Treating Hypertension: The Importance of Achieving and Sustaining Target Blood Pressure

By George Honos, MD, FRCPC, FACC

George Honos, MD, FRCPC, FACC
Associate Professor of Medicine,
University of Montreal
Chief of Cardiology,
Centre Hospitalier de l'Université de Montréal (CHUM)
Montreal, Quebec

Hypertension is a well known risk factor for a host of complications—microvascular (*e.g.*, nephropathy) and macrovascular (*e.g.*, stroke, myocardial infarction [MI]).[1] There is a wealth of compelling evidence that has demonstrated that lowering blood pressure (BP) is associated with a reduction in these risks. Based on these data, the authors of clinical practice guidelines have established treatment goals for systolic and diastolic BP. In Canada, statistics suggest that the implementation of the Canadian Hypertension Education Program (CHEP), established in 1999, has led to a significant improvement in the diagnosis and management of hypertension in this country.[2,3]

With a higher and higher proportion of patients with hypertension being treated and controlled, clinicians must not rest on their laurels, but aim to improve on the situation even further. While striving for 100% treatment and control for all people with hypertension in Canada, there are also other potential improvements to be made. First, efforts should be made to ensure that BP levels are optimally controlled throughout the day (*i.e.*, 24-hour BP control). Second, patients who achieve their targets need to be maintained at those lower-risk levels. Antihypertensive therapy should, therefore, be selected with these principles in mind. This review concludes with an examination of one class of antihypertensive agents, the angiotensin II receptor blockers (ARBs), which illustrates the potential differences between classes and between agents within a given class.

To begin, however, this paper briefly reviews some of the risks associated with uncontrolled BP and summarizes some of the key evidence documenting the major risk reductions associated with BP control.

The Risks Associated with Uncontrolled BP

The World Health Organization has identified hypertension as the leading contributor to death worldwide.[4] Numerous studies have shown that the risks of major vascular events (*e.g.*, stroke, death from ischemic heart disease) are increased substantially in patients with high BP. A meta-analysis published in 2002 evaluated data from one million adults with no previous vascular disease at baseline in 61 prospective observational studies of BP and mortality (12.7 million person-years at risk).[5] The investigators demonstrated a linear relationship between higher BP and higher risk of mortality from stroke and from ischemic heart disease (Figures 1A and 1B). The graphs show the relationship of systolic BP to

Figure 1
Association Between Systolic BP and Mortality from Stroke (A) and Ischemic Heart Disease (B) by Age[5]

