NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 4; Number 10 **July 2010**

RENIN ANGIOTENSIN SYSTEM DRUGS: THE CASE FOR FIRST LINE ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Key Points

- Angiotensin converting enzyme inhibitors (ACEI) and angiotensin 2 receptor antagonists (A2RAs) are used in a wide range of indications including hypertension, heart failure, treatment post-MI, diabetes and chronic kidney disease.
- NICE Guidance for each of these indications places ACEIs first line where a drug acting on the renin angiotensin system (RAS) is indicated; A2RAs are reserved for patients in whom RAS drugs are indicated but ACE inhibitors are not tolerated.
- It is a commonly held view that ACEIs are first line drugs within this class because of their lower cost. Whilst cost remains an important factor, ACEIs also have a much more robust evidence base than A2RAs across most indications and there is no evidence that A2RAs are more effective than ACEIs in any indication. ACEIs should be used first line in preference to A2RAs in hypertension, cardiovascular risk reduction, heart failure, post MI, diabetes and chronic kidney disease (CKD) (see below).
- The only advantage of A2RAs over ACEIs is their lower incidence of cough and even this tends to be over-stated. Concern that the patient may develop an ACEI related cough is not sufficient to justify first line A2RA use. A2RAs should only be used as an alternative where there is continuing intolerance to an ACEI (see below).
- Most ACEIs are available as low cost generics. Generic losartan tablets became available in March 2010, but the NHS reimbursement price has not yet fallen to reflect this. It is likely to be a few years before several low cost A2RAs become available and two of the key A2RAs used in Lincolnshire will remain under patent until 2017 (e.g. olmesartan and telmisartan). Practices currently using long patent life A2RAs are asked to review their practice as a matter of priority.
- A Better Care, Better Value indicator (BCBVI) related to prescribing of drugs affecting the renin angiotensin system (RAS) has been available for some time. NHS Lincolnshire prescribes 70.8% of RAS drugs as ACE inhibitors (Q3 2009-10). The associated productivity opportunity is £383,553 p.a. (saving realised if 74% target achieved).
- Practices that perform below the 74% target advocated by the NHS Institute should review their practice to ensure that where a RAS drug is indicated, a low cost generic ACEI (e.g. ramipril or lisinopril) is used first line and that patients who have inadvertently been started on an A2RA where an ACEI would have been preferable are reviewed and, where possible, their treatment changed. Support from the Prescribing and Medicines Management Team is available for practices that wish to implement these changes.

It is the purpose of this special issue of the *PACE Bulletin* to review the evidence base for ACEIs and A2RAs across a broad range of licensed indications.

ACEIs VERSUS A2RAs: THE EVIDENCE

Hypertension

A systematic review of studies comparing ACE inhibitors with A2RAs in essential hypertension found that both classes of therapy provide similar levels of BP control and seem to have an equivalent effect on death and CV events (1). Any differences between ACE inhibitors and A2RAs in major events or changes in risk factors are likely to be small.

NICE Clinical Guideline 34 *Hypertension* recommends that A2RAs should be considered if patients are ACEI intolerant. In the full text guideline it states that the Guideline Development Group 'felt that the benefits from ACE inhibitors and A2RAs were closely correlated and that they should be treated as equal in terms of efficacy (although because of cost differences, ACE inhibitors should be initiated first).'

PACEF Comment:
In essential hypertension there seems to be no justification for using an A2RA first line.

Cardiovascular Risk Reduction

Two well publicized major trials, HOPE involving ramipril (2) and EUROPA involving perindopril (3), established the evidence base for ACEIs reducing cardiovascular (CV) events in patients at risk. The ONTARGET study (4) found that telmisartan was non-inferior to ramipril in the prevention of cardiovascular events in patients with vascular disease or diabetes with end organ damage.

Assumption of equivalence of ACEIs and A2RAs in cardiovascular risk reduction has been compromised by concerns about a possible increased risk of MI associated with A2RAs (5). Recent systematic reviews and meta-analyses have found that A2RAs are not associated with an increased risk of MI compared with ACEIs (6,7). Conversely, A2RAs do not appear to significantly reduce the incidence of MI compared with placebo.

PACEF Comment:
On the basis of best evidence and CV event reduction, ACE inhibitors are preferred to A2RAs in cardiovascular risk reduction.

Heart Failure

ACE inhibitors have a large evidence base in heart failure which demonstrates that treatment with an ACE inhibitor improves ventricular function, symptoms, quality of life, exercise tolerance and performance and reduces hospitalisation for heart failure and increases survival.

