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Novel blood pressure targets in patients with high-normal levels and grade 1 hypertension: Room for monotherapy?

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ABSTRACT

The 2018 European and 2017 American guidelines recommend to start antihypertensive treatment with combinations of two or more drugs in most hypertensive patients, as a consequence of the suggested more ambitious blood pressure (BP) targets (systolic BP between 130 and 120 mmHg in most patients, diastolic BP between 80 and 70 mmHg).
Monotherapy, however, is still suggested as first choice in some specific classes of patients.
In this article, we analyze the subgroups of hypertensive patients that should properly started and even maintained on monotherapy, with a focus on subjects with BP in the high-normal range or grade 1 hypertension, young adults with estimated low cardiovascular risk, women during pregnancy or menopause, elderly patients aged >80 years or with frailty parameters.
Altogether, these subgroups cover a relatively large proportion of patients with hypertension. Thus, we conclude that, despite the upgrowing role of combination therapy, there is still ample room for the approach with monotherapy in clinical management of hypertension.

1. Introduction

The optimal blood pressure [BP] goals and the best antihypertensive strategy to choose still represent an unsolved dilemma for many physicians.

The 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines [1], consistent with the 2017 American guidelines [2], have recently modified the recommended targets, suggesting to reach systolic BP (SBP) values of 130 mmHg or lower, but not <120 mmHg, in most patients aged <65 years and between 130 and 140 mmHg in fit elderlies aged >65 years (provided that the treatment is well tolerated) and diastolic BP (DBP) values between 80 mmHg and 70 mmHg, independently from age. In view of these more ambitious BP targets as well as of the increasing evidence that initial combination therapy of two or more drugs is invariably more effective at BP lowering than monotherapy, with a more frequent BP control after 1 year, a better long-term adherence to the prescribed treatment and a lower risk of major cardiovascular events (MACEs) [3], current European guidelines have significantly shifted towards the recommended use of combination treatment in most patients [1].

Does this mean that it is time to put apart the use of monotherapy?

The same guidelines recommend monotherapy in specific groups, for instance high CV risk patients with high-normal BP (SBP between 130 and 139 mmHg, DBP between 80 and 89 mmHg) and grade 1 hypertensives at low-to-moderate CV risk.

In addition, in the 2017 American College of Cardiology/American Heart Association Hypertension (ACC/AHA) guidelines treatment should be initiated with two drugs having complementary mechanisms of action when BP is consistently >20/10 mmHg above goal. Otherwise, monotherapy should be prescribed as the first-line strategy [2].

So, according to the guidelines, it is not yet the time for "requiem" of monotherapy, but the space for this approach appears to be more restricted.

In this article, we will analyze in detail the subgroups of hypertensive patients that should properly started and even maintained on monotherapy according to European and US guidelines. In addition,

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association Hypertension; ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BP, blood pressure; CAD, coronary artery disease; CCBs, calcium-channel blockers; CVD, cardiovascular disease; DBP, diastolic BP; ESC/ESH, European Society of Cardiology/European Society of Hypertension; HF, heart failure; HMOD, hypertension mediated organ damage; ISH, isolated systolic hypertension; MACEs, major cardiovascular events; MI, myocardial infarction; MUCH, masked uncontrolled hypertension; NNT, number needed to treat; RAS, renin angiotensin-aldosterone system; SBP, systolic blood pressure.

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we will discuss whether there are other "grey zones" in the therapeutic management of hypertension that may indeed find an answer in the use of monotherapy.

2. High-normal BP range

In a pioneering study conducted in 2001 in one million adults, it was clearly shown that, for each decade of age, the risk of stroke, myocardial infarction (MI) and death progressively increases in relation to the increase of SBP already from 115 to 130 mmHg and further for increase from 130 to 140 mmHg [4]. A similar relation was found for increase in DBP.

More recently, a meta-analysis by Ettehad et al., which has enrolled 613,815 participants, has demonstrated that every10 mm Hg reduction in SBP significantly reduced the risk of MACEs, coronary artery disease (CAD), stroke, HF and all-cause mortality, irrespectively of mean baseline BP levels, also for SBP < 130 mmHg, without substantial differences related to the presence or absence of previous CV events [5].

