

# Hypertension data-focused commentary

1. Use of angiotensin converting enzyme inhibitors (ACE-inhibitors)
2. Use of angiotensin-II receptor antagonists (AIIIRAs)
3. Use of alpha-blockers
4. Use of calcium-channel blockers
5. Use of diuretics

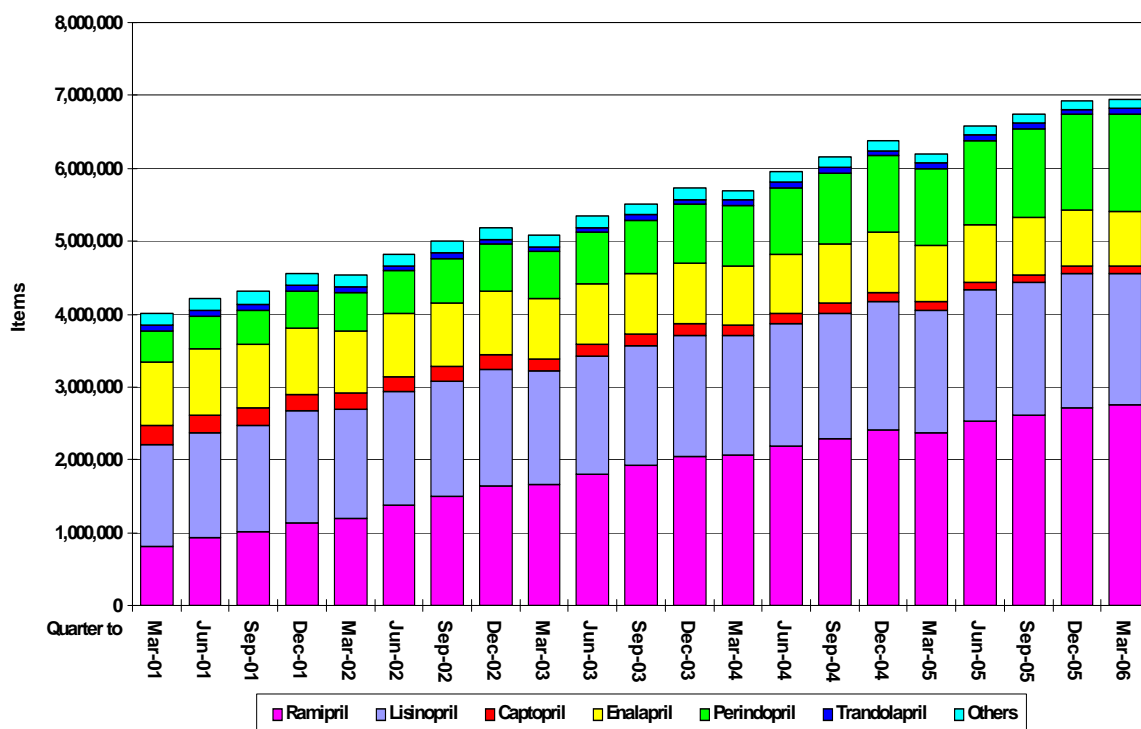
## 1. Use of ACE-inhibitors

ACE-inhibitors are used for several indications, notably heart failure, as well as hypertension. Interpretation of prescribing data is therefore limited in that information on the prescribed indication(s) is not available.

Over the last few years, the number of prescriptions for ACE-inhibitors has steadily increased, as the graph below shows:

### Prescriptions (items) for ACE-inhibitors in England (March 2001 to March 2006)

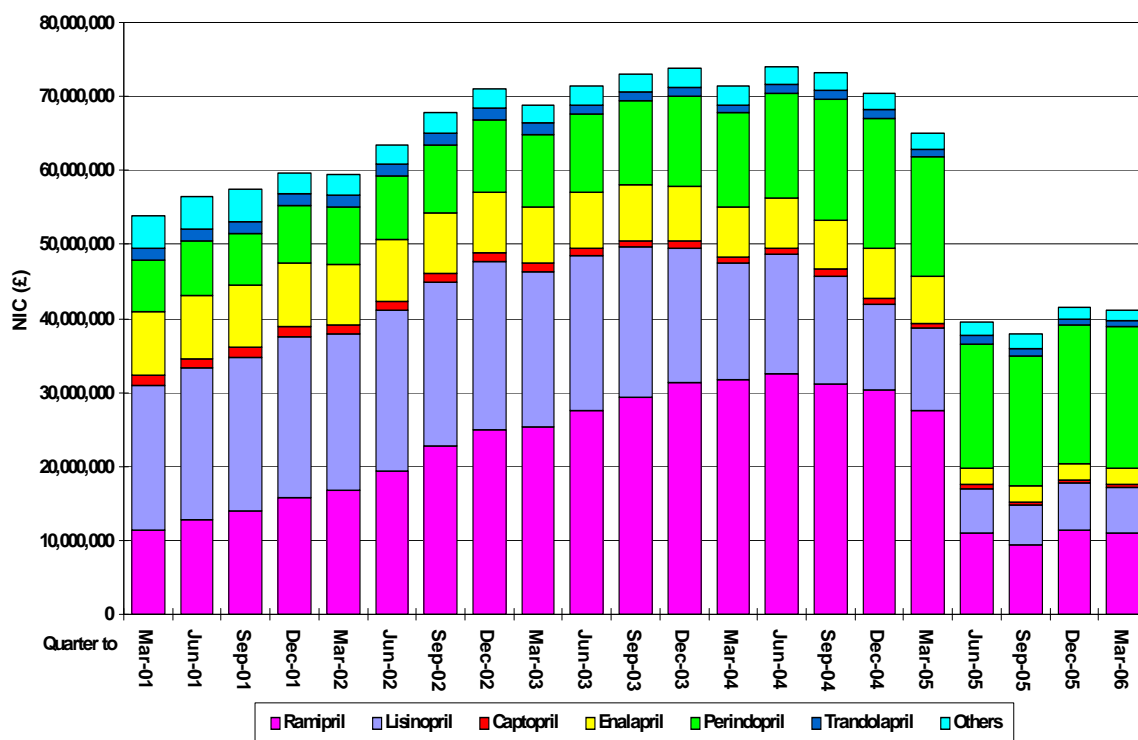
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The proportion of items which were for ramipril has increased significantly. Ramipril has a very strong evidence base, including the HOPE<sup>1</sup> study. There has been some increase in the use of perindopril, perhaps associated with marketing of trials such as EUROPA<sup>2</sup> and PROGRESS<sup>3</sup>, although there are still fewer prescriptions for perindopril than ramipril. The number of prescriptions for other products has remained more or less static. There is no reason to believe that perindopril has any superiority over ramipril or indeed other ACE-inhibitors.

