

FREE CONTINUING EDUCATION LESSON



APPROVED FOR
1 CEU

Approved for 1 CE unit by the Canadian Council on Continuing Education in Pharmacy. File # 727-0408. Not valid for CE credits after April 24, 2011.

OBJECTIVES

Upon successfully completing this lesson, the pharmacist will be able to:

1. discuss the importance of controlling hypertension.
2. describe the current Canadian Hypertension Education Program (CHEP) recommendations for the treatment of hypertension.
3. understand the mechanism of action of aliskiren and discuss its efficacy and safety in the management of hypertension.
4. understand the potential role of aliskiren in the treatment of diabetic nephropathy from the AVOID (Aliskiren in the eValuation of prOteinuria In Diabetes) study.
5. counsel patients on the administration and monitoring parameters of aliskiren.

INSTRUCTIONS

1. After carefully reading this lesson, study each question and select the one answer you believe to be correct. Circle the appropriate letter on the attached reply card or answer online at www.pharmacygateway.ca in the CE Online section, "More CCEP-Approved" area.
2. To pass this lesson, a grade of 70% (14 out of 20) is required. If you pass, your CEU(s) will be recorded with the relevant provincial authority(ies). (Note: some provinces require individual pharmacists to notify them.)

ANSWERING OPTIONS

- A. For immediate results, answer online at www.pharmacygateway.ca in the CE Online section, "More CCEP-Approved" area.
- B. Mail or fax the printed answer card to (416) 764-3937. Your reply card will be marked and you will be advised of your results within six to eight weeks in a letter from Rogers Publishing.

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Direct Renin Inhibitors: A new drug class for the management of hypertension

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JUNE 2008

The author, expert reviewers and Rogers Publishing have each declared that there is no real or potential conflict of interest with the sponsor of this CE lesson.

INTRODUCTION

Despite the availability of many antihypertensive agents, hypertension remains the major underlying factor causing death worldwide.¹ Complications of hypertension lead to stroke, cardiovascular disease and end-stage renal disease, creating a substantial burden on the healthcare system. It is estimated that 22% of Canadians aged 18–70, and 50% of Canadians above 65 years of age have hypertension. Among these patients, 22% are aware of their condition but remain untreated, and 21% are treated but their blood pressure (BP) remains uncontrolled.² Therefore, there are ample opportunities for clinicians to improve the management of hypertensive patients.

The renin-angiotensin-aldosterone system (RAAS) has been an important target of antihypertensives since the 1990s with the development of angiotensin-converting enzyme inhibitors (ACEI) and the angiotensin receptor blockers (ARB). A new class of antihypertensive targeting the RAAS, the direct renin inhibitors (DRI) has been developed to provide patients with another alternative for blood pressure control. This lesson introduces aliski-

ren, the first orally active direct renin inhibitor, with its unique mechanism of action, efficacy and safety in treating hypertension and renal complications.

IMPORTANCE OF CONTROLLING HYPERTENSION

Target organ damage involving the eyes, brain, heart, kidneys and peripheral blood vessels will occur if hypertension remains untreated or inadequately controlled. Stroke, coronary heart disease and end-stage renal disease (ESRD) are the primary causes of morbidity and mortality due to hypertension.³

It is well known that hypertension increases the risks of stroke and cardiovascular events. For example, a sustained elevation of diastolic pressure of 5–6 mmHg increases the risk of stroke by 34% and the risk of coronary heart disease by 21%.⁴ Achieving a sustained 12 mm Hg reduction in systolic blood pressure (SBP) over 10 years in patients with mild hypertension (140-159/<100 mmHg) will prevent one death for every 11 patients treated. In the presence of CVD or target organ damage, one death will be prevented for every 9 patients

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treated with the same BP reduction.³ A meta-analysis of observational studies demonstrated that even a 2 mmHg reduction in SBP would result in 10% lower stroke mortality and about 7% lower mortality from ischemic heart disease or other vascular conditions in middle age.⁵ Overviews of placebo-controlled randomized trials of ACEIs and calcium channel blockers (CCB) found that these agents reduced stroke and major cardiovascular events by 20–30% and 30–40%, respectively.⁶ In an overview comparing BP-lowering strategies of different intensity, it was found that the risks of stroke, coronary heart disease, and major cardiovascular events were reduced by 15–20% with the more intense regimens.⁶

Hypertension is also a strong independent risk factor for ESRD. Klag *et al.* assessed the development of ESRD in 332,544 men who were screened for entry into the Multiple Risk Factor Interventional Trial (MRFIT).⁷ The authors found a strong, graded relation between both systolic and diastolic blood pressure and ESRD, which is independent of age, race, income, use of medication for diabetes mellitus (DM), history of myocardial infarction, serum cholesterol and smoking. In this study, men with mild (140-159/<100 mm Hg), moderate (160-179/<110 mmHg), and severe (180-209/<120 mmHg) and very severe ($\geq 210/120$ mmHg) hypertension at baseline had adjusted relative risks of developing ESRD of 3.1, 6.0, 11.2 and 22.1, respectively ($p < 0.001$).

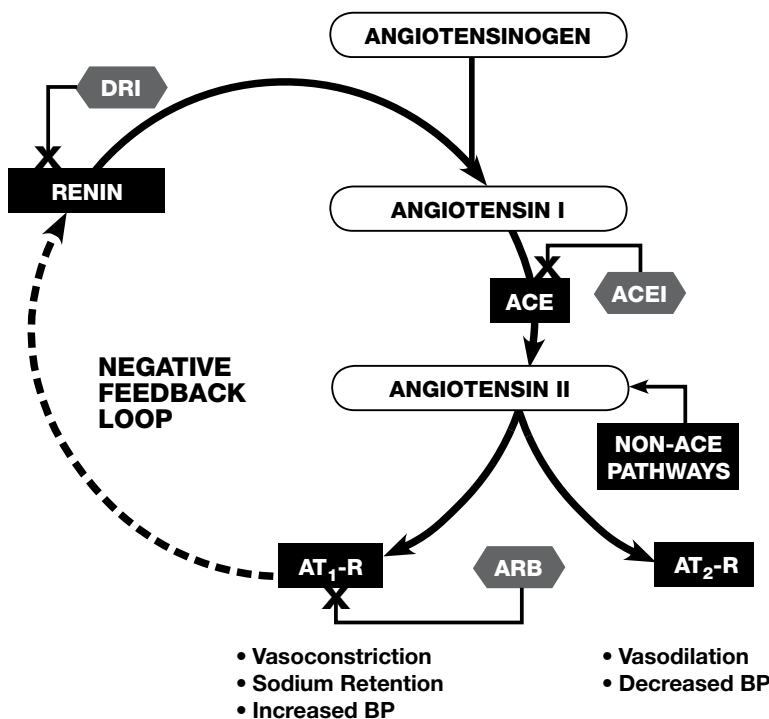
The CHEP 2008², JNC VII⁸ and the European Society of Hypertension guidelines⁹ all indicate that for effective BP control, combination therapies consisting of two or more agents are usually required. This is especially true in hypertensive diabetics or in patients with renal impairment. A review of six clinical trials revealed that patients with either diabetes or renal impairment required an average of 3.2 different antihypertensive medications per day to achieve BP endpoints.¹⁰

