Use of a New Antihypertensive Agent from a New Class in Canadian Real-life Clinical Practice

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The importance of reaching blood pressure targets is well established, but despite the wide variety of antihypertensive medications available, blood pressure has been shown to be uncontrolled in approximately 35% of Canadian patients.[1] In individuals with diabetes, blood pressure control rates are much lower, possibly due in part to the more stringent blood pressure targets for these high-risk patients. In fact, only 36.1% of such patients had blood pressure less than 130/80 mmHg.[1] Moreover, clinical trials have repeatedly demonstrated that most patients with hypertension require more than one pharmacological agent to reach blood pressure targets,[2] while hypertensive patients with diabetes or renal impairment require at least two or three pharmacological agents.[3] Within this context, the introduction of a new antihypertensive agent with a different mechanism of action might help increase rates at which blood pressure targets are achieved and ultimately improve patient outcomes.

Aliskiren, the first direct renin inhibitor,[4] is one of the most recent antihypertensive medications to be introduced in Canada. At the present time, aliskiren is indicated for the treatment of mild to moderate hypertension as a single agent or as an add-on to angiotensin-converting enzyme inhibitors (ACE-Is), diuretics or calcium channel blockers (CCBs). Long-term mortality and morbidity studies to demonstrate the benefits of aliskiren in cardiorenal protection and in the prevention of diabetes complications are ongoing.

This report describes the methodology and results of a retrospective chart review initiative. The goal of this project was to identify the types of patients who had been prescribed aliskiren in a "real-life" clinical setting and to characterize the change in blood pressure levels in these patients following a minimum of eight weeks of treatment with aliskiren.

METHODS

To characterize the types of patients prescribed aliskiren in Canadian clinical practice, primary care physicians and specialists (primarily endocrinologists, geriatric medicine specialists, internists and nephrologists) from Alberta, Ontario and Quebec were invited via fax or e-mail to participate in a chart review initiative. Participants were asked to provide information on their practice profile and to complete a questionnaire for each of five to 10 patients who had been treated with aliskiren according to its label indication for a minimum of eight weeks. The questionnaires collected information on patient demographics, body mass index (BMI), comorbidities, blood pressure before and after starting aliskiren, aliskiren dose and treatment length and concomitant antihypertensive medications. No identifying information, such as name, address or birth date, was collected, and all results are presented as aggregate data to maintain confidentiality.

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Participants were presented with the option of using paper forms or of completing the questionnaires online through a secure web portal. Completed hard-copy questionnaires were subsequently entered online in order to include the information in the database for analysis and the paper copies were subsequently destroyed.

RESULTS

A total of 439 primary care practitioners and 116 specialists were invited via fax or e-mail to take part in this initiative. Thirty-seven primary care practitioners and 10 specialists participated in the chart review, for response rates of 8.4% for primary care practitioners and 8.6% for specialists. All participating primary care practitioners and 70% of specialists worked in private offices or clinics rather than in community clinics or health centres. Approximately half of the participants were in solo practice in an urban setting. Only 10% of specialists and 14% of primary care practitioners worked in a semi-urban or rural setting.

Information on 417 patients was collected. The majority of patients (78%) were Caucasian, over half (58%) were between the ages of 51 and 70 years, and most were overweight or obese, as shown in Table 1. Nearly half the patients had type 2 diabetes, and albuminuria was another common comorbidity. There did not appear to be many differences in the types of patients in primary care vs. specialist practice, though patients of specialists were more frequently male than those of primary care physicians (67% vs. 54%) and were more likely to have diabetes (49% vs. 40%), microalbuminuria (43% vs. 22%) and other unspecified comorbidities (26% vs. 16%). Specialists also appeared to have had a higher proportion of overweight patients on aliskiren than primary care physicians (47% vs. 34%), but fewer severely or morbidly obese patients (13% vs. 24%).

