Editor's choice

Editor's Choice: Focus on diabetes
Fiona Godlee
BMJ 2007;335, doi:10.1136/bmj.39329.634931.47

Editorials

Screening for diabetes
Ronald P Stolk
(published 30 August 2007)

Self management of type 2 diabetes
Frank J Snoek
(published 30 August 2007)

Mild hypothermia for post cardiac arrest syndrome
Jasmeet Soar, Jerry P Nolan
BMJ 2007;335:459-460, doi:10.1136/bmj.39315.519201.BE

HIV phylogenetics
Deenan Pillay, Andrew Rambaut, Anna Maria Geretti, Andrew J Leigh Brown
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Pharmacovigilance in developing countries
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This week's letters

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NICE on childhood UTI: Author's reply
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BMJ 2007;335:463-464, doi:10.1136/bmj.39325.451933.3A

Improving stroke outcome: Apply science, not politics
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**Population growth:** Colonialism never dies
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**Unholy trinity:** Stance is worst type of spin
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**Unholy trinity:** Public trust in doctors undented
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**Unholy trinity:** Sticking to standards, not together
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BMJ 2007;335:465, doi:10.1136/bmj.39317.653125.BE

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**News**

Pathologist in Sally Clark case wins appeal against removal from government register
Clare Dyer
BMJ 2007;335:466, doi:10.1136/bmj.39328.472627.4

Parent warned to curb rise in measles cases by vaccinating their children
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Public support for hybrid embryos rises with knowledge, poll shows
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BMJ 2007;335:466-467, doi:10.1136/bmj.39329.482326.4E

Agency warns about dosing error for amphotericin after patients with cancer die
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Correction: GMC clears GP accused of giving court "junk science" on MMR vaccine
BMJ 2007;335:467, doi:10.1136/bmj.39328.514664.AD

In Brief: News

BMJ 2007;335:468, doi:10.1136/bmj.39328.691354.4E

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Mixed martial arts and boxing should be banned, says BMA
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Cancer expert attacks drug company’s funding of research paper
Caroline White
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Study shows paucity of female medical academics in UK
Roger Dobson
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Shortcuts from other journals: Global burden of COPD has been underestimated
BMJ 2007;335:472, doi:10.1136/bmj.335.7618.472

Shortcuts from other journals: Evidence for guidelines often lacks external validity
BMJ 2007;335:472, doi:10.1136/bmj.335.7618.472-a

Shortcuts from other journals: Saline may be better than albumin in severe traumatic brain injury
BMJ 2007;335:472, doi:10.1136/bmj.335.7618.472-b

Shortcuts from other journals: Hypogonadotropic hypogonadism may not need lifelong treatment
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Shortcuts from other journals: Whole grains help prevent type 2 diabetes
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Shortcuts from other journals: Be careful with claims that sex modifies genetic risk of disease

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Shortcuts from other journals: Selenium supplements may increase risk of type 2 diabetes

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Shortcuts from other journals: Cardiac support devices still cause serious adverse events

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Shortcuts from BMJPG journals: An apple a day keeps the wheeze away

BMJ 2007;335:474, doi:10.1136/bmj.39314.514792.AD

Shortcuts from BMJPG journals: Military personnel in 2003 Iraq war are free from depleted uranium

BMJ 2007;335:474, doi:10.1136/bmj.39314.514792.AD

Shortcuts from BMJPG journals: Cardiac care is poorer for patients with psychosis

BMJ 2007;335:474, doi:10.1136/bmj.39314.514792.AD

Shortcuts from BMJPG journals: ACE inhibitor fetopathy may have long term implications

BMJ 2007;335:474, doi:10.1136/bmj.39314.514792.AD

Shortcuts from BMJPG journals: It's safe to head a soccer ball

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Feature

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Emil J Freireich
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Head to head: Should terminally ill patients have the right to take drugs that pass phase I testing? No
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From the frontline: **Patient safety**
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Live from London: **The worrying world of eating disorder wannabes**
Deborah Cohen
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Between the lines: **The doctor writer’s handbook**
Theodore Dalrymple
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Medical classics: **Illness as Metaphor; AIDS and its Metaphors**
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This week’s obituaries

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**James Stokes Ellis**
Peter Ellis
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**Khaled ("Karl") Ghattas**
Alan Selwyn
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**Gerald Godfrey**
S Fathe-Azam, S Fellerman, A Godfrey, C Huston
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**Barbara Jones**
Louise Jones
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**Harold Gordon Mather**
Robert Mather
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**Edmund Eric Richey**
Ruth Richey
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**George Walter Scott**
M G Thorne
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J Cox, S Desai, K Callanan
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Fillers

Outside the comfort zone
Peter J Revington
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Life class lives again
H V Wyatt
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Endpiece: Evil in the United States in 1834

BMJ 2007;335:512, doi:10.1136/bmj.39069.591887.F7

Corrections

Long term results of compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR): randomised controlled trial

BMJ 2007;335, doi:10.1136/bmj.39323.661609.AD

Should eponyms be abandoned? No

BMJ 2007;335, doi:10.1136/bmj.39330.542569.AE

Preimplantation genetic screening reduces successful pregnancies after IVF

BMJ 2007;335, doi:10.1136/bmj.39330.553889.AE

Improving the outcome of stroke

BMJ 2007;335, doi:10.1136/bmj.39330.571748.AE

Career focus

Read this week’s articles on
Self management of type 2 diabetes

More efforts are needed to capture the patients’ perspective

The introduction of home blood glucose monitoring in the late 1970s was instrumental in shifting the focus of the management of diabetes from doctors to patients. It is now a common view that patients are primarily responsible for the daily management of their diabetes, which includes self monitoring, at least in patients treated with insulin. The usefulness of self monitoring in patients with type 2 diabetes not treated with insulin is controversial, a debate that was recently fuelled by the ADDITION study: proposed trial of the cost-effectiveness of an intensive multifactorial intervention on morbidity and mortality among people with type 2 diabetes detected by screening. Int Obes Relat Metab Disord 2006;24(suppl 3):S6-11.


The generalisability of the findings from this small qualitative study remains uncertain, although the reported experiences and attitudes seem all too realistic and common. The study reminds us of the importance of demographic, social, and psychological variables in explaining the observed interindividual differences. The question of how useful self monitoring is in patients not being treated with insulin remains, but those who did continue monitoring did so less frequently. Some patients expressed uncertainty about the meaning of the test results and how to act on them, while others found self monitoring to be reassuring and did it routinely. Most participants voiced concerns about the value health professionals placed on their readings. Doctors generally appeared to show little interest in patients’ test results after the initial phase, leading some patients to perceive self monitoring as not very important or even pointless. Interestingly, some patients continued to self monitor despite lack of guidance and the perceived health professionals’ disinterest.

The longitudinal qualitative study of the views of patients with type 2 diabetes about self monitoring, using a repeat interview design. The authors rightly point out that the patient’s view has been largely absent in discussions on self monitoring in type 2 diabetes. While self testing of blood glucose has the potential to empower patients, it is often viewed as complex and inconvenient. Finger pricks can be painful, and the repeated confrontation with unexpected outcomes and “bad” results can lead to frustration, guilt, and indeed “learned helplessness.”

These negative effects on patients’ wellbeing are probably responsible to a large extent for the low adherence to self monitoring seen in patients with both type 1 and type 2 diabetes.

Peel and colleagues previously reported from the same research project on patients views on self monitoring six months after diagnosis. Results suggested that patients with poorly controlled diabetes were more likely than those with good control to voice concerns and to have problems with self monitoring.

Three years after diagnosis, 18 of these patients (one on insulin) who had ever self monitored their blood glucose were contacted for a third interview round, to explore (changes in) their experiences and views of self monitoring. The relevance of a longitudinal approach is underscored by recent research showing that self monitoring practices change over time and may have different effects on glycaemic control in new and established users. Peel and colleagues found that fewer patients were self monitoring over time, and those who did continue monitoring did so less frequently. Some patients expressed uncertainty about the meaning of the test results and how to act on them, while others found self monitoring to be reassuring and did it routinely. Most participants voiced concerns about the value health professionals placed on their readings. Doctors generally appeared to show little interest in patients’ test results after the initial phase, leading some patients to perceive self monitoring as not very important or even pointless. Interestingly, some patients continued to self monitor despite lack of guidance and the perceived health professionals’ disinterest.

The generalisability of the findings from this small qualitative study remains uncertain, although the reported experiences and attitudes seem all too realistic and common. The study reminds us of the importance of demographic, social, and psychological variables in explaining the observed interindividual differences. The question of how useful self monitoring is in patients not being treated with insulin remains, but clearly Peel and colleagues’ study confirms the need to develop educational strategies that can help patients effectively use blood glucose monitoring and manage negative feedback. As the authors point out, self monitoring is apparently still surrounded with feelings of personal failure and self blame, particularly in female patients. Experience has shown that simply providing patients with a manual on how to overcome common emotional and behavioural barriers to self testing can have significant beneficial effects on psychology and glycaemic control. The second study, a systematic review by Ehrich and colleagues, assesses the optimum drug treatment for patients with type 2 diabetes and...
heart failure. The review used evidence from eight studies to look at the effects of various blood glucose lowering drugs, including oral drugs and insulin, on morbidity and mortality in patients with type 2 diabetes and heart failure. It found that metformin is the only antidiabetic drug that is not associated with any measurable harm in people with diabetes and heart failure. In fact, metformin was associated with reduced mortality.

A weakness of the review is that most of the data were observational and only one randomised trial was included. However, the review does complement a recently published systematic review on the effectiveness and safety of oral drugs for type 2 diabetes, which found that metformin and second generation sulphonylureas are similarly effective or even superior in terms of glycaemic effects to newer and more expensive agents.

Despite the new information provided by these reviews, more evidence is urgently needed on the benefits of newer antidiabetic drugs in different populations of patients. Future trials should not only include clinical end points, but also outcomes that are important to patients, in line with the draft guidance from the US Food and Drug Administration. Patients are experts on their own quality of life. It would seem wise therefore for the medical industry and scientists to ask patients to join them in designing clinical trials and choosing the most relevant outcomes to be reported by patients.

**Mild hypothermia for post cardiac arrest syndrome**

Is recommended by evidence based guidelines yet uptake remains poor

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failure. Complications of mild hypothermia include increased infection, cardiovascular instability, coagulopathy, hyperglycaemia, increased plasma amylase, hypophosphataemia, and hypomagnesaemia. Most of these complications are easy to treat in the intensive care unit or can be reduced by raising the patient’s temperature slowly by 1-2°C.

Despite the evidence and inclusion in guidelines, the uptake of mild hypothermia by intensive care units around the world is poor. Some clinicians remain sceptical about the evidence—just two relatively small unblinded controlled trials; one used pseudorandomisation to allocate treatments, the other enrolled just 8% of all the patients assessed for eligibility.

It is still not clear whether patients outside of the inclusion criteria used in the original trials would benefit from hypothermia (such as those with cardiac arrests occurring in hospital or non-ventricular fibrillation cardiac arrests). A randomised trial of hypothermia after resuscitation following in hospital cardiac arrest is ongoing (ClinicalTrials.gov identifier NCT00457431).

An effective and easy method to initiate cooling is rapid infusion of cold (4°C) intravenous fluid. Cooling should start as soon as possible. This means that for cardiac arrests occurring out of hospital, cooling should ideally be started at the scene of the arrest or in the ambulance or, at the very latest, in the emergency department. A randomised controlled trial assessing long term survival after prehospital induction of hypothermia with cold intravenous fluid is about to start (ClinicalTrials.gov identifier NCT00391469).

No consensus exists on the best way to maintain hypothermia, the optimum duration for hypothermia, or how best to rewarm the patient. In our experience, simple methods to maintain hypothermia—such as surface cooling with icepacks and fans—can work, but over-cooling and under-cooling are common. Intravascular cooling methods enable tighter temperature control, but insertion of large bore intravascular catheters has risks and the disposables are expensive.

Mild hypothermia is just one component of treatment for the post cardiac arrest syndrome. Other important components include early coronary reperfusion (percutaneous intervention or thrombolysis), controlled ventilation to achieve normal arterial blood oxygen and carbon dioxide tensions, cardiovascular support with vasoactive drugs, and, if necessary, an intra-aortic balloon pump, and intensive control of blood glucose.

Evidence suggests that implementing a systematic treatment protocol after resuscitation improves outcomes. Current guidelines recommend that unconscious adults with spontaneous circulation after out of hospital cardiac arrest should be cooled to 32-34°C for 12-24 hours when the initial rhythm was ventricular fibrillation. This treatment may be considered for unconscious adult patients with spontaneous circulation after out of hospital cardiac arrest with any other rhythm or after in hospital cardiac arrest. Many intensive care doctors, including ourselves, now cool most comatose patients admitted to intensive care after cardiac arrest.


HIV phylogenetics

Criminal convictions relying solely on this to establish transmission are unsafe

The recent flurry of criminal cases brought against people in the United Kingdom accused of infecting their sexual partner(s) with HIV has resulted in several convictions. This has caused concern among health professionals and community groups about the detrimental effect such cases may have on disclosure of HIV infection and uptake of voluntary HIV testing, which contrasts with the move to normalise HIV testing and clinical care. The potential negative effect of this on the public health programme to reduce transmission of HIV has been widely discussed in these pages and elsewhere.

Virological evidence, specifically HIV gene sequence data obtained from the defendant and complainant, has been used in these cases because a prerequisite for establishing criminal liability is that the
Andrew Rambaut senior research fellow, Institute of Evolutionary Biology, University of Edinburgh, Edinburgh EH9 3JT
Anna Maria Geretti consultant medical virologist, Royal Free Hospital, London NW3 2PF
Andrew J Leigh Brown professor of evolutionary genetics, Institute of Evolutionary Biology, University of Edinburgh, Edinburgh EH9 3JT

Competing interests: This article takes account of a discussion held by the UK Expert Advisory Group on AIDS (EAGA; www.advisorybodies.doh.gov.uk/eaga/). DP is a member of EAGA. ALB, AMG, and DP have acted as expert witnesses in relation to criminal transmission cases in recent years.
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Viral phylogenetics provides methods for assessing the relations between viruses from different people. A phylogeny is a hypothesis under which we can estimate the probability that viruses from two particular people have a recent common origin, but only in relation to other strains compared. The reliability of the conclusion depends both on the assumptions made in the statistical analysis and the data available for analysis.

Statistical tests (parametric, non-parametric, or Bayesian) are used to evaluate one such hypothesis against another, but if an inaccurate model is specified, or if the most relevant data are not included, these tests can, perhaps counterintuitively, give formal support to an incorrect conclusion. There are serious limitations on what can and cannot be inferred using phylogenetics alone and, in our view, a conviction that relies on such evidence to establish transmission is inherently unsafe. For these reasons, expertise should be sought before undertaking such analyses.7 8

The greatest difficulty lies with the nature of the data. Identifying a linkage between viruses from two people on its own says nothing about the direction of transmission (who infected whom?) without allied information for the individuals concerned, and multiple specimens may be needed from before and after infection. Secondly, it is unlikely that all sexual contacts of all HIV infected people will be available for viral testing; indeed some may not be diagnosed. Thus, it is extremely difficult to distinguish a direct transmission between two people from a transmission from a third party to both, or from the first to the second person indirectly through a third. Thirdly, because HIV infected people can be coinfected or superinfected with genetically diverse strains, interpretation of the phylogeny is even more complex. Finally, similarities in two virus genomes may occur as a result of convergent or parallel evolution. An example of such is the independent development of drug resistance mutations, which can erroneously link people with no history of direct contact.10 Now that this is known, genetic positions subject to mutation associated with drug resistance can be excluded, but other sources of convergent evolution, such as those that might be produced by the virus evolving to escape the immune system, are not as well characterised.

We therefore advise caution when interpreting such data because the strength of any apparent linkage between viruses will never approach the degree of certainty generally expected of “DNA” data in a criminal court, which juries are more familiar with. Phylogenetic evidence—together with clinical and epidemiological evidence regarding likely duration of infection, sexual history, and other relevant factors—can provide support for linkage between cases but cannot prove transmission.

In this context, the only safe use of virus gene sequences is in circumstances where the genetic differences between viruses are sufficient to make linkage between two people doubtful (or in the case of different HIV-1 subtypes, highly unlikely). This is equivalent to the ability of blood grouping to establish that two samples come from different people (when the blood group differs), but not that they come from the same person (when the blood group is the same).

Despite the difficulty in determining linkage between specific individuals, phylogenetics can provide important new insights in investigations. A recent example is a study of the timing of HIV-1 infections among Libyan children in hospital, which showed that most infections occurred before the arrival of the accused medical workers in the country.11 Within the UK, new diagnoses comprise imported infections, many from sub-Saharan Africa, together with a growing number of infections acquired within the UK, overwhelmingly in men who have sex with men. The speed with which imported infections, from Eastern Europe as well as Africa, will lead to ongoing spread within the UK is unknown, as is the future mixing of viruses between different risk groups (those practising heterosexual or homosexual sex).

Molecular epidemiological approaches, allied to existing surveillance of HIV, will allow sensitive real time monitoring of such trends to be established, thus guiding targeted and cost effective public health interventions.

It will be important that sufficient checks and balances are in place to allow full use of such data for public health benefit, without concern that the underlying purpose for identifying possible viral genetic linkage between people will be to support criminal proceedings.

References are on bmj.com
Pharmacovigilance in developing countries

Requires collaboration between stakeholders to develop novel models of funding

Efforts are increasing to ensure that resource poor countries, which bear almost 90% of the global disease burden, have access to effective medicines.1 As a result, drug companies are facing increased pressure from governments, the World Health Organization, and patient lobby groups to remove legal and financial barriers to access.2 However, although these campaigns are necessary and clearly laudable, they are not accompanied by the development or upscaling of processes for monitoring drug safety. Although many drugs have been extensively used and studied in developed countries (thus informing global practice), their safety profile cannot necessarily be generalised to developing countries, where the incidence, pattern, and severity of adverse reactions may differ markedly because of local environmental and genetic influences.2

After the thalidomide disaster in the 1960s, most Western countries developed national pharmacovigilance systems.3 These systems use spontaneous reporting or other pharmacoepidemiological methods to systematically collect and analyse adverse events associated with the use of drugs, identify signals or emerging problems, and communicate how to minimise or prevent harm. Although these processes are not perfect, as exemplified by recent problems,4 they do provide evidence that can be used to institute regulatory action to protect public health.

At the global level, the WHO programme for international drug monitoring at the Uppsala Monitoring Centre collates adverse drug reaction reports via the national pharmacovigilance centres of the 81 member countries (www.who-umc.org). However, currently only six sub-Saharan African countries (South Africa, Zimbabwe, Tanzania, Mozambique, Nigeria, and Ghana) are full members of the programme. In fact, less than 27% of lower middle income and low income economies have national pharmacovigilance systems registered with the WHO programme, compared with 96% of the high income countries in the Organisation for Economic Co-operation and Development. The main reasons for this are lack of resources, infrastructure, and expertise. Thus, although access to medicines is increasing in developing countries, there is a danger that their risk benefit profiles in indigenous populations will not be fully monitored and acted upon.

So what can be done to improve drug safety monitoring in developing countries? In the short term, we need to make better use of ongoing or planned studies. The ability to detect an adverse drug reaction depends on its frequency and the total number of people exposed to the drug.5 A logical approach would be to encourage collaboration between academic investigators, drug companies, and governments undertaking clinical studies to develop common adverse reaction reporting forms and to deposit the data into a single database. Similar partnerships could also be established with organisers of public health and drug access campaigns and with regional surveillance systems, such as the East African network for monitoring antimalarial treatment6 and the network for assessing health and demography in developing countries.7 The operational advantages of this approach are that data can be obtained from a range of studies and that pre-existing manual and technical infrastructures can be used to acquire the data. This would provide demographically relevant data from large (and less homogeneous) populations in a structured and systematic fashion, and these data could then be used to identify warning signals.

Individual investigators would still own their data and publish results of their trials, but the pooling of data on adverse drug reactions would add value to ongoing studies. This has already happened on a small scale. For example, an increased risk of serious neurological reactions was identified in people taking ivmercin who were infected with Loa loa before treatment started.8 Such pooling of data needs to be increased and considered for all drug classes within a formulary.

What role should the drug industry have in promoting pharmacovigilance? The current model for drug development in resource poor settings depends on public-private partnerships, such as the Medicines for Malaria Venture. These partnerships should be encouraged to continue beyond the point of obtaining a drug licence to developing a proactive phase IV programme. Such a programme could be designed to show the effectiveness of the drug in a real world situation, and through this obtain safety data in much larger cohorts of patients. A few examples of this approach already exist in Africa,9 but these need to become the norm rather than the exception.

In the long term, every country should develop its own national pharmacovigilance system, which contributes to a global database such as that held by the Uppsala Monitoring Centre. This will need an extensive infrastructure, however, which would be costly. In a climate where health resources are limited, funding a pharmacovigilance system will come second to other competing priorities such as implementing a new vaccine programme. The funding model for pharmacovigilance activities in the United States recently advocated by the Institute of Medicine10 is unlikely to work in developing countries if it increases drug costs, as this defeats the aim of increasing access to medicines. No easy answers are available, but WHO needs to lead a dialogue between the major stakeholders with the aim of developing a novel funding model that supports pharmacovigilance activities in developing countries.

The lack of local expertise in pharmacovigilance could be tackled through developing exchange programmes with the major drug regulatory agencies and sharing of best practices.

References are on bmj.com
The guideline from the National Institute for Health and Clinical Excellence (NICE) on urinary tract infections (UTI) in childhood\(^1\) was welcomed in a *BMJ* editorial.\(^2\)\(^3\) Most readers will assume it was based on evidence correctly analysed by medical statisticians, robustly peer reviewed, and openly debated. As this is a controversial subject, dependent more on small studies than randomised controlled trials, many will imagine that it represented consensus following wide consultation, as stated.\(^1\) Sadly, all these assumptions are wrong.

The NICE guideline committee signed highly restrictive secrecy agreements, and its two paediatric nephrologists did not consult with the British Association for Paediatric Nephrology, whose members hold diverse views. I was a peer reviewer but was not treated as one. My first draft review identified major flaws, was supported by the association, and delayed publication by six months. However, I was allowed to see the committee’s adjustments only after strong insistence, signing a secrecy document, and accepting that it would ignore my responses. The errors persist.

