

NEWSLETTER

Supporting the Derbyshire Health Community

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JAPC Update

The Joint Area Prescribing Committee (JAPC) is a countywide group covering Derbyshire County PCT and Derby City PCT. It provides recommendations on drugs and medicines management issues.

RED drugs are those where prescribing responsibility lies with a hospital consultant or a specialist. AMBER drugs are those that are initiated within a hospital/specialist setting but are suitable for shared care with a GP under a shared care agreement. GREEN drugs are regarded as suitable for primary care prescribing. BROWN drugs are those that JAPC does not recommend for use, except in exceptional circumstances, due to lack of data on safety, effectiveness, and/or cost-effectiveness.

The most recent updates are in the table below; the full list is available at

<http://www.derbyshirecountypct.nhs.uk/guidelines/default.asp>

The guidelines, formulary chapters, newsletters, etc can now be found via this link.

Drug	Date considered	Decision
Agomelatine tabs	July 2009	BROWN
n-Acetylcysteine tabs	July 2009	AMBER (with Derby Hospitals)
Beclometasone dip MR tabs	July 2009	RED
Cosopt, Duotrav, Ganfort, Trusopt eye drops	July 2009	GREEN (after consultant initiation)
Frovatriptan tabs	July 2009	GREEN (3 rd line use only)
Levamisole	July 2009	RED
Ondansetron tabs	July 2009	BROWN
Optive eye drops	July 2009	GREEN

Melatonin shared care

A shared care agreement for [melatonin](#) in the treatment of sleep disorders in children and adolescents with visual problems, learning difficulties, cerebral palsy and autistic spectrum disorders has recently been ratified by JAPC. Here is an extract:

- Circadin® 2mg M/R prolonged-release tablets is the only melatonin product licensed in the UK. It is licensed for short-term use in over 55s only. However, the MHRA have stipulated that licensed products should be used wherever possible, even if it means using a product off-label and outside its licensed indications. Hence, Circadin 2mg MR is the preferred option for children.
- If an immediate release form is required, there is at least one licensed product available within the EU. e.g. Bio-Melatonin 3mg. These tablets can be crushed and mixed with water if there are swallowing difficulties. In accordance with MHRA guidance, a letter confirming “special clinical need” will be required with orders.

- Various unlicensed UK Specials and imports, especially from the USA where melatonin is classed as a food supplement and where they may not be made according to good pharmaceutical manufacturing standards, are not recommended.

JAPC has discussed what to do with patients that are currently prescribed unlicensed products. The agreed advice is:

- When the dose of melatonin is equivalent to a dose of Circadin then they should be moved on to the same dose e.g. 6mg of unlicensed melatonin to 3 x 2mg of Circadin.
- For patients not on an equivalent dose, they should be put on the next nearest dose e.g. 2.5mg to 2mg; 3mg to 4mg Circadin.
- Those patients who have difficulty swallowing tablets and who open capsules should not be switched. If in doubt seek advice from the specialist who initiated treatment.

Guidelines update

The following guidelines and shared care agreements have recently been ratified by JAPC:

- Glucose control in type 2 diabetes
- Management of behavioural problems in dementia
- Bicalutamide 50mg/150mg tablets shared care (with Derby Hospitals)
- Colomycin shared care
- Melatonin shared care
- Exenatide shared care

HbA1c now reported in different units

From 1st June 2009, glycated haemoglobin (HbA1c) in all people with diabetes will be measured in millimoles per mol (mmol/mol) as well as by percentage (%). Measurements will be reported in both ways until 31 May 2011 when people with diabetes will receive their HbA1c measurement only in millimoles per mol. Health professionals need to understand this change, so as to be able to reassure patients and become familiar with the new units in anticipation of the switchover in 2011.

There is a linear relationship between HbA1c as a percentage and as millimoles per mol. A 0.5% difference in HbA1c is equivalent to a difference of about 5.5mmol/mol, and a 1% difference is equivalent to a difference of about 11mmol/mol. Note that these are rounded equivalents. The table below gives some common values, taken from the leaflet for laboratory staff.

