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THE MANAGEMENT OF HYPERTENSION: ASCOT IN PERSPECTIVE

The diagnosis and treatment of hypertension remains one of the biggest issues in chronic disease management. Trials suggest different treatment strategies or ever lower blood pressure targets. The results are frequently reported in lay media while national, international and local groups issue guidelines that may differ in many aspects. Gordon McInnes of the Western Infirmary is Vice President of the British Hypertension Society and has extensive experience of clinical trials, notably as a member of the steering committee of ASCOT, executive committee of VALUE and as UK National Co-ordinator of HOT. Here he presents an overview of recent developments to help place different trials in context. It is expected that the Greater Glasgow & Clyde Hypertension Guidelines will be updated in light of the NICE/ BHS guidance published at the end of June.

This is shortened version of a detailed review of recent advances in hypertension. The full version is available on the ADTC website (**www.glasgowformulary.scot.nhs.uk**).

Findings from over 60 observational studies indicate a continuous association between blood pressure (BP) and the risk of cardiovascular (CV) events. Prospective trials have demonstrated conclusively that small reductions in BP (10-12mmHg systolic/5-6mmHg diastolic) are associated with large reductions in stroke (38%), coronary heart disease (CHD, 16%) and all CV deaths (21%).

The landmark trials which established the benefit of BP reduction used thiazide or thiazide-like diuretics and, in a few cases, beta-blockers. No differences in CV outcomes were identified between drug groups in direct comparisons. More recently, calcium channel blockers and ACE inhibitors have shown benefits of a similar magnitude to those of thiazide-like diuretics in high-risk populations.

Rigorous BP control is critical in reducing the risk of CV events. In type 2 diabetes, a reduction in diastolic BP from 85 to 81mmHg was associated with a 51% reduction in CV events. High-risk patients are exquisitely sensitive to small BP differences. Even in lower-risk patients, a 4/3 mmHg difference was associated with 23% fewer strokes and 15% fewer CV events.

Recent landmark trials
ALLHAT, the largest ever trial in hypertension, randomised 33,357 patients aged at least 55 years with one other CHD risk factor to treatment based on chlortalidone (chlorthalidone), amlodipine or lisinopril.

No difference was observed between the three treatment groups for the primary end point (fatal CHD or non-fatal myocardial infarction (MI)). For the secondary endpoints compared to chlortalidone, heart failure was more common with amlodipine; CV disease, stroke and heart failure were more common with lisinopril. Systolic BP was lowest on chlortalidone and this can readily explain the slight advantage in secondary outcomes.

ASCOT
This study recruited 19,257 patients (mean age 63 years) with hypertension plus at least three other CV risk factors, but no prior cardiac disease. ASCOT compared regimens:

• contemporary (amlodipine 5-10 mg + perindopril 4-8 mg)
• conventional (atenolol 50-100 mg + bendroflumethiazide 1.25-2.5 mg)

Other drugs were added as required to achieve target BP. Over half of participants needed two or more drugs; 8% required at least four.

The study was discontinued prematurely after 5.5 years because of excess mortality in the conventional group. As a result, only 903 primary end-points occurred but 1,150 were needed for the study to have the intended statistical power. Some of the main findings were:

• There was a non-significant (10%) relative reduction in the primary end point (fatal CHD plus non-fatal MI) with contemporary therapy; perhaps because of insufficient statistical power.
• Absolute risk reductions were modest (from 4.93% to 4.45%; ARR=0.48%, 5-year NNT=209) but this may be misleading since it is not representative of lifetime treatment.
• Contemporary therapy was significantly better for most secondary end points including stroke.
• Conventional therapy was not significantly better for any end point and the findings were consistent in all pre-specified subgroup analyses of the secondary end-point of total CV events and procedures.
• BP was significantly lower on contemporary therapy (average 2.7/1.9 mmHg, with greater differences earlier in the trial). This might explain most of the difference in stroke outcomes.
• Adverse events were similar in both groups, with 25% of patients stopping therapy because of an adverse event.

What does it all mean?
Differences between randomised groups in achieved BP are closely related to observed differences in risk and preclude

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Alphabetical list of most recent ADTC decisions

For full details of SMC advice, visit **www.scottishmedicines.org** For previous ADTC decisions, visit **www.glasgowformulary.scot.nhs.uk**