The guidelines were derived from an inadequate review of the literature. The authors misused statistics and reached beyond the evidence to make erroneous conclusions based on flawed logic. Some seemed to reflect opinion rather than fact. The committee’s own figures showed that nitrite screening has a mean sensitivity of about 50%, so will miss half the cases, yet it\(^4\) and Watson\(^2\) advise its use unreservedly. Similarly, both promote the use of ultrasound rather than dimercaptosuccinic acid (DMSA) scans, despite their own data showing DMSAs to be much more sensitive; on average ultrasound misses half the scars. They also view DMSA as invasive even though it requires only a single venepuncture and has the radiation burden of one abdominal x ray. Both advise a temperature cut off of 38°C for investigating infants’ urines without clear evidence, and both assume that a lack of evidence for prophylactic antibiotics equates to evidence against their benefit, which many paediatricians dispute.

NICE guidelines result in uniformity of practice; clinicians “are expected to follow them.”\(^4\) Unifying practice before a consensus emerges is absurd. Scientific debates are not resolved by secrecy and decree but by patient research and genuinely open discussion. The premature imposition of inappropriate guidelines will stifle new clinical developments. For example, our unit runs a direct access service,\(^5\) which seems to be reducing renal scarring rates (despite Watson’s assertion that most scars are congenital). If we are all forced into one mould based on poor analysis of evidence, we will miss the opportunity to make important advances.

Malcolm G Coulthard, consultant paediatric nephrologist
Royal Victoria Infirmary, Newcastle NE1 4LP
malcolm.coulthard@nuth.nhs.uk

Competing interests: None declared.


**Author’s reply**

The guideline on urinary tract infection (UTI) in children from the National Institute for Health and Clinical Excellence (NICE) will precipitate debate, but hopefully cause less consternation than that expressed by Coulthard (previous letter). The published clinical guideline runs to 150 pages and 271 references with many systematic reviews.\(^1\)

We can all quote observational studies that don’t pass the scrutiny of evidence based medicine, but perhaps we should remember that the 1991 Royal College of Physicians guidelines were produced by 18 “experts” at a one day consensus meeting with medical audit in mind.

Achieving a further consensus has been difficult, with imaging modalities changing from intravenous urogram and micturating cystogram for all to ultrasound, radionuclide imaging, and more selective cystograms. At the same time, recognition has been increasing that a lot of what we called reflux nephropathy is reflux associated damage in association with congenital dysplastic and obstructive kidneys.

The algorithms that were devised didn’t really distinguish between upper tract and lower tract infection. As most children only have a single episode and recover there has been legitimate concern about over-investigation. The NICE guideline helps us focus on important groups—young people and patients with unexplained fever, atypical UTI, or recurrent UTI. Prompt diagnosis and treatment are emphasised, but debate will continue about the relative merits of microscopy and dipsticks. One point to bear in mind is that UTI is a combination of symptoms and growth of organisms from an appropriately taken urine sample. Clinical decision making can be difficult, but the NICE guidelines clearly state that “the guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.” This may certainly be appropriate in the debated area of antibiotic prophylaxis. A recent Cochrane review quoted only two small studies where no significant differences in risk for UTI were found between antibiotic prophylaxis and no treatment.\(^7\) We urgently need a controlled trial in this area, especially as compliance with long term prophylaxis is probably worse than we think and some
parents and carers express concern about long term usage. However, children are our priority and we must justify to them the taking of the nasty medicine and the need for potentially nasty invasive tests.

Alan R Watson consultant paediatric nephrologist Nottingham University Hospitals, City Hospital Campus, Nottingham NG5 1PB judith hayes@jinu.nhs.uk

Competing interests: None declared.


IMPROVING STROKE OUTCOME

Apply science, not politics

Markus leaps from a discussion about outcomes to a plea to reorganise acute stroke care to improve access to thrombolysis.1 Not one patient received thrombolytic treatment in the studies he quotes, but such subtleties will be lost in the political hubbub about the NHS letting us all down yet again. It is frustrating that after 25 years’ research, we have only one drug treatment, alteplase, which seems to work, and we only manage to give it to 2% of our patients, but we should not pull all our eggs in this basket.

About 1 in 8 patients would expect to obtain major benefit from thrombolytic treatment, so even if we could increase the proportion treated to 20%, about 1 in 40 patients would benefit overall. To achieve this, Markus suggests that patients receive “rapid ambulance assessment” and perhaps half would be transferred to “specialised stroke centres,” some distance away.2 What of the patients not transferred and condemned to “second class care” in their local hospital? This would presumably include anyone over 80 (over 30% of patients with acute stroke) as there is insufficient evidence of benefit for alteplase to be licensed in this age group. What of the many patients rushed to the specialist hospital in the hope of getting clot busting treatment but found to be unsuitable? The logistics are nightmarish, and the sense of frustration among those whose hopes are dashed would be fertile soil formedia mischief. Inevitably, the risks and limitations of alteplase would be ignored, and it would become yet another wonder drug being denied to thousands of NHS patients.

The only proved effective treatment for most patients with stroke is specialist, multidisciplinary team based, stroke unit care.2 Good coordination, communication, and continuity of care are essential ingredients, and these would be put at risk if large numbers of patients received acute care and rehabilitation in different trusts, looked after by different teams. There is no reason why patients with acute stroke, admitted to any reasonably sized hospital, should not have access to immediate brain scanning and expert assessment, if necessary via telemedicine links, but we need to develop these services quickly and quietly, without hyperbole and fuss.

David Barer professor in stroke medicine Queen Elizabeth Hospital, Gateshead, Tyne and Wear NE9 6SX d.h.barer@ncl.ac.uk

Competing interests: None declared.

1 Marcus H. Improving the outcome of stroke. BMJ 2007;335:56–6. (25 August.)

DRUG MISUSERS AND INCENTIVES

Methadone works if used properly

Stevenson, a senior British forensic doctor, observes that methadone treatment does not work, contrary to 40 years of high quality research showing that it does.1

The reason can be found in the lack of adherence to evidence based clinical guidelines in much of the United Kingdom.2 With some notable exceptions, UK addicts are routinely given dose schedules that are contrary to guidelines (such as mean doses of less than 40 mg daily in place of double that found in well run clinics). These advise strict dose supervision for new and unstable patients with an effective dose range from 60 mg to 120 mg daily after careful induction starting with no more than 40 mg daily.3

Hong Kong, Australia, and New Zealand may be the only places where methadone has been available for over 30 years under reasonably open access and with a largely evidence based approach. Uniquely, all three have very little HIV in their large injecting populations. Few would believe this is coincidental (although hepatitis C has been a different and as yet unanswered story).

The question of whether addicts should receive incentives in treatment should be decided by practical research, not moralist opinions.4 Methadone treatment is already one of the most cost effective things we do in medicine and probably compares with washing hands. It would seem logical to raise the abysmal standards of practice in the UK and then examine incentives to improve results still further if needed.

Andrew Byrne private addictions physician 75 Redfern Street, Redfern, NSW 2016, Australia abyrne@ozemail.com.au

Competing interests: AB charges a fee for administration of drugs in the treatment of addiction.

1 Stevenson RJ. Drug misusers are likely to abuse the system. BMJ 2007;335:317. (18 August.)
4 Burns T. Is it acceptable for people to be paid to adhere to medication? Yes. BMJ 2007;335:232. (4 August.)
5 Shaw J. Is it acceptable for people to be paid to adhere to medication? No. BMJ 2007;335:233. (4 August.)

POPULATION GROWTH

Colonialism never dies

Interesting to see that old colonial opinions still flourish at the BMJ. Having decided that African women are intelligent enough to hold down jobs but not to bottle feed safely, thereby putting countless babies at risk, they are now to be told to limit their families.1 Africans like having large families. No doubt that will change in time, but that should be determined by the people themselves, not by Europeans, who like having long haul holidays and driving large cars and are not prepared to give them up. The options suggested for limiting population growth include contraception, which presents problems with choice of method and access and “safe abortion.” If that takes off in Africa with the enthusiasm that it has in this country the annual health budget will be mopped up.

How about doing what the Africans want? In my experience, although the death of a child is mourned, it is, in time, accepted. Funds should be diverted from keeping children alive to ensuring optimum health for their parents by establishing some form of health facility in every area, supplying medical assistants with bicycles, ensuring a safe supply of front line drugs, and discussing, intelligently, the problem of safe childbirth—and maybe improve the roads so that women can get to hospital or teach village practitioners to do caesarean sections.

How about tackling the problem of the tsetse fly that devastates large areas of Africa, which not only causes trypanosomiasis (said to be increasing), but also means no draught animals and no dairy products? If
all conferences and advocacy groups were dismantled there might be enough money to free Africa of this scourge and liberate much productive land. But then there wouldn’t be much in it for the drug firms, conference centres, caterers, and all those agencies that keep academics in business.

Anne Savage retired, London NW3 5RA savage.ann@btinternet.com
Competing interests: None declared.

1 Richards T. The hitch hiker’s guide to population growth and climate change. BMJ 2007;335:374. (25 August.)

UNHOLY TRINITY

Stance is worst type of spin

I am not alone in my surprise at seeing Delamothe join Dearlove on the moral low ground to support his position on the public and professional impacts of Bristol, Alder Hey, and Shipman. Above the shuffling of closing medical ranks I can catch the words of Hampton’s 1983 editorial on the end of clinical freedom, “at best a cloak for ignorance, at worst an excuse for quackery.”

Dearlove demands evidence, as if an opiate. Lack of evidence of effect is not the same as evidence of lack of effect. The Department of Health’s MORI polls, whose responses are likely to be driven largely by recent direct medical contact, show that 14–17% of patients have reservations or negative opinions about the competence of doctors. In the British social attitudes surveys 16% of respondents expressed dissatisfaction with general practice and more with the NHS generally (www.data-archive.ac.uk/findingData/bsaTitles.asp). After Alder Hey, Cancer UK reported a sharp fall in donations of tissue to the national tumour bank for children’s cancer, and 3000 families joined in a legal action against the NHS.

To suggest that the political and professional responses to the unholy trinity were a conspiracy between the government and the media is as bizarre as failing to recognise that the actions of individual doctors and hospitals were not isolated events but the alarm symptoms of deeper problems. To caricature all this as an anti-medical machination of the Blair government seems to me the worst kind of medical spin.

Roger H Jones Wolfson professor of general practice Department of General Practice, King’s College, London SE11 6S roger.jones@kcl.ac.uk
Competing interests: None declared.

1 Delamothe T. Why this unholy trinity? Editor’s choice. BMJ 2007;335:0. (18 August.)

Public trust in doctors undented

The BMA does not take public trust in doctors for granted nor does it underestimate the potential for adverse reactions from the public or patients to events such as Bristol and Alder Hey. Accordingly, it has commissioned regular research via MORI on the issue and did so at intervals during the 1980s and 1990s and on an annual basis between 1999 and 2005. The findings support a conclusion of ongoing trust and belief in medical competence, with little deviation even at times of highly adverse publicity.

The public was asked whether it trusted a variety of professions and occupations to tell the truth. The figure (top) shows the findings for doctors over time. An additional question asked from 1999 to 2003 explicitly prompted respondents over negative publicity on doctors and asked whether in the light of this doctors did a good job. In 2000 specific reference was made to Bristol in the preamble and from 2001 onwards reference was also made explicitly to Alder Hey (figure (bottom)).

Neither set of findings seems to support the view that such events shook the foundations of public trust and professional confidence. Furthermore, respondents with experience of the NHS were more likely to state that they thought doctors did their job very well.

Jon Ford head, Health Policy and Economic Research BMA, London WC1H 9JP jon.ford@bma.org.uk
Competing interests: JF is employed by the BMA.

1 Delamothe T. Why this unholy trinity? Editor’s choice. BMJ 2007;335:0. (18 August.)

Sticking to standards, not together

If the profession continues to turn a blind eye to underperforming doctors we should not be surprised if the government takes action.

We have used locum doctors as part of the salvage process for a high health need, inner city practice over the past six months. Some of them missed potential red flags; had poor record keeping, prescribing, and referral practices; and proposed out of date management of chronic conditions. Some from elsewhere in Europe do not know how the NHS works, or how to work in the NHS. Perhaps not surprisingly—since locums are generally unsupervised and unsupported—most do not seem to reflect systematically on their clinical practice.

So far, in this one practice, over the past few months, we have referred one doctor to the National Clinical Assessment Service and another for formal investigation. Dozens of others have been referred to their host primary care trusts.

We are unusual in having an assertive quality process, routinely reviewing the day to day work of all our clinicians. And it takes up time and resources which we would rather spend on our patients.

Perhaps this explains why no one else has picked up these issues and these doctors. We think that there is widespread collusion between employers (often general practitioners, sometimes primary care trusts) who want holidays and other staff gaps filled; locum agencies that are apparently oblivious; and other doctors who seem to be in denial about poor performance even when they notice it.

Jones calls for professional unity. Surely this means sticking to standards rather than together?

Caroline Mawer general practitioner, Douglas Russell medical director, Tower Hamlets Primary Care Trust, Mile End Hospital, London E1 4DG caroline.mawer@gmail.com
Competing interests: None declared.

1 Delamothe T. Why this unholy trinity? Editor’s choice. BMJ 2007;335:0. (18 August.)
2 Jones R. The future of the medical profession. BMJ 2007;335:53. (14 July.)
Pathologist in Sally Clark case wins removal appeal

Clare Dyer BMJ

The pathologist for the prosecution in the Sally Clark murder case, who failed to disclose results of microbiological tests on her second baby, has won an appeal against his removal from the UK Home Office register of forensic pathologists.

An appeal panel of three people, headed by a retired appeal court judge, Sir Paul Kennedy, held that the ruling by a home office disciplinary tribunal in 2005 removing Alan Williams from the register was “unreasonable” (BMJ 2005;331:1355).

He was “a competent pathologist who made one serious error which he is unlikely to repeat,” said the panel, which substituted an 18 month suspension.

Because the suspension period has now expired, Dr Williams’s accreditation is now restored. But he is unlikely to be offered prosecution work because he will always be vulnerable to cross examination by the defence, said the panel.

In June 2005 the General Medical Council also barred him from undertaking Home Office pathology work or coroners’ cases for three years, although he was allowed to continue as a consultant histopathologist at Macclesfield General Hospital.

His appeal against the GMC’s finding of serious professional misconduct is expected to be heard by the High Court next month.

Mrs Clark was convicted in 1999 of killing her babies, Christopher and Harry, but cleared on a second appeal in 2003 after it emerged that the results of microbiological tests on body samples from Harry had not been disclosed in Dr Williams’s postmortem report. The samples showed the presence of Staphylococcus aureus in several body sites, including the cerebrospinal fluid.

The appeal panel said that Dr Williams had never sought to hide the results.

Several experts later said that S aureus was a postmortem contaminant, although an expert for the defence at the second appeal thought infection was the likely cause of death.

Parents warned to curb rise in measles cases by vaccinating their children

Roger Dobson ABERGAVENNY

Parents are being urged to have their children fully immunised with the combined vaccine against measles, mumps, and rubella (MMR) before school starts this month, after warnings that cases of measles are rising.

The latest figures from the Health Protection Agency show 480 confirmed cases of measles in the United Kingdom so far this year, compared with a provisional total of 756 cases for the whole of last year.

The measles increase is in communities where uptake of the MMR vaccine is low, such as travelling families

Public support for hybrid embryos rises, poll shows

Zosia Kmietowicz LONDON

The Human Fertilisation and Embryology Authority, the United Kingdom’s fertility watchdog, will decide this week whether to approve in principle the use of hybrid animal-human embryos for research.

Results of a public consultation on the matter, which were released before the authority’s decisive meeting that was due to be held on Wednesday 5 September, indicate a widespread lack of understanding among the public on the need and worth of creating hybrid embryos. However, support for hybrid research increases as people appreciate its possible applications.

Scientists are keen to develop hybrid embryos and a potential assured source of stem cells for research because the supply of human eggs and embryos is limited.

Results from an opinion poll show that 35% of respondents agreed that scientists should be able to create cytoplasmic embryos—those that use the shell of an animal egg—and implant human genetic material, making them 99.9% human.

But support for the use of cytoplasmic embryos rises to 61% if respondents think that the research may help understand some diseases, such as Parkinson’s disease and motor neurone disease.

For full results see www.hfea.gov.uk. See bmj.com for the outcome of the meeting.
Agency warns about dosing error for amphotericin

Nigel Hawkes LONDON

Two patients died in an oncology ward at Birmingham Heartlands Hospital in July after being treated with the wrong formulation of injectable amphotericin—a drug to treat fungal infections.

The National Patient Safety Agency (NPSA) has issued a warning over the use of the drug, but without disclosing where the two deaths referred to in its announcement had taken place. When questioned, the NPSA and the hospital confirmed that the deaths had taken place within hours of each other on 20 July (BMJ 2007;335:274).

Baljit Singh Sunner, aged 36, and Paul Richards, aged 35, were given the wrong dose of the drug. Amphotericin is available under several names and in different formulations—lipid and non-lipid—which have different recommended doses.

Confusion between the formulations can lead to a dose that is too high or too low, the agency said, leading either to inadequate treatment or a fatal outcome. It said that there had been 53 incidents involving the drug between January 2004 and July this year. Seven resulted in “low harm” to patients, one resulted in moderate harm, and 43 in no harm, it said.

Mark Goldman, chief executive of Heartlands Hospital, said, “A detailed investigation into the clinical care given to both patients has now been completed, the findings of which will be presented to the families in the next few weeks.

Phil Barnes, a solicitor representing the Richards family, said that they were considering legal action against the hospital on grounds of negligence.

Karol Sikora, a leading cancer specialist, was critical of the time it took the agency to issue its warning: “What I find bizarre is how slow this has been to get out,” he said. “The NPSA is not behaving in the way it advises—transparency, openness, and immediate transfer of information to the public domain.”

See: www.npsa.nhs.org

CORRECTION

GMC clears GP accused of giving court “junk science” on MMR vaccine

In this News article last week by Owen Dyer (BMJ 2007;335:416-7, 1 Sep), we wrongly stated that “the GMC panel concluded that all of the substantive charges against Dr [Jayne] Donegan were unproved except for the charge of quoting selectively from research.” Dr Donegan was in fact cleared on all six charges, the panel saying that in the reports that she provided she “did not fail to be objective, independent and unbiased.” The BMJ apologises to Dr Donegan for the error.
IN BRIEF

Alcohol poisoning increasing in the Netherlands: Since 2000 the total number of patients treated for alcohol poisoning in Dutch emergency care departments has more than doubled to about 1800 a year. Cases involving 10 to 14 year olds have also increased, to just fewer than 100. The study, published in the Dutch Medical Association journal, Medisch Contact, was based on a representative sample of one in five hospitals (www.medischcontact.nl).

Standards for record keeping produced: The Royal College of Physicians' health informatics unit has produced a national set of standards for record keeping for hospitals in a bid to improve patient care and reduce the risk of litigation (www.rcplondon.ac.uk).

Care of community mental health patients is improving: Mental health services in the community are improving, but concerns remain over social inclusion and access to counselling, a snapshot survey from the Healthcare Commission shows. The survey, of almost 160 000 service users at 69 trusts, shows that about one in three service users who wanted counselling or help with benefits did not receive it (www.healthcarecommission.org.uk).

Government to put graphic warnings on tobacco products

Amy Davis BMJ

The United Kingdom will be the first country in the European Union to use graphic warnings on tobacco products. The announcement coincides with figures released by the Department of Health that show England has 97% compliance with the ban on smoking in enclosed public places, which was introduced on 1 July.

97% of premises complied with banning smoking in enclosed spaces, and 79% displayed the correct signs

More than 88 000 inspections took place in the first two weeks of the smoking ban, including inspections of 1090 hotels, 6783 restaurants, and 9568 licensed premises. The local authority enforcement officers found that 97% of premises complied with banning smoking in enclosed spaces, and 79% displayed the correct signs. These figures are comparable to those for the first month of the smoking bans in Scotland and Ireland.

Dawn Primarolo, minister of state for public health, welcomed the statistics, “We predicted that it would be largely self enforcing based on experience elsewhere and the fact that three quarters of the British public supported the move.”

The department says that local authorities are continuing to work with local businesses to ensure that they understand the legal requirement to display “no smoking” signs at the entrance to all public buildings and workplaces.

Meanwhile, the health secretary, Alan Johnson, has said that he believes “picture warnings are the next vital step in reducing the number of people who smoke.” From autumn 2008 the packets of tobacco products in the UK will incorporate images that show the devastating effects tobacco can have on health.

“We hope this is a step towards the plain, generic packing of all tobacco products,” said Elspeth Lee, senior tobacco control manager at Cancer

NHS likely to end financial year with £1bn surplus

Adrian O'Dowd MARGATE

Clinicians and patients are paying the price for a predicted surplus in the NHS, it has been claimed.

The Department of Health in its latest quarterly report says that the NHS in England will have achieved a surplus of almost £1bn (£1.5bn; $2bn) by the end of this financial year.

The department said that most NHS trusts would be in balance by April of next year, with an overall forecasted surplus of £983m. This compares with an end of year surplus of £510m in 2006-7 and a deficit of £547m in 2005-6.

A small number of trusts will finish the year with a deficit, however. Hitchin-brooke Health Care NHS Trust is expected to have the largest deficit, of £17.5m, 24% of turnover.

There has been a cost to achieving the healthy financial position, however, said Hamish Meldrum, chairman of the BMA, who paid tribute to the staff who had worked hard to reach this point.

“You have to look at what trusts have done to get out of the red,” he said. “At the end of last year we saw services to patients being cut, with operations delayed, outpatient clinics cancelled, and referral management schemes—which were really only thinly disguised forms of rationing.

“There are still hospitals that are threatening to lay off hundreds of staff in order to break even. Budgets that used to be set aside for the training of doctors and nurses have been raided.”

Dr Meldrum told the BMJ, “There has been an impact on doctors and patients. I wouldn’t say doctors have been making sacrifices, but what has been happening has been affecting the way they can deliver best care to patients.

“There was poor financial management that allowed trusts to get into that state in the first place, but the timescale for which they were told they had to get out of it meant the measures they had to take were more extreme than we believed they needed to be, had they been given a longer timescale.

“We now want to work with government to ensure the money that now appears to be available is going back into the right areas.”

The quarterly report is available at www.dh.gov.uk.

One of the images to appear on cigarette packets from 2008
Mixed martial arts and boxing should be banned, says BMA

Caroline White LONDON

The BMA is renewing its calls for an outright ban on boxing, including mixed martial arts, ahead of a combat sport tournament to be held on Saturday 8 September in London’s East End.

