ASCOT: a tale of two treatment regimens

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hepatitis C, heralded by the chief medical officer last year,[4] have not been adequately implemented.

In 2004 I conducted a questionnaire survey on the staffing and facilities of 28 English hospital trusts identified as running hepatology services and known as "liver centres." Relatively few were able to provide a full range of liver services.[5] There were serious shortages of staff at all levels: a third of the centres lacked a designated consultant hepatologist, and in 11 of the 28 units general physicians were sharing the workload with gastroenterologists. Five centres did not have a single specialist nurse for hepatitis, and in four centres the only specialist nurses were for people with alcohol related disorders. Lack of dedicated beds for patients with liver disease was one of the most common limitations to the service. Waiting times for outpatient appointments were generally unacceptable too—more than 20 weeks in three hospitals, and between 11 and 20 weeks in 14. Only seven hospitals were able to offer an urgent appointment within two weeks. An earlier questionnaire survey on training by Ramage[6] also showed the need for a substantial increase in consultant hepatologists.

How can staffing in the United Kingdom be improved? The recent designation of hepatology as a subspecialty of gastroenterology, with one year of the current five years' training spent in a liver centre, is a step forward. So are the integrated training pathways proposed for academic doctors through the Modernising Medical Careers programme[7]—and the initiatives of the UK Clinical Research Collaboration,[8] which should both bring new recruits into academic hepatology.

Liver services need better funding as well as better staffing. The considerable costs of drug treatment and specialised procedures for treatment underline the need for an appropriate funding mechanism within the new national tariff system.[9] And much remains to be done in the commissioning of specialised liver services by primary care trusts.[10] The National Plan for Liver Services UK envisaged that some 10-15 hospital centres would provide specialised services through a series of managed clinical networks, evenly distributed around the country.[3] This is considerably less than the number of hospitals currently identified as liver centres, and these serve a variable number of primary care trusts (range of 1-14, median 6).

The six centres for liver transplantation in the United Kingdom—which receive dedicated funding—fared better than liver centres in last year's survey, with considerably more facilities for investigation and availability of expert staff.[6] Patients referred to these centres with liver disease not requiring transplantation (which accounted for 30-60% of the total referrals) will benefit from the better facilities. Increasing the number of transplant centres would be one way to provide liver services more widely in the United Kingdom. Large areas of the country currently lack a transplant centre, notably north west England (including Manchester and Liverpool) and the south west peninsula. Clearly, specialised services for liver disease and transplantation will have to improve substantially to meet the considerably increased burden of liver disease that is predicted for the next 20 years.

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1 Handslip P, Swindells M, Allan C, Clifton M, Thomas H. Information-clinical analysis. The data today. Real-time monitoring can alert trusts to clinical performance problems—before the star-ratings do it for them. *Health Serv J* 2004 Sep 2;114(suppl):6-8.
2 Department of Health. *Annual report 2001/2*. www.doh.gov.za/docs/reports/annual/2001-02/contents.html (accessed 4 Oct 2005).
3 Moore K, Thursz M, Mirza DF. *National plan for liver services—specialised services for hepatology, hepatobiliary and pancreatic surgery*. 2003. Report prepared for the British Association for the Study of the Liver. www.basl.org.uk/National%20Plan%20for%20Liver%20Services%20UK%20Final-May04.pdf (accessed 4 Oct 2005).
4 Department of Health. *Hepatitis C: action plan for England*. July 2004. www.hepc.nhs.uk/resources/documents/ACTIONPLAN.pdf (accessed 4 Oct 2005).
5 Williams R. Provision of specialist liver services in England. July 2004. www.bsg.org.uk/pdf_word_docs/hepservices.doc (accessed 4 Oct 2005).
6 Ramage J. Results of hepatology training questionnaire, 2002. www.bsg.org.uk/pdf_word_docs/hep_survey.doc (accessed 10 Oct 2005).
7 National Health Service. *Modernising medical careers: foundation programmes*. www.mmc.nhs.uk/pages/foundation (accessed 3 October 2005).
8 Department of Health, UK Clinical Research Collaboration. Government agrees new pathway to create the medical researchers of tomorrow. Press release, 30 March 2005. www.ukcrc.org/Documents/UKCRC_MMC_Report_Press_Release_30_March_2005.PDF.pdf (accessed 4 Oct 2005).
9 Department of Health. *Reforming NHS financial flows: introducing payment by results*. London: DOH, 2002. www.dh.gov.uk/assetRoot/04/06/04/76/04060476.pdf (accessed 4 Oct 2005).
10 Williams R. Direct and indirect constraints on commissioning specialist medical care. In: Grimley Evans J, Pollard S, Sikora K, Williams R, eds. *They've had a good innings: can the NHS cope with an ageing population?* London: CIVITAS, 2003:50-69.

ASCOT: a tale of two treatment regimens

Better blood pressure, fewer deaths, and less diabetes with newer antihypertensive agents

Papers p 873

Each year in the United Kingdom alone there are 20 000 preventable deaths from cardiovascular disease attributable to hypertension. Much of the excess mortality and associated morbidity arises from poor control of blood pressure among people known to have hypertension. For the past two years in the United Kingdom, general practitioners have had the prime responsibility for tackling this problem, along with financial incentives to meet targets for detecting and controlling high blood pressure. Yet, despite many clinical trials and guidelines, they may be unsure about which antihypertensive drug to use first and how to combine treatments.