It has been estimated that one-third of CV events occur in individuals with BP levels in the high-normal range, independently from the presence of concomitant CV risk factors, with a morbidity and mortality risk 1.6–2.0 greater than in normotensives with BP < 120/80 mmHg [6] and 150,000 excess CV events annually [7].

These data consistently indicate that the risk of CV events progressively rises even in the high-normal range, that high-normal BP is not such a benign condition, and that lowering BP in these subjects may be highly beneficial.

However, it has not been clearly established whether the benefits of pharmacological treatment of individuals with high-normal BP are independent from the coexistence of other risk factors and from estimated CV risk profile.

Thomopoulos et al. have demonstrated the efficacy of BP-lowering treatment in reducing fatal and non-fatal CV events in subjects with BP in the high-normal range and without history of MI, left ventricular dysfunction and HF [8].

Another meta-analysis, addressed to subjects with high-normal BP range, investigated 25 secondary CVD prevention studies including 64,162 non-hypertensive patients, showing a reduction in the incidence of stroke, MI, HF, composite CVD events and mortality in those treated with BP-lowering drugs [9].

In another study, 70,664 patients with BP values between 120 and 140 mmHg, impaired glucose tolerance, diabetes and microalbuminuria who received active antihypertensive treatment had a 22% reduction in the risk of stroke compared with placebo, with a number needed to treat (NNT) of 169 [10].

The main results of these meta-analyses are summarized in Table 1.

In the TROPHY study, 409 participants with high-normal BP were randomly assigned to receive candesartan 16 mg and 400 to receive placebo for a 2-year period, followed by another 2-year phase within all the patients received placebo [11]. At the end of the study, CV outcomes occurred in a significant smaller percentage of patients treated with candesartan compared to placebo (0.5% vs 1.5%).

Among patients with high-normal BP, the relative risk reduction due to antihypertensive treatment is similar among different estimated CV risk groups, whereas absolute risk reduction is greater with the increase of baseline risk and the estimated NNT to avoid one MACE in 5 years is inversely proportional to CV risk [12].

Other studies have demonstrated that antihypertensive medications prescribed to adults with BP in the high-normal range and history of CVD or diabetes produced a reduction of the RR of fatal and nonfatal stroke by 22–23%, MI by 20%, HF by 23%, and composite CV events and all-cause mortality by 15% [13,14].

Egan et al. suggested to start antihypertensive therapy in individuals with high-normal BP with an absolute 10-year CVD risk of 20% or between 10 and 19% in the presence of impaired fasting glucose, impaired glucose tolerance, microalbuminuria, obesity, metabolic syndrome, and hypertension mediated organ damage (HMOD) [7].

A lack of consensus exists on whether to treat adults with high-normal BP and without clinical CV disease, because of the low absolute risk, the high NNT, the costs and the still unproven benefits of pharmacological treatments.

Therefore, in patients with high-normal BP and estimated high or very-high CV risk, which may need pharmacological treatment because of the insufficient effect of lifestyle changes, the 2018 ESC/ESH guidelines suggest to start an antihypertensive treatment with a monotherapy strategy, since a SBP reduction of 10 mmHg is sufficient to achieve therapeutic targets [1].

3. Patients with grade 1 hypertension and low-to-moderate CV risk

Whether to treat and when to start antihypertensive treatment in patients with grade 1 hypertension at low or moderate CV risk (<5% cardiovascular death rate in 5 years) has been debated for many years, due to the lack of specific RCTs, because it would require many thousands of individuals and a very long follow-up to achieve meaningful findings. However, in the last decade, several meta-analyses have addressed this question and have univocally supported the advantages associated to the treatment of these patients.

The SPRINT study [15] has shown a significantly lower rate of the primary composite outcome [MI, acute coronary syndrome not resulting in MI, stroke, acute decompensated HF, or death from CV causes] in the intensive-treatment group than in the standard-treatment group (1.65% vs. 2.19% per year; hazard ratio [HR] with intensive treatment, 0.75) also in low-risk patients with grade 1 hypertension.

Significant absolute and relative reductions in most outcomes, including fatal events, was found for all hypertension grades, including patients with grade 1 hypertension at low-to-moderate CV risk, with

Table 1
Representative meta-analyses demonstrating the benefits of BP reduction in patients with high-normal BP.

