Brief Reviews

Have ALLHAT, ANBP2, ASCOT-BPLA, and So Forth Improved Our Knowledge About Better Hypertension Care?

Peter T. Sawicki, Natalie McGauran

One of the major milestones in medicine during the last 40 years has been strong evidence from well-designed clinical trials showing that blood pressure–lowering interventions reduce hypertension-related morbidity and mortality.1 Whereas initially these results were in most cases achieved with high-dose thiazide diuretics, subsequent research demonstrated that dose reduction, including combination with potassium-sparing agents, is effective and decreases the risk of adverse effects.2-3 Since then, several new antihypertensive agents have been developed, but meta-analyses have not indicated a superior beneficial effect of these agents over conventional ones.4,5 However, many hypertension experts do not recommend thiazide diuretics as first-line treatment for hypertension, and guidelines are inconsistent.6-8

There were 2 major reasons for this failure to transform sound scientific evidence into practice. Firstly, potential thiazide-induced metabolic effects (eg, a transient increase in serum cholesterol and a serum potassium–dependent slight increase in blood glucose levels) were thought to be responsible for the so-called shortfall in the reduction in cardiovascular events (the gap between the epidemiologically estimated decrease in the risk of hypertension-related events and the magnitude of the decrease actually achieved in intervention trials).9 Second, protective effects beyond the blood pressure–lowering effect were attributed to newer agents, which include α-blockers, calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), and, more recently, angiotensin receptor blockers. Despite the fact that this theory was not confirmed in head-to-head trials, the vigorous marketing of these agents, combined with a campaign against the use of diuretics, changed prescription habits worldwide.10 This controversy was the reason for the largest hypertension study ever conducted: the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT). The results and implications of ALLHAT and 2 other controversially discussed studies, namely, the Second Australian National Blood Pressure Study (ANBP2) and the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA), are discussed here. It should be noted that their comparability is limited by different study designs and by marked differences in baseline blood pressures and risk profiles. An overview of these studies is presented in Tables 1 and 2.

The ALLHAT, ANBP2, and ASCOT-BPLA Hypertension Trials

ALLHAT was sponsored by the US National Heart, Lung, and Blood Institute in conjunction with the Department of Veterans Affairs. The National Heart, Lung, and Blood Institute received financial support from Pfizer Inc, USA, and its responsibilities included the collection, interpretation, and analysis of data, and the decision to submit the article for publication. Study medications were supplied by Pfizer Inc and AstraZeneca, USA.11,12

This randomized, double-blind, controlled trial included 42 418 hypertensive patients aged ≥55 years who had ≥1 other coronary heart disease (CHD) risk factor. The study was conducted in 623 centers in North America. A subset of patients participated in a lipid-lowering trial. In the antihypertensive component, first-line treatment (titrated to a maximum dose) with amloidipine, lisinopril, or doxazosin was compared with chlorthalidone. Additional agents, the step 2 drugs atenolol, clonidine, or reserpine, and the step 3 drug hydralazine could be added if necessary. Open-label step 1 drugs were to be avoided unless maximum tolerated doses of the 3-step regimen had unsuccessfully been tried.

The doxazosin arm of the study was terminated early with a median follow-up of 3.3 years because of a significantly higher incidence of combined cardiovascular disease events (in particular, congestive heart failure); negative trends were also observed for combined CHD and stroke. No significant difference was observed for the primary end point (combined fatal CHD or nonfatal myocardial infarction) or for all-cause mortality.13

In the other 3 arms, the full study period was completed (mean length of follow-up, 4.9 years). With respect to the occurrence of the primary end point (6-year rates), the newer agents were not significantly superior to the conventional one (chlorthalidone, 11.5%; lisinopril, 11.4%; P=0.81; amlodipine, 11.3%; P=0.65). P values for secondary end points do not seem to have been adjusted for multiple testing. For secondary end points (6-year rates), more strokes occurred with lisinopril than with chlorthalidone (6.3% versus 5.6%; P=0.02); the same applies to combined cardiovascular dis-
ease events (33.3% versus 30.9%; \( P < 0.001 \)). Heart failure (a component of a secondary end point) was more frequent with the newer agents (chlorthalidone, 7.7%; amlodipine, 10.2%; \( P < 0.001 \); lisinopril, 8.7%; \( P < 0.001 \)). At 5 years, among participants in the diuretic, CCB, and ACEI groups, 80.5%, 80.4%, and 72.6%, respectively, were receiving the blinded study drug or a drug of the same class (with or without other antihypertensive medication).

