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GUIDELINES/CLINICAL TRIALS/META-ANALYSIS (WJ KOSTIS, SECTION EDITOR)

Legacy Effect in the Treatment of Hypertension: Persistent Cardiovascular Protection after Conclusion of Randomized Clinical Trials in Hypertension

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Abstract

Recent Findings Essential hypertension is the main determinant of cardiovascular morbidity and mortality worldwide. During the last decades, several antihypertensive drug therapies have been introduced and tested in clinical trials, both as monotherapies and combination therapies. The current recommended therapeutic approaches effectively reduce the lifetime risk of experiencing major cardiovascular outcomes and disabling comorbidities, such as myocardial infarction, stroke, and congestive heart failure. On the basis of multiple proofs, antihypertensive therapy is currently recommended for improving event-free survival rate and quality of life in different clinical settings and conditions. At the same time, other cardiovascular drugs, including novel lipid-lowering, anti-platelet, and anti-coagulation agents, have been made available and also contribute to reduce the incidence of atherothrombotic diseases.

Purpose of Review Beyond the beneficial aspects obtained by pharmacological treatment of major cardiovascular risk factors and comorbidities, including hypertension, several aspects remain to be defined. One major limitation linked to randomized, controlled clinical trials is represented by the relatively short duration of the studies, which usually ranges between 1 and 5 years. Whether antihypertensive therapy should be maintained for a longer time (after 5 years) and whether this is supported by sufficient evidence of a persisting benefit is supported by limited post-trial observations but mostly by findings derived from large clinical registries. The so-called *legacy effect* in the treatment of hypertension, in which patients who are treated with a given antihypertensive therapy may derive a long-term benefit after discontinuation of therapy, has been recently proposed on the basis of accumulating evidence and, in particular, on the availability of long-term post-trial observations in randomized controlled clinical trials.

Summary In this review, we discuss the evidence witnessing a legacy effect of antihypertensive therapy and whether this supports sufficiently lifetime drug treatment of hypertension.

Keywords Hypertension · Legacy effect · Randomized clinical trials · Myocardial infarction · Stroke · Cardiovascular prevention

Introduction

Essential hypertension is a major health care problem, being related to a persistently elevated burden of cardiovascular (CV) morbidity and mortality at the global level [1]. The clinical benefits obtained by lowering blood pressure (BP) levels to conventional therapeutic targets, namely systolic /diastolic BP (SBP/DBP) less than 140/90 mmHg for adult hypertensive outpatients and 140–150/90 mmHg in frail elderly individuals, have been demonstrated in numerous randomized clinical trials [2–5] and confirmed in several independent meta-analyses [6–8].

Previous sets of both European [9] and US [10] guidelines for hypertension management and control have proposed these goals to be achieved and maintained in treated hypertensive patients.

The most recent editions of US hypertension [11•] and European [12•] guidelines have consistently reassessed new

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and more stringent BP goals to be achieved under pharmacological therapies. Both guidelines also recommended to achieve these goals rapidly and to maintain the BP within the normal levels over time, an approach that has been associated with clinical benefits in terms of reduced risk of CV outcomes [13•].

Indeed, these recommendations are based on evidence derived from large, randomized, controlled clinical trials, which are often limited to the duration of these trials, which is often confined between 1 and 5 years. Whether antihypertensive therapy should be maintained for a longer time (after 5 years) and whether this is supported by sufficient evidence of a persisting benefit is more frequently sustained by findings derived from large clinical registries, beyond some findings originated by perspective evidence-based studies.

The legacy effect in the treatment of hypertension, in which patients who are treated with a given antihypertensive therapy may derive a long-term benefit after discontinuation of therapy, has been assessed on the basis of the availability of long-term post-trial observation in randomized controlled clinical trials.

A meta-analysis performed by Kostis WJ and colleagues in 2010, including 132,854 patients who took blood pressure–lowering medications for hypertension, myocardial infarction, and left ventricular systolic dysfunction, demonstrated that a significant decrease in overall mortality persisted after the end of clinical trials, when subjects in both the intervention and control groups were advised to receive active therapy [14].

However, it should be considered that the detection of this described legacy effect of antihypertensive therapy is influenced by a number of confounding factors, such as recommended therapeutic targets and the time to achieve BP control identified in previous studies, as well as the estimated cardiovascular risk of the enrolled populations.