Meta-analyses	CV risk	BP reduction	MACEs reduction RR [95% CI]	CAD reduction RR [95% CI]	Stroke reduction RR [95% CI]	HF reduction RR [95% CI]	All-cause mortality reduction RR [95% CI]	CV mortality reduction RR [95% CI]
123 RCTs (n = 613,815) [5]	Low-to-moderate and high or very-high	SBP 10 mmHg	0.8 [0.77–0.83]	0.83 [0.78–0.88]	0.73 [0.68–0.77]	0.72 [0.67–0.78]	0.87 [0.84–0.91]	
24 RCTs (n = 48,026) [8]	Low-to-moderate (n = 21,123)	SBP/DBP 10/5 mmHg	1.01 [0.86–1.20]	1.14 [0.89–1.46]	1.11 [0.68–1.81]		1.10 [0.93–1.31]	1.13 [0.84–1.52]
	High or very-high (n = 26,863)		0.96 [0.84–1.11]	1.00 [0.86–1.16]	0.69 [0.52–0.92]	0.92 [0.66–1.28]	0.92 [0.82–1.04]	0.87 [0.73–1.03]
25 RCTs (n = 64,162) [9]	High or very-high (secondary prevention)		0.85 [0.80–0.90]	0.80 [0.69–0.93]	0.77 [0.61–0.98]	0.71 [0.65–0.77]	0.87 [0.80–0.95]	0.83 [0.69–0.99]

BP, blood pressure; CAD, coronary artery disease; CV, cardiovascular; DBP, diastolic blood pressure; HF, heart failure; MACEs, major cardiovascular events; RCTs, randomized clinical trials; RR, relative risk; SBP, systolic blood pressure.

Table 2
Representative meta-analyses demonstrating the benefits of BP reduction in patients with grade 1 hypertension with estimated low-to-moderate CV risk.

Meta-analyses	BP reduction	MACEs reduction RR [95% CI]	CAD reduction RR [95% CI]	Stroke reduction RR [95% CI]	HF reduction RR [95% CI]	All-cause mortality reduction RR [95% CI]	CV mortality reduction RR [95% CI]
23 RCTs (n = 81,675) [16]	SBP/DBP 6.3/3.8 mmHg	0.84 [0.76–0.93]	0.90 [0.80–1.04]	0.67 [0.53–0.83]	0.82 [0.44–1.57]	1.00 [0.88–1.14]	1.19 [0.86–1.65]
6 RCTs (n = 8975) [17]			0.68 [0.48–0.95]	0.33 [0.11–0.98]	0.92 [0.66–1.28]	0.57 [0.32–1.02]	0.53 [0.35–0.80]
27 RCTs (n = 108,297) [18]	SBP/DBP 10/5 mmHg		0.79 [0.72–0.86]				0.54 [0.45–0.65]
BPLTTC 13 RCTs (n = 15,266) [19]	SBP/DBP 3.6/2.4 mmHg	0.86 [0.74–1.01	0.91 [0.74–1.12]	0.72 0.55–0.94]	0.80 [0.57–1.12]	0.78 [0.67–0.92]	0.75 [0.57–0.98]

BP, blood pressure; BPLTTC, Blood Pressure Lowering Treatment Trialists' Collaboration; CAD, coronary artery disease; CV, cardiovascular; DBP, diastolic blood pressure; HF, heart failure; MACEs, major cardiovascular events; RCTs, randomized clinical trials; RR, relative risk; SBP, systolic blood pressure.

no significant trend related to risk ratio changes with increasing baseline BP [16–18].

Moreover, the wide population examined in the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) meta-analysis has provided additional solid ground, since significant reductions in the risk of stroke, CV and all-cause deaths was found in patients with grade 1 hypertension in the absence of organ damage [19].

On the basis of these data, even if antihypertensive treatment induces greater absolute risk reductions in patients at higher CV risk level, there is clear evidence that the continuum BP lowering is beneficial whatever the grade and the stage of hypertension and that the absolute residual risk can be maintained low only if therapy is started early, most likely before the development of HMOD.

The main results of these meta-analyses are summarized in Table 2.

