

# DRUG UPDATE

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## ACE INHIBITORS

Angiotensin converting enzyme (ACE) inhibitors reduce mortality and/or morbidity in chronic heart failure, following myocardial infarction and in those at high cardiovascular risk for other reasons, including previous stroke and stable coronary artery disease. They also reduce disease progression in patients with diabetic nephropathy. Although they lower blood pressure, there is no evidence that clinical outcomes are improved compared with other antihypertensive drugs. ACE inhibitors should be chosen from a limited formulary agreed locally on the basis of clinical trial evidence, range of indications, cost and convenience.

### *What are they?*

There are eleven different angiotensin converting enzyme (ACE) inhibitors licensed in the UK.<sup>1</sup> All have been approved for the treatment of hypertension; eight have also been approved for the indication of heart failure or left ventricular dysfunction/heart failure post infarction (see table).<sup>1</sup> These drugs differ in their properties, including pharmacokinetics, lipophilicity, ability to block tissue ACE, and effects on endothelial function. It is not currently known if the beneficial effects shown for individual agents are affected by any of these ancillary properties or if they are a 'class effect' associated with ACE inhibition.

### *Hypertension*

All licensed ACE inhibitors are effective for lowering blood pressure but there is no consistent evidence that they improve clinical outcomes more than other antihypertensive drug groups. They are recommended as a second-line therapy in patients with a raised risk of new-onset diabetes who are not controlled on a low-dose thiazide diuretic.<sup>2</sup>

### *Heart failure*

A systematic review of 7105 patients (NYHA class II or worse) from 32 trials demonstrated that, compared with placebo, ACE inhibitors significantly reduced mortality (absolute risk reduction [ARR] 6%, 95% CI 4%-8%; odds ratio [OR] 0.77, 95% CI 0.67 to 0.88).<sup>3</sup> These data were largely derived from trials using enalapril, captopril, ramipril, quinapril or lisinopril. There was no statistically detectable heterogeneity of effect between these agents ( $p=0.87$ ) consistent with (but not proving) a class effect.

### *Following myocardial infarction*

In a meta-analysis including 3 trials involving 5966 patients with left ventricular dysfunction or heart failure following MI and an average follow-up period longer than 1 year (SAVE, AIRE, TRACE), ACE inhibitors (captopril, ramipril, trandolapril) significantly reduced mortality (OR 0.74, 95% CI 0.66-0.83), readmission for heart failure and re-infarction compared with placebo.<sup>4</sup> Statistical assessment for heterogeneity of effect between these three trials was not reported but broadly similar effects were seen with 3 agents studied.

### *Prophylaxis of cardiovascular events, stroke and coronary artery disease*

In the HOPE study ramipril 10mg daily was associated with a significant ARR of 3.8% in MI, stroke or CV mortality compared with placebo in patients at high risk of cardiovascular complications.<sup>5</sup> There were significant reductions in risk when each of these end-points were analysed separately.

In the PROGRESS trial involving patients with a recent stroke, the combination of perindopril (4 mg/day) and indapamide (2-2.5 mg/day) reduced further episodes of stroke (fatal and non-fatal) and major vascular events (vascular death, non-fatal MI, non-fatal stroke) with an ARR of 3.7%.<sup>6</sup> Significant benefits were not seen with perindopril monotherapy, although the study was not designed to address this specifically.

In the EUROPA study, involving patients with stable coronary artery disease, perindopril 8 mg daily was associated with a significant ARR of 1.9% in the combined primary endpoints of CV death, MI and cardiac arrest compared with placebo.<sup>7</sup> There was no significant reduction in total mortality or stroke.

It is not known if the result of ramipril and perindopril in the HOPE and EUROPA studies respectively can be achieved with other ACE inhibitors, or if ramipril and perindopril have similar benefits, since the HOPE and EUROPA trials studied different patient populations. The Prevention of Events with ACE Inhibition (PEACE) trial will evaluate the effect of trandolapril in preventing myocardial infarction and other ischaemic events in patients with normal ejection fractions providing further useful information.<sup>8</sup>

