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Perspectives on improving blood pressure control to reduce the clinical and economic burden of hypertension

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The clinical and economic burden of hypertension is high and continues to increase globally. Uncontrolled hypertension has severe but avoidable long-term consequences, including cardiovascular diseases, which are among the most burdensome and most preventable conditions in Europe. Yet, despite clear guidelines on screening, diagnosis and management of hypertension, a large proportion of patients remain undiagnosed or undertreated. Low adherence and persistence are common, exacerbating the issue of poor blood pressure (BP) control. Although current guidelines provide clear direction, implementation is hampered by barriers at the patient-, physician- and healthcare system levels. Underestimation of the impact of uncontrolled hypertension and limited health literacy lead to low adherence and persistence among patients, treatment inertia among physicians and a lack of decisive healthcare system action. Many options to improve BP control are available or under investigation. Patients would benefit from targeted health education, improved BP measurement, individualized treatment or simplified treatment regimens through single-pill combinations. For physicians, increasing awareness of the burden of hypertension, as well as offering training on monitoring and optimal management and provision of the necessary time to collaboratively engage with patients would be useful. Healthcare systems should establish nationwide strategies for hypertension screening and management. Furthermore, there is an unmet need to implement more comprehensive BP measurements to optimize management. In conclusion, an integrative, patient-focused, multimodal multidisciplinary approach to the management of hypertension by clinicians, payers and policymakers, involving patients, is required to achieve long-term improvements in population health and cost-efficiency for healthcare systems.

Keywords: blood pressure, blood pressure measurement modalities, hypertension, hypertension management barriers, single-pill combinations

Introduction

Hypertension is a chronic disease affecting more than one billion adults globally [1, 2]. The prevalence of hypertension has doubled between 1990 and 2019 [1, 2], and a further increase is expected, due to projected population growth, increases in body weight and ageing of the population, which contribute to hypertension risk. The burden of hypertension on society is correspondingly high, both in terms of life years lost due to cardiovascular and renal disease [3], and costs, which have continued to increase over recent years [4]. Not all regions are equally affected. In low- and

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middle-income countries, mean blood pressure (BP) and prevalence have been rising [5], whereas decreases have been observed in some high-income countries [5], although mean BP and prevalence remain high [6]. Within Europe, there is considerable variation in hypertension prevalence between countries [1, 7–9]. The prevalence is comparatively low across Western and Northern Europe, but high in most countries of Eastern and Southern Europe [1, 9].

Hypertension is regarded as a multifactorial disease, driven by genetic, environmental and lifestyle factors (e.g. unhealthy diets [high salt or calorie intake], smoking, exercise habits, alcohol consumption) [10, 11]. The modifiable risk factors for hypertension (e.g. weight gain/obesity, high salt consumption or a sedentary lifestyle) have a considerable cumulative impact on hypertension risk [10] and should be the target of population and individual strategies to reduce the burden of hypertension [12, 13]. Social factors may also play a role [14–18]. For example, both hypertension and cardiovascular disease are more prevalent in socioeconomically deprived populations. The Marmot reviews both in Europe [19] and in the UK [20, 21] report that social inequalities are important determinants of ill health. They highlight the social gradient in health inequalities, where people of poorer backgrounds non only die sooner but spend more of their lives with disabilities. Health inequalities arise from a complex interaction of many factors that include poor diet and nutrition, unhealthy behaviours, limited access to healthcare resources and poor health literacy. More recently, trauma and post-traumatic stress have been associated with high BP in regions of the world exposed to chronic violence and war [18] and deserve to be considered in the management of hypertension, particularly in migrants and refugees. Genetic and environmental factors lead to BP increase via derangement of neural and humoral mechanisms involved in BP regulation.

Uncontrolled hypertension is associated with a number of long-term consequences, which include coronary heart disease, stroke, heart failure [22], cardiovascular disease and death [23], as well as dementia, functional and structural organ damage or renal disease [24, 25]. In Europe, cardiovascular and renal diseases are among the most burdensome conditions, as well as the most preventable [26]. By reducing BP in patients with hypertension, the risks of major fatal and nonfatal cardiac events are significantly reduced [23, 27–29]; this is also the case for stroke [23, 27–29], diabetic or non-diabetic nephropathy [30] and also cognitive dysfunction [31], as reported by comprehensive systematic reviews, based on large numbers of trials. The beneficial effects of antihypertensive treatment have also been demonstrated in old and very old patients [32] and can be seen regardless of the cardiovascular risk level (primary or secondary prevention) [29], sex, ethnicity and comorbidities, such as diabetes mellitus, dyslipidaemia and advanced nephropathy [23]. Even modest reductions of BP of 5 mmHg have been shown to reduce the risk of major cardiovascular events by as much as 10% [29]. Most available interventions for the screening, treatment and management of hypertension are also associated with economic benefits and their implementation is highly cost-effective [33, 34].