Drug	Indication under consideration (There may be other licensed indications)	Glasgow decision
Bevacizumab (Avastin®)	First-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5 fluorouracil/folinic acid or intravenous 5-fluorouracil/folinic acid/irinotecan.	Non-*Formulary.*
Choriogonadotropin alfa (Ovitrelle®)	• Superovulation prior to assisted reproductive techniques such as *in vitro* fertilisation. • Treatment of anovulatory or oligo-ovulatory women.	Non-*Formulary.* Non-*Formulary.*
Ciclesonide (Alvesco®)	Control of persistent asthma in adolescents (aged at least 12 years and <18 years).	Non-*Formulary.*
Cinacalcet (Mimpara®)	Reduction of hypercalcaemia in patients with parathyroid carcinoma.	Non-*Formulary.*
Darbepoetin alfa (Aranesp® and Aranesp SureClick)	Treatment of symptomatic anaemia in adult cancer patients with non-myeloid malignancies receiving chemotherapy.	Non-*Formulary.*
Dorzolamide 2% preservative-free unit dose eye drops (Trusopt®)	Treatment of elevated intra-ocular pressure in ocular hypertension, open angle glaucoma and pseudo-exfoliative glaucoma.	*Formulary.* Acknowledge new formulation. Restricted to use in patients for whom dorzolamide is appropriate and who have proven sensitivity to the preservative benzalkonium chloride.
Epinastine (Relestat®)	Treatment of the symptoms of seasonal allergic conjunctivitis.	Non-*Formulary.*
Erlotinib (Tarceva®)	Treatment of patients with locally advanced or metastatic non small cell lung cancer after failure of at least one prior chemotherapy regimen.	Decision deferred to allow consultation with the Drugs in Oncology Group.
Escitalopram (Cipralex®)	Treatment of generalised anxiety disorder.	Non-*Formulary.*
Esomeprazole (Nexium®)	• Prevention of gastric and duodenal ulcers associated with NSAID therapy in patients at risk. • Healing of gastric ulcers associated with NSAID therapy.	Non-*Formulary.* Non-*Formulary.*
Fentanyl (Durogesic D Trans®)	Chronic intractable pain due to non-malignant conditions.	*Formulary.* Acknowledge new formulation. Reserved for patients whose pain has initially been controlled by oral means, the pain being stable. Its use should focus on patients who have difficulty swallowing or have problems with opiate-induced constipation.
Fondaparinux (Arixtra®)	•Treatment for the prevention of venous thrombo-embolic events. • Treatment of acute deep vein thromboembolic events and the treatment of acute pulmonary embolism.	Non-*Formulary.* Non-*Formulary.*
Interferon alfa 2b (Viraferon® and Intron A®) in combination with ribavirin (Rebetol®)	Treatment of children and adolescents 3 years of age or over, who have chronic hepatitis C, not previously treated, without liver decompensation and who are positive for serum HCV-RNA.	*Formulary.* Acknowledge new indication.
Letrozole (Femara®)	Adjuvant treatment of postmenopausal women with hormone receptor positive invasive early breast cancer. Treatment should continue for 5 years or until tumour relapse occurs, whichever comes first.	*Formulary.* Acknowledge new indication. Restricted to initiation by a breast cancer specialist.

Drug	Indication under consideration (There may be other licensed indications)	Glasgow decision
Olmesartan/ hydrochlorothiazide (Olmetec Plus®)	Treatment of hypertension	Non-*Formulary.*
Omalizumab (Xolair®)	Add-on therapy to improve asthma control in adult and adolescent patients (12 years of age and above) with severe persistent allergic asthma.	Non-*Formulary.*
Oxycodone (OxyNorm) injection	Treatment of post-operative pain.	Non-*Formulary.*
Palifermin (Kepivance®)	Treatment of oral mucositis in bone marrow transplantation.	Non-*Formulary.*
Pegvisomant (Somavert®)	Treatment of patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalise insulin-like growth factor 1 concentrations or was not tolerated.	Non-*Formulary.*
Pemetrexed (Alimta®)	Treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy.	Non-*Formulary.*
Posaconazole (Noxafil®)	Treatment of adults with specific invasive fungal infections refractory to, or intolerant of, specified antifungal agents.	*Formulary.* Restricted to specialist initiation.
Pramipexole (Mirapexin®)	Symptomatic treatment of moderate to severe idiopathic restless legs syndrome (RLS).	*Formulary.* Acknowledge new indication. Restricted to patients with severe RLS (causes chronic sleep loss/daytime fatigue or forces major lifestyle changes).
Sildenafil (Revatio®) CORRECTION	Treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity.	*Formulary.* Restricted to initiation by specialists working in the Scottish Pulmonary Vascular Unit (not Scottish Peripheral Vascular Unit as stated in PS33) and by physicians experienced in the management of pulmonary vascular disease.
Somatropin (Norditropin SimpleXx®)	Treatment of growth disturbance in short children born small for gestational age, with a birth weight and/or length below -2 standard deviations, who failed to show catch-up growth by 4 years of age or later.	*Formulary.* Acknowledge new indication. Restricted to initiation and monitoring by a paediatrician with expertise in managing childhood growth disorders and growth hormone therapy.
Trastuzumab (Herceptin®)	Treatment of patients with HER2 positive early breast cancer following surgery, chemotherapy and radiotherapy (if applicable).	*Formulary.* Acknowledge new indication. Restricted to use by breast cancer specialists. November 2005 protocol remains extant until further notice.
Triptorelin (Gonapeptyl® depot)	• Treatment of advanced, hormone-dependent prostate carcinoma. • Treatment of symptomatic endometriosis confirmed by laparoscopy when suppression of the ovarian hormonogenesis is indicated to the extent that surgical therapy is not primarily indicated.	Non-*Formulary.* Non-*Formulary.*

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ASCOT in perspective *contd from page 1*

a simple comparison of drug effects on outcome. Equivalent BP control is seldom achieved in studies. Thus, assumptions must be made about the contribution of small differences in BP.

