

NEWSLETTER

Supporting the North Derbyshire Health Community

Volume 5: Issue 5

August 2006

Further in this issue	Page 2	Recommendations for the safe use of LABAs Clenil Modulite
	Page 3	Rimonabant Restless legs syndrome
	Page 4	Induction of ovulation in women with PCOS The ACTIVE W trial
	Page 6	Absorption from iodine dressings HRT and urinary incontinence Black Cohosh and liver injury Research and audit newsletter Guidelines update
	Page 7	Measuring Blood Pressure – Top 10 Tips
	Page 8	Choosing drugs to lower blood pressure

PACEF update

The current Traffic Lights list can be accessed via your PCT website (www.chesterfieldpct.nhs.uk, www.highpeakanddalespct.nhs.uk, or www.northeasternderbyshirepct.nhs.uk) or the PACEF intranet site www.nodyis.nhs.uk/guidelines/pacef%20web.htm.

RED drugs are those where prescribing responsibility would normally lie with a hospital consultant or a specialist. AMBER drugs are those that although usually initiated within a hospital setting, could appropriately become the responsibility of the GP. This would normally be under a shared care agreement. GREEN drugs are regarded as routine for primary care prescribing. BROWN drugs are those that PACEF does not recommend for use (or only in restricted circumstances) due to lack of data on safety, effectiveness, or cost-effectiveness.

<u>Drug</u>	<u>Date considered</u>	<u>Decision</u>
Clenil Modulite (beclometasone cfc-free MDI)	August 2006	GREEN Prescribe by brand name
Celluvisc eye drops	August 2006	GREEN
Natalizumab	August 2006	RED
Rimonabant	August 2006	BROWN
Desloratidine	July 2006	BROWN
Levocetirizine	July 2006	BROWN
Pegaptanib injection	July 2006	RED
Rotigotine patch	July 2006	BROWN
Zaleplon	July 2006	BROWN
Zolpidem	July 2006	BROWN
Zopiclone	July 2006	BROWN
Formoterol cfc-free MDI (Atimos Modulite)	June 2006	GREEN
Letrozole	June 2006	AMBER
Acamprosate	April 2006	AMBER (moved from RED)
Ivabradine	April 2006	BROWN
Nebivolol	April 2006	BROWN
Revatio (sildenafil 20mg tablet for PAH)	April 2006	RED
Inhaled insulin (Exubera)	April 2006	RED

Recommendations for the safe use of LABAs

Following on from last month's article on the effect of long-acting beta-agonists on asthma exacerbations and asthma-related deaths, I am repeating the recommendations endorsed by PACEF for the safe use of these drugs. Informal discussions with primary care clinicians has revealed that the British Asthma Guideline may not be fully understood and that the recommendations in the North Derbyshire Asthma Guideline are not being followed. For instance, 400mcg/day beclometasone equivalent for adults at step 2 is not the automatic trigger for moving to step 3 and adding a LABA. Step down when at step 3, is not to reduce the inhaled steroid dose but to step back to step 2, i.e. maintain the ICS dose and stop the LABA.

Recommendations

- It is important to follow current guidelines and emphasise the use of ICS as the first-line treatment for patients with mild to moderate asthma symptoms. LABAs should not be used as initial therapy for any asthmatic patient.
- Make sure individuals are receiving an adequate dose of ICS. Escalate the dose of ICS to the levels recommended in the British Asthma Guideline (800mcg/day beclometasone equivalent in adults and 400mcg/day in children aged 12 and under) before considering a LABA. Do not jump to step 3 too early (this might be encouraged by the use of combination inhalers). If satisfactory control is not obtained at these doses then a LABA should be added.
- Do not move to step 3 without assessing inhaler technique and compliance. Encourage the use of spacer devices. Data show that in patients with more severe disease who still require two or more daily administrations of salbutamol in addition to adequate doses of ICS, symptoms in one third to one half may be explained by non-adherence to therapy or the coexistence of other conditions that are not responsive to beta-agonists¹.
- If at step 3, review regularly as recommended by the British Asthma Guideline, and consider stepping down back to step 2.
- It is important to carefully monitor patients on LABAs to identify those who do not respond or whose condition deteriorates in response to LABA therapy. Health professionals should be prepared to provide an alternative medication for patients in whom LABA therapy fails².
- Remember that the step 3 recommendation for children aged under 5 in the British Asthma Guideline is not a LABA.

