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Is early and fast blood pressure control important in hypertension management?

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ABSTRACT

Control of blood pressure (BP) in hypertension is recognized as a key measure in the management of cardiovascular (CV) risk and is a cornerstone of preventive strategies. It is not defined, however, whether an initiation of the antihypertensive treatment in the early stages of hypertension (such as prehypertension or high-normal BP), may bring benefits for the long-term prevention of CV events. In addition, it has not been thoroughly addressed the issue whether achievement of a prompt BP reduction in hypertensive patients may contribute to reduce CV damage and events.

The aim of this article is to critically examine data from studies exploring these important questions. Our conclusion is that the available evidence, though not very extensive, supports the prevailing benefits associated with early BP control. We also discuss the therapeutic strategies to achieve early control of BP. Finally, we believe that this aspect deserves to be more thoroughly addressed in upcoming international guidelines.

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1. Introduction

Hypertension is a major cardiovascular (CV) risk factor and blood pressure (BP) lowering therapies are able to reduce the incidence of myocardial infarction, stroke, heart failure, CV and all-cause mortality [1]. These findings have been recently confirmed by a large meta-analysis conducted by Ettehad et al., including 68 randomized clinical trials performed between 1966 and 2013 [2].

In view of the impressive growth of the number of hypertensive patients (from 594 million in 1975 to 1.13 billion in 2015) [3], the detection of elevated BP is a fundamental step of any CV prevention strategy and its treatment has outstanding health benefits. Many patients, however, are still unaware of their diagnosis, are untreated or do not receive therapeutic regimens adequate to control BP within normal limits [4].

A recent analysis of data from European registries [5] has shown that on average only 39% of hypertensive patients achieve an adequate BP control. The proportion of patients reaching therapeutic targets, however, is increasing worldwide (in Italy to about 61%), though remaining unsatisfactory [6].

Multiple reasons may be advocated to explain persistent poor control of BP. Among these reasons, late or ineffective treatment, leading to irreversible or difficult to reverse adaptations of the CV system, may play a role.

Thus, among the strategies which may be adopted to obtain more effective and long lasting BP reductions in hypertensive patients, one possible approach, that has been repeatedly suggested in the past, though never proved, relies on an early start of treatment and, even more, on the early achievement of BP control.

In this regard, one real challenge is to unequivocally establish when to initiate the treatment, if it is worth to pharmacologically treat all grades of hypertension, and if it is possible to define a timeframe, from the initiation of the treatment to the achievement of BP control, which may eventually impact on CV outcomes. On this aspect, guidelines have so far rather elusive, whereas a position seem to be appropriate and needed.

We review here the literature on the evidence of the effects of early and effective BP control in hypertension, keeping a focus also on the targets to reach. With this approach we attempt to provide physicians with the available data supporting the benefit of early BP control.

We also discuss pharmacological interventions which may promote early BP reduction in hypertensives.

Abbreviations: BP, blood pressure; CV, cardiovascular; CAD, coronary artery disease; HF, heart failure; MI, myocardial infarction; CCB, calcium channel blocker; ARB, angiotensin receptor blocker; VALUE, Valsartan Antihypertensive Long-term Use Evaluation; ALLHAT, Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial; ASCOT-BPLA, Anglo-Scandinavian Cardiac Outcomes Trial-BP Lowering Arm; SCOPE, Study on Cognition and Prognosis in the Elderly; REGARDS, Reasons for Geographic and Racial Differences in Stroke; MESA, Multi-Ethnic Study of Atherosclerosis; BPLTTC, BP Lowering Treatment Trialists' Collaboration; TROPHY, TRial Of Preventing Hypertension; HCTZ, hydrochlorothiazide; TRINITY, TRIple therapy with olmesartan medoxomil, amlodipine, and hydrochlorothiazide in patients study.

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2. Fast achievement of BP control

Although several trials have contributed to support the concept that prompt BP control may produce long-lasting BP reduction and decrease the incidence of CV events, a precise and univocal definition of the significance of early success and which early therapeutic strategies to choose are still lacking.

