Optimal Control in Hypertension: A Focus on the Role of Direct Renin Inhibition in Helping Reach BP Targets

by Sébastien Bergeron, MD, FRCPC; Pierre Nantel, MD, CSPQ; and Pavel Hamet, OQ, MD, PhD, FRCPC, FAHA, FRSM, FCAHS

Sébastien Bergeron, MD, FRCPC
Clinical Professor of Medicine,
Laval University
Cardiologist,
University Institute of Cardiology and Pneumology of Quebec (IUCPQ)

Pierre Nantel, MD, CSPQ
Nephrologist
Chief of Specialized Medicine,
Hotel-Dieu de Sorel
Secretary-Treasurer,
Quebec Hypertension Society

Pavel Hamet, OQ, MD, PhD, FRCPC, FAHA, FRSM, FCAHS
Professor of Medicine,
Université de Montréal
Canada Research Chair,
Predictive Genomics
Chief, Gene Medicine Services,
Centre Hospitalier de l'Université de Montréal

The potentially devastating consequences of uncontrolled hypertension are well known, and include increased risk of major cardiovascular (CV) events (*e.g.,* stroke, myocardial infarction), congestive heart failure, renal failure, peripheral vascular disease, dementia and atrial fibrillation.[1]

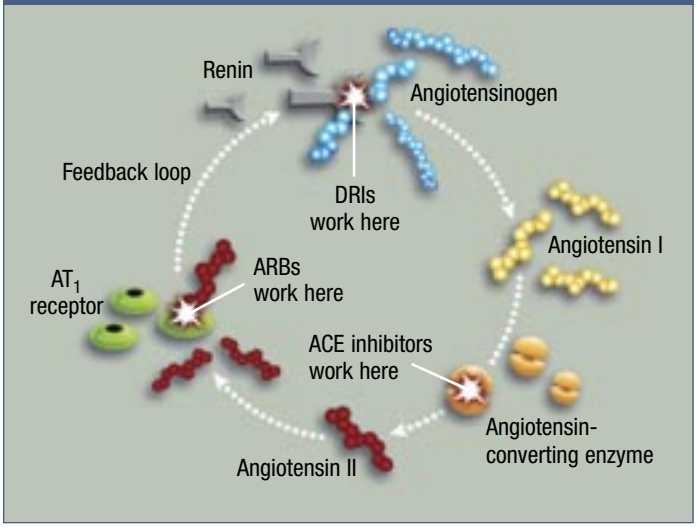
With this in mind, control of hypertension to target blood-pressure (BP) levels recommended by national guidelines is one of the most important goals for every hypertensive patient seen in clinical practice. For most patients, this means a systolic/diastolic BP of < 140/90 mmHg.[1] For some higher-risk populations (*e.g.,* those with diabetes or chronic kidney disease), the target is lower, at < 130/80 mmHg.

Reduction of BP is an integral part of providing vascular protection to people with diabetes. Because CV disease is the leading cause of death among patients with diabetes, the Canadian Diabetes Association (CDA) guidelines[2] make BP control a top priority. In fact, it has been estimated that more than 60% of people with diabetes die of CV causes and that up to 75% of specific diabetes complications are attributable to elevated BP.[1] Aside from its association with CV morbidity and mortality, diabetes is also the leading cause of blindness, end-stage renal failure and non-traumatic amputation in Canadian adults.[2] The optimal management of diabetes—including vascular protection, BP reduction and nephroprotection—is therefore a critically important specific goal within the Canadian healthcare system.

Pharmacologic agents that modulate the renin-angiotensin system (RAS) have been the cornerstone of hypertension management (and of vascular protection in patients with diabetes), and comprise the first-line options for lowering BP within national guidelines. It has also been long recognized that the majority of patients with hypertension require multiple antihypertensive agents in order to reach BP targets (especially those with comorbidities and even lower targets, such as patients with diabetes).

However, options for combining first-line agents are limited by the number of first-line agents available, and by contraindications, safety concerns, and limited efficacy data for certain combinations of different agents. This has been emphasized recently and termed by some as the "post-ONTARGET era," after the results of that study showed no additive benefit of using an ACE inhibitor and an ARB together vs. either agent alone for CV

FIGURE 1 The RAS and Site of Action of ACE Inhibitors, ARBs and DRIs



mortality. These limitations have led to uncertainty among many clinicians regarding how to best employ combination pharmacotherapy for optimal management of hypertension. This uncertainty has made way for discussing the important emerging role of direct renin inhibition within the antihypertensive armamentarium, especially within the RAS.

This review discusses the ways in which BP goals can be reached, drawing on evidence-based medicine and the recommendations of national guidelines. In particular, the review highlights the emerging role of direct renin inhibition as an optimal component of therapy to help achieve BP targets, particularly for patients with diabetes in need of enhanced RAS modulation, more effective BP control and prevention of diabetes complications.

