Diagnosis and management of hypertension in primary care

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Abstract

Raised blood pressure (BP) or hypertension is a major preventable cause of cardiovascular disease (CVD) and all-cause death. Among adults, the overall prevalence is around 30-45%, but hypertension becomes progressively more common with increasing age, up to a prevalence of more than 60% in people of 60 years and older. Moreover, it is well established that lowering BP can substantially reduce premature morbidity and mortality. However, BP control rates are often inadequate. Only about 40% of patients with hypertension are treated, and of these only about 35% achieve BP to a target of less than 140/90 mmHg.

This document aims to guide general practitioners (GPs) and other primary care physicians on how to manage vascular disease in hypertensive patients in primary care, including how to deal with challenges faced in clinical practice. The document considers discrepancies between international guidelines in definitions of hypertension and recommendations on when to start treatment. The European Primary Care Cardiovascular Society (EPCCS) supports the hypertension categories defined in the 2018 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines. Recent evidence that has influenced the guidelines is briefly discussed. Current recommendations on how to monitor BP and diagnose hypertension, and management options, both lifestyle modifications and pharmacotherapeutic options are provided.

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Introduction

In 2015, an estimate suggested a global prevalence of hypertension of 1.13 billion, with over 150 million cases in central and Eastern Europe (1). Among adults, the overall prevalence is around 30-45%, but hypertension becomes progressively more common with increasing age, up to a prevalence of >60% in people of 60 years and older. The high prevalence of hypertension is consistent across the world, irrespective of income status (2). According to the new American definition of hypertension (3), nearly half of US adults now have hypertension, as opposed to 1 in 3 based on the previous definition.

A huge and longstanding evidence-base shows that hypertension is a major preventable cause of cardiovascular disease (CVD) and all-cause death. Moreover, it is well established that lowering blood pressure (BP) can substantially reduce premature morbidity and mortality (4). However, BP control rates are often inadequate worldwide. Only about 40% of patients with hypertension are treated, and of these only about 35% achieve BP <140/90 mmHg (2).

Over the past decade, treatment targets have fluctuated, and methods of measuring and monitoring BP have evolved. More recently, hypertension recommendations have changed due to the publication of two new major international guidelines, which differ in their perspectives on how to define hypertension. While this EPCCS document largely follows the 2018 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) Guidelines for the management of arterial hypertension (4), it will also touch upon the major differences with the 2017 American ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (hereafter referred to as 2017 ACC/AHA Guidelines, (3)).

Before publication of the 2017 ACC/AHA Guidelines, most guidelines, including those from Europe (5), Canada (6), Great Britain (7) and Japan (8), and the previous edition of the ACC/AHA guidelines defined hypertension as systolic BP (SBP) >140 mmHg and diastolic BP (DBP) >90 mmHg as measured in the office. Alternatively, a threshold for hypertension of SBP/DBP >135/85 mmHg was used for home or ambulatory BP monitoring (HBPM or ABPM), taking into account that BP is generally slightly lower at home as compared to a clinic setting. Most guidelines distinguished several categories of BP, as shown in table 1 (example taken from 2013 and 2018 ESH/ESC guidelines (4, 5)). The 2017 ACC/AHA Guidelines have now shifted the definition of stage 1 hypertension down to SBP 130-139 mmHg or DBP 80-89 mmHg (3), levels still considered normal, albeit high normal, according to European and other international standards. The EPCCS considers the US lower diagnostic thresholds and targets premature and we support the hypertension categories defined in the 2018 ESH/ESC guidelines and table 1.

Table 1 | Blood pressure categories used in this guidance document (based on reference (4))

	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120-129	and/or	80-84
High normal	130-139	and/or	85-89
Grade 1 hypertension	140-159	and/or	90-99
Grade 2 hypertension	160-179	and/or	100-109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

This document aims to guide general practitioners (GPs) and other primary care physicians on how to manage vascular disease in hypertensive patients in primary care. This document is based on the summary evidence on how to manage hypertension and the associated vascular risk, presented during the 2018 European Primary Care Cardiovascular Society (EPCCS) Annual CV Summit, and the discussion thereafter among primary care physicians from across Europe. It provides a brief scientific background and practical guidance, focussing on challenges faced in clinical reality.

Multiple CVD risk and risk assessment

Though this guidance document focuses on management of hypertension and the associated CV risk, it is important to stress that for most patients a comprehensive risk factor management approach, or modifying all elevated risk factors simultaneously, is needed to help lower risk of a CVD event. Dyslipidaemia, hyperglycaemia (EPCCS

Guidance documents for primary care on these conditions are available on IPCCS.org) and high BP all contribute to CV risk, and national and international (9) guidelines consider the management options for all of these domains at once.

When should high blood pressure be treated?

The different SBP thresholds to define hypertension raise the question why the condition should be defined in the first place. Epidemiology has provided evidence that indicates that as SBP increases, risk of stroke or other CVD becomes greater (10), with a consistent relationship between SBP 120 and SBP 180 mmHg. Based on the log-linear relationship between usual SBP and CV risk, it could be argued that putting any threshold on the SBP spectrum is arbitrary, since there is no SBP at which risk suddenly appears. The absolute risk varies with SBP; estimates state that for every either increase or decrease in SBP of about 10 mmHg, the risk of stroke changes in the same direction by about 35% and risk of coronary heart disease (CHD) by about 20% (10-12).
Thus, thresholds for treatment may be based on the continuous risk associated with different BP levels, but they may also be guided by the level at which treatment becomes beneficial. The latter is particularly relevant in primary prevention. A meta-analysis of largely primary prevention studies established a lack of evidence of effect for treatment thresholds below SBP 140 mmHg (13). The ESH/ESC Task force chose the BP level at which drug treatment has been shown to be effective to improve outcomes, while the American ACC/AHA guideline writing committee chose the level at which lifestyle intervention pays off.

Take home messages

In Europe, hypertension is defined as SBP ≥140 mmHg and DBP ≥90 mmHg.

Risk of stroke and other CVD becomes greater with increasing SBP.

Diagnosis of hypertension

In previous ESH/ESC guidelines, screening and diagnosis was predominantly based on office BP, measured at least twice and on at least two visits. Since 2013, out-of-office BP measurement has also been recommended, to confirm diagnosis or identify the type of hypertension, detect hypotensive episodes and to maximise prediction of CV risk (5). Importantly, white coat hypertension can only be identified if out-of-office BP is measured. In the 2018 ESH/ESC guidelines (4), while diagnosis remained primarily based on office BP, recommendations included a wider use of out-of-office BP measurement, performed with ABPM or HBPM to confirm the diagnosis, detect white coat or masked hypertension and monitor BP control.

Challenges in accurate BP measurement

This change in emphasis for out-of-office measurement originated from the realisation that routine BP measurement is often flawed. BP varies throughout the day and between seasons (14). This seasonality is not taken into account; no season-specific targets are used, and no adjustments to medication are currently recommended in different seasons although this is standard practice in some Southern European countries. Many other factors also affect BP measurement (15): for instance, talking can increase SBP by 17 mmHg and DBP by 6 mmHg. Exposure to acute cold can induce increases of about 11 and 8 mmHg, respectively. Acute ingestion of alcohol can result in 8 and 7 mmHg higher SBP and DBP, respectively, which lasts about 3 hours.

Using the wrong cuff size has a similar magnitude of effect, and other suboptimal techniques affect the BP read-out to a lesser extent. An expectation bias of the measurer has also been documented; such that BP values are rounded to the nearest 5 or 10 mmHg value (15). Many physicians are nowadays aware that BP is lower when a nurse measures it, as opposed to a doctor. While this difference has been described to be 7 mmHg on average (16), there is no recommendation to use a different BP target depending on who performs the measurement.

BP measurement methods vary substantially in clinical practice. A “mystery shopper” study in the United Kingdom (UK) assessed BP measurement in practice, via an online survey among UK patient groups (17). The data showed that if the initial BP is within normal ranges, the GP leaves it at that and records it in the health record. When the initial reading is higher, more measurements are done and the BP tends to come down with subsequent readings (17). This may suggest that It is probable that the last or lowest reading is recorded thus meaning that routinely collected BP data that are used for

development of risk calculators are systematically biased. This could explain why BP does not come out as a strong risk factor.

White coat and masked hypertension

White coat hypertension is diagnosed when BP is normal on ABPM or HBPM but high on clinic measurements. CV risk of individuals with white coat hypertension is similar to but slightly higher than that of those with normotension. This is because those with white coat hypertension may have between 5 and 10 mmHg higher out-of-office SBP than a normotensive population. While individuals with white coat hypertension may still be in the normal range for ABPM/HBPM at diagnosis, they should be followed up, because their higher absolute BP means they are more likely to develop hypertension over time (18). When a person with previously diagnosed white coat hypertension goes on to develop hypertension, it is important to treat them based on home readings. Treating them based on the higher office readings may lead to adverse effects such as dizziness from treating too aggressively.

