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Benefits of ACE Inhibitors in Diabetes

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Abstract: Angiotensin-converting enzyme (ACE) inhibitors have been FDA-approved for treating refractory hypertension since 1981. Since then, clinical investigations support the benefits of ACE inhibition (ACE-I) in pathologies like congestive heart failure, myocardial infarction, diabetes mellitus, chronic renal insufficiency, and atherosclerotic cardiovascular disease. Both, clinical trials and animal models of type I and type II diabetes have shown that hyperactivity of the angiotensin II signaling pathway contributes to the development of diabetes and its complications, and that blockade of the renin-angiotensin system prevents new onset diabetes and reduces the risk of diabetic complications. Furthermore, ACE inhibitors are generally well tolerated and have few contraindications. This article describes ACE as a target molecule and gives an overview on the clinical evidence that supports the use of ACE inhibitors in diabetes.

Keywords: ACE inhibitor, renin-angiotensin system, ACE, diabetes

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Role of the Renin-Angiotensin System in Diabetes

The Renin-Angiotensin System (RAS) is an important component for the homeostasis of blood flow.¹ The existence of the RAS was recognized more than 100 years ago, after the discovery of renin by Tigerstedt and Bergman.² Renin is released from juxtaglomerular cells of the kidney in response to reduced renal perfusion pressure, reduced salt transport to the distal tubule, or increased renal sympathetic tone.³ The cascade of events that follows renin release is illustrated in Figure 1. The action of renin on its liver-generated substrate, angiotensinogen, generates the inactive decapeptide, angiotensin I (Ang I), which is hydrolyzed by angiotensin-converting enzyme (ACE) to the octapeptide, angiotensin II (Ang II). ACE conversion of Ang I occurs primarily in the lungs, producing changes in Ang II levels that vary in accordance to plasma renin levels.⁴ There is growing evidence that

local systems in various tissues and organs are capable of generating Ang II including the adrenal gland, brain, heart, kidney, vasculature, adipose, gonads, pancreas, prostate, retina, and liver.^{2,5-14}

Elements of the RAS act in concert to maintain exquisite balance of water homeostasis (Fig. 2). Deregulation or accumulation of any of these elements disrupts the balance, tilting the balance to one side and exacerbating or accelerating the onset of disease. Of the RAS elements shown in Figure 2, Ang II is perhaps the most biologically active, triggering elevation in blood pressure by direct vasoconstriction, the stimulation of thirst by causing vasopressin release,¹⁵ and the induction of aldosterone production leading to water retention and facilitation of sympathetic activity.¹⁶ Ang II has also been implicated in insulin resistance by inhibiting insulin receptor dependent PI3K signaling.¹⁵ Additionally, Ang II and can act on the AT1 receptor, thereby decreasing insulin-induced

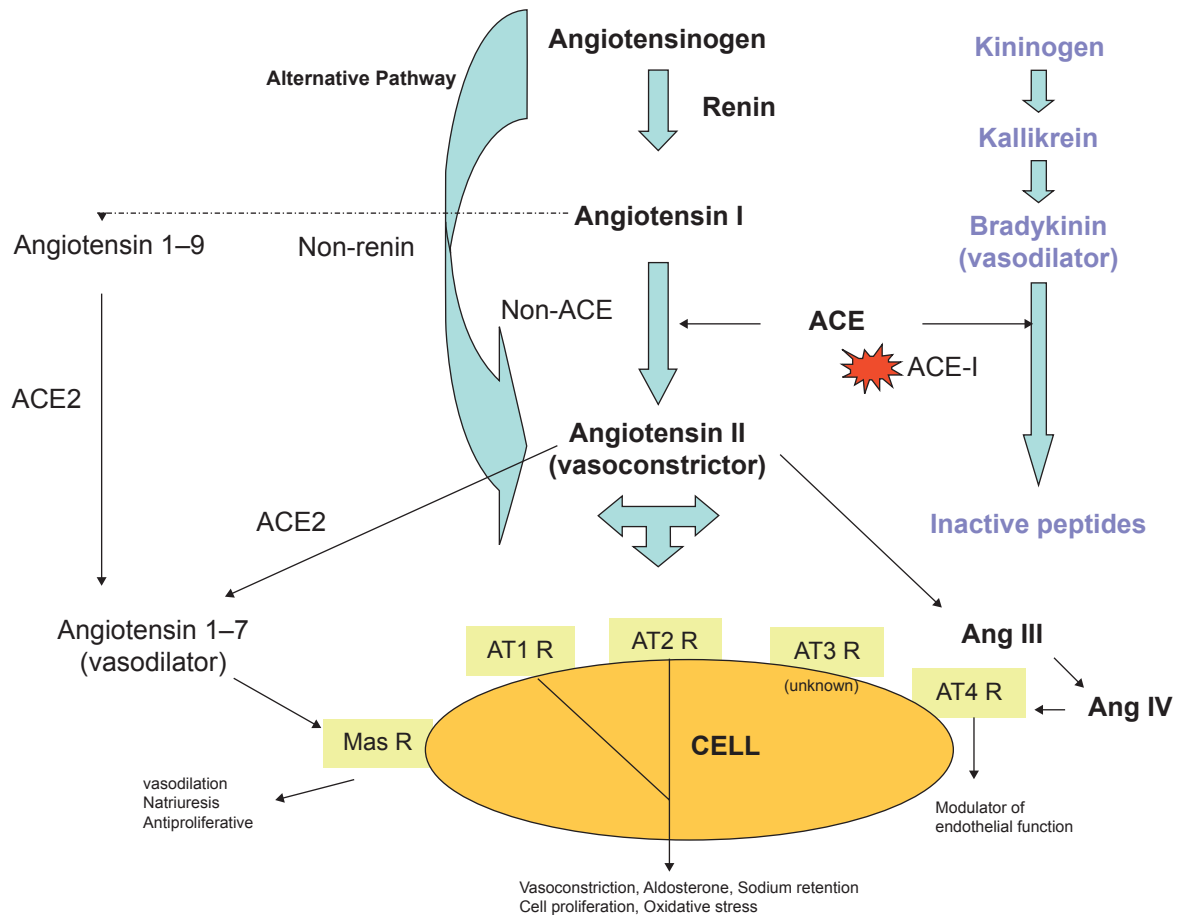


Figure 1. Schematic representation of the Renin-Angiotensin and Kinin-Kallikrein cascade.

