 μmol/L and eGFR 66 mL/min, but potassium was within normal at 4.3mEq/L. Thyroid-stimulating hormone (1.47mIU/L) was also normal.

As no secondary cause for hypertension was revealed, he was managed with adjustment of his medications. Doxazosin was initially increased to 8 mg od and reduced as his BP control improved. However, in attempts to adequately control his elevated BP over the subsequent years, the daily dose of diltiazem gradually increased to 300 mg. Bumetanide was replaced by bendroflumethiazide. He developed
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A dry cough attributed to the angiotensin-converting enzyme (ACE) inhibitor and was switched to the angiotensin receptor blocker losartan at a dose of 100 mg od. Despite these changes in his medications, his home BPs remained high and his clinic BP was 152/94 mm Hg.

It was decided to reinvestigate for secondary causes in 2016. At this point, renin was suppressed at 4.3 mU/L and aldosterone raised at 641 pmol/L, giving an elevated ARR of 149. He remained normokalemic (4.2 mEq/L). A saline suppression test confirmed failure to adequately suppress aldosterone following a 2-hour saline load. Adrenal magnetic resonance imaging (MRI) revealed bilateral adrenal body adenomas, measuring 11 mm on the right and 12 mm on the left.

At this point he was enrolled into the MATCH (Is Metomidate PET-CT superior to Adrenal venous sampling to predict outcome of adrenalectomy in Hyperaldosteronism?) study. He underwent successful adrenal vein sampling (AVS, Figure 1) which demonstrated raised aldosterone concentration in the right adrenal vein with an elevated lateralization index (LI) of 1.1. The cortisol-corrected aldosterone concentration is calculated in both adrenal veins and the LI is the ratio of the higher value over the lower. LIs greater than 2 to 4 (depending on the center) indicate unilateral disease.

Following AVS, he underwent 11C-metomidate positron emission tomography-computed tomography (PET-CT), which identified a single right-sided 14x14 mm tumor with SUV\textsubscript{max} of 1.18 (Figure 2). This corresponded to a medium probability of a right-sided aldosterone-producing adenoma (APA).

Both tests therefore suggested right-sided primary hyperaldosteronism (PHA). He underwent an uncomplicated laparoscopic right adrenalectomy and was discharged home 2 days later. He did not exhibit postoperative hypoadrenalism, nor did he require mineralocorticoid replacement.

In the weeks preceding his adrenalectomy, the patient’s plasma aldosterone concentration was 991 pmol/L and renin 1 mU/L. Home BPs averaged 180/95 mm Hg. 10 months post-adrenalectomy, his home BP was 134/91 mm Hg on average and his medications had reduced to losartan 50 mg od and lercanidipine 20 mg od. Aldosterone had reduced to 191 pmol/L and renin to 0.9 mU/L.

Whilst the patient tolerated the AVS and did not experience any adverse events or complications relating to this, he expressed a preference for the 11C-metomidate PET-CT scan as this was a more straightforward and familiar procedure which was relatively quick and noninvasive. Post-adrenalectomy, he was pleased that that the number of medications had reduced significantly and that his blood pressure was better controlled.

Discussion

An important stage in the management pathway for patients with suspected PHA is to subtype this as either unilateral or bilateral disease. The significance of identifying lateralization is in the subsequent management. In patients with unilateral disease, adrenalectomy can be offered with the potential to cure hypertension (in 30% to 60%)\textsuperscript{1} and/or correct hypokalemia.

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**Figure 1** Adrenal vein sampling from the left (a) and right (b) adrenal veins.

**Figure 2** Right adrenal adenoma (arrow). Images are CT alone (a), PET alone (b), and PET combined with CT (PET-CT; c). The adenoma shows avid uptake of the radiotracer 11C-metomidate.
In bilateral disease or in patients with unilateral disease who do not want or are not suitable for surgery, the management is targeted drug therapy with a mineralocorticoid receptor antagonist.1

The current gold standard investigation to differentiate unilateral from bilateral pathology is AVS, wherein the adrenal veins are catheterized and samples taken for cortisol and aldosterone measurement. An elevated aldosterone:cortisol ratio on one side indicates unilateral PHA, whereas elevation of this ratio on both sides indicates bilateral disease.2,3 AVS has a sensitivity of 95% and a specificity of 100% for detecting unilateral aldosterone excess.1