A correct diagnosis of hypertension is the essential first step to appropriate management. Hypertension can be diagnosed if there is a persistent elevation of office or clinic BP, and estimates suggest that more than half of patients with hypertension remain undiagnosed and unaware of their condition [35]. Among those with a diagnosis of hypertension, the majority (>85%) receive treatment, but only approximately a fourth are well-controlled [1]. Available data for Europe are broadly in line with global data; across Europe, approximately one quarter of patients with diagnosed hypertension do not receive treatment, and among those who are treated, control rates are low [36]. Delayed diagnosis of hypertension is common, and hampers timely management [37], which is believed to be a means to minimize the residual risk of cardiovascular and renal events that remains even in patients achieving BP control. In addition, a proportion of patients are misdiagnosed for several different reasons [38, 39].

In diagnosed and treated hypertensive patients, poor treatment adherence and persistence are increasingly considered the most important factor in the lack of appropriate BP control, besides treatment intensification inertia [11]. There is evidence that low adherence and persistence to antihypertensive drugs lead to increased cardiovascular risk and that; conversely, high adherence and treatment persistence are associated with better BP control and lower incidence of hypertension-related cardiovascular and renal events [40–43]. It should be noted that improvements in medical

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inertia are accompanied by a reduction in cardiovascular events, and that medication adherence benefits all patient groups, including elderly and frail populations [32]. A recent publication by the International Society of Hypertension discusses the global rise in hypertension, global disparities and potential solutions [44]. In the present review, we discuss barriers to optimal screening, diagnosis and management of hypertension, as well as possible solutions, at the patient-, physician- and healthcare system level, with a focus on Europe.

Current diagnosis of hypertension

Hypertension can be identified by opportunistic measurement of office BP or via the use of structured screening programmes, but often goes undetected. In structured screening programmes, over 50% of patients were previously unaware that they had hypertension. Current ESC/ESH guidelines specify that every adult should be aware of their BP and that BP should be documented in their medical record. Although precise evidence-based recommendations are not available, BP screening should be undertaken at regular intervals, with the frequency dependent on the BP level. For patients with high-normal BP (130–139/85–89 mmHg) or with masked hypertension (isolated elevation of out-of-office BP) the recommendation is for annual screening. Patients with a normal BP (120–129/80–84 mmHg) and patients with an optimal BP (<120/80 mmHg) should be remeasured at a minimum of every 3 and 5 years, respectively [11]. Most countries in Europe have a universal, primarily public healthcare system where it is possible to have BP measured by a pharmacist or other community-based healthcare professional. However, these BP measurements are not always reimbursed (Table 1 and Table S1) and should not be the basis for starting antihypertensive treatment – a decision to be taken after consultation with a physician. This also applies to BP measured with smartwatches and other electronic devices.

Due to the variability of BP, ESC/ESH guidelines recommend that the diagnosis of hypertension should be based on repeated office BP measurements in almost all patients. The frequency of visits should be inversely related to the severity of hypertension. Out-of-office BP measurements with ambulatory BP monitoring or home BP monitoring are also recommended by ESC/ESH guidelines, to confirm the diagnosis of hypertension, if these measurements are economically and logistically possible [11]. Out-of-office BP measurement is beneficial in detecting white-coat hypertension, a condition in which only office BP is elevated, carrying a greater cardiovascular risk than in normotension but a lower risk than that of in- and out-of-office hypertension. As mentioned above out-of-office measurements can also identify a BP elevation seen only outside the doctor's office (masked hypertension), where the cardiovascular risk is clearly higher than in normotensive individuals [45]. ESC/ESH guidelines also recommend the assessment of nocturnal BP and the dipping status [46], as nocturnal hypertension (defined as mean night-time or asleep BP ≥120 and/or ≥70 mmHg) [11] is a stronger predictor of future cardiovascular events than day-time BP [47]. Nocturnal hypertension is a common cause of masked hypertension [48] and frequent in people with diabetes, obesity, obstructive sleep apnoea, chronic kidney disease, high salt intake or old age [49].

Current management of hypertension

The evaluation of total cardiovascular risk impacts both the threshold for antihypertensive treatment initiation and the intensity of recommended treatment. Currently, recommended treatment thresholds do not differ by underlying disease and are ≥140/90 mmHg for those aged 18–79 years, and ≥160/90 for those aged ≥80 years [11]. The threshold is lowered to ≥130/85 mmHg for patients with a previous cardiovascular event (particularly myocardial infarction). Therapeutic objectives are largely dependent upon cumulative cardiovascular risk profile and age [50]. Office BP targets have been lowered, both in ESC/ESH guidelines (to <130 mmHg in most patients aged <65 years, and to <140 mmHg in older patients) [11] and in ACC/AHA guidelines (to <130 mmHg for virtually all patients) [14]. To enhance predictability, speed and efficiency of BP control, ESC/ESH guidelines recommend that treatment initiation should involve two drugs in a single-pill combination (SPC) – preferably a renin-angiotensin system (RAS) blocker with a diuretic or a calcium channel blocker (CCB) – for the majority of patients [11]. Several SPCs are available and reimbursed in Europe (Table 1). A reduction in the number of pills taken per day increases adherence to and persistence on treatment [51], with favourable effects on BP control [52–61] and, as shown in observational studies [62, 63], a greater degree of cardiovascular