With regard to the recommended goals, the results of the Systolic Blood Pressure Intervention Trial (SPRINT) [15•], a large, randomized, controlled clinical trial performed under the auspices of the National Institute of Health (NIH) have suggested that the incidence of a primary composite endpoint (myocardial infarction (MI), other acute coronary syndromes, stroke, heart failure (HF), or death from CV causes) and of all-cause mortality is reduced in an intensive treatment group (target SBP < 120 mmHg) than in a standard treatment group (target SBP < 140 mmHg). Although some former clinical studies had failed to demonstrate additional benefits of lowering further BP [16, 17], the need to aim for lower BP goals in hypertensive patients aging less than 65 years, especially when estimated risk profile is high, has been consistently recommended in the most authoritative international guidelines.

In this view, a first important issue to consider is the residual risk linked to BP levels, represented by the goals of BP predefined in numerous hypertension trials, which potentially affects BP legacy.

The residual risk of atherothrombotic events, despite an adequate BP control, is also influenced by baseline CV risk, remaining elevated in patients with high or very high risk [18•].

Thus, the greatest success of BP lowering is obtained in individuals with low-to-moderate risk, before the occurrence of hypertension-mediated organ damage [18•].

The results of a pioneering study performed in Sweden between 1970 and 1992 showed that, during a two-decade follow-up, hypertensive subjects, although a continuously adequate achievement of BP targets, had a significantly higher incidence of all-cause death (OR 1.6, 1.4 to 2.1), coronary heart disease (OR 1.9, 1.6 to 2.3), and mortality from stroke (OR 2.1, 1.4 to 2.7), compared with normotensives [19]. It is interesting that in this study the treated hypertensives showed an overall reduction of 40 mmHg but SBP remained on average greater than 145 mmHg.

Another compelling and very debated confounding factor is represented by the decision of when to start an antihypertensive therapy and whether to treat patients with low-to-moderate CV risk.

Although it has been demonstrated that the highest is the estimated CV risk, the greatest is the absolute risk reduction obtained by lowering BP, the results of several studies and meta-analyses have shown that the benefits on major CV outcomes are significant for any hypertension grade and stage [18•]. In addition, an analysis of available data indicates that the earlier the treatment is started and the earlier BP targets are achieved, the larger appears to be the benefit.

In fact, to reach the goal earlier and in a more effective way, new guidelines recommend to start with combination therapies on more than 70% of patients.

In the following sections of this review, we discuss the evidence supporting a legacy effect of antihypertensive therapy and whether this supports sufficiently lifetime drug treatment of hypertension.

Methodology of the Search

We reviewed the medical literature to identify randomized, controlled clinical trials, designed to test the long-term efficacy, safety, and tolerability of different antihypertensive therapies. In this perspective, a computerized literature search was carried out using the PubMed Medline database from January 2012 to May 2019. Only articles published in the English language on peer-reviewed journals and clinical trials performed in adults according to the recommendations of Good Clinical Practice were considered for the present review. The following key words were applied: “hypertension,” “high blood pressure,” “antihypertensive therapy,” “legacy effect,” “ACE inhibitors,” “angiotensin receptor blockers,” “antialdosterone agents,” “calcium channel blockers,” “beta-blockers,” “diuretics,” and “cardiovascular prevention.”

Long-Term Cardiovascular Protection in Hypertension Trials

The legacy effect has been observed in several randomized clinical trials performed with lipid-lowering therapies, mostly statins [20–25]. These trials demonstrated persistent benefits in patients previously assigned to statin treatment [20–25]. Several long-term observations of major hypertension trials have suggested similar beneficial effects of antihypertensive therapies after trial conclusion, though contrasting results have been also reported.

Legacy Effect in Trials Comparing Tight Versus Conventional Blood Pressure Control

The first evidence in favor of the legacy effect in hypertension derived from the findings of the Hypertension Detection and Follow-up Program (HDFP), which originally described a significant reduction in all-cause mortality after a 5-year follow-up period in the intensively treated (stepped care) group compared with (referred care) the control group [26••]. Six months after the close of the trial, a 2-year post-trial surveillance study, which extended mortality follow-up to 8.3 years, was conducted [26••]. The post-trial use of antihypertensive medications was reduced in the stepped and increased in the referred care groups, so that by the end of the post-trial period there was little difference in the percentages of participants taking antihypertensive medications between groups. Despite this aspect, BP control (as defined by mean diastolic BP and by percent of participants with a diastolic BP of 90 mmHg or less) was slightly better for stepped than for referred care participants (stepped care group, 86.5 mmHg and 68% controlled; referred care group, 87.8 mmHg and 62% controlled) [27••]. The absolute mortality advantage found at 6.7 years persisted and increased throughout the post-trial period of follow-up, despite discontinuation of the formal stepped care therapy program [27••].