However, there are significant disadvantages to AVS. It is an invasive and expensive investigation. There are substantial technical challenges, particularly regarding successful cannulation of the right adrenal vein, which is much smaller than the left and drains directly into the vena cava rather than into the renal vein.2 The right adrenal vein is successfully cannulated in 74% of procedures.1 The main complication is adrenal vein rupture, which occurs in 0.51% to 0.61% of cases.3

There is much heterogeneity in how AVS is performed and how results are interpreted. The adrenal veins can either be sampled simultaneously or sequentially, and sampling can be done with or without cosyntropin.2,3 Cosyntropin use minimizes stress-induced and time-related fluctuations in aldosterone secretion.3 Prior to the AVS, hypokalemia should be corrected, and medications known to stimulate renin should be stopped, which may prove challenging in patients with severe hypertension. If the AVS result shows that both adrenals were not successfully catheterized, the procedure may need to be repeated.3

Given the multiple challenges that AVS poses, eligible patients may not even undergo the procedure. These patients may be managed medically and not offered the unilateral adrenalectomy which could potentially cure them. There may also be a resistance from clinicians to initially screen for PHA but also to improve the willingness of clinicians to investigate for it.11C-metomidate PET-CT is a promising rival to the current gold standard of AVS.7 Historically, metomidate was used as a veterinary anesthetic but later found to be a potent inhibitor of the human adrenal steroidogenic enzymes CYP11B1 (11β-hydroxylase) and CYP11B2 (aldosterone synthase). Metomidate can be labeled as a PET radiotracer that selectively accumulates in tissue that secretes aldosterone to excess. The 11C-metomidate PET-CT combines noncontrast CT images with dynamic PET images to create standardized uptake value (SUV) maps. The maximum uptake (SUVmax) is higher in APAs than normal adrenal tissue.7,8 Dexamethasone can be given to suppress background adrenal CYP11B1, enhancing the selectivity of metomidate for CYP11B2, which is ACTH-independent and preferentially expressed in APAs.9 Several studies have assessed the usefulness of 11C-metomidate PET-CT in PHA subtyping.7-12 The largest study included 39 patients with PHA.12 The investigators determined that using an SUVmax ratio of 1.25 provided a specificity of 87% (95% CI 69-104) and a sensitivity of 76% (95% CI 59-93) for identifying APAs.12 In areas with a SUVmax >17, the specificity rose to 100%. This study concluded that 11C-metomidate PET-CT is non-inferior to AVS and should be considered as a noninvasive alternative.

Conclusion

We describe the case of a patient in which PHA was discovered over 45 years after his initial hypertension diagnosis. There were bilateral adrenal changes on
standard (MRI) imaging, but AVS and a novel investigation, 11C-metomidate PET CT, showed right-sided PHA, which was managed by adrenalectomy, with resultant improvement in blood pressure control.

For patients with unilateral PHA, adrenalectomy offers superior health outcomes compared to medical management alone. Proving lateralization with AVS has its challenges, however 11C-metomidate PET-CT may be a useful noninvasive alternative to this. Current available evidence for this imaging modality is based on small patient numbers, and further studies are required to determine its true usefulness in wider clinical practice. As a noninvasive investigation, it may prove to be a powerful tool to break down the barriers in detecting unilateral PHA in the hypertensive population and to better managing this underdiagnosed, potentially curable condition.

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Introduction

Hypertension is increasing in prevalence due primarily to an aging population, together with an increasing presence of comorbidities which predispose to the development of hypertension including diabetes, renal disease, obesity, and adverse lifestyle factors.

Effective treatment of high blood pressure, combining both medication and lifestyle interventions, significantly reduces the risk of cardiovascular events. A reduction of 10 mm Hg in systolic blood pressure lowers the risk of stroke by 38%, cardiovascular death by 21%, and coronary artery disease by 16%.

Conversely it is well recognized that up to 50% of patients treated with antihypertensive drugs do not achieve their target blood pressure. Poorly controlled hypertension confers an increased risk of stroke, myocardial infarction, heart failure, and end-stage renal disease.

A significant factor in suboptimal blood pressure control is poor adherence to both medication and lifestyle interventions. Nonadherence to antihypertensive medication is estimated to account for between 43% to 65% of patients with presumed “resistant” hypertension. Poor adherence therefore constitutes a major barrier to reducing cardiovascular mortality.

Factors influencing adherence to and persistence with antihypertensive medication and lifestyle interventions

The discrepancy between optimal blood pressure control rates achieved in clinical trial settings (up to 80% in the ACCOMPLISH trial achieved target blood pressure) and everyday clinical practice is due to a number of factors, including differences in medication-taking behaviour, ie, adherence to and persistence with drug therapy regimens.