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Table 1. *Healthcare system determinants of hypertension management in examples across Europe.*

Country	Health system	Insurance type (public, private and mixed)	Patient co-payment	Generic substitution	SPC			Home BP devices reimbursed	Pharmacist BP measurement		Nurse prescription
					Available	Reimbursed	First line use in clinical practice		Available	Reimbursed	
Belgium	Universal NHS	Mixed	Yes	Allowed, indicative	Yes	Yes	Yes	No	Yes	Yes	No
Czech Republic	Universal NHS	Public	Yes	Allowed, indicative	Yes	Yes	Yes	No	Yes (partly)	Free of charge	No
France	Universal NHS	Mixed	No	Allowed, indicative	Yes	Yes	Yes (low dose only)	No	Yes	No	Yes
Germany	Universal NHS	Mixed	Yes	Obligatory	Yes	Yes	Yes	Yes	Yes	No	No
Italy	Universal NHS	Public	Yes	Obligatory	Yes	Yes	Yes	No	Yes	No	No
Poland	Universal NHS	Public	No	Allowed, indicative	Yes	Yes	Yes	No	Yes	No	Yes
Spain	Universal NHS	Public	Yes	Obligatory	Yes	Yes	Yes	Yes	Yes	No	Yes
United Kingdom	Universal NHS	Public	Yes	Allowed in special circumstances	Yes, limited	Yes	No[a]	No[b]	Yes	Yes	Yes
Turkey	Universal NHS	Public and private	Percentage co-payment[c]	Not Obligatory	Yes	Yes	Yes	No	Yes	No	No

Note: See Table S1 for the details of other European countries.
Abbreviations: NHS, National Health Service, SPC, single-pill combination.
[a]As per 2019 NICE guidance [69].
[b]The UK NHS has funded a limited number of devices that can be loaned to patients, as a one-time emergency COVID-19 measure.
[c]For some drugs/therapies there are patient co-pay schemes.
Source: Expert knowledge.

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protection compared with the separate administration of the combination components. Thus, healthcare systems across Europe, and globally, should strive to encourage development and facilitate access to SPCs for eligible patients [64]. SPCs are widely recommended by guidelines for the majority of patients with hypertension [11, 14, 64]. Initial therapy with an SPC of an RAS blocker and a CCB or diuretic is currently recommended by the latest European guidelines [11]. Beta blockers should be considered when there is a specific indication for their use. According to the ESC/ESH guidelines, these indications are heart failure, angina, post-MI, atrial fibrillation, higher heart rate values, aortic dissection or in younger women with, or planning, pregnancy [11], although, in clinical practice, blockade of beta-adrenergic receptors is useful or necessary in many other cardiovascular or non-cardiovascular conditions frequently associated with hypertension [65]. Should BP not be controlled by a two-drug SPC, the use of a three-drug SPC, comprising an RAS blocker, a CCB and a diuretic is recommended. Unless contra-indicated, low-dose spironolactone is usually considered the fourth drug of choice in resistant hypertension, which is defined as failure to lower systolic and diastolic office BP values to <140 and/or 90 mmHg, respectively (and 24-h or home BP to <130/80 or 135/85 mmHg), despite confirmed adherence to a thiazide or thiazide-like diuretic, an RAS blocker and a CCB. Alternatives include an additional diuretic, central agents, beta blockers and alpha blockers [11]. Although in the past resistant hypertension has been reported to involve 15% or more of treated hypertensive patients [66, 67], its true prevalence, after consideration of individual circumstances like adherence, lifestyle or morbidity, is likely to be no more than 5% [68]. However, the high prevalence of patients under antihypertensive drug treatment translates into a high absolute number of individuals in whom multiple drug administration does not achieve BP control.

Hypertensive patients rarely exhibit isolated high BP; their cardiovascular risk profile is multifactorial, due to the coexistence of one or more important risk factors, such as an unhealthy lifestyle, diabetes, dyslipidaemia and obesity. Thus, patient management needs to address all potentially modifiable cardiovascular risk factors. Personalized advice on lifestyle changes is therefore always recommended alongside pharmacological treatment of the associated conditions [11].