Post-trial monitoring of patients in the United Kingdom Prospective Diabetes Study (UKPDS) [28••] examined whether risk reductions for microvascular and macrovascular disease, achieved with the use of improved BP control during the trial, would be sustained. Among 5102 UKPDS patients with newly diagnosed type 2 diabetes mellitus, 1148 patients with hypertension were randomly assigned to tight or less-tight BP control regimens. The 884 patients who underwent post-trial monitoring were asked to attend annual UKPDS clinics for the first 5 years, but no attempt was made to maintain their previously assigned therapies. Annual questionnaires completed by patients and general practitioners were used to follow patients who were unable to attend the clinic in years 1 through 5, and questionnaires were used for all patients in years 6 to 10. Seven pre-specified aggregate clinical endpoints were examined on an intention-to-treat basis, according to the previous randomization categories. Differences in BP between the two groups during the trial disappeared within 2 years after termination of the trial. Significant relative risk reductions were found during the trial for any diabetes-related endpoint, diabetes-related death, microvascular disease, and stroke in the group receiving tight, as compared with less tight, and BP control were not sustained during the post-trial follow-up. No risk reductions were seen during or after the trial for MI or death from any cause, but a risk reduction for peripheral vascular disease associated with tight blood pressure control became significant ($p = 0.02$).

The legacy effect was also investigated in the Second Australian National BP study (ANBP2) for those previously on pharmacotherapy and those who were not, as well as fatal events in the 6-year post-trial period [29••]. Study population consisted of ANBP2 participants without prior CV disease. In this study extension, it was observed that a higher in-trial CV and all-cause mortality rate and incidence of new-onset diabetes for those on previous treatment versus those who were treatment naive.

Legacy Effect in Trials Comparing Different Antihypertensive Drug Regimens

The legacy effect was also described for the long-term mortality rate of 4732 patients originally enrolled in the Systolic Hypertension in the Elderly Program (SHEP), who were randomized to a stepped care therapy with 12.5 to 25.0 mg/day of chlorthalidone or matching placebo (plus atenolol or matching placebo, if BP remained uncontrolled) [30••]. At a mean follow-up of 14.3 years, CV mortality rate was significantly lower in the chlorthalidone group than in the placebo group (adjusted HR 0.854, 95% CI 0.751 to 0.972). Presence of diabetes at baseline was associated with increased CV mortality rate (adjusted HR 1.659, 95% CI 1.413 to 1.949) and total mortality rate (adjusted HR 1.510, 95% CI 1.347 to 1.693). Also, new-onset diabetes was associated with increased CV adverse outcome (adjusted HR 1.562, 95% CI 1.117 to 2.184) and total mortality rate (adjusted HR 1.348, 95% CI 1.051 to 1.727), although only in the placebo group, while it did not have significant associations with CV mortality rate (adjusted HR 1.043, 95% CI 0.745 to 1.459) or total mortality rate (adjusted HR 1.151, 95% CI 0.925 to 1.433) in those patients treated with diuretics.

More recently, the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) trial was a prospective, multicenter, randomized, clinical trial, which enrolled 19,257 patients with hypertension and at least three other cardiovascular risk factors in the blood pressure–lowering arm (BPLA) [31••]. Since the trial has a factorial 2×2 design, 10,305 with non-fasting total cholesterol concentrations 6.5 mmol/L or less formed the Lipid-Lowering Arm (LLA) [32].

In the BPLA, patients were randomized to either an amlodipine-based regimen (amlodipine 5–10 mg plus perindopril 4–8 mg as required; $n = 9639$) or an atenolol-based regimen (atenolol 50–100 mg plus bendroflumethiazide 1.25–2.5 mg and potassium as required; $n = 9618$), while the LLA patients were randomly assigned additional atorvastatin 10 mg or placebo. Patients treated with the amlodipine-based regimen had lower BP values during the follow-up period than those allocated to the atenolol-based regimen. Similarly, atorvastatin-based therapy significantly reduced all lipid parameters compared with placebo.

As the trial was stopped prematurely, the primary endpoint of non-fatal MI and fatal coronary heart disease did not reach significance (hazard ratio (HR) 0.90, 95% confidence interval (CI) 0.79–1.02; $p = 0.1052$) in the BPLA [31••]. On the other hand, in the LLA, the primary endpoint occurred in 100 patients allocated to statin therapy and in 154 patients allocated to placebo, thus achieving statistical significance (HR 0·64 (95% CI 0·50–0·83), $p = 0{\cdot}0005$) [31••]. Beyond these aspects, the amlodipine-based regimen significantly reduced the primary and secondary endpoints of all-cause mortality (by 11%; $p = 0.0247$), CV mortality (by 24%; $p = 0.0010$), total CV events and procedures (by 16%; $p < 0.0001$), total coronary endpoints (by 13%; $p = 0.0070$), and fatal and non-fatal stroke (by 23%; $p = 0.003$), compared with the atenolol-based regimen [31••].