CHEP RECOMMENDATIONS

The 2008 Canadian Hypertension Education Program (CHEP) recommends a BP target of <140/90 mmHg for uncomplicated hypertension. For patients with diabetes and chronic kidney disease, the BP target is <130/80 mm Hg. Lifestyle modifications such as sodium intake restriction, healthy diet, regular physical activity, moderate alcohol consumption, smoking cessation, and weight management, remain an integral part for BP control. Regular home BP monitoring should be considered for those hypertensive patients with diabetes, chronic kidney disease, or suspected nonadherence. For a summary of techniques for accurate

FIGURE 1

Renin-angiotensin-aldosterone system including sites of action for the direct renin inhibitor (DRI), angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs)



The DRI acts at the rate-limiting step of the RAAS and prevents the conversion of angiotensinogen to angiotensin I by blocking the activity of renin. ACEIs can only block the production of angiotensin II through ACE pathways. ARBs act only on angiotensin II type 1 receptors (AT₁-R). Stimulation of AT₁-R leads to vasoconstriction, aldosterone secretion, sodium retention, activation of the sympathetic nervous system, cell growth and smooth-muscle hypertrophy. Stimulation of angiotensin II type 2 receptors (AT₂-R) counteracts AT₁-R activity by causing vasodilation, apoptosis and promotes cell differentiation.

TABLE 1: Techniques for accurate blood pressure assessment²

Dos for the patient	Don'ts for the patient
<ul style="list-style-type: none"> • Sit calmly for at least 5 minutes • Arm level with heart • Feet touching floor • Wear comfortable clothing • Free from stress or pain • Be bladder and bowel comfortable 	<ul style="list-style-type: none"> • Ingest caffeinated beverages 1 hour prior • Smoke about 30 minutes prior • Use any substances containing adrenergic stimulants (e.g. pseudoephedrine)

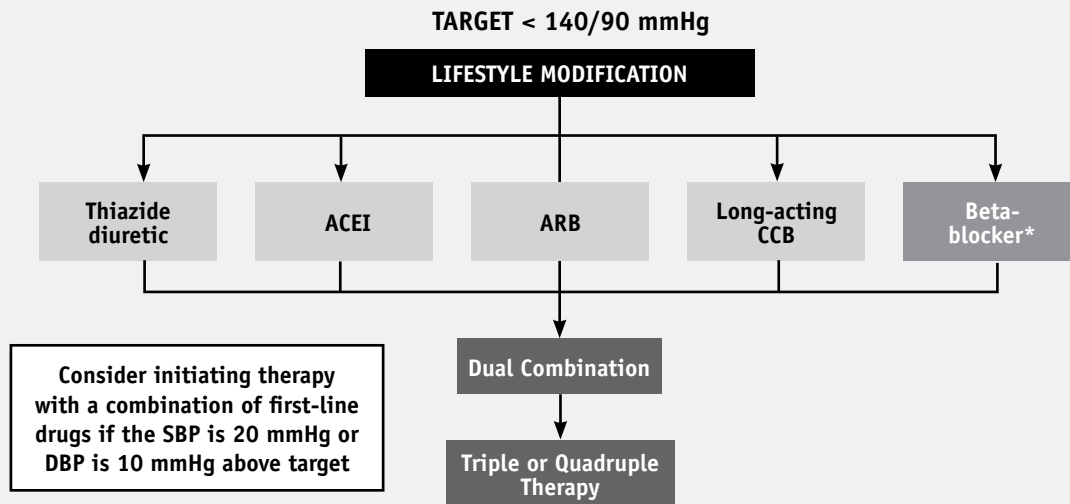
BP assessment see Table 1.²

Pharmacotherapy should be initiated when the average DBP is ≥ 100 mmHg or the average SBP is ≥ 160 mmHg.² Intervention should be strongly considered when the individual has an average DBP of ≥ 90 mmHg or an average SBP of ≥ 140 mmHg in the presence of macrovascular target organ damage. Thiazide diuretics, beta-blockers, ACEIs, ARBs, or long-acting CCBs are recommended as first-line monotherapy for individuals who have diastolic (with or without systolic) hypertension without other compelling indications. CHEP does not recommend using beta-blockers in patients 60 years of age or older. Also,

ACEIs are not recommended in black patients as first-line therapy for uncomplicated hypertension. Beta-blockers and ACEIs, however, may be used in patients with comorbid conditions or in combination therapy.²

As previously mentioned, many hypertensive patients are unable to reach target BP levels and require combination therapy. For a summary of the CHEP recommendations for the treatment of hypertension see Table 2. One combination that CHEP recommends avoiding is a non-dihydropyridine CCB with a beta-blocker to prevent bradycardia or heart block.² For the combination of potassium-sparing diuretics with ACEIs and/or ARBs, it is advised that serum

TABLE 2: CHEP Treatment summary of systolic-diastolic hypertension without other compelling indications (adapted from CHEP 2008)



ACEI and ARB are contraindicated in pregnancy and caution is required in prescribing to women of child-bearing potential.
 * Not indicated as first-line therapy over 60 years of age.

