

PRESCRIBING and CLINICAL EFFECTIVENESS NEWSLETTER



Supporting the
Derbyshire Health Community

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Happy New Year to all our readers

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JAPC Update

The Joint Area Prescribing Committee (JAPC) is a countywide group covering Derbyshire County PCT and NHS Derby. 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.derbyshiremedicinesmanagement.nhs.uk/home>

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

Drug	Date considered	Decision
Azarga eye drops (brinzolamide + timolol)	January 2010	GREEN (after consultant initiation)
Cabergoline (for hyperprolactinaemia)	January 2010	AMBER
Quinagolide (for hyperprolactinaemia)	January 2010	AMBER
Prasugrel	December 2009	GREEN (after consultant initiation)
Fentanyl nasal spray / tablet / lozenge	November 2009	BROWN
Saxagliptin	November 2009	BROWN
Mercaptamine	November 2009	RED
Voriconazole	November 2009	RED
Ulipristal acetate (ellaOne)	November 2009	GREEN (between 72 and 120 hours)

New Joint Derbyshire Medicines Management Website Launched

The Medicines Management Teams from NHS Derby and Derbyshire County PCT are pleased to announce the launch of this new collaborative NHS website. It is aimed at primary care NHS workers but is also available to other NHS sectors and the public. It can be found at www.derbyshiremedicinesmanagement.nhs.uk and there are links from the respective PCT main websites and from the Pulse intranet homepage.

This new website is the first port of call for information on local NHS decisions and guidance on medicines use. It includes: local prescribing formularies, JAPC decisions, traffic lights, shared care guidelines, medicines guidelines, newsletters, controlled drug resources, and other medicines management resources.

The new site improves upon previous sites in several ways. It is faster, more reliable, has its own search engine, and it is easier to find information. Content is constantly being updated and you can sign up for e-mail alerts to keep you up to date.

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Medicines Management are very keen to know what you think of the site and how it can be further refined for the benefit of all. Please use the [contact us](#) page on the website.

Beta-blockers in heart failure

There is now consistent evidence that (some) beta-blockers significantly improve mortality and reduce hospitalisation in patients with all grades of heart failure. Guidelines recommend the use of ACE inhibitors and beta-blockers as first- and second-line drugs for heart failure, unless they are contraindicated or not tolerated. Beta-blocker treatment should be started at a low dose and gradually increased to the target dose used in the trials or the highest tolerated dose. Studies have shown that many patients do not achieve target doses outside of specialist heart failure clinics. A meta-analysis has investigated whether the survival benefits of beta-blockers in heart failure are associated with the magnitude of heart rate reduction or the dose of beta-blocker¹.

Placebo-controlled RCTs of beta-blockers in patients with heart failure that reported mortality were eligible for inclusion. A total of 23 trials (n=19,209) were included in the review. The mean left ventricular ejection fraction ranged from 0.17 to 0.36, and more than 95% had systolic dysfunction. Most patients had NYHA class III or IV symptoms at baseline. Included studies assessed metoprolol, carvedilol, bisoprolol, bucindolol, nebivolol and atenolol. The great majority of patients (median 93%) received an ACE inhibitor and most also received digoxin (median 75%).

There was statistically significantly lower mortality in the groups treated with beta-blockers than in the control groups (RR 0.76, 95% CI: 0.68 to 0.84). The magnitude of the survival benefit was significantly affected by the choice of beta-blocker. Metoprolol, carvedilol and bisoprolol showed statistically significantly reduced death rates compared to placebo, but the comparisons were statistically non-significant for bucindolol, nebivolol and atenolol.

There was a statistically significant relationship between heart rate reduction and beta-blocker survival benefit. Meta-regression showed that for every 5 beats/minute reduction in heart rate with beta-blocker treatment the relative risk for death was reduced by 18% (95% CI: 6% to 29%). There was no statistically significant effect of beta-blocker dosing on mortality.