Barriers to effective hypertension management/reasons for poor control of hypertension

Physician-level barriers

Healthcare professionals tend to underestimate the impact of undetected or undertreated hypertension [70, 71]. This is sometimes due to an inadequate knowledge of the therapeutic goals [71] but several other apparently trivial factors, for example time pressure on physicians [72], with patients finding it difficult to obtain appointments when needed, are also responsible. Despite multiple existing therapeutic options, approximately two thirds of patients diagnosed with hypertension do not reach BP control [1]. This is partially due to therapeutic inertia: Many physicians are satisfied by the initial reduction of BP, even though this is not at target; some patients do not receive treatment at all (e.g. 21.2% in Spain [6]), and some patients are not offered the treatment intensification required [73–77]. Underdosing is also a major problem for antihypertensive drug treatment in the real-life setting; reasons include not only physician inertia but also tolerability concerns by physicians [78]. Failure to adapt therapy to patient age, ethnicity, metabolic profile and comorbidities, as well as appropriate dosing, can be a further barrier to optimal hypertension management [11, 14, 78, 79], with healthcare professionals not always adhering to guidelines [71]. In addition, lack of response to antihypertensive treatment can also be due to comorbidities, such as diabetes, dyslipidaemia, obesity, obstructive sleep apnoea or the metabolic syndrome [80], which make achievement of BP control more difficult. It is now well recognized that more intensive management of BP is needed [6, 11], such as the use of two or more antihypertensive drugs rather than monotherapy, which is still the most common type of antihypertensive treatment in several countries [81]. Use of combination treatment is strongly recommended by the ESH/ESC [11] and other hypertension guidelines [14, 82] for the majority of patients with hypertension.

Patient-level barriers

Low adherence and persistence to antihypertensive medication [83] are generally the main reasons for uncontrolled hypertension in those diagnosed and treated; they are also important driver of the clinical and economic burden of hypertension [43, 83, 84], the latter due to high resource use (e.g. in- and outpatient costs, hospitalizations or emergency department use). Drug cost can also be a

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barrier if patients need multiple drugs. The prevalence of non-adherence is estimated at approximately 50% after 1 year of treatment across different regions globally [66, 67, 85–89] and persistence at 75%–85% after 6–12 months [90–92]. The importance of long-term BP control in the outpatient setting has been recently demonstrated in a large-scale study (9361 randomized participants) of the long-term effects of 5-year intensive antihypertensive treatment, which showed the benefits of long-term BP control on cardiovascular and all-cause mortality and the need for consistent long-term management of hypertension [93].

The close relationship between adherence and the risk of cardiovascular events and mortality, which increases markedly in patients that discontinue antihypertensive treatment, further underscores the importance of adherence [40, 94]. The asymptomatic nature of hypertension, combined with limited health literacy [95, 96] additionally contributes to low adherence and persistence, particularly if treatment leads to side effects [97]. Across Europe, approximately half of people show limited health literacy [96], demonstrated by the general lack of understanding of the impact of hypertension and the importance of its management among patients [71].

Low adherence to and persistence on treatment are common [98], but difficult to measure, especially at the medical practice level [67]. Although a number of methods are available (patient interviews, questionnaires, pill count, prescription refill data, electronic monitoring or drug level tests in serum or urine), they each have limitations [67, 97, 99]. It is equally challenging for healthcare professionals to predict which patients are at high risk of non-adherence. Adherence and persistence are sensitive to patient-specific and general circumstances and may change over time. Older patients, and, in general, patients with previous cardiovascular or renal events, are often more likely to be adherent unless they have cognitive alterations [100]. In contrast, cancer, lung disease, rheumatic diseases or depression shift the priority away from hypertension, making treatment discontinuation and low adherence more likely [101]. Comorbidities often require multiple treatments resulting in a high overall pill burden for patients, which is associated with low adherence and persistence with treatment [61, 102]. Physician–patient interaction is an important element in supporting adherence, detecting non-adherence and finding solutions to improve it; patients who are satisfied with their physician interactions are more likely to exhibit good adherence and persistence [103, 104]. Psychosocial factors, such as altered expression of emotions and tendency to somatize, have also been associated with poor drug adherence, particularly in patients with apparently treatment-resistant hypertension [105], and deserve more attention.

Improving adherence measurements and offering measuring methods available to the doctor at the patient bedside, as well as home-based self-monitoring methods [106], is a research priority not only for hypertension but also for diabetes, dyslipidaemia and obesity, which are also plagued by low adherence.

Healthcare system-level barriers

Most healthcare systems place insufficient emphasis on the systematic screening, diagnosis and management of hypertension. As hypertension is asymptomatic, structured screening programmes, in addition to opportunistic measurement, are required [11]. Nevertheless, no European countries currently have national screening programmes for asymptomatic patients. The global May Measurement Month is the only large-scale screening initiative [107]. At the screening, diagnostic and monitoring level, the definition of hypertension can be an obstacle. In the ESC/ESH guidelines, hypertension is defined as an office BP $\geq$140/90 mmHg [11], which, with few exceptions, are the values above which drug treatment provides cost-effective protection. However, the correlation between BP, stroke, myocardial infarction and other cardiovascular or renal diseases is observed at much lower BP values [108], which justifies BP-lowering recommendations, albeit only lifestyle measures, appropriate in many individuals [109]. The problem is aggravated by the fact that the cut-off BP value at which no pharmacological intervention is needed may vary according to age and associated conditions [11]. Diagnosis and monitoring are also hampered by the challenge of BP measurement. Incorrect use of BP monitors is common, yielding incorrect results [38]. In the ESC/ESH guidelines, home and/or ambulatory measurements are recommended to confirm the diagnosis, as an alternative to repeated office BP measurements obtained at different visits [11]. Availability of out-of-office (and nocturnal) BP measurements may also increase the accuracy of cardiovascular risk quantification [110]. Home BP measurement has

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been reported to be associated with an improved adherence to treatment [111, 112], particularly if combined with telemetric transmission of the BP values [97]. However, large-scale integration of out-of-office BP measurements into clinical practice is complex and varies by country, not least due to limited accessibility, and cost and reimbursement issues (see Table 1).

