The Importance of Lowering Blood Pressure Quickly and Effectively in Hypertensive Patients

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Hypertension is a major risk factor for a host of cardiovascular (CV) and non-CV conditions. The association between rising blood pressure (BP) levels and increased risk of stroke, myocardial infarction (MI) and CV death is particularly illustrative of the importance of regulating BP levels.

Our understanding of the importance of BP-lowering for people with hypertension has prompted researchers to investigate the management of hypertension in considerable depth. Analysis of epidemiologic and clinical trial data have led to the current recommendations for BP goals and have provided invaluable insight into the kinds of therapies that are efficacious in lowering BP and reducing the risk of events. Furthermore, among strategies that have been proven effective, there is a growing body of evidence showing that certain regimens can produce more favorable outcomes than others. For example, regimens that lower BP more rapidly than others have been shown to be more effective in lowering the risk of major CV events. The most compelling data demonstrating this difference comes from the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study, the primary results of which were published in 2004.[1] In addition, the BP-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA) also provided evidence that faster BP lowering was associated with better outcomes.[2] These trials are reviewed in detail below. First, however, the importance of BP lowering in general, and the types of antihypertensive agents that can be used to lower BP, are briefly reviewed.

Importance of BP Lowering

Uncontrolled hypertension puts individuals at increased risk for a number of significant potential complications. The most important of these, as listed by the authors of the Canadian Hypertension Education Program (CHEP), are shown in Table 1.[3] The

Table 1
Conditions for Which Hypertension is a Major Risk Factor[3]

- Cerebrovascular disease
- Coronary artery disease
- Congestive heart failure
- Renal failure
- Peripheral vascular disease
- Dementia
- Atrial fibrillation

relationship between BP and risk for major vascular events is a linear one; for ischemic heart disease and stroke mortality, for example, risk rises in a steady slope from approximately 115 mmHg systolic and 75 mmHg diastolic.[4] Reductions below these BP levels have not been shown to result in additional reduction in risk.

Although benefits have been shown for having BP in the range of 115/75 mmHg, Canadian and international guidelines recommend a target BP of below 140/90 mmHg for most people, and below 130/80 mmHg for those with diabetes and/or chronic kidney disease. International guidelines suggest an optimal BP of 120/80 mmHg.

Treating hypertension to achieve these goals has been associated with significant reductions in risk for major events. The CHEP states that for individuals younger than 60 years, treating hypertension reduces the risk of stroke by 42% and the risk of a coronary event by 14%. For those older than 60 years, treating hypertension can be expected to reduce overall mortality by 20%, CV mortality by 33%, stroke by 40% and coronary artery disease by 15%.[3] For those with isolated systolic hypertension and older than 60 years, treating to target is associated with a 36% reduction in the risk of stroke and a 25% reduction in the risk of coronary events.

There do not appear to be any subgroups of individuals that do not benefit substantially from treating hypertension. The Blood Pressure Trialists' Collaboration (BPTC) has published a series of reports showing that significant reductions in risk for major CV events can be expected when BP is lowered in hypertensive patients, regardless of whether they are older or younger than 65 years,[5] whether they are men or women,[6] and whether or not they have diabetes.[7] The HYVET study,[8] in fact, recently demonstrated mortality benefit in octogenarians.

Antihypertensive Therapies

There are many different classes of antihypertensives available to treat hypertension, and many individual agents within those classes. The CHEP makes recommendations for which classes of agents to use as initial monotherapy depending on the individual patient's comorbidities. For example, for those who have systolic/diastolic hypertension without any compelling comorbidities, initial monotherapy can be selected from among five different classes of agents: angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, long-acting calcium channel blockers (CCBs) or thiazide diuretics (Figure 1).[9]

