

Diagnosis of peripheral arterial disease of the lower limb

Duplex ultrasound is safe, inexpensive, and accurate enough to guide management in most cases



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Andrew W Bradbury Sampson

Gamgee professor of vascular surgery and consultant vascular and endovascular surgeon

Donald J Adam senior lecturer and consultant vascular and endovascular surgeon, University Department of Vascular Surgery, Heart of England NHS Foundation Trust, Solihull Hospital, Birmingham B91 2JL

ann.murray@heartofengland.nhs.uk

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In this week's *BMJ* a systematic review by Collins and colleagues compares the diagnostic accuracy of duplex ultrasound, magnetic resonance angiography, and computed tomography angiography for assessing peripheral arterial disease of the lower limb.¹ The review also evaluates the impact of these assessment methods on patient outcomes. It found that contrast enhanced magnetic resonance angiography seemed to be more specific than computed tomography angiography (better at ruling out stenosis of 50% or more in a lower limb vessel) and more sensitive than duplex ultrasound (better at ruling in stenosis of 50% or more). Magnetic resonance angiography was also generally preferred by patients over contrast angiography. So what do these results mean for practising clinicians?

In developed countries up to a fifth of the population over the age of 60 has lower limb peripheral arterial disease, as defined by absent pulses or a reduced ankle brachial pressure index. About a quarter of these people have symptoms—most commonly intermittent claudication. This consists of pain in the leg (usually in the calf) on walking, as a result of atherosclerotic stenosis or occlusion, usually of the superficial femoral artery in the thigh.²

Only a small minority of patients with intermittent claudication undergo imaging with a view to open surgical (bypass, endarterectomy) or endovascular (angioplasty, stenting) intervention. Most claudicants are treated medically in primary³ or secondary care⁴—if they are treated at all.⁵ In contrast, most patients with severe limb ischaemia (rest pain, tissue loss) undergo imaging with a view to interventional treatment, usually by means of bypass surgery or angioplasty.^{6,7}

Imaging studies are of little use in peripheral arterial disease unless intervention is being considered and the imaging results are likely to influence the choice and nature of that intervention. In an era of “high tech” medicine we sometimes forget that the purpose of imaging is not just to obtain pleasing pictures but to answer specific clinical questions that have been thoughtfully framed after undertaking a careful history, thorough examination, and non-invasive assessments.⁸ Not surprisingly, Collins and colleagues found that the availability of appropriate clinical data increased the accuracy and quality of imaging interpretation.

The imaging modality should be carefully chosen, in an evidence based manner, so as to maximise the quality and relevance of information obtained, minimise the risk and inconvenience to the patient, and make the best

use of limited resources. But, as Collins and colleagues report, making such a choice can be difficult in people with peripheral arterial disease. They could find few comparative studies and many had serious methodological limitations. Most studies had several potential sources of bias resulting from the nature of the patient population being investigated, the delay between index and reference tests, and the inability to blind observers. Only one study compared patient outcomes. The rest compared diagnostic “accuracy,” which can be hard to define in a clinically meaningful way, especially when data are presented by arterial segment rather than by limb or by patient. Relative sensitivities and specificities, often with wide ranges, for various degrees of arterial stenosis, most commonly 50%—a level of disease with limited biological or clinical relevance—are hard to factor into everyday clinical decision making. In reality, as pointed out by Collins and colleagues, the choice of imaging may be more influenced by patient preference and tolerance as well as the availability of the test.

When a patient with peripheral arterial disease needs diagnostic imaging, it seems sensible to start with the simplest and safest modality, which is undoubtedly duplex ultrasound.^{1,2} Only if this proves insufficient should more sophisticated, potentially risky, and costly tests normally be considered. In practice, this is now unusual given the quality of the machines used and the skill of vascular technologists.

Intra-arterial digital subtraction angiography is the reference standard, but magnetic resonance angiography and computed tomographic angiography can provide more information and can be more accurate than ultrasound.¹ However, in many cases the extra information and accuracy has little effect on patient management and outcome. The only study in the review by Collins and colleagues that compared patient outcomes found no significant difference between duplex ultrasound and intra-arterial digital subtraction angiography.