RECOMMENDATIONS AND GUIDELINES FOR HYPERTENSION MANAGEMENT AND REDUCTION OF CV RISK

The primary guidelines for the management of hypertension in Canada are those provided by the Canadian Hypertension Education Program (CHEP), whose recommendations are updated annually. In recent years, other guideline committees working in related fields have collaborated to ensure that their messages and recommendations are in line with each other. This has been done in recognition of the fact that each group of experts has a similar ultimate goal: reduction of CV morbidity and mortality. Examples of guidelines that are complementary to the CHEP recommendations are the Canadian Cardiovascular Society (CCS) Guidelines for the Diagnosis and Treatment of Dyslipidemia and Prevention of Cardiovascular Disease,[3] the Canadian Society of Nephrology (CSN) Guidelines for the Management of Chronic Kidney Disease,[4] and the Clinical Practice Guidelines of the Canadian Diabetes Association (CDA).[2] The authors of these guidelines recognize that there is considerable overlap between their various areas of interest. For example, in the 2008 CDA guidelines, the authors state that "The first priority in the prevention of diabetes complications should be the reduction of CV risk by vascular protection through a comprehensive, multifaceted approach."[2] This includes optimal control of BP and lipid parameters. Furthermore, in addition to the specific recommendations of the CSN guidelines, the CHEP recommendations and the CDA guidelines recognize the potential of optimal therapy to prevent (or delay the progression of) renal disease.

UNMET NEEDS IN THE MANAGEMENT OF HYPERTENSION

In the late 1990s and early 2000s, Canadian physicians were made aware of the results of the Canadian Heart Health Surveys, which showed that a mere 13% of patients with hypertension were treated and optimally controlled.[5,6] At that time, the picture was even more bleak for patients with hypertension and diabetes; among that group, statistics showed that only 9% had their hypertension treated and controlled to target.[5,6]

Although a great deal of progress has been made since then, attributed in large part to the CHEP's efforts,[7,8] there is still much work to be done. More recent surveys have shown that the rates of diagnosis, treatment and control of hypertension are much higher now than those observed in Canadian Heart Health Surveys. Recently published results from Statistics Canada's Canadian Health Measures Survey,[9] for example, showed that about 80% of the 4.6 million adult Canadians with hypertension were being treated with antihypertensive drugs and that 66% of these people were being adequately controlled to BP targets. While this is a great improvement and an accomplishment to be lauded, it still leaves about one third of patients with hypertension uncontrolled. Additional reports of this national survey are forthcoming, but it can be noted that the data released thus far closely mirror those of an Ontario survey published in 2008.[10] In this survey, within the subgroup of patients with diabetes, among those whose BP was at least 130/80 mmHg, the proportion treated and controlled to BP target was only 34.7%.

Highlighting the importance of addressing this unmet need for BP control in diabetes, the CDA guidelines[2] provide detailed recommendations for optimal hypertension management. The guidelines acknowledge that most people with diabetes require multiple antihypertensive medications to reach target BP, and

indicate that additional antihypertensive drugs should be used if targets are not achieved using standard-dose monotherapy with a first-line agent.

TREATMENT OF HYPERTENSION: CURRENT CANADIAN RECOMMENDATIONS

The 2010 CHEP recommendations emphasize the importance of lifestyle modifications in helping patients reach their BP goals. These measures include regular physical activity, weight reduction, limiting alcohol consumption, consuming a balanced, low-sodium diet (*e.g.,* the DASH diet) and stress reduction. Successful implementation of these measures can have significant BP-lowering effects.

Antihypertensive pharmacotherapy. For patients who do not successfully implement lifestyle modifications or in whom these interventions are insufficient to achieve BP goals, and for those whose initial BP is markedly elevated, antihypertensive pharmacotherapy is indicated.

The 2010 CHEP guidelines recommend that, for systolic/diastolic hypertension without any compelling indication, the initial treatment agent can be chosen from among five classes of antihypertensive agents: ACE inhibitors (except in black patients), ARBs, beta-blockers (in patients younger than 60 years), long-acting calcium channel blockers (CCBs), or thiazide diuretics.[1]

CHEP also makes specific recommendations for patients with hypertension and other comorbidities (*e.g.,* diabetes, ischemic heart disease, renal disease). For patients with diabetes, for example, a RAS-blocking agent (ACE inhibitor or ARB) is recommended as first-line therapy.[1]

It should be emphasized, however, that the majority of patients treated with pharmacotherapy will require more than one agent to reach their BP goal. This is particularly true for higher-risk groups (*e.g.,* those with diabetes or renal disease), where the BP goal is lower. The current recommendation is to use a combination of two first-line agents when dual combination therapy is required. It is also suggested to start with a combination if systolic BP is more than 20 mmHg above target or diastolic BP more than 10 mmHg above target. The CHEP recommendations list some of the more useful dual combinations among the first-line agents. These include a thiazide diuretic or CCB in combination with an ACE inhibitor, ARB or beta-blocker. These combinations have complementary mechanisms of action and their combinations have been shown to provide clinically meaningful additional BP-lowering efficacy. There are also some combinations that are not recommended. In the 2010 CHEP recommendations, it is clearly stated that the combination of an ACE inhibitor and an ARB is not recommended (except in patients with heart failure and proteinuria), while caution should be exercised when combining a non-dihydropyridine CCB (*e.g.,* diltiazem, verapamil) and a beta-blocker.