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 normotension (19). However, so far there is no trial evidence to support treatment.

How should hypertension be diagnosed?

In addition to clinical measurement errors, another challenge is that patients may not see their GP regularly. This can cause a delay in initiation of treatment. Out-of-office BP measurement, by ABPM or HBPM, may give better information, and sooner. In ABPM, a balance needs to be found between burden for the patient and obtaining useful information; for instance half-hourly measurement during the day and hourly overnight. The 2018 ESH/ESC guidelines define HBP as the average of all BP readings performed with a semiautomatic, validated BP monitor, for at lease 3 days but preferably for 6-7 days before each clinic visit, with readings in the morning and the evening, taken in a quiet room after 5 minutes of rest, with the patient seated with their back and arm supported. Two measurements should be taken at each measurement session, performed 1-2 minutes apart (4). ABPM offers additional information over HBPM, for instance night vs. daytime BP and it correlates best with long-term outcomes such as end-organ damage, as compared with other methods. ABPM also allows identification of white coat hypertension and masked hypertension. Table 2 summarises how hypertension is defined, depending on whether it was measured in the office, or with ABPM or HBPM.

High 24-hour ABP variability is associated with poor CV outcomes (20). The 'smoothness index' as a measure for 24-hour BP variability may be relevant in the assessment of treatment efficacy (20, 21), but there is no consensus on how to measure or manage this.

Table 2 | Definitions of hypertension according to measurement method (based on reference (4))

	Systolic (mmHg)		Diastolic (mmHg)
Office BP	≥140	and/or	≥90
Ambulatory BP			
Daytime (or awake) mean	≥135	and/or	≥85
Night-time (or asleep)mean	≥120	and/or	≥70
24-hour mean	≥130	and/or	≥80
Home BP mean	≥135	and/or	≥85

Indeed, 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 lead to more appropriate targeting of treatment (19). A modelling study assessed 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. This study found that ABPM as a diagnostic strategy for hypertension was the most cost-effective strategy in men and women of all ages. Savings from better-targeted therapy counterbalanced additional costs associated with ABPM (22). This work has been recently updated by the 2019 NICE hypertension guidelines (National Institute for Health and Care Excellence, UK, see https://www.nice.org.uk/guidance/ng136).

Take home messages

Out-of-office BP measurement is recommended for diagnosis and on-going management of hypertension. Out-of-office BP is often lower than clinic BP.

BP measurement method and who measures BP affects the BP value recorded.

ABPM is becoming the gold standard for diagnosis. It is necessary to detect white coat and masked hypertension.

Repeated HBPM is a good alternative to ABPM, because it is simpler and much cheaper, but it cannot supply data on diurnal BP variation.

Recent evidence that has influenced the guidelines

Several important large BP-lowering trials have been published in recent years, which have influenced international guidelines. We briefly summarise the trial design and outcomes of some of these trials, considering how they have impacted clinical practice and recent guidelines.

SPRINT

The Systolic Blood Pressure Intervention Trial (SPRINT) (23) compared two SBP treatment targets, to assess their appropriateness to reduce CV morbidity and mortality. SPRINT included adults of at least 50 years old, with SBP between 130 and 180 mmHg, on a maximum of three antihypertensive medications and who were at increased CVD risk (clinical or subclinical CVD, CKD (chronic kidney disease, eGFR between 20 and 60 ml/min), 10-years CVD risk ≥15% or age ≥75 years). Patients with diabetes or prior stroke were excluded.

Almost 10,000 patients were randomized to either standard or intensive BP-lowering treatment, which were treatment targets of <140 mmHg or <120 mmHg, respectively. Importantly, if BP was too low in the standard treatment group (if SBP <130 mmHg or <135 mmHg twice), medication was down-titrated (reduced) to stay closer to the target of <140 mmHg. The primary outcome was a composite of myocardial infarction (MI), acute coronary syndrome, stroke, acute heart failure (HF) or death from CV causes (23). Recruitment was planned for two years, with a maximum of six years of follow-up.

SPRINT, however, was stopped prematurely after a median follow-up of 3.26 years, due to a significantly lower rate of the primary outcome in the intensive-treatment group than in the standard-treatment group (1.65% vs. 2.19% per year; HR: 0.75, 95%CI: 0.64-0.89, P<0.001). The intensive-treatment group also showed lower all-cause mortality (HR: 0.73, 95%CI: 0.60-0.90, P=0.003). The event curves for the primary outcomes separated after about one year, and for all-cause mortality after about two years. In subgroup analysis of participants 75 years or older, results were very similar but relatively few people over 80 were included.

The results hinted at more benefit for frail patients although overall levels of frailty were lower than in daily practice. The intensively treated group, however, also showed significantly higher rates of some serious adverse events, such as hypotension (2.4% vs. 1.4%), syncope (2.3% vs. 1.7%), electrolyte abnormalities (3.1% vs. 2.3%) and acute kidney injury or acute renal failure (4.1% vs. 2.5%)(23). Thus, SPRINT yielded a mortality benefit and a positive effect on the primary outcome, at the cost of more adverse events.

Debating SPRINT

The method of BP measurement in SPRINT has, however, been a topic of debate. They used automated clinic BP measurement. This was not mentioned in the initial paper that reported the main results (23). Three readings at 1-minute intervals were done, which were mostly unattended, after the patient had been left alone for five minutes. The mean of three readings was used. On average, a 9 mmHg drop was seen over the three readings. A later publication revealed that the measurement scenario varied between trial sites, with some sites leaving the participant alone during the entire measurement, while others never leaving them alone, or only during rest or during the BP measurement (24). The effect of intensive vs. standard treatment on the primary outcome was compared between measurement scenarios. The SPRINT researchers concluded that similar BP levels and CVD risk reduction were observed in participants in whom measurement took place primarily attended and unattended (24). However, other researchers tested the unattended BP compared to standard BP estimation and concluded that the difference between BP measurement in clinic using an automated device and the unattended SPRINT method was around 10/4mmHg, suggesting that the comparison in SPRINT was more like targets of 130 vs 150mmHg (25).

A common critique on the SPRINT BP measurement method by guideline groups, in editorials and on congress stages has therefore been that the treatment targets from SPRINT cannot be directly extrapolated to daily clinical practice.

The impressive reduction in the secondary outcome of HF (0.41% vs. 0.67% per year, HR: 0.62, 95%CI: 0.45-0.84, P=0.002) in the intensively treated group has also been questioned (Debate on SPRINT during ESC 2016 (26)). The observed difference may have been the consequence of up-titration and down-titration of diuretics in the intensively treated and control groups, respectively. In the latter group, diuretics were frequently discontinued, to keep SBP around the target of 140 mmHg. This may have unmasked the endpoint in participants at high risk of HF. In the intensively treated group, on the other hand, diuretics may have masked this endpoint.

ACCORD

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) blood pressure trial (ACCORD BP) (27) set-up resembled that of SPRINT, but was conducted in patients with type 2 diabetes (T2DM) at high risk for CV events (n=4733). Patients were randomly assigned to intensive therapy, targeting SBP <120 mmHg or standard therapy with a target of SBP < 140 mmHg. The primary outcome of ACCORD BP was a composite of nonfatal MI, nonfatal stroke or death from CV causes.

After a mean follow-up of 4.7 years, no significant difference in the occurrence of the primary outcome was seen between the two treatment regimens (1.87% per year with intensive therapy vs. 2.09% per year with standard therapy, HR: 0.88, 95%CI: 0.73-1.06, P=0.20). Secondary outcomes that did show a significant reduction with intensive treatment were any stroke (0.32% vs. 0.53% per year, HR: 0.59, 95%CI: 0.39-0.89, P=0.01) and nonfatal stroke (0.30% vs. 0.47% per year, HR: 0.63, 95%CI: 0.41-0.96, P=0.03). The intensively treated group showed a higher rate of serious adverse events that were attributed to BP medication (3.3% vs. 1.27%), such as hypotension (0.7% vs. 0.04%), bradycardia or arrhythmia (0.5% vs. 0.13%) and hyperkalaemia (0.4% vs. 0.04%) (27).

The SPS3 trial

Previous trials have shown that BP lowering has the largest effect on stroke. Optimal target levels to prevent recurrent stroke are, however, unknown. The Secondary Prevention of Small Subcortical Strokes (SPS3) trial therefore compared the effect of different BP targets on the rate of recurrent stroke in patients with recent, symptomatic, MRI-confirmed lacunar stroke. Eligible patients were at least 30 years of age and were normotensive or hypertensive. They did not have carotid artery stenosis, disabling stroke, haemorrhage or cortical stroke. 3,020 Participants were randomised to SBP target of 130-149 mmHg vs. SBP <130 mmHg. Forced up-titration and down-titration was used to achieve targets in both groups.