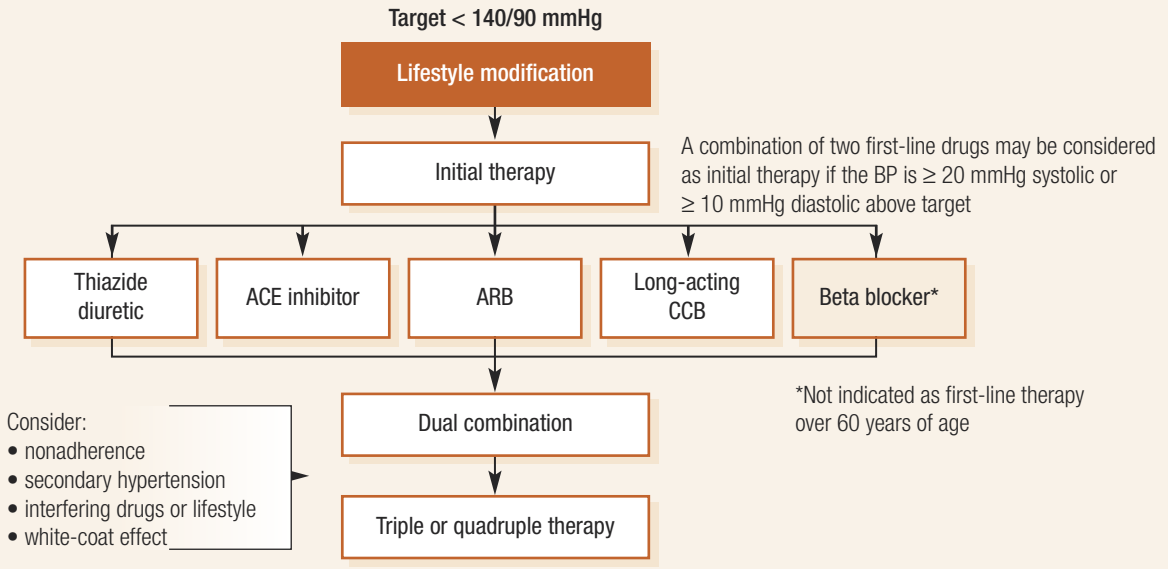
The presence of comorbidity narrows the therapeutic choices. For example, for patients with diabetes, the CHEP recommends an ACE inhibitor, ARB, thiazide diuretic or long-acting dihydropyridine CCB. For those with diabetes and evidence of nephropathy, the CHEP recommends using an ACE inhibitor or an ARB.

While the recommendations are quite specific in terms of recommended classes for initial monotherapy, they also emphasize the fact that combination therapy is most often required to achieve target BP. In fact, for those individuals who present with a baseline systolic BP of 20 mmHg or more above target, and/or a diastolic BP of 10 mmHg or more above target, the CHEP recommendations state that initial dual combination antihypertensive therapy can be considered, based in part on evidence from the ADVANCE trial.[10]

Effects beyond BP lowering. The main goal of antihypertensive therapy is to get the BP down to target, regardless of the agent or agents used. However, as suggested by the CHEP recommendations, it is recognized that there are differences between the antihypertensives in their impact on CV risk. These differences seem to be determined mainly by factors other than reduction of BP.

Indeed, there is a growing body of evidence demonstrating that certain antihypertensives have the ability to produce beneficial effects beyond their ability to lower

Figure 1
Treatment of Systolic/Diastolic Hypertension without Other Compelling Indications (CHEP Recommendations)[9]



BP. The majority of evidence of this type comes from studies involving agents that block the renin-angiotensin system (RAS: *i.e.*, ACE inhibitors and ARBs). The RAS is responsible for a number of processes that have an impact on CV disease. The deleterious effects of RAS overactivation are thought to be mediated through the binding of angiotensin II to the AT1 receptor. ARBs block this binding directly, while ACE inhibitors inhibit the formation of angiotensin II from angiotensin I.

These deleterious effects include vasoconstriction, sodium and water retention, and inflammatory and atherogenic responses. The effects are seen in various organs, including the heart, vasculature, brain and kidneys. There are also central effects: angiotensin II also promotes the release of norepinephrine, additional renin, endothelin, aldosterone and vasopressin.