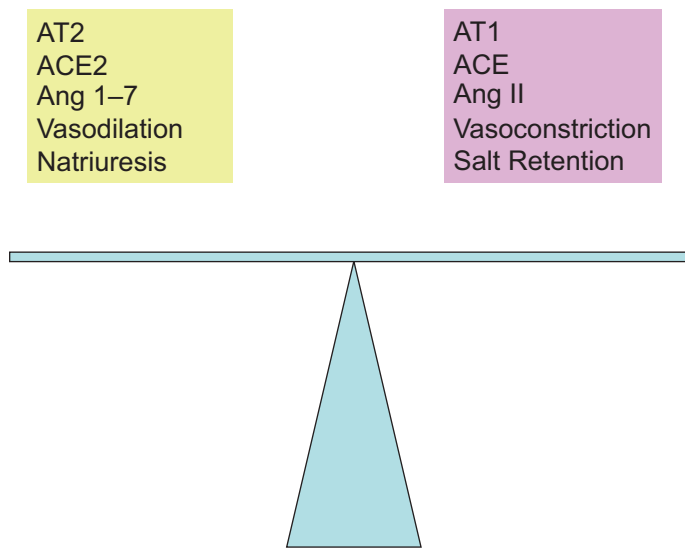


Figure 2. Balance activities in the RAS.

nitric oxide production and at the same time activating NADPH oxidase leading to enhanced production of other reactive oxygen radicals and enhancing inflammation.^{16,17} That hypertension is a common characteristic of insulin-resistant diabetes, with observed increases in tissue Ang II seen¹⁸ coupled with the inhibition of the vasodilator, nitric oxide, is not surprising. Further, it has been shown that in diabetic patients, therapeutic inhibition of the RAS increased nitric oxide activity in renal endothelium, having a positive influence on renal function, and possibly cardiovascular function as well.¹⁹

Therapeutic responses to RAS blocking agents indicate that maintenance of normal renin levels may contribute to blood pressure elevation, suggesting that renin-dependent mechanisms may be involved in more than 70% of patients with essential hypertension. On the other hand, 25%–30% of patients have evidence of low or suppressed renin levels, a finding that may reflect primary aldosteronism, sodium or volume excess.¹⁷ Low-renin hypertension is more common among older people with hypertension, women, African Americans, patients with chronic renal parenchymal disease and patients with type 2 diabetes.¹⁷ Although such patients often have lesser blood pressure-lowering benefit from RAS blocking agents, there is evidence that the circulating levels of plasma renin activity (PRA) might not reflect tissue activities of the system. One particular example is

the involvement of intrarenal Ang II in progression of renal damage and therefore substantial benefit of RAS blockage despite low circulating levels of renin and Ang II.¹⁷

The frequent association of diabetes mellitus with hypertension, retinopathy, nephropathy, and cardiovascular disease has implicated dysfunction of RAS in the initiation and progression of these disorders.^{2,18} Because the prevalence of diabetes is reaching epidemic levels, the potential importance of these agents in the prevention and control of diabetic complications is obvious.

Clinical trials have demonstrated the ability of RAS blockade to prevent new-onset diabetes and the development of diabetic complications.^{19–21} In the Heart Outcomes Prevention Evaluation study (HOPE), diabetes incidence was lower in the group treated with ramipril when compared with placebo.²⁰ In the Losartan Intervention For Endpoint Reduction in Hypertension study (LIFE), the use of losartan was associated with a reduction in the occurrence of new diabetes onset as compared with atenolol.²² RAS components, mostly Ang II, have a potential role in endothelial cell dysfunction, insulin resistance, inflammation, and proliferative effects.^{23–25} Meta analysis of several trials demonstrated that ACE inhibitors or Ang II receptor blockers (ARB) reduce the risk of diabetes by 25%.²⁶ Clinical evidence supports the idea that aggressive ACE-I treatment is warranted in diabetic patients. A subgroup of the United Kingdom Prospective Diabetes Study (UKPDS) was analyzed for the effect of aggressive versus less aggressive treatment of hypertensive diabetic patients with the ACE-I, captopril, or the beta-blocker, atenolol. This study found that patients treated more aggressively with either antihypertensive agent had reduced risk of complications associated with diabetes when compared to those treated less aggressively.^{27,28}

Targeting RAS

The Angiotensin-Converting Enzyme (ACE)

ACE is a zinc metallopeptidase expressed at the surface of many cells where it catalyzes the conversion of Ang I to Ang II and degrades bradykinin. Bradykinin is a potent vasodilator, acting through the release of



prostacyclin, nitric oxide, and endothelial derived hyperpolarization factor (Fig. 1). Clinical and experimental evidence show that blockage of ACE improves endothelial dysfunction.¹⁵

ACE inhibitors (ACE-I) are a family of drugs commonly prescribed to combat hypertension. The primary vasodilatory action of ACE-I is the blockage of ACE and thus the formation of Ang II. With long-term administration, ACE-I lower blood pressure, even in patients with low renin hypertension, suggesting that part of the effect is independent of a decrease in Ang II.¹ The contribution of bradykinin to the action of ACE-I has been debated.¹ Studies by Gainer et al²⁹ found that co-administration of the bradykinin receptor antagonist, icatibant acetate, significantly attenuated the hypotensive effect of the ACE-I captopril in normotensive and hypertensive subjects. Furthermore, Horning et al, showed that ACE-I increase flow-dependent, endothelial-mediated dilation in humans by bradykinin-dependent mechanisms.³⁰ In another study, bradykinin concentration in plasma was found to be increased or unchanged after ACE inhibition.¹ These studies suggest a potential contribution of bradykinin to the effect of ACE-I. Considering that the treatment with ACE-I also increases Angiotensin 1–7 levels,^{31,32} the beneficial action of ACE-I could also be in part due to Angiotensin 1–7 effects.^{33,34}

Currently, there are at least 10 ACE-I that have been approved for use in the US (Table 1 and Fig. 3).³⁵ Most of these drugs, with the exception of captopril and enalaprilat, are considered to be pro-drugs. The use of ACE-I has risen over the years, with the sales in the U.S. for angiotensin-II antagonists increasing from \$3.5 billion (US) in 2003, to \$6.6 billion (US) in 2007, while global sales were \$19.4 billion (US) in 2007.³⁶

Angiotensin Receptor Blockers (ARBs)

ARBs bind to the angiotensin type-1 receptors (ATR1) (Fig. 1) and block the physiological effects that result from binding of Ang II to these receptors. Similar to ACE-I, these agents reduce blood pressure, inflammation, cytokine generation, and prothrombotic factors.³⁷ Available ARBs include Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Telmisartan and Valsartan.