The trial that is paradigmatically quoted to support the beneficial effect of early BP control on major CV events is the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study [7], which compared the antihypertensive efficacy of the calcium channel blocker (CCB) amlodipine with the angiotensin receptor blocker (ARB) valsartan. Although the study was designed to assess the potential difference between the two arms, a prespecified, wide post-hoc analysis comparing the outcomes in "immediate" vs "non-immediate" responders was performed, and it revealed very interesting and provocative data. In fact, the achievement of systolic BP below 140 mm Hg within 6 months, defined as "immediate response", independently on the treatment adopted, was associated with a significant reduction of CV outcomes when compared to "non-immediate responders" (those who did not respond within the first 6 months). Even better results, in terms of combined cardiac events, stroke and all-cause mortality, were obtained in "immediate" responders, when identified with those previously untreated patients with a systolic BP reduction of 10 mm Hg within the first month, or patients previously controlled with other drugs, whose BP levels did not rise after the switch to the medications adopted in the trial [7].

These results are consistent with the findings of other large randomized trials.

Data derived from the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) suggest that the achievement of BP control within 6 months is associated with a significant reduction of stroke incidence. In this large study, non-immediate responders had a higher incidence of combined CV disease, coronary artery disease (CAD) and heart failure (HF) [8].

Also, the Authors of the Anglo-Scandinavian Cardiac Outcomes Trial-BP Lowering Arm (ASCOT-BPLA), that assessed the superiority of amlodipine-based vs. atenolol-base therapy, in reducing fatal and non-fatal stroke, total CV events and procedures and all-cause mortality, attributed this finding to the early BP lowering effect of amlodipine during the first year of treatment [9].

Consistent with these results, the Study on Cognition and Prognosis in the Elderly (SCOPE), which analyzed the effect of candesartan on preventing major events in 4964 hypertensives, demonstrated the benefits, in terms of reduction of stroke, of an early BP control within the first 3 months of treatment [10]. The beneficial effect of fast BP control, within 6 months but even more within 1-to-3 months, was confirmed also in patients at high CV risk [11]. The results of these studies are reported in Table 1. Indeed, they are strengthened by a recent meta-analysis that has shown that achievement within a year of a BP reduction of 10 mm Hg, for systolic values, and 5 mm Hg, for diastolic, reduced coronary artery disease events by 22% and stroke by 41%, this effect being maintained over the long term [1].

Altogether, these findings consistently support that the benefit of BP control is enhanced by rapidly achieving the response, and it can be speculated that the faster is the goal achievement, the more sustained is the CV protection.

If it might be true that earlier is better, evidence about the period of time within which is critical to reach therapeutic BP targets are still lacking.

3. BP control with drug treatment in mild hypertension and prehypertension

It is also not clear whether treating all grades of hypertension may be considered as part of an early therapeutic strategy and the debate about the need to start a prompt treatment in all patients at different levels of CV risk remains.

Major international guidelines [12,13,14,15,16] vary about the recommendations for drug treatment in grade 1 hypertension and in patients at lower levels of CV risk.

The issue remains controversial and challenging nowadays, whereas univocal recommendations have become a clinical need.

On the basis of the results of several studies and meta-analyses [17,18,19,20,21], which definitely support a more intensive control of systolic BP independently from CV risk levels, and regarding the new lower thresholds of BP normality (130/80 mm Hg) advocated by the recent North-American guidelines [22], the prompt initiation of antihypertensive therapies may contribute to the achievement of these proposed new therapeutic targets.

Current guidelines and risk prediction models take into account BP levels only at the moment when the risk prediction is performed, not considering the potential consequences of development of high BP levels earlier in life, and of the cumulative effect linked to the long-term exposure to high BP and to the associated risk over time.

Analyses from the Framingham Heart Study [23], the REGARDS study (Reasons for Geographic and Racial Differences in Stroke) [24] and the MESA (Multi-Ethnic Study of Atherosclerosis) [25] have shown that individuals with higher BP levels, even below the diagnostic threshold for hypertension, have an increased prospective risk of clinical and subclinical CV disease, especially when lifetime risk is estimated.

Loria et al. have demonstrated that BP levels in young adulthood better predict development of coronary calcium score 15 years later [26].

In the CARDIA study, adults with a longer exposure to higher BP showed an increased risk of organ damage, atherosclerosis, kidney disease and myocardial infarction (MI). These individuals may indeed have a low short-term, but a high lifetime, CV risk [19].

