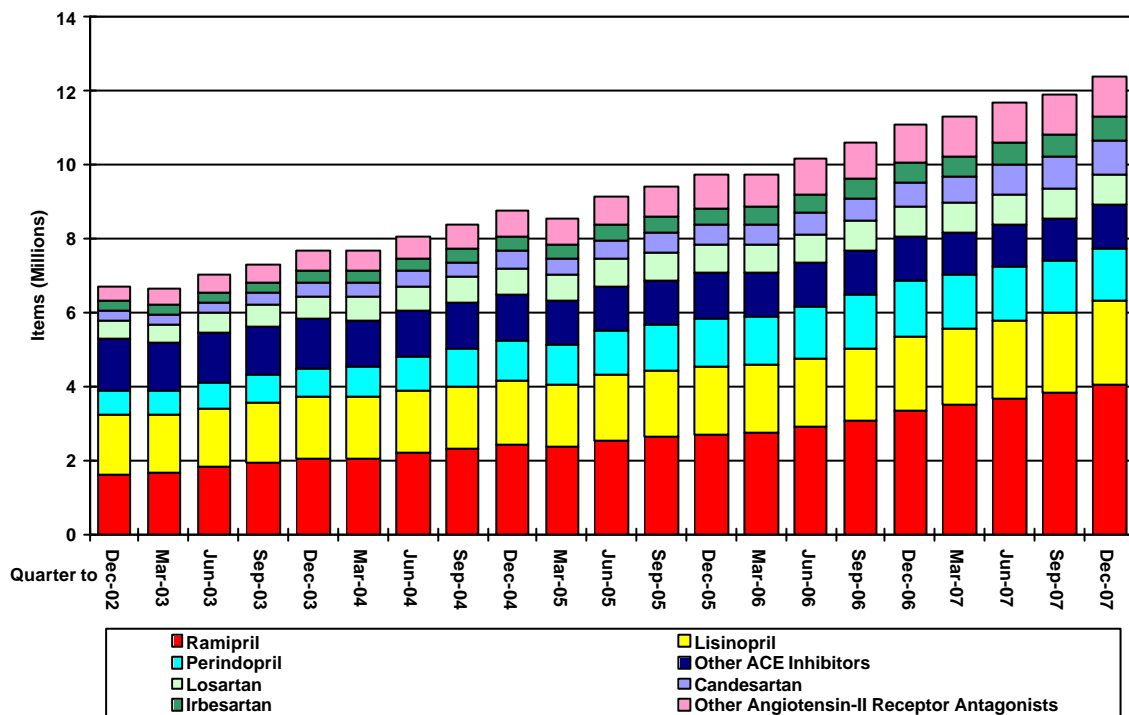


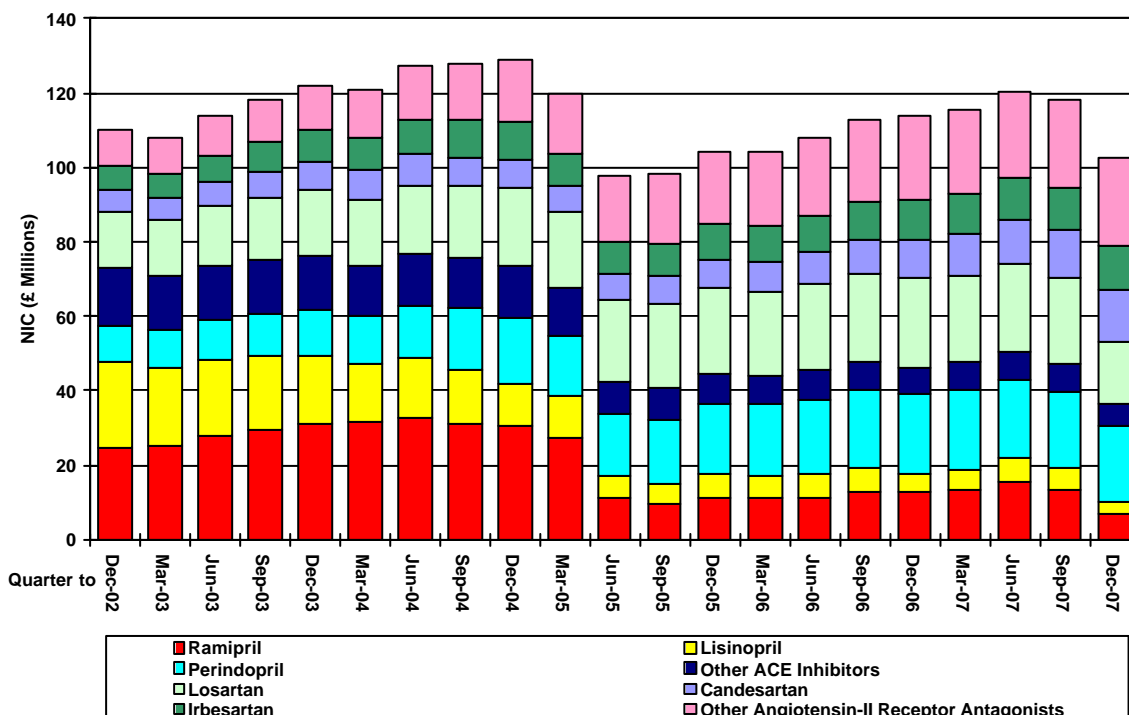
Prescribing of cardiovascular drugs has increased by 82% since 2000, when the National Service Framework for Coronary Heart Disease was published. This trend has been matched by increased prescribing of drugs acting on the renin-angiotensin system - that is, ACE inhibitors (ACEIs) and angiotensin-II receptor antagonists (ARAs). In *Prescribing Costs in Primary Care*, the National Audit Office estimated that £67 million could be saved by increasing the use of generic ACEIs in place of ARAs, which are more expensive and offer no advantage for most patients.<sup>1</sup> ACEIs currently account for 72% of prescribing but the proportion of prescriptions for ARAs has been increasing steadily (Chart 1). In the last three years, increases in cost have been limited by the introduction of generic ramipril, the leading ACEI (Chart 2). However, growth in prescribing of ARAs, which are more expensive than ACEIs, has continued to exert upward pressure on costs and ARAs now account for 65% of total costs for this class. There is also a trend for increased prescribing of perindopril which, even generically, is more expensive than ramipril (see Prescribing Data).

Although the licensed indications vary, ACEIs and ARAs are primarily prescribed for the treatment of hypertension and heart failure and for secondary prevention of cardiovascular events post-myocardial infarction.

Trends in Prescribing of Renin-angiotensin System Drugs in General Practice in England (Chart 1)



Trends in Spending on Renin-angiotensin System Drugs in General Practice in England (Chart 2)