Thus, both the 2017 ACC/AHA [2] and 2018 ESC/ESH guidelines [1] recommend to begin antihypertensive pharmacotherapy also in grade 1 hypertensives, whatever it is their estimated CV risk. In subjects with low-to-moderate risk, however, initial monotherapy may be a reasonable and sufficient choice, at least until it will be eventually demonstrated that a low-dose single pill combination therapy may be more effective also in this patients. As aforementioned, ACC/AHA guidelines recommend to start with the combination of two agents only when SBP/DBP exceeds 20/10 mmHg the BP target [2].

The existence of a continuous association between BP levels and incidence of CV events is shown in Fig. 1. In this figure, in particular, one may see the CV events double or triple in 8 years in the group of patients with SBP ranging between 140 and 149 mmHg [20].

Fig. 2 summarizes the suggested therapeutic strategies for grade-1 hypertension and high-normal BP levels with different characteristics and CV risk.

4. Masked and white-coat hypertension

In the last few years, several trials and meta-analyses have demonstrated that ambulatory and home BP measurements better predict CV morbidity and mortality than office BP, suggesting that masked and white-coat hypertension are not such a benign condition [21,22].

In particular, the analysis of data from a Spanish registry including 63,910 adults has shown that, among all the clinical phenotypes evaluated (sustained, masked and white coat hypertension and normotension), masked hypertension was associated with the highest risk of death (HR, 2.83) compared to sustained hypertension (HR,

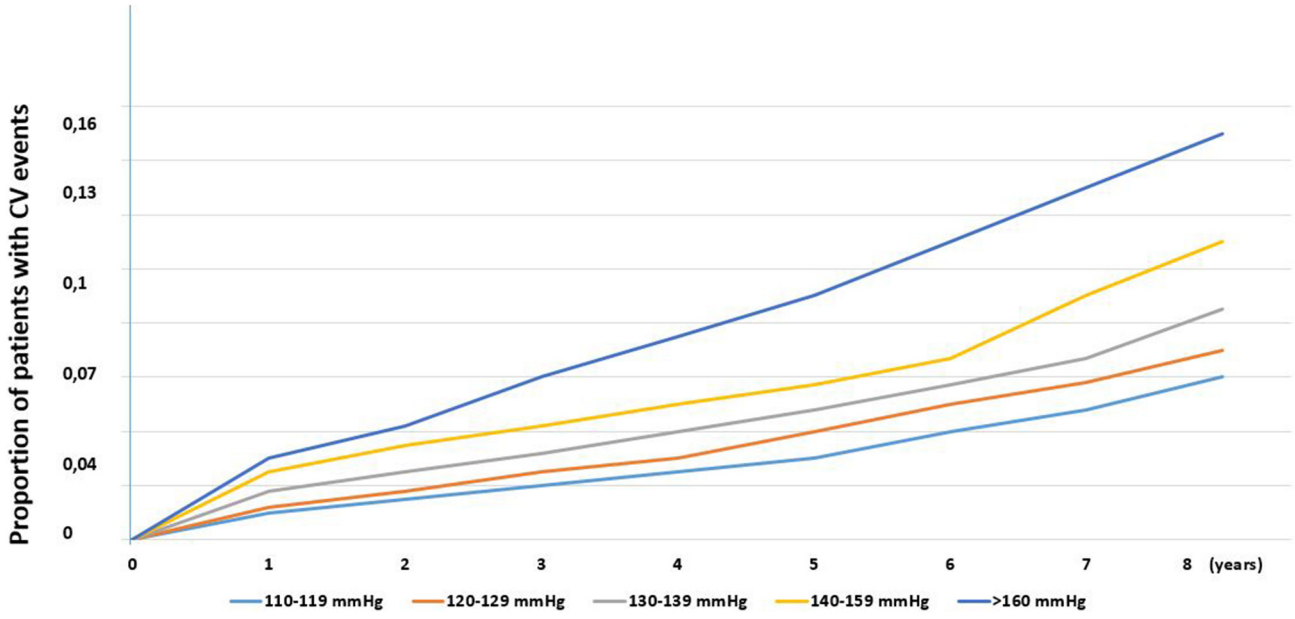

Fig. 1. Linear relationship between BP levels and incidence of CV events.
Modified from Ref [20].