Superior blood pressure control in the diuretic group (versus ACEI) is likely to have contributed to the better outcomes.12 Poorer blood pressure and cardiovascular outcomes (eg, stroke) were especially evident in blacks treated with the ACEI. However, despite these race-specific differences, the overall findings hold for the total study population.14

In a posthoc analysis in patients with a reduced glomerular filtration rate, the CCB and ACEI were comparable with the diuretic in reducing the rate of development of end-stage renal disease or a decline in glomerular filtration rate of \( \geq 50\% \).15 A further posthoc analysis indicated that the cardiovascular outcomes of ALLHAT applied independent of level of renal function.16

In conclusion, the ALLHAT study demonstrated that, when used as first-line antihypertensive agents, with regard to the primary outcome, newer antihypertensive agents were not superior to conventional thiazide-based treatment. The results of secondary comparisons and posthoc analyses should be interpreted with caution. However, these findings also do not support the superiority of newer agents: (1) the ACEI-, CCB-, and \( \beta \)-blocker–based regimens were less effective than the thiazide-based regimen in preventing heart failure events; (2) the ACEI- and \( \beta \)-blocker–based regimens were inferior to the thiazide-based regimen with regard to stroke prevention, in particular in blacks; and (3) the theory that newer agents have additional protective effects beyond a blood pressure–lowering effect (eg, renoprotective properties) was not supported by the data.

Positive or negative metabolic effects of antihypertensive agents (eg, a higher incidence of hyperglycemia, hypercholesterolemia, and hypokalemia with thiazide-based treatment) did not seem to have an effect on the incidence of hard clinical end points, such as cardiovascular events or all-cause mortality. However, these were medium-term outcomes. Long-term effects of diuretics were investigated in an extended follow-up (mean, 14.3 years) of the Systolic Hypertension in the Elderly Program (SHEP) study in 4732 subjects randomly assigned to chlorthalidone or placebo. Diabetes diagnosed during diuretic
TABLE 2. Overview of the ALLHAT, ANBP2, and ASCOT-BPLA Hypertension Trials: Results

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>ALLHAT</th>
<th>ANBP2</th>
<th>ASCOT-BPLA*</th>
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</thead>
<tbody>
<tr>
<td>Duration, y</td>
<td>4.9 (mean)</td>
<td>4.1 (median)</td>
<td>5.5 (median)</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Not significant</td>
<td>Unclear†</td>
<td>Not significant</td>
</tr>
<tr>
<td>Combined fatal CHD or nonfatal myocardial infarction:</td>
<td>ACEI vs DU: All cardiovascular events or death from any cause: 56.1 vs 59.8 per 1000 PY; HR: 0.89; 95% CI: 0.79 to 1.00; P=0.05</td>
<td>Nonfatal myocardial infarction (including silent) and fatal CHD: 8.2 vs 9.1 per 1000 PY; HR: 0.90; 95% CI: 0.79 to 1.02; P=0.105</td>
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<tr>
<td>DUS: 11.5%</td>
<td>ACEI: 11.4%</td>
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<tr>
<td>(RR, 0.99; 95% CI: 0.91 to 1.08; P=0.81)</td>
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<tr>
<td>CCB: 11.3%</td>
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<tr>
<td>(RR, 0.98; 95% CI: 0.90–1.07; P=0.65)</td>
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<tr>
<td>Secondary outcomes‡</td>
<td></td>
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<tr>
<td>Combined CVD:</td>
<td>33.3% (ACEI) vs 30.9% (DU)</td>
<td>28.9 (ACEI) vs 32.8 (DU) per 1000</td>
<td>14.6 vs 16.8 per 1000 PY; HR: 0.87; 95% CI: 0.79 to 0.96; P=0.007.</td>
</tr>
<tr>
<td>and single CV events</td>
<td>(RR, 1.10; 95% CI: 1.05 to 1.16; P&lt;0.001)</td>
<td>HR: 0.86; 95% CI: 0.74 to 0.99; P=0.03.</td>
<td>Total CV events and procedures: 27.4 vs 32.8 per 1000 PY; HR: 0.84; 95% CI: 0.78 to 0.90; P=0.0001.</td>
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<tr>
<td>DUs: 7.7%</td>
<td>ACEI: 7.7%</td>
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<tr>
<td>(RR, 1.38; 95% CI: 1.25 to 1.52; P&lt;0.001)</td>
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<tr>
<td>CCBs: 10.2%</td>
<td>ACEI: 8.7%</td>
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<td>(RR, 1.19; 95% CI: 1.07 to 1.31; P&lt;0.001)</td>
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<tr>
<td>Tertiary outcomes¶</td>
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<tr>
<td>Cerebral events</td>
<td>Stroke:</td>
<td>Fatal stroke:</td>
<td>Stroke:</td>
</tr>
<tr>
<td>(6.3% (ACEI) vs 5.6% (DU))</td>
<td>(RR, 1.15; 95% CI: 1.02 to 1.30; P=0.02)</td>
<td>(2.3 (ACEI) vs 1.2 (DU) per 1000 PY; HR: 1.91; 95% CI: 1.04 to 3.50; P=0.04)</td>
<td>(6.2 vs 8.1 per 1000 PY; HR: 0.77; 95% CI: 0.66 to 0.89; P=0.0003.</td>
</tr>
<tr>
<td>Mortality (all-cause)</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Peripheral arterial disease: 2.5 vs 3.9 per 1000 PY; HR: 0.65; 95% CI: 0.52 to 0.81; P=0.0001.</td>
</tr>
<tr>
<td>Tertiary outcomes¶</td>
<td></td>
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<td>Development of diabetes mellitus: 11.0 vs 15.9 per 1000 PY; HR: 0.70; 95% CI: 0.63 to 0.76; P&lt;0.0001.</td>
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<td>Blood pressure</td>
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<td>Changes from baseline in mean SBP/DBP, mm Hg</td>
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<td>Changes in mean SBP/DBP</td>
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<tr>
<td>Between baseline in mean SBP/DBP</td>
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<td>Differences between groups</td>
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<td>At year 5: SBP lower in DU group</td>
<td>Identical decrease in SBP/DBP from baseline to year 5 in both groups</td>
<td>Average difference in SBP/DBP throughout trial between groups: 2.71 (9 mm Hg (P&lt;0.0001 for both SBP and DBP)</td>
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<td>(vs CCB: 0.8 mm Hg, P&lt;0.03; vs ACEI: 2 mm Hg, P&lt;0.001)</td>
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<tr>
<td>At year 5: DBP lower in CCB group</td>
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<td>(0.8 mm Hg, P&lt;0.001)</td>
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CVD indicates cardiovascular disease; DBP, diastolic blood pressure; DU, diuretic; HR, hazard ratio; PY, patient years; RR, relative risk; SBP, systolic blood pressure.