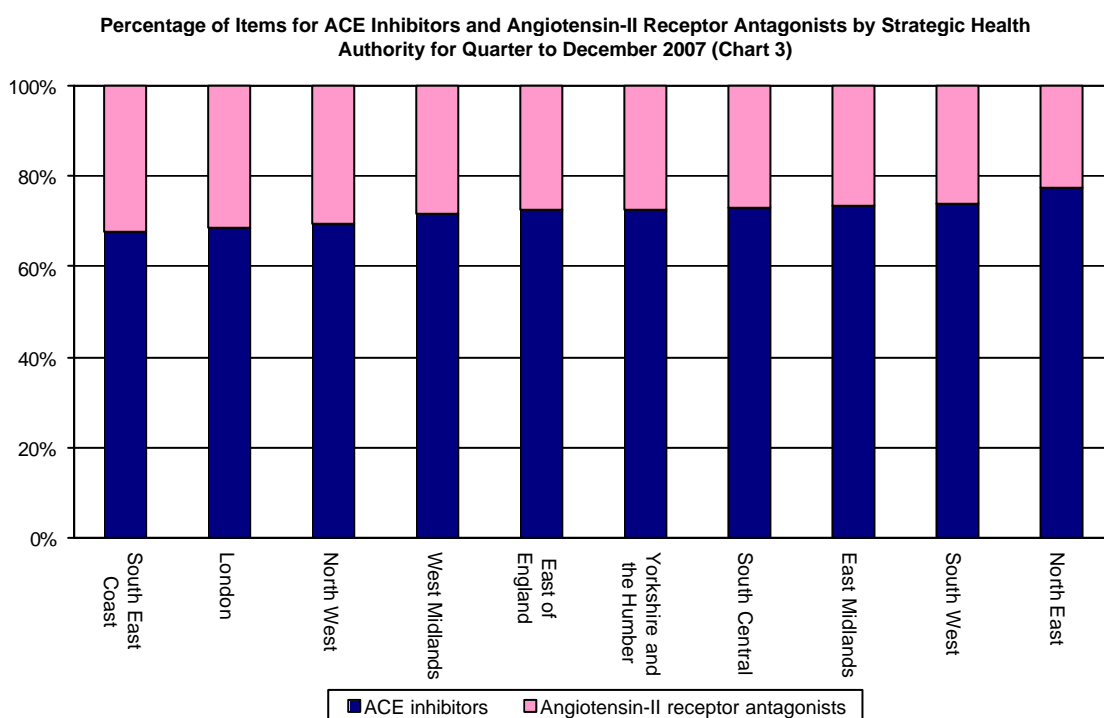


## Hypertension

The National Institute for Health and Clinical Excellence (NICE) clinical guideline on the management of hypertension, updated in 2006, states that hypertension should be treated as part of the overall management of cardiovascular risk in individual patients.<sup>2</sup> There is no evidence of clinically significant differences in overall efficacy between or within the various classes of antihypertensive drugs with the exception of beta-blockers, which reduce the risk of major events less effectively. The choice of initial treatment should therefore be made according to individual patient factors (e.g. age, comorbidity, ethnicity), the nature of adverse effects and cost. NICE recommends that initial treatment for patients aged over 55 years, or for those of African or Caribbean descent of any age, should be either a thiazide diuretic (D) or a calcium channel blocker (C). In patients under 55 years, the drug of first choice is an ACEI (A); if this is not tolerated, an ARA is appropriate. ACEIs are also the drugs of first choice to lower blood pressure (BP) in patients with diabetes who have microalbuminuria or proteinuria.<sup>3</sup> If combinations of two drugs are indicated, the recommended regimens are A+C or A+D; if three are needed, the recommended regimen is A+C+D. Combinations of four drugs may include a second diuretic, a beta-blocker or an alpha-blocker; specialist advice should also be considered. In clinical trials, about half of patients required treatment with more than one antihypertensive to achieve target BP.

ACEIs are preferred to ARAs because the long-term outcome data are stronger for ACEIs, they cost less, and there is no convincing evidence of clinical advantage. A meta-analysis of 48 clinical trials and 13 observational studies which compared ACEIs and ARAs found no consistent differences in BP control; as monotherapy they were both effective in about 55% of patients.<sup>4</sup> In these trials, reported rates of discontinuation due to adverse events varied between 1% and 41% for both ACEIs and ARAs and the data were of variable quality. The odds ratio for withdrawal due to adverse events for ARAs vs. ACEIs was 0.51 (95%CI 0.38 - 0.70) (median withdrawal rate 3.7% vs. 8.0%). The incidence of adverse effects was similar overall but cough was more frequent with ACEIs than ARAs. This difference was greater in clinical trials when patients were asked about it directly (9.9 vs. 3.2%) than was reported in cohort studies (1.7 vs. 0.6%). NICE's economic model of the cost effectiveness of treatment assumed, based on expert opinion, that ACEIs would account for 80% of prescribing and ARAs for 20%. However, it should be noted that this not an evidence-based assumption. Chart 3 shows that the percentage of items for ACEIs ranges from 68% to 78% across Strategic Health Authorities.

Clinical trials show that combining an ACEI and an ARA offers a further reduction in BP compared with monotherapy but the effect is small (3 - 4/2 - 3 mmHg<sup>5</sup>) and is probably also achievable by titrating the ACEI to the target dose. The adverse effects associated with long-term combined treatment have not been adequately quantified.<sup>5</sup> It is therefore preferable to add an antihypertensive from another class when target BP is not achieved with an ACEI.



