Therapeutic perspective: starting an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker in a diabetic patient

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Abstract: There are extensive data confirming involvement of the renin-angiotensin system in microvascular and macrovascular complications of diabetes. Blockade of the system with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) is regarded as the first-line approach to managing hypertension and end-organ protection in patients with diabetes. ACE inhibitors are still the preferred agents for most patients. Dose should be lower with renal impairment unless an agent which is not excreted by the kidneys is chosen. Dose should be titrated up to the maximum tolerated to optimize end-organ protection, and intermediate-acting agents should be given in a twice daily divided dose when higher doses are used. Electrolytes should be checked before commencing, 1–2 weeks later, and after each dose increment. A modest decrease in estimated glomerular filtration rate (eGFR) and increase in creatinine often occurs with ACE inhibitors or ARBs. The agents may need to be discontinued if eGFR decreases by >15%, if creatinine increases by >20%, or if hyperkalaemia develops. Cough occurs in 5–10% of patients taking ACE inhibitor, but not with ARBs. Angioedema is probably equally common with ACE inhibitor or ARBs. It is not widely appreciated that ACE inhibitors may precipitate hypoglycaemia in patients taking glucose-lowering medication. The combination of ACE inhibitor and ARB is not routinely indicated for either hypertension or end-organ protection. While patients should not be denied the undoubted benefits of these important classes of drugs, we should also guard against their indiscriminate use in patients with diabetes. We must also ensure that patients receive appropriate counselling and monitoring.

Keywords: diabetes, hypertension, renal impairment, hyperkalaemia, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, cough, angioedema

Introduction

After aspirin and statins, angiotensin-converting enzyme (ACE) inhibitors are the most commonly prescribed cardioprotective drugs in patients with diabetes. Extensive animal and human data confirm the role of the renin-angiotensin system in the pathogenesis of microvascular and macrovascular complications of diabetes [Braga *et al.* 2009]. ACE inhibitors are indicated for the treatment of hypertension, in cardiac failure and asymptomatic left ventricular dysfunction, to decrease mortality and cardiac events following myocardial infarction, and to decrease microvascular complications of diabetes. In recent years,

angiotensin II receptor blockers (ARBs) have been widely used for end-organ protection in patients with type 2 diabetes and in those intolerant of ACE inhibitors. ARBs are indicated for hypertension and evidence supports their use in cardiac failure when ACE inhibitors are not tolerated. The direct renin inhibitor aliskiren is now available in many countries and is indicated for the treatment of hypertension. The aldosterone antagonist spironolactone is used for mineralocorticoid and resistant hypertension and in patients with heart failure. Eplerenone, another aldosterone antagonist, has recently become available for patients with heart failure. Thus,

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the renin–angiotensin system can be inhibited by four separate mechanisms. The choice of drug class depends on the precise indication and a number of patient-related factors. Combination treatments may be useful for end-organ protection. The major benefit of ACE inhibitors and ARBs is in blood pressure reduction, which they achieve through decreasing vascular tone (and thus peripheral resistance) and decreasing salt and water retention. It remains uncertain to what degree they offer end-organ protection independent of their blood pressure reducing effect. Other potentially beneficial effects are in improving endothelial function, decreasing oxidative stress, anti-inflammatory effects, antithrombotic actions, and decreasing adverse vascular and cardiac remodelling. There are considerable data from trials and meta-analyses suggesting that inhibition of the renin–angiotensin system can prevent, or at least delay, the onset of diabetes. Widespread use of ACE inhibitors and ARBs has led to complacency about their potential side effects. Simple precautions have considerable potential to decrease adverse drug reactions and to increase benefit from these important drug classes.

Choice of agent

Captopril, the first ACE inhibitor to be marketed, contains a sulphydryl group that is responsible for the high incidence of metallic taste disturbance and skin rash. All other available ACE inhibitors contain a carboxyl group except for fosinopril, which contains a phosphoryl group. The commonly used ACE inhibitors are summarized in Table 1. Most ACE inhibitors are predominantly eliminated by the kidney and the dose should thus be decreased in patients with renal impairment. Exceptions are fosinopril, which is 50% eliminated by the kidney (and 50% by the liver) and