Some factors involved in low adherence are relatively easy to ascertain. These include pill burden and treatment complexity, which have been shown to be inversely related to adherence to and persistence with antihypertensive medication [41, 58, 61, 102, 113–115]. In particular, SPCs of two or three antihypertensive drugs have been shown to improve adherence and persistence in the general hypertensive population compared with separate administration of the combination components [59, 116], regardless the type of drugs included in the combination. Some healthcare systems are reluctant to grant their reimbursement, and even when they are prescribed, SPC prescriptions may be changed by the pharmacist who fulfils the prescription through the individual drug components, that is as multiple pills. Another easily identifiable factor is drug costs; however, in most European countries, the availability of all drug classes as generics, as well as reimbursement, has reduced the impact of cost on adherence [117, 118]. Most other factors remain undetermined, and some are probably due to multiple reasons that make access to persistent treatment more difficult in some individuals than in others. In a study on the general population of Lombardy, for example persistence to antihypertensive drugs was found to be inversely correlated with population density, with the lowest adherence in metropolitan areas [101]. The importance of the role of a functioning healthcare system has been dramatically documented during the COVID-19 pandemic, which has caused a collapse of the medical facilities for any other disease in 2020/2021, including cardiovascular disease and hypertension [119]. The consequences of this collapse for the treatment of hypertension and BP control have still to be documented, although an increase of BP values has been reported in 2020 compared with those in 2019 [120].

All of the issues discussed above are intricately linked with healthcare system capacity, particularly in primary care. Data from the US and Europe show that the number of healthcare professionals is largely insufficient to implement all measures recommended by guidelines, and equally, guidelines do not take clinician time needed for their implementation (time needed to treat) into account [121].

Solutions

Currently, many different options to improve BP control are available and others are under investigation. Many proposed approaches are multimodal and include individualized treatment, behavioural interventions, SPCs, devices, mobile health apps or online platforms, which recognize the central role of adherence to and persistence with treatment [11, 52–58, 122–128]. New strategies or policies are needed at the patient-, physician- and healthcare system level to overcome barriers and achieve good hypertension management.

Physician-level solutions

An integrative strategy that considers all healthcare professions and offers training and best practice protocols to all is required to implement an effective screening system. Guidance should include comprehensive information on risk factors, including risk factors like body weight or associated comorbidities, as well as social and psychological factors (e.g. post-traumatic syndrome and altered expression of emotions among migrant populations [18] but also in patients with apparently treatment-resistant hypertension [105]). In such a screening programme, there is a role not only for physicians but also pharmacists [129], nurses or carers.

Once a diagnosis is made, physicians face the challenging task of establishing a collaborative relationship, while taking several patient characteristics, needs and circumstances into account. These characteristics range from comorbidities to the level of health literacy, social situation and patient preference.

Clear consensual definitions and guidance, as those provided by the European Society of Hypertension [11], are needed to decrease treatment and treatment intensification inertia at the physician level. In addition, awareness of the burden of uncontrolled hypertension should be increased on both individual and societal levels. Possible solutions could comprise education, feedback, incentives or redesigned processes (e.g. a defined number of physician contacts over a period of time) [74, 75].

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Having determined a suitable management strategy, healthcare professionals need to monitor and support adherence and persistence, as well as intensify treatment if needed, in order to reach recommended BP goals. Among the many available monitoring options outlined earlier [67, 98], the strategy (or combination of strategies) should be chosen that is most feasible under the individual circumstances, which will vary by patient, country and healthcare system. Physicians need to differentiate direct and indirect monitoring of adherence and keep the limitations of each option in mind. For example, chemical adherence testing is most appropriate in patients who do not appear to respond to treatment or treatment intensification [99]. Furthermore, the fact that adherence will vary over time should be considered. Healthcare professionals should be offered training in the correct use of any monitoring programmes or devices. To support adherence in patients, healthcare professionals require additional time to provide education. Among the solutions, SPCs of two or more drugs are a valuable option for early achievement and maintenance of BP control, with improved adherence and persistence, as well as good tolerability.