The primary outcome of all stroke (including ischaemic strokes and intracranial haemorrhages) did not show a significant reduction at the lower SBP target (2.77% per patient-year vs. 2.25% per patient-year, HR: 0.81, 95%CI: 0.64-1.09, P=0.08). The lack of statistical significance may have been a power issue, with a sample size much smaller than SPRINT. No difference was seen between groups with regard to all deaths (1.74% vs 1.80% per patient-year, HR: 1.03, 95%CI: 0.79-1.35, P=0.82). No significant differences were seen in adverse outcomes, which may for some outcomes also reflect a lack of sufficient power.

HOPE-3

The Heart Outcomes Prevention Evaluation (HOPE)–3 trial looked at people at intermediate risk without CVD who did not receive antihypertensive treatment (28). The HOPE-3 trial studied the effect of both BP-lowering therapy with a fixed-dose combination of an angiotensin-receptor blocker (ARB) and a thiazide diuretic, of cholesterol-lowering therapy with a statin, and the combination of both therapies, in a 2-by-2 factorial design (28). This was essentially a ‘polypill’ study. Here we discuss the results of the BP-lowering intervention only. Nearly 13,000 persons were included; men aged ≥55 years and women ≥65 years, who had at least one of the following risk factors: raised waist-hip ratio, low HDL-c, smoker, dysglycaemia, family history of premature CVD or mild renal dysfunction. Women ≥60 years with at least two such risk factors could also be included.

No strict BP or lipid levels were mandated for entry in the study. Participants had no clear indication for antihypertensive therapy or statins. The co-primary endpoints were a composite of death from CV causes, nonfatal MI or nonfatal stroke, and this composite included resuscitated cardiac arrest, HF and revascularization as well. Median follow-up was 5.6 years.

On average, people were about 65 years old. Mean BP at baseline was 138.1/81.9 mmHg and the active treatment group achieved a 6.0/3.0 mmHg greater decrease than the placebo group. No statistically significant difference was seen between treatment groups in the first co-primary endpoint (4.1% vs. 4.4%, HR: 0.93, 95%CI: 0.79-1.10, P=0.40), nor in the second co-primary endpoint (4.9% vs. 5.2%, HR: 0.95, 95%CI: 0.81-1.11, P=0.51). A pre-specified analysis demonstrated a significant trend (P for trend= 0.02) for the co-primary endpoints across BP categories of participants with SBP ≤131.5 mmHg, 131.5-143.5 mmHg and >143.5 mmHg. Participants in the highest SBP category did show a significant reduction of the first co-primary endpoint (4.8% vs. 6.5%, HR: 0.73, 0.56-0.94)(28). However, this is unsurprising, given this group had a mean SBP of 154.1 mmHg, thus they should have already been treated with antihypertensive treatment.

Conclusions based on these recent BP-lowering trials

A meta-analysis combined all these data and compared three groups based on SBP: <140 mmHg, 140-159 mmHg and >160 mmHg, across a wide range of CV outcomes. The meta-analysis did not show evidence of a statistically significant benefit of primary preventive treatment to reach SBP below 140 mmHg on all-cause mortality, CV mortality, major CV events, CHD and stroke. Only in those with SBP >140 mmHg, was primary preventive BP-lowering treatment associated with reduced risk for death and CVD (13).

When comparing results of the above studies, it should be noted that SPRINT tested a lower BP target, but about 90% of participants were already on antihypertensive therapy. Thus, the baseline BP was not a true baseline BP. A consistent benefit of the lower treatment target was seen across subgroups, possibly with more benefit in older and frail individuals. When interpreting SPRINT data, however, it should be remembered that the unattended, automated BP measurement likely yielded lower BP values (10/4 mmHg) than commonly obtained in clinical practice.

Somewhat surprisingly, ACCORD and SPS3 showed different results, possibly because they were underpowered, as point estimates were consistent. In HOPE-3, about 80% were not treated for hypertension at baseline, thus in this study there was a true baseline BP. The benefit of treatment was indeed directly related to baseline BP and therapy was only associated with a lower risk of death and CVD if baseline SBP was >140 mmHg. The HOPE-3 results suggested that treatment of normotensive individuals at intermediate risk is not helpful. The meta-analysis does not support treatment of those with SBP <140/90 mmHg for primary prevention.

Additional relevant studies include a longitudinal cohort study that provided evidence on the effect of treatment in persons with mild hypertension (grade I) and low risk of mortality and CVD. During a median follow-up of 5.8 years, those prescribed antihypertensive treatment did not show lower mortality and CVD rates compared to those not prescribed therapy, while treatment was associated with a higher risk of adverse events, including hypotension, syncope, electrolyte abnormalities and acute kidney injury (29). Another meta-analysis assessed whether frailty affects the association between BP and clinical outcomes in older adults of 65 years and older. Based on data of nine observational studies, it was concluded that in people with frailty, SBP <140 mmHg was not associated with lower mortality as compared with SBP >140 mmHg. In the absence of frailty, a mortality benefit of SBP <140 mmHg was observed in these studies (30). These studies are, however, limited by their observational nature, which is inevitable considering the difficulties of conducting trials in these areas.

Take home messages

In SPRINT, intensively treating patients to SBP <120 mmHg (vs. <140 mmHg) was associated with a benefit on mortality and CV outcomes, but also with more adverse events. The BP measurement method likely led to lower BP values than obtained in routine care, thus BP values and treatment effects achieved in SPRINT cannot be extrapolated directly to clinical practice.

ACCORD showed no benefit of intensively treating T2DM patients to SBP <120 mmHg on the composite CV outcome, and more adverse events, but less stroke was observed, compared with those targeted to <140 mmHg.

Targeting treatment to <130 mmHg did not reduce the endpoint of all stroke compared with targeting 130-149 mmHg in patients with a recent stroke in the SPS3 trial.

The BP-lowering results of the HOPE-3 trial showed no significant effect of ARB plus a thiazide diuretic on the co-primary CV endpoints compared with placebo, in people at intermediate risk without CVD, without a clear indication for antihypertensive therapy.

Combined, the currently available data suggest that there is no benefit of primary preventive antihypertensive treatment if SBP <140 mmHg. Primary preventive BP-lowering therapy is associated with reduced CV and mortality risk if SBP ≥140 mmHg.

Therapeutic considerations

Both lifestyle interventions and drug treatment are well-established strategies to lower BP. While lifestyle interventions lower BP and in some cases CV risk, most patients with hypertension will also need pharmacotherapy to reach target BP (4). A large and solid evidence base is available on the effect of BP lowering on CV risk: large meta-analyses have shown that a 10 mmHg reduction in SBP or a 5 mmHg reduction in DBP is associated with reductions in all major CV events by about 20% and all-cause mortality by 10-15%, stroke by about 35%, coronary events by about 20% and HF by about 40% (11, 12). These findings are consistent, irrespective of baseline BP within the hypertensive range, CV risk level, comorbidities (e.g. diabetes and CKD), age, sex and ethnicity (11, 13). Recent meta-analyses show relative risk reductions similar to the original meta-analysis of BP-lowering effects on outcomes, published in 1994 (31). That suggests that the now widespread concomitant prescription of lipid-lowering and antiplatelet therapies have not attenuated the benefits of BP-lowering medication (4).

The following treatment recommendations are based on randomised clinical trial (RCT) outcome evidence. It should be noted that outcome RCTs often include a majority of older and high-risk individuals, to increase statistical power. Another limitation is that follow-up duration is relatively short; rarely longer than five years. As a consequence, establishing recommendations for life-long treatment for younger and lower-risk individuals involves extrapolation. Big data applications (based on registries, insurance databases, prolonged observational follow-up of RCTs) will help to fill the gap in the evidence (4).

When to initiate antihypertensive treatment

Debate continues whether BP-lowering treatment should be initiated based on the BP levels or on the level of total CV risk. The latter view is supported by findings that those at the highest risk show the greatest absolute benefit of BP-lowering treatment (32). These patients also have the highest residual risk, implying that treatment fails to fully protect them (12). The ESH/ESC Guideline Task Force therefore viewed this evidence as support for the benefit of earlier treatment of those with BP >140/90 mmHg, when they still have low-moderate risk. This should prevent hypertension-induced organ damage. Moreover, it can prevent the late treatment failure that could occur if treatment initiation is delayed if it were solely risk-based (4). However direct evidence of benefit from this approach is not established.

CV risk assessment, although not primarily used to guide decisions on BP-lowering therapy, is however, important because of the frequent co-existence of multiple CV risk factors in hypertensive individuals. CV risk assessment therefore informs the use of concomitant therapies (lipid-lowering, antithrombotic, antiglycaemic) for CV risk reduction (4). This is also relevant for people with borderline BP level, who are at high CV risk.

Guidelines generally agree that patients with grade 2 or 3 hypertension, as well as those with grade 1 with high CV risk or hypertension-mediated organ damage should receive antihypertensive drug-treatment, in addition to lifestyle intervention. Less consistency is seen on whether patients with grade 1 hypertension with low-moderate risk should be offered BP-lowering medication. Similarly, advice for older (>60 years old) patients with grade 1 hypertension, or patients with high-normal risk has varied. This is a consequence of the fact that these patient groups are rarely included in RCTs. New evidence has become available and will be discussed for each of these patient groups, along with updated management recommendations (based on the latest evidence, as well as the ESH/ESC 2018 guidelines (4), summarised in figure 1).