If BP remains uncontrolled despite dual combination therapy, any additional antihypertensives may be added to reach target.

Evidence for the benefits of traditional antihypertensive therapy in patients with diabetes has included results from the BP-control arm of the ADVANCE trial,[11] which showed that lowering BP with a fixed-dose combination of an ACE inhibitor and a diuretic (perindopril + indapamide) conferred a relative risk reduction vs. placebo + current therapy of 9% for major macrovascular or microvascular events ($p = 0.04$). The relative risk of overall mortality was reduced by 14% ($p = 0.03$). It should also be noted that the glucose-control arm of this study[12] demonstrated significant reductions in combined major macrovascular and microvascular events, as well as major microvascular events (due primarily to a reduction in the incidence of nephropathy), with intensive vs. standard glucose control.

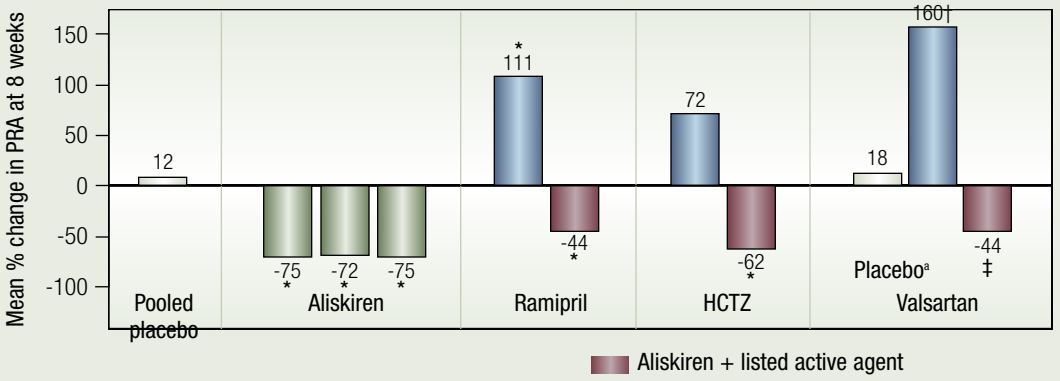
A NEW OPTION FOR HELPING PATIENTS REACH BP TARGETS: DIRECT RENIN INHIBITION

In 2007, Health Canada approved the first direct renin inhibitor (DRI), aliskiren, for use in Canada. This marked the first new antihypertensive class to be added to the therapeutic armamentarium since the introduction of the ARBs in the early 1990s. DRIs have a unique mechanism of action that makes them suitable for combination therapy with most of the other agents used to treat hypertension. Currently, aliskiren is indicated for use as monotherapy and in combination with ACE inhibitors, ARBs, CCBs or thiazide diuretics.[13] Clinical studies have validated the use of this agent in conjunction with each of these antihypertensive classes. In addition, aliskiren has been studied in several populations of patients at higher risk of CV events (*e.g.,* those with diabetic nephropathy or congestive heart failure). Furthermore, the agent is currently being investigated in a large and comprehensive clinical trial program examining its effects on morbidity and mortality in a variety of patient populations.

ALISKIREN: MECHANISM OF ACTION

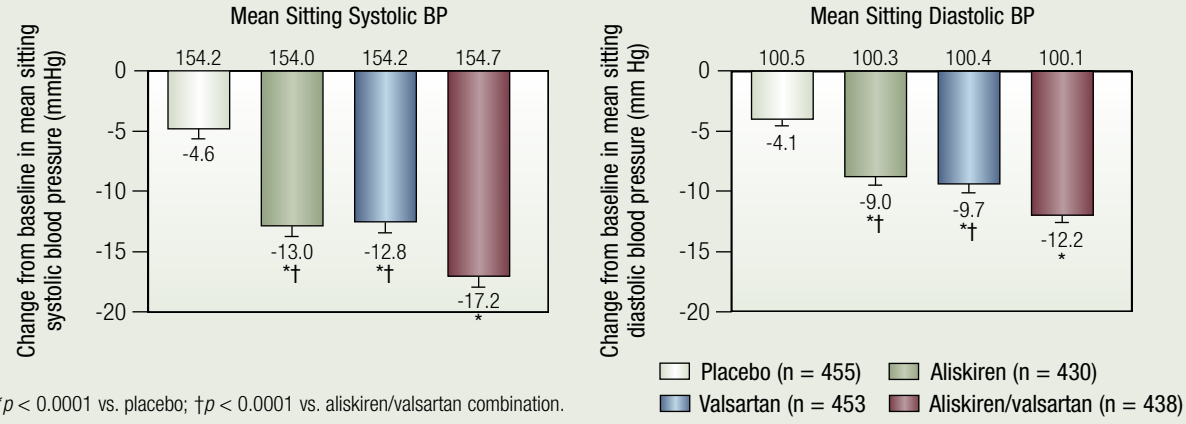
Aliskiren inhibits the ability of renin to cleave angiotensinogen to form angiotensin I. This is a distinctly different mechanism from that of ACE inhibitors or ARBs (Figure 1). By inhibiting this first rate-limiting step of the RAS, aliskiren suppresses plasma renin activity (PRA) and suppresses the production of angiotensin II. The reduction in angiotensin II trans-

FIGURE 2 **Aliskiren Neutralizes the Rise in PRA Induced by Agents That Stimulate Renin Release**[21]



*$p < 0.0001$ vs. pooled placebo; †$p < 0.001$, ‡$p < 0.0001$ vs. placebo[a]; [a]placebo from aliskiren/valsartan study.