A meta-analysis of 24 trials of A2RAs in heart failure was published in 2004 (8). A2RAs reduced hospital admission for heart failure compared to placebo but not compared to ACE inhibitors. For all cause mortality the reduction for ARBs compared

to placebo reached borderline significance; when compared with ACE inhibitors there was no significant difference in all cause mortality.

PACEF Comment:
On the basis of best evidence, ACEIs are preferred to A2RAs in heart failure.

Post Myocardial Infarction

ACE inhibitors have a large evidence base post-MI (with or without heart failure or left ventricular systolic dysfunction, LVSD) demonstrating improved survival, reduced re-admission for heart failure and reduced recurrence of MI.

There are no trials of A2RAs in patients with preserved LV function post-MI. Two trials compared A2RAs and ACEIs in patients with acute MI and LVSD.
The OPTIMAAL study compared losartan 50mg with captopril 150mg in post-MI patients with heart failure (9). There was a non-significant difference in total mortality (primary outcome) in favour of captopril and a statistically significant increase in CV mortality (a tertiary outcome) seen with losartan. The VALIANT study compared valsartan 80mg twice daily, captopril 50mg three times daily and combination therapy in post-MI patients with heart failure and/or LV dysfunction; all cause mortality was similar in all 3 groups (10).

PACEF Comment:
On the basis of best evidence, ACEIs are preferred to A2RAs post MI.

Diabetes and Chronic Kidney Disease (CKD)

The NICE Clinical Guideline on type 2 diabetes recommends that ACE inhibitors are used as first line blood pressure lowering agents in hypertensive diabetics and that A2RAs may be used if there is continuing intolerance to an ACEI. The full diabetes guideline explains that drugs acting on the RAS are first line agents in this patient group because of greater benefits in terms of renal outcomes rather than superior blood pressure lowering properties. They go on to recommend that on grounds of cost a generic once daily ACE inhibitor should be first line.

A Cochrane review in 2006 of 49 randomised controlled trials (RCTs) of ACEIs or A2RAs in patients with diabetic nephropathy found that ACEIs and A2RAs had similar beneficial effects on renal outcomes (doubling of creatinine, progression of microalbuminuria, remission to normoalbuminuria and progression to end-stage kidney disease) (11). All cause mortality was not significantly reduced with ACEIs or A2RAs compared with placebo.

Renal outcomes were reported as part of the ONTARGET study comparing telmisartan and ramipril in the large cardiovascular risk reduction study (4). The primary renal outcome was a composite of dialysis, doubling of serum creatinine and death; this was similar with telmisartan or ramipril.

PACEF Comment:
On the basis of best evidence, ACEIs are at least equivalent to A2RAs in the treatment of hypertensive diabetics. NICE guidance advocates low cost generic once daily ACEIs first line.

Cough

A2RAs are associated with a lower incidence of cough than ACEIs. A systematic review of studies directly comparing ACEI and A2RAs in hypertension suggested that in randomised controlled trials the rate of cough for ACE inhibitors was 9.9% compared to 3.2% for A2RAs. The rates observed in cohort studies were lower; 1.7% and 0.6% respectively (1).

In the ONTARGET study, which included more than 25,000 patients at high cardiovascular risk but without heart failure randomised to either telmisartan or ramipril or both treatments, 4.2% of ramipril patients stopped treatment due to cough compared with 1.1% in the telmisartan group (4). This is an absolute difference of 3.1% and suggests a Number Needed to Harm with ramipril of 32 over 56 months (i.e. 32 people need to be treated with telmisartan rather than ramipril for 4½ years to prevent one person having to stop treatment because of a cough).

PACEF Comment:
Evidence from studies suggests that ACEI related cough is not as common as often perceived. Concern that the patient may develop an ACEI related cough is not sufficient to justify first line A2RA use. A2RAs should only be used as an alternative where there is continuing intolerance to an ACEI.

Combination therapy: ACEI plus A2RA

Local audits suggest that combination A2RA and ACEI therapy is not uncommon. Combined use is based on the theory that an A2RA plus an ACEI blocks the RAS more completely than either drug alone and provides possible additional benefits. In the ONTARGET study, combination therapy with ramipril and telmisartan was no more effective than ramipril alone at reducing CV death, MI, stroke and hospitalisations due to heart failure, but was associated with significantly more discontinuations due to hypotension, syncope, diarrhoea and renal impairment (4). The full CKD guidance from NICE states that there is no evidence to suggest increased effectiveness of combining an ACEI with an A2RA over and above the maximum recommended dose of each individual drug.

Small trials of short duration suggest that dual blockade may be beneficial in the management of macroalbuminuria / proteinuria in diabetic and non-diabetic renal disease. There is less convincing evidence in microalbuminuria despite more trials. The Renal Association advises that combination therapy should only be initiated under specialist supervision (12). Local ULHT nephrologists advocate combination ACEI and A2RA use in patients with renal disease to achieve a reduction in proteinuria.