On the basis of these reports and in view of the direct relation between BP levels and CV events that have been demonstrated by several epidemiological studies, starting from values of 115/

Table 1
Reduction of CV outcomes with Renin Angiotensin System blockers-based therapies achieving early BP control (3–12 months) in large randomized control trials.

Trial	Number of patients	Timeframe to reach BP <140/90 mm Hg	Mean BP reduction (mm Hg)	CV outcomes	Reduction of CV outcomes in early BP response (%)
VALUE	14,400	6 months	12.3/6.1	Total CV events	12
				Stroke	17
				All-cause death	10
ALLHAT	42,418	6 months	6.7/4.4	Stroke	33
				Total CV events	21
				All cause death	16
				HF	22
ASCOT-BPLA	19,342	1 year	21.9/11.7	Fatal and non-fatal stroke	23
				Total CV events	16
				All-cause mortality	11
SCOPE	4964	3 months	21.7/10.8	Fatal and non-fatal stroke	24

70 mm Hg, it is reasonable to assume that initiating an early antihypertensive treatment, also in subjects with grade 1 hypertension or high-normal BP, may be associated with long-term clinical benefits [27].

A recent meta-analysis of the BP Lowering Treatment Trialists' Collaboration (BPLTTC) has analyzed data of grade 1 hypertensive patients with low-to-moderate CV risk from 10 randomized clinical trials. Pharmacological treatment was associated with a significant reduction of CAD, stroke and CV and all-cause mortality, independently from concomitant risk factors and baseline BP levels [28] (Fig. 1).

These data have been confirmed also in another meta-analysis of 68 trials, involving >245,000 individuals at different levels of risk, ranging from low-to-moderate to very-very high. This shows that relative reductions of all outcomes are comparable among groups, with absolute risk reductions increasing proportionally to the level of CV risk. The proportional decrease in disease events, for a given BP reduction, was the same irrespective of BP before treatment, thus supporting the advantages of the treatment also in grade 1 hypertensives [29]. Although the absolute beneficial effect of anti-hypertensive treatment is greater in the highest risk categories, the residual risk of major events, that occur even when adequate BP control is achieved, is proportional to the estimated baseline CV risk and the greatest success is reached in low-to-moderate risk patients, before the occurrence of overt organ damage [1,11].

Another challenging question is whether the incidence of hypertension can be decreased starting medications in subjects with prehypertension (systolic of 120–139 mm Hg or diastolic of 80–89 mm Hg), or high-normal BP (130–139/85–90 mm Hg) and if the residual risk can be further reduced in these categories.

Several studies have shown that about 60% of untreated prehypertensive patients will develop hypertension within 4 years, with a 3-fold greater risk than in subjects with BP values <120/80 mm Hg.

The role of pharmacological therapies in preventing the onset of hypertension has been investigated in the TRial Of Preventing HYpertension (TROPHY), which underlined the insufficiency of educational intervention in most of patients with BP above optimal threshold and other concomitant risk factors, and suggested that a long-term pharmacological strategy initiated in the prehypertensive stage may provide protective effect [30].

Several studies have demonstrated that prehypertensive individuals, who often present other associated CV risk factors, have an increased risk profile compared to those with optimal BP <120/80 mm Hg, independently of progression to hypertension, even if major events may occur many years later than in patients with established hypertension.

This goes along with the historical meta-analysis of Collins et al., showing that the risk of stroke and myocardial infarction progressively increases starting from 115 mm Hg systolic BP for each decade of age

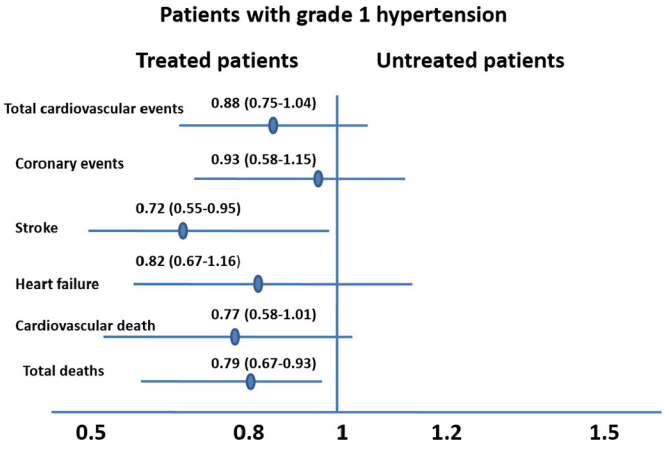

Fig. 1. CV outcomes in treated vs. untreated patients with mild hypertension. Modified from Ref 28.