Following the publication of the main papers [31••, 32], the ASCOT Legacy Study reports mortality outcomes after 16 years of follow-up of the 8580 UK-based patients originally involved in the ASCOT trial. Among these, 3282 (38.3%) died, including 1640 (38.4%) of 4275 assigned to atenolol-based treatment and 1642 (38.1%) of 4305 assigned to amlodipine-based treatment; also, 1768 of the 4605 patients in the LLA died, including 903 (39.5%) of 2288 assigned placebo and 865 (37.3%) of 2317 assigned atorvastatin. Of all deaths, 1210 (36.9%) were from CV-related causes. Among patients originally enrolled in the BPLA, there was no overall difference in all-cause mortality between treatments (adjusted HR 0.90, 95% CI 0.81–1.01, $p = 0.0776$), although significantly fewer deaths from stroke (adjusted HR 0.71, 0.53–0.97, $p = 0.0305$) occurred in the amlodipine- based treatment group than in the atenolol-based treatment group. There was no interaction between treatment allocation in the BPLA and in the LLA. However, in the 3975 patients in the non-LLA group, there were fewer CV deaths (adjusted HR 0.79, 0.67–0.93, $p = 0.0046$) among those assigned to amlodipine-based treatment compared with atenolol-based treatment ($p = 0.022$ for the test for interaction between the two blood pressure treatments and allocation to LLA or not). In the LLA, significantly fewer CV deaths (HR 0.85, 0.72–0.99, $p = 0{\cdot}0395$) occurred among patients assigned to statin than among those assigned to placebo.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [25] was a multicenter randomized double-blind, active-controlled clinical study which investigated whether fatal coronary heart disease or non-fatal MI (primary endpoint) and all-cause and cause-specific mortality, stroke, HF, CV disease, and end-stage renal disease (secondary endpoints) were reduced among 42,418 high-risk hypertensive patients treated with amlodipine, lisinopril, or doxazosin each compared with chlorthalidone. Participants in the chlorthalidone ($n = 15{,}255$), amlodipine ($n = 9048$), and Lisinopril ($n = 9054$) groups were followed for a mean of 4.9 years, whereas doxazosin-based therapy was terminated early (3.25 years) due to a 25% higher incidence of CV events.

No statistically significant differences were demonstrated in the primary endpoint among groups.

The incidence of HF was 38% higher in the amlodipine group and the rate of CV disease, stroke, and heart failure was increased (10%, 15%, and 19% respectively) in the lisinopril group, compared with chlorthalidone.

The ALLHAT extension study (entire follow-up 8 to 13 years) has investigated whether the results obtained in the principal trial remained constant or changed over time and the potential development of new beneficial effects [33••]. The increased risks of HF in the amlodipine group and of stroke mortality in the lisinopril group were the only major outcomes confirmed in the extension study. However, the rate of HF mortality was reduced in the amlodipine group compared with chlorthalidone (HR = 0.71; 95% CI, 0.51–0.98, $p = 0.02$ for heterogeneity comparing in-trial with post-trial). In addition, the incidence of CV disease was lower in patients treated with lisinopril than in the chlorthalidone group (HR = 0.92; 95% CI, 0.85–1.00, $p = 0.02$ for heterogeneity comparing in-trial with post-trial) [33••].

However, it should be underlined that post-trial analyses were no longer protected by the double-blind design and that the diminished differences in some major outcomes may be consequent to the fact that antihypertensive regimens most likely became similar among groups.

Conclusions

Several trials have demonstrated the beneficial effects of BP control on CV events and mortality even after the discontinuation of antihypertensive therapy, the so-called legacy effect in the treatment of hypertension.

On the basis of this evidence, the future international guidelines should not only recommend a tight achievement of BP goals but also should clearly advise to maintain antihypertensive therapy over time, with the aim of providing the best possible long-term CV protection.

The potential legacy effect of antihypertensive treatment should be assessed in further studies aiming to achieve contemporary goals in both low- and high-risk patients on optimal therapy, using intensive BP-lowering strategies to control early BP (before organ damage development) and BP effectively.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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