*Terminated prematurely. All noted differences in favor of the CCB (vs β-blocker).
†Primary end points according to the final publication (significance level: α=0.05). According to the protocol, death from any cause was not a primary end point.23
‡Outcomes with P<0.05 are presented here. ALLHAT and ANBP2: no adjustment for multiple testing; ASCOT: α=0.01.
§Component of a secondary outcome (other components not presented).
¶The final publication notes a significant reduction in all-cause mortality with amiodipine.25 This is contradicted by the protocol (α=0.01 for secondary and tertiary end points).24
¶Outcomes with P<0.01 are presented here.
therapy was not associated with an increased cardiovascular or total mortality risk. Furthermore, the course of diabetes was milder in patients who developed diabetes in the diuretics group compared with the placebo group.\textsuperscript{17} Diuretics-induced hypokalemia is related to poorer cardiovascular outcomes; this finding emphasizes the importance of monitoring serum potassium levels during therapy.\textsuperscript{18} The interchangeability of chlorthalidone and the more commonly prescribed hydrochlorothiazide has been queried; a literature review of studies investigating these agents did not show strong evidence in favor of chlorthalidone, and the use of either agent as a diuretic in antihypertensive therapy was recommended.\textsuperscript{19}

Shortly after the publication of ALLHAT, the results of ANBP2 were published. This trial was sponsored by the Australian Commonwealth Department of Health and Aging, the National Health and Medical Research Council of Australia, as well as Merck Sharp & Dohme (Australia), who provided support for infrastructure, including research nursing staff, data collection and analysis, and coordinating personnel. Data analysis and writing were performed independently, without the involvement of Merck Sharp & Dohme. Study medication was provided through the Australian Pharmaceutical Benefits Scheme.\textsuperscript{20–23}