The BMA’s Board of Science, which has issued a new report on the latest evidence of the damaging effects of boxing, says that the relatively new mixed martial arts format is just as dangerous.

Mixed martial arts involves various fighting techniques, in which a combination of wrestling, boxing, and martial arts is used to strike and grapple with opponents.

The sport was forced underground in the United States after sustained political pressure but has re-emerged there and is currently enjoying a surge in popularity, says the report.

London was set to host the Ultimate Fighting Championship, featuring the combat sport this weekend.

For the championship, which first started in 1993, contestants fight inside a metal cage. Each bout lasts three to five rounds of five minutes each until submission, knock-out, or disqualification, says the report.

“But because of its no holds barred nature, the [championship] fighters are open to a myriad of injuries, including subdural haematoma, thought to be one of the most common causes of injuries in boxing,” the BMA report says.

But contestants also risk fractures, tears, muscle and ligament sprains, as well as electroencephalographic abnormalities as a result of neck holding manoeuvres, it adds.

Supporters claim that this style of fighting is safer than boxing, and so far only one death has been reported.

But the report warns that “[mixed martial arts] tournaments, such as [the Ultimate Fighting Championship] are still in their infancy”; since 1993 there have been only 800 fights in 14 years, “it is still too early to draw any meaningful conclusions,” it says.

The BMA has been campaigning for the complete abolition of boxing on medical grounds since 1982.

The report, Boxing: An Update is available at www.bma.org.uk.

Cancer expert attacks research paper

Caroline White LONDON

A leading cancer epidemiologist has heavily criticised the funding and science of a report that compares different rates of cancer survival in 25 countries. The report linked cancer survival with access to new and innovative drugs.

The Karolinska 2 report, published earlier this year in the Annals of Oncology, concluded that access to cancer drugs affected survival and that the licensing process should be speeded up, with equitable access for all (2007;18(suppl 3):iii2-7).

But the epidemiologist Michel Coleman, who heads the cancer survival group of Cancer Research UK, has in the latest issue of the same journal questioned the credibility of the figures and methods used to arrive at these conclusions (2007;18:1433-5).

He says that estimates rather than actual survival rates were used. And the benefits of access to drugs were calculated using data for about 2003 but for patients who were diagnosed between 1990 and 1994, and the research concentrated on drugs that were not available at that time.

Contrary to what the report implies, he added, “For many adult malignancies, drugs are not the most important element of cancer survival.”

And he doubted that Roche Pharmaceuticals, which funded the research through an unrestricted educational grant, would have backed it if the “wrong conclusions” had been reached.

But a spokeswoman for Roche said that the company “has had no involvement in the analysis of data nor did it have any input into the report’s findings.”

In the same issue of the Annals of Oncology, the report’s authors, Bengt Jonsson, of the Stockholm School of Economics, Nils Wilking, of the Karolinska Institute, and Franck Lichtenberg, of the University of Columbia, New York, strongly refute any interference by drug companies in their research (pp 1585-7).

Dr Wilking told the BMJ that Professor Coleman had focused on “a very minor part” of the report. “We feel there is a political agenda behind this,” he said. “We used the data that were available.”
Proliferation of firearms is growing global health problem

John Zarocostas GENEVA

The growing number of civilians holding firearms is fuelling gun crime worldwide and is putting healthcare systems, especially in poor countries, under stress, an expert report says. Gun crime kills about 250000 people a year and injures many more.

“The proliferation of civilian gun arsenals is not likely to slow anytime in the foreseeable future,” says the report.

The study was conducted under the auspices of the Graduate Institute of International Studies, Geneva, and was funded by European governments; the United States; Canada; and United Nations agencies, including the World Health Organization.

The researchers estimate that civilians own about 650 million firearms, from handguns to assault rifles, worldwide—about 75% of the world’s 875 million known total. US citizens account for 270 million or 90 guns for every 100 citizens.

“There is a correlation between firearm ownership and firearm related injuries and death,” David Meddings, medical officer at WHO’s department of injuries and violence prevention, told the BMJ.

Keith Krause, programme director of the survey, says that a variety of factors are behind the increase in gun ownership among civilians.

“The main one is generally increasing wealth in some parts of the world that make people able to buy weapons, and, frankly, the failure of many states to provide for the security of individuals and their communities . . . leads to raising insecurity in urban zones, especially some parts of Africa and Latin America.”

The report says that 36091 deaths in Brazil in 2004 were related to firearms and adds that men in South America’s largest nation are 17 times more likely to be victims of gun violence in urban areas than women.

Dr Meddings said that gun related violence has a considerable effect on healthcare systems and pointed out that research in South Africa has showed that non-fatal shooting, such as serious abdominal gun shot injuries, require care that costs on average 13 times the per capita health expenditure.

Small Arms Survey 2007: Guns and the City is available at www.smallarmssurvey.org.

Balancing the books

Technically the US Food and Drug Administration goes out of business at the end of September. FDA commissioner Andrew von Eschenbach talks to Bob Roehr

Bob Roehr WASHINGTON, DC

It’s been a tough few years for the US Food and Drug Administration, as it grapples with the problem of partial funding from the drug industry, which may compromise its impartiality; potential conflicts of interest on advisory committees; and the increasing difficulties in assessing risks and benefits of drugs.

Congress is expected to pass a law to cover the FDA soon after it returns from its summer break. Meanwhile the FDA commissioner, Andrew von Eschenbach, a surgeon and friend of the Bush family, says he sees the controversies as part of a more fundamental shift. He thinks medicine is rapidly changing from the observation of symptoms of late stage disease to a molecular understanding of the mechanisms of earlier stages of disease, with interventions becoming increasingly early and pre-emptive.

“The challenge for us is to not be a barrier to that new future but to be a bridge to it,” the commissioner told a small group of reporters last month.

He acknowledges that the changes the agency must make may not be easy.

The commissioner says that the FDA has to be engaged in the full lifecycle of the drugs, devices, diagnostics, and foods that it regulates: “It has to begin to work much more effectively at the front end of the process and engage more actively in the discovery and development end of the continuum if it is going to succeed in its mission to protect and promote the health of every single American.”

The ongoing modernisation effort is known as the critical path initiative (see www.fda.gov/oc/initiatives/criticalpath). “Many of the pieces are intended to help us be able to work before the application, before that product even comes to us, to help build quality in, to help reduce the risk of failure, to be able to change the way that we are discovering, developing, testing, and bringing these products forward.”

He uses the example of pandemic flu. Under the old model the agency would sit and wait for a vaccine.
Gun related suicides fall in Austria, study shows

Jane Burgermeister VIENNA

The number of homicides and suicides involving firearms has fallen dramatically in Austria since gun control laws were tightened in 1997, concludes a study in the British Journal of Psychiatry (2007;191:253-7).

In 1997 the Austrian government tightened its legislation on firearms in line with a European Council directive on controlling the acquisition and possession of weapons.

The study found that the fall in the number of firearm related suicides was not associated with an increase in the number of suicides in which other methods were used.

A total of 1392 people, or 17 in 100,000, committed suicide in Austria in 2005, the lowest number since 1986. Before the more restrictive gun legislation the mean number of gun related suicides was 3.96 per 100,000 people, which fell to 2.67 per 100,000 in 2005.

Even after factors that increase the risk of suicide—such as unemployment and alcohol consumption—were taken into account the decrease remained significant.

The study recommends that countries with a high number of gun related suicides should tighten gun legislation as part of their national suicide prevention strategies.

“...If the weapon isn’t there there’s no possibility of using it,” she said. “There are some traumatic and dramatic events when even quite stable people might lose control, and that is when it is important to make sure there are no firearms about.”

She said that the legislation in Austria was effective because it was backed up by effective action. Police, for example, made regular spot checks to ensure that firearms in homes were kept locked away.

application, which might come at about the time of a pandemic itself, and “then start figuring out what was wrong with the application and what they had to go back and redo.”

But to truly protect public health “the FDA has to get out in front and start working with vaccine manufacturers [to] facilitate success and not simply try to eliminate failure.”

A controversial aspect of this is the programme known as the Prescription Drug User Fee Act, which began in 1992. It allows industry to pay a fee for expedited review of a licensing application. Those fees are used to hire additional FDA staff for that process. The agency has about 10,000 employees and had a $1.5bn (£800m; €1bn) budget in fiscal year 2007. The programme generates about 20% of the overall budget but about 40% of the budget for drug regulation.

Some critics say that the fee and accompanying “fast track” consideration of drug applications compromise the independence of the review—a charge that the agency denies. Congress has been unwilling to directly fund such expanded operations, however, because of financial constraints.

The FDA proposed increases in fees that would raise revenue to a projected $392.8bn a year for the next five years. Congress does not want to find $400m a year through cuts to other budgets or raising taxes.

“You can’t personalise a therapy until you have a personalised diagnosis; genetics and genomics is becoming an important part of the equation”

Von Eschenbach defends the programme: “It will allow us to be more much engaged in pre-application consultations with developers so that we are helping them get it right from the very beginning. That reduces risk; it makes the process much more effective and streamlined; it aligns things with us in the regulatory process.”

At the same time as this uncertainty, the FDA is grappling with scientific advances that affect its work. Tailoring drugs to personal genetic make-up is becoming important, for example, and is creating its own tensions.

“You can’t personalise a therapy until you have a personalised diagnosis; genetics and genomics is becoming an important part of the equation,” Von Eschenbach says. Increasingly, the FDA does not view products as drugs, biological agents, devices, or diagnostics, “It is beginning to see things as solutions that will almost invariably draw on the integration of those parts and pieces.”

The public’s perception of the agency is also a challenge. He says that for the FDA transparency means that the public must be able to understand the regulatory process: how the members of its advisory committees are selected and how the agency makes its conclusions. It does not necessarily mean that industry must make more proprietary information public. He argues that the FDA’s decisions are being made by dedicated professionals, and he uses the analogy of the doctor-patient relationship, in which “there has got to be a level of trust at some point.”

Because the fast track programme and its revenue will expire at the end of September, the FDA must begin the 60 day notification process to terminate employees’ positions that are funded through this mechanism. That should have begun on 1 August.

But the commissioner has resisted doing so because of possible effects on employee retention.

“There is nothing more important at the FDA than its people,” says von Eschenbach, calling the agency “an information management business that by its very nature is absolutely, critically dependent on intellectual capital.” That is reflected in the budget: 84% is spent on staff.

Later this year the FDA will announce a two year fellowship programme to recruit a thousand fellows a year at postdoctoral level.
Global burden of COPD has been underestimated

An international study set out to estimate the global prevalence of chronic obstructive pulmonary disease (COPD) and assess its risk factors. So far, 12 sites (from China, Turkey, Austria, South Africa, Iceland, Germany, Poland, Norway, Canada, United States, Philippines, and Australia) have completed data collection. More than 9400 people, aged 52 years or older, participated. Response rates differed between sites—from 14% to 87%.

The overall prevalence of stage II or higher COPD, according to the internationally agreed criteria, was 10.1% (11.8% in men and 8.5% in women), higher than in most previous studies. The risk of having stage II or higher COPD increased with age (risk doubled with each 10 years) and smoking. Still, people who never smoked had a similar risk for developing the disease as did people with a history of 0-10 pack years of exposure to cigarette smoke. In sites with the highest prevalence of the disease other risk factors seemed to be important—tuberculosis in Cape Town and occupational exposure to irritants, fumes, and vapours in Adana, Krakow, Lexington, and Manilla. Lancet 2007;370:741-50

Evidence for guidelines often lacks external validity

Guidelines for clinical practice have proliferated recently and most say they are backed up by research findings. A study of 338 recommendations from nine guidelines for management of cardiovascular risk found, however, that fewer than one third were supported by high quality evidence, as assessed by a grading scheme that considered the external relevance of the research to the target group and outcome, as well as its internal validity.

The study examined Canadian, European, and American guidelines for diabetes mellitus, dyslipidaemia, and hypertension and excluded recommendations for diagnosis and prevention, as well as those for pregnant women and people admitted to hospital. The quality of evidence was graded with a four point scale using the Canadian hypertension education programme (CHEP) scheme.

Overall, 231 (68%) of the recommendations were backed by randomised controlled trials, but in only 105 (45%) of these was the evidence from trials judged to be of high quality. Concern about the applicability of the study to the target population was the most common reason that evidence from randomised controlled trials was given a suboptimal grade under the CHEP scheme (64 of 126 recommendations, 51%). The use of surrogate outcomes, rather than patient oriented outcomes, led to downgrading in 59 of the 126 recommendations (47%).

A previous saline versus albumin fluid evaluation (SAFE) randomised trial of people admitted to intensive care for various conditions found no difference in survival at 28 days between patients randomised to fluid resuscitation with saline and those randomised to 4% albumin. However, a subgroup analysis of people with severe traumatic brain injury indicated that saline might be better than albumin for this subgroup of patients.

Saline may be better than albumin in severe traumatic brain injury

Adapted from N Engl J Med 2007;357:874-84

Hypogonadotropic hypogonadism may not need lifelong treatment

Boys with hypogonadotropic hypogonadism reach 18 years of age with incomplete or absent sexual maturation, low plasma concentrations of gonadotropins and testosterone, but no other abnormalities. The condition is treated with androgens, and it has always been assumed that lifelong hormone treatment is needed.

But a new study shows that hormone treatment should be discontinued periodically to see if the hormonal axis has matured and if adult amounts of sex hormones are being produced. The study describes 10 men in whom sustained reversal of hypogonadotropic hypogonadism was noticed after they stopped treatment because of failure to adhere, recruitment into neuroendocrine studies, or increased size of the testes while taking androgens.

Reversal was also seen in five of 50 men in whom hormones were stopped for a mean of six weeks. Testicular volume and concentrations of testosterone, luteinising hormone, and follicle stimulating hormone improved greatly, and spermatogenesis was active in all of the men. Six years later, 13 of the 15 men still had normal adult concentrations of sex hormones and did not need treatment. The mechanism of reversal is unclear. N Engl J Med 2007;357:863-73

A post hoc 24 month follow-up of the original SAFE trial included 460 people with traumatic brain injury. It confirmed that saline seems to be better than albumin for fluid resuscitation in those with severe injury (a score of 8 or less on the Glasgow coma scale). In the two years after randomisation, 71 of the 214 (33%) people with traumatic brain injury who received albumin died, compared with 42 of the 206 (20%) who received saline (relative risk 1.63, 95% CI 1.17 to 2.26). The corresponding numbers for the subgroup of people with severe injury were 61 of 144 (42%) and 32 of 146 (22%) (1.88, 1.31 to 2.70), but survival was not significantly different for people with Glasgow coma scores 9-12. N Engl J Med 2007;357:874-84

What’s new in the other general journals

Kristina Fister, associate editor, BMJ kfister@bmj.com

Weekly news round-up on general medical topics

BMJ | 8 SEPTEMBER 2007 | VOLUME 335
Whole grains help prevent type 2 diabetes

Women who participated in the nurses’ health studies I and II and did not have diabetes, cardiovascular disease, or cancer at baseline were followed up for 12-18 years. During this time, 6486 of the 1737 women were diagnosed with type 2 diabetes. These women self-reported eating fewer whole grains than women who did not get diabetes, but they also reported taking less physical activity, having a higher body mass index, smoking more often, drinking more alcohol and soft drinks, and eating more processed meats.

After extensive adjustment for these and other confounders, eating whole grains remained protective against type 2 diabetes. Associations for consumption of bran were similar to those for total consumption of whole grains, but after adjusting for bran no significant association was seen for consumption of germ.

The authors searched Medline and Embase databases for prospective cohort studies that looked at the association between whole grains and risk for incident diabetes. The resulting systematic review included four additional studies and had a total of 286 125 participants and 10 944 people with type 2 diabetes. It confirmed that the more whole grains people ate, the lower their risk of developing type 2 diabetes. The meta-analysis showed that increasing consumption of whole grains by two servings a day was associated with a 21% (95% CI 13% to 28%) decrease in the adjusted risk of developing type 2 diabetes. *PLoS Med* 2007;4:1385-95

Selenium supplements may increase risk of type 2 diabetes

Experiments on animals suggested that selenium might protect against type 2 diabetes, but a randomised trial now suggests that, rather than being protective, selenium may increase the risk of diabetes. A secondary analysis of a parent trial where diabetes was a secondary outcome comprised 1202 people without diabetes at baseline, who were randomised to 200 μg of selenium daily, or placebo. After an average follow-up of 7.7 years, 58 people taking selenium had type 2 diabetes, compared with 39 people in the placebo group, giving a hazard ratio of 1.55 (95% CI 1.03 to 2.33). Furthermore, higher plasma concentrations of selenium at baseline were associated with an increased risk for developing diabetes. People whose plasma concentration of selenium was in the highest third had a 2.7-fold increased risk of developing type 2 diabetes during follow-up compared with those in the lowest third.

Before selenium was found to be essential for immune function and thyroid function, and to protect against oxidative stress, it was thought to be highly toxic to animals and humans, says the linked editorial (p 271). Most people who live in the United States get enough selenium from food, and supplementation seems to be harmful. The editorial reminds us that no dietary supplements have yet been shown to prevent cardiovascular disease or cancer in Americans. *Ann Intern Med* 2007;147:217-23

Cardiac support devices still cause serious adverse events

A new study reports on 133 people with end stage heart failure who received mechanical cardiac support by a continuous flow pump (HeartMate II, Thoratec) while waiting for a heart transplant. The device is marketed as being small enough for women and adolescents; as having good mechanical reliability because only one part moves; and as being quieter than similar devices, making it more comfortable for patients.

Three quarters of the participants survived to 180 days and were either still eligible for transplantation and had a functioning mechanical circulation support, or they had received a heart transplant. At three months, people who received the device had better functional status and quality of life compared with baseline. None the less, adverse events were common, including postoperative bleeding, stroke, right heart failure, and percutaneous lead infection.

This observational study did not compare the procedure with any alternative approaches. The linked editorial (p 846) describes many similar devices, emphasises that no clinical trials have compared any of them head to head, and provides a guide on how to choose the most appropriate device for a given patient. *N Engl J Med* 2007;357:885-96

Be careful with claims that sex modifies genetic risk of disease

Experience from observational studies and randomised trials teaches us that sex was often misinterpreted as a modifying factor in the risk of disease or response to treatment. For example, on the basis of one underpowered subgroup analysis, we believed for more than a decade that aspirin didn’t work for secondary prevention of stroke in women, while we knew it worked for men.

A group of researchers now set out to test the reliability of claims about sex differences in genetic studies. Their systematic review found 77 relevant reports whose authors made 432 claims of gene-sex interactions. In two thirds of these claims, the analyses according to sex were prespecified, rather than post hoc, but just under 13% of the claims were appropriately documented and reported. The authors reanalysed the 188 comparisons for which they had raw data and found that 105 were not statistically significant. Of the 83 that were significant more than half had modest P values—between 0.01 and 0.05. Furthermore, of the 60 claims researchers deemed most internally valid, only one was repeated in at least two other studies.

Ideally, gene-sex interactions should be explored in prespecified and adequately powered subgroup analyses, but post hoc analyses can be useful too. The key to reaching valid evidence is in clear and complete reporting, and in repeated testing of results by several studies. *JAMA* 2007;298:880-93

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**INCREASED WHOLE GRAIN INTAKE AND RISK OF TYPE 2 DIABETES**

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyer</td>
<td>0.85 (0.75 to 0.96)</td>
</tr>
<tr>
<td>Fung</td>
<td>0.80 (0.71 to 0.90)</td>
</tr>
<tr>
<td>Montonen</td>
<td>0.80 (0.81 to 1.01)</td>
</tr>
<tr>
<td>van Dam</td>
<td>0.65 (0.55 to 0.78)</td>
</tr>
<tr>
<td>NHSI</td>
<td>0.70 (0.62 to 0.79)</td>
</tr>
<tr>
<td>NHSII</td>
<td>0.83 (0.69 to 0.98)</td>
</tr>
<tr>
<td>Combined</td>
<td>0.79 (0.72 to 0.87)</td>
</tr>
</tbody>
</table>

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**EFFECT OF SELENIUM SUPPLEMENTS ON INCIDENCE OF TYPE 2 DIABETES**

![Graph](Adapted from Ann Intern Med 2007;147:217-23)
Guideline for irritable bowel syndrome is published

A guideline on assessing and managing irritable bowel syndrome has been produced by the British Society of Gastroenterology after a systematic literature search, internal and external review (including from patients), and achievement of consensus.

It recommends categorisation by bowel habit, few investigations, being alert to alarm features, and attention to patients’ concerns, including psychological features. Trials are stated to have shown that benefit is gained from cognitive behaviour therapy and psychodynamic interpersonal therapy, which help patients to cope; antispasmodics and tricyclics, which may help pain; and ispaghula, which relieves pain and improves bowel habit. Other major benefits are shown to come from 5-HT, antagonists, 5-HT, agonists, and selective serotonin reuptake inhibitors. Ten suggestions are made for future research, in particular the need to identify which patients are likely to respond to specific treatments.

Gut 2007 doi: 10.1136/gut.2007.119446

Military personnel in 2003 Iraq war are free from depleted uranium

Urine samples from 369 UK military personnel involved in the major combat phase of the 2003 war in Iraq have shown no evidence of uptake of depleted uranium (238U), with normal ratios of 238U/235U (the latter representing natural uranium from dietary exposure). This was despite many subjects being in vehicles hit by a depleted uranium round, working in contaminated vehicles, or treating casualties exposed to depleted uranium. The investigators find the results reassuring, suggesting any uptake of depleted uranium in their study sample would be very unlikely to have any health implications.

Occ Environ Med 2007 doi: 10.1136/occenvironmed.2007.032599

Cardiac care is poorer for patients with psychosis

Records of 3.26 million patients from 485 UK general practices have shown that among the 701 patients with a diagnosis of both coronary heart disease and schizophrenia (and/or bipolar disorder), cholesterol concentration was less likely to be recorded and statins less likely to be prescribed than in those with coronary heart disease alone. The researchers found no differences between these patients and 127 000 patients with coronary heart disease, for other specified care indicators (smoking status and cessation advice; blood pressure recording; referral for those with angina; and treatment with a β blocker or antithrombotic). Patients with schizophrenia were 15% (95% confidence interval 8% to 20%) less likely to have a recent prescription for statins and 7% (3% to 11%) less likely to have had a recent record of cholesterol concentration despite having a higher rate of risk factors.