### **Heart failure**

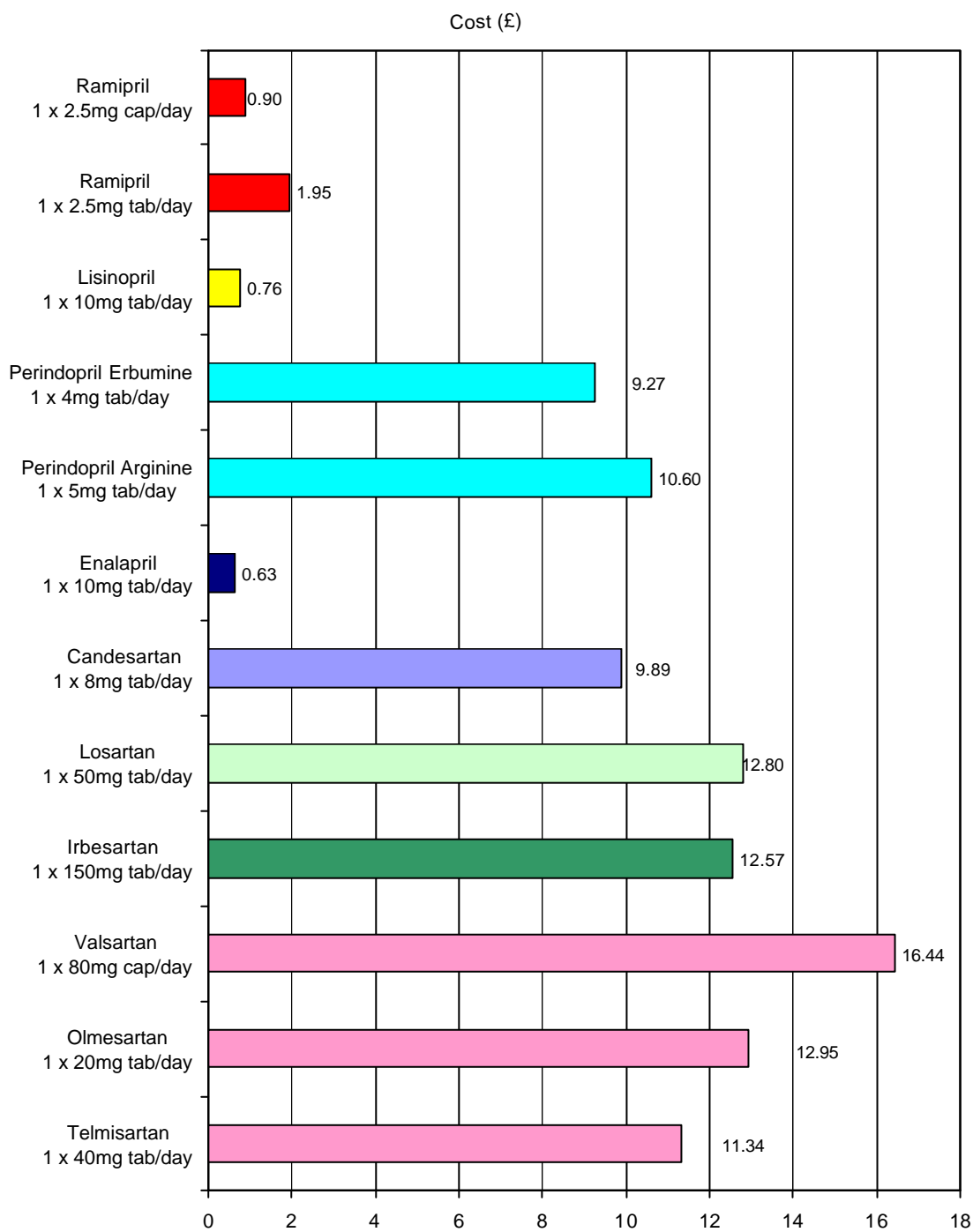
The NICE guidance on heart failure, published in 2003<sup>6</sup> is due to be updated in 2008. Recent data have been reviewed by the National Prescribing Centre.<sup>7</sup> Initial drug treatment in primary care includes an ACEI (or, if this is not tolerated, an ARA), a beta-blocker and a diuretic; patients who are symptomatic despite optimal therapy should be referred for specialist care. Compared with placebo, ACEIs reduce mortality (OR 0.80, 95%CI 0.74 - 0.87) and re-admission for heart failure (OR 0.67, 95%CI 0.61 - 0.74).<sup>8</sup> Treatment should be considered for all patients with heart failure due to left ventricular systolic dysfunction and introduced before a beta-blocker. The recommended target doses are relatively high: 10 mg/day for ramipril, 35 mg/day for lisinopril, 32 mg/day for candesartan and 160 mg twice daily for valsartan.<sup>7</sup> ARAs are also associated with reductions in mortality and admissions compared with placebo but are not more effective than ACEIs. A meta-analysis of 24 randomised trials involving 38,080 patients with mild to severe heart failure found no significant differences for ARAs compared with ACEIs for all-cause mortality (hazard ratio, HR, 1.06; 95%CI 0.90 - 1.26) or admissions for heart failure (HR 0.95, 95%CI 0.80 - 1.13).<sup>9</sup> This meta-analysis did not evaluate adverse effects but in the ELITE II trial, which accounted for 61% of the data, significantly fewer patients discontinued losartan than captopril due to adverse effects (9.7 vs. 14.7%) including 0.3 and 2.7% respectively for cough.<sup>10</sup>