Adherence is defined as appropriate use of therapy, including taking medication at the prescribed frequency, interval and dosage. Nonadherence may be either intentional, whereby the patient chooses to deviate from the treatment regimen, or unintentional,
when they may be careless or forgetful about adhering to the treatment regimen. Persistence, on the other hand, is defined as continuing the use of medication for a specified period.

With respect to antihypertensive treatment, a wide range of adherence rates have been reported. A study of 18,806 newly diagnosed hypertensive patients showed that only 8% were classified as high adherers (defined as adherence >80%) and 51% were low (adherence <40%) adherers. Typically, about 50% of patients discontinue their antihypertensive therapy after 1 year. At 10 years a persistence rate of 39% has been reported.

Adherence is a dynamic process, varying over time and influenced by a variety of factors. These include those related to the patient, physician, the condition, and the therapy, together with the impact of the health system and socioeconomic factors.

**Patient-related factors**

These include variable understanding or awareness of the long-term consequences of hypertension and the importance of optimal blood pressure control in reducing cardiovascular risk. This is particularly relevant as hypertension is asymptomatic, and life-long treatment is often necessary. Hypertension may also be perceived as a normal/natural consequence of aging. Physical and cognitive impairment may also significantly impact on adherence.

**Physician-related factors**

These potentially include a lack of awareness of recommended treatment targets. There may therefore be failure to modify therapy to achieve appropriate blood pressure goals. Regular appointments and follow-up are important, providing the opportunity to reinforce positive hypertension-related educational messages. It is also recognized that physicians often overestimate the success and impact of antihypertensive therapy, when compared with the clinical reality.

**Condition-related factors**

Adherence and persistence are typically low in the treatment of asymptomatic chronic disease, including hypertension. In addition treatment is often life-long and, from the patient’s perspective, there are no immediate consequences of discontinuing therapy.

**Therapy-related factors**

The complexity of the treatment regimen has an important bearing on adherence and therefore efficacy. Adherence decreases proportionally to dose frequency and therapeutic complexity. Adherence has been shown to be higher with angiotensin receptor blockers and lower with diuretics. Intentional nonadherence was more likely in diabetics and patients who reported at least five adverse effects which they attributed to their antihypertensive medications.

**Health system and socioeconomic factors**

These factors impact patients to varying degrees, and include social isolation or deprivation, employment status, lack of access to health care or poor continuity of care, together with adverse environmental/social factors.

**Improving adherence and outcomes with antihypertensive therapy**

Studies have shown that high adherers (adherence >80%) had a significantly lower risk of cardiovascular events when compared with low adherers (adherence <40%). This includes a 22% reduction in stroke incidence in patients with high adherence.

In addition, this association may, at least in part, be related to a “healthy adherer” effect, inasmuch as patients who take their medications regularly are also more likely to adhere to other healthy behaviors, including exercising regularly.

**Improving outcomes**

In terms of improving adherence with antihypertensive therapy, and hence outcomes, there are four important areas which need to be addressed which include:

**The patient**

It is imperative that the patient be involved in treatment decisions at all stages and has a good understanding of the long-term health implications, including the
asymptomatic nature of uncontrolled hypertension, and the adverse consequences of suboptimal blood pressure control.

A patient-centered approach and good communication skills will help identify any potential barriers from the patient’s perspective with regards to adherence and develop a personalized self-management plan. It may also be helpful to involve family or carers, depending on individual circumstances. Patient education can be enhanced using verbal, written, or visual tools.

The health care provider

A variety of strategies ensures the health care provider has an important role in supporting patient adherence. These include good communication and interpersonal skills which help establish trust between the health care provider and patient. This ensures they have a collaborative relationship which will help promote adherence.

Convenient and regular clinic reviews also provide the opportunity to reinforce hypertension-related educational messages.

The health care provider should be alert to identify conditions, eg, depression or cognitive impairment, which may impact on adherence. Treatment regimens may need to be tailored to the patient’s needs and simplified or adapted as necessary.

The treatment

Adherence is closely correlated to dosing schedule, decreasing from 84% for a once-daily dose to 59% for three times a day dosing.11 Ideally a once-daily dosing regimen is preferable, although, as approximately two-thirds of patients will require combination treatment to achieve satisfactory blood pressure control, the option of fixed-dose combinations should be considered in order to promote adherence. There is evidence that initiating treatment with low-dose combination therapy is better tolerated and more efficacious than uptitrating the dose of a single drug.