Patient-level solutions

Health literacy campaigns that target adequate education and avoidable risk factors for hypertension, like weight gain and obesity, high salt consumption and physical inactivity, and encourage dietary patterns rich in potassium, consumption of whole grain foods and plant-based proteins, are most likely to lead to population-wide improvements in hypertension and hypertension risk. In patients with hypertension, supporting health literacy is likely to improve healthcare behaviours [96]. People who understand both the importance of early diagnosis and adequate treatment, the consequences of uncontrolled hypertension and the rationale behind the specific treatment they receive will be more prone to exhibit good adherence and persistence. It is also probable that improving health literacy will encourage patients to invest the time and effort to monitor their condition appropriately and to address lifestyle factors that will support better BP control [130]. Extending health literacy support to specific training in the correct use of home BP measurement devices would provide clinically useful BP data, facilitating optimal management [125]. By allowing patients to measure their BP, home devices may improve treatment adherence and persistence. Making such devices more accessible to patients (access varies by country Table 1) could contribute to better adherence and persistence. Furthermore, access to 24-h BP data can help to identify masked hypertension, early-morning BP surge, reduced nocturnal BP, dipping, nocturnal hypertension or high variations in BP, which are associated with organ damage and poor cardiovascular outcomes [131, 132]. Given the importance of 24-h control, long-acting agents, which offer uniform BP control are an asset [133]. Increased use of SPCs could also be an option to improve 24-h BP control [134]. The better adherence associated with SPCs extends beyond hypertension [52, 116] and has recently been reported for the SPC of two lipid-lowering drugs (ezetimibe and a statin), with the additional finding of a relationship between improved adherence and a reduction of cardiovascular outcomes [135]. Treatment simplification may be especially useful in the case of polypharmacy regimens, for example in the elderly, or those presenting with several comorbid conditions requiring different co-treatments [59, 136]: Adherence has been shown to improve as the number of daily pills is progressively reduced from multiple to a single pill per day [137].

Empowering patients by engaging them in education on self-monitoring and self-management has been shown to improve adherence and overall BP control, with reduced involvement of physicians and nurses [125, 138, 139].

Patients could greatly benefit from individualized treatment. Depending on their age, sex, ethnicity, comorbidities, metabolic profile, previous experience with different drugs and personality aspects, individual treatment targets, lifestyle changes and antihypertensive drugs can be chosen more appropriately [140, 141]. Considerations of psychological and other social issues that can impact adherence [105] are likely to help improve BP control. Biomarkers can also help to optimize individual management [142, 143]. For example, tailored dietary approaches have been successful in patients with overweight/obesity [144].

A good patient–physician relationship, which empowers patients, provides adequate information and offers collaborative communication will facilitate management [98]. The shared-decision process when prescribing new treatments should be the rule, and patients' involvement in finding solutions to their treatment barriers should be reinforced. Because refill frequency can be

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also burdensome, facilitated refill procedures could improve adherence.

It has been shown that the first therapy a patient with hypertension receives has an important impact on adherence and persistence [145, 146], presumably due to adverse events, ease of use and perceived efficacy. Changes in therapeutic regimen have also been found to negatively impact adherence and persistence [145]. It is therefore of particular importance to pay special attention to determining the most suitable treatment choice for each patient when a diagnosis of hypertension is first made.

Healthcare system-level solutions

At the healthcare system level, more profound changes and an integrative approach are required to address the growing issue of hypertension [147]. Effective screening calls for a nationwide strategy led and coordinated by healthcare systems. In terms of management, it is well-recognized that multi-intervention programmes for hypertension treatment are more effective [148, 149] and cost saving [150] compared with an isolated pharmacological strategy. Multimodal interventions are more likely to induce long-term behavioural change in patients and physicians. A patient-centred, multidisciplinary team-based care approach needs to be adopted [11] that embraces new technologies [147]. Many different options beyond isolated pharmacological treatment are available or emerging:

- SPCs are supported by a wealth of clinical data, showing that they can help to achieve BP goals through improved adherence and persistence versus free combinations [41, 52–61, 151]. Improved adherence with SPCs has been shown to reduce cardiovascular event incidence and related hospitalizations [41, 60, 102, 152]. Patients on SPCs (vs. free combinations) are less likely to be prescribed additional hypertension therapies [102]. SPCs are also likely to be cost-effective and reduce healthcare resource use, not least because, in some instances, their cost is equal or even inferior to that of the drugs administered separately [41, 53, 55, 56, 60, 151, 152]. Furthermore, the availability of most SPCs in different doses of the combination components minimizes what in the past was regarded as an inconvenience that is the need to increase or reduce the dose of one drug only. Payers should encourage the development and increased use of SPCs, which requires that industry and payers come to a fair agreement on their price. Similarly, the polypill has shown promise in the integrative management of hypertension [153] and could be a particularly valuable option in low- and middle-income countries. There is a growing body of evidence on the advantages of the polypill, with the recent demonstration that the use of two antihypertensive drugs and a statin in a single tablet is accompanied not only by improved adherence to treatment but also by reduction of cardiovascular outcomes, which is reduced further if a low dose aspirin is also included. Originally limited to patients with a previous cardiovascular event, the protective effect of the polypill has now also been reported in the primary prevention setting [154], considerably expanding its potential use.
- A fundamental requirement for any antihypertensive treatment strategy is to lower BP throughout the between-dose interval, which means that the administered antihypertensive drugs should have a duration of action that is appropriate to the timing of drug administration. Whether it is preferable for the drugs to be taken in the morning or in the evening has been for years a debated issue because of the possibility that the timing of drug administration affects efficacy, indirectly influencing the degree of cardiovascular protection. In a recent randomized trial on a large number of patients, morning and evening dosing of antihypertensive agents did not result in any difference in the risk of cardiovascular events as well as in a variety of side effects [155]. This indirectly supports the recommendations of the European hypertension guidelines to leave the choice to the individual patient, based on his or her convenience [11].
- Besides medications, device-based treatments of hypertension are under investigation [156] and might be considered for national management strategies in the future, once full long-term evaluation has shown both efficacy on cardiovascular outcomes and cost-effectiveness [157], especially for patients with treatment-resistant hypertension. In particular, renal sympathetic denervation is supported by several randomized trials [158].
- Electronic health records, already in use in some countries, will be a key element in any