Evidence available since NICE guidance was published shows that, compared with an ACEI alone, adding an ARA to established treatment with an ACEI may further reduce hospital admissions for heart failure and cardiovascular events but not all-cause mortality.<sup>11,12</sup> Although optimal dosing of the ACEI was attempted in these studies the average doses achieved were low. It is therefore possible that similar benefits to combined treatment could have been achieved with target doses of ACEI monotherapy. Further, combined treatment was associated with a higher incidence of hyperkalaemia and renal impairment, and more discontinuations due to adverse events.

### **Post myocardial infarction**

Early treatment with an ACEI after acute myocardial infarction (MI) reduces mortality and reinfarction by approximately 10 - 20% (depending on left ventricular function) during the first 2 - 5 years, with a 10% reduction in all-cause mortality over 12 years.<sup>13</sup> NICE guidance recommends treatment with an ACEI, a beta-blocker, aspirin and a statin.<sup>14</sup> An ACEI should be initiated early after MI and the dose titrated as recommended for heart failure; treatment should continue indefinitely whether or not the patient is symptomatic. Patients who had an MI more than a year previously and are symptomatic should be treated according to NICE guidance on heart failure management; if they are asymptomatic, they should be offered an ACEI even if left ventricular function is preserved. NICE restricts the role of ARAs to intolerance of an ACEI; combined treatment is not recommended for routine use. There is no difference in efficacy between different ACEIs or between the ACEIs and ARAs in preventing recurrent MI or death after acute MI.<sup>15</sup> The VALIANT trial compared valsartan and captopril separately and in combination post-myocardial infarction.<sup>16</sup> The incidence of adverse events leading to treatment discontinuation was significantly lower with valsartan than captopril or combined treatment (5.8 vs. 7.7 and 9.0% respectively) but the difference in the incidence of cough leading to discontinuation was small (valsartan 0.6% vs. captopril 2.5%).

## Cost for 28 Days Treatment



Prices based on Drug Tariff May 2008, except for Perindopril Arginine which is based on information supplied by manufacturer. Dose based on WHO DDDs where possible, otherwise BNF stated dose. The WHO DDD is a unit of measurement based on the assumed average maintenance dose in adults. It may not necessarily reflect the actual dose used.