TABLE 3: Reasons for poor response to antihypertensive therapy²

Non-compliance
<ul style="list-style-type: none"> • Dietary • Medication
Associated Conditions
<ul style="list-style-type: none"> • Obesity • Cigarette smoking • Excessive alcohol consumption • Sleep apnea • Chronic pain
Drug Interactions
<ul style="list-style-type: none"> • NSAIDs • Oral contraceptives • Corticosteroids and anabolic steroids • Sympathomimetics and decongestants • Amphetamines • Erythropoietin • Cyclosporine, tacrolimus
Volume Overload
<ul style="list-style-type: none"> • Excessive salt intake • Renal sodium retention
Secondary Hypertension
<ul style="list-style-type: none"> • Renal insufficiency • Renovascular disease • Thyroid disease • Hyperaldosteronism • Pheochromocytoma

creatinine and potassium be monitored. If BP is still uncontrolled after the use of combination therapy, or there are adverse effects, other classes of antihypertensive drugs may be combined with the first-line agents. Alternate reasons why

an individual might not respond to antihypertensive therapy are listed in Table 3.²

TARGETING RAAS

The RAAS has an established role in the regulation of BP, fluid electrolyte balance and vascular growth through the action of angiotensin II (Ang II) (Figure 1).¹¹⁻¹³ Ang II is a potent vasoconstrictor and promotes aldosterone secretion, which results in an elevated BP.¹³ Targeting RAAS with ACEIs and ARBs has been shown to be beneficial in the treatment of cardiovascular disorders, including hypertension, left ventricular hypertrophy, myocardial infarction, stroke, heart failure, atherosclerosis and nephropathy.^{11,12} However, as Figure 1 demonstrates, suppression of the RAAS with ACEIs and ARBs is incomplete, since they interrupt the negative feedback loop of Ang II, causing an increase in renin release and plasma renin activity (PRA; measurement of Ang I generation).^{11,13} In addition, ACEIs cannot completely inhibit Ang II production because Ang II can also be produced from non-ACE pathways such as those mediated by chymase and chymotrypsin-like ACE, which is referred to as “ACE escape.”^{11,13} Aliskiren, the new DRI, also interferes with the negative feedback loop of the RAAS, but does not lead to an increase in PRA. Controlling PRA is important, since elevated levels have been associated with target organ damage.¹¹

ALISKIREN

Mechanism of action: Aliskiren is the first orally active direct renin inhibitor, which

inhibits the initial and rate-limiting step in the RAAS, preventing the formation of Ang I (Figure 1).^{11,14} Renin is secreted by the kidney in response to decreases in blood volume and renal perfusion. This response initiates a cycle that includes the RAAS and a homeostatic feedback loop. Despite causing a dose-dependent increase in plasma renin, aliskiren reduces PRA as it blocks the action of renin, resulting in a reduction of Ang I, Ang II and aldosterone.^{11,13} Aliskiren has been shown to reduce or prevent a rise in PRA when combined with other antihypertensive agents that normally increase PRA, such as ACEIs, ARBs and diuretics.¹⁵ It remains to be determined if these pharmacological differences would result in any clinically significant difference.¹¹ It has been observed that the reactive rise in plasma renin concentration is greater with aliskiren than with ARBs or hydrochlorothiazide (HCTZ).¹⁶ Some investigators have theorized that the compensatory rise in plasma renin concentrations may lead to an increase in BP in patients with hyperactive renin system. However, there is no evidence to support that a reactive rise in renin secretion observed with aliskiren is harmful. Data from more than 12,000 patients enrolled in various clinical trials confirm this, as there were no reports of any patient having a reactive rise in BP due to the rise in renin levels.^{17,18} See Table 4 for a description of the pharmacologic and pharmacokinetic properties of aliskiren.

Dose: The recommended initial dose of aliskiren is 150 mg once daily. If BP is not adequately controlled, the dose can be

increased to 300 mg. Plasma concentration is reduced significantly when aliskiren is administered with a high-fat meal.¹⁴ Therefore, patients should take aliskiren consistently, with respect to with or without food, to avoid fluctuations in absorption.¹¹ No initial dosage adjustment is required for elderly patients or for patients with mild-to-severe renal or hepatic impairment.¹⁴

Indication: Aliskiren is indicated for the treatment of mild-to-moderate essential hypertension. It may be used alone or concomitantly with thiazide diuretics, ACEIs or dihydropyridine CCB.¹⁴

Kinetics: Aliskiren has an oral bioavailability of about 2.6%, which is an improvement on other DRIs that have not made it to market.^{11,14} With an average elimination half-life of about 40 hours, aliskiren can be dosed once daily.¹⁴ It can take up to 8 days for the drug to reach steady state and about 4 weeks of therapy to achieve the maximum antihypertensive effect.^{11,14} About 90% of aliskiren is eliminated unchanged in feces while 1.4% of the drug is metabolized through the CYP3A4 enzyme.¹¹

Interactions: Aliskiren does not inhibit or induce the cytochrome P450 system. Since a small amount of aliskiren is metabolized, it has a low potential for drug interactions. Co-administration of aliskiren with amlodipine, digoxin, HCTZ, furosemide, metformin, ramipril, and valsartan did not result in any clinically significant changes in aliskiren exposure. Despite a reduction in the maximum plasma concentration of up to 50% for aliskiren, little effect on the AUC (area under the concentration curve) was found upon co-administration with irbesartan. An increase of about 80% and 50% in aliskiren plasma concentrations were observed upon the co-administration of ketoconazole or atorvastatin, respectively. Based on the overall safety profile of aliskiren, and less than a twofold increase in exposure, initial dose adjustment will not likely be required during co-administration. Co-administration of aliskiren with furosemide resulted in a reduction of furosemide AUC of about 30%. The concomitant use of cyclosporine and aliskiren is not recommended since the combination resulted in approximately a fivefold increase in AUC of aliskiren in healthy subjects.¹⁴

Adverse reactions: Aliskiren is generally well tolerated, with an adverse-event profile comparable to that of placebo.^{11,14} Common adverse events associated with aliskiren monotherapy include headache, nasopharyngitis, and diarrhea. Diarrhea and other gastrointestinal symptoms were more frequent at dosages greater than 300 mg or in individuals older