Heart 2007 doi: 10.1136/hrt.2006.110171

ACE inhibitor fetopathy may have long term implications

Long term follow-up of three children whose mothers in pregnancy had received the angiotensin converting enzyme (ACE) inhibitor enalapril found that two had impaired renal function, one had severe hypertension and proteinuria, and all three had polycythaemia.

One child was found to be hypertensive at age 10 years and by the age of 14 had mild renal failure (glomerular filtration rate 60 ml/min/1.73m2); between the age of 16 and 18 he required five phlebotomies for polycythaemia. Another child had shown a moderate fall in glomerular filtration rate since the age of 3 years (with a rate of 96 ml/min/1.73m2 at age 12.8 years) associated with mild proteinuria and isolated polycythaemia. The third child had normal renal function but low to normal concentrations of serum erythropoietin.

All three children had transient acute anuric renal failure as neonates (a recognised adverse effect of the mother taking an ACE inhibitor during pregnancy), hypoperfusion of the fetal kidney being a key mechanism in renal tubular dysgenesis. The authors recommend careful follow-up of all children with ACE inhibitor fetopathy.


It’s safe to head a soccer ball

Twenty three amateur soccer players repeatedly headed a ball, submitting to a lumbar puncture 7–10 days later. Cerebrospinal fluid biomarkers of neuronal injury (neurofilament light protein, total tau, glial fibrillary acidic protein, the calcium binding protein S100B, and albumin) were all normal.

Levels of the biomarkers did not correlate with the number of headers (10 in 10 players and 20 in 13 players, and none in 10 healthy controls). The authors point out that head injury in soccer is more likely to occur from head to head or head to goalpost collision.

Since 2003 the government has created a market in primary care and replaced the old general medical services contract governing general practitioners with a range of alternatives. The changes gave primary care trusts in England, health boards in Scotland, and local health boards in Wales new powers to negotiate contracts with commercial companies. Many of the changes to regulation were intended to facilitate the entrance of new providers to the healthcare market. General practitioners are no longer contracted directly to the NHS but to the firms or practices that contract with primary care trusts in the market. These bodies are in turn regulated largely through the market mechanism of commercial contracting. We explain how the reforms change the basis of government control and mechanisms for public accountability in primary care and the possible effects on staff and patients.

Breaking the monopoly

The primary care market is premised on the break-up of the general practitioners’ monopoly of the provision of primary care. From 1948 until 1997 GPs were contracted to work for the NHS under a general medical services contract between the secretary of state and the individual practitioner, on terms negotiated nationally. The contract was set out in the provisions of the Red Book, an extensive set of guidelines and regulations covering range and quality of services, staffing, and premises.

The national contract was broken in 1997 by the introduction of personal medical services contracts, which allowed local negotiations between general practitioners and commissioners about service specification. In 2003 the Health and Social Care (Community Health and Standards) Act ended the general practitioners’ monopoly over the provision of primary care to the NHS, allowing primary care trusts to commission care from “anyone capable of securing the delivery of such services.” The national agreement under which general practitioners were contracted directly to the secretary of state for health was replaced by four contracts:

- A new general medical services contract between practices and trusts
- An alternative provider of medical services contract
- A locally negotiated personal medical services contract
- A primary care trust medical services contract enabling trusts to employ general practitioners directly on salary.

General practitioners no longer have a direct contractual relationship with the state because the contract is between the practice or the company and the primary care trust. They may continue as partners in a practice; as employees of practices, trusts, or corporations; as directors or shareholders of commercial companies providing primary care; or as subcontractors to whatever entity holds the primary contract.

In March 2007 about 30 companies held commercial contracts to provide primary care services in England through their ownership of 74 health centres and general practices, excluding out of hours contracts (table). The companies comprise general practitioner owned and operated companies; international healthcare corporations, including drug companies; companies with commercial links to the drug industry and healthcare corporations; companies providing catering, cleaning, and laundry services under private hospital contracts; and some joint ventures between these.

General practitioners’ professional control over the range and provision of primary care services has been substantially reduced. Before the reforms doctors were contracted by the government to provide “all necessary and appropriate medical services of the type usually provided by general medical practitioners.” The arrangement specified doctors’ conditions of service to the NHS in terms that maximised professional autonomy. Under the new standard contract it is contractors, not general practitioners, who have the duty to provide services “appropriate to meet the reasonable needs of . . . patients.” It is the contractor’s duty to manage services required by patients registered with them, “offering a consultation and, where appropriate, physical examination for the purpose of identifying the need, if any, for treatment or further investigation; and the making available of such treatment or further investigation as is necessary.
The national contract was broken in 1997 by the introduction of personal medical services contracts

and appropriate.” Contractors may also determine the way in which services are delivered and determine, “in their reasonable opinion,” when home visits take place, when out of hours services are offered, who is removed from patient lists, and which serious incidents relevant to a contractor’s performance are notified to primary care trusts. Furthermore, the new system allows for contractors to manage specialist services formerly provided in hospitals but moved out into the community.

Change in legal basis for service provision

The introduction of commercial providers changes the legal basis of service provision, moving it from public law under direct government control to private commercial law. Whereas NHS contracts between primary care trusts and providers of primary medical services are non-legal agreements between NHS bodies—that is, trusts and strategic health authorities—commercial providers have commercial contracts that are enforceable in courts under private law.

Contracts with limited liability companies mean that the NHS cannot obtain redress beyond the value of the company’s shareholding if the company fails to deliver on its contracts or becomes bankrupt. The NHS commissioner has no recourse to other assets or income of the shareholders.

Unbundling primary care services

General practitioners are no longer bound to provide their patients with integrated and comprehensive services. The new contract has separated out primary care services into essential services, which are the minimum that must be provided to patients who are ill; additional services, such as screening, child health surveillance, and immunisation; and enhanced services, including such things as management of chronic diseases, minor surgery, and more specialist services currently provided in hospitals, which a practice can choose whether to provide.

An important consequence of this is that these services can be subcontracted to different providers. New entrants to the market are no longer committed to provide a full array of primary services to all patients but may select the services they wish to provide, if the primary care trust agrees.

Regulatory framework and professional control

The change from professional regulation and direct government control to commercial contracting has been introduced in advance of a system to regulate the new market, which was only being consulted on in November 2006. The Department of Health proposes that market forces should be the principal regulatory control on contractors. “Effective use of competition” and “healthy competition between different services users,” not “top-down performance management” is the preferred model, according to the consultation document. In this model regulation is chiefly through the contracts.

Although the proposals do not provide for a new primary and community services regulatory framework, several acts of deregulation accompany the reformed contracting system. Firstly, freedoms have been introduced to increase contractors’ ability to manage new financial risks by adjusting their cost base and restructuring their costs. For example, the government allows alternative primary care providers considerable freedom with respect to staff terms and conditions and the mix of staff employed. The contract prices, although negotiated locally with primary care trusts, are not necessarily bound by national agreements such as the terms of employment for salaried general practitioners or a requirement to guarantee NHS pensions for their employees, or detailed requirements about the way in which care is provided.

Secondly, the introduction of practice based commissioning gives contractors budgetary control over a wider range of services. Contractors can hold the NHS budget not just for primary care but also for acute hospital care and community services, making them both gatekeepers to and budget holders for services.

Thirdly, quality regulations do not apply to all providers. Service quality is the responsibility of the primary care trust and is regulated through the quality and outcomes framework. Although the quality and outcomes framework is the element of the new contract that has most exercised general practitioners, it does not apply to alternative contractors. These contractors therefore have greater latitude to adopt new models of care, change staffing patterns and skill mix, and allocate funding for services.

Fourthly, rules on the sale of goodwill have been lifted. Goodwill is defined as the practice of valuing a business on the basis of profits expected to flow from the contracts it holds, in addition to the value of tangible assets such as buildings and equipment. Sale of goodwill in primary care was banned in the NHS. In April 2004, however, the ban was lifted for all practices providing enhanced and additional services, allowing practices to be bought and sold on the basis of the number of patients they have and the income they represent.

Finally, providers have been given the power to devote part of their NHS budgets to advertising their services. A voluntary code of practice was published in 2006 allowing providers “to make more information about their services available to patients and referring clinicians in order to help them make choices and advise patients.” However, no limits were set on the proportion of NHS spending that can be devoted to advertising.

Implications of the reforms

John Reid’s statement that the new general practitioner contract “signals the most ambitious attempt to reform primary care services since the creation of the NHS” is fully justified. The government has moved away from direct government control and systems of professional regulation to a system where commercial contracts awarded to competing providers constitute the government’s preferred model of public service reform.

The changes raise important questions about government control and public accountability. Although primary care trusts are formally responsible for primary and community services, it is not clear how they will be able to influence the market when commercial contracts are in place.

The Department of Health proposes that management of financial performance will not be extended to privately owned providers but will be the responsibility of “their owners/trustees/shareholders.” This proposal is at odds with an earlier commitment by government to Lord Sharman’s recommendations that public money should remain publicly accountable even when it is channelled through private firms. So how will NHS spending be accounted for in the new primary care market?
Companies with commercial contracts to provide primary and community medical services to the NHS in England (March 2007)

<table>
<thead>
<tr>
<th>Company</th>
<th>Service, area covered, contract type (where known)</th>
</tr>
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<tbody>
<tr>
<td>Private healthcare corporations</td>
<td></td>
</tr>
<tr>
<td>BK Health UK</td>
<td>5 medical and health centres (4 practices run under PMS in England and 1 GMS Wales)</td>
</tr>
<tr>
<td>Care UK (formerly Anglia Secure Homes)</td>
<td>Out of hours provision across Essex</td>
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<tr>
<td></td>
<td>HM Prison/Young Offenders Institute, Chelmsford</td>
</tr>
<tr>
<td></td>
<td>HM Prison Wellingborough</td>
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<tr>
<td>Chivers McCrea (subsidary of Mercury)</td>
<td>23 general practices</td>
</tr>
<tr>
<td></td>
<td>Out of hours care</td>
</tr>
<tr>
<td></td>
<td>Variety of contract forms: GMS, PMS, and APMS</td>
</tr>
<tr>
<td>Concordia Health</td>
<td>2 general practices</td>
</tr>
<tr>
<td>IntraHealth</td>
<td>4 general practices (PMS)</td>
</tr>
<tr>
<td>Mercury (subsidary of Tribal Group)</td>
<td>1 primary care centre, City and Hackney primary care trust (integrated PMS and WIC this one not explained in footnote)</td>
</tr>
<tr>
<td>Nestor</td>
<td>Out of hours provider for 44 primary care trusts and 5 Welsh health boards</td>
</tr>
<tr>
<td></td>
<td>2 primary care centres</td>
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<tr>
<td></td>
<td>Forensic medical services—younger offender institutions, police authorities, detention centres</td>
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<tr>
<td>Serco</td>
<td>All out of hours care for Cornwall</td>
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<tr>
<td></td>
<td>Out of hours care in Cardiff</td>
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<td></td>
<td>Cardiff and Leicester prisons</td>
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<tr>
<td>United Healthcare</td>
<td>General practice, Derby</td>
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<tr>
<td>Drug company</td>
<td></td>
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<tr>
<td>Pfizer Health Solutions</td>
<td>Chronic disease management for North Birmingham and East Birmingham primary care trusts</td>
</tr>
<tr>
<td>Joint ventures</td>
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<tr>
<td>Hillingdon Healthcare/</td>
<td>General practice services in Hillingdon (APMS)</td>
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<tr>
<td>Hamoni</td>
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<td>Harmoni /WCI Group</td>
<td>Out of hours care for 11 primary care trusts</td>
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<tr>
<td></td>
<td>9 primary care centres</td>
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<tr>
<td>General practitioner providers</td>
<td></td>
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<tr>
<td>Aston Healthcare</td>
<td>General practice, Mansfield</td>
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<tr>
<td>Central Surrey Health</td>
<td>Community nursing</td>
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<td>Devon Doctors Cooperative</td>
<td>Out of hours service, Devon</td>
</tr>
<tr>
<td>GatDoc</td>
<td>Out of hours service, Gateshead</td>
</tr>
<tr>
<td>Hurley Group</td>
<td>Stennid Lane, Peckham</td>
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<tr>
<td></td>
<td>Riverside Medical Centre</td>
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<td>Hurley Clinic, Lambeth</td>
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<td>Local Care Direct</td>
<td>Out of hours service, West Yorkshire</td>
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<td>NEWDOC</td>
<td>Out of hours service, North Warwickshire and District</td>
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<td>Northern Doctors</td>
<td>Out of hours service, North Tyneside primary care trust</td>
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<td>Urgent Care</td>
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<tr>
<td>On Call Care</td>
<td>Out of hours service, Maidstone</td>
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<tr>
<td>Rushcliffe Mutual</td>
<td>Provision of services and practice based commission in Nottinghamshire (APMS with primary care trust)</td>
</tr>
<tr>
<td></td>
<td>21 general practices</td>
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<tr>
<td>SELDOC</td>
<td>Out of hours service Lambeth, Lewisham, and Southwark</td>
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<tr>
<td>Shropdoc</td>
<td>Out of hours service for Shropshire, Telford and Wrekyn, Powys and Wrexham</td>
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<tr>
<td>Thamesdoc</td>
<td>Out of hours service for Surrey primary care trust</td>
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<tr>
<td>Walsgrave</td>
<td>Surrey Heath and Woking local prison (APMS)</td>
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<tr>
<td>Wolverhampton Doctors on Call</td>
<td>Out of hours service for primary care trust</td>
</tr>
<tr>
<td>Widoc</td>
<td>Out of hours service for West Sussex, 7 out of hours surgeries</td>
</tr>
</tbody>
</table>

GMS= general medical services contract, PMS=personal medical services contract, APMS=alternative provider of medical services contract.

Recent inquiries by the National Audit Office and the public accounts committee into out of hours services\(^1\) and the consultants' contract\(^2\) suggest that primary care trusts and the Department of Health have insufficient information and knowledge to negotiate clinical care contracts. A National Audit Office survey of primary care trusts and out of hours services found that the majority of contract terms were drawn up by contractors not by commissioners. These findings are consistent with predictions from the economics literature that complex services, and clinical care in particular, cannot be successfully regulated through contracts because commissioners can never specify contract terms in sufficient detail to meet all contingencies.\(^3\)

Finally, the introduction of commercial contracts will see the jurisdiction for healthcare policy and law move away from national government to the European Union. However, the EU’s mandate is trade and commerce and not public health.\(^4\)

The government has allowed more firms to provide NHS funded primary and community care because it believes that competition will improve the public health. But nothing is yet known about the consequences for access, costs, quality, and accountability. It is surely time to evaluate the policy.

Allyson M Pollock professor, David Price senior research fellow, Elke Viebrock lecturer, Emma Miller research fellow, Centre for International Public Health Policy, University of Edinburgh, Edinburgh EH8 9AG, Graham Watt professor, Department of General Practice, University of Glasgow, Glasgow

Correspondence to: A M Pollock allyson.pollock@ed.ac.uk

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Should terminally ill patients have the right to take drugs that pass phase I testing?

Emil J Freireich

Professor, Special Medical Education Programs, University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA efreire@mdanderson.org

YES

Around half a million people will die from cancer related causes in the United States this year. In the US, as in much of the Western world, patients know their diagnosis and are often given a hopeless prognosis. For most, the option of participating in phase I and phase II clinical trials of new drugs that offer some promise helps them remain optimistic. Clearly, they should have the right to take drugs that have passed phase I testing.

The problem is that most cancer patients cannot participate in phase II trials because they are either ineligible or they are unable to fulfil the financial and social requirements for participating in such trials, such as staying in the centres conducting these trials, sometimes for many weeks or months. The problem is clearly not one of safety because these drugs have completed phase I clinical trials and there is sufficient information about them to justify a phase II trial to determine efficacy.

Phase II trials are designed to give the highest probability of a positive outcome. Thus, they have patient eligibility requirements which assure that only the healthiest patients at the earliest point in their disease are entered. These decisions are not based on any reasonable evidence that patients who are ineligible would not benefit, but are strictly designed to fulfil the regulatory requirements established by bodies such as the Federal Drug Administration (FDA) and the regulatory components of industry and academia that govern these clinical trials.1,2

Compassionate prescribing

In the modern electronic era, most of the patients with hopeless cancer diagnoses have access through the media and the internet to information about promising new drugs that are in phase II clinical trials. These patients would like very much to receive these drugs to offer them some hope, but for the reasons mentioned above are unable to participate in those trials. So why not offer these drugs to these patients on a compassionate basis?

The first reason given is usually the safety concerns. Without knowledge about how renal function, cardiac function, age, etc affect the action of the phase I drug, side effects might occur that could be harmful to the patient or, perhaps more importantly, the continued development of the drug. I think this objection is relatively minor since it simply states the benefit: risk ratio problem—that is, these patients are prepared to volunteer to expose themselves to increased risk because of their hopeless prognosis and because of the promise of the new drug.

The second objection is that it will interfere with the development of the drug. However, in the past, the FDA and the National Cancer Institute have allowed compassionate use of drugs and have found that it actually accelerates development. This is because when patients are offered compassionate use of an experimental drug, their doctors have to collect information as systematically as in the research protocol and submit it to the sponsor. Information is therefore available about use of the drug outside trial conditions. For example, if patients with impaired renal function not only tolerate the drug but respond, it will assist in drug development to have that knowledge collected systematically.

Drug industry profits

Another objection is that the drug industry might use this device to profit from investigation of a phase I drug. I believe this is a trivial objection because the usual strategy for compassionate use is that the drug is provided at cost. The last, and perhaps the most serious, objection is that expanded access would interfere with the clinical trial process. This certainly should not be the case. The clinical trial process is governed by the regulatory bodies in government, in industry, and in academic institutions. The unfortunate consequence of this is that physician scientists, who have the most experience, the most training, the most knowledge, the most productivity, and the most creativity, are completely excluded from this process. Because of the relationship between the regulatory organisations of government, industry, and academia, the academic physician scientist can only implement protocols that have been developed by the drug developer with direction from the regulatory agencies. Expanded access would bring the doctors back into the drug development process and, rather than damage the clinical trial system, would greatly expand its effectiveness and value.

In summary, patients with advanced cancer and limited life expectancy should have the same privilege as all individuals in a free society—that is, to decide their own benefit: risk ratio. It is tragic that regulatory bodies have created a circumstance where people have to live in an aura of hopelessness even though they have the will, the resources, and the ability to expose themselves to the risk of participating in investigational studies and to enjoy the potential for benefit. The solution is legislation or judicial action to permit expanded access to experimental treatments for patients with limited life expectancy.3,4

Competing interests: None declared.
The United States is considering allowing experimental drugs to be given to people at the end of life. **Emil J Freireich** believes patients should be able to judge the risks for themselves, and **Dean Gesme** counters that the use of such drugs outside trials will damage both individuals and science.

**NO**

Partially tested therapies cannot be allowed to substitute for good medical care. Hippocrates stated that our role as doctors is always to help or, at least, to do no harm. Those precepts apply equally to patients with minor ailments and those with terminal conditions.

In the United States, the Food and Drug Administration has proposed expanded access to investigational drugs for patients with terminal illnesses after initial safety (phase I) trials but before final approval for marketing. This would apply to selected drugs already in phase II and III testing. The legal action filed against the FDA by the Abigail Alliance seeks to make available drugs for which phase I trials are found unacceptable, and, of those approved, most provide incremental improvements rather than lifesaving treatments.

The allure of promising new drugs continues to engender false hope, which has all too often diverted time, resources, and attention from more appropriate efforts to minimise symptoms and enhance the quality of life for terminally ill patients and their families. Inappropriate expectations for untested new drugs are commonly promulgated by investigators eager for grant funding, companies searching for capital, writers eager for a good storyline, and uncomfortable practitioners who would rather avoid dealing directly with the complexity of end of life issues.

**Damage to clinical trials**

Patients may prefer to take partially tested drugs outside trials to avoid the constraints of a larger protocol study. However, this would subvert accrual of patients to phase II and III trials and ultimately delay the approval of those new drugs. Thus the needs of the many may become subservient to the desperate desires of the few.

False hopes for unproved drugs can also erode the clinical trials system by substituting clinical enthusiasm and wishful thinking for evidence based medicine. The best analogy may come from the many years in which autologous bone marrow transplant was considered standard treatment for advanced breast cancer despite the lack of data concerning efficacy. Well designed clinical trials failed to find willing participants as both patients and many doctors were convinced that this procedure was life saving. We now know that thousands of women experienced unnecessary toxicities, prolonged hospital stays, and lost time with families for what has now been shown to be inappropriate care. Rather than repeating this tragedy with each promising new drug, we should focus our clinical energies on the optimal use of existing treatments and the enhancement of the current clinical trials system.

Investigational drugs may not be accessible to patients even if government authorities grant patients the freedom to access them. Most doctors are likely to be unwilling or unable to assume the responsibility of obtaining adequate informed consent from patients who are desperate for treatment and often unable to assimilate the possible risks involved.

Similar issues of liability and oversight may stop institutions from allowing open access to partially tested drugs. The issue of defining who is, or is not, terminally ill can be most difficult, let alone delineating when existing therapies might offer no possible benefit. Indeed, who will decide which of the many investigational drugs would be best for an individual patient? Do we allow the marketplace to substitute for best practices and evidence based medicine?

Many drug firms have opted not to join current expanded access programmes for drugs in later stages of development and are opposed to providing investigational products outside of approved phase II trials. The costs of drug production can be high, with limited production early in a drug’s life. More importantly, there is concern that anecdotal toxicities for drugs used outside structured trials might lead to delayed approval, additional expensive testing, or adverse publicity that could jeopardise a process on which costs and profits of millions of dollars are in the balance.

Who will bear the costs of open access to these partially tested drugs? Will government and other payers who are now seeking to minimise payments for marginally beneficial therapies be willing to pay for unproved drugs outside of formal clinical trials?

Finally, while all doctors dream of the miracle cure for each of their terminally ill patients, we must accept the duty and responsibility to conform to both the principles of evidence based medicine and the precepts of appropriate end of life care. This includes the identification of false hopes and the substitution of realistic goals, enlightened hopes, and attainable expectations. This may be the greatest test for the truly caring and compassionate physician.

**Competing interests:** None declared.

All references are on bmj.com
Journalists: anything to declare?

Drug companies wouldn’t pay for the media to attend their events if they didn’t think it would affect coverage, yet journalists’ competing interests usually remain undeclared.