A paper entitled 'Asthma control in adults' notes that good control of asthma is desirable for short-term gains and probably for longer term outcomes but the approach to control needs to take account of patients' own aims and expectations for their asthma³. "It is not appropriate to define a fixed level of lung function or symptom control which must be achieved, as individual patients will have different goals and may also wish to balance these aims against the potential side-effects or inconvenience of taking the medication necessary to achieve perfect control"³.

If you would like help in organising an audit of LABA use, please contact your PCT prescribing adviser. If you would like a therapeutic workshop on the management of asthma (and/or COPD) held at your practice, then contact me.

1. N Engl J Med 2005; 353: 2637-9

2. Ann Intern Med 2006; 144: 936-7

3. BMJ 2006;332: 767-71

Clenil Modulite

A second CFC-free beclometasone pMDI has now been launched, with the proprietary name of Clenil Modulite. Because dissolving beclometasone in HFA results in ultrafine particles with better lung penetration, the first CFC-free beclometasone pMDI, Qvar, is twice as potent as CFC-containing beclometasone and is used at half the dose.

The beclometasone in Clenil Modulite is also dissolved in HFA but glycerol has then been added in order to manipulate the particle size back to that found in CFC-containing pMDIs. This means that Clenil Modulite achieves dose-for-dose equivalence with CFC-containing pMDIs. This results in a very practical problem. As two CFC-free products are now available that are not dose equivalent, a prescription for CFC-free beclometasone pMDI will at least cause confusion and possibly loss of asthma control or overdosing if the incorrect inhaler is supplied. This was discussed at PACEF and the conclusion reached that the only safe way to prescribe CFC-free beclometasone is by brand. If patients are already on Qvar please make sure the computer is set to prescribe Qvar and not generic. If starting new patients or switching existing patients please prescribe as Qvar (at half the dose) or Clenil Modulite (at the same dose equivalent).

Clenil Modulite is licensed for the prophylactic management of mild, moderate or severe asthma in adults or children. The licensed dose is 200-400mcg/day in children, and 400-2000mcg/day in adults, to be given in 2 to 4 divided doses per day. The SPC states that the Volumatic spacer device must always be used when Clenil Modulite is administered to adults and adolescents 16 years of age and older taking total daily doses of 1000 mcgs or greater and must always be used with the Volumatic when administered to children and adolescents 15 years of age and under, whatever dose has been prescribed.

Key point: Clenil Modulite and Qvar should be prescribed by brand name.

Rimonabant

Rimonabant has recently been launched with plenty of media hype to accompany it. It is an oral selective cannabinoid CB1 receptor antagonist. It is licensed as an adjunct to diet and exercise for the treatment of obese patients, or overweight patients with associated risk factor(s), such as type 2 diabetes or dyslipidaemia.

Efficacy

- Rimonabant used for up to 2 years, in addition to a calorie restricted diet, produced greater weight loss (around 4 to 6kg) compared with placebo in clinical trials. Most weight loss occurred in the first year and was only maintained if treatment was continued. Trial participants received a high level of support throughout treatment.