Failure to acknowledge the influence of small BP differences on CV outcomes in high-risk patients has led to both over- and under-estimation of treatment effects. HOPE and EUROPA reinforce the impact of small BP reductions in high-risk patients. ALLHAT may have underestimated the effect of ACE inhibitors and calcium channel blockers. Differences in outcomes may reflect BP differences or may highlight drug-specific effects. It is difficult, if not impossible, to adjust for the influences of BP differences in retrospect.

New onset diabetes

ASCOT confirmed a 30% relative risk reduction in the tertiary endpoint of development of diabetes (from 8.3% to 5.9%) for contemporary therapy compared with beta-blocker and/or diuretic treatment. In ALLHAT, the worsening of glycaemic control on chlortalidone was not associated with excess CV risk, but long-term observational studies suggest no difference between drug-induced and non-drug-induced diabetes with respect to CV outcomes. The increased risk due to new onset diabetes takes several years to become manifest so trials will underestimate the risks of diabetes and the benefits of maintaining normoglycaemia.

Diuretics and beta-blockers do not cause diabetes but appear to accelerate the progression to diabetes; newer drugs do not prevent diabetes but delay progression. The net time difference to diabetes between new and old drugs is only about 12 months. Not all hypertensive patients have the same risks of diabetes; low-risk patients have little to lose from conventional drugs and little to gain from newer agents.

The beta-blocker controversy

Two meta-analyses have questioned the place of beta-blockers first-line in hypertension. Compared with placebo, beta-blockers modestly reduce stroke but do not reduce MI. In comparative trials, beta-blockers are not different from other drugs in protection against MI but are significantly less effective in preventing stroke.

Were these meta-analyses flawed? Critically, allowances for BP differences were inadequate. The average BP difference between treatments in trials underestimates differences early in the trials when many events occur. The populations included were mainly elderly and beta-blockers perform poorly in systolic hypertension, the predominant problem in older subjects.

Beta-blockers remain reasonable first-line therapy for many younger patients, particularly those who are over-anxious or with hyperadrenergic responses. The increased risk of diabetes is unlikely to be a major issue in younger hypertensives. There is a real danger of throwing the baby away with the bath water. To achieve targets, all drugs need to be available. If BP is well controlled using a beta-blocker, there is little reason to change unless there is a high risk of developing new onset diabetes. The British Hypertension Society advocates this practical advice.

Conclusions

Interpretation of clinical trials is complicated by the BP differences between treatment arms. The beneficial effects of additional BP lowering far outweigh any postulated differential effects of drugs. In most patients, rigorous BP control necessitates the use of at least two drugs. Governments and health authorities must accept that antihypertensive drugs cannot be rationed and the pharmaceutical industry must acknowledge the clear conclusion that antihypertensive drugs work best when lowering BP without side effects – as it says on the label.

Drugs of choice update: Proton Pump Inhibitors

At the April 2006 meeting of the ADTC, lansoprazole capsules were added as the second drug of choice in the proton pump inhibitor section. Omeprazole capsules have been Glasgow's PPI of choice since inception of the scheme in 2004. There is no evidence that any PPI is more effective than another at equivalent doses and omeprazole had a significantly lower cost than lansoprazole in 2004. The ADTC planned to review the drug of choice status following the loss of the patent on lansoprazole in December 2005. For that reason, there has been no strategy to move patients away from lansoprazole to omeprazole in recent times. The drug of choice designation was intended to guide new prescribing.

Lansoprazole capsules have now been added to the Drug Tariff and the April PPI prices are shown below. The FasTab® formulation is significantly more expensive than generic lansoprazole capsules and remains non-*Formulary*. More than 90% of prescriptions for PPIs in primary care are for either omeprazole or lansoprazole.

Drug	Formulation	Strength	Cost/28
Lansoprazole	Capsules	15mg	£4.57
Lansoprazole	Capsules	30mg	£6.73
Omeprazole	Capsules	10mg	£5.32
Omeprazole	Capsules	20mg	£8.94
Omeprazole	Tablets	10mg	£14.08
Omeprazole	Tablets	20mg	£34.79

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