By contrast, the NHS spends much more on perindopril than any other ACE-inhibitor, as the graph below shows:

### Spend on ACE-inhibitors in England (March 2001 to March 2006)



<sup>1</sup> [The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Eng J Med 2000; 342: 145-153.](#)

<sup>2</sup> The EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 2003; 362: 782-788.

<sup>3</sup> Randomised Trial of a Perindopril-Based Blood-Pressure-Lowering Regimen among 6,105 Individuals with Previous Stroke or Transient Ischaemic Attack. Lancet 2001; 358: 1033-1041. (The PROGRESS Study).

The price of generic ramipril was substantially reduced in 2005 with the introduction of category M, but the price of generic perindopril is that of the branded product, and is considerably greater than generic ramipril<sup>4</sup>. Note also the important price differences between ramipril tablets and capsules: several PCTs have made substantial savings through programmes of switching to capsules, and optimising doses (e.g. prescribing one 5 mg capsule instead of two 2.5 mg tablets) (Personal communications).

**Cost of 28 days treatment** ([Drug Tariff](#) November 2006)

Perindopril 2 mg tablets (one daily)	£10.22
Perindopril 4 mg tablets (one daily)	£10.22
Perindopril 8 mg tablets (one daily)	£10.22
Ramipril 2.5 mg tablets (one daily)	£3.94
Ramipril 5 mg tablets (one daily)	£5.12
Ramipril 10 mg tablets (one daily)	£6.56
Ramipril 2.5 mg capsules (one daily)	£2.11
Ramipril 5 mg capsules (one daily)	£2.33
Ramipril 10 mg capsules (one daily)	£2.79

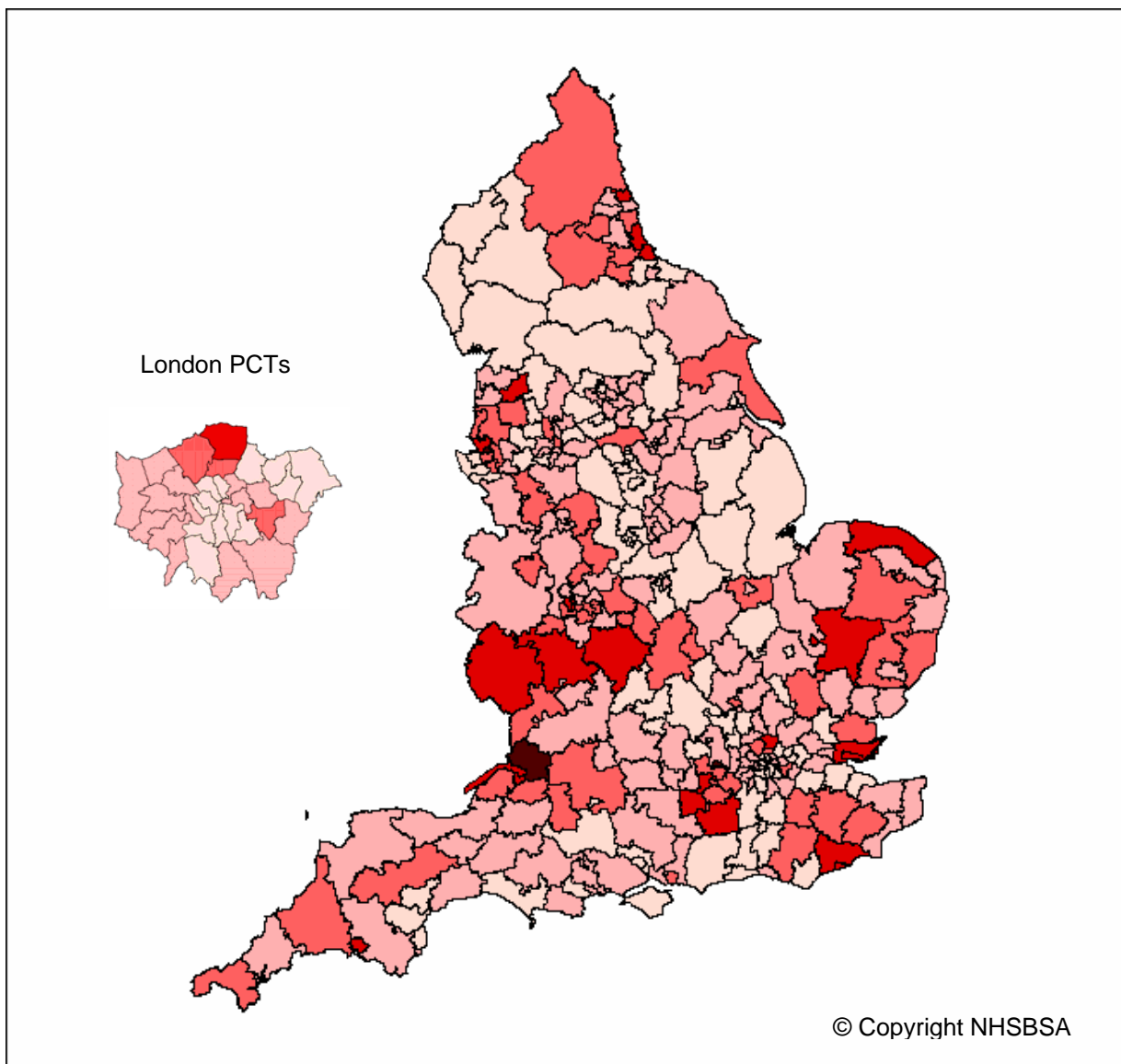
The map on the next page shows the relative spend on ACE-inhibitors by PCT in England. The differences in spend are due to differences in overall use of ACE-inhibitors as well as differences in product choice.