The authors acknowledge that because no heart failure trials have randomly assigned participants who receive beta-blockers to different target heart rates, the optimal heart rate (and thus target heart rate reduction) is unknown. The NPC² offers this advice: "Beta-blocker treatment should be introduced in a 'start low, go slow' manner, i.e. started at a low dose and titrated up to the target or highest tolerated dose. If heart rate has been reduced, patients can be reassured that beta-blocker treatment is beneficial for survival, even if the target dose has not been reached. However, in order to assess treatment efficacy in this way, clinicians will need to record baseline heart rate".

1. Ann Intern Med 2009; 150:784-94
2. www.npci.org.uk/blog/?p=619

ACEIs or ARBs in IHD

There is evidence of benefit for both ACE inhibitors and angiotension-2-receptor blockers (ARBs) for patients with heart failure and those who have had a myocardial infarction with ventricular dysfunction. It is less clear, however, whether there are benefits in patients with ischaemic heart disease (IHD) and preserved ventricular function.

A recent systematic review suggests that adding an ACE inhibitor to standard medical therapy improves outcomes in some of these patients but the evidence on ARBs is limited and combination of ACEI and ARB provides no additional benefits but does increase harms¹. The authors of this systematic review, carried out on behalf of the US Agency for Healthcare Research and Quality, defined three pre-specified questions:

1. In patients with stable ischaemic heart disease who have preserved ventricular function, what are the benefits and harms of adding ACE inhibitor or ARB to standard medical therapy compared with standard medical therapy alone?
2. In patients with stable ischaemic heart disease who have preserved ventricular function and are receiving standard medical therapy, what are the benefits and harms of combining ACE inhibitor and ARB compared with either an ACE inhibitor or an ARB alone?

3. What is the evidence that benefits or harms differ in pre-specified subpopulations?

Eight RCTs fulfilled the inclusion criteria for evidence of benefit, seven involving ACE-inhibitors and one involving an ARB (telmisartan) in patients with a history of ACE-inhibitor intolerance. Trial participants were more likely to be male (57% - 89%) and had mean ages between 57 to 67.

Seven trials reported total mortality: on pooled analysis, ACE-inhibitors reduced total mortality by about 13% (RR, 0.87; 95% CI: 0.81 to 0.94) compared to placebo. The single trial comparing an ARB to placebo found no significant difference in mortality between drug and placebo (RR, 1.05; 95% CI: 0.91 to 1.20). Compared to placebo, ACE-inhibitors were shown to reduce cardiovascular mortality (RR, 0.83; 95% CI: 0.70 to 0.98) and non-fatal MI (RR, 0.83; 95% CI: 0.73 to 0.94) in six trials; the single trial involving an ARB did not show an effect on cardiovascular mortality or non-fatal MI.

Analysis of harms found that patients were more likely to stop taking ACE-inhibitors due to adverse events than placebo (3 trials; RR, 2.30; 95% CI: 1.34 to 3.95), however actual reported withdrawal rates varied widely between 2-fold and 10-fold.

One trial reported the combination of ACE-inhibitor plus ARB with either drug alone. In this study, there was no significant difference in benefits between the combination and ACE-inhibitor alone, however combination therapy was associated with more harms (more discontinuations, and more discontinuations due to hypotension or syncope). This study also compared ARB alone with ACE-inhibitor alone; there were no significant differences in benefits, however ARB therapy was associated with fewer discontinuations for hypotension and cough.

Overall, the authors conclude that moderate to high-strength evidence indicates that in adults with stable IHD and preserved ventricular function, ACE inhibitors reduce relative risk for total mortality, cardiovascular mortality, nonfatal MI, and stroke. The benefits of ARB cannot be assessed because only one high-quality eligible trial was identified and this included only patients intolerant of ACE-inhibitors. Moderate-strength evidence in one trial suggested that combination treatment in this patient group did not increase benefits but was associated with greater harms.