Patients with high-normal blood pressure

New evidence strengthens the 2013 recommendation not to initiate antihypertensive treatment in persons with high-normal BP and low-moderate CV risk (28). Studies, including SPRINT (23), that did show reduction of major CV outcomes upon lowering 'baseline BP' in the high-normal range, determined 'baseline BP' on a background of antihypertensive treatment. The HOPE-3 trial (28), on the other hand, included a vast majority of patients who did not get antihypertensive treatment. In these patients with baseline SBP in the high-normal range, BP lowering did not give benefit on risk of major CV events (28).

Meta-analyses concluded that BP-lowering treatment was not effective at reducing CV risk if baseline SBP was already <140 mmHg (normal and high-normal) (13, 33). Primary preventive BP lowering was, however, associated with reduced risk for death and incident CVD if baseline SBP was ≥140/90 mmHg (13). Those with high-normal BP and established CVD, thus at very high risk, may

form another exception to the lack of benefit of BP-lowering in this BP range. A meta-analysis of RCTs in this patient group suggested that BP lowering by 4 mmHg reduced the risk of stroke, but not of other CV events (12). Another meta-analysis showed that BP treatment in a group with a mean baseline SBP of 138 mmHg and previous coronary artery disease (CAD), lowered risk of major CV events by 10%, but mortality was unaffected (13).

> EPCCS Recommendation:
Persons with high-normal BP (130-139 systolic) and low-moderate risk should be offered lifestyle advice, to reduce their risk of progression to established hypertension and possibly reduce their CV risk. They should not be offered BP-lowering pharmacotherapy. In patients with high-normal BP and established CVD (especially CAD), thus, at high risk, BP-lowering drug treatment may be considered, in which case monotherapy is likely to be sufficient.

Grade 1 hypertension and low-moderate CV risk

A meta-analysis of BP-lowering effects that was limited to RCTs in patients with grade 1 hypertension and low-moderate risk showed a significant reduction of all major CV events. An SBP reduction of about 7 mmHg was associated with 34% lower combined risk of stroke and CAD, and 19% lower risk of all-cause mortality (33). Another meta-analysis showed a benefit of BP lowering with regard to death and CVD in those with baseline BP ≥140/90 mmHg but not in those with lower BP at baseline (13). As described above, the HOPE-3 data corroborate these insights by showing a 27% reduction in major CV outcomes in patients with baseline SBP values in the grade 1 hypertension range, at intermediate CV risk, when drug treatment lowered SBP by a mean of 6 mmHg (28).

> EPCCS Recommendation:
In patients with grade 1 hypertension (140-149 mmHg systolic) at low-moderate risk, lifestyle advice should be accompanied by BP-lowering drug treatment after 3-6 months, if BP is not controlled by lifestyle interventions alone.

Older patients with grade 1 or 2 hypertension

The definition of 'old' varies between studies and over time. Chronological age is often a poor surrogate for biological age. Frailty and independence should be considered, as they affect the likely tolerability of BP-lowering medication in older people. The ESH/ESC Guidelines define 'old' as ≥65 years and 'very old' as ≥80 years. Notably, the previous guidelines (5) stated that all evidence on effect of BP lowering in older patients was obtained in those with baseline SBP >160 mmHg. Evidence clearly shows that these people should be offered BP-lowering pharmacotherapy (34, 35). The 2018 ESH/ESC Guidelines do not recommend starting primary prevention treatment in those over 80 years old with SBP <160 mmHg. Lifestyle intervention and drug treatment is recommended for those between 65 and 80 years old with grade 1 hypertension provided they are fit (4).

Evidence has been published on older people with SBP below this threshold, but this was often in the presence of background therapy. Thus, their true baseline SBP was probably higher, as described above for SPRINT (23). Other RCTs, including HOPE-3 (28) included older patients with mean SBP below 160 mmHg and without prior antihypertensive treatment, and showed a protective effect of BP-lowering treatment. It should be noted though, that the number of those over 80 years old was very low, given that the overall mean age was 66 (SD: 6) years.

BP-lowering medication should not be withdrawn based on age alone, because this leads to a marked increase in CV risk. A subgroup analysis of the Hypertension in the Very Elderly Trial (HYVET)(36) showed that in patients ≥80 years, CV risk reduction was greatest in those who continued treatment, as compared with those in whom treatment was discontinued (37).

Antihypertensive treatment is generally well-tolerated in older patients, although it should be noted that very few actual frail patients have been included in the studies. Moreover, SPRINT showed a higher rate of side effects in older patients (23). Attention should be paid to concomitant medication, considering drug-drug interactions, and to comorbidities, particularly postural hypotension.
The EPCCS congress in 2019 supported the use of shared decision-making in the very elderly, for whom the benefit of treatment might well be outweighed by the harms. This is particularly the case for the frail elderly.

> **EPCCS Recommendation:**
> *Older patients (>65 years, including persons >80 years) with SBP ≥160 mmHg (grade 2) should be offered BP-lowering treatment. Evidence now also justifies recommendation of BP-lowering treatment for old patients (>65 years but not >80 years) with grade 1 hypertension (SBP: 140-159 mmHg). In very old patients, shared decision-making is important. Initiation with monotherapy may be appropriate. In older patients, combination therapy should be started at the lowest available dose. Monitor possible occurrence of postural BP and hypotensive episodes with ABPM.*

Patients with grade 1 hypertension at high CV risk, or with grade 2 or 3 hypertension

> **EPCCS Recommendation:**
> *In patients with grade 1 hypertension at high risk or with hypertension-induced organ damage, drug treatment should be initiated alongside lifestyle interventions. The same strategy should be followed for patients with grade 2 or grade 3, for whom initial combination therapy may be appropriate.*

Recommendations for the management of different BP-categories and treatment thresholds are summarised in figure 1, along with treatment targets (discussed next). The presence of diabetes, CKD, CAD or stroke/transient ischemic attack (TIA) does not affect the treatment threshold for all age groups considered in the ESH/ESC guidelines and EPCCS supports this.

Therapeutic targets

While the 2013 ESH/ESC Guidelines stated that evidence showed no incremental benefit of lowering BP to <130/80 mmHg, new evidence has become available since then, including the findings of SPRINT (23), which, as described above, compared the effects of targeting SBP <120 mmHg with targeting SBP <140 mmHg. These data provide strong support for the benefit of more vs. less intensive BP-lowering treatment strategies in higher risk patients. They do not, however, reveal the optimal BP target, due to the method of BP measurement used in SPRINT. The newer recommendation in the 2018 ESH/ESC Guidelines that treated BP values should be targeted to 130/80 mmHg in most patients if treatment is well tolerated, is based on indirect evidence.

Two recent meta-analyses provide new insights on SBP and DBP targets for drug treatment. One meta-analysis (38) stratified achieved SBP into three SBP target ranges (149-140, 139-130 and <130 mmHg). It showed lower relative risk of all major CV outcomes (including mortality) at SBP <140 mmHg. Similar benefits were observed at SBP <130 mmHg (mean: 126 mmHg), even when the comparator group was SBP 130-139 mmHg. Analysis of achieved DBP showed lower CV risk at 90-80 or <80 mmHg (38). The other meta-analysis (11) concluded that every 10 mmHg reduction of SBP lowered the risk of CV events and death in patients with baseline SBP ranging from >160 mmHg to 139-130 mmHg. This also implies a benefit at achieved values <130 mmHg. This meta-analysis also showed an advantage of 10 mmHg SBP reduction in persons with baseline SBP <130 mmHg. It is important to note, however, that this group largely consisted of SPRINT patients with the unusually low achieved SBP. As discussed, comparison of effects of achieved BP in SPRINT and in other trials is difficult due to the differences in measurement method. Importantly, the analysis showed a consistent benefit from intensive BP lowering at all levels of risk, including in those with pre-existing CVD, stroke, diabetes and CKD (11).

It is important to note the risk level of the patients in these analyses. Evidence on the benefit of targets below 140 mmHg in low-risk primary prevention populations is scarce (13). In higher and high-risk populations, there is evidence for a benefit of SBP <140 mmHg, but these findings rely heavily on SPRINT data (11).

Nevertheless, the first meta-analysis further revealed that the incremental benefit of BP lowering on events was progressively less with lower SBP targets (38). In addition, permanent treatment discontinuation due to treatment-emergent adverse effects was more common in patients targeted to lower BP values (39). Thus, anticipated benefits of intensive BP lowering need to be balanced against the possible adverse effects, which may offset the limited incremental CV risk reduction at this BP level (4). In light of BP targets, it is noteworthy that less than half of patients treated for hypertension currently achieve a

target office SBP <140 mmHg (2, 40). Thus, there is ample room for improvement in CVD prevention in millions of people worldwide.