Renin blockers

Aliskiren inhibits the capacity of renin to form Ang I, and therefore Ang II (Fig. 1). It produces more complete RAS inhibition than the ACE-I or ARBs. Six randomized, double blinded placebo-control trials in >2,700 patients with mild to moderate hypertension demonstrated the blood lowering potential of this agent.³⁷ Further trials are under way to assess cardiovascular events and diabetic complications with aliskiren.

ACE-I Blockage and Diabetic Complications

In addition to their antihypertensive properties, for which these compounds were originally designed, ACE-I are also indicated (and prescribed) in a number of clinical situations (Table 1).^{38–46} There is strong evidence that ACE-I are effective in preventing cardiovascular disease and reducing morbidity and mortality in patients at high risk of cardiovascular disease or renal complications.^{47–52} Evidence is also mounting for other potential uses for these drugs.

Hypertension and cardiovascular diseases

Insulin resistance is related to hypertension and frequently is a comorbidity.⁵³ Patients with diabetes are more likely to be hypertensive than nondiabetics, and hypertension is linked with cardiovascular disease, stroke, progression of renal disease, and other complications.³⁷ The cardiovascular morbidity and mortality related to diabetes are very high.¹⁵ Clinical trials including the UKPDS, HOPE and MICRO-HOPE, Patients with Type 2 Diabetes and Microalbuminuria Study (IRMA2), and Reduction of Endpoints in Non-insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) have shown that prevention or reduction of proteinuria, blood pressure control, glycemic control, and particularly the blockade of RAS, are essential to prevent or delay the vascular diabetes complications in diabetics.¹⁵

Studies comparing the effect of ACE-I to other antihypertensive agents have been performed. The Captopril Prevention Project (CAPP) assessed diabetic patients at risk for cardiovascular disease, and found that patients who were treated with captopril had a significantly reduced incidence of cardiac events,

**Table 1.** ACE inhibitors.

Inhibitor	Indications (in addition to hypertension)	Typical dose range (mg/day)	Half-life (hours)	Monthly cost (US Dollars, 2005)*	FDA approved
Alacepril		12.5–75			
Benazepril	Non-diabetic neuropathy	5–80	10–12	22–44	1991
Captopril	Heart failure, post-MI left ventricular dysfunction, diabetic neuropathy, hypertensive emergency	25–450	1.5–3	30–271	1981
Cilazapril		2.5–5	30–50		
Delapril		30–60			
Enalapril	Heart failure, left ventricular dysfunction, diabetic neuropathy	2.5–80	2–11	18–111	1985
Enalaprilat	Hypertensive emergency	1.25/6 hrs by IV	35–38		1985
Fosinopril	Heart failure	10–80	12–14	35–47	1991
Imidapril		2.5–10	>24		
Lisinopril	Heart failure, Improved survival post-MI, migraine prophylaxis	2.5–40	11–12	18–61	1987
Moexipril		7.5–30	2–9	30–46	1995
Moveltipril					
Perindopril	Stroke prevention	4–16	3–10	48–68	1993
Quinapril	Heart failure	10–80	1–2	38–46	1991
Ramipril	Heart failure, reduce risk of MI, stroke, diabetic neuropathy, non-diabetic neuropathy	2.5–20	13–17	44–65	1991
Rentiapril					
Rescinnamine					1956
Spirapril		6	30–35		1994
Temocapril		1–4			
Trandolapril	Heart failure, post-MI left ventricular dysfunction	1–8	6–10	41–42	1996
Zofenopril	MI	30–60			

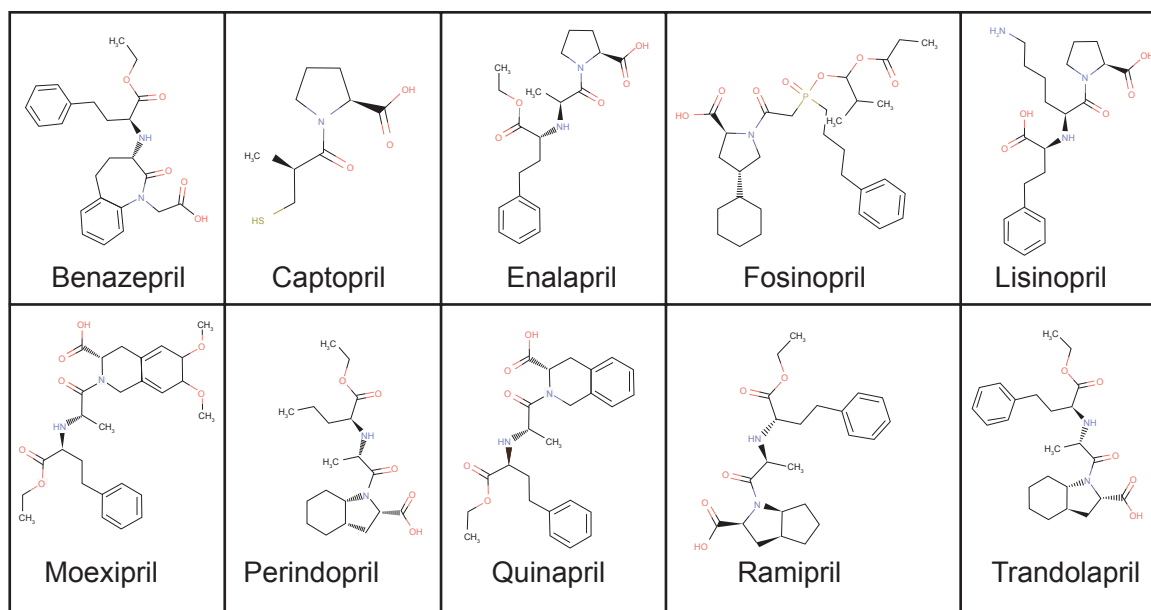
*Monthly cost depends on dose and brand name vs. generic.