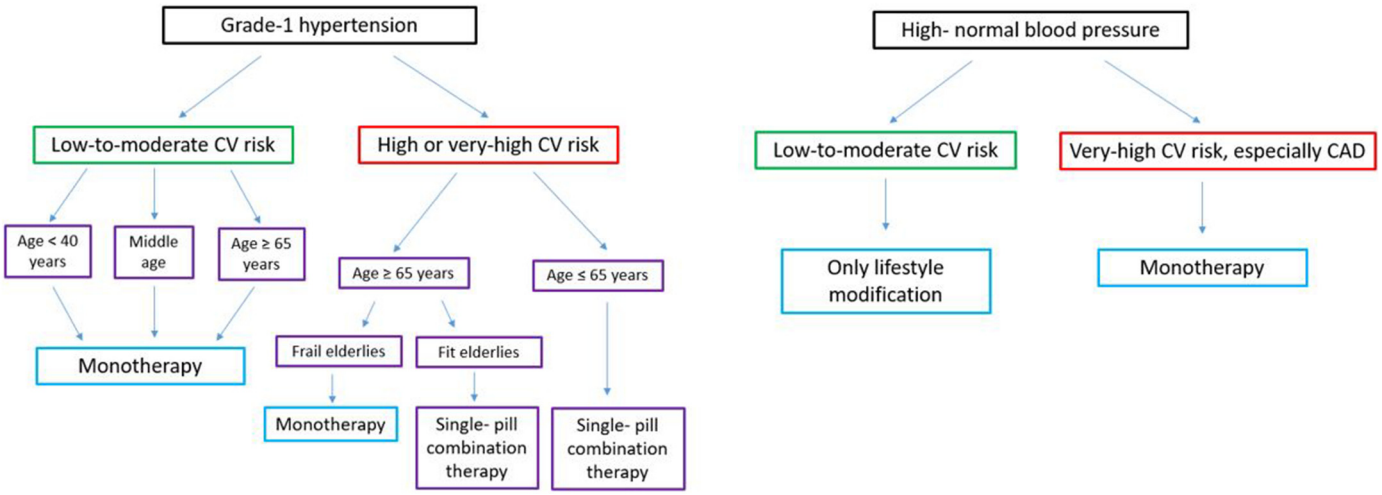

Fig. 2. Therapeutic algorithm in patients with grade-1 hypertension and high-normal BP. Adapted from Ref [1].

1.80) and white-coat hypertension (HR, 1.79) when adjusted for clinic blood pressure [23]. All-cause mortality and CV mortality were significantly greater in the group with uncontrolled masked hypertension compared with the group with controlled hypertension (adjusted HR 2.61 and 2.48, respectively).

On the basis of these results, patients with elevated out-of-office BP and diagnosis of masked uncontrolled hypertension (MUCH) may benefit of an early antihypertensive treatment, especially when lifestyle changes are not sufficient. In these patients, however, the adoption of a combination therapy as a starting strategy is not supported by current guidelines and a first-line monotherapy may represent an adequate and reasonable choice.

5. Hypertension in younger adults

There is clear evidence that grades 2 and 3 hypertension and grade 1 hypertension with HMOD should be promptly treated in all subjects, also in younger adults aged <50 years, performing a screening for secondary causes in the presence of clinical suspect [1].

On the other hand, the benefits of antihypertensive treatment in younger adults with uncomplicated grade 1 hypertension are not so well established, due to the absence of specific RCTs.

However, long-term epidemiological studies have demonstrated a clear relationship between BP and longer-term or lifelong risk of CV events and mortality in young adults with BP values above 130/80 mmHg, suggesting that an earlier treatment may prevent the progression of hypertension towards more severe forms and the development of HMOD and hypertension complications, thus reducing the risk of CV events [24]. According to these data, young adults may be eligible to treatment even when estimated risk is not immediately high, but lifetime estimated risk is unfavorable.

Young, healthy people, especially men, may present with isolated grade 1 systolic hypertension (ISH) (SBP between 140 and 159 mmHg and a normal DBP < 90 mmHg), with a normal central aortic SBP due to excessive peripheral systolic pressure amplification.