Table 4: Aliskiren drug information summary

MECHANISM OF ACTION
• Binds to the renin enzyme, preventing the conversion of angiotensinogen to angiotensin I
INDICATION
• Treatment of mild to moderate essential hypertension
DOSE
• Initial: 150 mg daily • Max: 300 mg daily
METABOLISM
• 90% eliminated unchanged in feces • about 1.4% metabolized by liver via CYP3A4
MAJOR INTERACTIONS
• cyclosporine and aliskiren combination is not recommended
ADVERSE EVENTS
Common (1-10%)
• nasopharyngitis, headache, and diarrhea
Less Common (<1%)
• cough, angioedema, hyperkalemia, and anemia
<i>For complete information on aliskiren, please refer to the most current aliskiren product monograph.</i>

than 65 years of age. Most adverse events were generally mild and transient in nature and have only infrequently required discontinuation of therapy. The incidence of cough with aliskiren was 1.1%, which was up to one-half the incidence of cough with ACEIs in similar trials. Angioedema rarely occurred during clinical trials. Increases in serum potassium levels were minor and infrequent (0.9% compared with 0.6% with placebo). However, when combined with ACEIs in patients with diabetes, the rate of hyperkalemia increased to 5.5%. Routine monitoring of potassium is suggested when this combination is used.¹⁴

Contraindications and precautions: As with any agent that directly affects the RAAS, aliskiren should be avoided during pregnancy, since they can all cause fetal and neonatal morbidity and death.^{11,14} It is unknown if aliskiren is excreted in human milk, therefore nursing mothers should use aliskiren with caution. Aliskiren should also be used with caution in patients with greater than moderate renal dysfunction (creatinine \geq 150 $\mu\text{mol/L}$ for women and \geq 176.8 $\mu\text{mol/L}$ for men and/or eGFR $<$ 30 mL/min), dialysis, nephritic syndrome, or renovascular hypertension, since they were excluded from clinical trials. Generally, hypotension was rarely observed (0.1%) when aliskiren was administered alone or in combination therapy ($<$ 1%). Drug-induced hypotension is more likely to occur in patients with an acti-

vated RAAS (e.g. volume- or salt-depleted patients), patients on dialysis, or those with fluid loss through diarrhea or vomiting.¹⁴

EFFICACY IN HYPERTENSION MANAGEMENT

Many clinical trials have been performed with aliskiren alone and in combination with diuretics, CCBs, ACEIs or ARBs to determine its efficacy in achieving BP control.^{14,19-23} The studies were generally conducted in adults with mild-to-moderate hypertension (excluding DBP \geq 110 mmHg and/or SBP \geq 180 mmHg). Several randomized, double-blind, placebo-controlled 8-week clinical trials demonstrated significant reductions in baseline DBP for both aliskiren 150 mg and 300 mg vs. placebo ($p <$ 0.05).^{14,24}

Gradman *et al.* conducted an 8-week, multicentre, randomized, placebo-controlled, double-blind, active-comparator, parallel-group study (n=652) to assess the efficacy of once-daily treatment of aliskiren (either 150 mg, 300 mg or 600 mg) compared with irbesartan 150 mg.¹⁹ It was found that the antihypertensive effect of aliskiren 150 mg was similar to that of irbesartan 150 mg ($p=0.69$). The higher doses of aliskiren (300 mg and 600 mg) lowered the mean sitting DBP significantly more than irbesartan 150 mg, but had no significant difference in the mean sitting SBP.

In another randomized, multifactorial, double-blind, 8-week study (n=2,776), Vilamil *et al.* assessed the effects of aliskiren (75–300 mg) as monotherapy and in combination with HCTZ (6.25–25 mg).²¹ All dosages of aliskiren and HCTZ monotherapy reduced mean sitting DBP significantly after 8 weeks compared with placebo ($p <$ 0.05). Combining aliskiren with HCTZ proved additional BP lowering over monotherapy with either drug. Responder rates (DBP of $<$ 90 mmHg and/or \geq 10 mmHg reduction) were significantly higher with aliskiren 300 mg (64%) and all combinations (58–81%) than with placebo (46%; all $p <$ 0.05).^{11,21,24}

Aliskiren was also compared with valsartan alone and in combination in a double-blind, randomized, 8-week study (n=1,797).²³ Patients were randomized to receive aliskiren 150 mg, valsartan 160 mg, aliskiren 150 mg with valsartan 160 mg, or placebo once daily. After 4 weeks of treatment, the dosages of the drugs were doubled for the remainder of the study. The researchers found that the combination therapy provided significantly greater BP reductions than either agent alone ($p <$ 0.0001). The greatest reduction in mean sitting SBP and DBP, 17.2 mmHg and 12.2 mmHg respectively, was found with the combination of aliskiren 300 mg with valsartan 320 mg.²³

In a randomized, double-blind, active-controlled parallel-group study, the antihypertensive efficacy of aliskiren as an add-on therapy to amlodipine was assessed.²² The effects of aliskiren were compared with maintaining or doubling the amlodipine dosage. After 4 weeks, for those patients who did not respond (i.e. did not have a DBP reduction to ≤ 90 mmHg) to amlodipine 5 mg were randomized to receive either addition of aliskiren 150 mg, continued amlodipine 5 mg, or amlodipine 10 mg, for 6 weeks. Drummond *et al.* found the addition of aliskiren 150 mg to amlodipine 5 mg produced significantly greater reductions in mean sitting DBP and SBP than continued amlodipine 5 mg monotherapy ($p < 0.0001$). Moreover, reductions in BP achieved with combination therapy were similar to that of amlodipine 10 mg. The proportion of patients achieving successful treatment response (mean sitting DBP < 90 mmHg and/or reduced by ≥ 10 mmHg) was significantly higher with combination therapy (64.2%) than with amlodipine 5 mg (45.2%; $p < 0.005$) and was similar to that of amlodipine 10 mg.^{22,24}

Sica *et al.* assessed the long-term efficacy and tolerability of aliskiren with optional addition of HCTZ in a one-year open-label, randomized, parallel-group, dose-escalation study.²⁵ Patients with mean sitting DBP 90–109 mmHg were randomized to once-daily aliskiren 150 or 300 mg. Patients with BP $\geq 140/90$ mmHg after 2 months received either a dose titration of aliskiren 150 mg titrated to 300 mg, or an addition of HCTZ (12.5 mg titrated to 25 mg if required) to aliskiren 300 mg.²⁵ This study demonstrates the long-term efficacy of aliskiren alone or in combination with HCTZ.^{24,25} Aliskiren also demonstrated persistence of effect after drug discontinuation. In this long-term study of aliskiren, a subgroup of patients remaining on aliskiren monotherapy at the 11th month was randomized to continue aliskiren or placebo during a 4-week double-blind withdrawal phase. The investigators found that there was a statistically significant difference between the two groups (5.99/3.87 mmHg; $p < 0.0001$, for mean sitting systolic and DBP), indicating that aliskiren continued to be effective in lowering BP after 11 months of treatment. There was no evidence of rebound hypertension in the placebo group following aliskiren withdrawal.²⁵