Approximately half of the patients included in this chart review initiative had received aliskiren for between eight and 12 weeks, while 25% had

TABLE 1 **Patient Characteristics**

	All patients (n = 417)	Patients from primary care practices (n = 325)	Patients from specialist practices (n = 92)
Gender (male)	57%	54%	67%
Age*			
< 40 years	4%	5%	3%
41-50 years	17%	17%	18%
51-60 years	28%	28%	28%
61-70 years	30%	28%	33%
71-80 years	15%	15%	15%
> 80 years	6%	6%	4%
Race*			
Asian	15%	13%	20%
Black	6%	6%	2%
Caucasian	78%	80%	75%
Other	1%	1%	3%
BMI*			
< 18.5 kg/m^2	0%	1%	0%
18.5-24.9 kg/m^2	14%	14%	14%
25.0-29.9 kg/m^2	38%	34%	47%
30.0-34.9 kg/m^2	27%	27%	26%
35.0-39.9 kg/m^2	11%	13%	5%
> 40.0 kg/m^2	10%	11%	8 %
Comorbid conditions			
Diabetes	47%	47%	49%
Microalbuminuria	27%	22%	43%
Macroalbuminuria	NA**	NA**	22%
Other	22%	16%	26%

*Percentages may not total 100% due to rounding
**This information was not collected from primary care practitioners
BMI = body mass index; NA = not available

been treated for between 13 and 24 weeks (refer to Table 2). The proportion of patients who had received aliskiren for more than 12 weeks was greater in specialist practices than in primary care practices (50% vs. 39%). Overall, slightly more patients were prescribed the 150 mg dose of aliskiren rather than the 300 mg dose. This trend most closely reflects the practice of primary care physicians, whose patients were most commonly prescribed the lower dose of aliskiren, rather than that of specialists, whose patients were more likely to be prescribed the 300 mg dose.

Aliskiren was most commonly used as a second, third or fourth add-on medication, but was used as a first-line medication in 17% of primary practice patients, 15% of specialist practice patients and 16% of patients overall. CCBs were the most commonly prescribed concomitant antihyperten-

TABLE 2 **Aliskiren Treatment Regimen**

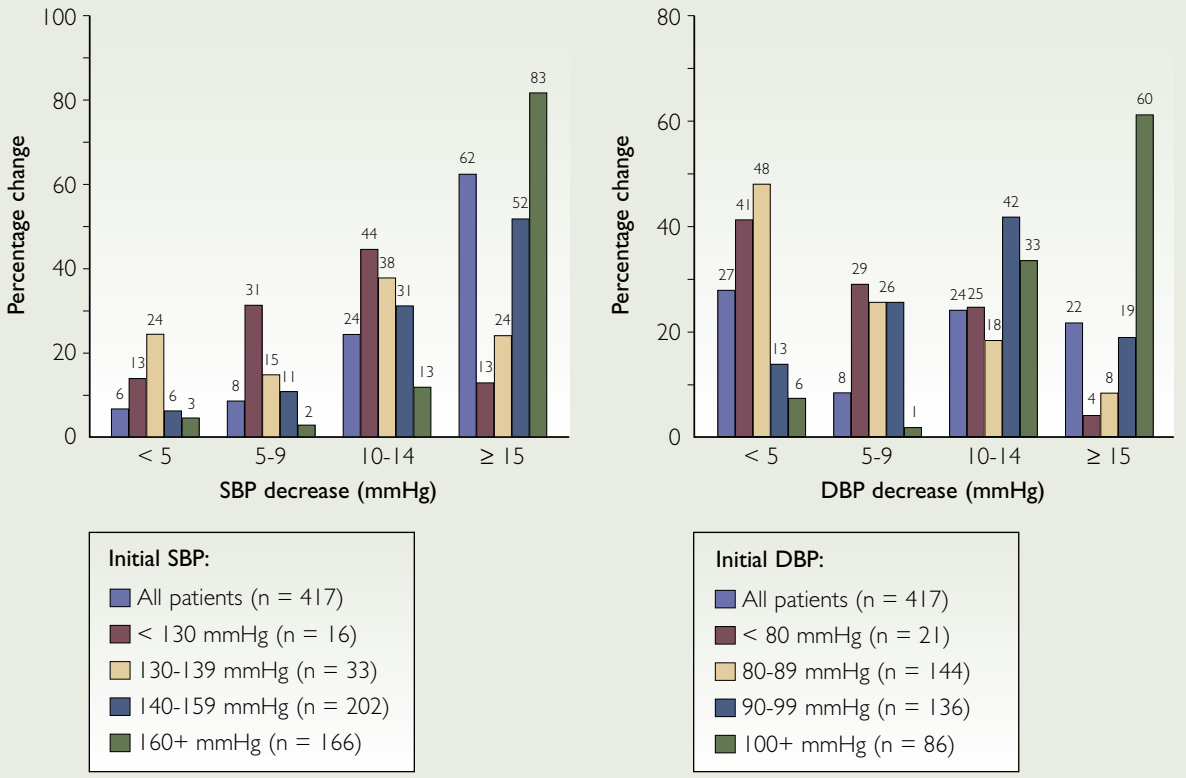
	All patients (n = 417)	Patients from primary care practices (n = 325)	Patients from specialist practices (n = 92)
Aliskiren dosage*			
150 mg	59%	66%	36%
300 mg	41%	34%	64%
Length of treatment with aliskiren*			
< 8 weeks	7%	6%	10%
8-12 weeks	52%	55%	40%
13-24 weeks	25%	25%	26%
25-36 weeks	10%	10%	13%
> 36 weeks	6%	4%	11%
Aliskiren used as:*			
First-line medication	16%	17%	15%
First add-on	15%	18%	5%
Second add-on	22%	18%	36%
Third add-on	22%	21%	24%
Fourth add-on	22%	22%	20%
Unknown	3%	4%	0%
Concomitant antihypertensive medications			
None	15%	17%	10%
Diuretic	26%	27%	20%
ACE inhibitor	15%	16%	13%
ARB	25%	24%	27%
CCB	50%	49%	54%
ACE inhibitor/HCTZ	7%	5%	13%
ARB/HCTZ	32%	30%	39%
Other	21%	20%	22%