FIGURE 3 **Aliskiren + Valsartan Combination vs. Component Monotherapies: BP Reductions**[28]



*$p < 0.0001$ vs. placebo; †$p < 0.0001$ vs. aliskiren/valsartan combination.

lates into a number of clinically important alterations, as angiotensin II is associated with vasoconstriction, left ventricular hypertrophy, inflammatory responses and atherosclerosis.[14] The suppression of PRA, which is unique to DRIs, seems to be an important aspect of the drug's activity; this makes it an attractive complementary agent to use with other other RAS-blocking agents (*i.e.*, ARBs and ACE inhibitors), whose mechanisms of action lead to an increase in PRA. High PRA has been associated with increased CV events in a number of different populations with CV disease.[15-22] Not only does aliskiren lower PRA when used in monotherapy, it has also been shown to neutralize the rise in PRA associated with other agents when used in combination with those agents (Figure 2).[23]

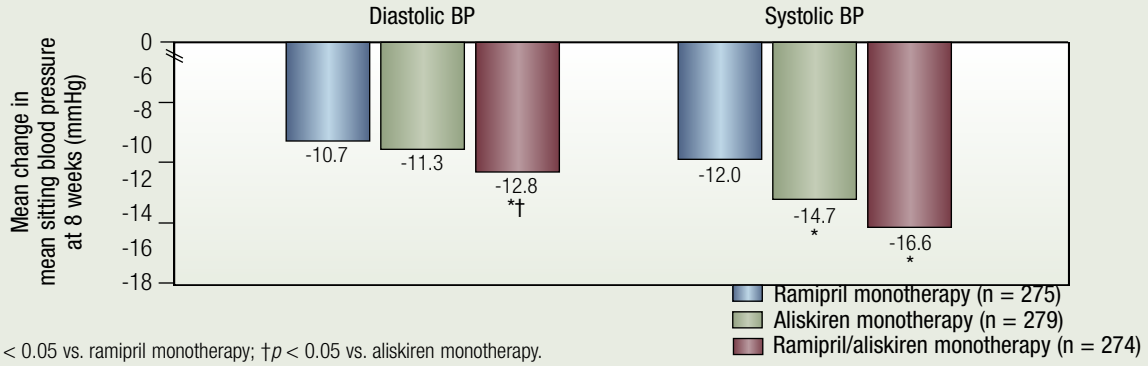
ALISKIREN: ANTIHYPERTENSIVE EFFICACY

Aliskiren is administered once daily at a dose of 150 mg or 300 mg.[13] It has been shown to be a true once-daily medication, with antihypertensive efficacy that extends beyond the 24-hour dosing window.[24]

Aliskiren has been studied extensively in monotherapy and found to be an efficacious BP-lowering agent.[13] In the current antihypertensive landscape, however, it is aliskiren's utility as a component of combination therapy that makes it an important addition to the therapeutic armamentarium. Aliskiren has been studied as part of dual combination therapy with hydrochlorothiazide (HCTZ), amlodipine, ramipril and valsartan.[25-28] In each of these studies, the combination was associated with significantly greater BP reductions than with the component monotherapies.

The studies in which aliskiren was combined with other RAS-blocking agents were particularly important, as other attempts at dual RAS blockade (*i.e.*, ACE inhibitor + ARB) have been associated with minimal additional BP-lowering efficacy and potential safety concerns (*e.g.*, hyperkalemia), and

FIGURE 4 **Aliskiren + Ramipril Combination vs. Component Monotherapies: BP Reductions[27]**



*$p < 0.05$ vs. ramipril monotherapy; †$p < 0.05$ vs. aliskiren monotherapy.

are not among the recommended choices for dual antihypertensive combination.[1]

In one double-blind randomized study evaluating the combination of aliskiren and valsartan among patients with mild-to-moderate hypertension,[28] the change in mean sitting BP at eight weeks with valsartan 320 mg alone was -12.8/-9.7 mmHg, while the change in BP with aliskiren 300 mg alone was -13.0/-9.0 mmHg. The change in BP with aliskiren 300 mg plus valsartan 320 mg was -17.2/-12.2 mmHg (Figure 3).

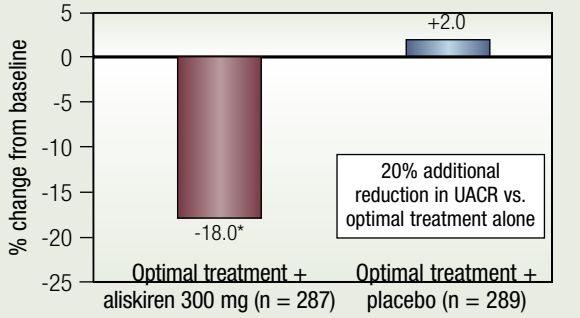
A trial evaluating aliskiren in combination with ramipril was conducted among patients with hypertension and diabetes.[27] After eight weeks (four weeks of randomized treatment plus four weeks following forced titration), the investigators reported changes in mean sitting BP of -12.0/-10.7 mmHg with ramipril monotherapy, -14.7/-11.3 mmHg with aliskiren monotherapy, and -16.6/-12.8 mmHg with the combination (Figure 4).