There is increasing evidence that ISH is associated with a higher risk for CVD and CV mortality compared with optimal or normal BP < 130/80 mmHg, independently from sex and associated CV risk factors [25].

The Chicago Heart Association Detection Project in Industry Study investigated the risk of CV events in a population of 15,868 men and 11,213 women aged between 18 and 49 years of age at baseline, free of CAD and antihypertensive therapy during an average follow-up period of 30.8 years (489,393 person-years) and 31.5 years (353,206 person-years), respectively [26]. In both sexes, cumulative CVD mortality was lower for those with optimal-normal BP, compared with subjects with ISH (Fig. 3).

In another analysis of data from the prospective cohort Coronary Artery Risk Development in Young Adults (CARDIA) study, 4851 individuals aged between 18 and 30 years were categorized, according to the most recent American guidelines classification [2], as having normal BP, elevated BP, stage 1 or 2 hypertension. The incidence of MACEs was significantly higher in the hypertensive groups (3.15 and 8.04 per 1000 person-years in stages 1 and 2 respectively) compared to those with normal or elevated BP (1.37 and 2.74 per 1000 person-year, respectively). The hazard ratios for elevated BP, stage 1 hypertension, and stage 2 hypertension compared to normal BP were 1.67, 1.75 and 3.49, respectively [27].

In a population-based cohort study from the Korean National Health Insurance Service including 2,488,101 adults aged 20–39 years and whose BP levels have been categorized according to American guidelines, patients with stage 1 hypertension had a significant higher risk of CVD, CHD and stroke compared to those with normal BP: CVD incidence was 215 vs 164 in men (HR 1.25) and 131 vs 91 in women (HR, 1.27); CHD incidence was 134 vs 103 in men (HR, 1.23) and 56 vs 42 in women (HR, 1.16); stroke incidence was 90 vs 67 in men (HR, 1.30) and 79 vs 51 in women (HR, 1.37) (all the outcomes defined as events per 100,000 person-years) [28].

Based on this evidence, it seems clear that treatment should be considered also for younger grade 1 hypertensive patients. In this regard, it is often required a pharmacological treatment whenever BP targets are not achieved with lifestyle changes. Given the BP and risk profile of this population, monotherapy may represent the rational first-line choice [1].

6. Pregnancy

Although young pregnant women with hypertension are supposed to have a low CV risk, a tight BP control is advised to reduce the immediate risk of uprising more severe hypertension, as well as the occurrence of pre-eclampsia and the subsequent risk of coronary events and stroke [29].

A BP target of <140/90 is suggested for pregnant women receiving antihypertensive therapy, even though consistent, solid data about the optimal BP goal in these subjects are still lacking.

Women with pre-existing hypertension may continue their current therapy, assuming that they do not take RAS inhibitors, which must be