This randomized, open-label, blinded end point, controlled study included 6083 hypertensive patients aged 65 to 84 years who otherwise had a relatively low cardiovascular risk profile. The study was conducted in 1594 family practices. Participants were followed for a median of 4.1 years. Treatment was initiated with either an ACEI-based or a diuretic-based regimen: enalapril and hydrochlorothiazide were the recommended agents; the choice of agent and dose was made by the family practitioner. The second-step therapy included \(\beta\)-blockers, CCBs, or \(\alpha\)-blockers. The third-step therapy recommended nonstep 2 drugs in both groups, or, according to the publication describing the protocol, \(\beta\)-blockers, CCBs, or other antihypertensive drugs were recommended.\textsuperscript{20–23} The information provided on the primary end point is consistent. According to the publication describing the protocol, “The primary endpoint of interest is total cardiovascular events (including cardiovascular deaths). Secondary endpoints include death and coronary heart disease events.”\textsuperscript{23} This is confirmed in an additional publication (“major comparison: total cardiovascular events [fatal and non-fatal]”).\textsuperscript{21} However, in the final publication, it is stated that “the primary endpoint was all cardiovascular events or death from any cause, both initial and subsequent fatal and nonfatal cardiovascular events were included. The 2 primary comparisons (all events and any first events) were tested at the 0.05 level of significance.”\textsuperscript{20} It, therefore, seems that the outcomes analyzed as primary end points were not defined as primary end points in the protocol. The respective rates were marginally significantly lower and nonsignificantly lower in the ACEI group (all cardiovascular events or death from any cause: 56.1 versus 59.8 per 1000 patient years [PY]; \(P=0.05\); first cardiovascular event or death from any cause: 41.9 versus 45.7 per 1000 PY; \(P=0.06\)).

Probability values for secondary comparisons were unadjusted for multiple testing to facilitate comparisons with other studies; it is noted in the final publication that the significance of these results should be judged cautiously.\textsuperscript{20} For cause-specific first events, the rate of myocardial infarction was lower in the ACEI group (4.7 versus 6.7 per 1000 PY; \(P=0.04\); with regard to fatal events, the rate of fatal stroke was higher (2.3 versus 1.2 per 1000 PY; \(P=0.04\)). The rate of first nonfatal cardiovascular events was lower in the ACEI group (28.9 versus 32.8 per 1000 PY; \(P=0.03\)); the rate of first nonfatal myocardial infarction was also lower (4.1 versus 5.8 per 1000 PY; \(P=0.05\)). At the end of the study, 58% of patients assigned to the ACEI group and 62% of patients assigned to the diuretic group were still receiving the assigned treatment (with or without other antihypertensive medication).

The finding that the relative benefits of an ACEI-based regimen were restricted to men is based on a posthoc gender-specific analysis; it is noted in the final publication that this observation should be interpreted with caution and requires confirmation.\textsuperscript{20} This result is, therefore, only suited to generate a hypothesis for future analyses.

In summary, the ANBP2 study does not prove the superiority of ACEIs over diuretics in hypertensive patients: (1) it is questionable whether the outcomes analyzed as primary end points were defined as primary end points in the protocol; (2) the open-label study design may have had an impact on additional therapeutic interventions and on the documentation of events (data collection was supported by the sponsor; issue of a potential conflict of interest); (3) the gender-specific subgroup analysis was conducted posthoc; and (4) diuretic agents for antihypertensive treatment were permitted in the ACEI group.

The results of ASCOT-BPLA have been published recently. This trial was mainly sponsored by Pfizer Inc, USA. According to the publication describing the protocol, “Funding has also been provided by Parke Davis, Ann Arbor, Michigan. Additional study medication was donated by the Servier Research Group, Paris, and Leo Laboratories, Copenhagen.”\textsuperscript{24} According to the final publication, “Funding was also provided by Servier Research Group, Paris, France. Drugs were supplied by Leo Laboratories, Copenhagen, Denmark, and Solvay Health Care, Southampton, UK.”\textsuperscript{25} The sponsors were not involved in the study design, or in the collection, analysis, or interpretation of data, or in the writing of the report.\textsuperscript{25}

This randomized, open-label, blinded end point, controlled study included 19,257 hypertensive patients aged 40 to 79 years who had \(\geq 3\) other cardiovascular risk factors. The study was conducted in 686 Scandinavian family practices and 32 British and Irish regional centers. A subset of ASCOT patients participated in a lipid-lowering trial. In the antihypertensive component, patients received initial treatment with amloidipine or atenolol, titrated to a maximum dose. If required, perindopril was added to amloidipine, and bendroflumethiazide and potassium to atenolol; further therapy consisted of adding doxazosin in both groups. The study was terminated prematurely after 5.5 years of median follow-up, despite the fact that the difference between groups with
regard to the primary end point, nonfatal myocardial infarction (including silent myocardial infarction) and fatal CHD, was not significant (amlodipine versus atenolol: 8.2 versus 9.1 per 1000 PY; \(P=0.105\)).