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integrated management strategy. They not only allow the collation of prescription and comorbidity data but can also be used to integrate information from smart packaging for adherence monitoring or could be linked to home BP measurements.

- E-health and telehealth solutions, which have gained greater importance accelerated due to the COVID-19 pandemic [159], can play an important role. Many studies of such interventions in different settings and populations are available and have been synthesized in systematic reviews and meta-analyses [124, 126–128, 159]. Interventions can range from something as simple as text message reminders [127] to telemonitoring [128] and wearable devices [160, 161] or ingestible sensors [124] and could be valuable for the recording of nocturnal BP. Mobile health, based on smartphone applications, has also found to improve some clinical outcomes [162] and may be an asset in an integrated strategy for hypertension management. For efficient deployment of these tactics, the training aspect must not be overlooked.

Health systems will need to support the development and validation of new protocols and pathways that include a range of strategies. Further research into their efficacy, effectiveness, feasibility and cost-effectiveness will be essential. The appropriate care pathways will have to be tailored to the population needs and the available budgets. Although low- and middle-income countries may need to design their care pathways differently, it may be possible for them to leverage some of the experience of high-income countries. A more precise quantification of the time that a physician can devote to a single patient in the context of their overall workload will be critical to any healthcare system-based improvement. Recently, attention has been drawn to the fact that the workload of general practitioners is close to saturation and that this is possibly the most important barrier to effective hypertension control and cardiovascular prevention in general [163]. Healthcare systems should not cope with this problem by issuing guidelines that rarefy the number of medical visits for cardiovascular prevention, as reasonably frequent visits are required to establish a good doctor–patient relationship, which is fundamental to achieve good adherence to treatment. The solution is to adjust the number of doctors up to their correctly calculated workload, which should include longer visits than at present. Another solution may also be to involve nurses more in cardiovascular preventive medicine, with tasks that go beyond BP measurements and involve instrumental examinations, explanations and delivery of both nonpharmacological and pharmacological treatment. Countries where this is common practice show that nurse involvement improves the healthcare quality [164].

Other blood pressure measurement modalities

There is evidence that patients on treatment with anti-hypertensive medications still have a considerable residual risk of the cardiovascular and renal events associated with BP, despite achieving target office BP values set by clinical guidelines, intended to maximize protection [165]. Several studies have shown that 24-h mean and home BP may be more sensitive prognostic markers than office BP, their addition to office BP leading to a considerable, albeit not marked improvement in the quantification of cardiovascular risk [110, 166]. Short BP phenomena (morning BP peaks, BP variability and morning BP surge) have been shown to adversely affect the incidence of cardiovascular outcomes independent of 24-h mean BP values. Night-time BP has been identified as a more important predictor of cardiovascular events and mortality than daytime BP, and several studies have shown that an attenuation of the physiological nocturnal BP fall (non-dipping) [167–169], a nocturnal BP rise (reverse dipping) [170, 171] or even an isolated nocturnal hypertension [172, 173] are more common than previously thought. However, these notions cannot be translated into management recommendations because no randomized clinical trial has been carried out to demonstrate additional cardiovascular benefits of focusing treatment on the correction of a raised nocturnal BP, an excessive BP variability or a marked BP increase at arousal. Lack of evidence extends to whether guiding treatment by 24-h and/or home BP increases protection against cardiovascular outcomes compared to treatment strategies based on office BP alone. Collecting evidence on these issues should be a priority for current and future medical research. Research will not be easy because BP phenotypes identified by ambulatory BP monitoring have a poor reproducibility, which means that their identification will require repeated out-of-office BP monitoring.