Blockade of these effects by ACE inhibitors and ARBs has been shown in numerous clinical trials to provide protective benefits beyond BP lowering. For example, studies examining the effects of ARBs in patients with diabetes and renal dysfunction have shown that treatment with these agents is associated with significantly reduced risk of major renal endpoints compared to optimal non-RAS-blocking antihypertensive therapy.[11-14]

Also, the authors of the Canadian Diabetes Association guidelines recognize the non-BP-dependent cardioprotective qualities of ACE inhibitors and ARBs in patients with diabetes at high risk of vascular events, recommending that these patients receive treatment with one of these agents, regardless of BP level.[15]

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In the CHEP guidelines, the proven utility and efficacy of these agents is reflected by the fact that they are recommended as first-line therapy for a wide variety of clinical situations (Table 2). These recommendations are supported by clinical-trial ev-

Table 2
Clinical Situations in Which ACE Inhibitors or ARBs are Recommended Among Choices for First-line Therapy[9]

Clinical Situation	ACE Inhibitor	ARB
Hypertension without other compelling indications	✓	✓
Isolated systolic hypertension without other compelling indications		✓
Diabetes with nephropathy	✓	✓
Diabetes without nephropathy	✓	✓
Ischemic heart disease	✓	✓*
Recent MI	✓	✓†
Left-ventricular systolic dysfunction	✓	✓†
Cerebrovascular disease	✓‡	
Left-ventricular hypertrophy	✓	✓
Nondiabetic chronic kidney disease	✓	✓†

* Expected addition to the 2009 recommendations, based on the results of the ONTARGET study.

† If ACE inhibitor is not tolerated.

‡ In combination with thiazide diuretic.

idence proving utility of these agents for management of hypertension in these respective situations.

In addition, the CHEP recommends that ACE inhibitors be prescribed for most patients with ischemic heart disease, regardless of BP level (the same recommendation is expected to be extended to ARBs, based on the findings of the ONTARGET study).