In 2004 the National Institute for Health and Clinical Excellence (NICE) recommended thiazide or thiazide-like diuretics as the first line treatment for most patients, with the addition of β blockers as the next step.[w1] This echoed the advice given in the US Joint National Committee's guidelines the previous year.[w2] Near simultaneous guidance from the British Hypertension Society, however, recommended for the first time drugs acting on the renin-angiotensin system—angiotensin converting enzyme (ACE) inhibi-

References w1-w12 are on bmj.com

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tors or angiotensin receptor blockers—as first line treatment for "younger, non-black" patients.[w3] In effect, the resulting confusion endorsed earlier European guidelines which advocated leaving the choice of drug to individual practitioners.[w4]

An eclectic approach to prescribing would make sense if all antihypertensive agents were equal. But they are not, according to results published last month from the largest antihypertensive trial ever conducted in Europe, the Anglo-Scandinavian cardiac outcomes trial (ASCOT).[w5] The trial compared strategies combining more expensive newer drugs with cheaper older ones. Nearly 20 000 patients with hypertension and at high risk of cardiovascular disease, aged 40-79, were randomised to two treatment regimens (rather than drug classes, as in most preceding trials).

The newer regimen comprised a calcium channel blocker (amlodipine) with an angiotensin converting enzyme inhibitor (perindopril) if required, while the older regimen comprised a β blocker (atenolol) with or without a diuretic (bendroflumethiazide). An extended release formulation of the α blocker doxazosin (4-8 mg) was added for all patients whose blood pressure did not reach the target value of $<140/90$ mm Hg, or $<130/80$ mm Hg for patients with diabetes. The trial was well conducted over a median follow-up of 5.4 years, with fewer than 2% of patients lost to follow-up and a high proportion continuing the treatment regimen to which they had been randomised.

The study was designed to stop after 1150 fatal or non-fatal coronary heart disease (primary endpoint) events in participants, but it was halted early after 903 such events, when the data and safety monitoring board reported that patients on the atenolol-based regimen were being increasingly disadvantaged as the trial progressed. In the final analysis, rates of fatal and non-fatal coronary heart disease were lower in patients on the amlodipine-perindopril regimen (by 10%), although this was not statistically significant ($P=0.1052$). However, clinically and statistically significant reductions in rates of the main secondary end points occurred, including all cause mortality (11%) and cardiovascular mortality (24%), as well as all coronary events (13%) and fatal and non-fatal stroke (23%).

Owing to changes in cardiological practice over the duration of the trial the ASCOT investigators added an end point in the final analysis, combining the primary end point with coronary revascularisation. This modified primary end point was reduced significantly by 14%. Moreover, a combined end point of cardiovascular death plus non-fatal myocardial infarction and stroke similar to that used in many previous hypertension trials was 16% lower in patients taking the newer rather than the older drugs ($P<0.0003$).

Were the better outcomes among patients allocated to the amlodipine-perindopril regimen attributable only to differences in achieved blood pressure or were they due to other effects of the drug classes used? The initial fall in blood pressure with the newer agents was brisker, with a difference of 5.9/2.4 mm Hg at three months and an overall mean difference at the end of the trial of 2.7/1.9 mm Hg. An analysis reported in an accompanying paper matched patients who had achieved similar blood pressures on the two regimens in ASCOT and compared outcomes, adjusting for baseline differences.[w6] This analysis found it was unlikely that all the benefits seen in the patients allocated to the amlodipine-perindopril regimen were attributable solely to more effective systolic blood pressure lowering.

Other potential benefits of the newer drugs in ASCOT included a statistically significant 30% reduction in the incidence of type 2 diabetes mellitus. Conversely, β blockers may have promoted the development of diabetes among participants in ASCOT, or this may have represented an interaction between β blockers and thiazides.[w1] Insulin resistance is closely associated with atherogenesis and is potentially modifiable by agents which block the renin-angiotensin system, such as perindopril. Reduced incidence of type 2 diabetes has been reported in several recent trials of ACE inhibitors and of angiotensin receptor blockers. Although concerns were raised in an editorial last year regarding the safety of angiotensin receptor blockers as a class,[w7] a systematic review in this issue (p 873)[w8] provides solid support for a previous rebuttal.[w9]

Recent meta-analyses have shown that four or five cases of type 2 diabetes will be prevented when 100 patients are treated for 10 years with newer rather than older antihypertensive drugs.[w1 10] In a similar population over 10 years, four coronary heart disease events and two strokes will be prevented by lowering blood pressure.[w1] A cost effectiveness analysis of ASCOT, which is clearly needed, should take into account the prevention of type 2 diabetes and its associated long term morbidity and mortality as well as the falling costs of generic calcium channel blockers and ACE inhibitors.

It makes sense for the British Hypertension Society and NICE to develop joint UK guidelines to help practitioners control their patients' blood pressure, with the aim of reducing unnecessary deaths from hypertension.[w11] Both bodies are set to collaborate, probably recommending more frequent prescription of ACE inhibitors or angiotensin receptor blockers plus calcium channel blockers as first line treatments and in combinations. Thiazides will probably be used mainly for adjunctive treatment to achieve targets for lowering blood pressure (particularly in useful combination, fixed dose preparations), while initial treatment with atenolol will be questionable.[w12]

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