Much as I like to think that I am cynical and worldly, being a doctor and a journalist, the world still holds some surprises for me. Conflict of interest is a subject that creates heat and concern, not least among journalists, who often stumble on a banal and openly declared interest and use it to build fantasies of medical corruption and Pulitzer prizes.

Although there is good evidence for the venality of drug companies in the way they conduct their public relations—and the success of this PR in influencing published academic work—it is often tempting to point out that the entire culture of academic funding has changed over the past 20 years and that politicians, journalists, and the public themselves might take some responsibility for the fact that governments choose not to fund academic work.

But that’s a digression. Given the puritanical stance of so many journalists, I was surprised last week by an email circular I received from a science writers’ mailing list. It was from the Aspirin Foundation, a group funded by the drug industry, and it was offering—on behalf of Bayer Healthcare—to pay expenses for journalists to attend the European Society of Cardiology’s conference in Vienna.

Now aspirin is without doubt an excellent and cheap drug. But in my naivety I had no idea such things went on. I pinged off a few emails to friends and colleagues. Most poked fun at my innocence—quite rightly—but some were helpful. Not only is it extremely common for journalists to take money from drug companies, but there have been some astonishing cases in recent history, including one memorable case where a PR company invited journalists to “an exclusive preview” of new laser eye technology, with the offer to “discuss free treatment in return for editorial features.”

“I organise the media programmes for a number of medical conferences run by scientific societies,” said one person who, without wishing to be melodramatic, has asked to remain anonymous, “and I reckon at least 50% of the journalists present are paid for by drug companies. They get pretty well looked after too—first class travel, five star hotels, posh dinners, etc. Some of them indulge in double dipping, where they are paid by the day by the drug company and then by the publication that takes whatever they have written. Sometimes they don’t even use the press room, spend all their time in company hospitality suites, and just go to company sponsored satellite sessions and press conferences.”

What was more striking was the range of responses I had: some laughed at my naivety; some expressed outrage at the venality of their colleagues; and some were emotive and defensive, playing down the idea that there was anything to worry about and explaining that journalists could detach themselves from such ties and remain impartial. In fact the arguments almost exactly mirrored those among medics, played out in editorials and letters about conflict of interest in academia, about 15 years ago.

Then, as now, it’s easy to become hysterical about conflicts of interest (or “competing interests,” to give them their more considered name). A conflict of interest is “a situation not a behaviour,” and simply receiving funding or jollies does not mean that you will change your mind. But it’s a discussion worth having: only one journalist friend had seen a declaration of competing interests appearing next to their article (it was in the Guardian), and few journalists I spoke to could think of any explicit policies on the subject.

Furthermore, there are real dangers in being too close to PR people: lovely though they may be, their trade is, by definition, manipulation. Drug companies are businesses, with responsibilities to their shareholders, and they wouldn’t pay for journalists to attend their events if they didn’t think it would affect media coverage of their product. After all, a journalist’s article is far more credible than a paid advertisement, for anybody’s money, and more likely to be read by potential consumers.

As we know from medicine and academia the ways of conflicting interests can be subtle. Not just money, hotels, and free eye surgery, but also the “revolving door”—the free movement between “mass media journalist” and “industry copywriter” is every bit as worrying as, for example, the gay dance from the US Food and Drug Administration to drug company.

But most often it is simply about fostering a relationships. To take a passing example, in 1982 the Aspirin Foundation of America—a body similar to the one offering money from Bayer—fought a successful media campaign against a US government proposal to put warning labels on aspirin packages. As you may remember, the possible link between Reye’s syndrome, which affects children and is often fatal, and aspirin had recently become prominent.

It’s much easier to get someone to take your calls when they’ve taken your money. And I, for one, will in future read outraged media reports of academic conflicts of interest with a wry smile indeed.

Ben Goldacre is a doctor and writer, London ben@badsience.net
Families of patients with premature coronary heart disease: an obvious but neglected target for primary prevention

Risk of premature coronary heart disease is increased in the families of affected patients. C K Chow and colleagues argue that targeting relatives for primary prevention would be an effective policy.

First degree relatives of patients with premature coronary heart disease are at increased risk of the disease. Compared with the general population, siblings have at least double the risk, because of shared lifestyle risk factors and genetic predisposition. Offspring and partners are also at increased risk. Relatives have an increased prevalence of modifiable risk factors including hypertension, dyslipidaemia, and smoking. Some guidelines recommend screening of relatives, but surveys indicate that this does not occur in practice. We propose that first degree relatives of patients admitted for premature myocardial infarction should be identified and then offered screening and treatment for risk factors of coronary heart disease.

Sources and selection
We searched OVID, Medline, and PubMed databases using combinations of the terms “family history”, “coronary heart disease”, “sibling”, “relative”, “premature coronary heart disease”, and “cardiovascular risk factors”. We cross checked the reference lists of papers identified as relevant. We undertook a web search using the same terms and searched the publication lists of relevant organisations such as the British Heart Foundation, European Society of Cardiology, and American Heart Association.

Increased risk of coronary heart disease
Coronary heart disease aggregates in families. In a cross sectional European survey (Euroaspire II), 10% of the siblings of 1289 patients with premature coronary heart disease also had the disease. In another study, 16% of first degree relatives of survivors of myocardial infarction reported previous myocardial infarction, compared with 9% of the relatives of controls. Similarly, 12% of siblings of 325 patients with premature coronary heart disease in a Danish registry already had the disease, and 30% had substantial risk (≥20% at 10 years) of a cardiovascular event.

Family history of coronary heart disease significantly increases risk of the disease in all first degree relatives. Myocardial infarction in a sibling increases the risk of coronary heart disease by twofold to 15-fold (table 1). Risk varies according to age at presentation, number of relatives affected, and degree of genetic concordance.

Premature coronary heart disease—before 55 years in men and 60 in women—is more likely to reflect a genetic predisposition, so relatives of patients with premature onset are at greater risk than those of patients with late onset disease. Among 45 317 health professionals, paternal history of myocardial infarction before 70 years conferred a relative risk of 1.7, whereas a paternal history before 50 years carried a relative risk of 2.3. The corresponding figures for maternal history were 2.2 and 3.6. Increased risk is also due to shared lifestyle. Mothers exert a greater influence over the lifestyle of their offspring than fathers, which accounts for the higher risk associated with maternal family history.

Risk is higher if more than one first degree relative is affected. In a study of 1310 people with myocardial infarction, the odds ratio was 1.8 for a history of coronary heart disease in one family member, compared with 3.5 for a history in two. In a study of 21 004 twins, the risk among dizygotic twins (odds ratio 2.2) was similar to other first degree relatives (table 1) but was much higher among monozygotic twins (14.9).

In another study, the relative risks of coronary heart disease in young men were 3.9 for a family history of premature coronary heart disease, 5.9 for a history of the disease in more than one relative, and 12.7 if both were true. The corresponding figures in an Italian case-control study were 2.7, 3.5, and 20.0; these results suggest that the combined effects of these factors may be more than additive.

Increased prevalence of modifiable risk factors
The relative contributions of genetic predisposition and shared lifestyle are unclear and probably vary between families. None the less, the high prevalence of modifiable risk factors suggests that affected families would benefit from modifying risk factors. High levels of cardiovascular risk factors have been noted in siblings, children, and even partners of patients with premature coronary heart disease. In Euroaspire II, 30% of siblings smoked, 20% were obese, 23% had hypertension, and 8% had diabetes. One study compared mean levels of risk factors between siblings of patients with premature coronary heart disease and the general population of the United States. Total cholesterol concentrations, low density lipoprotein...
ANALYSIS

cholesterol concentrations, and systolic and diastolic blood pressure were all higher in siblings. The offspring of patients with premature coronary heart disease also have higher levels of modifiable risk factors than age and sex matched controls. Of 87 asymptomatic offspring of women with such disease, 29% of sons and 30% of daughters exceeded their age and sex specific risk for developing the disease within 10 years.15 Carotid intima media thickness, an indicator of global cardiovascular risk, is higher in offspring of patients with premature coronary heart disease.27 28 The role of shared lifestyle is clearly shown by studies of unrelated family members. Wives of patients with myocardial infarction had significantly higher levels of modifiable risk factors than wives of healthy men.29

Guidelines versus current practice
Several published guidelines have recommended screening of first degree relatives of patients with premature coronary heart disease (table 2).19-23 Surveys suggest that this is not done in practice. Among siblings of 325 patients with premature coronary heart disease in a Danish registry, only 83% of those with hypertension and 33% of those with hypercholesterolaemia were receiving medical treatment.2 Further-

more, treatment targets were reached in only 28% and 7%, respectively. When 859 siblings of 490 patients with premature coronary heart disease in the John Hopkins study were compared with the US general population, siblings had a lower awareness about hypertension (60% v 69%), its treatment (45% v 53%), and its control (16% v 24%).35 In Euroaspir II, 54% of siblings and 71% of offspring had not been screened. Where screening had occurred, it was mostly opportunistic—part of a general check-up.24 In an international survey of patients with myocardial infarction, only 61% of relatives had altered their lifestyle; only 39% had reduced or quit smoking and less than half had reduced their fat intake.35 Few studies have examined why relatives are not screened, but lack of public awareness and lack of systems to identify them may play a part. Of 5553 patients admitted with coronary heart disease to 53 US hospitals, less than 1% had a discharge plan recommending screening of family members.36 Only 20% of the 5553 patients had family members screened within six months. Predictors of screening were education level, cholesterol value, marital status, smoking status, and ethnic group.36

Table 1 | Risk of coronary heart disease associated with a family history of premature coronary heart disease

<table>
<thead>
<tr>
<th>Reference</th>
<th>Location</th>
<th>Number</th>
<th>Relationship</th>
<th>Risk factor adjustment</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Overall</td>
</tr>
<tr>
<td>Case-control studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nora 19801</td>
<td>USA</td>
<td>207 cases, 621 controls</td>
<td>1st degree relatives</td>
<td>No</td>
<td>10.4</td>
</tr>
<tr>
<td>Ten Kate 19822</td>
<td>USA</td>
<td>145 cases, 145 controls</td>
<td>1st degree relatives</td>
<td>No</td>
<td>2.1</td>
</tr>
<tr>
<td>Shea 19844</td>
<td>USA</td>
<td>223 cases, 57 controls</td>
<td>1st degree relatives</td>
<td>Yes</td>
<td>2.1</td>
</tr>
<tr>
<td>Friedlander 19857</td>
<td>Israel</td>
<td>123 cases, 921 controls</td>
<td>1st degree relatives</td>
<td>No</td>
<td>1.7</td>
</tr>
<tr>
<td>Roncaglioni 19928</td>
<td>Italy</td>
<td>916 cases, 1106 controls</td>
<td>1st degree relatives</td>
<td>No</td>
<td>2.0</td>
</tr>
<tr>
<td>Roncaglioni 19928</td>
<td>Italy</td>
<td>916 cases, 1106 controls</td>
<td>1st degree relatives</td>
<td>No</td>
<td>3.1</td>
</tr>
<tr>
<td>Ciruzzi 19979</td>
<td>Argentina</td>
<td>1060 cases, 1071 controls</td>
<td>1st degree relatives</td>
<td>Yes</td>
<td>2.5</td>
</tr>
<tr>
<td>Leander 200110</td>
<td>Sweden</td>
<td>954 cases, 1351 controls</td>
<td>Offspring/siblings</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Cohort studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sholtz 197511</td>
<td>USA</td>
<td>3524</td>
<td>Offspring</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Barrett-Connor 198612</td>
<td>USA</td>
<td>4014</td>
<td>1st degree relatives</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>Colditz 198613</td>
<td>USA</td>
<td>117156</td>
<td>Offspring</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Myers 199014</td>
<td>USA</td>
<td>4847</td>
<td>Offspring</td>
<td>Yes</td>
<td>1.3</td>
</tr>
<tr>
<td>Colditz 199115</td>
<td>USA</td>
<td>45317</td>
<td>Offspring</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Marenberg 199416</td>
<td>Sweden</td>
<td>7310</td>
<td>Twins</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Marenberg 199416</td>
<td>Sweden</td>
<td>13694</td>
<td>Twins</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Jousilahti 199617</td>
<td>Finland</td>
<td>15620</td>
<td>Offspring</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Boer 199918</td>
<td>Netherlands</td>
<td>46356</td>
<td>1st degree relatives</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>Boer 199918</td>
<td>Netherlands</td>
<td>46356</td>
<td>1st degree relatives</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Andresdottir 200219</td>
<td>Iceland</td>
<td>19390</td>
<td>1st degree relatives</td>
<td>No</td>
<td>—</td>
</tr>
<tr>
<td>Hawe 20033</td>
<td>UK</td>
<td>2827 men</td>
<td>Any relatives</td>
<td>Yes</td>
<td>1.9</td>
</tr>
<tr>
<td>Hawe 20033</td>
<td>UK</td>
<td>2827 men</td>
<td>Any relatives</td>
<td>No</td>
<td>1.7</td>
</tr>
</tbody>
</table>
Primary prevention strategies
In the past, the main approach to primary prevention was to identify and treat very high levels of individual risk factors. This approach was ineffective at a population level because most events occur in people with moderate levels of risk.37 A small shift in the population distribution of a risk factor, such as blood pressure, prevents more deaths.37 Recently, a hybrid approach has been championed, whereby people are treated for one or more risk factor on the basis of their overall cardiovascular risk. Targeting interventions in this way is more than twice as effective as treating individual factors.38 Similarly, studies of the “polypill concept” (a pill combining low doses of many cardiovascular preventative drugs) suggest that this multifactorial approach could be very effective—reducing the risk of a cardiovascular event in high risk subgroups by up to 88%.39

The cost effectiveness of this strategy depends on how easily we can identify asymptomatic people with high overall risk. Few people have occupational health checks. Socioeconomically deprived people are at highest risk but are least likely to be screened. Opportunistic screening while patients visit primary care for another reason is possible, but middle aged men visit infrequently. Inviting unselected people for primary care screening is feasible,40 but the yield is low. Such an approach is of borderline cost effectiveness,41 but the overall cost may be prohibitive.42

Family history can identify a large proportion of people at high overall risk. In the Utah family health tree study, the 14% of families with a positive family history accounted for 48% of all coronary heart disease events and 72% of all premature coronary heart disease events.43 Targeting relatives of patients with premature coronary heart disease would improve yield and cost effectiveness. Attempts have been made to identify high risk families via school based, work based, or online questionnaires. We believe that wide coverage could be achieved by identifying relatives whenever someone is admitted to hospital for premature myocardial infarction. Such people may be motivated by their relative’s illness to modify their lifestyle.

Burden of preventable disease
The 2001 census shows that 29.2 million adults may be at risk of premature myocardial infarction in England and Wales (men 20-54 years, women 20-64 years; figure). In 2004, 15 616 hospital admissions for a principal diagnosis of myocardial infarction occurred in this age group (Hospital Episode Statistics (www.hesonline.nhs.uk); Scottish Morbidity Record (www.isdscotland.org))—20% of all admissions for myocardial infarction.

By applying the results of a northern European cohort study, we estimated that 2.5% (7.3 million) of people in this age group had a family history of coronary heart disease, and that their relative risk of this disease was 1.7 for men and 2.1 for women.43 By applying these relative risks to the age and sex specific population incidence, we estimated that people with a family history had 7369 premature myocardial infarctions in 2004.

On the basis of the polypill study, aggressive cardiovascular risk management might have decreased the risk by up to 88%40 and prevented 6485 premature myocardial infarctions in 2004. Thus, screening and treating middle aged people with a family history of coronary heart disease could have prevented 42% of premature myocardial infarctions and 8% of all myocardial infarctions.

Potential impact of a hospital admission strategy
We estimated the potential impact of using hospital admissions for premature myocardial infarction to identify and screen high risk relatives. Data from a population based family cohort study were used to determine the average numbers of live siblings by age-sex strata.44 We calculated that the 15 616 patients admitted for premature myocardial infarction in 2004 had a total of 32 074 siblings (mean 2.4). Using relative risks of 4.3 and 2.2 for male and female siblings, respectively,15 and the population age specific incidence of myocardial infarction, we calculated that 218 siblings would have premature myocardial infarction within one year of the index admission and 1148 within five years (figure). By applying the polypill risk reduction,39 we estimated

Table 2 | Guidelines recommending screening of first degree relatives of patients with premature coronary heart disease

<table>
<thead>
<tr>
<th>Year</th>
<th>Organisation</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>Second report of the National Cholesterol Education Program (NCEP) ATP II</td>
<td>Family history of premature coronary heart disease (definite myocardial infarction or sudden death before 55 years of age in father or in other male first degree relative, or before 65 years of age in mother of other female first degree relative) is a high risk category for cholesterol monitoring and lowering41</td>
</tr>
<tr>
<td>1994</td>
<td>Task force of the European Society of Cardiology, European Atherosclerosis Society, and European Society of Hypertension</td>
<td>Close relatives of patients with premature coronary heart disease or other atherosclerotic vascular disease are a high risk group requiring action to reduce their risk factor levels41</td>
</tr>
<tr>
<td>1998</td>
<td>Second joint task force of European and other societies on coronary prevention</td>
<td>Close relatives of patients with premature coronary heart disease (men &lt;55 years and women &lt;65 years) should be screened for coronary risk factors as they are at increased risk of developing coronary heart disease43</td>
</tr>
<tr>
<td>2002</td>
<td>American Heart Association guidelines for primary prevention of cardiovascular disease and stroke</td>
<td>Risk factor assessment in adults should begin at age 20 years; family history of coronary heart disease should be regularly updated33</td>
</tr>
</tbody>
</table>

Potential impact of using hospital admissions for premature myocardial infarction to identify and screen high risk relatives based on data from 2004 in England and Wales

Number of admissions for premature myocardial infarction each year (n=15 616)

Siblings (n=32 074)

Over one year

Premature myocardial infarctions (n=218)

Preventable myocardial infarctions (n=191)

Over five years

Premature myocardial infarctions (n=1148)

Preventable myocardial infarctions (n=1011)
that for every 14 patients admitted with premature myocardial infarction, one additional premature myocardial infarction could be avoided in siblings within five years. Inclusion of other first degree relatives would increase the yield further.

Conclusions
Primary prevention of coronary heart disease should be targeted at people with a high overall risk. Identifying such people from the general population is difficult. First degree relatives of patients admitted with premature myocardial infarction have a high overall risk and account for a large proportion of premature myocardial infarctions. At risk relatives could be identified easily at the time the index patient presents to hospital. Patients with premature coronary heart disease usually present acutely to the accident and emergency department or are referred to the outpatient clinic. Such patients could be flagged in these settings as needing family counselling. A similar practice is in use for inherited cancers, where relatives are identified, counselled, and offered screening. Motivation to attend cancer screening is higher in people with a positive family history. However, familial risk in cardiovascular disease is complex, and overemphasising the genetic component may reduce motivation to change lifestyle. Further research is needed to identify barriers and determine the most effective approach. In England and Scotland alone, 7369 premature myocardial infarctions occur each year in people with a family history of the disease, and 6485 may be preventable. First degree relatives are an obvious, but neglected, group at which primary prevention should be targeted.

Contributors and sources: AFD has a longstanding research interest in genetics of cardiovascular disease. JPP has a longstanding research interest in cardiovascular epidemiology and health services research. CKC is a cardiologist with a research interest in cardiovascular epidemiology. ACHP has considerable experience of managing patients with premature coronary heart disease. AW and COD have a longstanding interest in the health economics of cardiovascular disease. JPP and ACHP had the original idea. CKC and JPP did the literature review. CKC, JPP, AW, and COD agreed the model. CKC and JPP obtained the data for the model. CKC did the modelling. CKC and JPP drafted the paper. All authors helped with redrafting and agreed the final version. JPP is guarantor.

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Competing interests: None declared.

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5 Nora JJ, Lartscher RH, Spangler RD, Nora AH, Kimberling WJ.

Summary Box

Prevention of coronary heart disease is most effective if targeted at people with high overall risk.

First degree relatives of patients with premature myocardial infarction have double the risk of the condition.

In the UK, about 20% of all admissions for myocardial infarction occur in patients with premature myocardial infarction.

More than a third of admissions for premature myocardial infarction could be prevented by screening and treating first degree relatives.

30 Summary of the second report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel II). JAMA 1993;269:3015-23.
39 Wald NL, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ 2003;326:1419.
Psychological impact of screening for type 2 diabetes: controlled trial and comparative study embedded in the ADDITION (Cambridge) randomised controlled trial

Helen C Eborall, post-doctoral research fellow,1 Simon J Griffin, programme leader,2 A Toby Prevost, medical statistician,1 Ann-Louise Kinmonth, professor of general practice,1 David P French, reader in health behaviour interventions,3 Stephen Sutton, professor of behavioural science1

ABSTRACT
Objective To quantify the psychological impact of primary care based stepwise screening for type 2 diabetes.
Design Controlled trial and comparative study embedded in a randomised controlled trial.
Setting 15 practices (10 screening, five control) in the ADDITION (Cambridge) trial in the east of England.
Participants 7380 adults (aged 40-69) in the top fourth for risk of having undiagnosed type 2 diabetes (6416 invited for screening, 964 controls).
Interventions Invited for screening for type 2 diabetes or not invited (controls), incorporating a comparative study of subgroups of screening attenders. Attendees completed questionnaires after a random blood glucose test and at 3-6 months and 12-15 months later. Controls were sent questionnaires at corresponding time points. Non-attenders were sent questionnaires at 3-6 months and 12-15 months.
Main outcome measures State anxiety (Spilberger state anxiety inventory), anxiety and depression (hospital anxiety and depression scale), worry about diabetes, and self rated health.
Results No significant differences were found between the screening and control participants at any time—for example, difference in means (95% confidence intervals) for state anxiety after the initial blood glucose test was −0.53, −2.60 to 1.54, at 3-6 months was 1.51 (−0.17 to 3.20), and at 12-15 months was 0.57, −1.11 to 2.24. After the initial test, compared with participants who screened negative, those who screened positive reported significantly poorer general health (difference in means −0.19, −0.25 to −0.13), higher state anxiety (0.93, −0.02 to 1.88), higher depression (0.32, 0.08 to 0.56), and higher worry about diabetes (0.25, 0.09 to 0.41), although effect sizes were small. Small but significant trends were found for self rated health across the screening subgroups at 3-6 months (P = 0.047) and for worry about diabetes across the screen negative groups at 3-6 months and 12-15 months (P = 0.001).
Conclusions Screening for type 2 diabetes has limited psychological impact on patients. Implementing a national screening programme based on the stepwise screening procedure used in the ADDITION (Cambridge) trial is unlikely to have significant consequences for patients’ psychological health. Trial registration Current Controlled Trials ISRCTN99175498.