1-yr weight loss from baseline, rimonabant 20mg/day vs. placebo	
RIO-Europe (2 yr study, n=1,507)	6.6kg vs. 1.8kg
RIO-North America (2 yr study, n=3,040)	6.3kg vs. 1.6kg
RIO-Lipids (1 yr study, n=1,036, all with dyslipidaemia)	8.6kg vs. 2.3kg
RIO-Diabetes (1 yr study, n=1,045, all with type 2 diabetes)	5.3kg vs. 1.4kg

- Improvements in some metabolic parameters were reported as secondary endpoints (not LDL-C or total-C). No morbidity or mortality data are available. Effects beyond 2 years are unknown. No trials have compared rimonabant against other drugs.
- If prescribing rimonabant, it will be necessary to make arrangements to offer advice, support and counselling on diet, exercise and behavioural strategies, along with monitoring to check that appropriate weight loss is occurring and to identify side effects. As it is a black-triangled drug, it is important to report all adverse events via the yellow card system.

Patient and safety aspects

- Almost twice as many people discontinued rimonabant compared with placebo because of adverse events (13.8% vs. 7.2%). These consistently involved psychiatric disorders (8.5% vs. 3.2%), including depression and anxiety. Other common side effects included insomnia, nausea, vomiting, diarrhoea and fatigue. Patients will need to maintain motivation and commitment to ongoing exercise and diet, and monitoring and support.

Existing alternatives are orlistat and sibutramine and NICE has issued specific guidance on their use. PACEF has classified rimonabant as a BROWN drug (only in restricted circumstances) for third line use.

Key point: Rimonabant is a BROWN drug

Restless legs syndrome (Ekbom’s syndrome)

Patients with restless legs syndrome suffer from a range of sensory and motor symptoms affecting their legs during rest and/or while asleep. The sensory disturbance encompasses such symptoms as burning, cramps, paraesthesia, or weakness. In general, these symptoms can be temporarily relieved by moving the legs.

There is no diagnostic test for the syndrome but to be categorised as having restless legs syndrome four criteria must be satisfied:¹

1. The patient must have an urge to move the legs, usually accompanied by an unpleasant sensation in the legs.
2. Restless legs syndrome symptoms must be aggravated by rest.
3. Restless legs syndrome symptoms must be alleviated by movement and, in particular, walking.
4. Restless legs syndrome symptoms must be worse in the evening or night (either currently or when the condition first started).

There are a number of self-help measures that can be tried and the DTB² recommends that a full explanation of restless legs and reassurance that they are not typically a feature of a life-threatening underlying disorder, coupled with self-help measures, are usually sufficient to enable a patient to cope with the condition. Measures employed to help prevent attacks include: advice on improving sleep (e.g. by avoiding caffeine before bedtime); keeping cool (e.g. by wearing loose clothes); and avoiding standing or sitting for long periods. Wherever possible, drugs that can aggravate symptoms of restless legs (e.g. CNS stimulants, diuretics, tricyclic antidepressants, calcium antagonists, phenytoin) should be avoided. Anecdotal evidence suggests that during an episode of restless legs the following activities may help to bring relief: walking and stretching; taking a bath; relaxation exercises (e.g. biofeedback, yoga); and massaging the affected limbs. Patients with iron deficiency anaemia should have the cause investigated and be treated accordingly.

A patient information leaflet is available from www.patient.co.uk and includes advice on self-help measures.

Ropinirole (Adartrel) and pramipexole (Mirapexin) are now licensed for the symptomatic treatment of moderate to severe idiopathic RLS. We have discussed their place in therapy at PACEF. It was noted that the Scottish Medicines Consortium accepts them for use within NHS Scotland only for people with a specific score on the International Restless Legs Scale (IRLS). PACEF agreed to recommend the same criteria.

After non-drug therapy has been tried ropinirole is appropriate for people with a baseline score of 24 points or more on the IRLS and pramipexole is appropriate if the baseline score is 15 points or more.

The IRLS is a 40-point scale derived from 10 questions. You can access the IRLS via the PACEF intranet site.