SPECIAL POPULATION

Aliskiren demonstrated antihypertensive efficacy regardless of age or gender in several pooled analyses of randomized, placebo-controlled trials.²⁶ Other pooled data analysis revealed that aliskiren has antihypertensive efficacy in patients with obesity, diabetes and

impaired renal function.^{27–29}

In an 8-week, double-blind study, Uresin *et al.* randomized diabetic patients with hypertension to aliskiren 150 mg, ramipril 5 mg or aliskiren/ramipril 150/5 mg.³⁰ After 4 weeks, all patients had their respective doses doubled for an additional 4 weeks. The investigators found that both aliskiren and combination therapy were superior to ramipril in reducing mean sitting SBP (14.7/16.6/12.0 mmHg respectively; $p < 0.05$). Reductions in mean sitting DBP were similar for both aliskiren and ramipril monotherapy. Combination therapy provided significant reductions in mean sitting DBP compared with either monotherapy. Responder rates for mean sitting DBP were significantly greater with combination (74.1%) and aliskiren monotherapy (73.1%) than with ramipril alone (65.8%; $p < 0.05$).³⁰

PATIENT CASE

JN is a 48-year-old obese male with type 2 diabetes for the past 5 years. His BP has been averaging 125/90 over the past several visits. JN and his doctor have been concerned about JN's worsening kidney disease. JN's proteinuria is on the rise and his estimated glomerular filtration rate has reduced from 52 to 45 mL/min/1.73 m², within the past 6 months. Other lab values are unremarkable. His medication profile is the following:

- Intermediate-acting insulin 20 units twice daily
- Atorvastatin 10 mg at bedtime
- ASA enteric coated 81 mg every morning
- Valsartan 160 mg each morning
- Ferrous fumarate 300 mg at bedtime
- Alfacalcidol 0.25 mcg three times a week
- Calcium carbonate 500 mg with supper
- Replavite® at bedtime

JN has tried ramipril and enalapril previously but discontinued both agents due to a "dry hacking cough." JN has no other significant past medical history. JN's doctor calls you to ask what you recommend to slow down JN's kidney disease progression.

Which of the following agents would you recommend?

- a) lisinopril
- b) hydrochlorothiazide
- c) metoprolol
- d) amlodipine

Several guidelines would confirm that any one of these agents could be used for the treatment of proteinuria.^{2,31,32} ACEIs or ARBs are first-line for slowing the progression of kidney disease,^{2,31} and the combination normally will not cause any further hypotensive effects.³² However, JN is likely to develop a cough with the addition of lisinopril (since he developed a cough on two other ACEIs previously).

HCTZ may not be an effective option in JN's case since the kidney perfusion of the drug is limited when the estimated glomerular filtration rate is less than 50 mL/min/1.73 m².³³ The addition of either metoprolol or amlodipine could be problematic for this patient since we may not want to lower his BP any further. Potentially, there might be another option for JN.

AVOID STUDY

Albuminuria has been shown to be a risk factor for cardiovascular and kidney disease in patients with hypertension.³⁴ The prevalence of albuminuria in patients with DM is about 30%.^{24,34} There is emerging data that the treatment of albuminuria leads to improvement in risk profiles of patients. Microalbuminuria is defined as 30–300 mg of albumin in a 24-hour collection of urine, whereas macroalbuminuria is defined as 300 mg/24 h of albumin or greater. Since albuminuria represents about 40% of total urinary protein excretion, patients with macroalbuminuria or albuminuria also will have overt proteinuria.³⁴

The Aliskiren in the Evaluation of Proteinuria In Diabetes (AVOID) trial looked at the effect of aliskiren in patients with hypertension, proteinuria and DM.³⁵ This was a 24-week, double-blind, randomized placebo-controlled study in 599 patients. Patients initially received 12–14 weeks of losartan 100 mg once daily, with optional addition of other antihypertensive agents as necessary to achieve BP target of 130/80 mmHg. Those patients with BP $< 150/95$ mmHg after the 12–14 week period were randomized to receive aliskiren 150 mg or placebo, in addition to previous therapy. After 12 weeks, the aliskiren dose was doubled for another 12 weeks. The primary objective was to assess the percentage change in urinary albumin-to-creatinine ratio (UACR) from baseline. Secondary objectives included proportion of patients with $\geq 50\%$ reduction in UACR, effect of treatment on BP, effect on UAER (urinary albumin excretion rate) and estimated glomerular filtration rate (eGFR), and safety and tolerability of treatment.³⁵

Parving *et al.* found that in patients who received losartan 100 mg plus optimal therapy, the addition of aliskiren 300 mg provided significant reductions in UACR after 24 weeks of treatment ($p < 0.001$).³⁵ Overall, the study demonstrated that aliskiren provided a 20% reduction in UACR compared with placebo, beyond ARB-based therapy. When compared with the placebo group, a significantly greater proportion of patients in the aliskiren 300 mg group had a $\geq 50\%$ reduction in UACR (24.7% vs 12.5%; $p < 0.0005$). Patients who received aliskiren in addition to optimal therapy had

a decline in eGFR compared to the placebo group. However, the decline was not statistically significant.³⁵

Referring back to JN, a potential alternative for him would be to add aliskiren to his existing therapy. Extrapolating the AVOID data along with the mechanism of action of aliskiren on the RAAS, JN can potentially benefit from this therapy to slow down the progression of his kidney disease.

STUDIES ON THE HORIZON

Aliskiren possesses several features of an optimal antihypertensive agent.¹¹ The Aspire Higher program is a series of clinical trials designed to compare aliskiren for the treatment or prevention of cardiovascular and renal disease to established therapies that is presented in Figure 2.