They note that the review has limitations: it was not possible to assess the possibility of publication bias for some outcomes, and the evidence has reduced generalisability due to the predominance of men and limited age range in the trials. Reporting on harms was incomplete and inconsistent. Overall, they consider that adding ACE-inhibitor treatment to existing therapy has benefits in the patient population studied, but more trials are needed to assess the place of ARB.

The NPC² concludes that this systematic review adds to the weight of evidence supporting the use of ACE inhibitors in addition to standard medical treatments in patients with stable ischaemic heart disease and preserved ventricular function. Most patients in the included trials were already receiving aspirin and statins, and about half were being treated with beta-blockers.

The NPC recommends that **ACE inhibitors are the evidence-based first-line choice over ARBs in all situations where a renin-angiotensin system drug is indicated**. ARBs should be reserved for the small number of patients in whom an ACEI has to be discontinued because of cough. Combination therapy with ARB plus an ACEI would appear to have a very limited role. It may be a specialist option in patients with heart failure who are still symptomatic despite optimised ACEI and beta-blocker therapy. However, this requires very careful monitoring for adverse effects, including worsening renal function².

1. Ann Intern Med, published online October 19 2009

2. www.npci.org.uk/blog/?p=799

Prasugrel

In May 2009, JAPC reviewed the evidence for the new antiplatelet agent prasugrel. JAPC classified prasugrel as a BROWN drug as it is less cost-effective than current standard therapy (clopidogrel) and potentially not a priority for investment. In June 2009, the Midlands Therapeutics Review and Advisory Committee (MTRAC) published their review of prasugrel and gave it a Q4 rating – lower place, weaker evidence¹.

MTRAC stated “The evidence for the efficacy of prasugrel, based on one double-blind RCT comparing it with clopidogrel for the treatment of acute coronary syndrome managed with percutaneous coronary intervention, was considered to be relatively weak. Significantly fewer patients in the prasugrel group experienced the primary endpoint (a composite of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke) compared with those in the clopidogrel group. However, the loading dose of clopidogrel used in the study was lower than the dose commonly used in clinical practice in the UK. Concerns about the safety of prasugrel give it a low place in therapy. Although patients considered to have an increased risk of bleeding were excluded from the study, more bleeding events (including life-threatening bleeding) occurred with prasugrel than with clopidogrel in the overall cohort of patients.” The difference in the primary outcome was mainly due to a significantly lower incidence of non-fatal MI.

MTRAC recommends “Prasugrel may be suitable for a limited number of patients (e.g. patients who require immediate percutaneous coronary intervention or patients who have experienced stent thrombosis despite previous clopidogrel treatment). However, for each individual, the potential benefits of prasugrel must be carefully balanced against the risk of bleeding. Prasugrel is not recommended for patients over the age of 75 years or patients weighing less than 60kg because these patients have a high risk of bleeding. It is contraindicated in patients with a history of stroke or transient ischaemic attack.”

An Australian review² of prasugrel puts some numbers on the risk/benefit ratio compared with clopidogrel:

Outcome	Difference with prasugrel over clopidogrel
Primary endpoint	22 fewer events per 1000 people
Major bleeding (non-CABG)	6 more events per 1000 people
Non-fatal life-threatening bleeding	2 more events per 1000 people
Fatal bleeding	3 more events per 1000 people

This review points out that the benefit-harm profile may change over time – “The effect of prasugrel in preventing the first atherothrombotic event was greatest in the 30 days after the acute coronary syndrome compared with clopidogrel. The difference in bleeding incidence between treatments continued to diverge after this time.”

NICE has now issued a technology appraisal guidance (No. 182, October 2009) on the use of prasugrel. It says “Prasugrel in combination with aspirin is recommended as an option for preventing atherothrombotic events in people with acute coronary syndromes having percutaneous coronary intervention, only when:

- immediate primary percutaneous coronary intervention for ST-segment-elevation myocardial infarction is necessary **or**
- stent thrombosis has occurred during clopidogrel treatment **or**
- the patient has diabetes mellitus.”