trandolapril, which is only 15% eliminated by the kidney. For intermediate-acting ACE inhibitors (enalapril, fosinopril, lisinopril and ramipril) dividing the daily dose should be considered when higher doses of the drug are used. ACE inhibitors and ARBs have been very widely prescribed to prevent nephropathy and retinopathy. Recent data [Mauer *et al.* 2009] with normotensive, normoalbuminuric type 1 diabetic patients suggest that they may not prevent nephropathy developing even if they do retard its progress once it has developed. We should be wary of indiscriminate prescription of these drugs that are not indicated in all patients with diabetes. Also, although they are often used as first-line therapy for diabetic patients with hypertension, they do not always markedly decrease blood pressure in the volume overloaded, low-renin patient. In older patients with isolated systolic hypertension, vasodilators including calcium channel blockers (CCBs) are often more effective because decreased vascular compliance makes a major contribution to elevated blood pressure. There is an important synergy between ACE inhibitors and diuretics in lowering blood pressure, and many of the commonly used agents are marketed as combinations with hydrochlorothiazide (12.5 mg). Diuretics are often regarded as first-line treatment for hypertension in the elderly. Hypertension is not adequately controlled in many patients with diabetes, and underuse of diuretics may be a factor [Sweileh, 2009]. Diuretic use on its own diminishes the expanded plasma volume, which is a feature of many hypertensive patients, but in so doing leads to reflex activation of the renin–angiotensin system and this may attenuate vascular protective benefits. For many patients, a combination of an ACE inhibitor and a diuretic is the ideal initial approach to managing hypertension, with the addition of CCBs if systolic pressure, in particular, is not well controlled. Recent trials confirm a useful synergy between ACE inhibitors and CCBs [Reboldi *et al.* 2009].

The only specific indication for ARBs is where inhibition of the renin–angiotensin system is deemed desirable and ACE inhibitors are not tolerated. For all other indications, there is a more robust evidence base supporting the use of ACE inhibitors. There is evidence that ARBs slow progression of nephropathy in type 2 diabetes but they have not been demonstrated to be superior to ACE inhibitors in this regard. The commonly used ARBs are summarized in Table 2.

Table 1. Examples of commonly used Angiotensin-converting enzyme inhibitors.

Drug	$t_{1/2}$ *	Dose (mg)
Captopril	2	25–50 three times daily
Enalapril	11	5–40
Fosinopril	12	10–40
Lisinopril	12	10–40
Perindopril	25	5–10
Quinapril	4	20–40 twice daily
Ramipril	15	5–20
Trandolapril	18	2–4
*Effective halflife in hours (drug + metabolites).		

Table 2. Examples of commonly used Angiotensin receptor blockers.

Drug	$t_{1/2}$ *	Dose (mg)
Candesartan	8	8–16
Eprosartan	7	600–800
Irbesartan	13	150–300
Losartan	2	50–100
Olmесartan	13	20–40
Telmisartan	24	40–80
Valsartan	6	80–320

*Effective halflife in hours (drug + metabolites).

Protocol for starting an ACE inhibitor or ARB

The same warnings and precautions apply to ACE inhibitors and ARBs. As confidence in these drugs has grown, the vast majority of patients initiate treatment themselves at home. Special precautions are required with severe renal or cardiac failure, where there is hypotension (systolic <90 mmHg), and where the patient is either hypovolaemic or taking high-dose diuretic (equivalent to more than 80 mg frusemide daily). Otherwise, the following protocol is suggested.

1. Before starting. Check baseline urea and electrolytes. Consider whether the patient could have renal artery stenosis (and thus at risk of worsening renal function with an ACE inhibitor); patients with diabetes and peripheral vascular disease are at increased risk, listen for renal bruits. Be clear about the indication(s) and explain them to the patient.
2. The first dose may cause hypotension. For this dose only, a subtherapeutic dose (typically around a quarter of the daily maintenance) is prescribed and the patient instructed to take it on retiring to bed at night. For those already taking diuretics, consider withholding or decreasing them for 2–3 days before initiating an ACE inhibitor.
3. If there are no problems with the first dose, the maintenance dose should be started. As the first dose is usually given in the evening, it is common for subsequent doses to be given at the same time. For hypertension control where an ACE inhibitor is often combined with a diuretic, it is preferable to administer in the morning. After the test dose, the ACE inhibitor can be omitted the following day and the first maintenance dose administered on the morning of the third day. If morning blood pressure is not controlled with the ACE inhibitor and diuretic, add a long-acting CCB at night.