INTRODUCTION
Type 2 diabetes mellitus, the fourth leading cause of death in the United Kingdom,1 fulfils many of the criteria for screening yet important uncertainties remain. As with any screening programme the overall benefits should outweigh any physical and psychological harm associated with the programme. Consequently it is important to quantify possible adverse psychological effects of screening, and the consequent diagnosis and treatment. Given that a small adverse effect for most participants who will screen negative may outweigh a large benefit to the few diagnosed as having the condition, it is important to assess potential harms among all those invited to participate in screening.

Evidence from studies of screening for other conditions shows that people who screen positive can show reactions such as reduced perceptions of health and have increased absenteeism from work. A systematic review of prospective studies of the psychological harms that can arise from screening across various conditions found that anxiety is often raised, at least in the short term, when a positive result is received, although it is unlikely to be raised by receiving a negative result. However, few controlled trials of the psychological effects of screening have been published that would enable the psychological impact of being invited to screening and subsequent participation to be estimated. Furthermore, there are few evaluations of screening procedures that involve people undergoing a series of tests over time. These multistage screening programmes have the potential to cause increased distress because of prolonged uncertainty in the screening process.

A recent review concluded that the psychological impact of screening for type 2 diabetes is limited; slightly increased short term levels of anxiety were reported in two studies. A further study has reported
Box 1 | Screening procedure used in ADDITION (Cambridge) trial
Fifty four general practices in the east of England were randomly allocated to control, screening followed by routine care of screen detected cases according to national recommendations,16 and screening followed by intensive multifactorial intervention. Automated searches of computerised general practice records were carried out to identify those in the top fourth of risk of having prevalent but undiagnosed type 2 diabetes.17

Screening arms

- Individuals at high risk were invited by letter to attend their local general practice for capillary blood tests for random blood glucose (HemoCue glucometer; HemoCue, Angelholm, Sweden) and glycaated haemoglobin
- Patients were excluded if they already had type 2 diabetes, were pregnant or lactating, or had a psychotic illness or an illness with a prognosis of less than one year
- Patients with a blood glucose level of 5.5 mmol/l or more were invited to return for a fasting (capillary) blood glucose test
- Patients with a fasting blood glucose level of 6.1 mmol/l or more or 5.5-6.1 mmol/l and a glycaated haemoglobin of 6.1% or more were invited to attend an outpatient centre for a standard 75 g oral glucose tolerance test17 and clinical, anthropometric, and biochemical measures
- Diagnosis of type 2 diabetes was made according to World Health Organization criteria18
- Results were faxed to the patient’s doctor for discussion with patients in consultations

Control arm

- Neither practitioners nor patients were informed of the risk score

Table 1 | Baseline characteristics of screening and control participants. Values are percentages (numbers) of participants unless stated otherwise

<table>
<thead>
<tr>
<th>Variables</th>
<th>Screening group (n=6416)</th>
<th>Control group (n=964)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of practices</td>
<td>10</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) practice list size</td>
<td>7810 (3026)</td>
<td>7160 (2527)</td>
<td>0.68</td>
</tr>
<tr>
<td>Women</td>
<td>34.6 (2220)</td>
<td>35.6 (343)</td>
<td>0.57</td>
</tr>
<tr>
<td>Mean (SD) age (years)</td>
<td>57.6 (7.9)</td>
<td>58.7 (7.8)</td>
<td>0.25</td>
</tr>
<tr>
<td>Mean (SD) body mass index*</td>
<td>30.5 (6.7)</td>
<td>30.6 (4.9)</td>
<td>0.39</td>
</tr>
<tr>
<td>Body mass index &gt;30*</td>
<td>47.0 (2747)</td>
<td>48.5 (430)</td>
<td>0.38</td>
</tr>
<tr>
<td>Prescribed steroids</td>
<td>6.1 (390)</td>
<td>4.4 (42)</td>
<td>0.42</td>
</tr>
<tr>
<td>Prescribed antihypertensives</td>
<td>46.6 (2992)</td>
<td>49.0 (472)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

*Data not available from general practice records for 9% screening and 8% control participants.

similarly low distress levels after diagnosis in screen detected patients but noted that a significant number had clinically relevant anxiety and depression.9 Previous studies have been limited by non-randomised designs comparing just two groups: people with newly diagnosed type 2 diabetes and those who screen negative.7,10,11 Only one study reported distress levels for participants, grouped according to their level of risk.8 Another limitation of previous studies is the use of general anxiety measures. Studies on the impact of cancer screening suggest no detectable effect on measures of general anxiety but a substantial effect on disease specific measures.12,13 The review of screening for type 2 diabetes identified the need for controlled trials on large samples.6

The Anglo-Danish-Dutch study of intensive treatment in people with screen detected diabetes in primary care15 (the ADDITION trial) is evaluating the cost effectiveness of screening and intensive treatment of screen detected cases, with 34 general practices being included in the Cambridge arm. The current study was embedded in the ADDITION (Cambridge) trial and used validated measures to assess the short term and long term psychological effects of screening in a large well defined cohort of people at high risk of developing type 2 diabetes. More specifically it investigated the psychological impact of being invited to attend screening for type 2 diabetes at a general practice and of the screening tests and results. We formulated the following hypotheses for one of the outcome measures, anxiety. Similar hypotheses were specified for the other outcomes (depression, diabetes specific worry, self rated health): participants invited to screening would report higher anxiety than those not invited; participants who screen positive at the first test (and thus are invited to return for further tests) would report higher anxiety than those who screen negative; and within the screening group there would be a dose-response effect of level of risk (from number of tests and results) on anxiety—each stage of the screening process would be associated with an increase in anxiety.

METHODS

The study design was a controlled trial comparing those invited for screening with non-invited controls, incorporating additional comparisons between subgroups of screening attenders, embedded in the ADDITION (Cambridge) trial. In that trial, practices were randomly allocated to screening or control arms. The psychological impact substudy included all five control practices in the main trial and a sample of 10 of the screening practices. It was not possible to randomly select the screening practices because the substudy started later than the main trial and by this time many of the practices had finished screening; three of the 10 screening practices included in the substudy were part way through screening.

The screening procedure is summarised in box 1. The figure shows the design of the psychological impact study and the flow of participants through the screening programme, with response rates.

Participants in the 10 screening practices who attended the initial glucose test (n=4370) were given a questionnaire to complete and return by post to the study centre; subsequent questionnaires were sent at 3-6 months and 12-15 months after this initial appointment. Screening non-attenders in these practices (n=2046) were sent the questionnaire at 3-6 months and 12-15 months after the date of their scheduled random blood glucose test. Postal questionnaires were sent from the practices and returned to the study centre.

In each of the five control practices 25% (n=964) of those with a high risk score were randomly sampled to be sent questionnaires at equivalent times to 3-6 months and 12-15 months. [Four hundred and eighty four of these were randomly assigned to also
being sent a questionnaire at the initial time point for a substudy on measurement effects.)

For the screening attenders, consent for participation in the psychological impact study was obtained during attendance at the initial test. Control participants and non-attenders received an information sheet, consent form, and covering letter from their surgery with their first questionnaire.

At each wave, participants who had not returned a questionnaire after about three weeks were sent one reminder (including a copy of the questionnaire). Control participants and non-attenders who did not return their questionnaire after one reminder were not sent questionnaires at subsequent waves for ethical reasons.

At the initial time point screening attenders were classified according to their random blood glucose test result. At 3-6 months and 12-15 months participants were classified according to the point at which they had tested negative or positive or failed to attend (Box 2).

Measures

We studied five main outcome measures. State anxiety was measured using the six item short form state scale of the Spielberger state anxiety inventory; scores of 6-24 were prorated to range from 20-80 to correspond with the full form of the scale. General anxiety and depression were measured with the 14 item hospital anxiety and depression scale, comprising two subscales resulting in scores of 0-21 each for anxiety and depression. Disease specific worry was measured using a six item scale for worry about developing diabetes, adapted from the Lerman cancer worry scale; sum scores result in scores of 6-24. A single item was used to measure self reported general health; response options were excellent, very good, good, fair, and poor. The questionnaire also included basic demographic information and further measures not directly relevant to the current study.
Sample size

The study size was based on the Spielberger state anxiety inventory, informed by a pilot study providing a standard deviation of 12, an intrapraction correlation coefficient of 0.48, and plausible effect differences of 3 to 7 units from state anxiety scores of 34.1 (control), 37.6 (screening), 33.1 (negative at first test), and 41.7 (after further testing). With samples of 2500 patients from those eligible for screening in 24 screening practices and 500 patients from four control practices, and allowing for 20-40% of dropouts depending on group and wave, the study had 80% power, with two sided tests at the 5% level of significance, to detect a difference in mean state anxiety between screening and control (hypothesis 1) of 4.3 units (n=1800 v n=350, design effect 4), between screen negative and screen positive groups (hypothesis 2) of 1.6 units (n=900 v n=900), and between the two smallest fully screened groups of 5.0 units (n=80 v n=120) at 3-6 months and 5.5 units (n=64 and n=96) at 12-15 months (hypothesis 3). To coincide with the timing of the main screening study, for the practicality of involving all rather than a sample of eligible patients in the screening practices, and because the prevalence of undiagnosed diabetes was lower than expected, we altered the study size to five control practices and 10 screening practices, with 964 and 6416 eligible patients. The study numbers and measure variability provided 80% power to detect effect differences of 3.2 units, 1.4 units, 5.7 units, and 5.4 units, respectively (3.2 units equates to a difference between adjacent response categories—for example, “not at all” and “somewhat”—on three of the 20 items on the full form of the scale).

Analyses

We assessed cross sectional comparisons between groups and dose-response trends across testing groups using a linear mixed effects model, with practice as random effect to account for clustering. Effect sizes were summarised with 95% confidence intervals, and we assessed hypotheses using two sided tests at the 5% level of significance. These were adjusted for clustering and for age and comorbidity (use of antihypertensives) to allow psychological effects to be attributed to screening rather than to pre-existing comorbidity or age differences that might arise from the practices being selected or being part way through screening (in the event the effect of covariate adjustment made no difference to the overall conclusions). The size of the difference in means between groups was interpreted in terms of the response categories of the scale and by comparison with the standard deviation, using Cohen’s guidelines for interpreting standardised differences in means (0.2 is small; 0.5 is medium, 0.8 is large). Analysis was primarily by intention to treat although we followed the explanatory nature of the hypotheses by excluding those who did not return a questionnaire until after their subsequent test in the screening programme.

RESULTS

At the time of the initial random blood glucose test 82% of 1787 patients who screened positive for type 2 diabetes, 81% of 2583 patients who screened negative, and 54% of 484 control participants responded. To ensure that data at this time captured the impact of the random test only, 310 questionnaires from screen positive patients that were completed or returned after the date of the second test were excluded, providing amended response rates of 65% for the patients who screened positive and 74% for the screened group (participants who screened positive plus participants who screened negative).

Response rates at 3-6 months were 66% among screening attenders, 18% among non-attenders, and 47% among controls. At 12-15 months response rates were 67%, 11%, and 40%. To ensure that analysis at these times captured the impact of the oral glucose tolerance test result, questionnaires received from attenders of this test before they had received their result (3-6 months, n=10; 12-15 months, n=4) were excluded.

The screening and control groups were comparable at baseline on the measures used to calculate the diabetes risk score and for practice size (table 1).

Impact of being invited to screening

At the time of the random test no significant differences were found between the screening attenders and

Table 2 Differences in outcome between screening attenders and control participants, and between participants who screened positive and those who screened negative (random blood glucose test), at initial time point*. Values are means (standard deviations) unless stated otherwise

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control, non-screening</th>
<th>Screening attenders</th>
<th>Difference† (95% CI), P value‡</th>
<th>Screen negative at RBG</th>
<th>Screen positive at RBG</th>
<th>Difference§ (95% CI), P value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selfreported health</td>
<td>3.14 (0.85), n=253</td>
<td>3.10 (0.88), n=3199</td>
<td>-0.02 (-0.18 to 0.14), 0.81</td>
<td>3.17 (0.87), n=2057</td>
<td>2.97 (0.89), n=1142</td>
<td>-0.19 (-0.25 to -0.13), &lt;0.001</td>
</tr>
<tr>
<td>State anxiety</td>
<td>32.7 (11.5), n=199</td>
<td>32.7 (11.6), n=2468</td>
<td>-0.53 (-2.60 to 1.54), 0.62</td>
<td>32.4 (11.4), n=1594</td>
<td>33.1 (11.9), n=874</td>
<td>0.93 (0.02 to 1.88), 0.05</td>
</tr>
<tr>
<td>HADS anxiety</td>
<td>6.42 (4.39), n=255</td>
<td>6.04 (3.79), n=3140</td>
<td>-0.46 (-0.99 to 0.07), 0.12</td>
<td>6.07 (3.75), n=2016</td>
<td>5.97 (3.87), n=1124</td>
<td>-0.00 (-0.28 to 0.27), 0.99</td>
</tr>
<tr>
<td>HADS depression</td>
<td>4.52 (3.48), n=256</td>
<td>4.24 (3.31), n=3161</td>
<td>-0.37 (-0.93 to 0.18), 0.21</td>
<td>4.14 (3.24), n=2032</td>
<td>4.41 (3.43), n=1129</td>
<td>0.32 (0.08 to 0.56), 0.01</td>
</tr>
<tr>
<td>Worry about diabetes</td>
<td>7.95 (2.44), n=255</td>
<td>8.04 (2.20), n=3127</td>
<td>0.03 (-0.36 to 0.42), 0.90</td>
<td>7.97 (2.19), n=2019</td>
<td>8.18 (2.21), n=1108</td>
<td>0.25 (0.09 to 0.41), 0.002</td>
</tr>
</tbody>
</table>

HADS=Hospital anxiety and depression scale; RBG=Random blood glucose test.
*Immediately after initial (random blood glucose) test for screening attenders, first contact for control participants.
†Screening attenders minus controls.
‡Adjusted for age and comorbidity (use of antihypertensives).
§Participants who screened positive minus participants who screened negative.
control participants on any of the five outcome measures—for example, for state anxiety, difference in means −0.19, −0.25 to −0.13; P<0.001, higher state anxiety (0.93, −0.02 to 1.88; P=0.05), higher depression (0.32, 0.08 to 0.56; P=0.01), and higher diabetes specific worry (0.25, 0.09 to 0.41; P=0.002) than participants who screened negative (table 2). No significant difference was found on general anxiety. Thus, the second hypothesis, that participants who screened positive would have worse general anxiety. Thus, the second hypothesis, that being invited to a screening programme has an adverse psychological impact was not supported.

Immediate impact of initial screening test results
After the initial test the participants who screened positive reported significantly poorer general health (difference in means −0.19, −0.25 to −0.13; P<0.001), higher state anxiety (0.93, −0.02 to 1.88; P=0.05), higher depression (0.32, 0.08 to 0.56; P=0.01), and higher diabetes specific worry (0.25, 0.09 to 0.41; P=0.002) than participants who screened negative (table 2). No significant difference was found on general anxiety. Thus, the second hypothesis, that participants who screened positive would have worse outcomes than those who screened negative, was supported for four of the five outcome measures. The effect sizes were, however, small.

Impact of a recent diagnosis of type 2 diabetes
A significant linear trend across the subgroups of screening attenders was found on two measures (table 4). At 3-6 months self reported health declined across groups according to the number of tests before testing negative, with the poorest general health reported by those testing positive at the final test—that is, those with newly diagnosed type 2 diabetes (P=0.047). The effect was no longer evident at 12-15 months. Secondly, the more screening tests that a participant underwent before testing negative, the higher the diabetes specific worry reported at 3-6 months and 12-15 months (P=0.001 in both cases). No significant trend was found across groups for the anxiety and depression measures. Thus, support was limited for the hypothesis of a dose-response effect of length of involvement with the screening programme on psychological costs.

Non-attenders
Those invited for screening included two further groups (table 5): screening non-attenders (for the initial test) and dropouts (participants who tested positive at the initial test but did not attend for further tests and so never received their final result). Both had poor response rates (18% and 38% at 3-6 months, 11% and 37% at 12-15 months). Compared with screening attenders, non-attenders had significantly higher scores on diabetes specific worry at 3-6 months (difference in means 0.26, 0.01 to 0.50; P=0.04) and 12-15 months (0.35, 0.03 to 0.66; P=0.03), but the effect sizes were small. Participants who screened positive at the initial test but who dropped out were compared with those who screened positive at the initial test but attended for subsequent tests. Dropouts had significantly poorer self reported health at 12-15 months (−0.26, −0.46 to −0.06; P=0.01) and significantly higher diabetes specific worry at 12-15 months (1.25, 0.66 to 1.83; P<0.001), a medium sized effect.

Table 3 | Differences in outcome between screening and control participants at 3-6 months* and 12-15 months†. Values are means (standard deviations) unless stated otherwise

<table>
<thead>
<tr>
<th>Time</th>
<th>Self-reported health:</th>
<th>Screening group (attenders and non-attenders)</th>
<th>Difference ‡ (95% CI), P value §</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Control, non-screening</td>
<td>Differences in means (standard deviations)</td>
<td></td>
</tr>
<tr>
<td>3-6 months</td>
<td></td>
<td>3.14 (0.80), n=443</td>
<td>3.13 (0.88), n=3211</td>
</tr>
<tr>
<td>12-15 months</td>
<td></td>
<td>3.21 (0.81), n=383</td>
<td>3.15 (0.87), n=3093</td>
</tr>
<tr>
<td>State anxiety</td>
<td></td>
<td>31.8 (11.4), n=358</td>
<td>33.5 (12.0), n=2504</td>
</tr>
<tr>
<td>12-15 months</td>
<td></td>
<td>32.8 (11.8), n=304</td>
<td>33.5 (12.2), n=2377</td>
</tr>
<tr>
<td>HADS anxiety</td>
<td></td>
<td>5.97 (3.86), n=442</td>
<td>5.91 (3.89), n=3159</td>
</tr>
<tr>
<td>12-15 months</td>
<td></td>
<td>5.81 (3.87), n=377</td>
<td>5.85 (3.87), n=3034</td>
</tr>
<tr>
<td>HADS depression</td>
<td></td>
<td>4.18 (3.38), n=444</td>
<td>4.24 (3.40), n=3177</td>
</tr>
<tr>
<td>12-15 months</td>
<td></td>
<td>4.03 (3.35), n=378</td>
<td>4.28 (3.40), n=3049</td>
</tr>
<tr>
<td>Worry about diabetes</td>
<td></td>
<td>7.87 (2.35), n=428</td>
<td>7.79 (2.15), n=3041</td>
</tr>
<tr>
<td>12-15 months</td>
<td></td>
<td>8.08 (2.30), n=365</td>
<td>7.75 (2.21), n=2889</td>
</tr>
</tbody>
</table>

HADS=hospital anxiety and depression scale.
*Time since initial or scheduled (random blood glucose) test for screening group, 3-6 months since first contact or equivalent for control group.
†Time since initial or scheduled (random blood glucose) test for screening group, 12-15 months since first contact or equivalent for control group.
‡Screening group minus control group.
§Adjusted for age and comorbidity (use of antihypertensives).
Sensitivity to missing data
The analysis at the initial test included only those participants who had screened positive and who had completed or returned their questionnaire before the second test, but included all responders who screened negative at the initial test. To mirror the exclusion criterion applied to the screen positive group, the analysis was repeated with a reduced screen negative group, excluding those who took a long time to return the questionnaire (matching the mean return time of the screen positive group). The only change in conclusion from this further analysis was that participants who screened positive scored higher than those who screened negative on state anxiety. (difference in means 1.22, 0.25 to 2.18; P=0.01). The effect size remained small.

Completion rates for all items constituting the hospital anxiety and depression scale and measures for worry about developing diabetes were high (97%, 98%, 94%), but only 76% of participants completed all items constituting the state anxiety measure. At the initial test non-completers of the state anxiety measure had higher mean general anxiety (hospital anxiety scale) than completers, by 1.36 units in controls and by 0.79 units in participants who screened negative and 0.62 units in those who screened positive, with the same completion rate across groups. Inclusion of non-completers for state anxiety would therefore be expected to reduce the difference in scores between the group who screened positive and those who screened negative (table 2).

To investigate bias arising from dropout between the initial test and 3-6 months, non-responders to the questionnaire at 3-6 months were compared with responders at the initial test. For each outcome measure non-response rates were similar across the three main groups from the initial test to 3-6 months (within 7%). Non-responders had a mean outcome worse than responders; this was greater in the control group and at a similar level in the groups who screened negative or positive (data not shown). If non-responders had responded similarly at 3-6 months the effect would be relatively to worsen the outcomes in the control group and reduce the evidence in favour of a psychological impact of screening.

**DISCUSSION**
Our finding that the psychological impact of screening for type 2 diabetes seems to be limited is in line with previous research. Firstly, no significant differences were found on any of the five outcome measures (state anxiety, anxiety, depression, diabetes specific worry, and self rated health) between the screening attenders and control participants at the initial random blood glucose test or between those invited for screening and controls at 3-6 months and 12-15 months. This was important to address, as previous studies have not included such a control group at similar risk of having undiagnosed type 2 diabetes.

Previous studies have also not dealt with the immediate impact of patients screening negative at a first random blood glucose test compared with screening positive and thus being required to return for further tests. Those who screened positive at this initial test did report significantly poorer general health and higher state anxiety and depression and worry about developing type 2 diabetes than those who screened negative. These effects were, however, small and the mean scores were not clinically relevant (anxiety and depression) or relatively high (diabetes specific worry). It can be concluded that being required to return for further tests after an initial positive test result has a small negative psychological impact that is unlikely to be of clinical significance.