There is also some evidence supporting the use of combination therapy in heart failure. The CHARM-added study reported that adding candesartan to an ACE inhibitor reduced cardiovascular death. As a result of the CHARM-added study, heart failure guidance from SIGN recommends that patients who remain symptomatic despite optimised ACEI and beta-blocker therapy may benefit from the addition of candesartan following specialist advice.

PACEF Comment:
The evidence base supporting combination ACEI and A2RA use is limited and conflicting. Combination therapy should only be initiated in response to specialist advice.

Acknowledgements

Many thanks to the National Prescribing Centre who undertook the review of the published evidence that formed the basis for this *Bulletin*. Also thanks to Dr Richard Andrews and Dr David O'Brien, Consultant Cardiologists at United Lincolnshire Hospitals Trust who kindly peer reviewed the text. Also thanks to ULHT nephologists for their contribution to the section on combination therapy.

References

(1) Matchar DB et al. Ann Intern Med 2008; 148: 16 – 29
(2) HOPE Investigators. N Engl J Med 2000; 342:145 – 153
(3) EUROPA Investigators. Lancet 2003; 362: 782 – 788
(4) ONTARGET investigators. N Engl J Med 2008; 358:1547 – 1549
(5) Verma S et al. BMJ 2004; 329:1248
(6) McDonald MA et al. BMJ 2005; 331: 873
(7) Volpe M et al. J Hypertens 2009;27:941 – 946
(8) Lee VC et al. Ann Int Med 2004; 141: 693 – 704
(9) Dickstein K et al. Lancet 2002; 360: 752 – 760
(10) Pfeffer MA et al. N Engl J Med 2003; 349:1893 – 18906
(11) Strippoli GFM et al. Cochrane Review 2006
(12) UKMI Medicines Q&As. Q&A 295.1 (CKD)

Appendix 1

Costs of selected ACE inhibitors

	Dose range (hypertension)	Cost / 28 days (DT May 10)
Enalapril	2.5 – 40mg once daily	£1.29 – 2.78
Lisinopril	2.5 – 80mg once daily	£1.00 – 5.56
Perindopril erbumine (g)	2 – 8mg once daily	£2.29 – 2.45
Perindopril arginine	2.5 – 10mg once daily	£8.27 – 11.02
Ramipril capsules	1.25mg – 10mg once daily	£1.17 – 1.59

Costs of A2RAs

		Cost for 28 tabs / caps DT May 10
Candesartan	2mg	£13.56
	4mg	£9.25
	8mg	£9.89
	16mg	£12.72
	32mg	£16.13
Eprosartan	300mg	£7.31
	600mg	£14.31
	800mg	£15.77
Irbesartan	75mg	£9.69
	150mg	£11.84
	300mg	£15.93
Losartan	12.5mg	£8.09
	25mg	£16.18
	50mg	£12.80
	100mg	£16.18
Olmesartan	10mg	£10.95
	20mg	£12.95
	40mg	£17.50
Telmisartan	20mg	£8.00
	40mg	£12.50

	80mg	£17.00
Valsartan	40mg	£13.97
	80mg	£13.97
	160mg	£18.41
	320mg	£20.23

Appendix 2

Patent expiry dates

Taken from UK Medicines Information Central Patent Expiry database

Drug	Patent Expiry
Losartan	March 10
Valsartan	May 11*
Candesartan	April 12
Irbesartan	Oct 13
Olmesartan	Feb 17
Telmisartan	Jan 17
Eprosartan	Apr 12

*A paediatric investigation plan (PIP) has been approved. If completed this allows an additional 6 months patent protection

Appendix 3

Licensed indications

Drug name	BP	HF	Post MI prophylaxis	Post MI with LV failure	Diabetic nephropathy Type 1	Diabetic nephropathy Type 2	CV risk reduction [1]
Captopril	√	√	√	√	√		
Cilazepril	√	√					
Enalapril	√	√					
Fosinopril	√	√					
Imidapril	√						
Lisinopril	√	√	√			√	
Moexipril	√						
Perindopril	√	√	√	√			
Quinapril	√	√					
Ramipril	√	√	√	√			√
Trandolapril	√		√	√			
Candesartan	√	√					
Eprosartan	√						
Irbesartan	√					√	
Losartan	√	√				√	√
Olmesartan	√						
Telmisartan	√						√
Valsartan	√	√		√			

1. See SPC for precise licences (http://emc.medicines.org.uk)

Stephen Gibson
Head of Prescribing and Medicines Management

Gill Kaylor
Prescribing Adviser July 2010