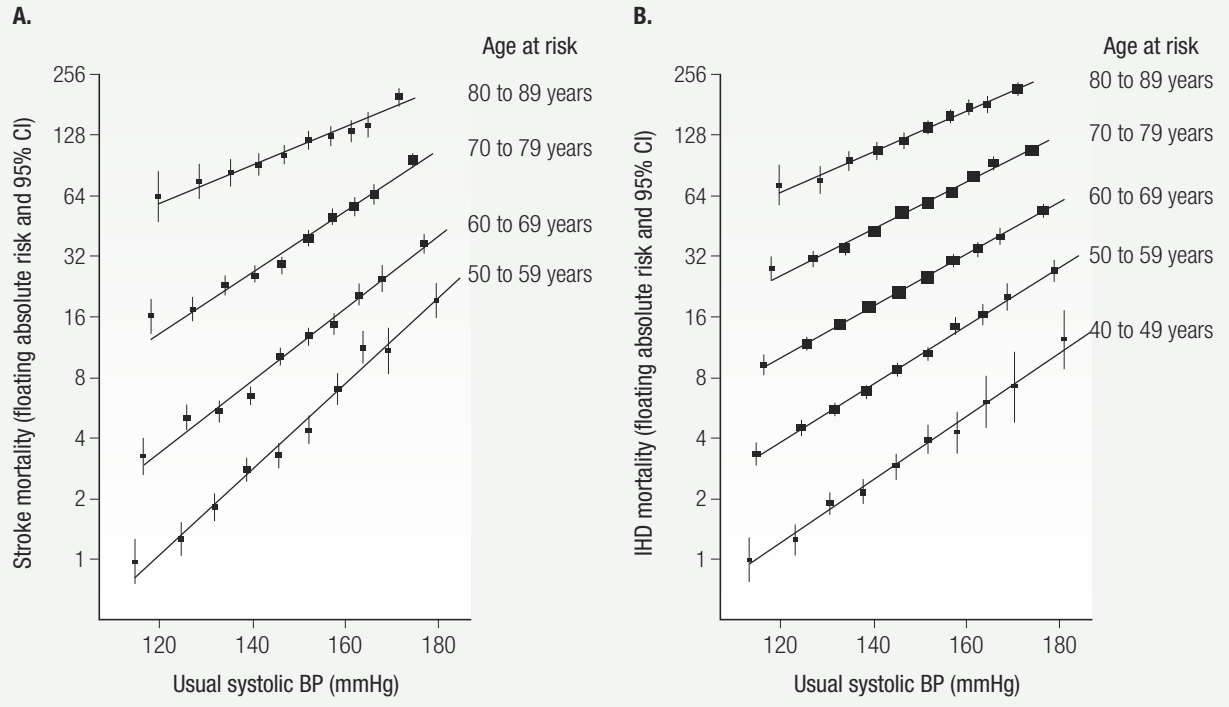
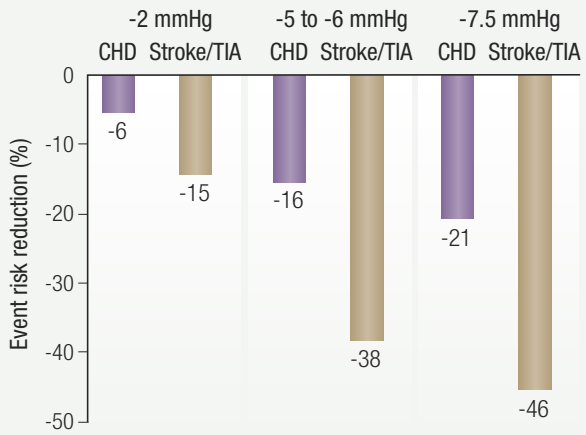


Figure 2
Effect of Diastolic BP Lowering on CV Events[9]



mortality; although not shown, the same significant patterns were also demonstrated with diastolic BP.

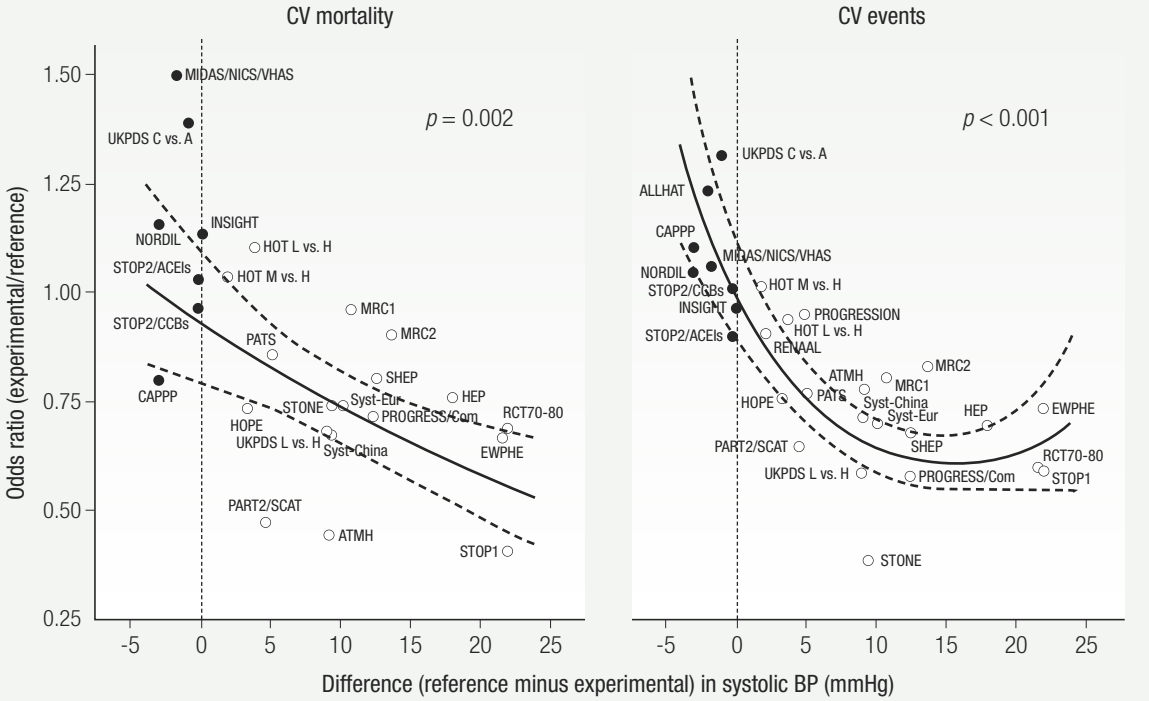
In terms of the microvasculature, a similar relationship exists between higher BP and increasing risk. For example, the presence and the development of retinopathy signs are strongly related to elevated BP.[6] Patients with hypertension are, for example, 50% to 70% more likely to have retinal hemorrhages than those with normal BP.[7]