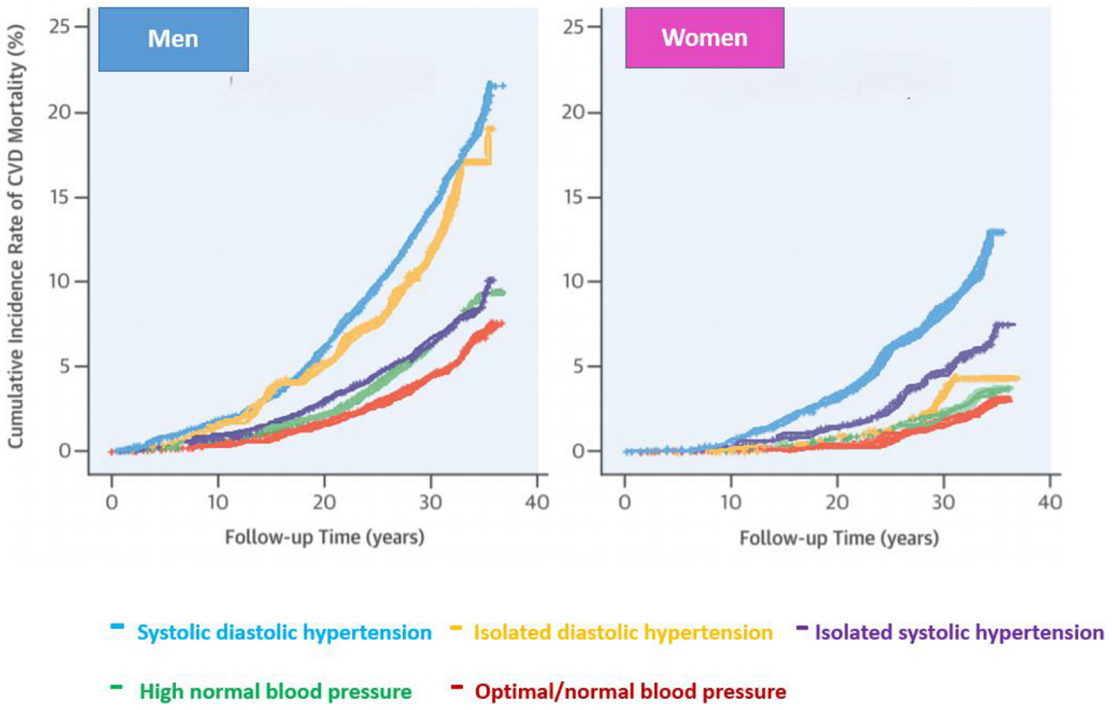

Fig. 3. Sex specific cumulative incidence of CV disease mortality for each hypertension subtype. Modified from Ref [26].

withdrawn and switched to another drug class to avoid adverse fetal and neonatal outcomes [1].

In women with new-onset mild hypertension, after a reasonable attempt to implement lifestyle measures, particularly sodium intake reduction and body weight control, monotherapy represents the most feasible and accurate strategy. Today, the recommendations on which drug should be used are mostly based on a few and relatively small studies. Among the drugs suggested in the 2018 European guidelines, methyldopa, labetalol, and calcium-channel blockers (CCBs) are preferred [1].

7. Middle-aged women in menopause

Hypertension rates have been described to rise after the occurrence of menopause, at an average age of 51 years. Post-menopausal and perimenopausal women have higher SBP at baseline compared to younger ones, the decreased arterial compliance, increased arterial stiffness, activation of the renin angiotensin-aldosterone system (RAS), oxidative stress, being proposed as responsible mechanisms [30].

Compared to age-matched men, BP levels are lower in premenopausal women, whereas this trend seems to be inverted after menopause, the incidence of hypertension rising more sharply in women than men after middle age with a pronounced increase in both SBP and pulse pressure [31,32]. However, the risk of CV events remains lower in women than in men, regardless the postmenopausal state and type and adjustment for concomitant risk factors [33].

Thus, middle-aged grade-1 hypertensive women without adjunctive risk factors may be considered at low-to-moderate CV risk and may benefit from a monotherapy strategy.

In this group of patients, all 5 principal drug classes may be used, although the typical side effects of dihydropiridinic CCBs (leg edema and flushes) can be amplified and metabolic adverse effects of beta-blockers (BBs) and thiazide-like diuretics may combine with the natural higher occurrence in the menopause. Therefore, angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEi) monotherapies are the preferred first-line therapy.

8. Hypertension in the elderly

The benefits of treating BP also in older patients aged >65 years are well established and have been confirmed by the current European guidelines, which have devoted particular attention to frailty parameters (increased vulnerability resulting from aging-associated decline in reserve and function across multiple physiologic systems) [34], adherence issues and potential side effects of the therapy.

In view of these three important issues related to the management of hypertension in the elderly, it is evident that there is room for considering monotherapy to start drug therapy in these patients.

Recent analyses and meta-analyses of RCTs have further substantiated the advantages of treating hypertension in the elderly.

In the SPRINT SENIOR trial, a subgroup analysis of patients aged >75 years enrolled in the SPRINT trial, intensive BP treatment is associated with a significant reduction of non-fatal and fatal CV events and all-cause mortality, in the absence of an increased incidence of adverse events [35].

A meta-analysis of 10,857 patients [36] has investigated data from the SPRINT SENIOR study, the JATOS (Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients) trial in patients aged >65 years [37], the VALISH (Valsartan in Elderly Isolated Systolic Hypertension) trial [38] and from a study conducted by Wei et al. in subjects aged above 70 years [39], demonstrating that BP-lowering treatment significantly reduced MACEs by 29%, CV mortality by 33%, HF by 37% and, although without statistical significance, MI and stroke by 21% and 20% respectively [36].