In summary, the available data,¹ supported by everyday clinical experience, suggest that duplex ultrasound is the only imaging test needed in most patients. If ultrasound is not sufficient, then most clinicians would probably choose magnetic resonance angiography rather than computed tomographic angiography because it is more versatile, more accurate, is not as affected by arterial calcification,^{1,8} and does not involve exposing patients to ionising radiation.^{9,10}

Diagnostic imaging continues to evolve and improve at an astonishing rate. There is a growing consensus

that invasive techniques should not be used to visualise the arterial system unless a therapeutic intervention is intended. Thus, diagnostic intra-arterial digital subtraction angiography is likely to become a thing of the past, with open and endovascular treatments for peripheral arterial disease being planned almost exclusively on the basis of duplex ultrasound and, where necessary, magnetic resonance angiography.^{11 12}

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Provision of primary care in different countries

Priorities of patients should not be overpowered by economic and political incentives



PATRICK WARD/JALAMY

Primary care has an important part to play within healthcare systems.¹ The World Health Organization defines the main aim of healthcare systems as the improvement of health, but it notes that financing should be fair and systems of care ought to respond to people's expectations.² Countries whose healthcare delivery focuses on the role of the specialist tend to fare less well in surveys that take account of these three goals.³ Primary care seems to offer important advantages within healthcare systems in terms of cost containment, health status of the population, and a range of other health related outcomes—the value of a strong primary care base within national healthcare systems is recognised by WHO.⁴ How can cross national studies provide insight into the optimal organisation of health care?

In this week's *BMJ*, Bindman and colleagues⁵ use data from national surveys in Australia, New Zealand, and the United States to compare mix of patients, scope of practice, and duration of visits in primary care. Previous studies have compared patient morbidity and patients' expectations of care between countries.^{6 7} This study differs in that it examines case mix and exposure to primary care in three countries using rigorous and innovative ways to analyse large nationally representative datasets.

In primary care, length of consultation has been proposed as a marker of quality of care, with longer consultations increasing patients' satisfaction and being more comprehensive and more responsive to patients' needs.^{8 9} Few studies have reported exposure to primary care in populations or have used such a measure to investigate differences between groups of individuals with regard to the experience or outcome of health care.

In the United Kingdom, a recent national survey of primary care provision¹⁰ reported a median consultation length of 13.3 minutes for general practitioners in 2003.

UK patients have an average of 4.5 consultations each year, so these figures imply a per capita annual exposure to primary care physicians of around 60 minutes each year—an increase of 28% in just five years.¹¹ Bindman and colleagues highlight a substantial variation in such exposure between the three countries they studied—from 29.7 minutes each year in the US to 83.4 minutes each year in Australia.

Similar methods to those used by Bindman and colleagues to define case mix have been used to investigate the relative contribution of social class and case mix in modelling the use of home visits in primary care settings.¹² The methodological approach used in the current study to assess differences in case mix is sophisticated; it draws on a diagnostic coding system developed at Johns Hopkins Hospital, which has been validated for use in primary care. It has the potential to compare case mix in primary care in countries that extensively use morbidity coding systems, such as those of the International Classification of Disease or READ coding system.

A limitation of Bindman and colleagues' study is that only administrative or preventive care codes were recorded in up to 20% of consultations, and these were excluded from the analysis. While the role that doctors play in society varies in different countries, the authors are right to note that such consultations should be included in the overall assessment of case mix. This would enhance the generalisability of the findings and provide a more comprehensive overview of the contribution of primary care to the healthcare system within the country.