[31]. The rate of CV events is increased also in "stage 1" prehypertension (BP 120–129/80–84 mm Hg), although their incidence is halved compared to individuals with "stage 2" hypertension. In absolute terms, the estimated rate of CV events is 1.0%/year in the high-normal BP range, compared to 0.5%/year in persons with normal BP.

In the Strong Heart Study, the incidence of CV disease was 1.8 fold higher in the prehypertensive cohort and even higher (2.1 fold) in patients with high-normal BP levels, even after demographic adjustments [32].

Thompson et al. have investigated the effects of BP lowering therapy in patients with normal or high normal BP levels, without a background of antihypertensive treatment, on fatal and nonfatal CV events in a large cohort of 64,162 patients from 25 randomized clinical trials. Antihypertensive treatment was able to reduce the incidence of stroke, MI, HF, CV and all-cause mortality [33].

Thus, prehypertension needs to be clinically monitored and eventually treated especially when high total risk is estimated. Therefore, prevention strategies need to be carefully considered and extended to all CV risk categories.

Since CV disease often reflects a multifactorial disorder, additional risk factors often cluster in hypertensive patients, with a greater prevalence compared to normotensive individuals, as documented by several epidemiological studies.

The coexistence of several risk factor exponentially increase the incidence of major CV events, 6-fold greater in hypertensive men with elevated cholesterol concentrations and smoking habit compared to subjects with high BP nonsmokers with normal cholesterol levels [34,35].

Due to the continuum of CV risk, it is reasonable to postulate that earlier BP treatment, by reducing the cumulative exposure to high BP levels, may contribute to prevent, or at least delay, the development of end organ damage and may abolish, in the absence of other risk factors, or at least reduce, if additional risk factors are present, the excess of CV risk.

4. Therapeutic strategies for early BP control

For patients without a compelling indication for a specific class of antihypertensive medication, according to current Guidelines [15,22], physicians may start and maintain therapies with diuretics, beta-blockers, CCBs, angiotensin-converting enzyme inhibitors and ARBs, either as monotherapy or in combinations. However, different classes provide different CV protection, independent of BP reduction, as paradigmatically observed in some large trials [36,37].

In addition, it must be considered that a single-drug therapeutic regimen is often insufficient to reach an early BP control, especially in patients with higher baseline BP levels and other CV risk factors.

Several studies have demonstrated that initiation with a dual combination, especially as a single-pill, is associated with a faster and greater antihypertensive effect and a more persistent BP control at one-year follow-up. An adequate BP control was more likely to be obtained during the first year of therapy in patients initially treated with single-pill combination than in those who began with free combinations or monotherapy, with a better adherence and a greater persistence on therapy [38,39,40].

Due to their favourable role in prevention of major CV events, and to the good tolerability profile and to their pathophysiological synergies with other pharmacological classes, drugs blocking the Renin-Angiotensin-System, e.g. ARBs are frequently used as first-line therapy and represent the basis of single pill combinations.

In particular, among available ARBs, there is growing evidence of the higher efficacy of the long-lasting compounds, such as olmesartan medoxomil, in achieving an early and sustained BP control.

Several studies have demonstrated that a greater percentage of patients treated with olmesartan achieved BP targets, compared to those who received initial doses of losartan, candesartan, valsartan

and irbesartan, with a significant greater reduction of both clinical and ambulatory systolic and diastolic BP levels, already after 1,2, 4 and 8 weeks of therapy, both in naïve and previously treated patients and independently from the grade of hypertension [41,42,43,44,45,46] (Fig. 2).

Olmesartan has a greater efficacy than irbesartan, valsartan, losartan and candesartan in reducing 24-h ambulatory systolic and diastolic BP after 8 weeks treatment [39]. The proportion of patients treated with olmesartan, who were normalized, was higher compared to those who received losartan 50 mg, irbesartan 150 mg or valsartan 80 mg, with a greater reduction of both systolic and diastolic BP [43].

These data have been confirmed by a large meta-analysis of 22 randomized controlled trials which assessed the better antihypertensive efficacy of olmesartan, in the absence of an increased risk of adverse events [47].