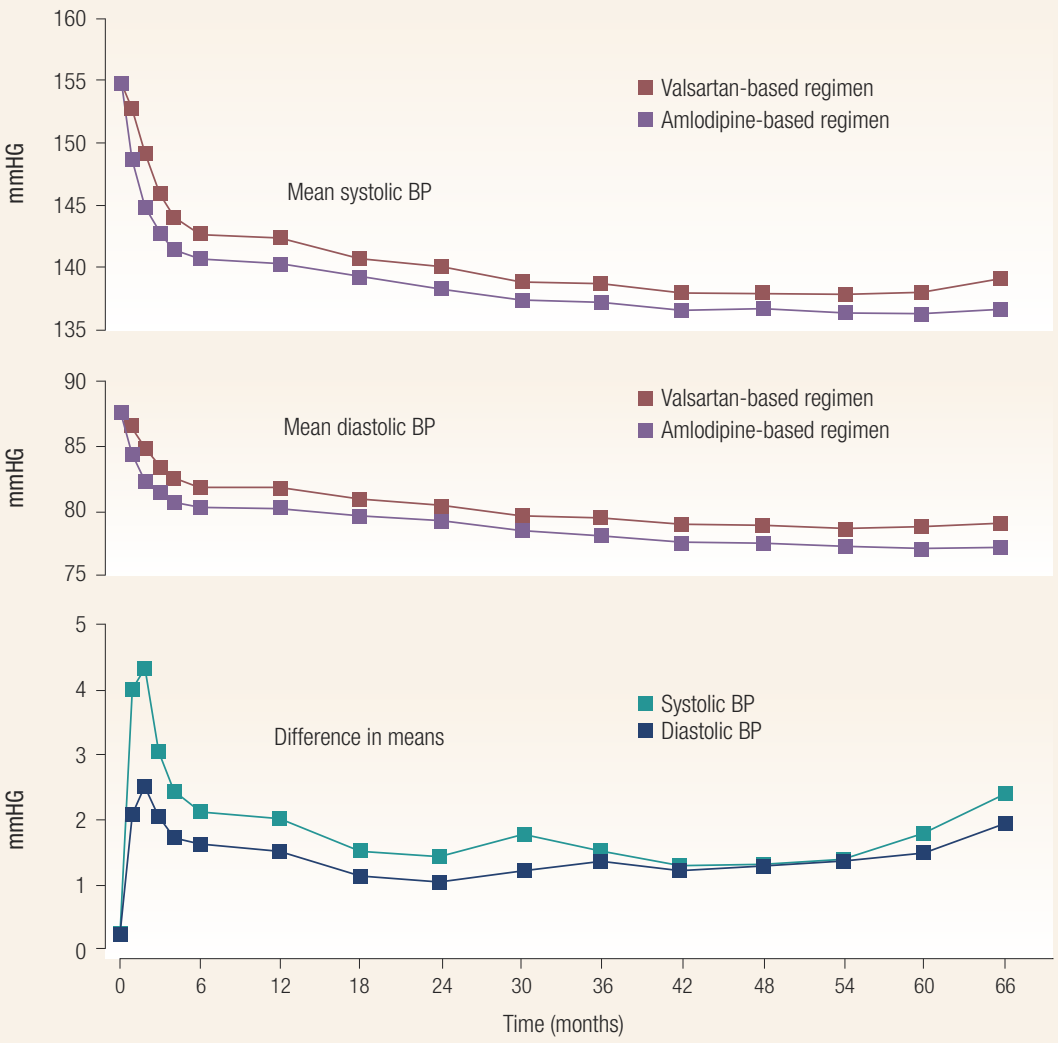
Importance of Rapid BP Lowering: Clinical Trial Evidence

The above discussion indicates that there may be important differences between antihypertensives in terms of BP-independent effects. Another important consideration is the observation that there may be differences in terms of the rapidity with which BP is lowered. Clinical-trial data demonstrate that these differences may also have a significant impact on outcomes.

VALUE. The VALUE trial was a large, double-blind, randomized, controlled study involving more than 15,000 patients with hypertension and high risk of CV events.[1] The subjects were randomized to either CCB (amlodipine)-based therapy or ARB (valsartan)-based therapy and followed for a mean of 4.2 years. The primary objective of the study was to determine whether valsartan-based therapy would reduce cardiac morbidity and mortality more than the amlodipine-based therapy. The regimens were designed such that the level of BP control would be equal in the two arms. First, study physicians were allowed to titrate the initial agent, then add and titrate hydrochlorothiazide, then add any other antihypertensive (except CCBs, ACE inhibitors or ARBs) to achieve the desired BP control (< 140/90 mmHg).

The primary outcome was a composite of cardiac mortality and morbidity: sudden cardiac death, fatal MI, death during or after percutaneous coronary intervention or coronary artery bypass graft, death due to heart failure, and death associated with recent MI on autopsy, heart failure requiring hospital management, non-fatal MI, or emergency procedures to prevent MI. For this endpoint, there were no significant differences found between the two therapies; it occurred in 10.6% of the valsartan-based group and 10.4% of the amlodipine-based group ($p = 0.49$). There was, however, a difference in

Figure 2
Mean Achieved BP in the VALUE Study[1]