The Benefits of Treating Hypertension

The evidence supporting the use of antihypertensive therapy to treat hypertension is unequivocal. There are numerous examples of well designed studies in the literature that document risk reductions for treated patients. Furthermore, the degree of benefit is associated with the degree to which BP is lowered (*i.e.*, the lower the better). For example, in the Hypertension Optimal Treatment (HOT) study (n = 18,790), patients were randomized to be treated to a target diastolic BP of < 90 mmHg, < 85 mmHg or < 80 mmHg.[8] The achieved mean diastolic BP in each of the three groups was 85.2 mmHg, 83.2 mmHg and 81.1 mmHg, respectively. Although there was only an approximate 2 mmHg difference between each group, the difference in MI rate was significant between the groups: 3.6 per 1,000 patient-years in the group targeted to < 90 mmHg and 2.6 per 1,000 patient-years in the group targeted to < 80 mmHg ($p < 0.05$ for trend). The difference between groups was more remarkable in the subgroup of patients with diabetes (n = 1,501). In that group, the rate of major cardiovascular (CV) events was 24.4 per 1,000 patient-years in the group with the < 90 mmHg target and 11.9 per 1,000 patient-years among those with a < 80 mmHg target.

The BP-dependent risk reduction for major CV events was also investigated in large, population-based studies in the United States. One such analysis used data from the Fram-

Figure 3
Staessen Model of Relationship Between BP and CV Mortality and Events[12]



ingham Heart Study and the National Health and Nutrition Examination Survey (NHANES) II to examine the impact of a population-wide strategy aimed at reducing diastolic BP by an average of 2 mmHg.[9] The investigators determined that such a reduction would lead to a decrease in stroke or transient ischemic attack (TIA) of 15%, and of coronary heart disease (CHD) of 6%. A reduction of 5 mmHg to 6 mmHg in diastolic BP was found to be associated with a reduction in stroke/TIA of 38% and in CHD of 16%. A 7.5 mmHg reduction was associated with relative reductions of 46% and 21% for stroke/TIA and CHD, respectively (Figure 2).

A meta-analysis by Staessen et al, published in 2001,[10] plotted the odds reductions for CV mortality and other major endpoints, relative to systolic BP reductions. These plots were updated in 2003[11] and again in 2005.[12] The result, shown in Figure 3, is now well known as the Staessen model. Reductions in systolic BP were associated with a reduction in events, up to a certain level of BP lowering.