HbA1c %	HbA1c mmol/mol
4.0	20
5.0	31
6.0	42
6.5	48
7.0	53
7.5	59
8.0	64
9.0	75
10.0	86

Aspirin for primary prevention – ASCEND trial

The Antithrombotic Trialists' Collaboration has recently published a collaborative meta-analysis of individual participant data from randomised trials on aspirin in the primary and secondary prevention of vascular disease¹. They conclude that in primary prevention, aspirin is of uncertain net value as the reduction in occlusive events needs to be weighed against an increase in major bleeds. Over one year the NNT to prevent a non-fatal MI was 2000, whereas the NNH for a major gastrointestinal or extracranial bleed was 3333. Their analysis showed that

risk factors for CHD are also risk factors for bleeding. This new meta-analysis supports the JAPC recommendation not to prescribe aspirin for primary prevention.

The authors point out that most of the patients in the primary prevention trials were not taking a statin, which would have reduced their CV risk. The NNT of 2000 would be even higher in those taking a statin and the absolute benefit of adding aspirin would likely be too small to warrant the increased risk of bleeding. In the discussion section, the authors state 'drug safety (like vaccine safety) is of particular importance in public health recommendations for large, apparently disease-free populations; there should be good evidence that benefits exceed risks by an appropriate margin.'

JAPC does not recommend the use of aspirin for primary prevention in people with (or without) diabetes. There has never been a sufficiently powered study to comprehensively address the question. ASCEND is an ongoing RCT intended to answer the question 'should aspirin be used routinely in people with diabetes but no vascular disease?' It aims to recruit 10,000 people and follow them up for 5 years. A study of this size should have excellent power to detect a 20% proportional reduction in the cardiovascular event rate, should one exist. They are currently recruiting patients for this trial in Derbyshire. JAPC supports this study and asks that GPs do so as well, by agreeing, if asked, for patients who meet the criteria to be recruited.

1. Lancet 2009; 373: 1849-60

Evidence for rosuvastatin?

People with CKD are at a greater risk of CV disease than the general population. However, the pattern of CV disease in such people differs from that in people without CKD, as does their dyslipidaemia. Some observational studies have suggested that statin therapy is associated with improved survival among patients with end-stage renal disease or those undergoing haemodialysis but others have suggested that hypercholesterolaemia is actually protective and associated with greater survival among dialysis patients.

The AURORA study¹ was a multicentre, randomised, double-blind, prospective trial intended to answer this question. 2776 patients, 50 to 80 years of age, with end-stage renal disease and undergoing maintenance haemodialysis, were randomised to rosuvastatin 10mg or placebo daily. The primary endpoint was a composite of CV death, non-fatal MI, or non-fatal stroke. After 3 months, the mean reduction in LDL-cholesterol levels was 43% in those receiving rosuvastatin. After a median follow-up of 3.8 years there was no statistically significant effect on the primary endpoint (HR 0.96 [CI 0.84 to 1.11], p=0.59). Rosuvastatin had no effect on the individual components of the primary endpoint. There was no significant effect on all-cause mortality.

An accompanying² editorial to AURORA suggests that the disappointing results with rosuvastatin in this study add statins to the group of "promising but ineffective" interventions for improving survival and CV outcomes in patients undergoing dialysis. This is despite their beneficial effects on surrogate markers, in this case LDL-cholesterol. The lack of benefit of rosuvastatin in AURORA was observed despite a mean 43% reduction in LDL-cholesterol at three months.

The NPC suggest the following action in their rapid review³:

"Patients with chronic kidney disease are at increased risk of cardiovascular disease. It remains uncertain whether the administration of statins to patients or subgroups of patients with CKD prevents CV events. Prescribers should continue to follow the recommendations in the NICE clinical guideline on chronic kidney disease. This recommends that statins should be offered to all people with CKD for the **secondary prevention** of CV disease, irrespective of baseline lipid levels. However, for the **primary prevention** of CV disease in people with CKD, the use of statin therapy should not differ from its use in people without CKD. Framingham-based risk tables underestimate CV risk in people with CKD and clinical assessment may be necessary as a basis for decision making."

This is the third RCT showing that rosuvastatin had no significant effect on patient-orientated outcomes. The JUPITER study was reported in the January 09 edition of this newsletter. In a population with raised high sensitivity C-reactive protein levels, rosuvastatin 20mg/day provided a very small absolute benefit. For every 1000 people treated for 2 years, 8 people avoided having an MI or a stroke or dying from CV causes, but 6 people developed diabetes who would not have done so otherwise. JAPC concluded that this study should not change practice.