Therapeutic interventions

The wider health environment will also potentially impact on the patient’s perception and confidence with regard to the management of their hypertension. It is important to supervise treatment and positively reinforce adherence with drug and lifestyle interventions. Involving a family member, carer, nurse, or pharmacist may also be helpful in supporting the patient and improving adherence. In this setting a “multidisciplinary team” approach has the potential to improve outcomes.

Patients should be active participants in their own treatment and encouraged to monitor their blood pressure at home. There is evidence that home monitoring improves treatment adherence and may also motivate patients to adopt healthy lifestyle interventions.12

Conclusion

Managing hypertension successfully presents a variety of challenges, not least due to the condition’s increasing prevalence, ensuring that we need to identify and adopt effective strategies in order to realize the benefits of improving cardiovascular outcomes. These include recognizing the positive impact of long-term adherence with regard to both medical therapy and lifestyle interventions. It is important that the health care provider and patient work in partnership, potentially also including family and carers, to ensure optimal outcomes and quality of life are achieved.

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Will the polypill be the solution?

Michael Marber, MBBS, PhD, FRCP
King's College London BHF Centre of Research Excellence, Cardiovascular School of Medicine and Sciences, The Rayne Institute, St Thomas' Hospital, London, UK

Correspondence: Michael Marber, The Rayne Institute, 4th Floor Lambeth Wing, St Thomas' Hospital, 1 Westminster Bridge Road, London SE1 7EH, UK
E-mail: mike.marber@kcl.ac.uk

Abstract: The polypill is a fixed-dose combination of individual drugs given to reduce the risk of future cardiovascular events. The idea is very attractive, but currently there are several unknowns that make it difficult to implement. These unknowns include the exact constituent drugs, the baseline cardiovascular risk at which treatment becomes acceptable, and the added value of titration of drugs to achieve risk factor targets. The debate regarding the individual and societal benefits of the polypill has been raging for the last 15 years and there are currently several ongoing trials. These may provide clearer future guidance.

Keywords: cardiovascular risk; polypill

Introduction

"Will the polypill be the solution?" Before attempting to answer the question, we need to define the relevant treatment group and the precise contents of the polypill. These are needed to know the baseline cardiovascular risk and therefore the risk:benefit ratio of each drug in the polypill combination. The original idea proposed and modelled by Wald and Law in 2003 was that the pill was for primary prevention and contained six active ingredients.1 The absolute benefit of the polypill was increased by selecting people thought to be at moderate risk based on age greater then 55 years. The original polypill contained a fixed-dose combination (FDC) of statin, three blood pressure-lowering drugs (a thiazide, a β-blocker, and an angiotensin-converting enzyme inhibitor [ACEI]), folic acid (0.8 mg) and aspirin (75 mg).1 At the time this seemed reasonable since the evidence base for using statins, ACEIs, and β-blockers in patients following an acute coronary event was overwhelming; so, the case for secondary prevention was mandated in guidelines. On the other hand, the case for primary prevention was as controversial then as it is now.

The main problem is that the risk associated with a drug is often independent of its absolute benefit. So, whether a component of the polypill is "efficacious" will be determined by the baseline risk of events in the population being treated. A clear example that illustrates this is the use of aspirin against placebo, the subject of three recent large primary prevention trials (ASCEND, ARRIVE, and ASPREE).2 In both covering Editorials and a timely meta-analysis, the conclusions were that the risk of major bleeding with aspirin was higher than the small but definite reduction in cardiovascular events (ischemic stroke and myocardial infarction); with a number needed to harm of 210 and number needed to treat of 265.2,3 This balance in favor of harm occurred despite a moderately high 9.2% average risk of CV events over 10 years in the combined study populations (n=164 225).3 One could therefore argue that if the baseline risk of events was just a bit higher aspirin would be of net benefit and should therefore be included in a polypill. However, baseline risk is largely driven by age and it is also age that drives the bleeding risk of aspirin!4 We can’t therefore assume higher-risk patients will derive a net benefit. For this reason, the hypothesis that as-
pirin could be of net benefit for primary prevention in higher risk populations still needs to be tested prospectively.4

The example of aspirin reveals additional problems for the polypill idea. Once baseline cardiovascular risk exceeds 10% many guidelines, like those in the UK, recommend the use of a statin5 and also the treatment of stage 1 hypertension. So these would have to be mandated as a background therapy. In addition, these recommendations can be very pragmatic, those in the UK being for 20 mg of atorvastatin.5 This reduces the flexibility of the FDC in the polypill and also introduces difficulties for once-daily dosing (statin at night versus diuretic in the morning).