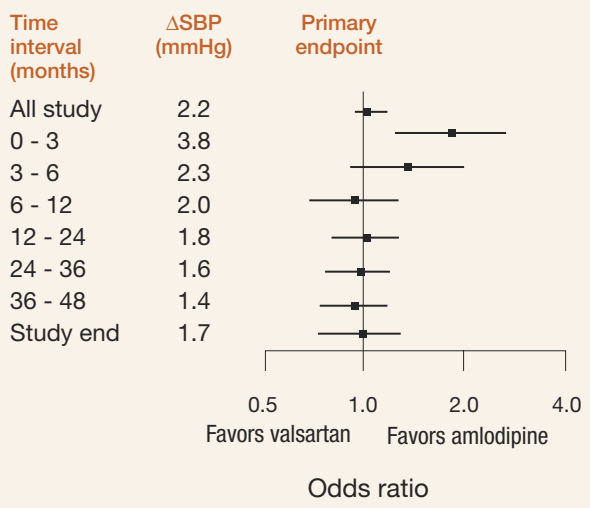


favor of amlodipine-based therapy in terms of MI (11% relative risk reduction; $p = 0.02$). The authors attributed the between-group differences to a significant observed difference in BP between the two arms, which was most notable during the first three months of the study (Figure 2). The difference from baseline to study's end in mean BP was an additional 2.1/1.7 mmHg in favor of amlodipine-based therapy. During the first three months, the mean difference was 4.2/2.2 mmHg.

These observations led the VALUE investigators to examine the primary outcome by time interval. They observed that during the first three months, when the BP differences were most pronounced, there was a statistically significant 78% increase in risk for the primary endpoint with valsartan-based therapy compared to amlodipine-based therapy (odds ratio 1.78; 95% confidence interval 1.22-2.60; Figure 3). There were no significant differences between groups during any other subsequent period in the study. The authors concluded that based on their findings, "recommended BP goals need to be reached within a relatively short time (weeks rather than months), at least in patients with hypertension who are at high CV risk."[1]

The impact of the early BP differences were further examined in a post-hoc analysis of the VALUE study.[16]

Figure 3
Odds Ratio for the Primary Endpoint in VALUE, by Time Period in the Study, with Mean Differences in Systolic BP[1]



Using the statistical technique of serial median matching, the investigators created two new groups out of the entire VALUE cohort, for whom the mean achieved BP was identical. This narrowed the population from the overall 15,245 patients in the actual VALUE study to 5,006 comprehensively matched patients in the post-hoc analysis. When these groups were compared, the investigators observed that most outcomes, including the primary endpoint, were closely similar for valsartan-based and amlodipine-based regimens, although significantly fewer hospitalizations for heart failure occurred among valsartan-treated patients. While this method significantly narrowed the VALUE population to one third of its original size and, thus, does not provide the same strength of evidence as a prospectively designed trial, its results are nonetheless informative and suggest that the major differences observed in the first three months of the VALUE trial were driven by differences in achieved BP.

ASCOT-BPLA. This study has also provided valuable data that supports the importance of rapidly achieving BP goals. ASCOT-BPLA was a multicentre, prospective, randomized controlled trial that included 19,257 patients with hypertension at high risk for CV events.[2] The regimens to which subjects were randomized were based either on amlodipine (with or without perindopril; n = 9,639) or atenolol (with or without bendroflumethiazide and potassium; n = 9,618). Patients were followed for a median of 5.5 years. The primary endpoint was a composite of non-fatal MI and fatal CHD. Like VALUE, the trial was designed so that the achieved BP would be similar in both groups. If the initial agent (amlodipine or atenolol) was not sufficient to achieve goal, the second element was added (perindopril or bendroflumethiazide + potassium). If this combination was insufficient, the protocol called for the addition of an alpha blocker (doxazosin).