### Table 4 | Trends across four subgroups of screening attenders, at 3-6 months and 12-15 months since initial random blood glucose test. Values are means (standard deviations) unless stated otherwise

<table>
<thead>
<tr>
<th>Time</th>
<th>Screen negative RBG</th>
<th>Screen positive RBG, screen negative FBG</th>
<th>Screen positive RBG, screen negative OGTT</th>
<th>Screen positive RBG, screen positive OGTT</th>
<th>Test for trend P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self reported health:</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>3-6 months</td>
<td>3.16 (0.87), n=1718</td>
<td>3.11 (0.87), n=865</td>
<td>3.08 (0.87), n=103</td>
<td>2.99 (0.82), n=103</td>
<td>0.047</td>
</tr>
<tr>
<td>12-15 months</td>
<td>3.18 (0.87), n=1701</td>
<td>3.13 (0.87), n=880</td>
<td>3.16 (0.83), n=111</td>
<td>3.17 (0.78), n=110</td>
<td>0.77</td>
</tr>
<tr>
<td>State anxiety:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-6 months</td>
<td>33.6 (11.9), n=1341</td>
<td>33.0 (11.8), n=666</td>
<td>32.4 (12.6), n=85</td>
<td>34.4 (13.8), n=85</td>
<td>0.94</td>
</tr>
<tr>
<td>12-15 months</td>
<td>33.5 (12.0), n=1297</td>
<td>33.2 (11.9), n=682</td>
<td>32.3 (11.7), n=86</td>
<td>32.9 (13.3), n=90</td>
<td>0.72</td>
</tr>
<tr>
<td>HADS anxiety:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-6 months</td>
<td>5.76 (3.95), n=851</td>
<td>5.76 (3.79), n=862</td>
<td>5.94 (3.91), n=107</td>
<td>5.32 (4.18), n=109</td>
<td>0.46</td>
</tr>
<tr>
<td>12-15 months</td>
<td>5.89 (3.90), n=1673</td>
<td>5.76 (3.79), n=862</td>
<td>5.94 (3.91), n=107</td>
<td>5.32 (4.18), n=109</td>
<td>0.46</td>
</tr>
<tr>
<td>HADS depression:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-6 months</td>
<td>4.14 (3.36), n=1695</td>
<td>4.28 (3.31), n=859</td>
<td>4.50 (3.66), n=100</td>
<td>3.99 (3.63), n=104</td>
<td>0.47</td>
</tr>
<tr>
<td>12-15 months</td>
<td>4.20 (3.33), n=1678</td>
<td>4.26 (3.36), n=866</td>
<td>4.80 (3.86), n=110</td>
<td>3.92 (3.86), n=111</td>
<td>0.44</td>
</tr>
<tr>
<td>Worry about diabetes:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-6 months</td>
<td>7.69 (2.02), n=1678</td>
<td>7.68 (2.06), n=858</td>
<td>8.75 (3.09), n=101</td>
<td>—</td>
<td>0.001</td>
</tr>
<tr>
<td>12-15 months</td>
<td>7.61 (2.07), n=1654</td>
<td>7.79 (2.26), n=856</td>
<td>8.07 (2.35), n=110</td>
<td>—</td>
<td>0.001</td>
</tr>
</tbody>
</table>

RBG=random blood glucose; FBG=fasting blood glucose; OGTT=oral glucose tolerance test.
*Adjusted for age and comorbidity (use of antihypertensives).
At 3-6 months rather than comparing those with and without screen detected type 2 diabetes we compared participants according to the point in the screening process at which they screened negative or positive, to examine the impact of the tests as well as the diagnosis. A marginally significant dose-response effect was found on self reported health in the hypothesised direction—those screening negative at the initial test reported the best health and those with a diagnosis of diabetes reported the poorest health; the trend was, however, no longer evident at 12-15 months. Within the screen negative group the more screening tests that participants had before screening negative the higher was their worry at 3-6 months about developing type 2 diabetes; this trend was maintained at 12-15 months. Although this trend is in the direction hypothesised the level of worry was relatively low\(^{11,12}\). The mean score for those screening negative after three tests equated to being “sometimes” worried on three items and “not at all or rarely” worried on the other three items on the scale. No trends were found for the anxiety and depression measures. Thus the hypothesis of a dose-response effect across the screening groups was only partially supported.

Only a small proportion of non-attenders for the initial test returned questionnaires but those who did had higher scores on diabetes specific worry than the attenders. The non-attender group comprised 32% of those invited for screening, so an adverse impact in this group is a potential concern. The effect size was, however, small. Another important group of non-attenders was the 11% of participants who screened positive at the initial test but who failed to attend for further tests. These dropouts were more worried about diabetes at 12-15 months than those who completed subsequent tests. The findings for non-attenders should be interpreted with caution because of the poor response rates in these groups.

Most comparisons in this study provided no statistically significant differences between groups. As a consequence of the large sample size, the estimates of differences in means had narrow confidence intervals and these can be interpreted as robust negative findings. When significant differences between groups were observed, in almost every case the effect size was small, as judged both for standard deviation of the measure and for response categories of the scale. The largest effect we observed was for diabetes specific worry at 12-15 months in the comparison between participants who screened positive at the initial test who dropped out of the screening programmes and those who attended for subsequent tests (table 5).

The current study had several limitations. Firstly, the screening practices were not randomly selected from those in the Cambridge arm of the Anglo-Danish-Dutch study of intensive treatment in people with screen detected diabetes in primary care (ADDITION) trial. Nevertheless, the screening and control groups were comparable on the baseline measures used to calculate the diabetes risk score and for practice size. Secondly, the study did not include a true baseline measure of anxiety and other psychological measures assessed before participants were invited for screening. This was a deliberate decision to avoid the possibility that the uptake of screening would be influenced by sending patients a questionnaire. It means, however, that to attribute the observed differences between groups to differences in their screening experience (number of tests, test

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**Table 5** Differences in outcome between screening attenders and non-attenders (for random blood glucose test) and, within screen positive group (random blood glucose), between those who attended all subsequent tests and dropouts, at 3-6 months and 12-15 months since initial or scheduled random blood glucose test. Values are means (standard deviations) unless stated otherwise.

<table>
<thead>
<tr>
<th>Time</th>
<th>Screen positive RBG, attended all</th>
<th>Screen positive RBG, dropped out</th>
<th>Difference (95% CI)</th>
<th>P value†</th>
<th>Difference (95% CI)</th>
<th>P value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self reported health:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-6 months</td>
<td>3.13 (0.87), n=2860</td>
<td>3.09 (0.94), n=351</td>
<td>-0.05 (-0.15 to 0.05)</td>
<td>0.32</td>
<td>3.10 (0.87), n=1071</td>
<td>2.93 (0.93), n=71</td>
</tr>
<tr>
<td>12-15 months</td>
<td>3.16 (0.86), n=2874</td>
<td>3.08 (0.94), n=219</td>
<td>-0.07 (-0.19 to 0.05)</td>
<td>0.24</td>
<td>3.14 (0.86), n=1101</td>
<td>2.88 (0.90), n=72</td>
</tr>
</tbody>
</table>

**HADS anxiety:**

<table>
<thead>
<tr>
<th>Time</th>
<th>Screen positive RBG, attended all</th>
<th>Screen positive RBG, dropped out</th>
<th>Difference (95% CI)</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-6 months</td>
<td>33.2 (11.9), n=2225</td>
<td>34.5 (12.7), n=279</td>
<td>0.30 (-1.20 to 1.81)</td>
<td>0.69</td>
</tr>
<tr>
<td>12-15 months</td>
<td>33.3 (12.0), n=2210</td>
<td>35.3 (13.8), n=167</td>
<td>1.33 (-0.58 to 3.25)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

**HADS depression:**

<table>
<thead>
<tr>
<th>Time</th>
<th>Screen positive RBG, attended all</th>
<th>Screen positive RBG, dropped out</th>
<th>Difference (95% CI)</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-6 months</td>
<td>5.83 (3.86), n=2833</td>
<td>5.94 (3.91), n=211</td>
<td>-0.17 (-0.71 to 0.37)</td>
<td>0.53</td>
</tr>
<tr>
<td>12-15 months</td>
<td>4.22 (3.39), n=2833</td>
<td>4.68 (3.53), n=216</td>
<td>0.27 (-0.20 to 0.74)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

**Worry about diabetes:**

<table>
<thead>
<tr>
<th>Time</th>
<th>Screen positive RBG, attended all</th>
<th>Screen positive RBG, dropped out</th>
<th>Difference (95% CI)</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-6 months</td>
<td>7.76 (2.10), n=2701</td>
<td>8.08 (2.40), n=340</td>
<td>0.26 (0.01 to 0.50)</td>
<td>0.04</td>
</tr>
<tr>
<td>12-15 months</td>
<td>7.76 (2.18), n=2683</td>
<td>8.16 (2.52), n=206</td>
<td>0.35 (0.03 to 0.66)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

RBG=random blood glucose; HADS=Hospital anxiety and depression scale.

*Adjusted for age and comorbidity (use of antihypertensives).
†Dropped out minus attended all subsequent tests.
results), it is necessary to assume that they were similar at baseline for anxiety and the other psychological measures. Even without a true baseline, however, the findings are informative. For example, that attenders for screening are no more anxious immediately after their first test than non-invited controls is an important finding, even if we do not know how anxious the attenders were before receiving their invitation for screening.

A third limitation is the low questionnaire response rates among the screening non-attenders, an almost universal finding in the literature on screening participation.25 This affects the comparison between those invited for screening and controls. If screening non-attenders who do not return questionnaires are more anxious (as a result of receiving an invitation) than those who do, we may be underestimating the adverse impact of being invited for screening.

Despite these limitations this study provides strong evidence on the psychological impact of screening for type 2 diabetes. The findings confirm the emerging position that screening for type 2 diabetes does not cause psychological costs.6-11 Implementing a national screening programme based on the stepwise screening procedure used in the ADDITION (Cambridge) trial is unlikely to have significant consequences for patients’ psychological health. A prospective qualitative study26 with ADDITION (Cambridge) trial participants helps to illuminate the findings from this quantitative study by showing how participants’ perceptions changed as they progressed through the stepwise screening process.

We thank the participants and the practices; the Cambridge ADDITION trial coordination team, in particular Kate Williams (trial manager), Lincoln Sargeant (clinical epidemiologist), Ryan Butler (data manager), Tom Fanshawe (medical statistician), Lewis Moore, Peshiya Doubleday, Ros Baring, and Nick Wareham (principal investigator, ADDITION trial); and the Medical Research Council field epidemiology team, in particular Sandra Bovan, Liz White, Christine May-Hall, Rosi Robbins, Muriel Hood, Georgina Lewis, Kate Westgate, and Ros Stevenson (leads: Sue Hemmings and Paul Roberts).

Contributors: SS, DPF, ATP, A-LK, and SJG conceived and designed the original protocol. All authors were involved in amending the protocol. HCE coordinated the study through data collection. Data entry was carried out by Wymam Dillon Ltd, Lewis Moore, and HCE. HCE cleaned the data and ran preliminary analysis with input from Tom Fanshawe. ATP analysed the data. ADDITION trial data were supplied by Lincoln Sargeant and Kate Williams. HCE wrote the first draft of the manuscript with ATP and SS. All authors contributed to subsequent and final drafts. HCE is guarantor of the paper.

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Competing interests: None declared.

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Patients’ experiences of screening for type 2 diabetes: prospective qualitative study embedded in the ADDITION (Cambridge) randomised controlled trial

Helen Eborall, post-doctoral research fellow; Richard Davies, director of general practice studies; Ann-Louise Kinmonth, professor of general practice; Simon Griffin, programme leader; Julia Lawton, senior research fellow

ABSTRACT
Objectives To provide insight into factors that contribute to the anxiety reported in a quantitative study of the psychological effect of screening for type 2 diabetes. To explore expectations of and reactions to the screening experience of patients with positive, negative, and intermediate results.

Setting Seven general practices in the ADDITION (Cambridge) trial in the east of England.
Participants 23 participants (aged 50-69) attending different stages in the screening process.
Results Participants’ perceptions changed as they progressed through the screening programme; the stepwise process seemed to help them adjust psychologically. The first screening test was typically considered unimportant and was attended with no thought about its implications. By the final diagnostic test, type 2 diabetes was considered a strong possibility, albeit a “mild” form. After diagnosis, people with screen detected type 2 diabetes tended to downplay its importance and talked confidently about their plans to control it. Participants with intermediate results seemed uncertain about their diagnosis, and those who screened negative were largely unaware of their remaining high risk.

Conclusions This study helps in understanding the limited psychological impact of screening for type 2 diabetes quantified previously, in particular by the quantitative substudy of ADDITION (Cambridge). The findings have implications for implementing such a screening programme in terms of timing and content.

INTRODUCTION
Type 2 diabetes mellitus is a progressive disease, which can lead to considerable morbidity and mortality as a result of cardiovascular, renal, and retinal complications. Disease onset may occur up to 12 years before clinical diagnosis so many patients are asymptomatic. Screening by measuring blood glucose concentrations can diagnose type 2 diabetes and identify people with impaired fasting glucose or impaired glucose tolerance who are at risk of developing the condition. Evidence suggests that earlier detection and treatment may lead to improved health outcomes, and that behavioural and drug interventions in people with impaired glucose tolerance can reduce progression to type 2 diabetes. However, it is not clear whether the potential population benefits outweigh the possible costs, which include adverse psychological effects of screening and subsequent treatment.

The Anglo-Danish-Dutch study of intensive treatment in people with screen detected diabetes in primary care (the ADDITION trial) is evaluating the cost effectiveness of screening and intensive treatment of screen detected cases. A substudy of the ADDITION (Cambridge) trial investigating the psychological impact of screening reported minimal adverse effect overall—no significant differences were found between the screening and control participants on psychological measures. People who screened positive at the first test reported a significantly greater psychological effect than those who screened negative, but effects were small and mean scores were not clinically relevant. At three to five months (after participants had completed the screening process) and 12-15 months, the more tests a participant had before screening negative, the more they worried about developing diabetes. However, levels of worry were low and effect sizes small.

Recent qualitative research has highlighted considerable diversity in the emotional reactions of people diagnosed with type 2 diabetes through routine testing (compared with those diagnosed after illness) and a lack of understanding of their risk of cardiovascular disease. Only one qualitative study has explored screening for type 2 diabetes from patients’ perspectives. This highlighted a lack of understanding of the meaning of raised blood glucose. Few diagnosed patients thought their diabetes was a potentially severe condition, and those who received negative results (but were still at high risk) reported reassurance and no plans to change their lifestyle. This study was limited by a retrospective design, which could not...
capture the temporal relation between patients’ expectations and experiences of the screening process or which aspects of screening may have fostered the low levels of anxiety observed. Furthermore, it only looked at people with positive or negative results, not those with intermediate results (impaired glucose tolerance or impaired fasting glucose).

We devised a prospective qualitative study to provide insight into the factors that contribute to anxiety during screening, as noted in the quantitative psychological impact substudy of ADDITION (Cambridge), and to provide insight into expectations and reactions to the screening experience of patients with positive, negative, and intermediate results.

**METHOD**

Our qualitative approach enabled us to identify themes during data collection, rather than test predetermined hypotheses. We incorporated a prospective component to capture participants’ experiences and views at different stages during the screening process and to explore whether and how these changed after receiving their results.

**Participants**

We were keen to capture the experience of patients through the entire stepwise screening process (box 1). Because only 7% of people in ADDITION (Cambridge) who took the first test (random blood glucose) went on to take the final test (oral glucose tolerance) we sampled at three stages:

1. We began by sampling at the point of referral for the final test; all patients with oral glucose tolerance tests scheduled during a defined period were invited for interview \((n=65)\). The resulting sample comprised 13 participants who were interviewed both before this test and again after receiving their test results.

2. A second group of participants \((n=21)\) was purposively invited for interview after their final test results to redress the uneven balance of sex and diagnosis achieved in the first group. The resulting sample comprised five participants who were interviewed once (after test results).

3. To capture the views of participants at the initial test (random blood glucose), we invited all patients attending for tests during one practice session \((n=15)\). The resulting sample comprised five participants who were interviewed once, shortly after their test.

All participants were patients at seven ADDITION (Cambridge) study practices; recruitment was by invitation letter with an opt-in reply slip. The table provides a breakdown of participants’ sex and diagnosis.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Type 2 diabetes</th>
<th>Impaired glucose tolerance or impaired fasting glucose</th>
<th>Negative (random or fasting blood glucose only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>5</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
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<td></td>
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<td></td>
<td>3</td>
</tr>
</tbody>
</table>

**Box 1 | The ADDITION (Cambridge) trial screening programme**

A stepwise screening procedure in people aged 40-69 years without known diabetes. People identified in the top quartile of risk of having prevalent undiagnosed type 2 diabetes by automated search of medical records are invited by letter to attend their local general practice for screening.

**Screening procedure**

Visit 1: random whole blood (capillary) glucose and glycosylated haemoglobin tests
- If random blood glucose 5.5-11.0 mmol/l proceed to visit 2
- If random blood glucose ≥11.1 mmol/l proceed to visit 3

Visit 2: fasting whole blood (capillary) glucose
- If fasting blood glucose ≥6.1 mmol/l or fasting blood glucose 5.5-6.0 mmol/l and glycosylated haemoglobin ≥6.1% proceed to visit 3

Visit 3 at hospital outpatient centre: oral glucose tolerance test and clinical, anthropometric, and biochemical measures
- Diagnosis of type 2 diabetes was made according to the World Health Organization criteria
- A second (confirmatory) oral glucose tolerance test was needed if a patient had tested 5.5-11.0 mmol/l at random blood glucose, 5.5-6.0 mmol/l at fasting blood glucose, and glycosylated haemoglobin ≥6.1%
- Results were faxed to the patient’s general practitioner for discussion with patients

**Data collection**

HE conducted all interviews in participants’ homes or workplaces. All patients gave written consent. Interviews covered the different stages of the screening process (box 2). The initial question, “Thinking back to when you received the invitation to screening what were your initial feelings?” encouraged participants to tell their story of the screening experience from the beginning. Interviews were audio recorded and transcribed verbatim.

**Analysis**

The analysis was informed by grounded theory, involving concurrent data collection and analysis, together with systematic efforts to check and refine emerging categories of data. Themes were not predetermined; rather, those that emerged in early interviews were discussed in team meetings (HE, RD, JL) and
were used to inform subsequent interviews and analysis. Throughout the interview and analysis phases, team meetings focused on exploring patients’ underlying reasoning, discussing deviant cases, and reaching agreement on recurrent themes and findings. HE and RD independently read through and cross compared all transcripts. We used NVivo7 (QSR International), a qualitative data indexing package, to help in data coding and retrieval.

RESULTS
Participants’ accounts of their screening experience showed how their perceptions of type 2 diabetes and their own personal risk changed over the course of the stepwise screening programme (box 1). Participants seemed to undergo a process of psychological adjustment, typically from attending the first screening test without considering its implications, to the final test where they confronted the possibility of having diabetes, as demonstrated by these contrasting quotes:

Patient 5 (male, impaired glucose tolerance, age 69) “I wasn’t concerned at all, you know I thought, well I’ll just go along and if I can help well okay all well and good, go and see what happens.”

Patient 18 (female, impaired glucose tolerance, age 64) “So I go for number one, I go for number two and then I have to go to number three. So it’s a build up all the time, making me think, well OK there’s a possibility you know . . . there’s a strong possibility you know’ in that sense [...] you’ve gone through the three, so your brain’s adjusted anyway.”

Initial stages of the screening process
Participants’ reflections on the initial ADDITION invitation letter highlighted an unquestioning perception of screening being “good” (box 3). Most participants seemed to have considered the initial test “routine” and thought little about the implications of the possible results, an attitude typified by one patient’s comment that “it can only be a good thing.” Attendees rarely expected to test positive, except for one woman who had a family history of diabetes. At this point in the screening process, some participants drew attention to their perceived lack of risk factors such as not having a sweet tooth, whereas others downplayed risk factors such as being overweight. Some participants did not know why they had been invited.

Most participants who tested positive on the first occasion reported being “not unduly worried.” A high random blood glucose concentration was often attributed to the food consumed for breakfast or the previous evening, or a healthy fluctuation. Participants typically reported expecting the next (fasting) test to be negative. Indeed the participants interviewed after the first test all said they were not worried. Accounts of the health professionals’ reassuring manner in giving results, particularly their use of the term borderline, seemed to contribute to this lack of concern in some cases.

Prediagnostic test expectations
After testing positive at the second (fasting) test some participants still expected to test negative at the oral glucose tolerance test, one hypothesising that the large number of patients referred for this test meant that only a few would be diabetic. Others had moved to accepting the possibility of type 2 diabetes, albeit a “mild” easily controlled type, often justifying this belief on the absence of symptoms.

All but one participant interviewed before their oral glucose tolerance test seemed to have taken in information about type 2 diabetes from the media or from health professionals, friends, and family at this stage. Some participants (without a family history) had identified people with type 2 diabetes within their own
Patient 8 (male, impaired glucose tolerance, age 64) "I didn’t really think too much about it ‘cause I’m a great believer in preventive medicine if you like. It’s like preventive maintenance on the car ‘cause if you do it beforehand it saves you a lot of problems later down the line"

Patient 102 (female, random blood glucose only, age 69) "I mean it’s only been a pin prick up to now hasn’t it?"

**Expectations of initial test results**

Patient 2 (male, type 2 diabetes, age 67) "I honestly thought I’d have a clear, I can’t remember ever suffering from anything, effects of diabetes or anything. I’m grossly overweight but apart from that"

Patient 17 (female, normal, age 58) "I thought I’ll just go along and I’d no reason to think there might be anything [diabetes] . . . I’ve never had a particularly sweet tooth"

Patient 4 (female, type 2 diabetes, age 58) "I had been given these tests before from my doctor, because of my family. My grandmother and grandfather both had diabetes and nine out of their 11 children had it, including my mother. And my cousins have got it so I would not be surprised if—it wouldn’t be a shock anyway"

**Reflections on reason for being invited**

Patient 11 (male, type 2 diabetes, age 55) "I suppose the criteria they put forward was over 40 and overweight . . . I certainly unfortunately fit into that"

Patient 3 (male, normal, age 69) "No. No. I don’t know why I was invited, I think maybe it’s because I’ve had hypertension ‘cause they say that it can lead to diabetes, I don’t know"

Patient 103 (male, random blood glucose only, 53) "It just said in the letter that I was just picked at random"

**Unimportant event**

Patient 3 (male, normal, age 69) "I know it [random blood glucose] was quite high. But I’d rather a big meal the night before [. . .] a great big plate of ice cream and two bananas which I imagine put the blood sugar up quite a lot"

Patient 5 (male, impaired glucose tolerance, age 69) "I was surprised at that initial test, that it was higher than the ones I had before from my doctor, because of my family. My grandmother and grandfather both had diabetes and nine out of their 11 children had it, including my mother. And my cousins have got it so I would not be surprised if—it wouldn’t be a shock anyway"

Patient 1 (male, type 2 diabetes, age 61) "[The nurse] said, ‘You’ll probably be quite all right but you’re on the borderline so we’ll get you back just in case”

**Prediagnostic test expectations**

Patient 2 (male, type 2 diabetes, age 67) "I’ve set my mind that I will probably fail (be diagnosed) tomorrow. But if you catch it early enough you can probably get rid of most of it just by dieting or looking after [yourself]"

Patient 1 (male, type 2 diabetes, age 61) "If I have got diabetes or any form of diabetes, it’s very light anyway, you can control it quite easily. It’s not—I don’t think for one minute I’ve got it life threatening. I would be dead by now wouldn’t I?"