ALISKIREN: BP-INDEPENDENT PROTECTION IN HIGH-RISK POPULATIONS

Diabetic nephropathy. The AVOID study was conducted to evaluate the BP-independent renoprotective effects of aliskiren when added to optimal therapy in patients with diabetic nephropathy.[29] A total of 599 patients were included in the trial. All were receiving the maximal recommended dose of the ARB, losartan (100 mg daily), in addition to optimal antihypertensive therapy to reach a goal BP of < 130/80 mmHg. The patients were randomized to receive additional aliskiren 150 mg daily (titrated to 300 mg after three months) or placebo.

At the conclusion of the trial (six months), the group receiving add-on aliskiren fared significantly better than those who received placebo, in terms of the primary study endpoint of urinary albumin:creatinine ratio (UACR). The mean change from baseline was -18% with aliskiren, which was significantly superior

FIGURE 5 **AVOID: Mean Change from Baseline UACR with Added Aliskiren or Placebo[29]**



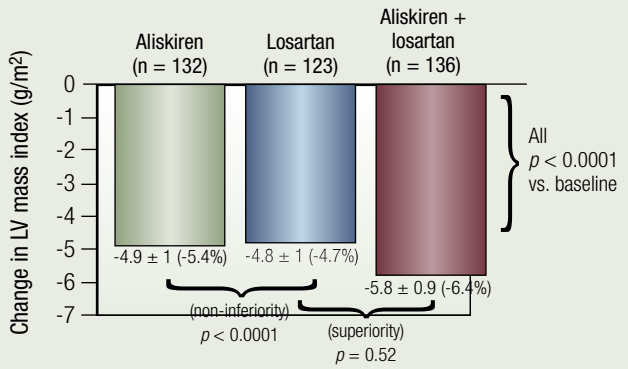
*$p < 0.001$ vs. optimal care + placebo.

to the increase of 2% observed in the placebo group (Figure 5), which represented an additional 20% reduction in UACR vs. optimal treatment with losartan. Notably, BP was similar in both groups throughout the study, suggesting that the benefits of aliskiren in this population were independent of BP effects.

The CDA guidelines,[2] which as mentioned set vascular protection as the first priority in the prevention of diabetes complications, point out that progression of diabetic nephropathy can be slowed by using medications that disrupt the RAS. While the guidelines list ACE inhibitors and ARBs as preferred initial agents for preventing progression of renal disease, the complementary mechanism of action of aliskiren outlined above makes this a very compelling option for optimal modulation of the RAS and prevention of renal complications.

Left-ventricular hypertrophy. The ALLAY study was designed to compare the effects of aliskiren with those of losartan or the combination of both on the reduction of left-ventricular (LV) mass in overweight patients with hypertension patients.[30] A total of 465 patients with hypertension, increased ventricular-wall thickness, and body mass index > 25 kg/m^2 were ran-

FIGURE 6 **ALLAY: Reduction in LV Mass with Aliskiren, Losartan or Their Combination**[30]



Mean (± SEM) for the efficacy population.

domized to receive aliskiren 300 mg, losartan 100 mg, or their combination daily for nine months.

BP was controlled to a similar extent in each group, with non-RAS-blocking add-on antihypertensive therapy allowed as needed. The investigators observed a significant reduction from baseline in LV mass in all treatment groups (Figure 6). There were no significant differences between the treatment groups, although the combination was associated with a numerically larger reduction (-5.8 g/m^2) than either of the monotherapies (-4.9 g/m^2 and -4.8 g/m^2 for aliskiren and losartan, respectively).

Heart failure. The ALOFT study was conducted to assess the safety and tolerability of aliskiren 150 mg when given in addition to standard therapy in patients with hypertension and stable congestive heart failure.[31] The subjects were 302 patients with New York Heart Association class II to IV heart failure, current or past history of hypertension, and plasma brain natriuretic peptide (BNP) concentration > 100 pg/mL. All patients had been treated with an ACE inhibitor (or ARB) and a beta-blocker. They were randomized to receive either aliskiren 150 mg daily or placebo for three months.

No statistically significant differences between aliskiren and placebo were observed in terms of prespecified safety assessments or adverse events. This included similarly low rates of renal dysfunction, symptomatic hypotension and hyperkalemia. As well, no statistically significant differences between aliskiren and placebo were observed in terms of biochemical abnormalities (elevated urea, creatinine or potassium).

For the study's primary efficacy outcome, the addition of aliskiren 150 mg to standard heart failure therapy provided significant reductions from baseline in plasma N-terminal proBNP (NT-proBNP) and BNP compared with placebo ($p < 0.05$; Figure 7).