**Questions for reflection**

- a. **What is the pattern of ACE-inhibitor use in my practice / locality / PCT? Could it be more cost-effective?**
- b. **What barriers prevent it being more cost-effective?**
- c. **How can I go about improving the cost-effectiveness? Who do I need to work with?**

<sup>4</sup> Department of Health. [Department of Health: The Drug Tariff](#). October 2006

Variation between Primary Care Trusts in spending on ACE-inhibitors (Quarter to March 2006)



**NIC (£) per 1000 Renin-Angiotensin System STAR(01)-PUs**

230.7 to 268.1	(3)
193.1 to 230.6	(23)
155.5 to 193.0	(59)
117.9 to 155.4	(126)
80.2 to 117.8	(92)

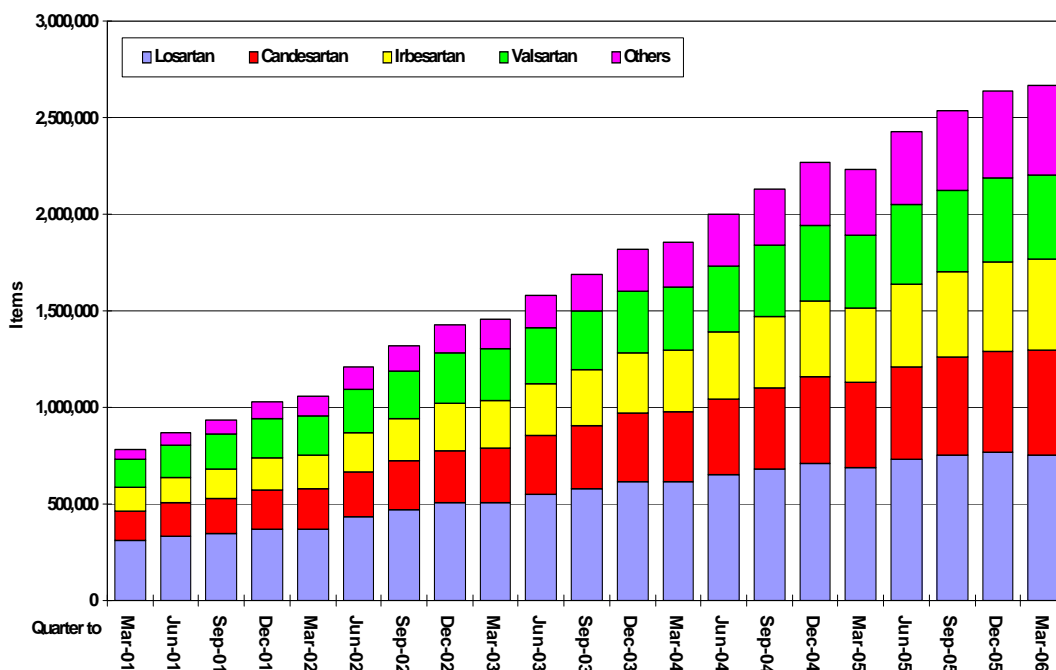
Spend is a proxy for number of prescriptions. The number of Renin-Angiotensin System STAR(01)-PUs is a measure of population, taking into account age and sex demographics. For more information on STAR-PUs and other prescribing measures, see the [Prescribing Support Unit website](#)

## 2. Use of Angiotensin-II receptor antagonists (AIIARs)

AIIARs have grown considerably in popularity over the last few years, as the graph below shows. This is despite the lack of any good evidence to suggest any advantages over ACE-Is. AIIARs should only be considered where an ACEI is indicated but not tolerated. The most common reason for intolerance is a dry cough, which occurs in about 5–10% of people. There is no compelling evidence to suggest that AIIARs offer any clinical advantage over ACEIs, or that there are differences between individual agents, and AIIARs are considerably more costly than ACEIs. There is also insufficient evidence to suggest any synergistic or clinically significant effect of using an ACEI and an AIIAR in combination. (Ref: MeReC Bulletin. The management of hypertension in primary care: updated guidance from NICE. Volume 17. Number 1. September 2006).

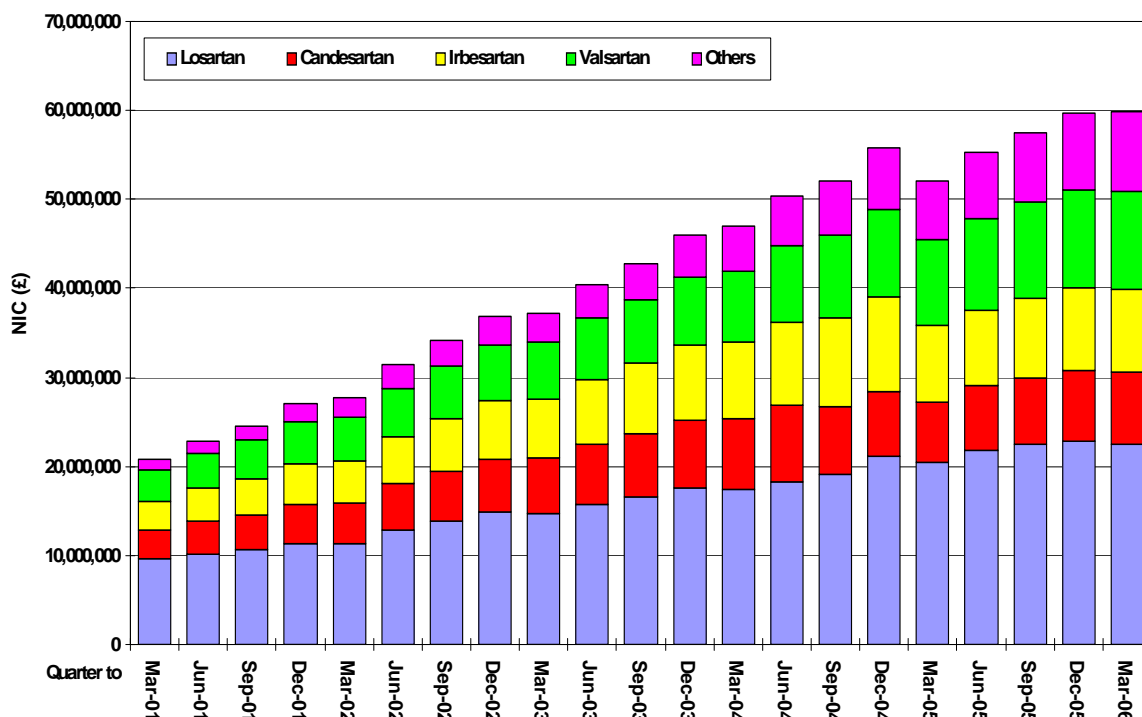
### Prescriptions (items) for AIIARs in England (March 2001 to March 2006)