Even in patients aged >80 years, the HYVET (Hypertension in the Very Elderly Trial) study has formerly provided data supporting benefits in CV risk reduction [40].

On the basis of these results, the 2018 ESC/ESH guidelines recommend a BP-lowering treatment in elderly patients with SBP > 140 mmHg, with a therapeutic target between 130 and 140 mmHg, provided that it is well tolerated [1]. In frailer individuals or in very-elderlies aged >80 years, monotherapy represents the most reasonable choice in terms of benefit/risk ratio [1].

Table 3
Specific conditions and first choice antihypertensive drugs for monotherapy. (Based on Refs. [1, 44]).

Clinical conditions	Preferred classes of drugs
High-normal BP and high or very-high CV risk	ACEi/ARBs or BBs in CAD
Grade 1 hypertension and low-to-moderate CV risk	ACEi/ARBs or CCBs or diuretics
Masked and white coat hypertension	ACEi/ARBs or CCBs or diuretics
Younger male adults	ACEi/ARBs or CCBs or diuretics
Pregnancy or women programming pregnancy	BBs or CCBs or alpha-methyldopa
Middle-age women in menopause	ACEi/ARBs
Elderly	ACEi/ARBs, CCBs or diuretics

In elderly patients with CAD, BP should be lowered slowly, in order to limit or to avoid the occurrence of J-curve-related risk of myocardial ischemia as a consequence of reduced coronary blood flow [41].

An increased risk of recurrent cerebrovascular events has also been described in elderlies with recent ischemic stroke and SBP maintained in a low-normal range (<120 mmHg), due to a significant reduction in cerebral perfusion [42]. For these reasons, monotherapy can be identified as the best therapeutic option for these categories of patients.

9. Benefits from the five major classes of antihypertensive drugs

The five major classes of antihypertensive drugs, including ACEi, ARBs, diuretics (thiazides, chlortalidone and indapamide), CCBs and BBs have been demonstrated to be effective in reducing CV outcomes and may be used as first-choice treatment, both as monotherapy and combination therapy [43].

However, some classes of drugs should be preferred in specific clinical conditions, as reported in Table 3 which is largely based on European guidelines [1,44].

Among all these pharmacological classes, ARBs display the most favorable tolerability profile, since they do not have any adverse metabolic effects and they cause cough and angioedema only in a minority of cases. They can be prescribed once daily in most patients, have been associated with the lowest rate of therapy discontinuation and with the best adherence. On the basis of these practical considerations, this pharmacological class probably represents the most suitable approach for patients who may start antihypertensive treatment with a monotherapy strategy. This is particularly true for long-lasting ARBs [45].

Among these ARBs, olmesartan is the compound with the widest documented antihypertensive effect both as monotherapy or in combination and at different dosages, probably related to its more prolonged receptor binding, associated with an “insurmountable” AT1 receptor inhibition, which characterize its long-lasting BP lowering effect, which is desirable when monotherapy is chosen [46].

Several studies have demonstrated that olmesartan produced a significant greater and faster BP reduction and a higher percentage of patients achieving BP goal compared to other ARBs [47–49].

In addition, olmesartan has been demonstrated to produce a sustained BP lowering, even during the last hours of the inter-dose period, with a significantly greater reduction of night-time and 24-hour SBP and DBP, also in low-risk patients without HMOD [50].

10. Conclusions

Although there is increasing evidence about the benefits of combination antihypertensive therapy in improving BP control and reducing CV events, even as first-line choice, some categories of subjects, in particular those with high-normal BP, elderly patients and grade 1 hypertensives with low-to-moderate CV risk or aged <50 years without other comorbidities, may still benefit from an early BP-lowering treatment based on a monotherapy strategy.

Among the five major classes of antihypertensive drugs, ARBs present the most favorable tolerability and adherence to the treatment profile.

Conflicts of interest

Massimo Volpe has received honoraries as a speaker from Menarini International and Daiichi Sankyo.

Giuliano Tocci lectured for Daiichi Sankyo and Menarini.

Giovanna Gallo has no conflicts of interest to disclose.

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