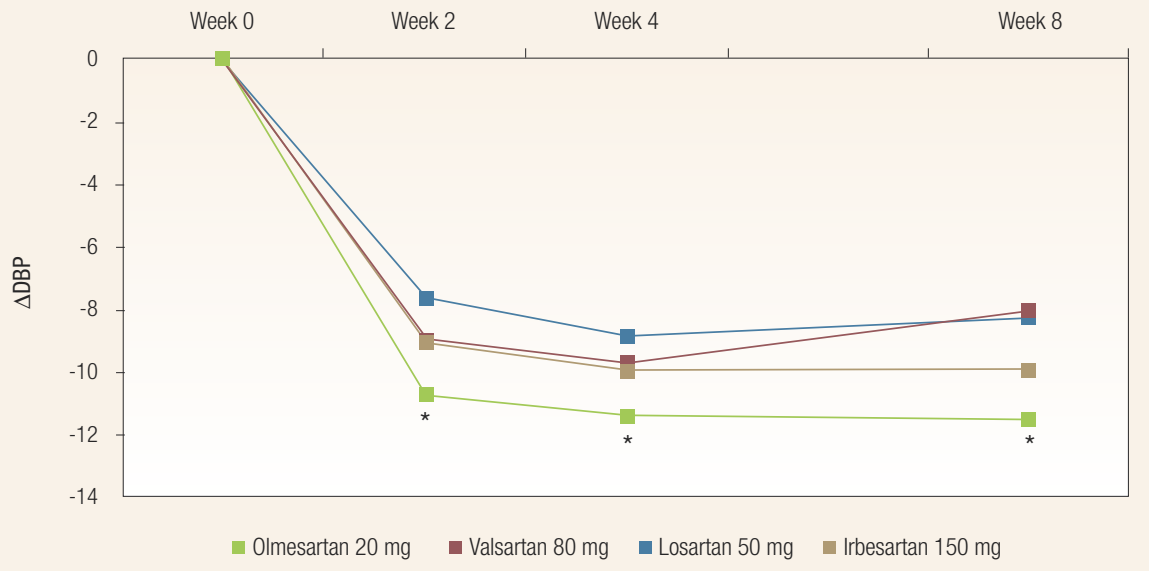
In the primary-endpoint analysis, there was a non-significant trend towards a higher risk with the beta-blocker/diuretic arm compared to the CCB/ACE-inhibitor arm (occurred in 9.1 per 1000 patient-years in the former group and 8.2 per 1000 patient-years in the latter; p = 0.1052). The differences in favor of the CCB/ACE-inhibitor group were significant for several of the secondary endpoints, including: non-fatal MI (excluding silent) and fatal CHD; total coronary events; total CV events and procedures; all-cause mortality; CV mortality; and fatal and non-fatal stroke

Just as was observed in VALUE, there were significant differences in achieved BP in ASCOT-BPLA, which were most pronounced in the early part of the study, but persisted throughout. Over the entire study, amlodipine/perindopril-based therapy was associated with an additional 2.7/1.9 mmHg drop in BP, while the difference during the first three months was 5.9/2.4 mmHg.

The authors of the ASCOT-BPLA paper concluded that the more "effective blood-pressure lowering achieved in ASCOT-BPLA by the amlodipine-based regimen, particularly in the first year of follow-up, is likely to have contributed to the differential CV benefits."[2] However, they also suggested that BP differences were likely only responsible for part of the observed differences, suggesting that there were also BP-independent improvements with the CCB/ACE inhibitor combination relative to the beta-blocker/diuretic combination.

In the same issue of the *New England Journal of Medicine* as the original ASCOT-BPLA paper, the investigators also published an analysis examining the various possible reasons for the difference in outcomes observed in their

Figure 5
Changes Over Time in Sitting Cuff Diastolic BP with Four Different ARBs[18]



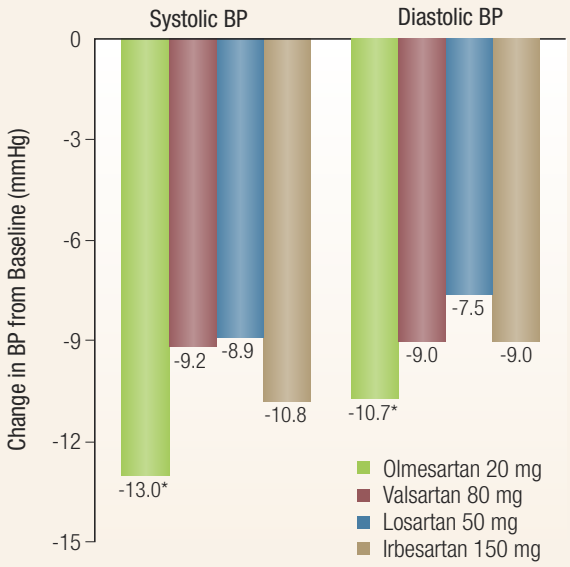
*$p < 0.05$ vs. irbesartan, losartan and valsartan