A second report from JUPITER has been published⁴. In this paper, venous thromboembolism was the reported endpoint. Over a median follow-up period of 1.9 years, rosuvastatin 20mg daily reduced the incidence of symptomatic VTE by 43% compared to placebo (0.34% vs 0.67%), hazard ratio 0.57 (CI 0.37 to 0.86), P=0.007. However, because the baseline risk of VTE in the control group was low the number needed to treat was high: 342 people would need to take rosuvastatin 20mg for 1.9 years for one to benefit.

Rosuvastatin did not statistically significantly reduce the incidence of pulmonary embolism: HR 0.77, (CI 0.41 to 1.45), P=0.42, although it did reduce the incidence of deep vein thrombosis: 0.19% vs 0.43%, HR 0.45, (CI 0.25 to 0.79), P=0.004, NNT=424.

The NPC conclude⁵ “This study does not seem to justify the use of statins for prophylaxis of VTE in the general population and insufficient information is presented to evaluate their usefulness in patients at higher risk”.

1. N. Engl J Med 2009; 360:1395-407
2. N. Engl J Med 2009; 360:1455-57
3. www.npci.org.uk/blog/?p=323
4. N. Engl J Med 2009; 360:1851-61
5. www.npci.org.uk/blog/?p=324

Cancer and palliative care

The Regional Drug and Therapeutics Centre up in Newcastle¹ have recently published two useful articles in their Drug Update series – ‘[Opioid analgesia in cancer](#)’ and ‘[Laxative use in palliative care](#)’. Here are extracts.

Opioid analgesia

Oral morphine is still recommended as the first-line strong opioid for use in the control of cancer-associated pain despite the introduction of non-morphine opioid analgesics and novel formulations. There is no consistent evidence to support the use of non-morphine opioid analgesics for first-line opioid therapy. There is only limited evidence for a benefit of switching between opioid drugs in patients experiencing adverse effects, tolerance or inadequate analgesia, although this may be the only practical option in some situations.

Compared with morphine, transdermal (TD) fentanyl is a costly option yet it accounted for over one fifth of primary care prescriptions for strong opioid analgesics in England in the financial year 2007/08. A 2007 systematic review of morphine included three studies that compared morphine MR with TD fentanyl in cancer pain. No differences in efficacy were found although other differences were observed: more patients required rescue medication in the fentanyl group and the fentanyl dose required titration upwards more commonly. Fentanyl did however appear less sedating than morphine both during the day and at night, and patients on fentanyl were significantly less constipated.

Factors to consider when using TD fentanyl:

- It usually takes 36 to 48 hours to achieve steady-state plasma concentrations, during which time other analgesic cover will be required.
- Once a patch has been removed drug elimination occurs slowly with a terminal half life ranging from 22 to 25 hours and significant blood levels persist for at least 24 hours.
- TD fentanyl is therefore inappropriate for unstable pain and dose titration should proceed cautiously.
- Despite a reduced dose frequency of 72 hours vs. a typical 12-hour interval with morphine MR there is no evidence of improved compliance with TD fentanyl in cancer pain.
- Despite an apparent reduction in the incidence of constipation, individual patient responses are highly variable. It is not often possible to avoid morphine entirely, e.g. for breakthrough analgesia.
- Fatalities and life-threatening adverse effects have been reported with incorrect use of TD fentanyl. Patients should be counselled on correct patch application and dose. The passage of fentanyl through skin is affected by temperature and patients should be advised to avoid excessive heat sources.

Pain control is highly subjective and it is essential that treatment is tailored to individual patient needs. Evidence to support switching to an alternative opioid is generally anecdotal or based on observational and uncontrolled studies. However, opioid switching may be the only practicable option for patients who experience inadequate analgesia or intolerable and unmanageable adverse effects. There is insufficient evidence to recommend a specific sequencing of opioids.

Opioid drugs are the mainstay of management of moderate to severe cancer-associated pain. Morphine is the recommended first-line treatment option. Other opioid drugs should only be used for patients who cannot tolerate or fail to achieve adequate analgesia with morphine. TD preparations may be useful for the small number of patients without oral access.

Laxative use

Constipation is a common and often debilitating problem in palliative care and laxative treatment is frequently required. A fully optimised combination of stimulant and softening laxative agents is often the most appropriate option for chronic constipation in palliative care, while macrogols and dantron may be less suitable, and bulk-forming laxatives should be avoided. Regular laxative therapy should always be prescribed for patients receiving strong opioid analgesics. Methylnaltrexone should be restricted to palliative care specialists for exceptional use when maximal conventional laxative therapy is ineffective.