This is despite some comments in the main document³ “because of the difficulty in relating the results of the TRITON-TIMI 38 trial to clinical practice in England and Wales it was therefore difficult to determine the relative effectiveness of prasugrel compared with clopidogrel” and “the Committee agreed that there was considerable uncertainty about whether prasugrel was clinically superior to clopidogrel in terms of the net clinical benefit for the licensed or the target population as proposed in the manufacturer’s submission”.

NICE TAGs are mandatory on PCTs (other forms of NICE guidance are not) and for now JAPC has changed the traffic light classification to GREEN (after consultant initiation). Eligible patients will be discharged with a supply of prasugrel and GPs may be asked to prescribe the rest of the course. Prasugrel is a black-triangled drug and in light of the evidence base you might want to consider if it is the best option for your patient.

Taking into account the fine balance of benefit and harms with this treatment, JAPC are liaising with the East Midlands Cardiac Network to clarify if patients have the option of switching to clopidogrel following the first month of prasugrel as a matter of routine.

1. [MTRAC review of prasugrel](#), June 2009
2. [NPS RADAR review of prasugrel](#), December 2009
3. [NICE TAG 182](#), October 2009

Opioids for osteoarthritis

A Cochrane review to determine the effects on pain and function and the safety of oral or transdermal opioids as compared with placebo or no intervention in patients with OA of the hip or knee has been published¹. Studies of tramadol were excluded. Ten trials with 2268 participants were included in the review. Oral codeine was studied in three trials, transdermal fentanyl and oral morphine in one trial each, oral oxycodone in four, and oral oxymorphone in two trials.

Overall, opioids were more effective than control interventions in terms of pain relief (SMD -0.36, 95% CI: -0.47 to -0.26) and improvement of function (SMD -0.33, 95% CI: -0.45 to -0.21). They did not find substantial differences in effects according to type of opioid, analgesic potency (strong or weak), daily dose, duration of treatment or follow up, methodological quality of trials, and type of funding. Adverse events were more frequent in patients receiving opioids compared to control. The pooled risk ratio was 1.55 (95% CI: 1.41 to 1.70) for any adverse event (4 trials), 4.05 (95% CI: 3.06 to 5.38) for dropouts due to adverse events (10 trials), and 3.35 (95% CI: 0.83 to 13.56) for serious adverse events (2 trials). Withdrawal symptoms were more severe after fentanyl treatment compared to placebo (SMD 0.60, 95% CI: 0.42 to 0.79; 1 trial).

Authors' conclusions

The small to moderate beneficial effects of non-tramadol opioids are outweighed by large increases in the risk of adverse events. Non-tramadol opioids should therefore not be routinely used, even if osteoarthritic pain is severe.

From the plain language summary:

Best estimate of what happens to people with osteoarthritis who take opioids

Pain

- People who took opioids rated improvement in their pain to be about 3 on a scale of 0 (no pain) to 10 (extreme pain) after 1 month.
- People who took a placebo rated improvement in their pain to be about 2 on a scale of 0 (no pain) to 10 (extreme pain) after 1 month.

Another way of saying this is:

- 35 people out of 100 who use opioids respond to treatment (35%).
- 31 people out of 100 who use placebo respond to treatment (31%).
- 4 more people respond to treatment with opioids than with placebo (difference of 4%).

Physical Function

- People who took opioids rated improvement in their physical function to be about 2 on a scale of 0 (no disability) to 10 (extreme disability) after 1 month.
- People who took a placebo rated improvement in their physical function to be about 1 on a scale of 0 (no disability) to 10 (extreme disability) after 1 month.

Another way of saying this is:

- 29 people out of 100 who use opioids respond to treatment (29%).
- 26 people out of 100 who use placebo respond to treatment (26%).
- 3 more people respond to treatment with opioids than with placebo (difference of 3%).