ALISKIREN SAFETY AND TOLERABILITY

As mentioned, the efficacy of aliskiren in combination with other therapies is only part of the reason why this agent is an attractive option for combination with a variety of commonly used antihypertensive agents from other classes. The tolerability and safety of aliskiren are also highly favorable. In monotherapy, aliskiren has been shown to be associated with a tolerability profile similar to that of placebo.[13]

In a 54-week, open-label study designed to investigate the safety of aliskiren in combination with valsartan, 601 patients with mild-to-moderate hypertension were enrolled.[32] The subjects were administered a combination of open-label aliskiren 150 mg plus valsartan 160 mg once-daily for two weeks, after which the doses of both agents were doubled for the remainder of the study. Patients whose BP remained uncontrolled received optional HCTZ 12.5–25 mg.

At the six-month interim analysis, long-term treatment with aliskiren 300 mg plus valsartan 320 mg combination therapy (with or without optional HCTZ) was generally well-tolerated. Overall, 66.2% of patients reported at least one adverse event (AE) during long-term combination treatment, and the rate of discontinuation for AEs was 6.0%. The most frequently reported AEs were headache, dizziness and nasopharyngitis.

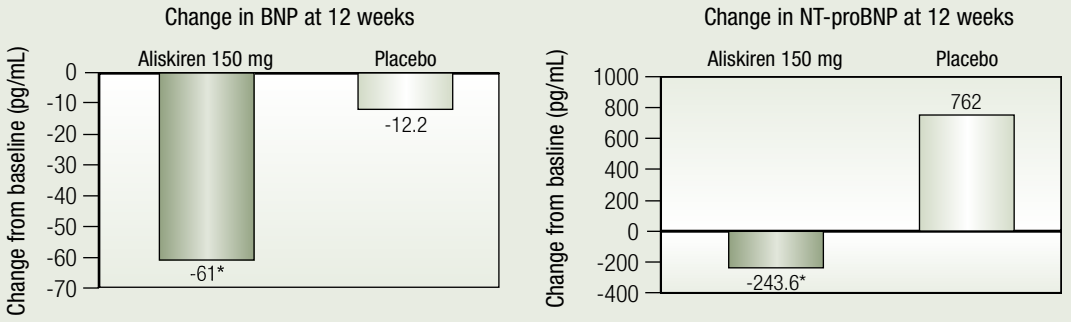
Hyperkalemia, which had been reported to be a concern with ACE inhibitor plus ARB combinations,[33,34] has not been a concern in the various clinical trials involving aliskiren in combination with an ACE inhibitor or ARB,[27-31] including the study involving an aliskiren plus losartan combination in patients with diabetic nephropathy.[29]

Of note, aliskiren has also demonstrated the potential to reduce the incidence of AEs associated with other antihypertensive agents when used in combination with those other agents. For example, in the study evaluating ramipril, aliskiren and their combination, the incidence of dry cough (a common AE of ACE inhibition) was 4.7% with ramipril alone, but only 1.8% with the aliskiren + ramipril combination.[27] Similarly, in the study evaluating aliskiren, amlodipine or their combination, the incidence of peripheral edema (a common adverse effect of CCB therapy) was 11.2% with amlodipine 10 mg, 3.4% with amlodipine 5 mg and 2.1% with the aliskiren 150 mg + amlodipine 5 mg combination (Figure 8).[26]

ONGOING STUDIES INVESTIGATING EFFECTS OF ALISKIREN ON MORBIDITY AND MORTALITY

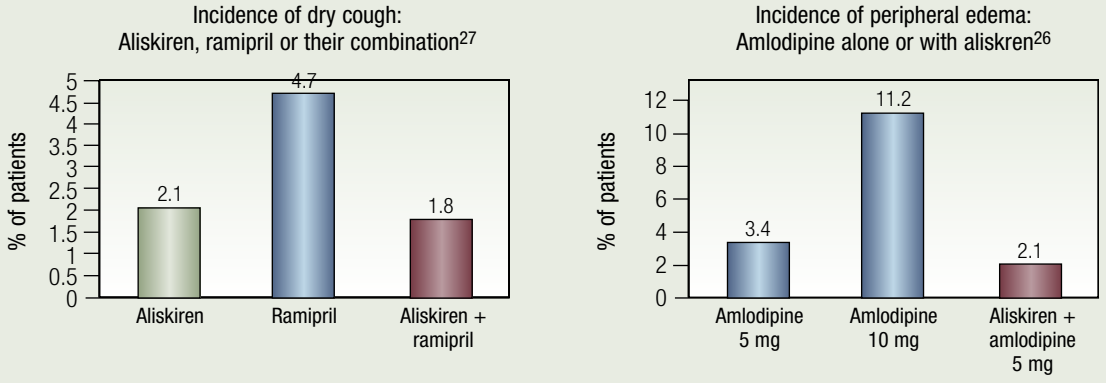
Traditional inhibitors of the RAS (*i.e.,* ACE inhibitors, ARBs) have become standard therapy for

FIGURE 7 **ALOFT: Changes in BNP and NT-proBNP with Aliskiren vs. Placebo[31]**



*$p < 0.05$ vs. placebo.