*Percentages may not total 100% due to rounding
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; HCTZ = hydrochlorothiazide

sive medication, followed by angiotensin II receptor blockers (ARBs) and diuretics. Interestingly, 7.4% of patients were already taking an ACE-I plus an ARB when they were prescribed aliskiren. This may not be surprising as this chart review initiative was performed very shortly after the publication of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) results,[5] and, the indication for the ACE-I and ARB combination was still unclear at that time.

Prior to initiating aliskiren therapy, 40% of all patients had a systolic blood pressure (SBP) of at least 160 mmHg and 48% had an SBP of 140 to 159 mmHg, while only 8% and 4% had SBP of 130 to 139 mmHg and less than 130 mmHg,

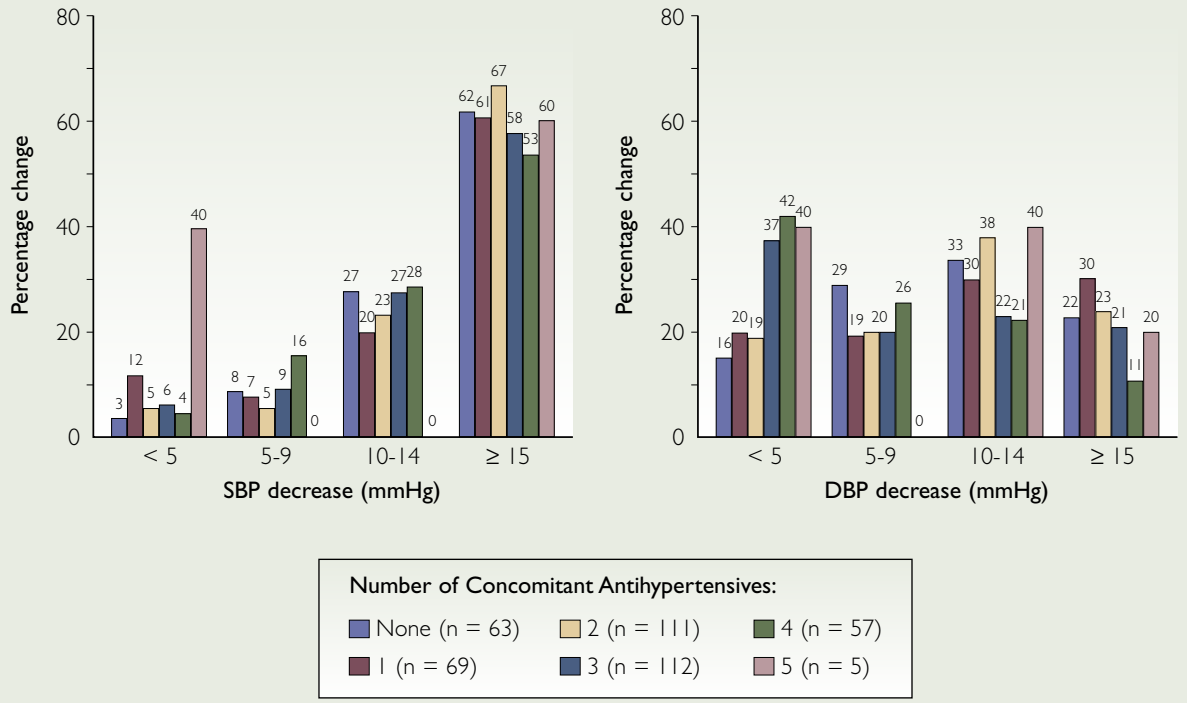
FIGURE 1 **Change in Blood Pressure Between Measurements Taken Prior to Initiating Aliskiren Therapy and Those Taken Afterwards According to Initial Blood Pressure Level**