**Prescribing data (reporting quarter = October-December 2007, index quarter = October-December 2002)**

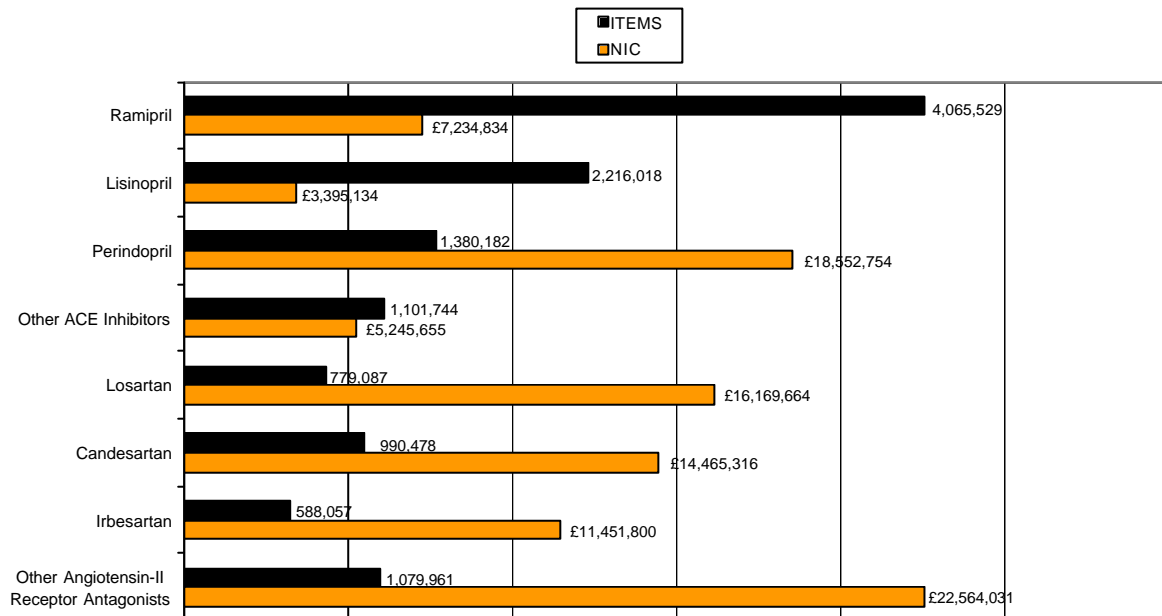
Prescription items for drugs affecting the renin-angiotensin system have increased by 85% in the last 5 years to 12.4 million items, whereas cost has decreased by 7% to £103 million. Prescribing of ACEIs has increased by 68% (to 8.9 million items), whilst cost has decreased by 51% (to £36 million). ACEIs now account for 72% of prescribed drugs affecting the renin-angiotensin system but only 35% of the cost. Ramipril represents 45% of all ACEI items and 19% of cost, while lisinopril accounts for 25% of ACEI items and 9% of cost. Whereas prescribing of ramipril has risen by 147%, its cost has fallen by 72%. Prescribing of ramipril is predominantly in the form of capsules (94% of items and 83% of the cost), which are cheaper than tablets. Perindopril accounts for 16% of ACEI items (1.4 million) but 57% of cost (£20.4 million). The patent on perindopril erbumine (Coversyl) expired in June 2003 and generic versions of perindopril erbumine have been available in the UK since July 2007. The manufacturers of Coversyl have announced that it is to be discontinued and replaced with Coversyl Arginine which has a different equivalent dose (2mg perindopril erbumine is equivalent to 2.5mg perindopril arginine). For patients taking Coversyl, prescribers will have two choices: either to prescribe perindopril erbumine as the generic product so patients stay on the same dose and formulation, or switch patients to Coversyl Arginine with the appropriate dose change. Prescribing of ARAs has increased by 145% (to 3.5 million items) with cost rising by 80% (to £67 million). At present there are no generic presentations of ARAs. The most frequently prescribed ARA is candesartan (28% of items and 21% of cost). This represents an increase in prescribing of over 250% and an increase in spending of 137%. 23% of ARA items are for losartan (25% of cost).

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**Summary**

- The National Audit office estimates that £67 million could be saved by increasing the use of generic ACEIs in place of ARAs.
- ACEIs are preferred to ARAs for hypertension, heart failure and secondary prevention after MI because the long-term outcome data is stronger for ACEI.
- For the treatment of hypertension, the first choice in people aged over 55 years, or those of African or Caribbean descent of any age, is either a thiazide diuretic or a calcium blocker. In patients under 55 years, the first choice is an ACEI or ARA.
- For the treatment of heart failure, initial treatment should be with an ACEI (or ARA, if not tolerated), a beta-blocker and a diuretic.
- For post MI, the recommended drug regimen is an ACEI, a beta-blocker, aspirin and a statin.
- The incidence of adverse effects is similar between ACEIs and ARAs except for cough, which is more frequent with ACEIs.

**Prescribing and Spending on Drugs affecting the Renin-angiotensin System  
in England for Quarter to March 2008**



Quarter to Mar 08  
National

	ITEMS/1000 PUs	NIC/1000 PUs
ACE Inhibitors	123.42	£484.88
Angiotensin-II Receptor Antagonists	48.41	£910.52