study.[17] They identified a number of potential confounders, including higher baseline BMI, serum triglycerides, creatinine concentrations, and fasting blood glucose values, as well as lower HDL-cholesterol concentrations, in the atenolol-based group. However, they also noted that the outcome differences were at least partially mediated by the early differences in BP between the two groups. The authors of the post-hoc analysis stated that "...early differential BP control rates might have an important long-term effect on CV event rates."

Rapid BP lowering: Evidence for Differences Within Antihypertensive Classes

When applying the lessons of the trials like VALUE and ASCOT-BPLA to clinical practice, it is important to consider that there may be differences between agents within classes in terms of rapidity of BP lowering. Not all CCBs, for example, may lower BP as quickly as amlodipine, just as some ARBs may lower BP more rapidly than valsartan. In fact, researchers have shown that there are indeed differences in the rapidity of BP-lowering activity among ARBs. This may be an important consideration, considering the versatility of these agents for treating hypertension in a number of clinical situations (Table 2).

Figure 4
Early BP Changes with Four Different ARBs: Reductions in Sitting Cuff BP After Two Weeks[18]



*$p < 0.05$ vs. irbesartan, losartan and valsartan

A double-blind, randomized, controlled trial involving 588 patients with hypertension compared the BP-lowering effects of four different ARBs at their recommended starting doses: irbesartan 150 mg, losartan 50 mg, olmesartan 20 mg and valsartan 80 mg (all once daily).[18] The subjects, whose mean baseline BP was 157/104 mmHg, were treated for eight weeks. The primary efficacy variable of this study was sitting cuff diastolic BP at eight weeks.

For the primary analysis, the investigators found that the BP reductions were significantly greater (all $p < 0.05$) for olmesartan 20 mg (-11.5 mmHg) than for losartan (-8.2 mmHg), valsartan (-7.9 mmHg) or irbesartan (-9.9 mmHg).

In terms of rapidity of effect, the investigators also noted significant differences between the groups at the two-week assessment. At that point, the mean change with olmesartan was -13.0/-10.7 mmHg. For systolic and diastolic BP, the reductions were significantly greater than those observed with any of the other three agents (Figure 4). While the differences in diastolic BP changes persisted at weeks 4 and 8 (Figure 5), the numerically larger reductions in systolic BP seen with olmesartan compared to the three other ARBs were no longer statistically significant at week 4.

Conclusions

Uncontrolled hypertension is a major risk factor for many undesirable complications, including stroke and MI. Treating hypertension to target is associated with significant reductions in this risk. Current guidelines recommend treating to a target of < 140/90 mmHg for most patients and < 130/80 mmHg for those with diabetes and/or chronic kidney disease.

While lowering BP is an effective risk-reduction strategy regardless of the agent used, there is evidence to suggest that some antihypertensive agents and regimens are better than others at obtaining optimal outcomes. This is reflected by the CHEP recommendations to preferentially use certain agents over others in particular clinical situations.

Furthermore, the data from VALUE and ASCOT-BPLA demonstrate that achieving BP reductions early in the course of therapy is associated with improved outcomes. To apply these lessons, one should employ powerful BP-lowering agents from among the recommended antihypertensive classes. Regardless of the antihypertensive class chosen to treat hypertension, one should try to choose the agent within the class that is known to be the most powerful for reducing BP effectively and quickly (where evidence of such differential effects exists).

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