1. BJGP 2004, 54:960-61
2. DTB 2003; 41:81-83

Induction of ovulation in women with PCOS

Further to the article in the June edition of this newsletter on the use of metformin in PCOS, an RCT has investigated the use of clomifene plus metformin versus clomifene alone (plus placebo)¹.

The addition of metformin to clomifene did not improve the ovulation rate but did increase the number of women discontinuing treatment because of side effects (16% vs 5%). The authors conclude that metformin is not an effective addition to clomifene as the primary method of inducing ovulation in women with PCOS.

The accompanying editorial recommends that, at present, it is advisable to restrict metformin to second line treatment for women whose anovulatory infertility is resistant to clomifene².

1. BMJ 2006; 332: 1485-89
2. BMJ 2006; 332: 1462-3

The ACTIVE W trial (Lancet 2006; 367:1903-12)

Atrial fibrillation is a common cardiac arrhythmia in the elderly and increases the risk of stroke and other vascular events. Warfarin reduces the stroke risk by two-thirds but is not patient friendly, needs regular monitoring, and is associated with a risk of severe bleeding. It is currently the treatment of choice for patients at high risk of stroke.

Aspirin reduces the risk of stroke in patients with AF but is inferior to warfarin. Hence it is only indicated in patients not eligible for warfarin or in those at very low risk of stroke. Would a more intensive antiplatelet therapy be as effective as warfarin? This trial assessed whether aspirin plus clopidogrel was non-inferior to oral anticoagulation for prevention of vascular events in AF.

Method

- Patients were eligible for ACTIVE W if they had ECG evidence of AF and at least one additional risk factor for stroke.
- Patients were randomised in a 1:1 ratio to clopidogrel (75mg) plus aspirin (75-100mg) both daily or oral anticoagulation (INR 2.0 – 3.0).
- The primary outcome was the first occurrence of stroke, non-CNS systemic embolism, MI, or vascular death.
- *Major bleeding* was defined as any bleeding requiring transfusion of at least 2 units of red blood cells or equivalent of whole blood, or which was severe. *Severe bleeding* was bleeding associated with, among other things, death, intraocular bleeding leading to substantial loss of vision, bleeding requiring surgical intervention, and symptomatic intracranial haemorrhage. *Minor bleeding* was any other bleeding requiring modification of the study drug regime.
- Patients had a mean age of 70 years, 66.5% were male and the mean CHADS-2 score was 2.0. Most patients (77%) were receiving oral anticoagulation before randomisation.

Results

- The study was stopped early because of clear evidence of superiority of oral anticoagulation therapy. Median follow-up duration was 1.28 years.
- Patients on oral anticoagulation therapy had INR values in the therapeutic range (2.0 – 3.0) 63.8% of the time. INRs were below 2.0, 20.8% of the time and above 3.0, 15.4% of the time.
- The annual risk for the primary outcome was 3.90% for oral anticoagulation and 5.60% for clopidogrel plus aspirin; RR 1.44 (CI 1.18 to 1.76), $p=0.0003$. This gives an NNT of 59.
- Total mortality rates were similar in the two groups, RR 1.01 (0.81 to 1.26), $p=0.91$.
- Rates of major haemorrhage were also similar in the two groups but significantly more minor bleeds occurred with clopidogrel plus aspirin than with oral anticoagulation; RR 1.23 (1.09 to 1.39); $p = 0.0009$. This gives a NNH of 47. Total bleeds were also significantly more likely with clopidogrel plus aspirin, RR 1.21 (1.08 to 1.35), $p = 0.001$ (NNH=46).
- The net benefit (primary outcome event plus major haemorrhage) favoured oral anticoagulation; RR 1.41 (1.19 to 1.67), $p<0.0001$ (NNT = 47).
- 77% of patients were receiving oral anticoagulation therapy at the time of study entry. The groups who were and were not on oral anticoagulation at study entry responded differently to oral anticoagulation therapy during the study. Although rates of discontinuation of clopidogrel plus aspirin were similar, the rates of discontinuation of oral anticoagulation therapy was significantly lower for patients who entered the study already on oral anticoagulation compared with those who did not – 1-year discontinuation rates of 8.7% and 15.3% respectively ($p=0.008$). INR control was significantly better ($p<0.0001$) for patients entering the study on oral anticoagulation therapy – for example, at 3 months INR values were therapeutic in 62.4% and 57.2% of patients respectively. The results for the primary outcome (RR 1.27 [0.85 to 1.89], $p=0.24$) and the net benefit (RR 1.10 [0.78 to 1.55], $p=0.57$) were not statistically significantly different for those not on oral anticoagulation therapy at entry. It has to be stressed that this is sub-group analysis. Only 23% were not on oral anticoagulation at study entry and hence the sub-group is not appropriately powered.