One such study, the ALOFT study, (ALiskiren Observation of Heart Failure Treatment) is a 12-week study designed to evaluate the safety and tolerability of aliskiren when given in addition to standard therapy (beta-blockers with either an ACEI or an ARB) for heart failure.^{11,24} The ALiskiren Left ventricular Assessment of hYpertrophy (ALLAY) study is a 36-week study designed to evaluate the effect of aliskiren/losartan combination therapy on left ventricular regression. The 36-week ASPIRE (Aliskiren Study in Post-MI patients to Reduce Remodelling) study will compare aliskiren to standard therapy (beta-blockers, either ACEIs or ARBs, a statin, and an anti-platelet agent) in the treatment of acute myocardial infarction. The 8-week Aliskiren and Valsartan to reduce NT-proBNP via renin-

TABLE 5: Studies on the horizon

Name	Patient	Study Population	Duration	Status
ALOFT	• Heart failure	302	12 weeks	Complete
ALLAY	• LVH	480	36 weeks	Complete
ASPIRE	• Myocardial Infarction	800	36 weeks	Ongoing
AVANT GARDE	• Acute coronary syndrome	1100	8 weeks	Ongoing
ALTITUDE	• Type 2 diabetes • History of CVD • Kidney disease*	8600	4 years	Ongoing

*LVH=Left ventricular hypertrophy; CVD=Cardiovascular disease; *Kidney disease=estimated glomerular filtration rate between 30-60 mL/min/1.73m²*

angiotensin-aldosterone-system blockade (AVANT-GARDE) is designed to determine whether aliskiren or valsartan reduce levels of NT-proBNP. The ALTITUDE (Aliskiren Trial In Type 2 diabetes Using cardio-renal Disease Endpoints) is a 4-year study that will determine whether aliskiren, when added to conventional treatment delays the occurrence of cardiovascular and renal complications in patients with DM.^{11,24} See Table 5 for a summary of these aliskiren trials.

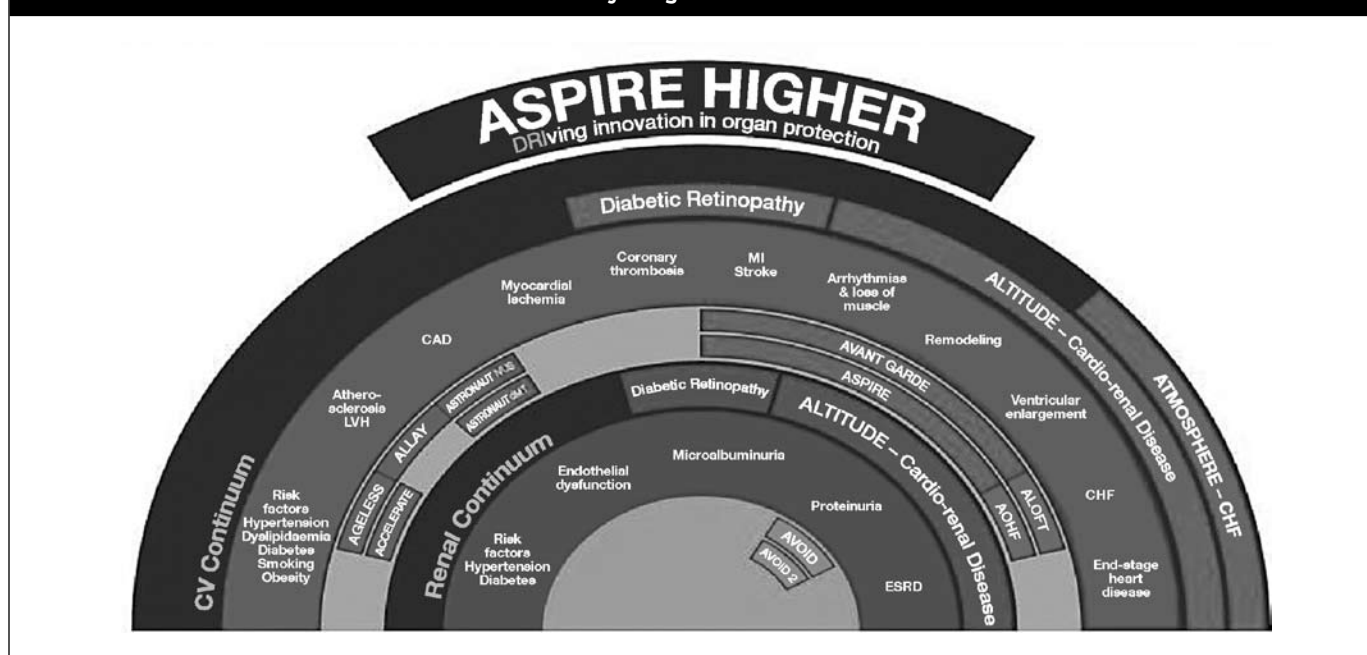
SUMMARY

Hypertension treatment remains a challenging issue despite advances. Pharmacists need to encourage patients to take an active role in managing their hypertensive disorder and to promote patients' adherence to pharmacological therapy along with lifestyle modification, self-monitoring of BP, and awareness of their BP status. Controlling hypertension is important since it can potentially prevent end-organ

damage such as stroke, myocardial infarction, and kidney failure. In many cases, patients require a combination of antihypertensive agents from different classes to achieve and sustain the BP targets established by CHEP. With one-fifth of Canadians continuing to have uncontrolled hypertension, there is an obvious need for novel and effective treatment alternatives for hypertension.

Aliskiren, the first direct renin inhibitor, provides an effective alternative for the management of hypertension whether used as monotherapy or in combination with thiazide diuretics, ACEIs, ARBs, and CCBs. This agent has also been shown to be well tolerated and safe with a low risk of drug interactions. It appears promising that the unique mechanism of action of aliskiren provides a more complete suppression of the RAAS when compared to ACEIs and ARBs. The reduction in PRA may prove to be beneficial for the prevention of end-organ damage beyond BP control. From

FIGURE 2: Overview of ASPIRE HIGHER Clinical Study Program³⁶



the results of the AVOID trial, comparative trial with ramipril in diabetics along with other pooled data, aliskiren may have a potential benefit in patients with diabetic nephropathy. Given its effect on the RAAS, aliskiren may be a useful therapy in cardiovascular and renal diseases. The results from other large-scale randomized controlled trials will further clarify its therapeutic significance.