and the incidence of diabetes was lower in the captopril treated group compared to those treated with other agents.⁵⁴ When compared to diuretics and beta-blocker therapies, patients receiving ARB or ACE-I had a 25%–30% lower risk of developing new-onset diabetes despite similar reduction in blood pressure.^{55,56}

Other studies have also shown that calcium antagonists (another antihypertensive drug class) are less effective than ACE-I in preventing cardiovascular events in diabetic hypertensive patients.⁵⁷ The Appropriate Blood Pressure Control in Diabetes

Trial also found that diabetic patients treated with ACE-I had lower incidence of MI and overall cardiac events compared to patients treated with a calcium antagonist.²⁸ However, recent large prospective randomized studies showed an opposite effect.⁵⁷

Diuretics, the gold standard treatment in hypertension have been used singly and in combination with ACE-I. However, they have been shown to actually impair glucose tolerance and thereby accelerate the development of diabetes mellitus.^{58,59} The effect of treating diabetics with



(Not Traditional/Not FDA Approved)

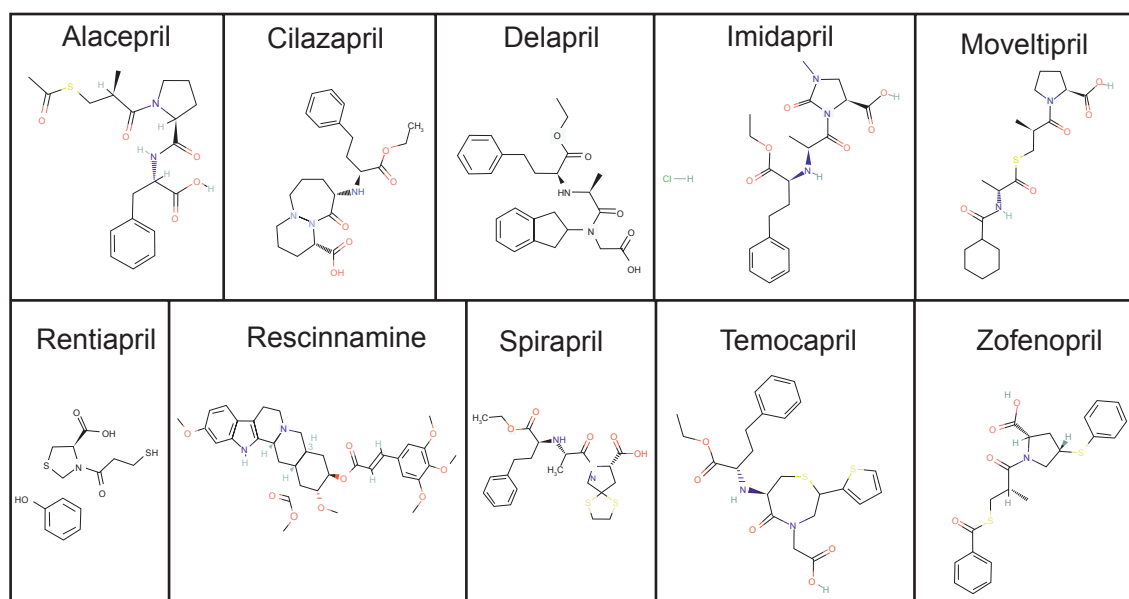


Figure 3. ACE Inhibitor Chemical Structures (FDA Approved).

thiazide diuretics may be detrimental to their health by affecting the action of insulin.⁵⁸ Thiazide diuretics were also associated with increased cardiovascular mortality in diabetic patients except at low-medium dose.⁵⁷ When given in combination with ACE-I, it was shown that ACE-I alone provided better health benefit than when combined with thiazide diuretics. In the CAPP study, captopril reduced the relative risk of diabetes by 22%

in previously untreated patients compared with diuretic and/or beta-blocker treatment.⁵⁴

The combination of ACE-I and ARB is controversial. Some experts believe there are advantages to the combination to further reduce blood pressure.⁶⁰ According to The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), combination therapy



of ACE-I and ARB showed a modest effect of lowering blood pressure in diabetic patients, but the added risk of adverse events attributable to the combination therapy makes them not recommendable in the treatment of hypertension.⁶¹ However, it was suggested that the ACE-I and ARB combination therapy maybe beneficial to patients having proteinuria or diabetic patients without concomitant diseases.⁶¹ There also appears to be a substantial benefit in heart failure and renal disease.^{62,63} In the Candesartan and Lisinopril Microalbuminuria (CALM) study in hypertensive patients with type 2 diabetes and microalbuminuria, the combination was more effective in reducing blood pressure and the urinary albumin:creatinine ratio than either agent alone.⁶⁴ The combination of an ACE inhibitor and an ARB produced no significant clinical benefit in preventing vascular events in high-risk patients in ONTARGET. But, the risk of adverse events, including hypotension, syncope, renal dysfunction, and hyperkalemia, was increased with combination therapy.

The American Diabetes Association (ADA) recommends that all patients with diabetes and hypertension receive an ACE-I or ARB as part of their antihypertensive regime.⁶⁵ ACE-I is a strong first-line therapy for diabetic patients having hypertension, but it is recognized that hypertension may best be combated by multi-therapy.^{66,67}

Renal complications

The relative risk of developing end-stage renal disease increases with higher systolic blood pressure.^{68,69} Ang II produces renal vasoconstriction and antinatriuresis, therefore, targeting the RAS is a logical approach to reducing renovascular risk.³⁷ National guidelines recommend ACE-I or ARB therapy in patients with diabetes who also have hypertension and/or proteinuria to retard the progression of renal damage.^{65,70,71} One of the main characteristics of essential hypertension is nephrosclerosis, the first clinical sign of which is protein in the urine. Proteinuria is the main predictor of cardiovascular disease in patients with type 2 diabetes as well as progressive renal disease in type 1 diabetes and in patients with overt diabetic nephropathy.¹ Renoprotective effects of captopril are reported in diabetic neuropathy,⁷² the ACE-I ramipril, exhibited vascular and renal protective effects in high risk diabetic patients with previous

history of cardiovascular events,⁷³ and the ACE-I, benazepril was shown to inhibit the deterioration of renal function in patients with glomerular disease.^{1,74} Treatment with ACE-I has been shown to consistently reduce proteinuria in these patients, as compared to other antihypertensive agents.^{75,76}