Side effects

- 23 people out of 100 who used opioids experienced side effects (23%).
- 15 people out of 100 who used a placebo experienced side effects (15%).
- 7 more people experienced side effects with opioids than with placebo (difference of 7%).

This gives an NNT for pain of 25, NNT for physical function of 33, and an NNH for side effects of 14.

This review excluded tramadol but there is a separate review of tramadol in OA².

From the plain language summary:

What are the results of this review?

People in the studies took 200 mg of tramadol per day or a placebo (fake tablets or powder) or an NSAID or a different pain reliever. People took the drugs for up to one week to three months.

Benefits of tramadol

In people with osteoarthritis:

tramadol may decrease pain more than a placebo

- pain may decrease by 8.5 more points on a scale of 0 to 100 with tramadol

tramadol may improve overall well-being more than placebo

- 50 out of 100 people may improve when taking a placebo
- 69 out of 100 people may improve when taking tramadol

tramadol may slightly decrease stiffness and slightly improve function more than placebo

- function may improve by 0.32 more points on a scale of 0 to 10 with tramadol

It is not known whether tramadol improves symptoms of osteoarthritis more than other drugs. It is also not known whether tramadol still works well after long use. This is because the follow-up of the studies was short.

Harms of tramadol

In people with osteoarthritis:

tramadol may cause minor side effects in more people than placebo, such as nausea, vomiting, dizziness, constipation, tiredness, and headache

- 18 out of 100 people may have minor side effects when taking a placebo
- 39 out of 100 people may have minor side effects when taking tramadol

tramadol may cause major side effects that would make people stop taking it

- 8 out of 100 people had major side effects when taking a placebo
- 21 out of 100 people had major side effects when taking tramadol

It is not known whether tramadol causes more side effects than other drugs for osteoarthritis.

The NNT for moderate improvement is 6. The NNH for minor side effects is 5 and for major side effects it is 8. See the JAPC guidance on [pharmacological management of osteoarthritis](#).

1. *Cochrane Database of Systematic Reviews*, Issue 4, 2009.
2. *Cochrane Database of Systematic Reviews*, Issue 3, 2006

Fifty years of thiazide diuretics

Two extensive reviews of thiazide diuretics for hypertension have recently been published^{1,2}. “Few pharmacological discoveries have advanced the treatment of any disease in such a profound and enduring manner” concludes one². The role of thiazides in lowering blood pressure was discovered in the late 1950s and serendipity played a big part. The precise mechanism of long-term action of thiazides remains unknown, except that a natriuretic effect initiates the process¹.

Key points from the evidence base:

- Thiazides reduce blood pressure when administered as monotherapy, enhance the efficacy of other antihypertensive agents, and reduce hypertension-related morbidity and mortality.
- On average, after adjustments for reductions seen with the use of placebo, thiazides induce a reduction in the systolic and diastolic blood pressures of 10 to 15 mmHg and 5 to 10 mmHg, respectively.
- Compared with placebo, thiazide-based therapy reduces relative rates of heart failure (by 41 - 49%), stroke (by 29-38%), CHD (by 14 - 21%), and death from any cause (by 10 - 11%), with results consistent across age and sex strata.
- Low doses are usually well tolerated and have been shown to improve quality-of-life measures.
- While the possible metabolic effects of diuretics, especially hypokalaemia and hyperglycaemia, have been repeatedly emphasised in the literature, they appear to have been overemphasised and do not obviate the benefit of thiazide use.
- To date, no analyses of ALLHAT data have indicated that the development of diabetes obviates the benefit of the thiazide. Similar findings have been reported in a large meta-analysis and in long-term follow-up data of the SHEP cohort.