Discussion

- This study shows that oral anticoagulation therapy is superior to clopidogrel plus aspirin for prevention of vascular events in patients with AF at high risk of stroke who do not have contraindications to oral anticoagulation therapy.
- Warfarin remains the first-line choice for reducing the risk of stroke in AF.
- As the accompanying editorial points out, ACTIVE W adds to the list of long-term studies with double-antiplatelet therapy when bleeding can be a problem. Whereas the benefit of aspirin plus clopidogrel outweighs the bleeding risk in trials of a year or less, in longer-term aspirin plus clopidogrel studies this benefit is not seen¹.
- Whether aspirin plus clopidogrel is a better option than aspirin alone in AF when warfarin is not suitable is not known, and would need to be tested in a randomised controlled trial.

1. Lancet 2006; 367:1877-78

Key point: warfarin remains the first-choice for reducing the risk of stroke in AF.

Absorption from iodine dressings

I have been asked whether iodine is absorbed when iodine-containing dressings are used and if this can affect thyroid function.

Povidone-iodine and cadexomer-iodine contain about 1% available iodine. On contact with exudates, these complexes break down, making iodine available for absorption. Instructions for Iodoflex give a maximum treatment duration of 3 months, after which patients should stop treatment for a week when iodine will then be excreted. If necessary, it can then be restarted.

The BNF states that Iodoflex and Iodosorb should be avoided in people with thyroid disorders and cautions against use in people with a history of thyroid disorders. There is no such warning for Inadine but the manufacturer suggests monitoring if the patient is on thyroxine.

HRT and urinary incontinence

According to an analysis from the HERS study women taking combined HRT were more likely to develop incontinence than women taking placebo¹. Using the data for women who reported no incontinence in the week before the start of the trial, they found that during 4 years of treatment 64% on HRT and 49% on placebo were classified as incontinent at least once (OR 1.6, p<0.001). This is an excess risk of 15% or a NNH of 7.

Urge and stress incontinence were both more common among women taking HRT. Numbers needed to harm for urge and stress incontinence were 9 and 6 respectively.

1. BMJ 2006; 332:bmjupdates+ (18th February)

Black Cohosh and liver injury

The MHRA and EMEA have announced that there is a potential connection between Black Cohosh and hepatotoxicity. Black Cohosh is widely available and used to treat menopausal symptoms.

The EMEA has issued the following advice:

Advice to patients:

- Patients should stop taking *Cimicifugae racemosae rhizoma* (Black Cohosh, root) and consult their doctor immediately if they develop signs and symptoms suggestive of liver injury (tiredness, loss of appetite, yellowing of the skin and eyes or severe upper stomach pain with nausea and vomiting or dark urine).
- Patients using herbal medicinal products should tell their doctor about it.

Advice to healthcare professionals:

- Health care professionals are encouraged to ask patients about use of products containing *Cimicifugae racemosae rhizoma* (Black Cohosh, root).
- Suspected hepatic reactions should be reported to the national adverse reaction reporting schemes.