Other complications

ACE-I therapy is now commonly prescribed to diabetic patients and has been associated with a lower likelihood of other complications including a history of cancer and peptic ulcers.⁷⁷ Also, clinical studies have detected inhibition of diabetic retinopathy by ACE-I. The EURODIAB Control Trial of Lisinopril in Insulin-Dependent Diabetes Study Group investigated the effect of the ACE-I, lisinopril, on retinopathy in normotensive type I diabetic patients. They found a 50% reduction in the progression of retinopathy in lisinopril treated subjects compared to controls.⁷⁸ After 9 years follow-up, the UKPDS clinical trial similarly reported that the ACE-I captopril inhibited the two-step progression of retinopathy by 34%.⁷⁸ Despite the evidence that the use of ACE-I does not have long-term or irreversible effects in most cases, there is literature stating that ACE-I are still underprescribed.^{79,80} A recent study using 30,750 patients with diabetes (68.7% with hypertension and/or proteinuria) suggested a potential underuse of ACE-I and ARB in elderly patients with diabetes. Of the whole sample, only 50.7% of potential users were administered an ACE-I or ARB in the quarter studied. In multivariate analysis, failure to administer either agent was associated significantly with older age, male sex, chronic lung disease, depression, dementia and other mental illness.⁷⁰

Generally, this family of drugs has the effect of increasing plasma levels of renin, and decreasing aldosterone secretion. The effects of a single dose treatment with ACE-I, such as ramipril have been shown to be long-lasting, maintaining up to 80% inhibition 24 hours after administration.^{81,82} They are additionally thought to have effects separate from the ACE effects, as they have been shown to also increase kinins and N-acetyl-seryl-aspartyl-lysyl-proline, a tetrapeptide that has anti-fibrotic and anti-inflammatory effects.^{83,84}

Overall, ACE-I are effective as antihypertensive agents, have utility in prevention of cardiac remodeling



following myocardial infarct (MI), inhibition of heart and kidney disease, prevention of cancer and diabetes, and their use has even been associated with decreased mortality in patients hospitalized with community-acquired pneumonia.^{50,51,58,77,80,83,85-93}

ACE-I Side Effects and Limitations

ACE inhibitors are generally well tolerated and have few contraindications.⁹⁴ However, the use of ACE-I does come with side effects and warnings. The most common side effects in adults are a dry, persistent cough attributed to accumulation of substance P (which is normally degraded by kininase II),¹⁷ dizziness, fatigue and nausea. Other side effects include hypotension, hyperkalemia, hypoglycemia, renal failure and angioedema.⁴⁴ ACE inhibitors are not nephrotoxic, but an increase of up to 20 percent in the serum creatinine level is not uncommon. During the first four weeks of treatment, serum potassium and creatinine levels should be monitored closely.⁹⁵ Hypotension can occur in patients with hyponatremia or volume depletion, those taking vasodilators, those in acute heart failure or dialysis. Patients with high plasma renin level are vulnerable to first dose hypotension.⁹⁵ Cough occurs in 5–20 percent of patients, more frequently in women than men, and more frequent in blacks than whites. It develops within one week to six months and resolves within four days of cessation.⁹⁵ Hyperkalemia generally occurs in patients with renal insufficiency or diabetes. Patients taking potassium, salt substitutes, potassium-sparing diuretics, beta blockers, and NSAIDs are susceptible.⁹⁵

It has been shown that black people received less benefit from ACE-I than do white people.⁷¹ Also, other RAS blockers like the ARBs are generally better tolerated than ACE-I across large populations, particularly in black people, cigarette smokers, and people who might be susceptible to the effects of bradykinin.⁹⁶ There is some evidence that with long-term ACE-I treatment, circulating Ang II levels may return to pretreatment levels, perhaps through activation of the so-called alternative pathway (Fig. 1), although the studies are controversial.^{17,37}

The absolute contraindications for ACE-I are: 1) angioneurotic edema which occurs in approximately 0.1–0.2 percent patients, 2) ACE-I must be avoided by pregnant women, as major congenital malformations

have been seen in fetus exposed to ACE-I following the first trimester,⁹⁷⁻¹⁰⁰ 3) renal artery stenosis and 4) previous allergy to ACE inhibitors.

Conclusions

The RAS is involved in a wide range of adverse effects that contribute to metabolic diseases. ACE-I are effective as antihypertensive agents, have utility in prevention of cardiac remodeling following myocardial infarct (MI), inhibition of heart and kidney disease, prevention of diabetes, and their use has even been associated with decreased mortality in patients hospitalized with community-acquired pneumonia. Furthermore, evidence is starting to accumulate for further beneficial uses of these drugs in diabetic patients. In spite of the accumulating evidence on the benefits of ACE-I therapy, there is an underuse of ACE-I in patients with diabetes.^{80,101}

Disclosures

The authors report no conflicts of interest.