  
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AllIRAs can be more expensive than ACE-inhibitors. The graph below shows the relative spend on AllIRAs:

### Spend on AllIRAs in England (March 2001 to March 2006)

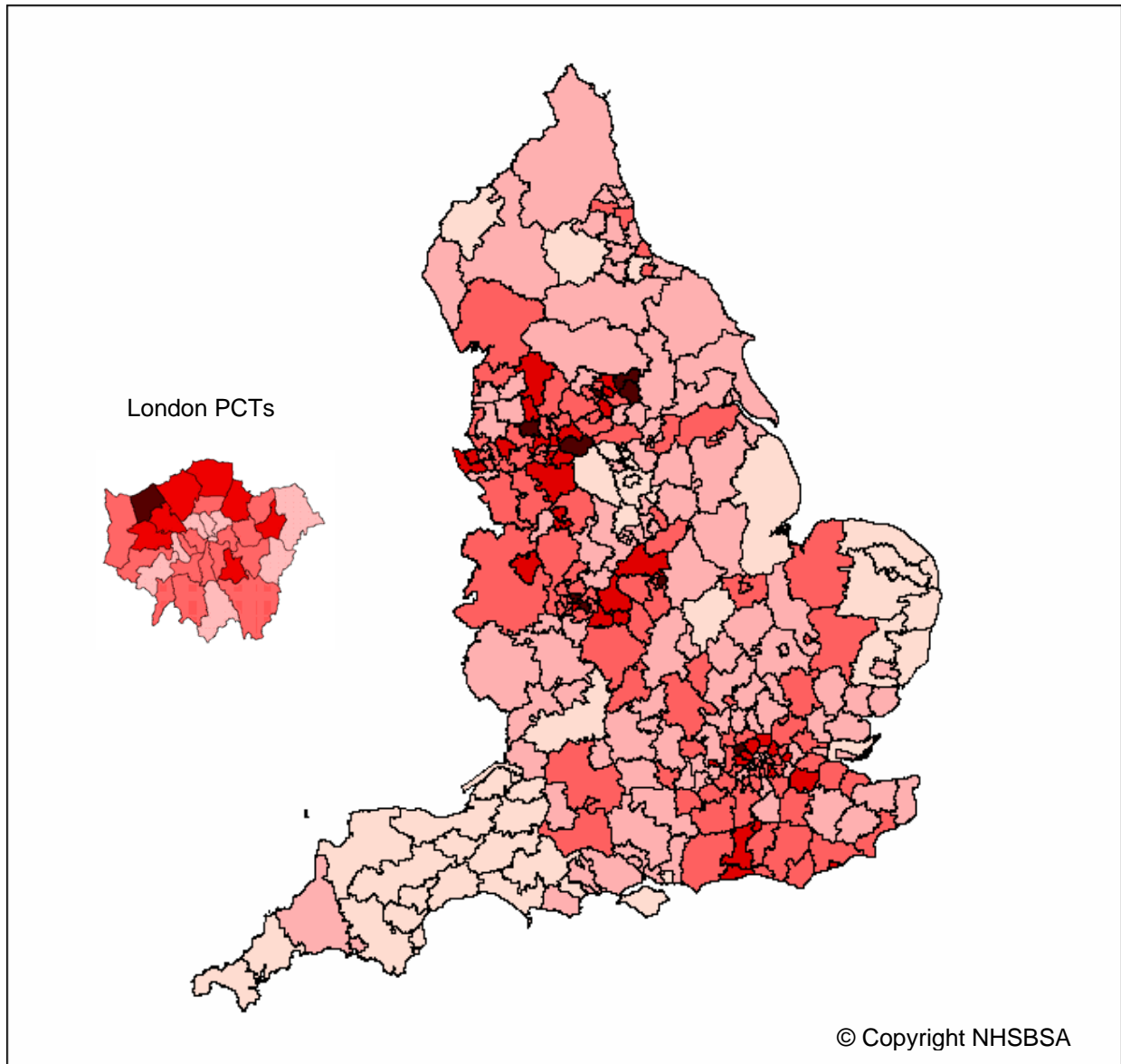


The map below shows the relative spend on AllIRAs by PCT in England. The differences in spend are due both to differences in overall use of AllIRAs and differences in product choice. Assuming an intolerance to ACEi of 10%, we might expect a ratio of ACEi: AllIRA items of 9:1. Nationally there are around 7 million ACEi items and 2.5million AllIRA items prescribed in primary care in England each quarter, so there may be a little more than 1.5million items of AllIRAs each quarter that might be instead be ACEis. An initial approach might be to see if there are patients taking an AllIRA who do not have contraindications to an ACEi and who have never been on an ACEi.

#### Questions for reflection

- What is the pattern of AllIRA use in my practice / locality / PCT? Is it appropriate and cost effective?
- What barriers prevent it being more appropriate and cost effective?
- How can I go about improving the appropriateness and cost effectiveness of prescribing? Who do I need to work with?

Variation between Primary Care Trusts in spending on AIIIRAs (Quarter to March 2006)



**NIC (£) per 1000 Renin-Angiotensin System STAR(01)-PUs**

269.6 to 310.6	(9)
228.6 to 269.5	(35)
187.6 to 228.5	(101)
146.6 to 187.5	(113)
105.5 to 146.5	(45)

Spend is a proxy for number of prescriptions. The number of Renin-Angiotensin System STAR(01)-PUs is a measure of population, taking into account age and sex demographics. For more information on STAR-PUs and other prescribing measures, see the [Prescribing Support Unit website](#)

### 3. Use of alpha-blockers

The alpha-blocker doxazosin was included in the landmark hypertension study, ALLHAT. Patients with hypertension and at least one other coronary heart disease (CHD) risk factor were randomised (double blind) to initial treatment with one of four drugs: amlodipine, chlortalidone, doxazosin or lisinopril (with open label treatment with other drugs if necessary) to try to achieve target blood pressure of 140/90 mmHg or less.