Benefits of Achieving BP Targets

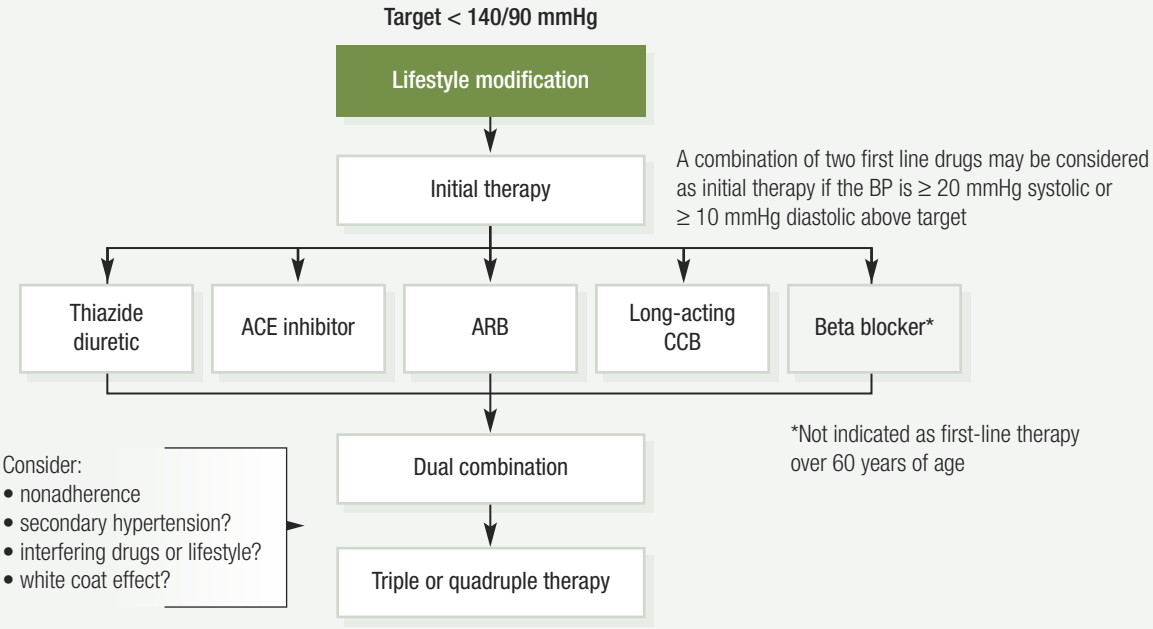
Canadian and international experts recommend that, for most hypertensive patients, BP should be reduced to below 140/90 mmHg.[1,13,14] For those in higher-risk groups, (*e.g.*, those with diabetes, chronic kidney disease), the target is set to below 130/80 mmHg.

These recommendations are based on observations accumulated over the course of the 20th century. In the The Multiple Risk Factor Intervention Trial (MRFIT), for example, while there was a continuum of increasing CV risk with increasing BP, there seemed to be a notable increase in the slope of the graph depicting CV disease risk in treated hypertensives around the 140 mmHg systolic and 90 mmHg diastolic points.[15]

> Furthermore, the degree of benefit is associated with the degree to which BP is lowered (*i.e.*, the lower the better).

The most compelling evidence supporting the lower threshold recommended for patients with diabetes comes from the HOT study, in which patients with a diastolic BP goal of < 80 mmHg had significantly lower risk of CV events than those who were treated to a target diastolic BP of < 90 mmHg or < 85 mmHg.[8] This is despite the fact that the group with the 80 mmHg target did not, on average, attain that goal. The United Kingdom Prospective Diabetes Study (UKPDS) and the Blood Pressure Lowering Treatment Trialists' (BPLTT) Collaboration meta-analyses have also shown that targeting a lower diastolic BP achieved significantly lower rates of macro- and mi-

Figure 4
2008 CHEP Recommendations for the Treatment of Hypertension Without Any Compelling Indications[1]



crovascular complications among patients with diabetes.[16-18]

In addition to clinical trial findings, patients with diabetes are already known to be at higher risk of CV disease irrespective of the presence of hypertension; this provides the rationale for more aggressively lowering BP than one would advocate for a patient without this additional burden of risk.

The thresholds for hypertension diagnosis and control have, however, been recognized as somewhat arbitrary and disputed by many experts, who argue that the risk of CV events continues to decrease with lower BP levels. The European Society of Hypertension's 2007 Guidelines for the Management of Arterial Hypertension, for example, state that the relationship between BP and CV risk is continuous down to systolic and diastolic levels of 115 mmHg to 110 mmHg and 75 mmHg to 70 mmHg, respectively.[14] That being said, however, the authors of those recommendations retained the standard 140/90 mmHg and 130/80 mmHg treatment targets.

Achieving target BP will equate to a different risk reduction for different patients, depending on the BP at which they started. For example, a patient whose BP was lowered from 155/100 mmHg to below 140/90 mmHg will have a greater relative risk reduction compared to a patient whose BP was lowered to target from a starting point of 142/92 mmHg (see the Staessen curves in Figure 3). However, as discussed above, even modest reductions in BP are associated with significant reduction in the risk of complications, and the 140/90 mmHg threshold, while somewhat arbitrary, remains the target recommended in evidence-based guidelines.

Importance of 24-hour Control

BP naturally rises and falls over the course of a 24-hour period, with a notable peak upon awakening. Also, the effects of antihypertensive therapy wears off over time. Both these phenomena can lead to large variability in BP over 24 hours. One of the goals of antihypertensive therapy is to bring the overall mean BP down, but also to reduce the daily variability.