It may be surprising to general clinicians providing "comprehensive" first line care that 75% of the workload of US primary care physicians' comprises just 46 conditions. Also, this number rose to only 57 conditions

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John L Campbell professor of general practice and primary care Peninsula Medical School, St Luke's Campus, Exeter EX1 2LU jlcampbell@pms.ac.uk

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for family doctors in New Zealand, a country that is much more orientated towards primary care than the US, and which has healthcare structures similar to those of the UK National Health Service. Some substantial differences were seen between national populations in primary care case mix—women in the US had lower rates of attending primary care for gynaecological problems, but attendance for endocrine and cardiovascular problems was much higher in the US than in Australia and New Zealand. Such observations may reflect differences between countries in access to care and in the gatekeeping role of family doctors, but they may also result from cultural differences between populations in their interpretation of symptoms and in their use of health services.

Even in Western healthcare systems, inequalities in health status and experience of care exist between individuals. Squandering of resources through failure to provide a strong primary care base within national health systems is likely to reinforce divisions within society, worsen the health status of individuals, and create a healthcare system that is unresponsive to the needs of the population. Cross national comparative studies have the potential to inform the development of services, but they need to take account of the beliefs and values of the people served as well as the ambitions and resources of their health professionals and politicians.

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Transition of care in children with chronic disease

Healthcare teams need to adapt to change as much as patients and their families



SIMON FRASER/VSPL

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Colin Wallis consultant respiratory paediatrician, Great Ormond Street Hospital for Children NHS Trust, London WC1N 3JH
c.wallis@ich.ucl.ac.uk

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In this week's *BMJ*, a woman with cystic fibrosis describes her experience of living with the disease from childhood to adulthood.¹ Among the many challenges she describes is the “rocky road” of transition from paediatric to adult health care. She says that she would have given anything to attend a transition clinic when she was 16 years old, instead of going straight to an adult clinic at another hospital.

Cystic fibrosis was previously considered a lethal disorder of childhood, but as survival improves, the need for continuous care into adulthood becomes more important. For the past two decades the global cystic fibrosis community has recognised the importance of transferring care from paediatric to adult services, and has set an example for services in other chronic conditions to follow.²

Transition to adult care for any child with a chronic life limiting illness should not consist of just transfer to a doctor who treats adults. It should be a clinical and psychosocial process. Adolescence is a time of great change—a normal journey of transition from childhood to adulthood. It is a difficult and exciting time as shifts occur in emotional attachments, autonomy, self identity, sexuality, physical shape, philosophy of life, and vocation. For those with a chronic illness, this developmental stage is complicated further as the teenager takes responsibility for care and faces problems associ-

ated with morbidity, mortality, and limitations to life's options. Coping with these extra problems on top of the normal challenges of adolescence is an immense challenge, which is made worse by being cut off by the paediatric care team that the patient knows and trusts.

Fundamental differences exist between paediatric and adult chronic care. Paediatric care is often multidisciplinary, prescriptive, and family focused. It requires parental direction and consent. Adult care tends to be patient focused, and it encourages autonomy in making decisions about treatment and life choices. Professionals in adult care are familiar with the difficulties associated with sex, pregnancy, work, and raising a family in the context of chronic ill health.³

A successful transition process has defined stages. Firstly, the needs and benefits of a move to adult care are explained and discussed with the young adult patient and the parents. A combined clinic is then held where the patient and family meet with the “receiving” team for a multidisciplinary handover. An orientation tour of the adult centre is an important part of the journey. Finally, there is the last goodbye—a visit to ensure that all aspects of transition have been covered.⁴

Surveys show that patients and parents have a positive opinion of such transition clinics.⁵ The parents' biggest concern was whether their child would be able to care for their illness independently, although this concern

was not always shared by the children.

Transition services have been developed for children with other chronic conditions, such as diabetes,⁶ renal disease,⁷ and complex congenital heart disease,⁸ in addition to transplants recipients.⁹ The principles are similar, although local resources and the underlying condition determine the details of care.

In the United Kingdom, as in many countries, transition occurs when patients are between 16 and 18 years of age, and it ties in with the educational curriculum and social needs. Although timing is generally determined by age, it may require review in people who are less able to care for themselves as a result of mental capacity or severe ill health.¹⁰

The hurdles for transition medicine lie as much with the healthcare teams as with the patients and their families. The attitude towards transition and the relationship between the paediatric and adult clinics is central to success.¹¹ Some paediatric units find it hard to let go of children they have looked after for so long. But holding on to patients who could benefit from the expertise of an adult orientated service causes as many problems as treating transition just as an administrative event.