In January 2000, after an interim analysis (median 3.3 years) the study's independent data review committee recommended discontinuing the doxazosin treatment arm based on comparisons with chlortalidone<sup>5</sup>. Although the drugs had similar effects on the study's primary outcome (CHD death or non-fatal MI), doxazosin was associated with significantly higher risks of other adverse outcomes.

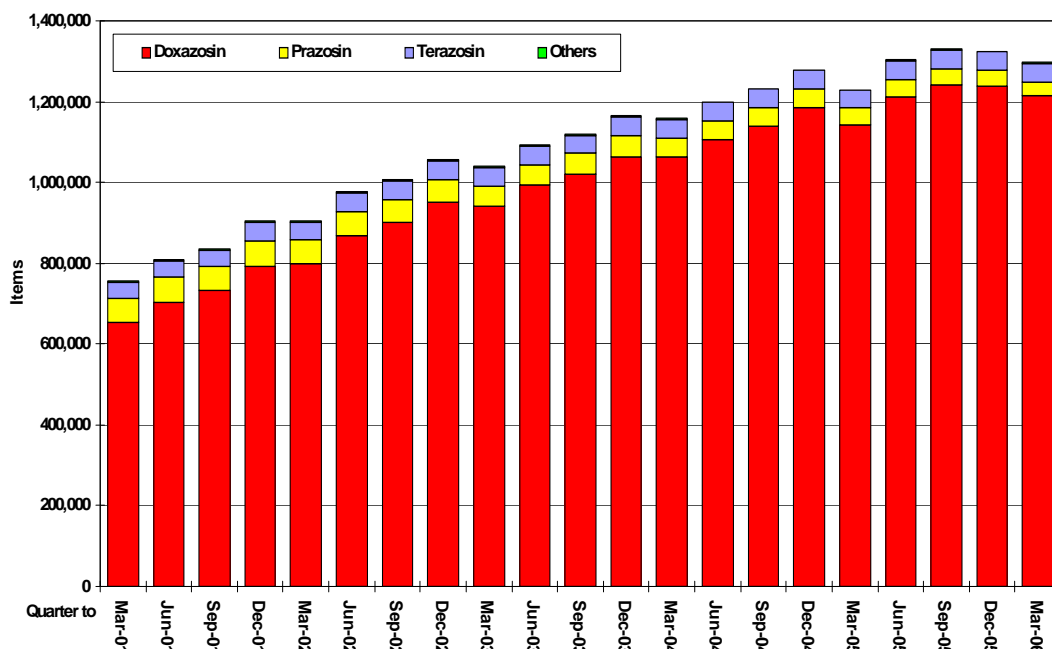
Compared with chlortalidone, doxazosin was associated with a 19% higher risk of stroke and a 25% higher risk of the combined cardiovascular disease endpoint. Considered separately, the risk of heart failure was doubled and the risk of angina, coronary revascularization, and peripheral arterial disease was also increased (by 16%, 15% and 7% respectively).

NICE guidance [CG 34, June 2006](#) advises that alpha-blockers should normally be reserved for fourth line use, after combination therapy with diuretic, ACE-inhibitor and calcium channel blocker has failed to control blood pressure adequately.

However, use of alpha-blockers, especially doxazosin, has risen steadily over the last few years, and the findings of the ALLHAT study referred to above have made little if any impact on the amount used.

#### Prescriptions (items) for alpha-blockers in England (March 2001 to March 2006)

  
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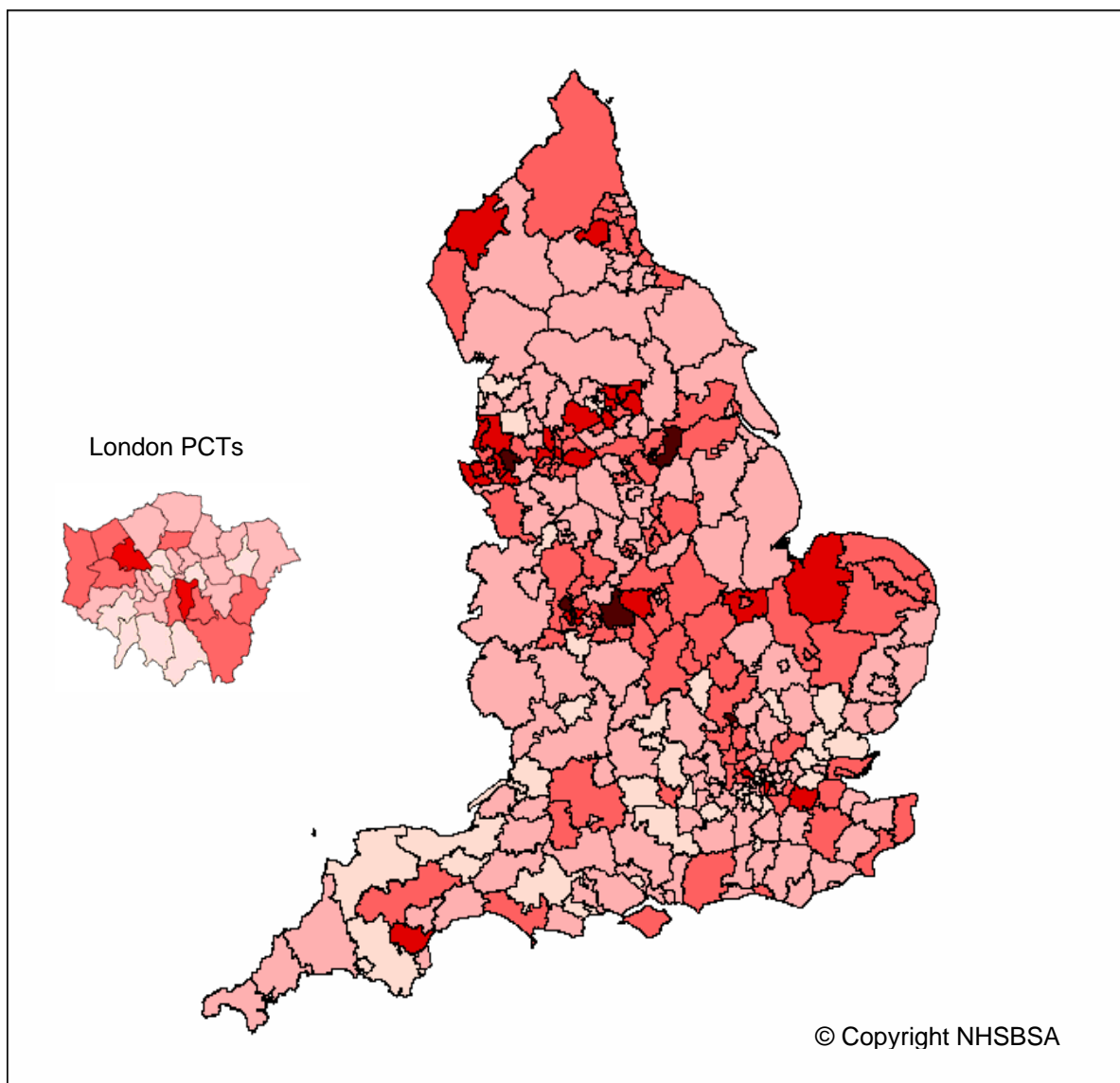
<sup>5</sup> The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs. chlortalidone. JAMA 2000; 283: 1967-1975.