Research and audit newsletter

I would like to bring these to your attention, as they may be a useful resource. They are produced by Derbyshire Mental Health Services NHS Trust and have now been made available on the PACEF intranet site. The last three issues covered substance misuse, psychosis, and depression respectively.

Guidelines update

PACEF has recently ratified the following guidelines. These and all the other guidelines/policies are available on the PACEF intranet site and the PCT websites.

- Head lice management (update)
- Oral anticoagulation (update)
- Referral to rapid access chest pain clinic
- Statin policy (update)
- Infertility referral
- Aciclovir in recurrent genital herpes (update)
- Chlamydia management (update)
- Diagnosing VTE (update)
- Clopidogrel guidance (update)
- Use of hip protectors
- Use of VAC (vacuum assisted closure)
- Leg ulcer referral
- Shared care – acamprosate
- Shared care – apomorphine (update)
- Shared care – DMARDS in RA (update)
- Shared care – venlafaxine (update)

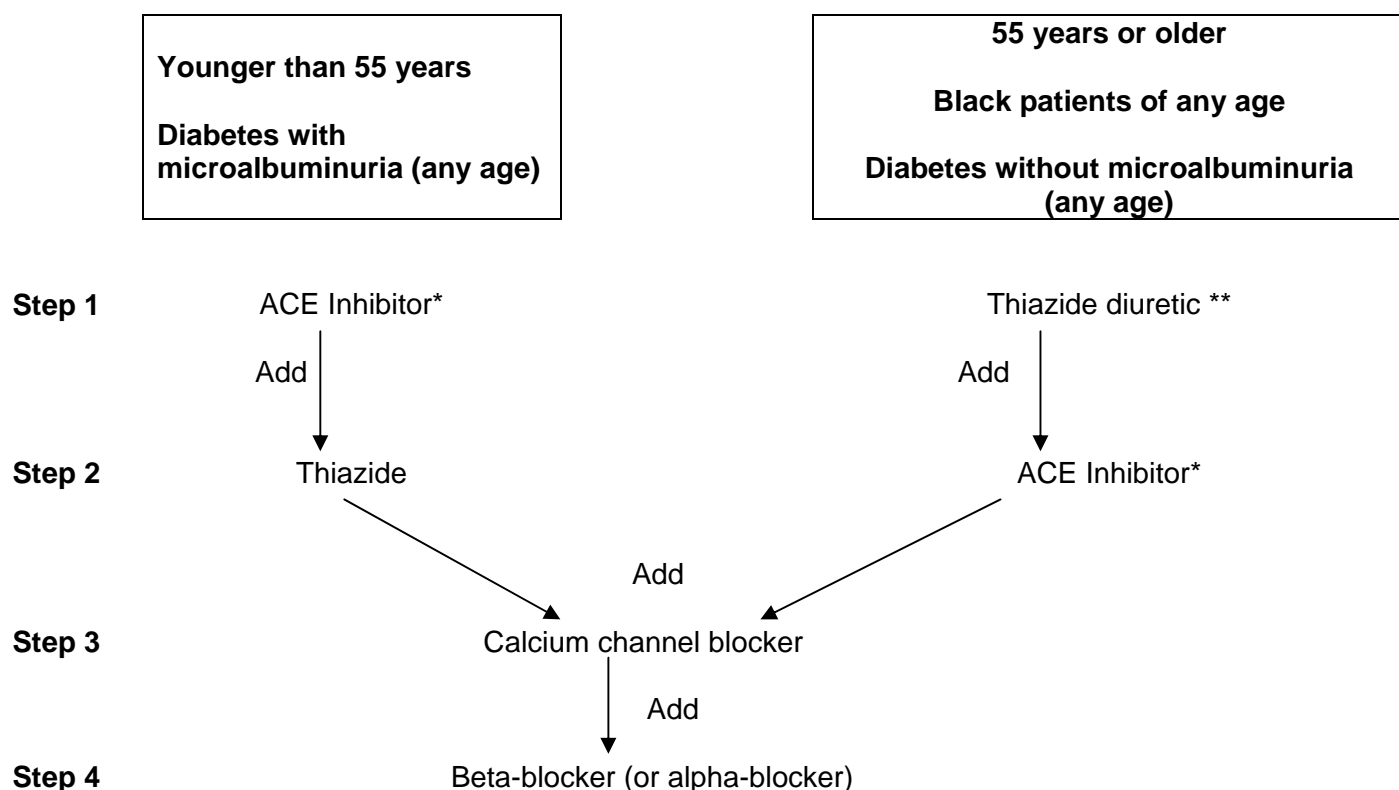
Measuring Blood Pressure – Top 10 Tips

The MHRA has issued a leaflet for health professionals containing the following advice:

- 1. Ensure that only clinically validated equipment is purchased for use and that all sphygmomanometers are regularly checked – mercury devices at least annually and aneroid devices at least twice a year.** Automated devices should only be used if re-calibration is undertaken in accordance with the manufacturer's instructions. It is good practice to delegate the task of ensuring regular calibration checks and maintenance to a designated individual.
- 2. Ensure each consulting room has both large and regular cuffs as this reduces the likelihood of cuffs being inappropriately used.** 'Miscuffing' can introduce large errors in measurement. 'Undercuffing' (either too narrow or too short a bladder) can lead to overestimation of BP, while 'overcuffing' (too wide or too long a bladder) may lead to underestimation.
- 3. Raised blood pressure should not be discounted on the basis of suspected anxiety.** If there is doubt about the relevance of readings during a consultation, the measurements should be repeated on a couple of occasions. The patient should be allowed to rest, sitting for at least 5 minutes before undertaking the initial measurements. While measuring blood pressure, the patient should not be talking or have their legs crossed. Three measurements should usually be taken, discarding the first. If there is still a large discrepancy (>10mmHg systolic) then ambulatory blood pressure monitoring (ABPM) should be considered.