> **EPCCS Recommendation:**
> *When initiating BP-lowering medication, the first objective should be to lower BP to <140/90 mmHg in all patients. If treatment is well tolerated, treated BP values may be targeted to 130/80 mmHg or lower in patients who want maximal control. Treated SBP should not be targeted to <120 mmHg.*

Treatment targets in specific patient groups

- Type 2 diabetes mellitus: In those receiving BP-lowering drugs, it is recommended to target office BP to SBP of 130 mmHg, and lower if tolerated. In older (>65 years) patients, the SBP target range should be 130-140 mmHg. SBP should not be lower than <120 mmHg. DBP should be lowered to <80 mmHg. Visit-to-visit BP variability is associated with increased CV and renal risk and reduced CV protection, thus consistency of BP control should be aimed for (Evidence supporting these recommendations is summarised in reference (4)).

- Older patients: In those over 80 years old, treatment should be recommended if SBP >160 mmHg, with a target of 130-140 mmHg. It should be considered that, with increasing age, individual variation in functional status and independence varies. This can affect the patient's ability to tolerate treatment. Thus, initiation of treatment should be based on shared decision-making, weighing benefits against possible adverse events.

Take home messages

The decision to offer BP-lowering therapy should be based on both BP levels and risk, as those with the highest risk show greatest benefit of BP-lowering treatment.

Persons with high-normal BP and low-moderate risk should be offered lifestyle advice. If persons have established CVD, drug treatment (usually monotherapy) may be considered.

In **persons with grade 1 hypertension and low-moderate risk**, lifestyle advice should be offered, and BP-lowering treatment if BP is not controlled after 3-6 months.

Older patients (>65 years, including the very old >80 years) with grade 2 hypertension should be offered BP-lowering therapy. **Patients between 65 and 80 years with grade 1 hypertension** can also benefit from treatment. Monitor postural BP and hypotensive episodes with ABPM. Shared decision-making and weighing risks against benefits is important in the very elderly.

Patients with grade 1 hypertension at high risk, or those with **grade 2 or 3**, should be advised lifestyle interventions and drug treatment should be offered.

When initiating BP-lowering therapy, treatment target should be <140/90 mmHg, and 130/80 mmHg if therapy is well-tolerated. In older people, SBP should be 130-140 mmHg.

Management options to lower blood pressure

Non-pharmacological management options

Effective lifestyle changes can prevent or delay the onset of hypertension and reduce CV risk (4, 9). They may be enough to delay or prevent the need for drug therapy in those with grade 1 hypertension. Healthy lifestyle choices can also enhance the effects of BP-lowering drugs, thus may enable reductions in dose or number of agents used. Lifestyle measures that have been shown to reduce BP, and thus that are recommended, are listed below.

Dietary sodium restriction

Evidence suggests a causal relationship between sodium intake and BP (41). Indeed, sodium restriction had a BP-lowering effect in many trials. A meta-analysis suggested that at reduction of about 1.75 g sodium per day (˜4.4 g salt per day) is associated with a mean SBP/DPB reduction of 4.2/2.1 mmHg. In people with hypertension, the effect was more pronounced, with 5.4/2.8 mmHg BP reduction (42). Moreover, black people, older people and patients with diabetes, metabolic syndrome or CKD show greater BP-lowering effect of sodium restriction.

The effect of sodium reduction on CV events is less clear. A J-curve has been described, suggesting a higher risk of all-cause and CV mortalities and CV events at sodium intake below about 3 g per day in the general population and in hypertensive individuals (43). The mechanism underlying this phenomenon is unclear, and epidemiological studies have not revealed harm associated with very low sodium intake. Thus, the J-curve phenomenon may result from confounding by reverse causation. No prospective RCT's

have provided definite evidence about the optimal sodium intake in light of minimizing CV events and mortality. It should be noted that potassium intake is inversely associated with BP, and this may modify the relation between sodium intake, BP and CVD (44).

> **EPCCS Recommendation:**
> *Sodium intake should be limited to about 2 g per day (~5 g salt per day) in the general population and in hypertensive people.*

Moderation of alcohol consumption

A well-established positive linear relation exists between alcohol intake, BP, prevalence of hypertension, and CVD risk. Binge drinking can have a strong pressor effect. A mendelian randomisation study of epidemiological studies suggested that reduction of alcohol consumption might be beneficial for CV health, even in light-moderate drinkers (45). The PATHS study suggested a modest BP-lowering effect of an intervention to lower alcohol consumption (46).

> **EPCCS Recommendation:**
> *Hypertensive men are advised to limit alcohol consumption to 14 units per week, and women to 8 units (1 unit equals 125 mL of wine or 250 mL of beer). Moreover, it is recommended to have alcohol-free days and to avoid binge-drinking.*

Other dietary changes

A **healthy balanced diet** containing vegetables, legumes, fresh fruits, low-fat dairy products, wholegrain products, fish and unsaturated fatty acids (especially olive oil), and low intake of red meat and saturated fatty acids should be advised to hypertensive patients. The Mediterranean diet follows most of these recommendations, with moderate consumption of alcohol, mostly wine during meals. Following the Mediterranean diet has been shown to be associated with lower ambulatory BP, blood glucose and lipid levels (47) and even a reduction of CV events and mortality (48).
While **coffee** has an acute pressor effect, coffee consumption has also been associated with CV benefits (49). **Green or black tea** consumption also appears to have modest BP-lowering effects (50, 51). Consumption of sugar-sweetened beverages should be discouraged, considering the associations of regular consumption with becoming overweight, metabolic syndrome, T2DM and higher CV risk.

> **EPCCS Recommendation:**
> *Adopting a healthy, balanced diet may assist in BP reduction and lower CV risk.*

Weight reduction

Excessive weight gain is associated with hypertension, and both being overweight and obese are linked to increased risk of CV death and all-cause death (52). A meta-analysis suggested SBP/DBP reduction of 4.4/3.6 mmHg with an average weight loss of 5.1 kg (53). Weight loss can improve the efficacy of BP-lowering medication and the CV risk profile.

> **EPCCS Recommendation:**
> *Weight reduction is recommended in overweight and obese hypertensive patients for control of metabolic risk factors. Maintenance of a healthy body weight (BMI: 20-25 kg/m2 in persons <60 years old, higher in older people) and waist circumference (<94 cm for men and <80 cm for women) is recommended for non-hypertensive people to prevent hypertension, and for those with hypertension to reduce BP.*

Regular physical activity

While BP rises acutely during physical activity, afterwards BP briefly drops to below baseline. Epidemiological studies have suggested that regular aerobic physical activity may exert benefits for preventing or treating hypertension, and that it may improve the CV risk profile. A meta-analysis of (unblinded) RCT's showed that endurance training, dynamic resistance training and isometric training reduced resting SBP/DBP by 3.5/2.5, 1.8/3.2 and 10.9/6.2 mmHg, respectively, in general populations (54). Endurance training has a larger effect in hypertensive individuals (-8.3/5.2 mmHg).

> **EPCCS Recommendation:**
> *Hypertensive persons should be advised to participate in at least 30 minutes of moderate-intensive dynamic aerobic exercise on 5-7 days each week. Adding resistance exercises on 2-3 days per week may also be advised.*

Smoking cessation

ABPM studies have shown that both normotensive and hypertensive smokers have higher daily BP values than non-smokers (55), but smoking cessation does not appear to lower office BP. Nevertheless, smoking cessation is probably the most effective lifestyle change to prevent CVD.

> **EPCCS Recommendation:**
> *Hypertensive smokers should be counselled about smoking cessation. Pharmacological measures can be considered, with best results for varenicline and a combination of nicotine replacement therapies (56). Success rates are increased when pharmacotherapy is combined with behavioural support, as compared with brief advice alone.*

Using behaviour change techniques (BCTs) that focus on how an individual thinks about themselves, their behaviour and circumstances and how they can modify their way of life, can be effective to stimulate adoption of a healthy lifestyle. It is generally more effective when more than two strategies are used. Ingredients of successful BCTs include:

- Realistic goal setting and translation of goals into meaningful action.
- Self-monitoring, for instance with health apps or other means of regular monitoring of health data
- Involving others (with partner, family or a buddy)
- Targeting automatic behaviour: developing positive associations with healthy behaviours and inhibiting behavioural impulses
- Attitude of the PC professional: assess and reinforce progress towards goal achievement

(For more information: see also the EPCCS Guidance on 'Stimulating health behaviour changes to reduce cardiovascular risk in primary care', available at IPCCS.org).

Device therapy

Device-based therapy to lower BP is emerging, but has not yet been proven to be an effective treatment option, and will therefore not be discussed in this document aimed at guidance in the primary care setting.