Due to the wide variety of laxatives available and the lack of defined treatment regimens, therapy can be complex, costly and sometimes sub-optimal. Unsuccessful treatment for constipation in palliative care can be due to:

- Failure to fully optimise treatment, or maximally titrate the laxative dose, as required.
- Failure to use a combination of laxatives.
- Failure to allow sufficient time e.g. 72 hours, for some laxatives to become effective.
- Failure to administer laxatives regularly, rather than 'as required'.
- Failure to recognise progression of underlying disease, ileus or faecal obstruction.

Palliative care laxative combinations (doses divided per day according to individual patient response)			
	Starting dose	Maintenance dose	Maximum dose
SENNA (tablets or syrup)	7.5 mg	7.5-15 mg	15-45 mg (>30mg daily)*
OR			
BISACODYL (tablets)	5 mg o.n	5-10 mg b.d (>10mg daily)*	10-15 mg t.d.s*
PLUS			
DOCUSATE (capsules)	100 mg	100-200 mg	200-300 mg
OR			
LACTULOSE	10 ml o.n	10-20 ml b.d (>30 ml daily)*	10-20 ml t.d.s (>30 ml daily)*

*off licence dose

1. www.nyrdtc.nhs.uk

Drug safety update

This can be found at www.mhra.gov.uk/publications/safetyguidance/drugsafetyupdate/index.htm

Here are some key points from the June issue.

Antipsychotics: risk of venous thromboembolic events

Advice for healthcare professionals:

- Antipsychotic use may be associated with an increased risk of VTE
- At present there are insufficient data available to determine any difference in risk between atypical and conventional antipsychotics, or between individual drugs
- All possible risk factors for VTE should be identified before and during antipsychotic treatment and preventive measures undertaken

Chloral hydrate (Welldorm) and Triclofos: not first-line options for insomnia

Advice for healthcare professionals:

- Welldorm and Triclofos are indicated only for the short-term treatment of severe insomnia which is interfering with normal daily life and where other therapies have failed, as an adjunct to non-pharmacological therapies
- The use of hypnotics in children and adolescents is not generally recommended, and if used should be under the supervision of a specialist. Welldorm elixir can be used in children aged 2 years or older as an adjunct to behavioural therapy and sleep-hygiene management, usually for less than 2 weeks.

Topical ketoprofen: reminder on risk of photosensitivity reactions

Topical ketoprofen causes photosensitivity reactions, and users should avoid direct sunlight, ultraviolet rays, and sunbeds or sunlamps. Ketoprofen should be stopped and medical attention sought if skin reactions develop.

Advice for healthcare professionals: Healthcare professionals, particularly pharmacists, are reminded to advise users to:

- Avoid direct sunlight, ultraviolet (UV) rays, sunlamps, and sunbeds while using topical ketoprofen, and to exercise caution for 2 weeks after stopping treatment.
- Stop using ketoprofen gel and see a healthcare professional or go to hospital if they experience a skin reaction to sunlight, sunlamps, or sunbeds.

Hay fever management in pregnant or breastfeeding women

As the hay fever season progresses, questions arise about the management of symptoms in women who are pregnant or breastfeeding. Two useful *Medicines Q&A* documents provide advice^{1,2}.

Pregnancy summary¹

Women with intermittent allergic rhinitis (IAR) during pregnancy can be treated with a number of medicines without increasing the risk of an adverse pregnancy outcome. However, the decision to treat should always be based on a risk versus benefit assessment of each case.

The choice of agent should be based on symptoms, severity, evidence of foetal safety, efficacy as well as patient preference. Rhinitis and especially rhinitis during pregnancy is not always due to allergens and may not respond to standard therapies.

Treatment:

- Avoid/minimise precipitating allergens, if known and if practical.
- Assess risk and benefits – particularly in relation to trimester.
- Intranasal corticosteroids are the treatments of choice during pregnancy especially when nasal congestion predominates.
- If an intranasal corticosteroid does not fully relieve symptoms or is not tolerated consider an oral antihistamine. Loratadine is the antihistamine now recommended for use during pregnancy.
- For mild or intermittent nasal symptoms an oral or topical antihistamine may be used. If considering an oral antihistamine loratadine is now recommended in pregnancy.
- Sodium cromoglycate eye drops and nasal sprays are suitable for use during pregnancy however they require frequent application.
- Oral and systemic decongestants are of limited efficacy in IAR and are not usually recommended.
- Any medication prescribed during pregnancy should be at the lowest effective dose for the shortest time necessary.