- 4. BP should initially be measured in both arms and the arm with the higher values should be used for subsequent measurements.** A difference in blood pressure between the arms can be expected in about 20 per cent of patients. If the difference between the arms is more than 20mmHg for systolic or 10mmHg for diastolic pressure on three consecutive readings the patient should be considered for referral for further evaluation.
- 5. Arm support is very important.** Muscle contraction in an unsupported arm can raise diastolic BP by as much as 10 per cent while raising the arm above heart level leads to an underestimation by as much as 10mmHg. The arm should be supported in a horizontal position with the cuff at the level of the heart as denoted by the midsternal level.
- 6. Try to measure BP at the same time of day where practically possible.** BP rises with waking and then tends to fall through the day. Current guidelines do not make specific recommendations regarding the time when it should be measured but it seems sensible to try to measure it at a consistent time.
- 7. When interpreting the results of ABPM it should be remembered that average daytime values are approximately 10/5 mmHg lower than surgery measurements.** Thresholds and targets for treatment which are based on clinic values should be adjusted accordingly.
- 8. Be alert to 'white coat effect'.** BP readings can increase in both normotensive and hypertensive patients, (untreated and treated) when the measurement is taken by a healthcare professional.
- 9. Remember BP variability is large and studies have shown it can vary from the mean by a standard deviation of 12/8mmHg in the same patient on different days.** In one study, 15 readings (over five different days, three readings per occasion) were required to reduce variability by 80 per cent.
- 10. Measurement of blood pressure by any method is less reliable in the presence of arrhythmias such as atrial fibrillation.** This is because there can be large beat to beat variation when heart rhythm is irregular. Although current guidelines do not recommend auscultatory endpoints in these situations, using a greater than usual number of readings may not only improve precision but also increase the agreement between oscillometric and mercury measured blood pressures.

Choosing drugs to lower blood pressure and reduce cardiovascular risk (endorsed by PACEF)

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