Do we really need a transition service for all chronic

paediatric conditions? The case for chronic disorders with an advancing morbidity and the need for large multidisciplinary input is clear and these services have been adopted in many countries worldwide, such as the United States, Australia, South Africa, and many countries within Europe.¹² However, the natural history of many childhood conditions has changed with modern treatment. For example, children with HIV find the transition particularly difficult as they move into a world with few adolescents and a healthcare environment mainly focused on the needs of homosexual men.¹³ And for some conditions there are no existing adult teams, such as immunodeficiency diseases like chronic granulomatous disease.

Some clinical teams and families remain reluctant to buy into the concept of transition medicine.¹⁴ But the considerable financial and emotional input in caring for the child with a chronic condition should not be lost in a failed transition process. This is not just about paediatric teams being unduly precious about the children they have steered through 17 difficult years. This is about preventing adults looking back and saying, "I would have given anything to attend a transition clinic when I was 16."

Tamiflu and neuropsychiatric disturbance in adolescents

The case is not proved but caution is advisable



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In March 2007 the Japanese authorities advised against prescribing oseltamivir (Tamiflu, Roche) to adolescents aged 10-19 years.¹ This unusually severe measure resulted from the separate suicides of two 14 year olds who jumped to their deaths while taking oseltamivir; 52 other deaths (14 in children or adolescents) have been associated with the same drug. So far, similar action has not followed in Europe. When a regulatory authority warns doctors not to prescribe a drug but decides not to retract its marketing authorisation prescribers and patients are entitled to be concerned and a little confused.

Oseltamivir is a sialic acid analogue that inhibits influenza type A and type B neuraminidase, the viral enzyme that allows the release of virus from infected cells. Its main licensed indications are the treatment of flu, short term postexposure prophylaxis after contact with a diagnosed case of flu, and more prolonged (up to six weeks) "seasonal" prophylaxis when flu is circulating in the community. The licence was extended in 2005 to include children aged 1-12 years.

When used to treat otherwise healthy people, oseltamivir reduces the duration of symptoms by 1-1.5 days if started within 48 hours of first symptoms, irrespective of vaccination status, although it may be less effective in those with chronic diseases.^{2,5} It also provides a modest reduction in complications such as pneumonia, otitis media in children, and hospital admission.^{4,5} As postexposure prophylaxis, the protective efficacy of oseltamivir was 80-90% in the family contacts of index cases.^{2,3,6,7}

As seasonal prophylaxis, the protective efficacy was 74% in healthy people aged 18-65⁶ and even higher in frail elderly people in residential care.⁸

The National Institute for Health and Clinical Excellence advises that oseltamivir should not be prescribed for otherwise healthy people because the health gain in this group is modest.^{4,6} However, oseltamivir is recommended for treatment and postexposure prophylaxis in people who are at increased risk of complications because of age or comorbid conditions (box). This restricted recommendation in the United Kingdom has limited prescription of oseltamivir to only a few thousand people.⁹ In contrast, an estimated 45 million patients have received oseltamivir worldwide.¹ This has been partly boosted by encouragement from the World Health Organization, as a way to gain familiarity with antiviral agents before the outbreak of a pandemic.¹⁰ Several governments have been stockpiling supplies in preparation for such an event.

So far, oseltamivir has been thought to be well tolerated and safe. The most common adverse effect is dose related nausea, which occurs twice as frequently as with placebo when used as prophylaxis.⁵ Post-licensing monitoring has revealed very rare reports of raised liver enzymes and hepatitis and of serious skin reactions, including Stevens-Johnson syndrome and erythema multiforme.¹¹ However, the recent events in Japan have prompted a reappraisal.