References

1. Dzau VJ, Bernstein K, Celermajer D, Cohen J, Dahlof B, Deanfield J, et al. The relevance of tissue angiotensin-converting enzyme: manifestations in mechanistic and endpoint data. *Am J Cardiol*. 2001;88(9A):1L–20L.
2. Hunyady L, Catt KJ. Pleiotropic AT1 receptor signaling pathways mediating physiological and pathogenic actions of angiotensin II. *Mol Endocrinol*. 2006;20(5):953–70.
3. Thomas MC, Tikellis C. ACE2; and ACE up the sleeve. Current enzyme inhibition. 2005;1:51–63.
4. Ryan JW. Processing of endogenous polypeptides by the lungs. *Annu Rev Physiol*. 1982;44:241–55.
5. Lavoie JL, Cassell MD, Gross KW, Sigmund CD. Localization of renin expressing cells in the brain, by use of a REN-eGFP transgenic model. *Physiol Genomics*. 2004;16(2):240–6.
6. Lavoie JL, Sigmund CD. Minireview: overview of the renin-angiotensin system—an endocrine and paracrine system. *Endocrinology*. 2003;144(6):2179–83.
7. Nielsen AH, Schausser KH, Poulsen K. Current topic: the uteroplacental renin-angiotensin system. *Placenta*. 2000;21(5–6):468–77.
8. Sernia C. A critical appraisal of the intrinsic pancreatic angiotensin-generating system. *Jop*. 2001;2(1):50–5.
9. Spat A, Hunyady L. Control of aldosterone secretion: a model for convergence in cellular signaling pathways. *Physiol Rev*. 2004;84(2):489–539.
10. Danser AH, Schalekamp MA. Is there an internal cardiac renin-angiotensin system? *Heart*. 1996;76(3 Suppl 3):28–32.
11. Paul M, Poyan Mehr A, Kreutz R. Physiology of local renin-angiotensin systems. *Physiol Rev*. 2006;86(3):747–803.
12. Baltatu O, Silva JA Jr, Ganten D, Bader M. The brain renin-angiotensin system modulates angiotensin II-induced hypertension and cardiac hypertrophy. *Hypertension*. 2000;35(1 Pt 2):409–12.
13. Tikellis G, Robman LD, Harper A, McNeil JJ, Taylor HR, McCarty CA. Methods for detecting age-related maculopathy: a comparison between photographic and clinical assessment. *Clin Experiment Ophthalmol*. 2000;28(5):367–72.



14. Lau T, Carlsson PO, Leung PS. Evidence for a local angiotensin-generating system and dose-dependent inhibition of glucose-stimulated insulin release by angiotensin II in isolated pancreatic islets. *Diabetologia*. 2004;47(2):240–8.
15. Ribeiro-Oliveira A Jr, Nogueira AI, Pereira RM, Boas WW, Dos Santos RA, Simoes e Silva AC. The renin-angiotensin system and diabetes: an update. *Vasc Health Risk Manag*. 2008;4(4):787–803.
16. Muscogiuri G, Chavez AO, Gastaldelli A, Perego L, Tripathy D, Saad MJ, et al. The crosstalk between insulin and renin-angiotensin-aldosterone signaling systems and its effect on glucose metabolism and diabetes prevention. *Curr Vasc Pharmacol*. 2008;6(4):301–12.
17. Atlas SA. The renin-angiotensin aldosterone system: pathophysiological role and pharmacologic inhibition. *J Manag Care Pharm*. 2007;13(8 Suppl B):9–20.
18. Giacchetti G, Sechi LA, Rilli S, Carey RM. The renin-angiotensin-aldosterone system, glucose metabolism and diabetes. *Trends Endocrinol Metab*. 2005;16(3):120–6.
19. Schmieder RE, Delles C, Mimran A, Fauvel JP, Ruilope LM. Impact of telmisartan versus ramipril on renal endothelial function in patients with hypertension and type 2 diabetes. *Diabetes Care*. 2007;30(6):1351–6.
20. Yusuf S, Gerstein H, Hoogwerf B, Pogue J, Bosch J, Wolfenbutter BH, et al. Ramipril and the development of diabetes. *Jama*. 2001;286(15):1882–5.
21. Vijayaraghavan K, Deedwania PC. The renin angiotensin system as a therapeutic target to prevent diabetes and its complications. *Cardiol Clin*. 2005;23(2):165–83.
22. Lindholm LH, Ibsen H, Dahlof B, Devereux RB, Beevers G, de Faire U, et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359(9311):1004–10.
23. Watanabe T, Barker TA, Berk BC. Angiotensin II and the endothelium: diverse signals and effects. *Hypertension*. 2005;45(2):163–9.
24. Matayoshi T, Kamide K, Takiuchi S, Horio T, Yoshihara F, Nakamura S, et al. Relationship between insulin resistance and the renin-angiotensin system: analysis for patients with essential and renovascular hypertension. *Clin Exp Hypertens*. 2007;29(7):479–87.
25. Furuhashi M, Ura N, Takizawa H, Yoshida D, Moniwa N, Murakami H, et al. Blockade of the renin-angiotensin system decreases adipocyte size with improvement in insulin sensitivity. *J Hypertens*. 2004;22(10):1977–82.
26. Abuissa H, Jones PG, Marso SP, O'Keefe JH Jr. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for prevention of type 2 diabetes: a meta-analysis of randomized clinical trials. *J Am Coll Cardiol*. 2005;46(5):821–6.
27. Group UPDS. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *Br Med J*. 1998;317:703–13.
28. Estacio RO, Schrier RW. Antihypertensive therapy in type 2 diabetes: implications of the appropriate blood pressure control in diabetes (ABCD) trial. *Am J Cardiol*. 1998;82(9B):9R–14R.