Breastfeeding summary²

- Breast feeding mothers with seasonal allergic rhinitis can be treated with a number of pharmacological agents to control symptoms without concern of untoward effects on the nursing infant. However, the decision to treat should always be based on a risk versus benefit evaluation in each individual case. The choice of agent should be based on severity or symptoms, distribution into breast milk, as well as efficacy.
- In general, medications should be avoided by mothers breast feeding premature or low birth weight infants, or in infants who have any underlying medical conditions.

In addition:

- Avoid precipitating allergens, if known.
- Consider whether the mother's hay fever is sufficiently severe to warrant treatment.
- If a medication is prescribed, it should be at lowest effective dose and for the shortest period of time.
- Initially use topical treatment: intranasal corticosteroids and/or sodium cromoglycate eye drops.
- Cetirizine or loratadine are the oral antihistamines recommended for a breast feeding mother.

1. UKMi [Q&A 29.3](#)

2. UKMi [Q&A N26.3](#)

ALLHAT findings revisited

Thiazide diuretics are unsurpassed as initial therapy for reduction of cardiovascular (including stroke) and renal risk, a review of ALLHAT¹ has concluded. ALLHAT, still the largest hypertension study conducted, compared a thiazide diuretic-based regimen with regimens based on an alpha-blocker, an ACE-inhibitor or a calcium channel blocker. The diuretic-based regime was superior at preventing heart failure, and new-onset diabetes associated with thiazides does not increase the risk of cardiovascular outcomes.

In summary, more complete ALLHAT analyses and subsequent trial and meta-analytic data are consistent in confirming initial ALLHAT findings that (despite having more favourable effects on glucose and lipid levels and other surrogate variables) neither the alpha-blocker, ACE inhibitor, nor the CCB surpasses the thiazide-type diuretic as initial therapy for control of BP or reduction of cardiovascular or renal clinical outcomes (when compared at appropriate dosage). Although initial unveiling of ALLHAT findings met with a number of questions and some controversy, further analyses of ALLHAT data and findings from subsequent trials continue to support the original findings. In conclusion, extensive further analyses from ALLHAT and data from other sources underscore the original conclusions from ALLHAT that thiazide-type diuretics remain the preferred first-step therapy in most patients with hypertension.

Thiazides are superior in preventing heart failure, and new-onset diabetes associated with thiazides does not increase CVD outcomes.

1. Arch Intern Med 2009; 169:832-42

Antiepileptic drugs and suicide risk

All antiepileptic medicines have recently been found to be associated with a small risk of suicidal thoughts and behaviour (incidence increased by about 2 additional patients per 1000). The European Medicines Agency (EMA) has recommended that the product information for these agents is updated to warn of this.

Action

Healthcare professionals should continue to follow MHRA advice and NICE guidance on epilepsy. Patients taking antiepileptics (and their carers) should be advised to seek medical advice if they develop any mood changes, distressing thoughts or feelings about suicide or self-harm at any point during treatment. Such patients should be referred for appropriate treatment if necessary and advised against stopping or switching treatment without talking to a healthcare professional first.

Treatments for neuropathic pain

A Canadian Health Technology Assessment report¹, concludes that there is no statistically significant difference in clinical response rates between tricyclic antidepressants, anticonvulsants and serotonin-norepinephrine reuptake inhibitors (SNRIs).

This meta-analysis (28 RCTs) assessed the clinical response rates in adults diagnosed with neuropathic pain who were taking tricyclic antidepressants (e.g. amitriptyline), SNRIs (duloxetine, venlafaxine) or anticonvulsants (gabapentin, pregabalin) compared with placebo.