respectively. Diastolic blood pressure (DBP) levels were slightly more evenly distributed with 21% of patients having a DBP of at least 100 mmHg, 33% falling between 90 and 99 mmHg, 35% having a DBP of 80 to 89 mmHg and 12% falling below 80 mmHg. There appeared to be some differences between patients in primary care and specialist practice in terms of initial blood pressure levels. Specialists appeared to start more patients with an SBP of less than 130 mmHg on aliskiren than did primary care practitioners (11% vs. 2%), and, conversely, fewer patients with an SBP of greater than or equal to 160 mmHg (29% vs. 43%). Similar differences between patients in specialist and primary care practice were seen in terms of initial DBP levels, with 29% of patients in specialist practice having an initial DBP of less than 80 mmHg as compared to 8% of primary care patients and 11% having an initial DBP of at least 100 mmHg vs. 24% in primary care.

Clinical trials have repeatedly demonstrated most patients with hypertension require more than one pharmacological agent to reach blood pressure targets,[2] while hypertensive patients with diabetes or renal impairment require at least two or three pharmacological agents.[3]

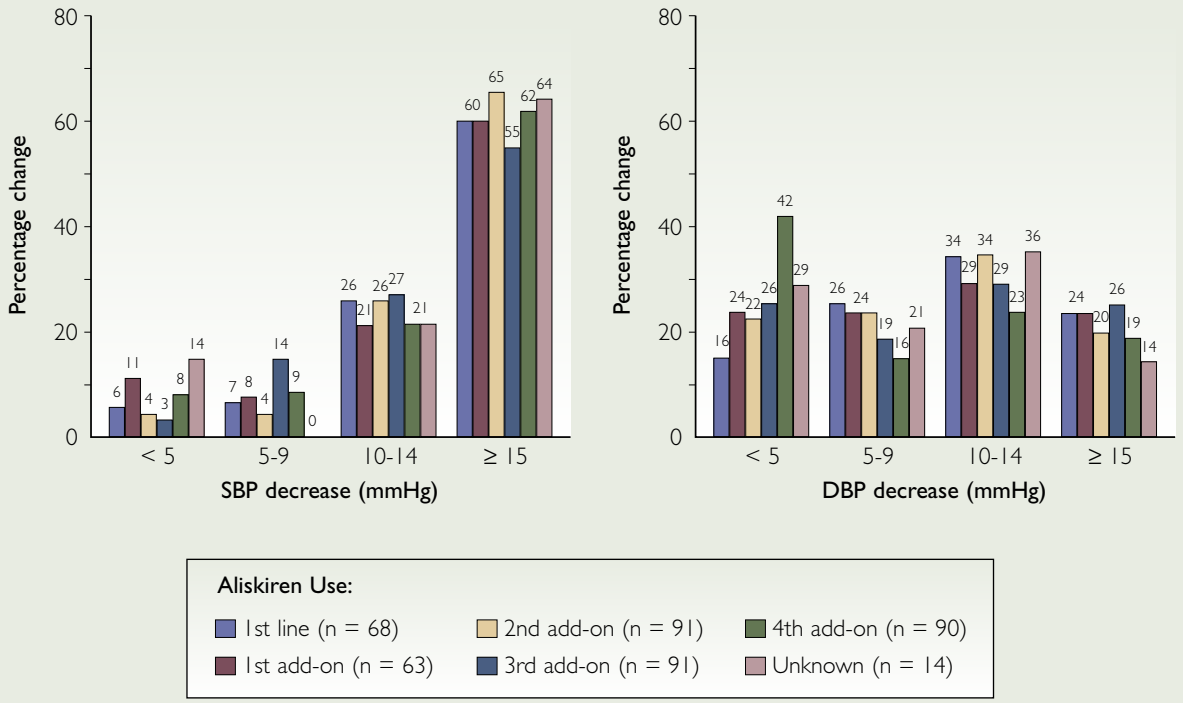
FIGURE 2 Change in BP Between Measurements Taken Prior to Initiating Aliskiren Therapy and Those Taken Afterwards According to Number of Concomitant Antihypertensive Agents