29. Gainer JV, Morrow JD, Loveland A, King DJ, Brown NJ. Effect of bradykinin-receptor blockade on the response to angiotensin-converting-enzyme inhibitor in normotensive and hypertensive subjects. *N Engl J Med*. 1998;339(18):1285–92.
30. Hornig B, Kohler C, Drexler H. Role of bradykinin in mediating vascular effects of angiotensin-converting enzyme inhibitors in humans. *Circulation*. 1997;95(5):1115–8.
31. Campbell DJ. The renin-angiotensin and the kallikrein-kinin systems. *Int J Biochem Cell Biol*. 2003;35(6):784–91.
32. Simoes e Silva AC, Diniz JS, Pereira RM, Pinheiro SV, Santos RA. Circulating renin Angiotensin system in childhood chronic renal failure: marked increase of Angiotensin-(1–7) in end-stage renal disease. *Pediatr Res*. 2006;60(6):734–9.
33. Chappell MC. Emerging evidence for a functional angiotensin-converting enzyme 2-angiotensin-(1–7)-MAS receptor axis: more than regulation of blood pressure? *Hypertension*. 2007;50(4):596–9.
34. Santos RA, Ferreira AJ. Angiotensin-(1–7) and the renin-angiotensin system. *Curr Opin Nephrol Hypertens*. 2007;16(2):122–8.
35. Wishart DS, Knox C, Guo AC, Cheng D, Shrivastava S, Tzur D, et al. DrugBank: a knowledgebase for drugs, drug actions and drug targets. *Nucleic Acids Res*. 2008;36(Database issue):D901–6.
36. IMS Health Incorporated. In: IMS Health Incorporated; 2009.
37. Berra K, Miller NH. Inhibiting the renin-angiotensin system: why and in which patients. *J Am Acad Nurse Pract*. 2009;21(1):66–75.
38. Sennesael J, Ali A, Sweny P, Vandenburg M, Slovic D, Dratwa M, et al. The pharmacokinetics of perindopril and its effects on serum angiotensin converting enzyme activity in hypertensive patients with chronic renal failure. *Br J Clin Pharmacol*. 1992;33(1):93–9.
39. Litt JZ. *Litt's Drug Eruption Reference Manual Including Interactions*. 14th ed: Informa UK Limited; 2008.
40. Turkoski L, Bonfiglio. *Drug Information Handbook for Advanced Practice Nursing*. 7th ed: Lexi-Comp; 2006.
41. Price D, Della Rocca G, Guo C, Ballo M, Schwinn D, Luttrell L. Activation of extracellular signal-regulated kinase in human prostate cancer. *J Urology*. 1999;162:1537–42.
42. Deptala A, Bedner E, Gorczyca W, Darzynkiewicz Z. Activation of nuclear factor kappa B (NF-kappaB) assayed by laser scanning cytometry (LSC). *Cytometry*. 1998;33:376–82.
43. Whitehurst A, Wilsbacher J, You Y, Luby-Phelps K, Moore M, Cobb M. ERK2 enters the nucleus by a carrier-independent mechanism. *Proc Natl Acad Sci U S A*. 2002;99:7496–501.
44. Consumer Reports Best Buy Drugs. In: Consumer Reports; 2006.
45. Hockings N, Ajayi AA, Reid JL. Age and the pharmacokinetics of angiotensin converting enzyme inhibitors enalapril and enalaprilat. *Br J Clin Pharmacol*. 1986;21(4):341–8.
46. *Drug Facts and Comparisons 2009*: Wolters Kluwer Health; 2008.
47. Lonn EM, Yusuf S, Jha P, Montague TJ, Teo KK, Benedict CR, et al. Emerging role of angiotensin-converting enzyme inhibitors in cardiac and vascular protection. *Circulation*. 1994;90(4):2056–69.
48. Sleight P. Angiotensin II and trials of cardiovascular outcomes. *Am J Cardiol*. 2002;89(2A):11A–6A; discussion 16A–7A.
49. Solski LV, Longyhore DS. Prevention of type 2 diabetes mellitus with angiotensin-converting-enzyme inhibitors. *Am J Health Syst Pharm*. 2008;65(10):935–40.
50. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med*. 2000;342(3):145–53.
51. Cooper ME, Jerums G, Chattington PD. Treatment of hypertension in diabetes. *Saudi J Kidney Dis Transpl*. 1999;10(3):325–32.
52. Weir MR. Effects of renin-angiotensin system inhibition on end-organ protection: can we do better? *Clin Ther*. 2007;29(9):1803–24.
53. Olsen MH, Fossum E, Hoiegggen A, Wachtell K, Hjerkind E, Nesbitt SD, et al. Long-term treatment with losartan versus atenolol improves insulin sensitivity in hypertension: ICARUS, a LIFE substudy. *J Hypertens*. 2005;23(4):891–8.
54. Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPP) randomised trial. *Lancet*. 1999;353(9153):611–6.
55. Niklason A, Hedner T, Niskanen L, Lanke J. Development of diabetes is retarded by ACE inhibition in hypertensive patients—a subanalysis of the Captopril Prevention Project (CAPP). *J Hypertens*. 2004;22(3):645–52.
56. Vermes E, Ducharme A, Bourassa MG, Lessard M, White M, Tardif JC. Enalapril reduces the incidence of diabetes in patients with chronic heart failure: insight from the Studies Of Left Ventricular Dysfunction (SOLVD). *Circulation*. 2003;107(9):1291–6.
57. Grossman E, Messerli FH. Long-term safety of antihypertensive therapy. *Prog Cardiovasc Dis*. 2006;49(1):16–25.
58. McLaughlin DM, Atkinson AB, Ennis CN, Browne J, Hunter SJ, Sheridan B, et al. Comparison of effects of combined ACE inhibitor and low-dose thiazide diuretic with ACE inhibitor alone on insulin action in patients with hypertension and Type 2 diabetes: a double-blind crossover study. *Diabet Med*. 2008;25(5):631–4.
59. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288(23):2981–97.