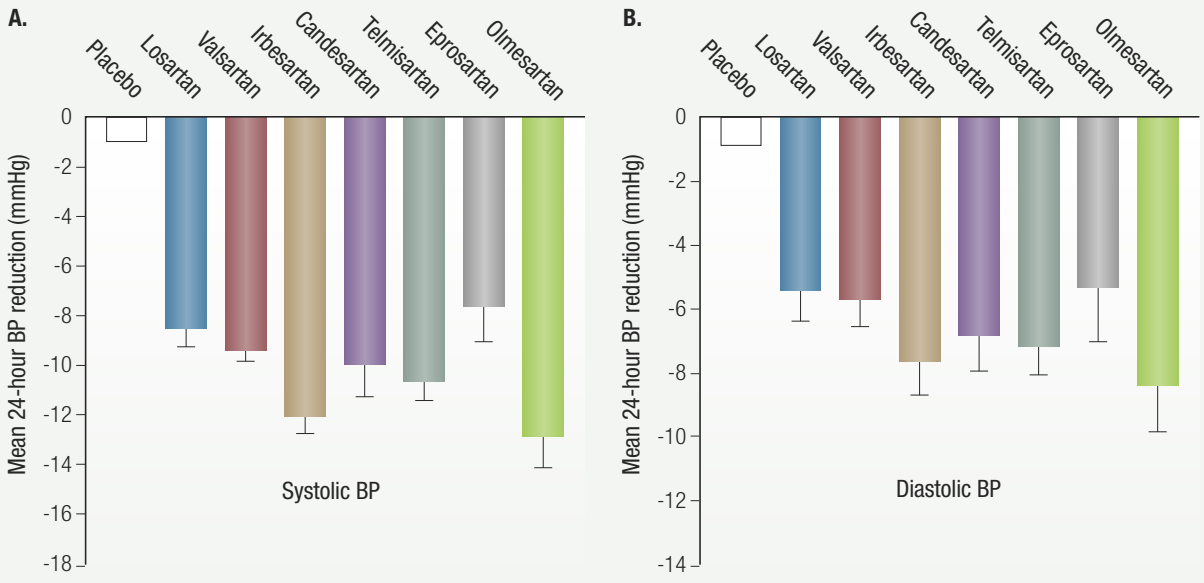
BP variability has been associated with a significant increase in CV mortality.[19] Furthermore, several studies have shown that night time BP is a better predictor of CV events than daytime BP.[20-22] Since it is highly impractical to measure nighttime BP clinically, these observations illustrate the need to provide therapy that controls BP over the full 24-hour period. To verify such control, ambulatory BP monitoring devices have been employed in clinical trials and may be used clinically.

Importance of Maintaining Control

The risks associated with uncontrolled hypertension do not recede over time. It is most often a condition that patients live with for the duration of their lives. Given that it is also largely an asymptomatic condition, it presents challenges in keeping patients motivated to adhere to the therapeutic regimen and keep their BP under control.

Adherence is an important therapeutic consideration.

Figure 5
Mean 24-hour Systolic (A) and Diastolic (B) BP Reductions: Placebo-controlled Trials of ARBs[24]



Studies have shown that patients with poor adherence to antihypertensive therapy are at dramatically increased risk for events compared to those who take their medication as directed. For example, the risk of stroke has been found to be six-fold higher among patients who are not adherent to their medical therapy.[23]

To improve the likelihood of adherence, the 2008 CHEP recommendations list a number of potential strategies.[1] These include: assessing adherence to pharmacologic and non-pharmacologic therapy at every visit; teaching patients to take their pills on a regular schedule associated with a routine daily activity (*e.g.*, brushing teeth), simplifying medication regimens using agents that are long-acting and are dosed once daily; using fixed-dose combination pills, using unit-of-use packaging (*e.g.*, blister packaging); encouraging greater patient responsibility/autonomy in regular monitoring of their BP; and educating patients and their families about hypertension and their treatment regimens, both verbally and in writing.[1]

One of the key determinants of adherence is adverse effects of therapy. The occurrence of such events can lead to interruptions in medication adherence, leaving the patient vulnerable to the effects of uncontrolled BP.[24] Selecting a treatment agent least likely to cause adverse effects should be a consideration for antihypertensive therapy.