In the final publication, it is stated that there was a significant reduction in all-cause mortality (a secondary end point) in the amlodipine group.\(^2^4\) However, for secondary and tertiary end points, a significance level of 0.01 was pre-defined.\(^2^4\) Hence, the difference between groups with regard to all-cause mortality was not significant according to the statistical methods of this trial (amlodipine versus atenolol: 13.9 versus 15.5 per 1000 PY; \(P=0.025\)). For secondary and tertiary end points, \(P\leq0.01\) were shown in favor of the amlodipine group for the total coronary end point (14.6 versus 16.8 per 1000 PY; \(P=0.007\)), total cardiovascular events and procedures (27.4 versus 32.8 per 1000 PY; \(P<0.0001\)), cardiovascular mortality (4.9 versus 6.5 per 1000 PY; \(P=0.001\)), stroke (6.2 versus 8.1 per 1000 PY; \(P=0.0003\)), peripheral arterial disease (2.5 versus 3.9 per 1000 PY; \(P=0.0001\)), and development of diabetes mellitus (11.0 versus 15.9 per 1000 PY; \(P<0.0001\)). It is noticeable that both systolic and diastolic blood pressure were significantly reduced in the amlodipine group, which is likely to have contributed to the better cardiovascular outcomes.\(^2^5\) On average, 83% and 79% of patients were taking amlodipine and atenolol as allocated, respectively; 50% and 55% were taking the combination of amlodipine/perindopril and atenolol/bendroflumethiazide as allocated, respectively (in all regimens: with or without other antihypertensive drugs).

This study raises several issues, resulting in the conclusion that, in hypertensive patients, ASCOT-BPLA is not suited to prove the superiority of an amlodipine-based regimen over a \(\beta\)-blocker–based regimen including a thiazide diuretic: (1) the comparator of amlodipine was atenolol, a hydrophilic \(\beta\)-blocker, which may be less effective in antihypertensive therapy than other \(\beta\)-blockers and/or thiazide diuretics;\(^2^6^–2^7\), (2) only 55% of the patients in the atenolol group were treated with a combination of a diuretic and a \(\beta\)-blocker; (3) the differences between groups with regard to the primary study end point and all-cause mortality were not significant; (4) the open-label therapy might have influenced the treatment of patients and the documentation of events; and (5) the premature termination of the trial might have influenced the outcome, particularly because criteria for the termination of the study were not prospectively published, which may render the results noninterpretable.\(^2^8\)

### Discussion

In view of the poor quality of hypertension control, our supposed wealth of pharmacological knowledge is exposed as poverty. The sad truth is that whereas most people with hypertension around the world are untreated, and most of those treated are insufficiently controlled, we are performing megatials to find out whether in those treated and controlled patients (presumably numbering \(<10\%)\) a change in the initial conventional antihypertensive treatment to newer and much more expensive agents would provide additional benefits. This may be comparable to a fire brigade that starts cleaning windows while the house is burning down.
We should instead focus on how to realize widespread clinically and cost-effective hypertension care. To this end: (1) people need to be aware of their blood pressure levels; (2) patients with a diagnosis of hypertension need to be informed about the risk of untreated hypertension, the benefits of lifestyle changes, and the potential benefits and harms of treatment; (3) treated hypertensive patients need to know how to play an active role in therapy; and (4) physicians need to reconsider any preconceptions about antihypertensive agents.

In addition to screening programs, to enable patients to make well-informed choices about antihypertensive medication, new information technology solutions, training programs for physicians and patients, and reimbursement schemes are needed. Structured teaching and treatment programs aiming at better control in treated patients have been conducted previously. The results of these new ways to improve the quality of hypertension care are promising, but there is still a lack of evidence about the results of these new ways to improve the quality of hypertension care models tailored to meet the needs of both patients and physicians.

Further comprehensive programs are under way; ALLHAT researchers are currently launching a physician and patient education program to improve hypertension control in the United States.

Perspectives

Powerful therapeutic means to control hypertension effectively have been available for decades. However, the results achieved are insufficient; the lack of screening programs, as well as inadequate physician and patient education, may have contributed to this unsatisfactory situation. It is unlikely that there is a pharmacological magic bullet to solve these problems. We should, therefore, shift our focus toward narrowing the gap between theory and clinical practice by implementing programs to achieve effective hypertension control in the population. To make substantial improvements in this major field of medicine, further research is necessary into the development of new hypertension care models tailored to meet the needs of both patients and physicians.

Disclosures

None.

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