Before 2007, there had already been more than 100 reports of neuropsychiatric events (including delirium,

Simon R J Maxwell senior lecturer, Clinical Pharmacology Unit, University of Edinburgh, Queen's Medical Research Institute, Edinburgh EH16 4TJ
s.maxwell@ed.ac.uk
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Patients at high risk of complications after flu

- People over 65 years of age
- People with chronic respiratory disease (including asthma and chronic obstructive pulmonary disease)
- Patients with cardiovascular disease (excluding those with hypertension only)
- Patients with chronic renal disease
- Immunocompromised patients
- People with diabetes mellitus

convulsions, and encephalitis) with oseltamivir in children, almost entirely from Japan, which has the highest usage of oseltamivir worldwide. However, these disturbing events had to be seen in the context of the millions of prescriptions worldwide and the fact that abnormal behaviour could also be due to flu or disease related complications. Indeed, a Food and Drug Administration (FDA) review of clinical trial and postmarketing data concluded that these events were not clearly drug related but might be related to higher rates of flu related encephalitis in Japan.¹² Since last November, the FDA has required that doctors be warned that patients should be closely monitored for signs of abnormal behaviour throughout the treatment period and the European Medicine Evaluation Agency (EMA) took similar steps in February.

The controversy about oseltamivir is a further reminder that, although common adverse effects of a drug may emerge in prelicensing studies, the detection of rarer and potentially more serious events has to await exposure of large numbers of patients. In the UK, oseltamivir is a “black triangle” drug, so it remains under more intensive surveillance. Doctors and other healthcare professionals should report all minor as well as serious adverse events via the yellow card scheme.

In the light of these concerns how should prescribers proceed? There seems little doubt that oseltamivir reduces the number and seriousness of flu episodes when used as treatment and prophylaxis. However, the impact of such events in otherwise healthy people is usually modest and of short duration. They should be encouraged to use conservative strategies such as resting, increasing fluid intake, and taking simple analgesics and over the counter symptomatic remedies. In people at higher risk of serious complications the potential

benefit of treatment seems greater, although convincing evidence about reductions in hospital admission or mortality is still awaited. In these groups, vaccination still offers a cost effective first line of defence.⁶

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Rosiglitazone and implications for pharmacovigilance

Postsurveillance data should be systematically collected and publicly available



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On 21 May 2007, the *New England Journal of Medicine* published a meta-analysis of 42 trials of rosiglitazone (Avandia, GlaxoSmithKline) for treating type 2 diabetes mellitus. It found that the drug was associated with an increased risk of myocardial infarction (odds ratio 1.43; 95% confidence interval 1.03 to 1.98; $P=0.03$) and death from cardiovascular causes (1.64; 0.98 to 2.74; $P=0.06$).¹

Rosiglitazone, a thiazolidinedione, is an agonist at the peroxisome-proliferator activated receptors in cell nuclei. These receptors modulate the expression of a host of genes, and glycaemic control is achieved primarily through increased insulin sensitivity in peripheral tissues. Rosiglitazone was approved by the US Food and Drug Administration (FDA) in 1999 and by the centralised process of the European Medicines Agency (EMA) in 2000. Its popularity has increased steadily, with more than one million prescriptions written in the one year period ending March 2006 in England alone—a 22%

increase over the previous year.² However, the recently published meta-analysis raises serious questions about the drug's safety.

Meta-analyses have unique strengths and weaknesses and this one is no exception.³ Its singular strength is the statistical power generated by data on 15 560 patients from published and unpublished trials. However, it includes clinically heterogeneous trials and criteria used by individual trials to classify adverse events are somewhat unclear. Only summary data are available in the public domain—for example, whether or not a person had a myocardial infarction, not when it occurred—which makes time to event analyses impossible. Also, the total number of adverse events was small, so that misclassification of a few events could alter the conclusions.