Selection of an Antihypertensive Agent: Focus on ARBs

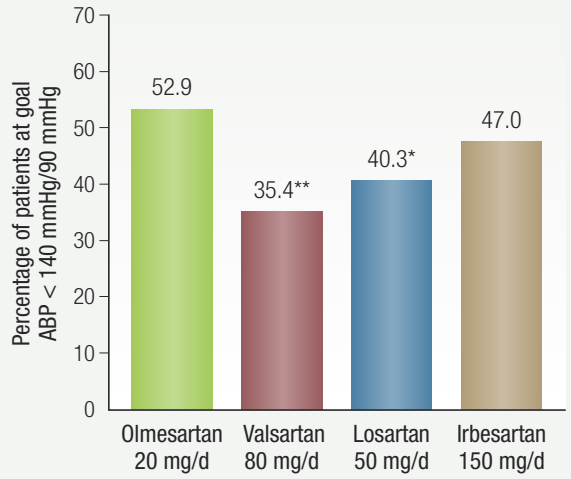
The current Canadian (CHEP) recommendation for a first-line antihypertensive monotherapy is to select a treatment agent from among the five main classes of antihypertensives: ARBs, angiotensin-converting enzyme (ACE) inhibitors, beta blockers, calcium channel blockers (CCBs) and diuretics (Figure 4).[1] The CHEP recommendations further specify that patients whose hypertension remains inadequately controlled with first-line monotherapy should be prescribed combinations of first-line agents (with the exception of ARB + ACE inhibitor combinations, which should be reserved for special poplulations).

While each of the first-line classes of agents has been shown to have BP-lowering efficacy that, alone or in combination, can help patients achieve their BP goals, there may be differences between classes and/or between agents within classes with respect to potency of BP lowering, 24-hour control and tolerability. As discussed above, each of these differences may have an impact on the clinical success of the antihypertensive regimen. The discussion below focuses on the ARB class, touching on BP efficacy differences within the class and tolerability of the class relative to other antihypertensives.

Researchers have shown that even within antihypertensive classes, there may be differences in potency of BP lowering.

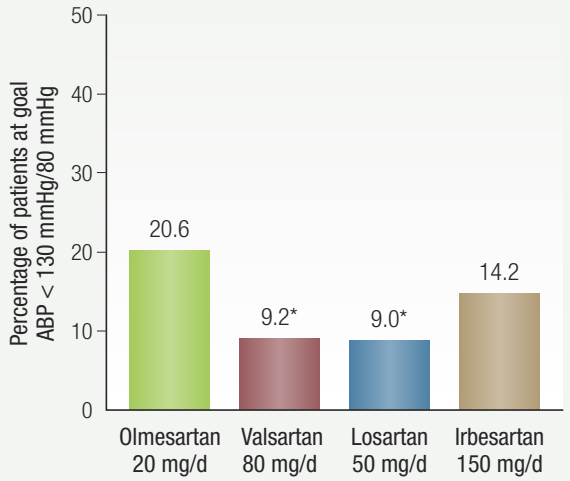
Potency of BP lowering. Researchers have shown that even within antihypertensive classes, there may be differences in potency of BP lowering. For example, researchers undertook a systematic review of studies using ambulatory

Figure 6
Proportion of Patients Achieving Systolic/diastolic BP Control (< 140 mmHg/< 90 mmHg) with Various ARBs[27]