### *Nephropathy*

ACE inhibitors should be started and titrated to full dose in all adults with confirmed nephropathy (including those with microalbuminuria alone) and type 1 diabetes.<sup>9</sup> Antihypertensive therapy slows the progression of nephropathy in hypertensive patients with type 2 diabetes; however, it is unclear whether ACE inhibitors have a specific renoprotective action beyond BP reduction in overt nephropathy complicating type 2 diabetes.<sup>10</sup> A recent meta analysis showed that ACE inhibitors significantly reduced the risk of progression from microalbuminuria to

macroalbuminuria by about 55% (n=2010) and increases the rate of regression from microalbuminuria to normoalbuminuria by about 3.4-fold (n=1888), these effects were independent of the type of diabetes or stage of diabetic nephropathy.<sup>11</sup> A meta-analysis involving 1860 patients demonstrated that the renoprotective properties of ACE inhibitors extend to patients with non-diabetic nephropathy.<sup>12</sup>

### What dose of ACE inhibitor to use?

It is important to prescribe the ACE inhibitor at an adequate dose. Lisinopril 32.5 mg to 35 mg daily significantly reduced the combined endpoint of all cause mortality and hospitalisation for any reason compared with lisinopril 2.5 to 5 mg daily in patients with heart failure.<sup>13</sup> Ramipril 10 mg but not 1.25 mg daily was effective in preventing CV mortality in patients at high cardiovascular risk or diabetic nephropathy.<sup>5,14</sup>

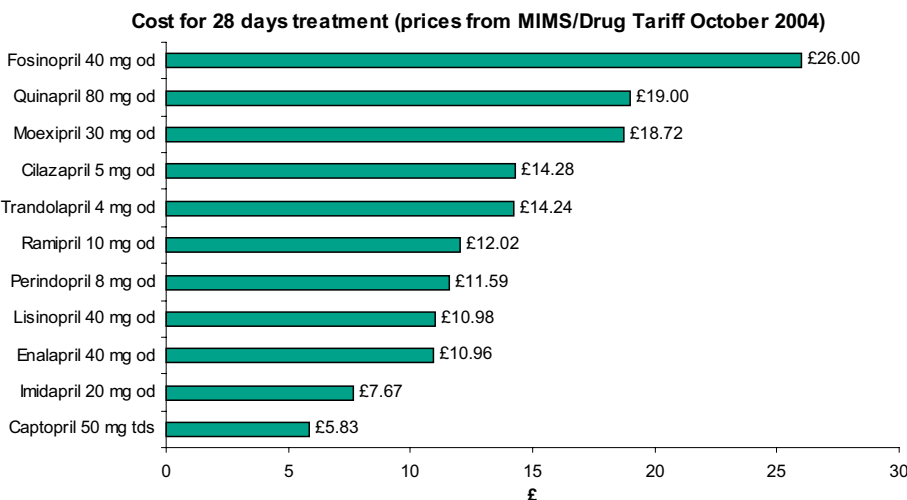
### Are there differences between ACE inhibitors in clinical effects?

There is no evidence for differences in efficacy between ACE inhibitors, although direct comparative trials are lacking. There is no conclusive evidence that ancillary properties affect clinical outcome or of differences in adverse effects between individual agents. There is less evidence of long term safety for newer ACE inhibitors and for those that have not been studied in long term clinical trials.

### Which ACE inhibitors should be used?

It is appropriate to prescribe from a locally agreed formulary of 2 or 3 ACE inhibitors chosen on the basis of the clinical trial evidence available, range of indications, and other factors such as cost, availability of generic preparations and convenience. Individual prescribers can then decide which of these ACE inhibitors is indicated for individual patients.

## Licensed indications for individual ACE inhibitors and their cost



	HYPERTENSION	CHF	LVD / CHF post MI	MI	CV risk reduction	Diabetic type 1 nephropathy
Fosinopril 40 mg od	✓	✓				
Quinapril 80 mg od	✓	✓				
Moexipril 30 mg od	✓					
Cilazapril 5 mg od	✓	✓				
Trandolapril 4 mg od	✓		✓			
Ramipril 10 mg od	✓	✓	✓		✓	
Perindopril 8 mg od	✓	✓				
Lisinopril 40 mg od	✓	✓		✓		zestril ✓
Enalapril 40 mg od	✓	✓				
Imidapril 20 mg od	✓					
Captopril 50 mg tds	✓	✓	✓	✓		✓

N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence. It should be noted that captopril, enalapril, lisinopril, and ramipril are available generically. It is expected that the cost of these drugs will fall further.

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KEY RCT - randomised controlled trial, CT - controlled trial, G - guideline, O - open study, MA - meta analysis, R - review, U - unpublished, Abs - abstract, E - editorial

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