From indirect comparisons, as the 95% confidence intervals all overlapped, no significant difference was seen between the three drug classes in terms of partial or full response when these were adjusted against placebo rates. A partial response (30% reduction in pain on a visual analogue scale) [adjusted] was seen in 49.7% (95% CI 43.4% to 56.0%) of patients taking an SNRI, 54.4% (95% CI 49.9% to 59.0%) of patients taking an anticonvulsant, and 59.4% (95% CI 42.4% to 76.5%) of patients taking a tricyclic antidepressant. For full response (50% reduction in pain on a visual analogue scale) the adjusted rate was 38.3% (95% CI 33.1% to 43.5%) for SNRIs and 42.3% (95% CI 38.3% to 46.3%) for anticonvulsants. The adjusted and prorated rate for full response with tricyclic antidepressants was 46.0% (95% CI 32.8% to 59.2%).

The dropout rates due to adverse drug reactions were similar between the three drug classes: 12.3% for anticonvulsants, 12.0% for SNRIs and 11.7% for tricyclic antidepressants.

There appears to be no evidence to distinguish between tricyclic antidepressants, anticonvulsants and SNRIs on the basis of safety or effectiveness. Therefore, as with all medicines where this is the case, choice should be

based on both individual patient preference and cost. As they are likely to be the least costly, the meta-analysis suggests that tricyclic antidepressants should be the first-line treatment option in patients whose neuropathic pain is not controlled using simple analgesia. See the JAPC guideline on neuropathic pain management.

1. CADTH Technology Report 116 December 2008.

Treatment of intermittent claudication

Peripheral artery disease of the lower extremities affects more than one in 10 people aged over 55 years. Half of those affected present with leg symptoms that limit physical activity and impair quality of life. The most feared complication is loss of limbs, but only 1-3% of those presenting with intermittent claudication progress to amputation over five years. Myocardial infarction and stroke resulting from progressive atherogenesis in other vascular beds are far more common – 15% to 30% of people presenting with peripheral artery disease die within five years, mainly from cardiovascular causes¹.

A meta-analysis based on individual patient data has assessed the effectiveness of naftidrofuryl compared with placebo in treating the symptoms of intermittent claudication². In the analysis of responders, therapeutic success was defined as an improvement of walking distance at baseline by at least 50%.

The ratio of relative improvement in pain-free walking distance after use of naftidrofuryl compared with placebo was 1.37 (95% confidence interval 1.27 to 1.49). The difference in response rate was 22.3% (95% confidence interval 17.1% to 27.6%) and the number needed to treat for relief of symptoms during six months of treatment was 4.48 (95% confidence interval 3.62 to 5.85). The authors concluded that naftidrofuryl has a clinically meaningful effect compared with placebo in improving walking distance in patients with intermittent claudication.

The linked editorial¹ points out that most of the trials included in the meta-analysis were performed in the 1980s and early 1990s, before the widespread use of antiplatelet agents and statins, which can both prevent cardiovascular events and improve walking distance. It is unclear whether naftidrofuryl provides incremental benefit in patients with peripheral artery disease receiving antiplatelet treatment, a statin, blood pressure lowering treatment, and an angiotensin converting enzyme inhibitor. Naftidrofuryl was evaluated for a mean of only 6.3 months in the trials included in the meta-analysis, and it is unclear whether the benefits are sustained in the long term.

The authors of the editorial state that first line medical treatment of peripheral artery disease should consist of interventions that effectively relieve symptoms and reduce CV risk (table).

Effect of behaviour modification and medical treatments for peripheral artery disease on cardiovascular risk reduction and claudication symptoms

Drug or intervention	Cardiovascular risk reduction	Improvement in claudication
Smoking cessation	Yes	Yes
Exercise	Yes	Yes
Antiplatelet treatment (such as aspirin, clopidogrel)	Yes	Yes
Statins	Yes	Yes
Blood pressure reduction	Yes	Yes
Angiotensin converting enzyme inhibitors	Yes	Possibly
Cilostazol	No	Yes

“Patients should be encouraged to “stop smoking and keep walking,” and drugs should include aspirin (or clopidogrel), a statin, a blood pressure lowering agent, and angiotensin converting enzyme inhibitor. Unfortunately these drugs are underused in patients with peripheral artery disease. Vasodilators such as naftidrofuryl or cilostazol might be considered in patients who have claudication symptoms that are refractory to conventional treatment. However, their role will probably remain uncertain until it is shown in RCTs that they provide incremental benefit in patients receiving currently established treatments that reduce systemic complications and leg symptoms”¹.

1. BMJ 2009; 338:671-2

2. BMJ 2009; 338:6603