4. Check urea and electrolytes 1–2 weeks after the first dose and after any subsequent dose increment. Consider specialist referral or discontinuing the ACE inhibitor if potassium is greater than 5.5 mmol/l, or if creatinine increases by 20% or more or if the estimated glomerular filtration rate (eGFR) decreases by 15% or more.
5. In patients with diabetes, ACE inhibitors are used as much for organ protection as for blood pressure control. The blood pressure may not therefore be a good guide to the optimal dose. The drug should be titrated up to the maximum tolerated dose, using divided doses for agents with intermediate duration of action.
6. Patients with diabetes and hypertension or emerging microvascular disease are at high risk. Check electrolytes, renal function and albumin excretion every 3 months.

Adverse effects and precautions

Worsening of renal function should be considered significant when eGFR falls by more than 15% or when plasma creatinine increases by more than 20% (some guidelines suggest 30%). The possibility of worsening renal function should be particularly considered under the following conditions: pre-existing poor renal function (eGFR <30 ml/min/1.73 m², i.e. Chronic Kidney Disease [CKD] stage 4 or worse); where renal artery stenosis is suspected; hypovolaemia (e.g. high doses of diuretics in heart failure patients); hyponatraemia (plasma sodium <130 mmol/l); hyperkalaemia (plasma potassium >6.0 mmol/l).

ACE inhibitors and ARBs decrease tone in renal arterioles. They have a greater effect on postglomerular efferent vessels than on afferent vessels. The result is a lowering of glomerular hydrostatic pressure and thus a decrease in GFR. A modest decline in renal function is thus to be expected on starting the drugs, and probably correlates with long-term benefit.

Hyperkalaemia is more likely to occur in patients with chronic renal impairment. It necessitates stopping treatment in less than 1% of patients. There is a similar incidence of hyperkalaemia with ACE inhibitors and ARBs. For patients with hyperkalaemia dietary potassium intake should be limited, potassium-sparing agents stopped (amiloride, triamterene and spironolactone), and potentially nephrotoxic drugs should be stopped (e.g. nonsteroidal anti-inflammatory

drugs [NSAIDs]). Use of diuretics decreases the incidence and severity of hyperkalaemia. If these measures fail or if hyperkalaemia is severe (as evidenced by the presence of electrocardiography features or values >5.5 mmol/l), the ACE inhibitor or ARB may need to be discontinued.

Cough is the most common side effect of ACE inhibitors, occurring in 5–10% of patients. The cough is dry and persistent. The effect of ACE inhibitors in causing coughs is not dose dependent. It typically occurs between a week and a few months after starting therapy and usually disappears within 5 days of stopping the ACE inhibitor, but can persist for weeks. If the cough is mild, the ACE inhibitor can be continued and the cough may resolve within 1–2 months. It is equally common with all members of the class but does not occur with ARBs. The cough is due to increased bradykinin; ACE also inhibits kininase. Tachykinins, substance P and prostaglandins may also be involved. Women, black or Asian patients, and those with ACE genotype II are at increased risk. The cough can be treated with disodium chromoglycate, local anaesthetic (nebulized bupivacaine), theophylline and NSAIDs (particularly sulindac). If ACE inhibitors are deemed to be absolutely necessary a repeat trial can be justified once the drug has been withdrawn and the cough has resolved. For the vast majority, prescription of an ARB is the best option.

Angioedema occurs in 0.1–0.2% of patients treated with an ACE inhibitor. It also occurs, but perhaps less commonly, in patients treated with ARBs or aliskiren. It can occur at any stage of treatment, but is most likely within 1 week of starting treatment and is more likely to be severe if it occurs early in treatment. It should always be taken seriously as repeat episodes are often more severe than the initial one. Although it can be severe, it is seldom fatal. Angioedema is thought to occur because of increased bradykinin, which might explain the relationship with ACE inhibitor treatment but not with ARBs or aliskiren. An increased incidence has been reported in African Americans and it is also more likely to occur in patients with idiopathic angioedema [Ricketti *et al.* 2007]. Despite the possible involvement of increased bradykinin, no relationship with ACE inhibitor-induced cough has been reported. The oedema is typically periorbital or perioral. More severe cases affect the tongue and throat. Less than 50% of cases

require hospital treatment and less than 10% require intubation. Bradykinin is also metabolized by the enzyme dipeptidyl peptidase IV (DPP-IV), which is inhibited by the gliptins (e.g. sitagliptin, saxagliptin and vildagliptin). DPP-IV has been reported to be decreased in patients with ACE inhibitor-induced angioedema [Lefebvre *et al.* 2002], and concurrent use of ACE inhibitor and DPP-IV inhibitor may be associated with up to a five-fold increase in risk of angioedema compared with ACE inhibitor alone [Brown *et al.* 2009].