REFERENCES

- Ezzati M et al. Selected major risk factors and global and regional burden of disease. *Lancet* 2002; 360:1347-60.
- Canadian Hypertension Education Program (CHEP) 2008. Available at <http://www.hypertension.ca/chep/en/slidekts.asp>. Accessed on March 7, 2008.
- Saseen JJ and Carter BL. Hypertension. In: DiPiro JT, et al., eds. *Pharmacotherapy - a pathophysiologic approach*. 6th ed. New York: McGraw Hill, 2005. p.185- 217.
- Nally JV Jr. Essential Hypertension. In: Greenberg A, ed. *Primers on Kidney Diseases*, 2nd ed. San Diego: National Kidney Foundation, 1998. p. 496-500.
- Levington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903-13.
- Neal B, MacMahon S, Chapman N, for the Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium channel antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomized trials. *Lancet*. 2000;356:1955-64.
- Klag MJ, Whelton PK, Randall BL, et al. Blood pressure and end-stage renal disease in men. *N Engl J Med* 1996;334:13-18.
- Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42:1206-52.
- 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003;21:1011-53.
- Bakris GL, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis* 2000;36:646-61.
- Frampton JE, Curran MP. Aliskiren: A review of its use in management of hypertension. *Drugs* 2007;67 (12):1767-1792.
- Ferrario CM, Straw WB. Role of the renin-angiotensin-aldosterone system and proinflammatory mediators in cardiovascular disease. *Am J Cardiol* 2006;98:121-8.
- Reid IA. Vasoactive peptides. In: Katzung BG, eds. *Basic and clinical pharmacology*. 10th ed. New York: McGraw Hill, 2007. p 277-93.
- Novartis Pharmaceuticals Canada Inc. Rasilez (aliskiren fumarate) product monograph. Dorval, QC: February 28, 2008.
- O'Brien E, Barton J, Nussberger J, et al. Aliskiren reduces blood pressure and suppress plasma renin activity in combination with a Thiazide diuretic, an angiotensin-converting enzyme inhibitor, or an angiotensin receptor blocker. *Hypertension* 2007;49:276-84.
- Sealey JE, Laragh JH. Aliskiren, the first renin inhibitor for treating hypertension: reactive renin secretion may limit its effectiveness. *Am J Hypertens*. 2007;20:587-97.
- Hollenberg NK. A brief response to Sealey and Laragh. *JRAAS*. 2007;8(2):63.
- Menard J, Azizi M. The difficult conception, birth and delivery of renin inhibitor: controversies around aliskiren. *J Hypertens*. 2007;25:1775-82.
- Gradman AH, Schieder RE, Lins RL, et al. Aliskiren, a novel orally effective renin inhibitor, provides dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients. *Circulation*. 2005;111:1012-18.
- Oh B-H, Mitchell J, Herron JR, et al. Aliskiren, an oral renin inhibitor provides dose dependent efficacy and sustained 24-hour blood pressure control in patients with hypertension. *J Am Coll Cardiol*. 2007;49:1157-63.
- 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.
- Drummond W, Munger MA, Essop MR, 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*. 2007;9:742-50.
- Oparil S, Yarows SA, Patel S, et al. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension. *Lancet*. 2007;370:221-9.
- Uresin Y, Bozkurt MM, Sabirli S, et al. Aliskiren, the future of renin-angiotensin system blockade? *Expert. Rev. Cardiovasc. Ther.*. 2007;5(5):835-49.
- Sica D, Gradman A, Lederballe O, et al. Aliskiren, a novel renin inhibitor, is well tolerated and has sustained BP-lowering effects alone or in combination with HCTZ during long-term (52 weeks) treatment of hypertension. 2007;25(Suppl),121 (Abstract P797).
- Dahlöf B, Anderson DR, Arora V, et al. Aliskiren, a direct renin inhibitor, provides antihypertensive efficacy and excellent tolerability of age or gender in patients with hypertension. *J Clin Hypertens* 2007;9(Suppl A):(Abstract P376).
- Pescott MF, Bush C, Arora V, et al. Aliskiren, a direct renin inhibitor, provides effective BP lowering with placebo-like tolerability in obese patients with hypertension. *Int J Obes*. 2007;31(Suppl 1):S99 (Abstract P88).
- Taylor AA, Anderson DR, Arora V, et al. Antihypertensive efficacy of the direct renin inhibitor aliskiren in patients with diabetes: pooled analysis of 10 randomized trials. Poster 0483 presented at the 67th Annual Scientific Sessions of the American Diabetes Association, 22-26 June 2007, Chicago, IL, USA.
- Weir MT, Anderson DR, Arora V, et al. Safety and blood pressure-lowering efficacy of the direct renin inhibitor aliskiren in patients with hypertension and impaired renal function. *WCN 2007 Book of Abstracts*: 384-T-PO-1162.
- Uresin Y, Taylor A, Kilo C, et al. Aliskiren, a novel renin inhibitor has a greater BP lowering than ramipril and additional lowering when combined ramipril in patients with diabetes and hypertension. *J Hypertens*. 2006;24(Suppl 4):S82(Abstract P269).
- American Diabetes Association (ADA) Recommendations 2007. Available at: <http://www.diabetes.org/for-health-professional-and-scientists/cpr.jsp>. Accessed on Jan 21, 2008.
- Caring for Australians with Renal Impairment (CARI) Guidelines. Available at: <http://www.cari.org.au/Reducing%20proteinuria.pdf>. Accessed on Jan 21, 2008.
- Micromedex. Available at: <http://www.micromedex.com/products/subscribers>. Accessed on Jan 25, 2008.
- Basri S, Lewis JB. Microalbuminuria as a target to improve cardiovascular and renal outcomes. *Am J Kidney Dis*. 2006; 47(6):927-46.
- Parving H-H, et al. (AVOID steering committee). Oral presentation at ASN, San Francisco, USA. November 4, 2007.
- Aspire Higher Program. Novartis Publications. March 8, 2008.

QUESTIONS - Answer online at www.pharmacygateway.ca, CE section, "More CCCEP-approved" dept.

1. What is the percentage of Canadians with uncontrolled hypertension despite treatment?

- a) 8%
- b) 11%
- c) 21%
- d) 22%
- e) 28%

2. Untreated, or inadequately controlled, hypertension can lead to which of the following organ damage?

- a) heart
- b) eyes
- c) kidneys
- d) brain
- e) all of the above

3. As little as a 2 mmHg reduction in systolic blood pressure would result in 10% lower stroke mortality and about 7% lower mortality from ischemic heart disease.

- a) true
- b) false

4. Which of the following statements is correct regarding the Canadian Hypertension Education Program (CHEP)?

- a) BP target for uncomplicated hypertension is less than 140/90 mmHg.
- b) BP target is less than 130/80 mmHg for patients with diabetes or chronic kidney disease.