“In conclusion, thiazide diuretics have stood the test of time for more than 50 years in the management of hypertension. Their use as monotherapy or in combination with other antihypertensive agents has resulted in dramatic decreases not only in cerebrovascular but also in CV events. Comparative data with other antihypertensive medications with different mechanisms of action indicate that diuretics are as, and in some instances more, effective in event reduction than other antihypertensive drugs.”¹

The JAPC algorithm for choosing drugs to lower blood pressure is included on page 8.

1. Arch Intern Med 2009; 169:1851-56
2. N Engl J Med 2009; 361:2153-64

Use of NICE appraised medicines

A report from the NHS Information Centre assessed the variation in the use of 26 medicines positively approved by NICE in 13 technology appraisals. In 7 of the 12 appraisals where a comparison could be made, observed use was higher than expected by NICE. In 5 cases use was lower than predicted, but in 2 of these cases safety warnings, issued since the publication of the guidance, had resulted in drug withdrawal or restricted use.¹

The appraisals where observed use **exceeded** the predicted use in 2008 were:

- Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease
- Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia
- Entecavir for the treatment of chronic hepatitis B
- Zaleplon, zolpidem and zopiclone for the short-term management of insomnia
- Varenicline for smoking cessation
- Hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer
- Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women, plus alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women

Many of these drugs are prescribed in primary care. Opportunity cost is harm to those patients whose care is then displaced.

1. www.npci.org.uk/blog/?p=609

Drug Safety Update

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

These are some key points from the December issue.

Ciclosporin: must be prescribed and dispensed by brand name

Patients should be stabilised on a single brand of ciclosporin because switching between formulations without close monitoring may lead to clinically important changes in bioavailability. All products that contain ciclosporin are interchangeable only if careful therapeutic monitoring takes place. Prescribing and dispensing of ciclosporin should be by brand name to avoid inadvertent switching.

Finasteride: potential risk of male breast cancer

Cases of male breast cancer have been reported for finasteride. Patients should be advised to promptly report to their doctor any changes in their breast tissue such as lumps, pain, or nipple discharge

Warfarin: product information to be amended to give clearer, up-to-date advice

The Summaries of Product Characteristics (SPCs) for all warfarin products are to be amended to give clearer and up-to-date advice to healthcare professionals. This update will also result in improved patient leaflets to ensure patients have consistent and appropriate information on this important medicine.

In particular, the core SPC provides advice on:

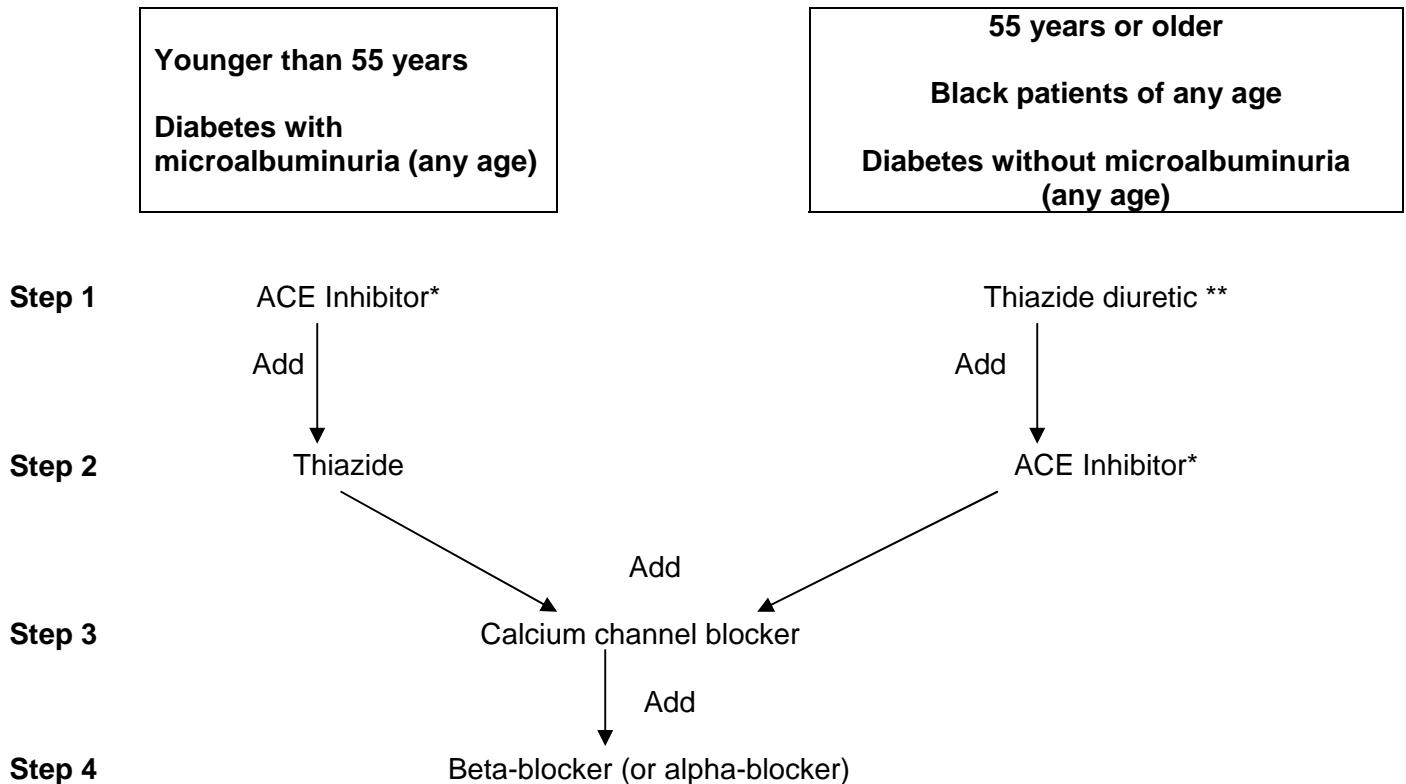
- Timing of warfarin treatment after ischaemic stroke
- Management of the patient before surgical or dental procedures
- Patients at particular risk of haemorrhage
- Interactions with herbal products, foods, and food supplements
- Management of patients with significantly raised INR and/or haemorrhage

In particular, healthcare professionals should ensure that they understand the contraindications to warfarin therapy, the relevant warnings, and the clinically significant drug interactions. Serious and unexpected adverse effects relating to warfarin should continue be reported via the Yellow Card Scheme (www.yellowcard.gov.uk).

Hypertension algorithm

Choosing drugs to lower blood pressure and reduce cardiovascular risk

Thiazides remain first-line in most people needing treatment for raised blood pressure



* use angiotensin-II antagonist if ACEI intolerant (as the evidence for using an ACEI first-line in those aged <55 years is not strong, a thiazide could be considered in this group of patients before changing to an A-II antagonist) ACEIs and A-II antagonists are contraindicated in pregnancy and should be avoided in women of childbearing potential (or ensure effective contraception)

** use calcium channel blocker if thiazide contraindicated or not tolerated (except in diabetes – straight to step 2 if cannot use thiazide)

Beta-blockers

- are no longer preferred as a routine initial therapy for hypertension
- may be appropriate for those who have another indication for beta-blocker therapy – angina, previous MI, heart failure
- should be considered for some younger people, particularly:
 - women of childbearing potential
 - patients with evidence of increased sympathetic drive
 - patients with intolerance of or contraindications to ACE inhibitors and angiotensin-II antagonists

Target clinic BP

The aim is to reduce blood pressure to target, adding drugs as needed, *until further treatment is inappropriate or declined.*

No diabetes – 140/90 mmHg or less

With diabetes – less than 140/80 mmHg

Diabetes with microalbuminuria/proteinuria (ACE inhibitor first-line [or A-II antagonist if not tolerated])

- 135/75 mmHg or less