60. Weinberg MS, Weinberg AJ, Zappe DH. Effectively targetting the renin-angiotensin-aldosterone system in cardiovascular and renal disease: rationale for using angiotensin II receptor blockers in combination with angiotensin-converting enzyme inhibitors. *J Renin Angiotensin Aldosterone Syst.* 2000;1(3):217–33.
61. Schindler C. ACE-inhibitor, AT1-receptor-antagonist, or both? A clinical pharmacologist's perspective after publication of the results of ONTARGET. *Ther Adv Cardiovasc Dis.* 2008;2(4):233–48.
62. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet.* 2003;362(9386):767–71.
63. Nakao N, Yoshimura A, Morita H, Takada M, Kayano T, Ideura T. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. *Lancet.* 2003;361(9352):117–24.
64. Mogensen CE, Neldam S, Tikkanen I, Oren S, Viskoper R, Watts RW, et al. Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. *BMJ.* 2000;321(7274):1440–4.
65. Standards of medical care in diabetes—2008. *Diabetes Care.* 2008;31 Suppl 1:S12–54.
66. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA.* 2003;289(19):2560–72.
67. Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, et al. Guidelines for management of hypertension: report of the fourth working party of the British Hypertension Society, 2004-BHS IV. *J Hum Hypertens.* 2004;18(3):139–85.
68. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE, et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Ann Intern Med.* 2003;139(4):244–52.
69. Pohl MA, Blumenthal S, Cordonnier DJ, De Alvaro F, Deferrari G, Eisner G, et al. Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: clinical implications and limitations. *J Am Soc Nephrol.* 2005;16(10):3027–37.
70. Winkelmayer WC, Fischer MA, Schneeweiss S, Wang PS, Levin R, Avorn J. Underuse of ACE inhibitors and angiotensin II receptor blockers in elderly patients with diabetes. *Am J Kidney Dis.* 2005;46(6):1080–7.
71. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003;42(6):1206–52.
72. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med.* 1993;329(20):1456–62.
73. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet.* 2000;355(9200):253–9.
74. Maschio G, Alberti D, Janin G, Locatelli F, Mann JF, Motolese M, et al. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. The Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. *N Engl J Med.* 1996;334(15):939–45.
75. Kasiske BL, Kalil RS, Ma JZ, Liao M, Keane WF. Effect of antihypertensive therapy on the kidney in patients with diabetes: a meta-regression analysis. *Ann Intern Med.* 1993;118(2):129–38.
76. Gansevoort RT, de Zeeuw D, de Jong PE. Additive antiproteinuric effect of ACE inhibition and a low-protein diet in human renal disease. *Nephrol Dial Transplant.* 1995;10(4):497–504.
77. Ramos-Nino ME, Maclean CD, Littenberg B. Association of angiotensin-converting enzyme inhibitor therapy and comorbidity in diabetes: results from the Vermont diabetes information system. *BMC Endocr Disord.* 2008;8:17.
78. Chaturvedi N, Sjolie AK, Stephenson JM, Abrahamian H, Keipes M, Castellarin A, et al. Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes. The EUCLID Study Group. EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus. *Lancet.* 1998;351(9095):28–31.
79. Masoudi FA, Rathore SS, Wang Y, Havranek EP, Curtis JP, Foody JM, et al. National patterns of use and effectiveness of angiotensin-converting enzyme inhibitors in older patients with heart failure and left ventricular systolic dysfunction. *Circulation.* 2004;110(6):724–31.
80. McConnell KJ, Zadvorny EB, Denham AM, Kasten SL, Hutka KA, Koetting CR, et al. Angiotensin-converting enzyme inhibitor therapy for coronary artery disease and diabetes mellitus. *Am J Manag Care.* 2007;13(10):560–6.
81. Mosby's Drug Consult: Mosby Elsevier; 2007.
82. Levitt DG, Schoemaker RC. Human physiologically based pharmacokinetic model for ACE inhibitors: ramipril and ramiprilat. *BMC Clin Pharmacol.* 2006;6:1.
83. Carretero OA. Novel mechanism of action of ACE and its inhibitors. *Am J Physiol Heart Circ Physiol.* 2005;289(5):H1796–7.
84. Peng H, Carretero OA, Raji L, Yang F, Kapke A, Rhaleb NE. Antifibrotic effects of N-acetyl-seryl-aspartyl-L-lysyl-proline on the heart and kidney in aldosterone-salt hypertensive rats. *Hypertension.* 2001;37(2 Part 2):794–800.
85. Bozkurt O, Verschuren WM, van Wieren-de Wijer BM, Knol MJ, de Boer A, Grobbee DE, et al. Genetic variation in the renin-angiotensin system modifies the beneficial effects of ACE inhibitors on the risk of diabetes mellitus among hypertensives. *J Hum Hypertens.* 2008;22(11):774–80.
86. Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. *N Engl J Med.* 2008;359(15):1565–76.
87. Kim JH, Yu YS, Cho CS, Kim KW. Blockade of angiotensin II attenuates VEGF-mediated blood-retinal barrier breakdown in diabetic retinopathy. *J Cereb Blood Flow Metab.* 2009;29(3):621–8.
88. Lopez-Sendon J, Swedberg K, McMurray J, Tamargo J, Maggioni AP, Dargie H, et al. Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease. The Task Force on ACE-inhibitors of the European Society of Cardiology. *Eur Heart J.* 2004;25(16):1454–70.
89. Ruggenenti P, Iliev I, Costa GM, Parvanova A, Perna A, Giuliano GA, et al. Preventing left ventricular hypertrophy by ACE inhibition in hypertensive patients with type 2 diabetes: a prespecified analysis of the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT). *Diabetes Care.* 2008;31(8):1629–34.
90. Siegmund T, Schumm-Draeger PM, Antoni D, Bibra HV. Beneficial effects of ramipril on myocardial diastolic function in patients with type 2 diabetes mellitus, normal LV systolic function and without coronary artery disease: a prospective study using tissue Doppler. *Diab Vasc Dis Res.* 2007;4(4):358–64.
91. Zidek W, Schrader J, Luders S, Matthaehi S, Hasslacher C, Hoyer J, et al. First-line antihypertensive treatment in patients with pre-diabetes: rationale, design and baseline results of the ADaPT investigation. *Cardiovasc Diabetol.* 2008;7:22.
92. Mortensen EM, Restrepo MI, Anzueto A, Pugh J. The impact of prior outpatient ACE inhibitor use on 30-day mortality for patients hospitalized with community-acquired pneumonia. *BMC Pulm Med.* 2005;5:12.
93. Jarmuzewska EA, Rocchi R, Guidoni A, Mangoni AA. ACE inhibitor-based treatment and antihypertensive effects in patients with type 2 diabetes. *Panminerva Med.* 2008;50(3):207–16.
94. Bicket DP. Using ACE inhibitors appropriately. *Am Fam Physician.* 2002;66(3):461–8.
95. Bindom SM, Lazartigues E. The sweeter side of ACE2: Physiological evidence for a role in diabetes. *Mol Cell Endocrinol.* 2008.



96. Moser M, Rosendorff C, White WB. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers: is there a difference in response and any advantage to using them together in the treatment of hypertension? *J Clin Hypertens (Greenwich)*. 2008;10(6):489–96.
97. Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. *N Engl J Med*. 2006;354(23):2443–51.
98. Barr M Jr. Teratogen update: angiotensin-converting enzyme inhibitors. *Teratology*. 1994;50(6):399–409.
99. Buttar HS. An overview of the influence of ACE inhibitors on fetal-placental circulation and perinatal development. *Mol Cell Biochem*. 1997;176(1–2):61–71.
100. Quan A. Fetopathy associated with exposure to angiotensin converting enzyme inhibitors and angiotensin receptor antagonists. *Early Hum Dev*. 2006;82(1):23–8.
101. Brown LC, Johnson JA, Majumdar SR, Tsuyuki RT, McAlister FA. Evidence of suboptimal management of cardiovascular risk in patients with type 2 diabetes mellitus and symptomatic atherosclerosis. *Cmaj*. 2004;171(10):1189–92.

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