Usage also varies from one PCT to another, as the map below shows

### Questions for reflection

- d. What is the pattern of alpha-blocker use in my practice/ locality/ PCT? Is it appropriate, safe and cost effective?
- e. What barriers prevent it being more appropriate, safe and cost effective?
- f. How can I go about improving the appropriateness, safety and cost effectiveness of prescribing? Who do I need to work with?

  
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NIC (£) per 1000 PUs		
	269.2 to 317.9	(6)
	220.4 to 269.1	(29)
	171.6 to 220.3	(97)
	122.8 to 171.5	(128)
	73.9 to 122.7	(43)

Spend is a proxy for number of prescriptions, although different formulations of doxazosin are more expensive than others. The number of PUs is a measure of population, taking into account age demographics. For more information on STAR-PUs and other prescribing measures, see the [Prescribing Support Unit website](#)

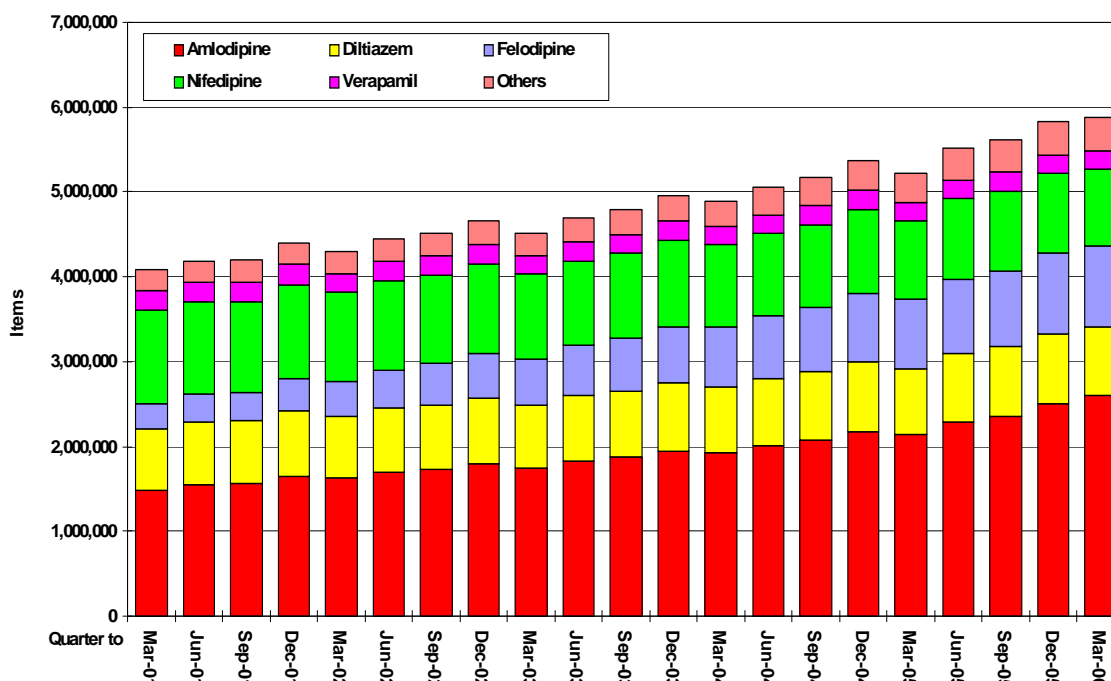
#### 4. Use of calcium-channel blockers

In the landmark ALLHAT study referred to above, primary treatment with the calcium-channel blocker amlodipine was compared with treatment with lisinopril and chlortalidone (and doxazosin) in patients with hypertension and at least one other CHD risk factor<sup>6</sup>. Amlodipine-based treatment **was no more effective** than chlortalidone-based treatment with regard to on the study's primary outcome (CHD death or non-fatal MI). Patients in the amlodipine-based treatment arm were **more** likely to develop heart failure as those in the chlortalidone-based arm (10.2% vs. 7.70%, RR=1.38, 95%CI 1.25 to 1.52, NNH=40 over 6 years). An analysis based on baseline glycaemic status of patients in ALLHAT<sup>7</sup> showed that patients with impaired fasting glucose (IFG) randomised to amlodipine had a 73% higher risk of fatal CHD or non-fatal MI than those taking chlortalidone (RR 1.73, 1.10 to 2.72, P=0.01).