Overall, 62% of patients experienced SBP decreases of at least 15 mmHg and 22% of patients experienced DBP decreases of at least 15 mmHg between measurements taken prior to initiating aliskiren therapy and those taken afterwards, as shown in Figure 1. Not surprisingly, a greater proportion of patients with an initial SBP of greater than or equal to 160 mmHg experienced SBP reductions of at least 15 mmHg than those with a lower initial SBP. Similarly, a greater proportion of patients with an initial DBP of at least 100 mmHg experienced DBP reductions greater than or equal to 15 mmHg than those with a lower initial DBP. A smaller proportion of patients in specialist practice experienced decreases of at least 15 mmHg than did those from primary care practice (51% vs. 64%), possibly reflecting their slightly lower initial blood pressure level.

There did not appear to be a relationship between the magnitude of blood pressure reduction between measurements taken prior to initiating aliskiren therapy and those taken afterwards and either the presence of diabetes or the BMI category. Similarly, the number of concomitant antihypertensive medications a patient received did not appear to affect the magnitude of SBP reduction (refer to Figure 2). However, a greater proportion of patients on three or more classes of concomitant antihypertensive medications experienced DBP reductions of less than 5 mmHg than those receiving fewer agents. The magnitude of blood pressure reduction between measurements taken prior to initiating aliskiren therapy and those taken afterwards appeared to be similar regardless of whether aliskiren was used as first-line therapy or as a first, second, third or fourth add-on medication (refer to Figure 3).

FIGURE 3 Change in BP Between Measurements Taken Prior to Initiating Aliskiren Therapy and Those Taken Afterwards According to Type of Aliskiren Use



DISCUSSION

Based on the results of this chart review initiative, it appears that the typical patient treated with aliskiren in Canadian clinical practice was between 51 and 70 years old (58%), overweight or obese (65%) and frequently had diabetes (42%). There appeared to be some differences in the types of patients prescribed aliskiren by specialists vs. by primary care practitioners, with a greater proportion of patients from specialist practices tending to be male, obese, have diabetes and suffer from albuminuria or other comorbidities. However, due to the small number of specialists who participated in this initiative, it is difficult to draw any firm conclusions.

Aliskiren was most commonly used as a second, third or fourth add-on antihypertensive medication (66%) and was often prescribed to patients taking CCBs (50%), ARB/hydrochlorothiazide fixed-dose combinations (32%), ARBs (26%) and/or diuretics (26%). Even though two-thirds of patients prescribed aliskiren were previously treated with at least two other antihypertensive medications, the majority of patients (62%) experienced SBP decreases of greater than or equal to 15 mmHg between measurements taken prior to initiating aliskiren therapy and those taken after at least eight weeks of therapy. This suggests that aliskiren may be effective in terms of lowering blood pressure in hypertensive patients whose blood pressure is uncontrolled despite the use of multiple antihypertensive medications. However, caution is needed in interpreting this information as a temporal association does not necessarily entail causality. Additionally, it should be noted that factors not captured by the patient profile, such as lifestyle changes or the introduction of other

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medications, may have also played a role in accentuating the blood pressure response.

Other limitations of this study include the facts that it was retrospective in nature and lacked a comparator or placebo group. There may have been some regression to the mean blood pressure values even in untreated patients that was not captured by this analysis. In addition, no information on adherence to medication or tolerability profile was collected. Finally, it is possible that there was some bias in terms of patient selection as no guidance was provided to participating physicians regarding which patients to select. However, despite these limitations, this chart review initiative enabled the characterization of the use of aliskiren in Canadian real-life clinical practice and provided insight into the potential benefits of this new class of antihypertensive medication. The considerable improvements in hypertension control and the magnitude of blood pressure reduction observed in many subgroups in this study is in keeping with a prior meta-analysis of this class of antihypertensive agents.[6] Furthermore, the results are being validated in a prospective national Canadian registry of 15,000 patients.

Disclosures. *Dr. Andrew Steele has accepted honoraria for talks from numerous pharmaceutical companies, including Novartis, AstraZeneca, sanofi-aventis, Pfizer, Boehringer Ingelheim and Servier. Marie Claude Laplace, Dr. Jean-Marie Leclerc and Dr. Denis Vézina are employees of Novartis Pharmaceuticals Canada Inc.*

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