In response to the concerns raised by this meta-analysis, an unplanned interim analysis of a large, manufacture sponsored, randomised, open label, non-inferiority trial specifically designed to investigate the cardiovascular

Dhruv Kazi internal medicine physician, London School of Economics, London WC2A 2AE d.s.kazi@lse.ac.uk

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safety of rosiglitazone was recently released.⁴ Compared with patients taking metformin and a sulphonylurea, people taking a regimen that included rosiglitazone had no significant increase in the risk of myocardial infarction (hazard ratio 1.16, 0.75 to 1.81), although they had a significantly increased risk of heart failure (2.24, 1.27 to 3.97). **When these new data are added to the trials in the previous meta-analysis, rosiglitazone is associated with an increased risk of myocardial infarction (odds ratio, 1.33; 1.02 to 1.72).**⁵

To summarise, the meta-analyses show a significantly increased risk for myocardial infarction, whereas several individual prospective trials do not. More data would certainly help to clarify the matter, but the emerging safety concerns question the prudence of continuing ongoing trials. Notwithstanding the ethical concerns, it may be impossible to prevent an exodus of patients from these trials in light of the ongoing “trial by media” of the drug.

The broader question is how this reflects on regulatory processes used to monitor drug safety. Postmarketing surveillance, or pharmacovigilance, remains the weakest link in the regulatory process on both sides of the Atlantic. The current approach—the FDA’s adverse event reporting system and the European EudraVigilance programme—relies heavily on passive surveillance, and it is based on reports of unusual adverse events from consumers, practitioners, manufacturers, and national regulatory authorities. At best, this creates a case series, one of the weakest forms of epidemiological evidence,⁶ that would be insensitive to an increase in common events like myocardial infarcts in diabetics.

Alternatively, the regulatory authorities may require systematic phase IV trials after market authorisation, but these are often not completed in a timely manner. In the United States, completion dropped from 62% in the 1970s to 24% in recent years,⁶ and the FDA is ill equipped to act against defaulters. As of September 2006, 930 (74%) of the 1259 postmarket studies were pending or delayed.⁷

This results in a fractured regulatory process, where the preapproval phase is marked by stringent requirements for safety and efficacy data, but performance in postmarketing surveillance falls short of the standards the agencies set for themselves. This is exemplified by the case of rosiglitazone. Rosiglitazone comes from a family of drugs with well documented side effects,^{8,9} and itself is associated with increased heart failure, anaemia, and raised low density lipoprotein concentration. However, postmarketing safety data seven years after regulatory approval consist of a patchwork of heterogeneous manufacturer sponsored trials, many of which are unpublished. Of note, a similar meta-analysis submitted by the manufacturer to the EMEA and the FDA in August 2006 showed an increased risk in ischaemic events (hazard ratio, 1.31, 1.01 to 1.70).¹⁰ The EMEA updated the product label of the drug,¹¹ but no specific communication to healthcare professionals was issued. The FDA did neither.

The system needs to be fixed. The Institute of Medicine recommends a life cycle approach to drug

evaluation.¹² This would involve a systematic effort to monitor the safety and efficacy of a drug before and after approval using data from well designed clinical trials to inform ongoing risk-benefit analyses. This process could be made more systematic by requiring regulatory authorities to periodically and independently re-evaluate all data gathered after approval for all new molecular entities—particularly drugs with high sales.

In addition, the lack of transparency in the current system needs to be dealt with. There should be a legal requirement for all phase II-IV trials to be registered in a centralised database, such as the National Library of Medicine’s clinicaltrials.gov or an equivalent. Complete datasets from these trials, systematic analyses of the results, and reports of periodic evaluations by the regulatory agencies must be publicly available.

A radical change is needed in the culture of existing regulatory institutions that regard postmarketing surveillance as their secondary mandate. This will require systematic rethinking of the existing regulatory and funding processes, and expediting changes currently in the pipeline.¹³ Progress will entail empowering the regulatory agencies with additional authority and resources.

The manufacturer and the FDA will share the spotlight as congressional investigation into the matter starts. In the meantime, what are the implications for patients currently on rosiglitazone? Doctors will need to revisit the indication for the drug on a case by case basis, bearing in mind that several alternatives are cheaper, supported by robust evidence, and now perhaps safer.¹⁴ The decision to switch drugs must be tempered by the fragility of the available evidence and the risks associated with altering patients’ medical regimens. Needless to say, the ongoing use of rosiglitazone merits careful deliberation.

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