NICE guidance [CG 34, June 2006](#) advises that calcium-channel blockers and diuretics are equal first choice in non-diabetic Black hypertensive people of any age and non-diabetic hypertensive people of other ethnicity aged 55 and older. If there are no other compelling reasons to favour one over the other, a diuretic is preferable because of the lower drug acquisition cost<sup>8</sup>. NICE guidance on management of blood pressure in people with type 2 diabetes, [ICG H, 2002](#), advises that calcium-channel blockers should be reserved for second-line treatment in patients who have not achieved target blood pressure on monotherapy with, for example, a diuretic or an ACEi.

Use of calcium-channel blockers, mainly amlodipine, has increased over the last few years, as the graph shows.

#### Prescriptions (items) for calcium-channel blockers in England (March 2001 to March 2006)



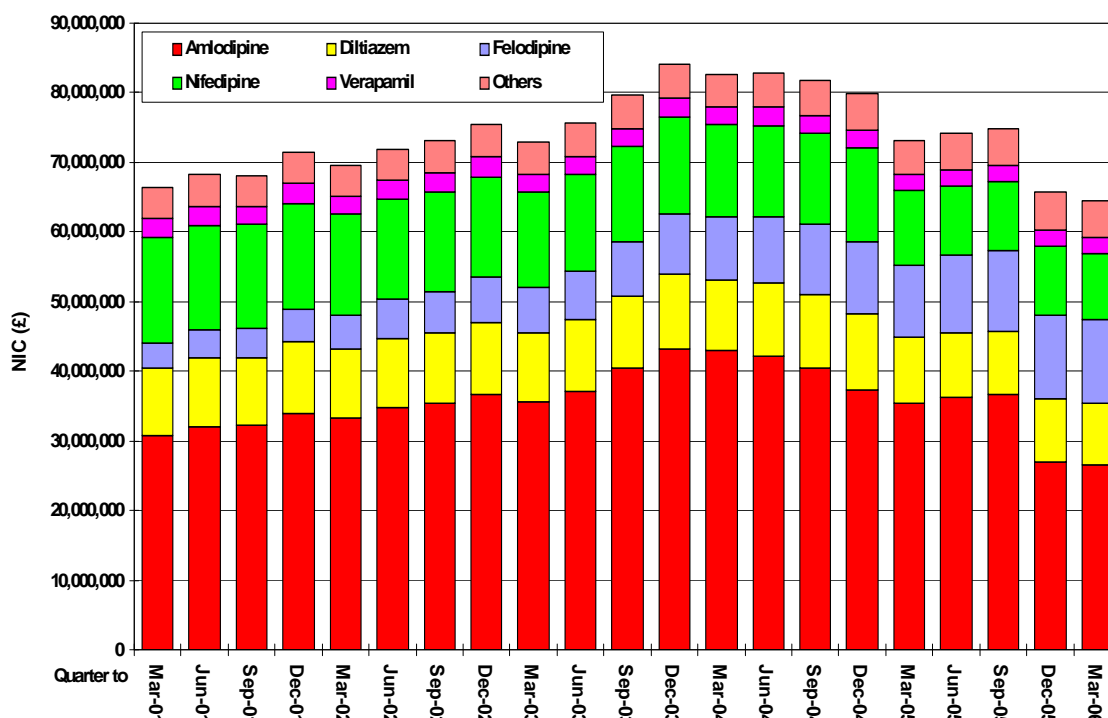
<sup>6</sup> The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. [Major outcomes in high-risk hypertensive patients randomised to ACE inhibitor or calcium channel blocker vs diuretic – The ALLHAT Trial. JAMA 2002; 288: 2981-2997.](#)

<sup>7</sup> Whelton P et al. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration and normoglycaemia (ALLHAT) Arch Intern Med 2005; 165:1401-1409

<sup>8</sup> NPC. MeReC Bulletin 2006; 17 (1). The management of hypertension in primary care – updated guidance from NICE

Since amlodipine has been available as a generic product, and been placed in Category M of the Drug Tariff, costs of calcium channel blockers have fallen (see graph). It is important to note there are substantial price differences between amlodipine besilate (the branded product, Istina<sup>®</sup>) and amlodipine maleate: it is important that prescribers do not inadvertently specify the branded product by prescribing amlodipine besilate.

### Spend on calcium-channel blockers in England (March 2001 to March 2006)



### Questions for reflection

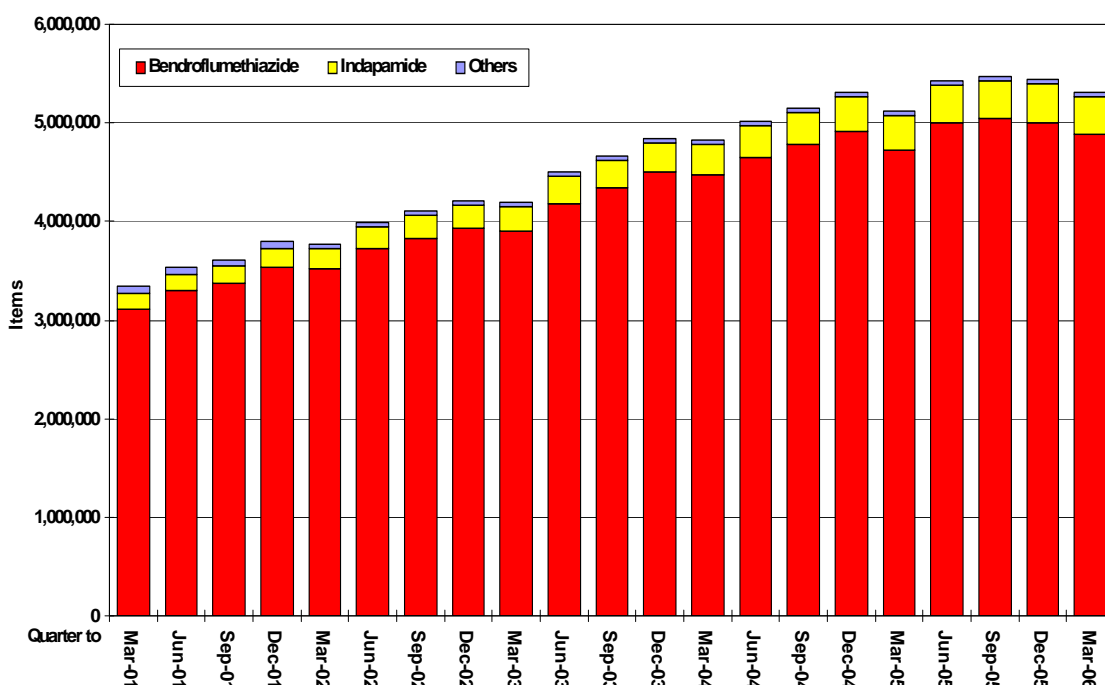
- g. What is the pattern of calcium-channel blocker use in my practice/ locality/ PCT? Is it appropriate and cost effective?
- h. What barriers prevent it being more appropriate and cost effective?
- i. How can I go about improving the appropriateness and cost effectiveness of prescribing? Who do I need to work with?