Recent ACE inhibitor trials [Kintscher and Kintscher, 2009; Black *et al.* 2008] have shown that ACE inhibitor use is associated with a decreased risk of developing diabetes and with improved glycaemic control in those with diabetes [Matfin and Pratley, 2010]. This appears to be a major advantage in using this drug class to treat hypertension. However, it is often forgotten that ACE inhibitors may increase the risk of hypoglycaemia in patients who are also having glucose-lowering therapy [Rave *et al.* 2005]. Risk of hospitalization for hypoglycaemia may be increased three-fold in patients taking ACE inhibitor [Morris *et al.* 1997]. There is no defect in counter-regulatory hormones in patients taking ACE inhibitor [Oltmanns *et al.* 2003], and the increased risk of hypoglycaemia appears to be due to increased insulin sensitivity [Rave *et al.* 2005].

ACE inhibitors are teratogenic with the potential to cause oligohydramnios, pulmonary hypoplasia, renal dysgenesis and foetal growth retardation. They are not contraindicated in women of reproductive age but should be used with caution if there is risk of unplanned pregnancy. If a hypertensive patient is likely to want to become pregnant in the foreseeable future, it is probably best to control blood pressure from the start with an agent that could be continued throughout pregnancy. ACE inhibitors should be used with caution in patients with aortic stenosis or hypertrophic obstructive cardiomyopathy. They occasionally cause neutropaenia and can increase risk of toxicity in patients taking lithium.

Conclusion

Inhibition of the renin–angiotensin system has proved to be a very effective approach to managing hypertension and end-organ protection in patients with diabetes. The four classes of agent used to inhibit the renin–angiotensin system are

Table 3. Comparison of drugs that inhibit the renin–angiotensin system.

	ACE inhibitor	ARB	DRI	Aldosterone antagonist
Side effects				
Cough	++	–	–	–
Angioedema	+	+	+	–
Renal function	+	+	+	–
Hyperkalaemia	+	+	+	+
Cost	+	++	++	+
Indications				
Hypertension	++	++	++	+
Heart failure	++	++ [‡]	–	++
Post myocardial infarction	++	++ [‡]	–	–
Nephropathy	++	++ [§]	–	–

ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DRI, direct renin inhibitor (aliskiren).

*Used as a fourth-line agent in those with resistant hypertension and in mineralocorticoid hypertension.

[‡]Used when ACE inhibitors are not tolerated.

[§]There is good evidence to support use in type 2 diabetes but no evidence to support an advantage over ACE inhibitors.

compared in Table 3. We should guard against indiscriminate use of these drugs in patients with diabetes. When they are prescribed, the practitioner should explain the indication, as well as the potential benefits and risks to the patient. They should be specifically warned about the risk of cough as this is common and often overlooked in review consultations. Also, angioedema is a sufficiently common and serious adverse effect that the patient should be aware of the condition, especially if they are in a high-risk group (including those using gliptins). The risk of hypoglycaemia with ACE inhibitors is not widely appreciated. There is no evidence that other renin–angiotensin blocking drugs cause hypoglycaemia. Patients often do not receive an effective dose of ACE inhibitor, and it is not uncommon to see patients taking a dose that is only equivalent to the initial test dose. Patients are also now commonly prescribed a combination of an ACE inhibitor and ARB. While this can be justified in some circumstances, it should be avoided routinely as the combination increases the risk of adverse effects without generally enhancing the end-organ protective effect of either class prescribed alone [Cowan *et al.* 2009; Mann *et al.* 2008]. In conclusion, while ACE inhibitors are generally a very safe and effective class of drug, they are a common cause of adverse drug reaction and care needs to be taken to ensure that they are appropriately prescribed and that the patient receives the necessary counseling and monitoring that should accompany their use.

Conflict of interest statement

None declared.

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