The efficacy and safety profile of olmesartan has been demonstrated also in combination therapies, with both CCs and diuretics, producing faster and lager reductions in both systolic and diastolic BP compared to associations based on irbesartan, telmisartan and valsartan [48].

In a treat-to-goal study conducted by Volpe et al., the triple-combination therapy of olmesartan, amlodipine and HCTZ resulted in incremental reduction of BP and in a significantly higher percentage of therapeutic goal achievement compared to the dual combinations [49].

Similar results have been obtained in the BP CRUSH and the TRINITY (the TRIple therapy with olmesartan medoxomil, amlodipine, and hydrochlorothiazide in hyperteNsIve patients studY) trials, which have demonstrated that both seated systolic and diastolic BP reductions were faster and greater with triple combination therapy of olmesartan, amlodipine and HCTZ, compared with those of dual combination therapies [50,51]. In all these studies the rate of early responders largely exceeded 60%, ranging on 67.5% in the presence of a rate of 1.2% of adverse effects [52].

Of course, other long-lasting compounds in the class, such as azilsartan, appear to have a similar effective profile in effectively reducing BP in hypertensives in a fast and sustained fashion.

The use of fixed-dose combination therapies represents a very attractive strategy for improving BP control and represents today one of the key elements for a successful large-scale hypertension program with the aim of obtaining BP control in the large majority of hypertensive patients, as well as higher levels of adherence and persistence of the treatment [53]. In this view, a platform approach has been proposed to help physicians in making the most appropriate choice, with therapies founded on single-pill fixed dose combination of two or three drugs, on the basis of grade of hypertension, concomitant risk factors and organ damage and comorbidities [54,55].

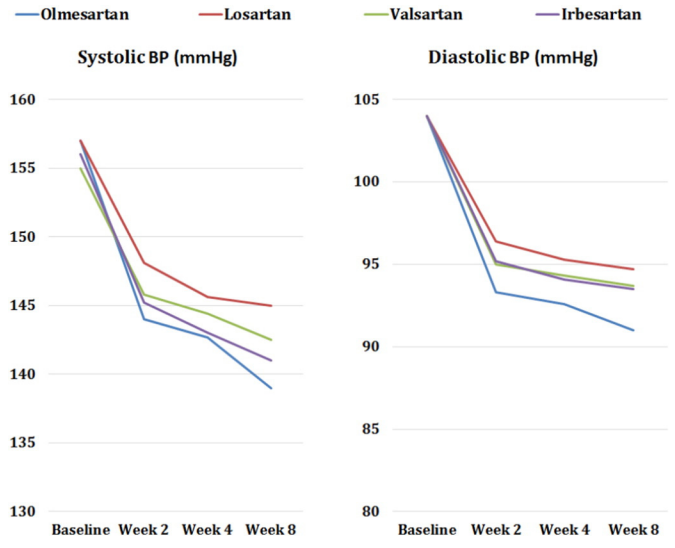

Fig. 2. Different speed of BP reductions of different drugs at initial dosages within the same class (ARBs).

Since initial treatment with two or more agents is associated not only with an earlier and more effective antihypertensive control, but also to more lasting results in terms of CV prevention, it is desirable that clinicians consider more and more frequently this strategy as first-line choice, especially in high or very-high risk categories.

Accordingly, international guidelines are progressively moving towards an extensive implementation of single-pill combination therapies in the clinical practice to achieve early and sustained control of BP.

5. Conclusions

Early start of an antihypertensive treatment is associated with a more effective and more lasting BP control and may reduce the impact of cumulative CV risk exposure. In addition, a fast achievement of BP control univocally leads to greater CV benefits. In this regard, more effective compounds within the same class, and even more, the early use of fixed-combination therapies, especially in single pill, can be preferred to achieve the objective.

Further perspective studies in this area are required and international guidelines will need to address this issue.

The Latin poet Horace wrote that "*Dimidium facti, qui coepit, habet*": "*A good start is half of the battle*": this appears to be suitable for a better hypertension management.

Conflicts of interest statement

Massimo Volpe has served in the speaking bureau and advisory board of Daiichi Sankyo, Menarini International, MSD, Novartis Pharma.

Giovanna Gallo has no conflicts of interest to disclose.

Giuliano Tocci lectured for Daiichi Sankyo and Menarini.

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