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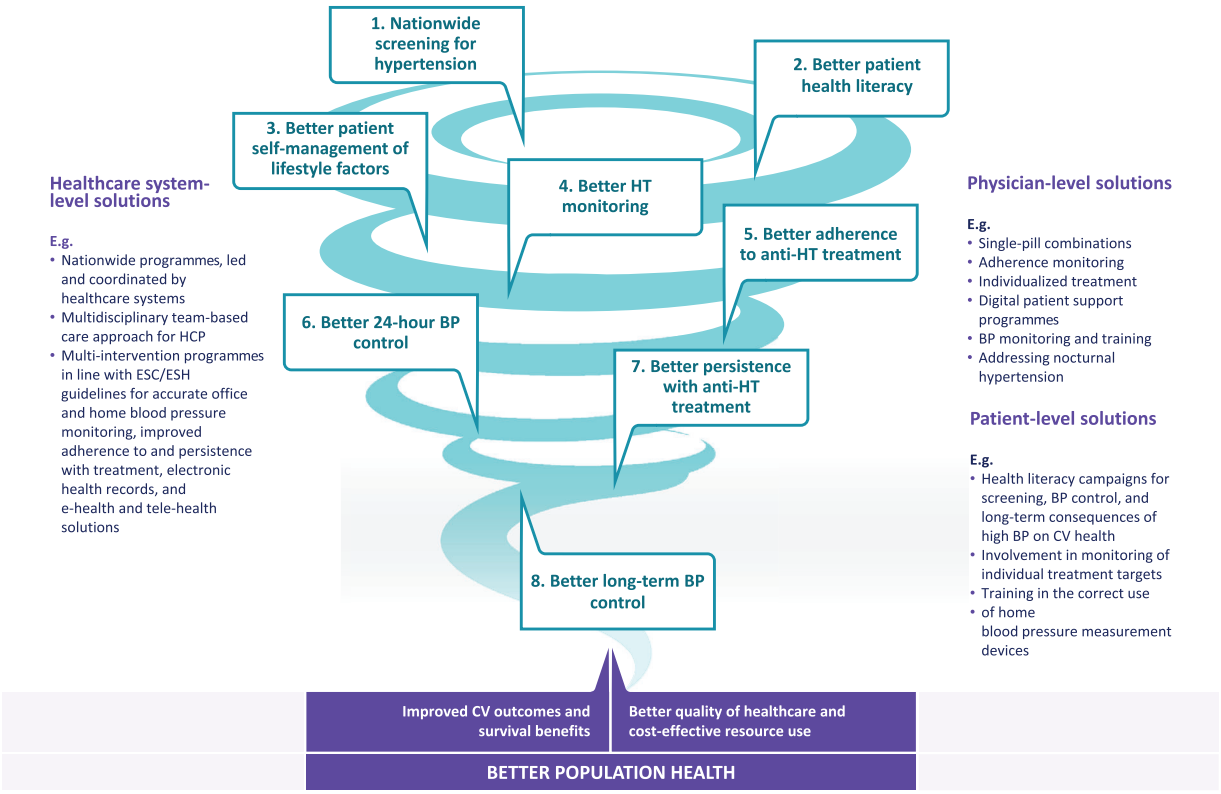

Fig. 1 *Virtuous spiral of hypertension screening and management: areas of improvements. BP, blood pressure; CV, cardiovascular; ESC, European Society of Cardiology; ESH, European Society of Hypertension; HCP, healthcare professional; HT, hypertension.*

The most advanced documentation on markers of treatment-related reduction of cardiovascular risk that may usefully complement mean BP reduction is those reflecting the consistency of BP control between visits and the conceptually related measure of visit-to-visit BP variability in patients on antihypertensive treatment. Evidence from post hoc analyses of trials has shown that treatment-related outcomes decrease progressively as the number of visits in which BP targets are achieved is reduced and that this is the case also when adjustment is made for the mean BP values during the treatment period [174–176]. Studies in hypertension and other clinical conditions have shown an independent relationship between the magnitude of visit-to-visit BP variations and cardiovascular outcomes or mortality [177, 178]. Recent evidence shows that combined use of on-treatment mean BP and visit-to-visit variability quantifies the benefit of treatment more accurately compared with the use of either BP marker alone [179]. This emphasizes the importance of regularly being at the recommended target BP for patients' protection, a concept now referred to as on-treatment 'time to target' and also quantified as the overall BP load [180]. Consistency of BP control is a highly desirable goal to achieve, because, at present, the number of patients with regular BP control visit after visit is less than one third of that of patients exhibiting control at any given visit [181].

Call to action

Hypertension is a key risk factor for cardiovascular disease and a neglected condition, associated with burdensome long-term consequences on patient health and costs. This impact is often underestimated by patients, physicians and healthcare systems.

Given that hypertension is the main driver of cardiovascular events [1, 29], clinicians, payers and policymakers need to adopt an integrative, patient-focused, multimodal and multidisciplinary

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approach to the management of hypertension, in order to realize and maintain long-term patient health improvements and cost-effectiveness of healthcare systems across Europe and globally (Fig. 1). Strategies need to be adapted to local circumstances. Besides the management of high BP, population-wide initiatives are required to prevent or delay hypertension onset. However, few such nationwide initiatives exist [182]. Hence, there is an urgent call for concerted action on avoidable risk factors and to increase patient understanding of adapted health behaviour in everyday life. Comprehensive approaches may also help to limit the residual cardiovascular risk in patients whose hypertension is well controlled. Finally, research suggests that other ways of measuring BP, like nocturnal measurements or measurements that provide information on short- and long-term variability, might improve measures of treatment-related protection, given the current lack of evidence around optimal management.

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