FIGURE 8 **Reduced Incidence of Common AEs with Aliskiren Combination vs. Monotherapy[26,27]**



a number of populations due not only to their BP-lowering efficacy, but also through their ability to reduce the risk of morbidity and mortality, which has been demonstrated over the years in clinical trials in a number of populations.

Investigators are currently accumulating this same type of evidence with aliskiren. The ASPIRE HIGHER clinical trial program consists of a series of large, well-designed clinical trials with morbidity and mortality as primary study endpoints. The ALTITUDE study is seeking to determine whether dual RAS blockade with aliskiren plus an ACE inhibitor or ARB will reduce major morbidity and mortality in a broad range of high-risk patients with type 2 diabetes.[35] The ATMOSPHERE study's primary endpoint is time to first occurrence of either CV death or heart-failure hospitalization in patients with chronic heart failure and systolic dysfunction, randomized to aliskiren, enalapril or their combination.[36] The ASTRONAUT study is evaluating the effects of aliskiren on death and recurrent hospitalization in the six months following hospital admission for decompensated heart failure.[36] The APOLLO trial is examining the effects of aliskiren in primary and secondary prevention of major CV outcomes in elderly patients.[37]

CONCLUSIONS

Direct renin inhibition with aliskiren provides clinicians with an important new tool for helping their patients reach target BP. Its mechanism of action (inhibition of renin, the first rate-limiting step in the RAS cascade) makes it a versatile drug that can be used alone or in combination with ACE inhibitors, ARBs, CCBs or thiazide diuretics. Given that most patients prescribed antihypertensive pharmacotherapy will require at least two agents to reach BP goal, the availability of such a versatile agent is a welcome addition to the pharmacologic landscape.

The observation that aliskiren lowers PRA is an important one; it also neutralizes the reactive rise in PRA caused by other agents when used in combination. With elevated PRA having been identified as a measure of RAS activity leading to increased BP and also associated with adverse CV outcomes, this makes aliskiren's mechanism of action complementary to that of ACE inhibitors, ARBs and CCBs, all of which raise PRA when given alone.

The complementary benefit of aliskiren also extends to tolerability; the finding that ACE-inhibitor-related cough and CCB-related peripheral edema are reduced when these agents are combined with aliskiren is significant. Better-tolerated regimens are more likely to be associated with treatment adherence. Reducing the risk of these potentially limiting AEs is an important benefit of combining aliskiren with ACE inhibitors and CCBs.

For certain high-risk groups, aliskiren represents a particularly attractive option. For those with diabetic nephropathy, for example, the addition of aliskiren to ACE-inhibitor or ARB therapy should be strongly considered as the optimal choice. This agent has been proven to be effective and safe in combination with both types of agents for patients with diabetes and, among those with diabetic nephropathy, has a significant additional BP-independent effect on UACR.

The clinical-trial evidence with this novel agent has been accumulating very rapidly, demonstrating its efficacy and safety in a number of populations and in combination with a number of agents. Clinicians should feel comfortable prescribing this agent as a component of combination therapy that will help their patients reach their BP targets. In addition, the ongoing ASPIRE HIGHER program will provide further important information regarding this agent's ability to reduce major CV morbidity and mortality, which will provide further guidance on the precise role of aliskiren within the antihypertensive armamentarium.

References:

1. Canadian Hypertension Education Program. 2010 Canadian Hypertension Recommendations. Available at: *www.hypertension.ca*.
2. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes 2008; 32(suppl 1):S1-S201.
3. Genest J, McPherson R, Frohlich J, et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult – 2009 recommendations. Can J Cardiol 2009; 25(10):567-79.
4. Levin A, Hemmelgarn B, Culleton B, et al. Guidelines for the management of chronic kidney disease. CMAJ 2008; 179(11):1154-62.
5. Joffres MR, Ghadirian P, Fodor JG, et al. Awareness, treatment, and control of hypertension in Canada. Am J Hypertens 1997; 10(10 Pt 1):1097-102.
6. Joffres MR, Hamet P, MacLean DR, et al. Distribution of blood pressure and hypertension in Canada and the United States. Am J Hypertens 2001; 14(11 Pt 1):1099-105.
7. Onysko J, Maxwell C, Eliasziw M, et al. Large increases in hypertension diagnosis and treatment in Canada after a healthcare professional education program. Hypertension 2006; 48(5):853-60.
8. McAlister FA, Feldman RD, Wyard K, et al. The impact of the Canadian Hypertension Education Programme in its first decade. Eur Heart J 2009; 30(12):1434-9.
9. Wilkins K, Campbell NRC, Joffres MR, et al. Blood pressure in Canadian adults. Statistics Canada Health Reports 2010; 21(1):1-10.
10. Leenen FH, Dumais J, McInnis NH, et al. Results of the Ontario survey on the prevalence and control of hypertension. CMAJ 2008; 178(11):1441-9.
11. Patel A, MacMahon S, Chalmers J, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007; 370(9590):829-40.
12. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358(24):2560-72.
13. Novartis Canada Inc. Rasilez Product Monograph, 2010.
14. Kim S, Iwao H. Molecular and cellular mechanisms of angiotensin II-mediated cardiovascular and renal diseases. Pharmacol Rev 2000; 52(1):11-34.
15. Bair TL, May HT, Prescott MF, et al. Association between baseline levels of plasma renin activity and risk of cardiovascular events. J Am Coll Cardiol 2009; 53:A383 [Abstract].
16. Bair TL, May HT, Prescott MF, et al. Association between baseline plasma renin activity and risk of cardiovascular events in coronary artery disease patients. J Clin Hypertens 2009; 11(Suppl A):88 [Abstract].
17. Rouleau JL, Packer M, Moyé L, et al. Prognostic value of neurohumoral activation in patients with an acute myocardial infarction: effect of captopril. J Am Coll Cardiol 1994; 24:583-9.
18. Latini R, Masson S, Anand I, et al. The comparative prognostic value of plasma neurohormones at baseline in patients with heart failure enrolled in Val-HeFT. Eur Heart J 2004; 25:292-9.
19. Vergaro G, Fontana M, Poletti R, et al. Plasma renin activity is an independent prognostic factor in chronic heart failure. Eur Heart J 2008;29(Suppl.):393 [Abstract].
20. Alderman MH, Ooi WL, Cohen H, et al. Plasma renin activity: a risk factor for myocardial infarction in hypertensive patients. Am J Hypertens 1997;10:1-8.
21. Masson S, Solomon SD, Angelici R, et al. Plasma renin activity retains a strong prognostic value in patients with chronic HF, independent of ACE inhibitor or beta-blocker therapy. Data from the Valsartan Heart Failure (Val-HeFT) trial. Eur Heart J 2009; 30:163 [Abstract].
22. Verma S, Gupta M, Holmes DT, et al. Plasma renin activity is associated with increased cardiovascular events and mortality in the HOPE Study. Circulation 2009; 120:S453 [Abstract].
23. Taylor AA, Anderson DR, Arora V, et al. Renin system suppression with the oral direct renin inhibitor aliskiren administered alone or in combination: a pooled analysis of 1093 patients with hypertension. J Am Coll Cardiol 2007; 49(9 Suppl A):370A [Abstract].
24. Ruilope LM, Anderson DR, Arora V, et al. Aliskiren, a direct renin inhibitor (DRI), provides smooth, sustained 24-h blood pressure control as monotherapy or in combination with valsartan or ramipril in patients with hypertension. Eur Heart J 2007; 28:868 [Abstract].
25. Villamil A, Chrysant SG, Calhoun D, et al. Renin inhibition with aliskiren provides additive antihypertensive efficacy when used in combination with hydrochlorothiazide. J Hypertens 2007; 25:217-226.
26. Drummond W, Munger MA, Rafique Essop M, et al. Antihypertensive efficacy of the oral direct renin inhibitor aliskiren as add-on therapy in patients not responding to amlodipine monotherapy. J Clin Hypertens (Greenwich) 2007; 9(10):742-50.
27. Uresin Y, Taylor AA, Kilo C, et al. Efficacy and safety of the direct renin inhibitor aliskiren and ramipril alone or in combination in patients with diabetes and hypertension. J Renin Angiotensin Aldosterone Syst 2007; 8(4):190-8.
28. Oparil S, Yarows SA, Patel S, et al. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial. Lancet 2007; 370(9583):221-9.
29. Parving HH, Lewis JB, Lewis EJ, et al. Aliskiren combined with losartan in type 2 diabetes and nephropathy. N Engl J Med 2008; 358:2433-46.
30. Solomon SD, Appelbaum E, Manning WJ, et al. Effect of the direct renin inhibitor aliskiren, the angiotensin receptor blocker losartan, or both on left ventricular mass in patients with hypertension and left ventricular hypertrophy. Circulation 2009; 119(4):530-7.
31. McMurray JJ, Pitt B, Latini R, et al. Effects of the oral direct renin inhibitor aliskiren in patients with symptomatic heart failure. Circ Heart Fail 2008;1(1):17-24.
32. Chrysant SG, Murray AV, Hoppe UC, et al. Long-term safety, tolerability and efficacy of aliskiren in combination with valsartan in patients with hypertension: a 6-month interim analysis. Curr Med Res Opin 2008;24(4):1039-47.
33. Jennings DL, Kalus JS, Coleman CI, et al. Combination therapy with an ACE inhibitor and an angiotensin receptor blocker for diabetic nephropathy: a meta-analysis. Diabet Med 2007; 24(5):486-93.
34. MacKinnon M, Shurraw S, Akbari A, et al. Combination therapy with an angiotensin receptor blocker and an ACE inhibitor in proteinuric renal disease: a systematic review of the efficacy and safety data. Am J Kidney Dis 2006; 48(1):8-20.
35. Parving HH, Brenner BM, McMurray JJ, et al. Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE): rationale and study design. Nephrol Dial Transplant 2009; 24(5):1663-71.
36. Pinto R, Gradman AH. Direct renin inhibition: an update. Curr Hypertens Rep 2009; 11(6):456-62.
37. Verdecchia P, Angeli F, Mazzotta G, et al. The renin angiotensin system in the development of cardiovascular disease: role of aliskiren in risk reduction. Vasc Health Risk Manag 2008; 4(5):971-81.