Guideline-recommended pharmacotherapeutic management options

In most patients, drug therapy will be needed in addition to lifestyle changes, to achieve optimal BP control. The 2018 ESH/ESC Guidelines recommend the same five classes of drugs as the 2013 edition to form the basis of antihypertensive therapy: angiotensin-converting-enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs) and diuretics (thiazides and thiazide-like diuretics) and beta-blockers (4). The recommendations are based on their proven ability to reduce BP and placebo-controlled evidence that they reduce CV events and mortality. Overall, effects of initial therapy with each of the classes are similar, although specific differences of their effects on outcomes exist. Moreover, contraindications vary among the classes. Additional specific indications are discussed below for each of the classes.

Renin-angiotensin system (RAS) blockers: ACEi and ARBs

ACEi and ARBs reduce albuminuria more so than other BP-lowering drugs and are effective at delaying the progression of both diabetic and non-diabetic CKD. In fact, RAS blockers are the only antihypertensive agents that have been shown to reduce risk of end-stage renal disease (33). ACEi and ARB also seem to be beneficial for preventing or regressing hypertension-mediated organ damage (57). Furthermore, they reduce incident atrial fibrillation (57).

ACEi and ARBs should not be used simultaneously, because of a lack of added benefit on outcomes. Moreover, it incurs a higher risk of renal adverse events (58, 59). ARBs show the lowest treatment discontinuation rates for adverse events, as compared with other antihypertensive therapies (60). ACEi are associated with a slightly higher risk of angioneurotic oedema, especially in people of black African origin, in whom an ARB may be preferred.

Calcium channel blockers

The class of calcium channel blockers (CCBs) is heterogeneous. Most RCTs that have demonstrated a

benefit on CV outcomes have evaluated dihydropyridines, especially the long-acting CCB amlodipine. No substantial differences in effectiveness have been found when compared with non-dihydropyridines (verapamil and diltiazem) and with other drugs (57).

The effect of CCBs on stroke reduction is greater than what may be expected based on the BP reduction achieved (57). CCBs have been shown to be more effective as compared with beta-blockers in slowing progression of carotid atherosclerosis and in reducing left ventricle hypertrophy and proteinuria (5).

Thiazide/thiazide-like diuretics

The effectiveness of diuretics in preventing all types of CV morbidity and mortality is well-established (61), and they also seem particularly effective at preventing HF (57). The thiazide-like diuretics chlorthalidone and indapamide have been shown to be more potent than the classical thiazide hydrochlorothiazide in lowering BP, with longer duration of action, without increasing side-effects (62). Lower-dose thiazide-like diuretics as typically used in modern antihypertensive treatment regimens also show more evidence of lowering CV events and mortality than lower dose thiazide diuretics (63). However, a recent meta-analysis of placebo-controlled trials suggested a similar effect on CV outcomes of thiazides, chlorthalidone and indapamide (61). Hence, in the absence of direct comparative evidence, thiazides, chlorthalidone and indapamide are all considered suitable antihypertensive drugs by the 2018 ESH/ESC guidelines (4).

The side effect profile of thiazide and thiazide-like diuretics is less favourable than that of RAS blockers, and they are associated with a higher rate of treatment discontinuation. They may also reduce serum potassium (57, 61). Plus, dysmetabolic effects that increase insulin resistance and the risk of new-onset diabetes may occur (64). These dysmetabolic effects may be reduced by potassium.

When estimated glomerular filtration rate (eGFR) is <45 mL/min, thiazides and thiazide-like agents are less effective than other antihypertensive therapies, and when eGFR drops below 30 mL/min, they become ineffective altogether. In such instances, thiazides and thiazide-like diuretics should be replaced by loop diuretics.

Beta-blockers

Beta-blockers are mainly indicated for third-line treatment of hypertension in specific conditions such as symptomatic angina, for heart rate control, post-MI, HFrEF and as an alternative to ACEi or ARBs in younger hypertensive women of child-bearing age.

As compared with other BP-lowering drugs, beta-blockers are generally equivalent in preventing major CV events, but they are consistently shown to be less effective at preventing stroke (33). Beta-blockers are also somewhat less effective at preventing or regressing left ventricular hypertrophy, carotid intima media thickness, aortic stiffness and small artery remodelling than RAS blockers and CCBs. Beta-blockers, in particular when combined with diuretics, are associated with increased risk of new-onset diabetes in predisposed individuals. The side-effect profile is a bit less favourable than that of RAS blockers and are associated with a higher rate of treatment discontinuation (65).

Different types of beta-blockers exist. Use of vasodilating beta-blockers such as labetalol, nebivolol, celiprolol and carvedilol has become more common in recent years. Nebivolol has been shown to have more favourable effects on central BP, aortic stiffness and endothelial dysfunction, without a negative effect on the risk of new-onset diabetes. The side-effect profile is more favourable (66, 67). Bisoprolol, carvedilol and nebivolol have been shown to improve outcomes in RCTs in heart failure. However, no RCTs have been published yet that evaluate outcomes with these beta-blockers in hypertensive patients.

Other antihypertensive drugs

Mineralocorticoid receptor antagonists (MRAs) may be considered as fourth line agents in resistant hypertension, when proven combinations of the antihypertensive classes do not control BP. The PATHWAY 2 study showed that blockade of the biological effects of aldosterone with spironolactone up to 50 mg/day could help control BP (68). As efficacy and safety of spironolactone has not been established yet in people with significant renal impairment, the use of this agent should be restricted to patients with eGFR ≥45 mL/min and a plasma potassium concentration of ≤4.5 mmol/L, until data from ongoing trials become available.
Centrally active drugs are less commonly used now, because of their poorer tolerability relative to the

drugs described above. Antihypertensive agents other than members of the five major classes are no longer recommended for routine management of hypertension. Only in rare cases of drug-resistant hypertension, in which all other treatment options have failed, other agents may be used as add-on therapy.

Treatment strategy

As opposed to the previous ESH/ESC Guideline that recommended initiating treatment with sequential use of different monotherapies, the 2018 edition focuses on the more effective and less time-consuming stepped-care approach. This means that treatment is initiated with different therapies simultaneously, followed by sequential addition of other agents until BP control is achieved. In uncomplicated hypertension, the preferred initial combination is a RAS blocker with a CCB or a diuretic. If this is insufficient to control BP, the three agents may be combined. In case of resistant hypertension, spironolactone may be added, unless contraindicated. Alternatively, another diuretic, alpha-blocker or beta-blocker may be added (4)..

> EPCCS Recommendation:
Based on currently available evidence, the most effective treatment strategy to improve BP control is one that (4):
1. uses combination therapy in most patients,
2. stimulates adherence by using single pill combination therapy in most patients, and
3. follows a treatment algorithm that is simple, applies to all patients and is pragmatic.
Thus, single-pill combination therapy is recommended as initial therapy for most patients, except those with BP in the high-normal range and in frail older patients (4).

Referral to hospital-based care
While most patients with hypertension will be managed in the primary care setting, some circumstances require referral for routine hospital-based evaluation and treatment. Such situations include, according to the 2018 ESH/ESC hypertension guidelines: patients in whom secondary hypertension is suspected, younger patients (<40 years) with grade 2 or more severe hypertension in whom secondary hypertension should be excluded, patients with treatment-resistant hypertension, patients in whom more detailed assessment of hypertension-mediated organ damage would influence treatment decisions, patients with sudden onset of hypertension when BP has previously been normal, or in other circumstances when the referring doctor thinks specialist evaluation is needed (4).

Take home messages

Effective lifestyle changes may be sufficient to delay or prevent development of hypertension and the need for drug therapy, as well as enhance the effects of BP-lowering.

Lifestyle measures that have been shown to lower BP are dietary sodium restriction, moderation of alcohol consumption, consuming a healthy balanced diet, weight reduction, regular physical activity and smoking cessation.

Using behaviour change techniques that focus on how individuals think about themselves, their behaviour and circumstances and how they can modify this, can be effective to stimulate a healthier lifestyle.

Most hypertensive patients will need drug therapy in addition to lifestyle changes. Effects of initial therapy with each of the antihypertensive drug classes are similar, but they vary in terms of their effect on specific outcomes.

A more effective and less time-consuming stepped-care approach is now recommended: starting with different therapies simultaneously, followed by sequential addition of other agents until BP control is achieved.

Challenges faced in clinical practice

Reasons for the currently suboptimal BP control rates in patients with hypertension include physician or treatment inertia, leading to too many patients remaining on monotherapy and/or suboptimal doses, even though their BP is inadequately controlled. Moreover, combination treatment is insufficiently used, although BP is regulated through various pathways, which are best targeted simultaneously to reduce BP. Poor patient treatment adherence is also a common problem. But it all starts with adequate measurement and diagnosis, which is not always straightforward. Some of these challenges are discussed in more detail below.

Practical aspects regarding blood pressure measurement

Despite its advantages, ABPM comes with some challenges, as not everybody tolerates it. ABPM is perceived as particularly disturbing sleep and usual activities, as compared with clinic and home readings, suggested a study that tested all three methods in the same population in the UK West Midlands. Interestingly, ABPM was worse tolerated in some minority ethnic groups (Indian, Pakistani, Bangladeshi) (69).