The aspirin illustration above demonstrates how the original proposal by Law and Wald has to be updated by evidence. It would be difficult to argue for the inclusion of aspirin in today’s polypill. Similarly, the supposed benefit of folic acid has not been realised and that of β-blockers questioned. On the other hand, some newer medications that have come off patent merit further study (ezetimibe, for example) as do some old medications based on new evidence (metformin, for example). The constituents of the FDC of the polypill are therefore in a constant state of flux. Furthermore, it is not possible to assume that just because an individual constituent drug has a benefit when compared with placebo that this benefit will endure when added to another active constituent of the polypill. Similarly, the risks associated with the coadministration of drugs maybe higher than the additive risk of each constituent alone (diuretics and ACEIs on renal function, for example). It is therefore necessary to determine the risk:benefit ratio of the actual FDC proposed in the polypill. However, trials of the polypill still need to allow an estimate of the contribution to risk:benefit for each individual component. To achieve this, by necessity, their design is complex often involving serial 2 x 2 factorial randomizations that can cloud data interpretation.5

The debate continues as to whether we should adopt a “fire and forget” or “treatment to target” philosophy in primary prevention. On the basis of SPRINT, there seems to be merit in titrating antihypertensive patients to achieve lower blood pressure targets.7 The same maybe true of LDL-cholesterol in primary prevention. Adopting an agile and personal approach to primary prevention does not sit well with the “one size fits all” polypill approach; despite the latter being less demanding on health care resources.

The title of this Hot Topic poses a simple question; the simple answer is “no,” at least for the moment. The main drawbacks are that we still don’t know the ideal components of the polypill. Furthermore, the very nature of medicine is that it is in a constant state of evolution and the inflexibility of the polypill reduces the room for change in the face of new evidence. The FDC doesn’t offer the flexibility to personalize treatment to individual patient characteristics whether this is baseline cardiovascular risk, side effects, response to treatment and/or achievement of targets. Despite this view, the outcome of a number current polypill trials8 is awaited which may change the balance of the argument.

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Ambulatory blood pressure measurement (ABPM)
Ambulatory blood pressure measurement (ABPM) refers to the measurement of blood pressure at specified intervals, typically over a 24-hour period, during the course of normal daily activities. ABPM is usually recorded with a portable blood pressure monitoring device. ABPM is used in the diagnosis of sustained hypertension, and can detect white-coat hypertension and masked hypertension.

Adrenal vein sampling (AVS)
Adrenal vein sampling (AVS) is a procedure used to collect blood via catheterization from the adrenal veins. AVS is the gold standard for localizing aldosterone-secreting adenomas from bilateral adrenal hyperplasia in patients with primary hyperaldosteronism, and can guide further treatment.

Aldosterone:renin ratio (ARR)
The aldosterone:renin ratio (ARR) is derived from the serum, or plasma concentration of aldosterone, relative to plasma renin activity, or renin concentration. ARR is used to detect primary hyperaldosteronism, the most prevalent cause of secondary hypertension. However, it is a highly variable test due to within-subject variation, differences in sampling protocols, laboratory assays, reporting units, effects of therapeutics, and population characteristics utilized to establish decision thresholds.

Fixed-dose combination (FDC)
A fixed-dose combination (FDC) (also known as a single-pill combination or polypill) is represented by a single medication that combines two or more active ingredients that act on different targets, and can thus produce additive or synergistic effects, as well as improve tolerability by decreasing adverse effects. By reducing pill burden for patients FDCs can increase adherence relative to patients taking therapeutic agents separately. Hypertension represents a setting where FDCs are used most commonly, as many patients require multiple antihypertensive medications to meet blood pressure targets.

Home blood pressure monitoring (HBPM)
Home blood pressure monitoring (HBPM) involves the use a home blood pressure monitoring device and represents a type of self-measured blood pressure useful for the diagnosis of sustained hypertension, white coat hypertension, and masked hypertension.

Masked hypertension
Masked hypertension is hypertension when an individual has normal blood pressure readings at the clinic/doctor’s office, but will experience increases in blood pressure at other times of the day (eg, at work) or in different settings (eg, at home).

Single-pill combination (SPC)
See definition for fixed-dose combination above.

Polypill
See definition for fixed-dose combination above.

White-coat hypertension
White-coat hypertension is the converse scenario to masked hypertension, where an individual experiences an increase in blood pressure specifically in the clinic/doctor’s office, but has otherwise normal blood pressure in other settings (eg, at work or at home).