## 5. Use of diuretics

In the landmark ALLHAT study referred to above, primary treatment with the diuretic chlortalidone was compared with treatment with amlodipine and lisinopril (and doxazosin) in patients with hypertension and at least one other CHD risk factor<sup>9</sup>. Not only was chlortalidone-based treatment just as effective as treatment based on the other drugs, with regard to the study's primary outcome (CHD death or non-fatal MI), chlortalidone-based treatment was unsurpassed with regard to any secondary outcomes (unlike the other drugs, see above) and in any patient subgroup (Black people<sup>10</sup>, people with diabetes<sup>11</sup>, etc). Use of diuretics has increased over the past few years, but so has their cost.

### Prescriptions (items) for diuretics in England (March 2001 to March 2006)

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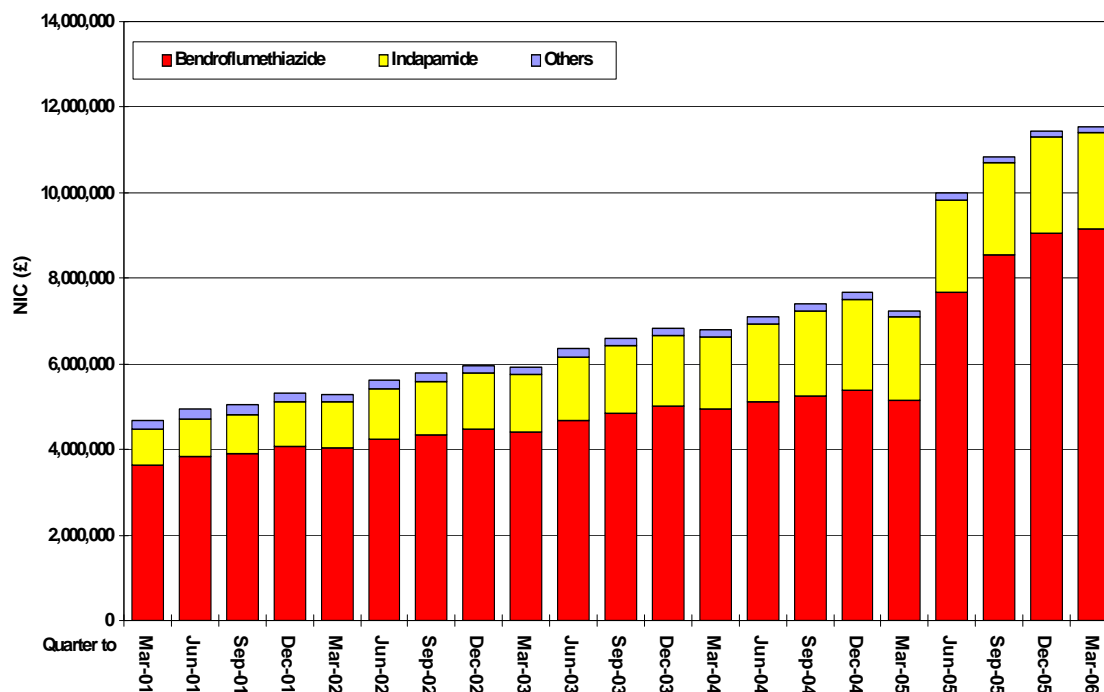


<sup>9</sup> The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. [Major outcomes in high-risk hypertensive patients randomised to ACE inhibitor or calcium channel blocker vs diuretic – The ALLHAT Trial. JAMA 2002; 288: 2981-2997.](#)

<sup>10</sup> Wright TJ, et al. Outcomes in hypertensive black and nonblack patients treated with chlortalidone, amlodipine, and lisinopril. JAMA 2005 ;293:1595-608

<sup>11</sup> Whelton P et al. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration and normoglycaemia (ALLHAT) Arch Intern Med 2005; 165:1401-1409

## Spend on diuretics in England (March 2001 to March 2006)



Indapamide, particularly when the modified release version is used, is more expensive than bendroflumethiazide but there is no reason to suppose it is any more effective.

### Cost of 28 days treatment ([Drug Tariff](#) November 2006)

Bendroflumethiazide 2.5 mg tablets (one daily)	£1.15
Indapamide 2.5 mg tablets (one daily)	£2.47
Inpadamide modified release tablets 1.5 mg (NatriliX SR, one daily)	£4.20

Even with recent price changes due to Category M fluctuations, diuretics are still a highly cost-effective treatment for hypertension. NICE guidance [CG 34, June 2006](#) advises that calcium-channel blockers and diuretics are equal first choice in non-diabetic Black hypertensive people of any age and non-diabetic hypertensive people of other ethnicity aged 55 and older. If there are no other compelling reasons to favour one over the other, prescribers and patients may prefer the diuretic as they are generally well tolerated and significantly less costly than calcium-channel blockers<sup>12</sup>. NICE guidance on management of blood pressure in people with type 2 diabetes, [ICG H, 2002](#), advises that calcium-channel blockers should be reserved for second-line treatment in patients who have not achieved target blood pressure on monotherapy with, for example, a diuretic or an ACEi.

<sup>12</sup> NPC. MeReC Bulletin 2006; 17 (1). The management of hypertension in primary care – updated guidance from NICE

## Questions for reflection

- j. What is the pattern of diuretic use compared to other antihypertensive drugs in my practice/ locality/ PCT? Is it appropriate and cost effective?**
- k. What barriers prevent it being more appropriate and cost effective?**
- l. How can I go about improving the appropriateness and cost effectiveness of prescribing? Who do I need to work with?**