A study evaluated whether pre-screening can determine when ABPM will be most appropriate in reaching a diagnosis. The Predicting Out-of-Office BP (PROOF-BP) study (70) screened patients with an apparatus that measures BP six times at one-minute intervals. These data were compared with a week of home monitoring data from the same patients. People who showed a white-coat effect, also had quite a steep reduction in BP over the six clinic readings, while this reduction was lower in those in whom home and clinic readings were fairly similar. In patients with masked hypertension, thus with higher BP in home readings, BP first went up during the clinic readings, to then decrease to end at a reading similar to the beginning (70). The hypothesis was taken further to explore the question whether clinic BP can be combined with other factors to reduce the need for ABPM. A statistical model suggested indeed that the clinic BP changes could to some extent predict a difference between home and clinic BP, but also some clinical and demographic characteristics.

Based on these factors, an online calculator was developed (https://sentry.phc.ox.ac.uk/proof-bp/). The PROOF-BP calculator asks for three BP readings, age, sex, height, weight, diabetes status and date of diagnosis, whether they receive treatment and if they have CVD. Then a predicted out-of-office BP comes out. If the predicted BP is clearly normal or definitely high, treatment can be based on the clinic readings. When it is intermediate (between 130/80 and 144/89 mmHg), ABPM is indicated to guide treatment (for algorithm, see reference (71)). This group can also include masked hypertension. Indeed, the PROOF-BP performs better at correctly identifying patients with hypertension than other strategies such as that of NICE and ESH/ESC (71).

When should treatment be based on out-of-office BP measurements? The TASMINH4 trial looked at whether GP's who titrate antihypertensive medication based on self-monitored BP ended up with better control as compared with on the basis of clinic BP readings (72). Two previous studies with 12 months follow-up in which physicians used self-monitored BP to explicitly titrate antihypertensive medication demonstrated worse BP control as compared with using clinic BP (73, 74). In those studies, the physicians were blinded to the method of BP measurement. Importantly, a common target BP was used for both home and clinic readings (140/90 mmHg), instead of using a lower target for home measurements, typically 135/85 mmHg, as recommended by the ESC/ESH and NICE hypertension guidelines (75). Therefore, a different approach was taken in TASMINH4, in which the 135/85 mmHg target was applied for home measurements and 140/90 mmHg for clinic readings. Two self-monitoring groups were included: one simply self-monitoring, by means of noting the BP on paper, and one that involved telemonitoring, via a relatively simple text-based method. After a year, the self-monitoring groups had a lower SBP than those in usual care (mean: 140.4, SD: 16.5 mmHg), with a slightly lower SBP in the telemonitoring group (mean: 136.0, SD: 16.1 mmHg, adjusted mean difference from usual care: -4.7 mmHg, 95%CI: -7.0 to -2.4) than in the self-monitoring group (mean: 137.0, SD: 16.7 mmHg, adjusted mean difference from usual care: -3.5 mmHg, 95%CI: -5.8 to -1.2). The two self-monitoring groups did not significantly differ. At 6 months, however, the telemonitoring group showed better BP control, while the self-monitoring group did not differ significantly from usual care. Importantly, no differences in adverse events were seen between clinic and home-measured groups (72).

A systematic review and individual patient data meta-analysis also suggested that self-monitoring is associated with lower BP or better BP control, as long as it is used in conjunction with co-interventions such as medication titration by doctors, pharmacists or patients, education or lifestyle counselling (76). When a patient is using their own BP measuring device at home, it is worth comparing their reading with the physician's during a clinic visit.

Treatment-resistant hypertension

Treatment-resistant hypertension is defined as when the recommended treatment strategy fails to lower office SBP and/or DBP values to <140 mmHg and/or <90 mmHg despite at least three antihypertensives including a diuretic. Inadequate BP control should be confirmed by

ABPM or HBPM after treatment adherence of the patient has been confirmed. Pseudo-resistant hypertension and secondary causes of hypertension should be excluded. Pseudo-resistant hypertension refers to a seemingly inadequate response to treatment due to one of the following situations: poor adherence to prescribed medicines (probably the major cause), white coat hypertension, poor office BP measurement technique, marked brachial artery calcification, or clinical inertia. The major secondary causes of hypertension are primary aldosteronism or atherosclerotic renal artery stenosis (particularly in older patients or patients with CKD).

Resistant hypertension may be caused by lifestyle factors such as obesity or large weight gains, excessive alcohol consumption and high sodium intake. Intake of vasopressor or sodium-retaining substances or drugs prescribed for other conditions, or some herbal remedies or recreational drugs may also cause resistant hypertension. Obstructive sleep apnoea, commonly associated with obesity can also interfere with treatment. Finally, one needs to be aware of undetected secondary forms of hypertension and advanced hypertension-mediated organ damage (CKD or large-artery stiffening). The prevalence of true resistant hypertension is estimated to be <10% of treated patients. Truly treatment-resistant patients are at higher risk of hypertension-mediated organ damage, CKD and premature CV events (77).

Diagnosis of treatment-resistant hypertension

When treatment-resistant hypertension is suspected, establishing a diagnosis requires detailed information about the patient's history, including lifestyle characteristics (intake of alcohol, sodium, drugs, and sleep history) and the type and dosing of antihypertensive treatment. A physical examination should be done, with focus on determining presence of hypertension-mediated organ damage and signs of secondary hypertension. Out-of-office BP measurement needs to be performed (ABPM or HBPM) to confirm treatment resistance. Electrolyte abnormalities (hypokalaemia), associated risk factors (diabetes), organ damage (advanced renal dysfunction) and secondary hypertension should be checked for by means of laboratory tests. Finally, adherence to BP-lowering therapy needs to be confirmed (4).

Management of treatment-resistant hypertension

Reducing pill burden and improving treatment adherence by replacing current drugs with a single pill combination is recommended. While the optimal drug treatment of resistant hypertension has been poorly studied, it seems most effective to add more diuretic treatment to decrease volume overload, with concomitant salt restriction. Evidence is accumulating that the fourth-line treatment should involve blockade of aldosterone effects by means of a mineralocorticoid receptor antagonist (MRA) such as spironolactone (68, 78-80).

Non-adherence

Non-adherence to prescribed medication is common among patients being treated for hypertension, which puts patients at higher risk of CV events. In fact, evidence points in the direction that poor treatment adherence, in addition to physician inertia, is the most important cause of poor BP control (65, 81-83).
Early recognition of poor treatment adherence may prevent unnecessary costs of investigations and procedures and prescription of unnecessary drugs. Thus, it is important to enquire about adherence to treatment at each visit and to motivate the patient to take the medication. The 2018 ESH/ESC guidelines list a number of interventions that may improve patient adherence to treatment, at the physician, patient, drug and health system level (4).