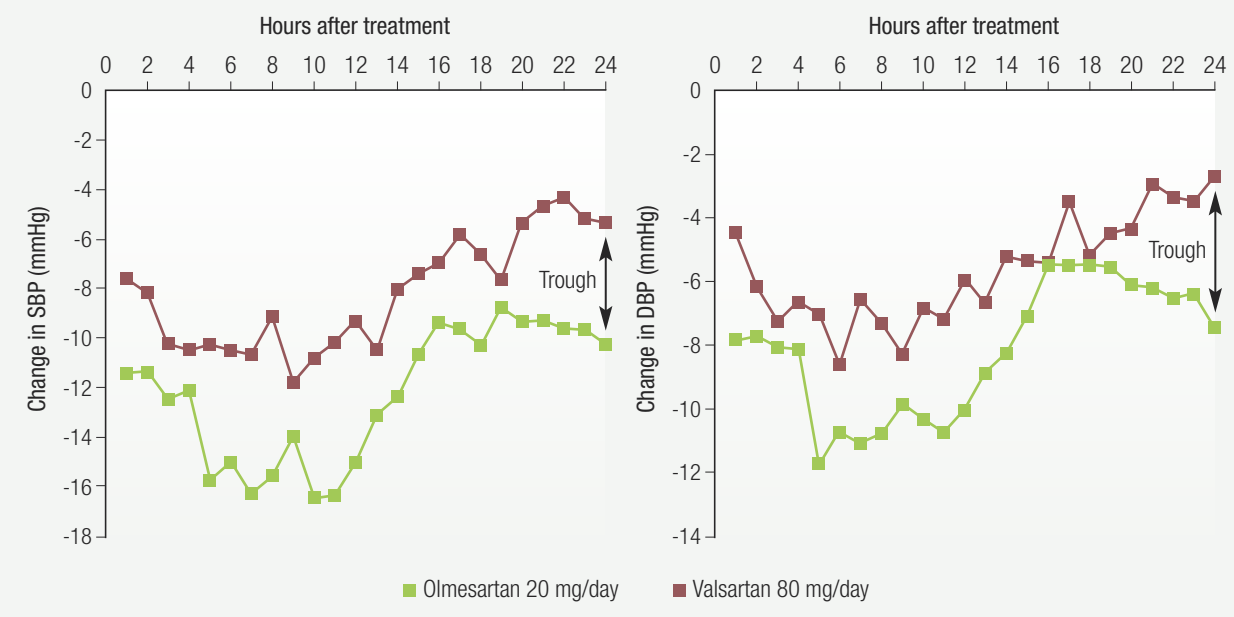
*$p < 0.05$ vs. olmesartan; **$p < 0.01$ vs. olmesartan

Figure 7
Proportion of Patients Achieving Systolic/diastolic BP Control (< 130 mmHg / < 80 mmHg) with Various ARBs[27]



*$p < 0.01$ vs. olmesartan

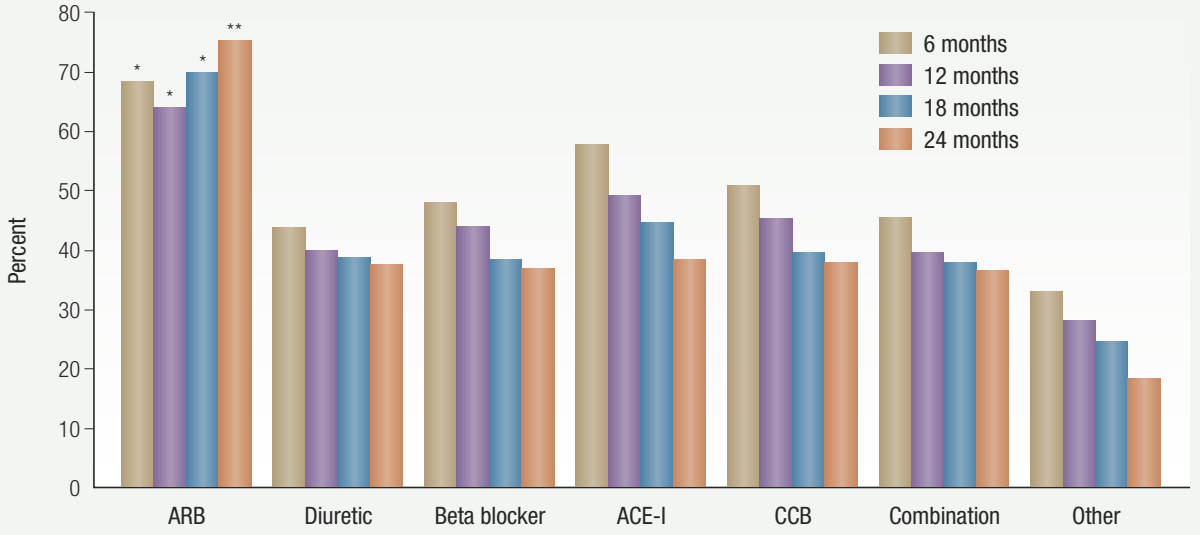
Figure 8
24-hour BP Responses to Olmesartan or Valsartan[27]



24-hour BP monitoring, comparing ARBs to placebo or other controls. There were a total of 36 studies involving 47 patient cohorts receiving ARBs in monotherapy, 10 with placebo, 10 with amlodipine, and five with enalapril.[25] The investigators reported that there were statistically significant differences observed between the BP-lowering efficacy of the various ARBs studied, in terms of clinical 24 hour mean BP reductions. This was true for both systolic and diastolic BP (Figures 5A and 5B). The differences were not related to dosage. The rank order of the agents in terms of potency in lowering systolic BP was, from most potent to least potent: olmesartan, irbesartan, telmisartan, candesartan, valsartan, losartan and eprosartan. Similar trends were observed for office BP measurement.