- c) BP target for hypertension is less than 120/90 mmHg.
- d) BP target for hypertension is 110/70 mmHg.
- e) a) and b)

5. Which of the following statements is incorrect regarding CHEP?

- a) Beta-blockers are first line of treatment in patients 60 years of age or older.
- b) Alpha-blockers are not recommended as first-line agents for uncomplicated hypertension.
- c) ACEIs and ARBs are contraindicated in pregnancy.
- d) Combination therapy of first-line agents could be initiated if SBP is more than 20 mmHg above target.
- e) a) and c)

6. CHEP recommends the following combination therapies except:

- a) Felodipine plus amlodipine
- b) Valsartan plus HCTZ
- c) Amlodipine plus lisinopril
- d) Diltiazem plus metoprolol
- e) a) and d)

7. Regarding accurate blood pressure assessment, which of the following statements is incorrect?

- a) Sit calmly for at least 5 minutes.
- b) Do not ingest caffeinated beverages 1 hour prior.

- c) Keep arm at shoulder level.
- d) Be bladder and bowel comfortable.
- e) Don't smoke about 30 minutes prior.

8. Which of the following statement(s) are correct?

- a) Ang II is a potent vasoconstrictor that promotes aldosterone secretion.
- b) ACEIs, ARBs and aliskiren interrupt the feedback loop of Ang II.
- c) ACEIs and ARBs cause an increase in PRA, whereas aliskiren reduces it.
- d) Aliskiren binds to the renin enzyme, thereby blocking the conversion of angiotensinogen to Ang I.
- e) All of the above.

9. All the following drug classes increase PRA except:

- a) ACEIs
- b) ARBs
- c) Thiazide diuretics
- d) DRIs
- e) c) and d)

10. Which of the following statement(s) are correct?

- a) ACEIs block all pathways of Ang II production
- b) ARBs are selective for AT₁-R only
- c) Aliskiren binds to renin, preventing Ang I production
- d) b) and c)
- e) All of the above

PATIENT CASE APPLIES TO Q11 – Q14

SV comes to your community pharmacy with a prescription for aliskiren 150 mg daily. His current medication history includes:

- ASA enteric coated 81 mg daily
- Metformin 500 mg twice daily
- HCTZ 25 mg each morning
- Enalapril 10 mg daily
- Simvastatin 20 mg at bedtime
- Celecoxib 100 mg daily
- Ranitidine 150 mg twice daily

He tells you that his BP at the doctor's office was 148/95 mmHg.

11. Possible explanation(s) for SV's uncontrolled BP include:

- a) non-compliance with either lifestyle modifications or medications
- b) celecoxib use
- c) simvastatin use
- d) a) and b)
- e) a) and c)

12. SV questions being given a prescription for a third BP medication. Your possible response could be one of the following:

- a) I will call your doctor because he probably made a mistake.
- b) Your BP is still not at target and many people require an average of three BP medications to achieve target.
- c) Hypertension is an uncontrollable disease no matter how many medications are used.
- d) You must be doing something wrong because one medication is usually enough.
- e) Your BP would be at target if you would only listen to the advice provided by me and your doctor.

13. Which of the following statements is true regarding the administration of aliskiren?

- a) You must take aliskiren with food.
- b) You may need to take aliskiren twice daily to reach full effect.

- c) You should be consistent with regards to aliskiren administration with food.
- d) You must take aliskiren on an empty stomach.
- e) You must take aliskiren at bedtime.

14. SV is curious about the side effects that are associated with this new drug he is given. Which of the following response(s) are correct?

- a) Most common side effects can include blurred vision or diarrhea.
- b) Most common side effects can include headache or swelling in the extremities.
- c) Most common side effects can include headache or diarrhea.
- d) Most common side effects can include cough or ringing in the ears.
- e) Most common side effects can include chest pain or swelling in the extremities.

15. Which of the following statement(s) regarding drug interactions with aliskiren are incorrect?

- a) Aliskiren has a low potential for interactions since most of the drug is excreted unchanged with little metabolism.
- b) Co-administration of irbesartan with aliskiren results in a clinically insignificant change in AUC for aliskiren.
- c) Initial dose adjustments for aliskiren is required upon the co-administration of either atorvastatin or ketoconazole.
- d) The combination of aliskiren with cyclosporine is not recommended.
- e) b) and c)

16. Which of the following statement(s) regarding aliskiren are correct?

- a) No initial dose adjustments are required for patients with renal or hepatic impairment.
- b) It has a short half-life and should be dosed twice daily.
- c) About 90% of the drug is metabolized through CYP3A4.
- d) a) and c)
- e) All of the above

17. Which of the following statement(s) are correct?

- a) Aliskiren monotherapy has demonstrated at least as well or better antihypertensive efficacy as thiazide diuretics, ACEIs, ARBs, or CCBs.
- b) Aliskiren has demonstrated better antihypertensive efficacy in men who are older than 65 years of age.
- c) Aliskiren was not shown to cause rebound hypertension following its withdrawal.
- d) a) and c)
- e) All of the above

18. Which of the following statement(s) are correct with regards to the AVOID trial?

- a) Aliskiren was found to provide an additional 20% reduction in urinary albumin-to-creatinine ratio beyond losartan-based therapy.
- b) A significantly greater proportion of patients in the aliskiren 300 mg treatment group had a >50% reduction in urinary albumin-creatinine ratio compared to the losartan-based therapy.
- c) Losartan-based therapy had a significantly greater reduction in BP compared to the aliskiren group.
- d) a) and b)
- e) a) and c)

19. The term "ACE escape" refers to the production of Ang II from non-ACE pathways such as those mediated by chymase and chymotrypsin-like ACE which limits the pharmacological effects of ACEIs.

- a) true
- b) false

20. By targeting RAAS, aliskiren, ACEIs and ARBs inhibit which of the following:

- a) aldosterone secretion
- b) activation of sympathetic nervous system
- c) smooth-muscle hypertrophy
- d) vasoconstriction
- e) all of the above

FACULTY: Direct Renin Inhibitors: A new drug class for the management of hypertension

About the author

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Reviewers

All lessons are reviewed by pharmacists for accuracy, currency and relevance to current pharmacy practice.

Continuing Education Project Manager

Sheila McGovern, Toronto, Ont.

This lesson is valid until April 24, 2011. Information about direct renin inhibitors may change over the course of this time. Readers are responsible for determining the

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