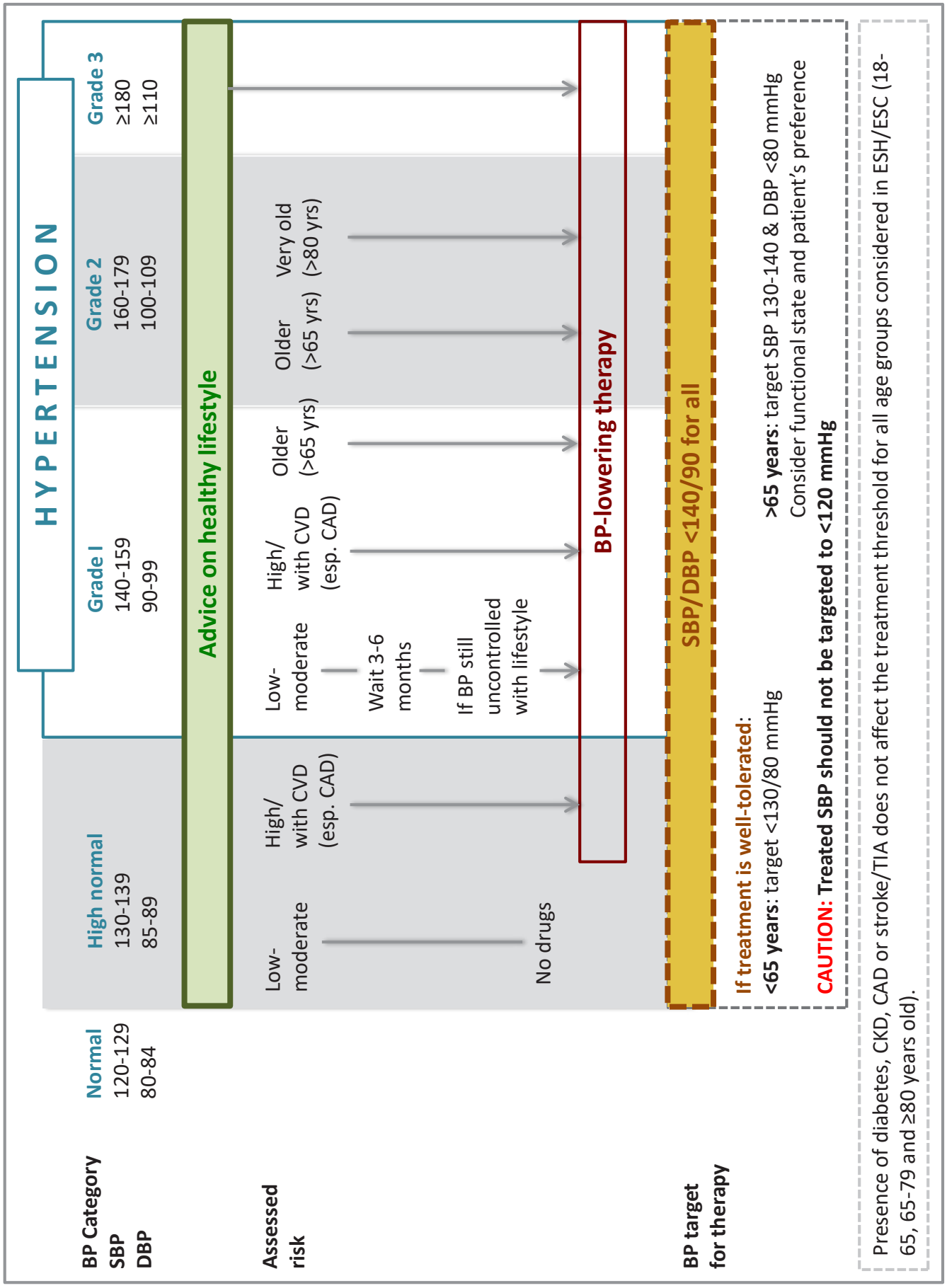
Take home messages

ABPM is not available for or tolerated by all. Using the PROOF-BP algorithm is one means of reducing the need for ABPM.

Home (/self) monitoring now has a firm evidence base for on-going management. It is important to apply a different target BP for home measurements than for clinic BP readings.

Treatment-resistant hypertension can have many causes. Reasons for pseudo-resistant hypertension need to be explored and excluded. Secondary causes of hypertension should be excluded. Patients with truly treatment-resistant hypertension are at higher risk of organ damage, CKD and premature CV events.

Establishing a diagnosis of treatment-resistant hypertension requires detailed history, physical examination, out-of-office BP measurement and laboratory tests.


BP Category
SBP
DBP
Normal
120-129
80-84
High normal
130-139
85-89
HYPERTENSION
Grade I
140-159
90-99
Grade 2
160-179
100-109
Grade 3
≥180
≥110
Assessed risk
Advice on healthy lifestyle
Low-moderate
High/ with CVD (esp. CAD)
No drugs
Low-moderate
Wait 3-6 months
If BP still uncontrolled with lifestyle
High/ with CVD (esp. CAD)
Older (>65 yrs)
Older (>65 yrs)
Very old (>80 yrs)
BP-lowering therapy
BP target for therapy
SBP/DBP <140/90 for all
If treatment is well-tolerated:
<65 years: target <130/80 mmHg
>65 years: target SBP 130-140 & DBP <80 mmHg
Consider functional state and patient's preference
CAUTION: Treated SBP should not be targeted to <120 mmHg
Presence of diabetes, CKD, CAD or stroke/TIA does not affect the treatment threshold for all age groups considered in ESH/ESC (18-65, 65-79 and ≥80 years old).

BOX 1 | Take home messages

INTRODUCTION

- In Europe, hypertension is defined as SBP ≥140 mmHg and DBP ≥90 mmHg.
- Risk of stroke and other CVD becomes greater with increasing SBP.

DIAGNOSIS OF HYPERTENSION

- Out-of-office BP measurement is recommended for diagnosis and on-going management of hypertension. Out-of-office BP is often lower than clinic BP.
- The BP measurement method and who measures BP affects the BP value recorded.
- ABPM is becoming the gold standard for diagnosis. It is necessary to detect white coat and masked hypertension.
- Repeated HBPM is a good alternative to ABPM, because it is simpler and much cheaper, but it cannot supply data on diurnal BP variation.

RECENT EVIDENCE THAT HAS INFLUENCED THE GUIDELINES

- In SPRINT, intensively treating patients to SBP <120 mmHg (vs. <140 mmHg) was associated with a benefit on mortality and CV outcomes, but also with more adverse events. The BP measurement method likely led to lower BP values than obtained in routine care, thus BP values and treatment effects achieved in SPRINT cannot be extrapolated directly to clinical practice.
- ACCORD showed no benefit of intensively treating T2DM patients to SBP <120 mmHg on the composite CV outcome, and more adverse events, but less stroke was observed, compared with those targeted to <140 mmHg.
- Targeting treatment to <130 mmHg did not reduce the endpoint of all stroke compared with targeting 130-149 mmHg in patients with a recent stroke in the SPS3 trial.
- The BP-lowering results of the HOPE-3 trial showed no significant effect of ARB plus a thiazide diuretic on the co-primary CV endpoints compared with placebo, in people at intermediate risk without CVD, without a clear indication for antihypertensive therapy.
- Combined, the currently available data suggest that there is no benefit of primary preventive antihypertensive treatment if SBP <140 mmHg. Primary preventive BP-lowering therapy is associated with reduced CV and mortality risk if SBP ≥140 mmHg.

THERAPEUTIC CONSIDERATIONS

- The decision to offer BP-lowering therapy should be based on both BP levels and risk, as those with the highest risk show greatest benefit of BP-lowering treatment.
- **Persons with high-normal BP and low-moderate risk** should be offered lifestyle advice. If persons have established CVD, drug treatment (usually monotherapy) may be considered.
- In **persons with grade 1 hypertension and low-moderate risk**, lifestyle advice should be offered, and BP-lowering treatment if BP is not controlled after 3-6 months.
- **Older patients (>65 years, including the very old >80 years) with grade 2 hypertension** should be offered BP-lowering therapy. **Patients between 65 and 80 years with grade 1 hypertension** can also benefit from treatment. Monitor postural BP and hypotensive episodes with ABPM. Shared decision-making and weighing risks against benefits is important in the very elderly.
- **Patients with grade 1 hypertension at high risk**, or those with **grade 2 or 3**, should be advised lifestyle interventions and drug treatment should be offered.
- When initiating BP-lowering therapy, treatment target should be <140/90 mmHg, and 130/80 mmHg if therapy is well tolerated. In older people, SBP should be 130-140 mmHg.

BOX 1 | Take home messages - continued

MANAGEMENT OPTIONS TO LOWER BLOOD PRESSURE

- Effective lifestyle changes may be sufficient to delay or prevent development of hypertension and the need for drug therapy, as well as enhance the effects of BP-lowering.
- Lifestyle measures that have been shown to lower BP are dietary sodium restriction, moderation of alcohol consumption, consuming a healthy balanced diet, weight reduction, regular physical activity and smoking cessation.
- Using behaviour change techniques that focus on how individuals think about themselves, their behaviour and circumstances and how they can modify this, can be effective to stimulate a healthier lifestyle.
- Most hypertensive patients will need drug therapy in addition to lifestyle changes. Effects of initial therapy with each of the antihypertensive drug classes are similar, but they vary in terms of their effect on specific outcomes.
- A more effective and less time-consuming stepped-care approach is now recommended: starting with different therapies simultaneously, followed by sequential addition of other agents until BP control is achieved.

CHALLENGES FACED IN CLINICAL PRACTICE

- ABPM is not available for or tolerated by all. Using the PROOF-BP algorithm is one means of reducing the need for ABPM.
- Home (/self) monitoring now has a firm evidence base for on-going management. It is important to apply a different target BP for home measurements than for clinic BP readings.
- Treatment-resistant hypertension can have many causes. Reasons for pseudo-resistant hypertension need to be explored and excluded. Secondary causes of hypertension should be excluded. Patients with truly treatment-resistant hypertension are at higher risk of organ damage, CKD and premature CV events.
- Establishing a diagnosis of treatment-resistant hypertension requires detailed history, physical examination, out-of-office BP measurement and laboratory tests.

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Acknowledgements

We thank all those who attended the 10th and 11th Annual EPCCS meetings, held in Barcelona, Spain (March, 2018) and Lisbon, Portugal (March, 2019), respectively, for their contribution to active discussion during the meeting. JRB and FDRH drafted the first paper but all authors contributed to editing and final approval. The corresponding author is FDRH, who acknowledges part support from the NIHR School for Primary Care Research (SPCR), the NIHR Collaboration for Leadership in Applied Research in Health and Care (CLARHC) Oxford, and the NIHR Biomedical Research Centre (BRC), Oxford.

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This document has been produced by MEDCON International, Heemstede, The Netherlands (Publisher). No external funding was received for the production of this document.