Achieving BP targets. A separate study has also reported similar findings. In a 12-week comparison of four ARBs

Figure 9
Compliance to Antihypertensive Classes at 6, 12, 18 and 24 Months



*p = 0.001 vs. each of the other clases (Chi-Square)
**p = 0.030 vs. diuretic, p = 0.002 vs. other (Fisher's Exact Test 2-tailed)

at their typical starting doses (olmesartan 20 mg, irbesartan 150 mg, losartan 50 mg or valsartan 80 mg once daily; total n = 588), the investigators measured the proportion of patients in each group who achieved BP targets.[26-27] As shown in Figure 6, 52.9% of the 136 patients treated with olmesartan achieved a BP of < 140/90 mmHg. This was significantly greater than the control rates observed with valsartan (35.4%; $p < 0.01$) or losartan (40.3%; $p < 0.05$). Also, as shown in Figure 7, 20.6% of the 136 patients treated with olmesartan achieved a BP of < 130 /80 mmHg—once again significantly greater than the control rates with valsartan (9.2%; $p < 0.01$) or losartan (9.0%; $p < 0.01$)—and more than twice as many patients achieved 130/80 mmHg on olmesartan than on valsartan or losartan.

24-hour BP control. In the comparative ARB study discussed above,[23] the investigators also examined the effect of irbesartan, losartan, olmesartan and valsartan on 24-hour BP control. They observed notable differences between the agents. In general, olmesartan maintained BP at a lower level than valsartan, losartan or irbesartan throughout the 24-hour period. The exception was that irbesartan led to more substantial BP reductions during the first few hours after dosing. At all other time points, mean BP was lower with olmesartan. This included a 3 mmHg to 5 mmHg difference in systolic and diastolic BP between olmesartan and each comparator agent at the end of the dosing interval (trough drug levels). Figure 8 shows the 24-hour BP curves for olmesartan and valsartan.

Tolerability. Because there are tolerability differences between the various antihypertensives, the selection of a particular agent should take into account the possibility for adverse effects and the degree to which an individual patient might tolerate these effects.[24]

ARBs have been associated with a placebo-like tolerability profile in clinical trials, as monotherapy and in combination with other agents. This favorable profile may be one of the reasons why these agents have been associated with enhanced adherence and persistence compared with agents from other antihypertensive classes. For example, using data from the Saskatchewan Health Database, investigators assessed the rates of persistence to different classes of antihypertensive agents. Patients were defined as persistent if the original prescription was refilled within 21 days of the target months.

The investigators observed statistically significant differences in persistence at all time points in favor of ARBs compared to all other antihypertensive classes. Persistence remained relatively consistent for ARBs, while all other classes experienced a decrease in persistence over time (Figure 9).[28] Thus, for patients with uncontrolled HTN on monotherapy, combinations of first-line agents are recommended, with the exception of an ACE inhibitor ARB combination, which is specifically not recommended—except perhaps in patients with associated systolic heart failure and NYHA class III-IV symptoms on background ACE inhibitor + beta-blocker therapy, in association with careful follow-up.

Conclusions

Hypertension is a condition with a significant potential impact on individual sufferers and on the healthcare system; uncontrolled hypertension is associated with a significant

burden of morbidity and mortality. Evidence is clear, however, that treatment of hypertension to targets recommended by clinical practice guidelines, is associated with a significant attenuation of risk.

When selecting a pharmacologic agent or agents to help achieve these BP goals, the ability to reach the BP targets, the ability to protect against circadian variation in BP and the likelihood that the patient will tolerate the therapy and adhere to treatment, should be taken into consideration.

As illustrated with the example of the ARBs, there are significant potential differences in BP-lowering characteristics between agents within the same class. These differences should be kept in mind when selecting the course of therapy.

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