Patient 8 (male, impaired glucose tolerance, age 64) "My cousin’s wife went along [. . ] but it was off the Richter scale. I mean [her blood glucose level] was like 31 for Christ’s sake. And even now with it controlled . . . it’s about 13. I said, ‘No I was something like 7.1 I think or 7”

Patient 6 (male, impaired fasting glucose, age 50) "Obviously I hope I’m not diabetic and have to inject myself. I’ve got a couple of friends who are diabetic that do that. But it doesn’t seem to have slowed them up too much or worry them"

Networks, sometimes using them as a benchmark against which to make favourable comparisons. Others reported how diabetes did not seem to affect their friends’ lives, furthering positive perceptions of it being a controllable condition.

**Reactions after diagnosis (box 4)**

**Newly diagnosed type 2 diabetes**

The most common reaction to being diagnosed with type 2 diabetes was to downplay its importance; only one participant reported shock. Testing positive at the first two tests seemed to lead participants to adjust their expectations from testing negative to an increased likelihood of having diabetes. A few participants reported symptoms, previously not considered relevant (such as tiredness and thirst), that they now linked to type 2 diabetes.

The one participant to describe shock was also afraid about the severe consequences of type 2 diabetes. In contrast, the rest emphasised the lack of severity they associated with the disease. All newly diagnosed patients talked confidently about their plans to control the disease; in some cases a diet-only regimen fuelled the perception that their diabetes was mild. Furthermore, most of this group reported being grateful that the screening programme had identified their diabetes at a treatable stage; indeed one patient described it as “a wake up call” to change his lifestyle.

**Intermediate and negative results**

Participants with intermediate (impaired fasting glucose or impaired glucose tolerance) or negative oral glucose tolerance test results suggested that they had known they did not have diabetes despite their earlier high readings. Some stated that they would have been surprised if they had been diagnosed, which contrasts with the lack of surprise reported by those who were. Often this belief was reinforced by lack of symptoms, despite being apparently aware of the disease’s early asymptomatic period.

Many participants diagnosed with an intermediate condition seemed confused. They appeared to be unaware of this diagnostic label or struggled to explain its meaning, or had received seemingly confused messages from their general practitioner. Most patients seemed unconcerned by their result, often normalising the condition, and reported feeling reassured by their general practitioner or nurse who had recommended simply annual checks. This diagnosis had not triggered lifestyle change even in those who had expressed intentions to change if diagnosed with type 2 diabetes in the pretest interview. For example, one patient said before his oral glucose tolerance test, “One knows there’s a chance of it and I think one can then say, right, well if that’s the case how do I deal with it and try and take sensible precautions.” But after diagnosis he said, “And so I was relieved not to have to have something else to worry about.”

Only one participant, unhappy with his general practitioner’s explanation, wanted further information about impaired glucose tolerance. Participants diagnosed with intermediate conditions had mixed views about their likelihood of getting type 2 diabetes in the future. Some patients accepted that lifestyle change would affect their risk of developing diabetes, but none appeared to be aware of the risk of cardiovascular disease associated with impaired fasting glucose or impaired glucose tolerance.
Box 4 | Reaction to diagnosis

Type 2 diabetes
Patient 9 (female, age 58) “Last time I saw you when we’d done the first interview, I think I was quite sort of blasé . . . Since I’ve been diagnosed I’m trying to get my head around it, and I’m finding it difficult. [. . .] To put it plainly I’m scared”
Patient 10 (male, age 66) “I rather suspected that once having got as far as having to go to [hospital], that [type 2 diabetes] was gonna be the outcome”
Patient 16 (female, age 63) “And I think there’s—that was where the tell-tale sign that I had trouble . . . [my husband] used to say to me, ‘you drink too much bloomin’ water’”
Patient 10 (male, age 66) “It’s not like you’re being told you’ve got cancer, it’s only diabetes for goodness sake innit? I mean, I must admit that everybody else seems to be taking it much more seriously than I am”
Patient 2 (male, age 67) “He [general practitioner] explained that people call it a mild form of the actual thing. But it wasn’t mild, that it was wrong, it was a type. And there was two ways of controlling it which was either tablets or diet, and they decided to go on the diet this time with me” “and if that don’t work well obviously it’s medication. But . . . I’m quite confident that in myself that the diet will control it”
Patient 1 (male, age 61) “If it wasn’t for [ADDITION] it wouldn’t have been picked up when it was, which means in a few years time I could be in some mess and it would be far too late to do anything then”

No diabetes
Patient 3 (male, normal, age 69) “I didn’t really think that I’d got diabetes, ‘cause I mean you can usually get symptoms don’t you?”
Patient 13 (male, impaired fasting glucose, age 69) “There was one little glitch where something showed up and it was very technical, about how quickly the blood can absorb sugar or something”
Patient 14 (male, impaired glucose tolerance, age 69) “I come out okay, well I come out—I come out with glucose intolerance, glucose impaired tolerance, which is below, right? It means you’re not diabetic but you could be—if you go down the path of—you know—that will bring you to it. And lots of people have got it haven’t they?”
Patient 15 (male, impaired glucose tolerance, age 53) “He [general practitioner] said, ‘Yeah, you’re fine, no problem . . . You’ve got a slight intolerance to glucose . . . No problem, you’re just like the man next door.’ I said, ‘Yeah, but it all depends on what the man next door’s like doesn’t it?’”
Patient 5 (male, impaired glucose tolerance, age 69) “I suppose depending upon what I eat and do and that sort of thing, I suppose that’s the things that affect it and . . . I suppose could tip it over into being a positive reading then”

DISCUSSION
This prospective qualitative study highlights the fluid and changing nature of participants’ perceptions at different stages of a stepwise screening programme for type 2 diabetes. The data indicate that participants underwent a process of psychological adjustment as they progressed through the programme. The findings help to explain the low levels of anxiety seen among participants in the ADDITION (Cambridge) screening programme, including those eventually diagnosed with the disease.6

Although participants talked about diabetes screening being a good thing—enabling the disease to be detected at an early, supposedly treatable stage—on a personal level most tended to downplay or not engage with their individual risk. Many participants, for instance, talked about attending the first test without considering the possibility of testing positive. Upon receipt of a positive test, there was a tendency to use an explanation other than diabetes and expect the next test to be negative.

By the time of the final diagnostic (oral glucose tolerance) test, participants had had time (nine to 10 weeks) to take in diabetes related information from the media or through conversations with friends, family, or health professionals. They had typically moved to accepting the increased possibility of being diagnosed with type 2 diabetes, but of a mild and controllable type. Minimising the threat of type 2 diabetes in this way may have helped participants prepare themselves mentally for a positive diagnosis, and helps account for the lack of anxiety seen in the participants who reached this stage of the programme.6

After diagnosis, the confidence that those diagnosed with type 2 diabetes expressed in their plans to control their disease seemed to be related to several perceptions and factors: the disease having been discovered “at an early stage”, a lack of severe complications,16 and being on a diet-only regimen.16 Our findings suggest that the duration and stepwise nature of the screening process is also salient, enabling gradual psychological adjustment. However many stages there are in a screening programme, people will have to go through a process of readjusting their expectations of personal risk. In the absence of a stepwise screening process, psychological reactions might be different. Hence, future research should compare the effect of a stepwise screening programme with a one-off diagnostic oral glucose tolerance test.

Patients with intermediate and negative results
Participants with impaired fasting glucose or impaired glucose tolerance tended to lack awareness of this diagnosis or struggled to explain the meaning and its implications. These participants, and those with a negative final test result, also expressed no intentions to change their lifestyles, despite having high blood glucose concentrations in the first few tests and the increased cardiovascular risk associated with impaired glucose tolerance or impaired fasting glucose. Given that many participants had not realised about these risks earlier in the screening process, this finding is unsurprising. It may also indicate a lack of accepted professional understanding and management protocols for treating patients at increased metabolic and cardiovascular risk, a problem previously raised by a qualitative study with general practitioners.17

Implications
The findings have important implications for people who implement screening. Even patients who tested negative at the first two tests remain at high risk of developing type 2 diabetes (as the risk score identified them in the top quarter for risk).12 Hence, the minimal importance attached to the first test, and relief arising from a negative random or fasting blood glucose test, could undermine the population benefit of a screening programme if these people do not realise that their risk remains high.18 Thus, patients should be made aware of the risk factors that led to their screening invitation. Furthermore, the lack of intentions to change lifestyle in participants who did not test positive at the final diagnosis raises questions of when and how “risk of
WHAT IS ALREADY KNOWN ON THIS TOPIC

- Quantitative studies have reported a limited psychological effect of screening for type 2 diabetes.
- Qualitative work has shown that patients with screen detected type 2 diabetes tend to think their disease is not serious.

WHAT THIS STUDY ADDS

- Participants’ perceptions of type 2 diabetes and their risk of developing the disease changed over the course of a diabetes screening programme.
- The stepwise nature of the screening programme seemed to facilitate psychological adjustment.
- Participants were uncertain about the meaning of intermediate screening results, and those with negative results were unaware they remained at high risk.

diabetes” might be effectively conveyed to patients to motivate changes in lifestyle. The interviews carried out before the oral glucose tolerance test indicate that this stage might be a useful point at which to give patients information about the consequences of a positive or negative test, so that those not diagnosed with type 2 diabetes are made aware of their risk of developing diabetes and cardiovascular disease.

The lack of anxiety associated with the screening programme may suggest a low psychological cost to implementing screening nationally. However, the tendency not to perceive type 2 diabetes as a serious condition is a potential concern. The information conveyed to participants about their screening result is key to their understanding. A challenge for health professionals is to convey enough information about the potential consequences of the disease to justify lifestyle change, without raising anxiety sufficiently to cause disengagement. The ADDITION (Cambridge) trial produced protocols outlining the form of words to be used when giving out results, but without observing the tests it is impossible to know what was actually said. Hence, future research could look at diagnostic consultations between health professionals and people with screen detected type 2 diabetes and impaired fasting glucose or impaired glucose tolerance.

Strengths and limitations of the study

The study was strengthened by its prospective component, enabling investigation of participants’ views before and after their final diagnosis. An additional strength is its focus on reactions to intermediate results as well as positive and negative diagnostic results. The study’s generalisability may be limited by its reliance on an opt-in procedure and low response rate. However, while it is impossible to establish whether participants were more or less anxious about their health than non-participants, the findings concur with previous literature and the larger quantitative study.

We are grateful to the participants for their time and involvement. We thank the ADDITION (Cambridge) trial coordination team, in particular Kate Williams (trial manager), the practices, the healthcare professionals, and the MRC field epidemiology team who helped with recruitment. Interviews were transcribed by Academic Transcriptions (Cambridge).

Contributors: The study was conceived and designed by all authors. HE coordinated the study and conducted all interviews. HE and RD analysed and interpreted the data with supervision from JL. HE wrote the first draft of the paper with input from JL and RD. All authors contributed to the final draft. HE is guarantor.

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Ethical approval: Eastern medical research ethics committee (Q2/5/54).

References


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We are grateful to the participants for their time and involvement. We thank the ADDITION (Cambridge) trial coordination team, in particular Kate Williams (trial manager), the practices, the healthcare professionals, and the MRC field epidemiology team who helped with recruitment. Interviews were transcribed by Academic Transcriptions (Cambridge).
Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review

Dean T Eurich, research associate,1 Finlay A McAlister, associate professor,2 David F Blackburn, assistant professor,3 Sumit R Majumdar, associate professor,2 Ross T Tsuyuki, professor,4 Janice Varney, librarian,1 Jeffrey A Johnson, professor5

ABSTRACT

Objective To review the literature on the association between antidiabetic agents and morbidity and mortality in people with heart failure and diabetes.

Design Systematic review and meta-analysis of controlled studies (randomised trials or cohort studies) evaluating antidiabetic agents and outcomes (death and admission to hospital) in patients with heart failure and diabetes.

Data sources Electronic databases, manual reference search, and contact with investigators.

Review methods Two reviewers independently extracted data. Risk estimates for specific treatments were abstracted and pooled estimates derived by meta-analysis where appropriate.

Results Eight studies were included. Three of four studies found that insulin use was associated with increased risk for all cause mortality (odds ratio 1.25, 95% confidence interval 1.03 to 1.51; 3.42, 1.40 to 8.37 in studies that did not adjust for diet and antidiabetic drugs; hazard ratio 1.66, 1.20 to 2.31; 0.96, 0.88 to 1.05 in the studies that did). Metformin was associated with significantly reduced all cause mortality in two studies (hazard ratio 0.86, 0.78 to 0.97 compared with other antidiabetic drugs and insulin; 0.70, 0.54 to 0.91 compared with sulfonylureas); a similar trend was seen in a third. Metformin was not associated with increased hospital admission for any cause or for heart failure specifically. In four studies, use of thiazolidinediones was associated with reduced all cause mortality (pooled odds ratio 0.83, 0.71 to 0.97, I²=52%, P=0.02). Thiazolidinediones were associated with increased risk of hospital admission for heart failure (pooled odds ratio 1.13 (1.04 to 1.22), I²=0%, P=0.004). The two studies of sulfonylureas had conflicting results, probably because of differences in comparator treatments. Important limitations were noted in all studies.

Conclusion Metformin was the only antidiabetic agent not associated with harm in patients with heart failure and diabetes. It was associated with reduced all cause mortality in two of the three studies.

INTRODUCTION

Worldwide, more than 171 million people have diabetes, and its prevalence is expected to double by 2030.1 People with diabetes are at increased risk of developing heart failure;2,3 with the relative risk increasing by 10-15% per unit increase in glycated haemoglobin.4-7 Conversely, heart failure is present in 25-40% of all adults with diabetes.2,6-12 Moreover, people with heart failure have worse outcomes if they also have diabetes,13-15 and it has been suggested that any level of hyperglycaemia is associated with increased rates of hospital admission, even in patients without manifest diabetes.16

How best to achieve glycaemic control in patients with diabetes and heart failure is therefore an important clinical question. Many antidiabetic drugs are now available to control hyperglycaemia. However, their role in managing diabetes in patients with heart failure is uncertain,17 and considerable controversy exists about the overall effect of antidiabetic agents on outcomes in people with comorbid diabetes and heart failure.18-26 Even the level of optimal glucose control in patients with diabetes and heart failure remains uncertain, and some evidence suggests that tight glycaemic control (glycated haemoglobin ≤7%) may be associated with worse survival than less tight control in patients with heart failure, irrespective of the agent used.18 As a result, outcomes are possibly affected not only by the choice of antidiabetic agent, but also by the degree of glycaemic control achieved with the agent.

Because of the lack of evidence around these matters, current recommendations are based on pathophysiological rationale, clinical experience, and expert consensus. A better understanding of the effects of antidiabetic agents on the health of people with heart failure and diabetes is needed.17 Thus, we conducted a systematic review to examine the relation between antidiabetic treatment and outcomes in people with heart failure and diabetes.

METHODS

week of 16 July 2007 for studies with contemporaneous comparison groups (such as randomised controlled trials or cohort studies) that evaluated the association between antidiabetic agents and clinical outcomes of hospital admission or mortality (or both) in patients with diabetes and heart failure (appendix on www.achord.ca). In addition, we also manually searched reference lists from original studies and review articles and contacted experts and authors of included studies. The search was not restricted by language or quality of study. We did not assess the risk of developing heart failure associated with antidiabetic drugs.

Two reviewers (DTE and DFB) independently identified relevant citations and included them if they described original research, included subjects with both diabetes and heart failure, evaluated the effects of antidiabetic agents on health outcomes (mortality, all cause hospital admission, and hospital admission for heart failure), and included a contemporaneous control group for comparison. Discrepancies were resolved by consensus after review by a third investigator (JAJ). All data were extracted and DTE and DFB independently assessed the methodological quality of included studies using a validated quality checklist. The maximum score on the quality checklist is 32, with a score of 12 (38%) or greater considered to be acceptable quality.20

**Statistical analysis**

To summarise the effects of antidiabetic drugs on outcomes of interest (all cause mortality or hospital admission), we abstracted the risk estimates and 95% confidence intervals from each study. For studies with insufficient information, we contacted the primary study authors to acquire and verify data where possible. If appropriate, we then pooled data across studies using random effects models if excessive statistical heterogeneity did not exist (measured using the $I^2$ statistic and defined a priori as $P < 0.10$ or $I^2 \geq 50\%$).21 We used Cochrane Review Manager 4.2 for all analyses.

**RESULTS**

Our search yielded 10 091 citations, and eight studies met our inclusion criteria—one randomised controlled trial, two post hoc subgroup analyses from randomised trials, four retrospective cohort studies, and one prospective cohort study (fig 1).21-25 Interobserver agreement was $k=0.84$ for study inclusion.

Of the eight studies, three had more than two comparison groups. As a result, four studies evaluated the effect of insulin treatment in patients with heart failure ($n=9104$), three examined metformin ($n=3327$), four evaluated thiazolidinediones ($n=3409$), and two studies ($n=8918$) compared sulfonylureas with other agents. No studies specifically evaluated the effects of alpha glucosidase inhibitors (such as acarbose and miglitol) or non-sulfonylurea insulin secretagogues (such as repaglinide and nateglinide) in patients with heart failure. The box and table 1 summarise the eight studies and their key findings. Overall, the studies were of acceptable quality, with a methodological quality score ranging from 13 (41%) to 22 (69%) (box); the median quality score was 16 (50%).

Table 2 summarises the statistical heterogeneity of the studies. A formal meta-analysis was not performed for the effects of insulin or metformin on all cause mortality because of significant statistical heterogeneity. With respect to hospital admission, meta-analyses could only be interpreted for the effects of metformin on all cause hospital admission and thiazolidinediones on hospital admission for heart failure (table 2).

**Insulin**

Outcomes with insulin were evaluated in a subgroup analysis of 496 patients with diabetes and left ventricular dysfunction (ejection fraction <40% after acute myocardial infarction) from the survival and ventricular enlargement (SAVE) trial (box).26-28 After multivariate adjustment, compared with 328 patients not treated with insulin (but treated with diet, sulfonylurea, or metformin), the 168 patients treated with insulin had significantly increased risk of all cause mortality (adjusted hazard ratio 1.66, 95% confidence interval 1.20 to 2.31), and cardiovascular morbidity (hospital admission for heart failure or prescription of an open label.
Table 1 | Results of studies assessing antidiabetic agents in the treatment of diabetes in patients with heart failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Study agent (n)</th>
<th>Comparator (n)</th>
<th>Outcome</th>
<th>Crude events (n) (treatment/controls)</th>
<th>Unadjusted risk estimates (95% CI)</th>
<th>Adjusted risk estimates (95% CI)</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murcia et al (2004)\textsuperscript{w1}</td>
<td>Insulin (n=168)</td>
<td>Diet, sulfonylurea, metformin (n=328)</td>
<td>All cause mortality</td>
<td>69/86</td>
<td>1.96 (1.33 to 2.90)</td>
<td>1.66 (1.20 to 2.31)</td>
<td>Patients with diabetes who survive a myocardial infarction with left ventricular dysfunction are at increased risk of subsequent mortality or cardiovascular events. Patients treated with insulin are at higher risk than those given other antidiabetic agents</td>
</tr>
<tr>
<td>Pocock et al (2006)\textsuperscript{w2}</td>
<td>Insulin (n=706)</td>
<td>Diet, sulfonylurea, metformin, thiazolidinediones (n=1454)</td>
<td>All cause mortality</td>
<td>245/435</td>
<td>1.25 (1.03 to 1.51)</td>
<td></td>
<td>In patients with systolic dysfunction and with preserved systolic function, the presence of diabetes and diabetes treated with insulin was highly prognostic of all cause mortality, death from cardiovascular disease, or hospital admission for heart failure</td>
</tr>
<tr>
<td>Smooke et al (2006)\textsuperscript{w3}</td>
<td>Insulin (n=43)</td>
<td>Diet, sulfonylurea, metformin, thiazolidinediones (n=89)</td>
<td>All cause mortality at 1 year</td>
<td>13/10</td>
<td>3.42 (1.40 to 8.37)</td>
<td></td>
<td>Insulin was associated with a pronounced increase in mortality. No increased risk of mortality was seen for non-insulin treated diabetes</td>
</tr>
<tr>
<td>Masoudi et al (2005)\textsuperscript{w4}</td>
<td>Insulin (n=8187)</td>
<td>Sulfonylurea, non-sulfonylurea secretagogues, alpha glucosidase inhibitors, metformin, TZDs (n=8230)</td>
<td>All cause mortality at 1 year</td>
<td>2891/2637</td>
<td>1.16 (1.09 to 1.24)</td>
<td>0.96 (0.88 to 1.05)</td>
<td>Insulin was not associated with an increased risk of mortality</td>
</tr>
<tr>
<td>Inzucchi et al (2005)\textsuperscript{w5}</td>
<td>Metformin (n=406)</td>
<td>Sulfonylurea, non-sulfonylurea secretagogues, alpha glucosidase inhibitors, metformin (n=2184)</td>
<td>All cause mortality at 1 year</td>
<td>93/768</td>
<td>0.55 (0.43 to 0.70)</td>
<td>0.92 (0.72 to 1.18)</td>
<td>In the subgroup of patients with left ventricular dysfunction, metformin did not increase the risk of mortality</td>
</tr>
<tr>
<td>Masoudi et al (2005)\textsuperscript{w1}</td>
<td>Metformin (n=1861)</td>
<td>Sulfonylurea, non-sulfonylurea secretagogues, alpha glucosidase inhibitors, insulin (n=12 069)</td>
<td>All cause mortality at 1 year</td>
<td>460/4345</td>
<td>0.58 (0.52 to 0.65)</td>
<td>0.86 (0.78 to 0.97)</td>
<td>Metformin was associated with reduced mortality, all cause hospital admission, and heart failure related hospital admission. Metformin did not increase the risk for hospital admission for lactic acidosis</td>
</tr>
<tr>
<td>Eurich et al (2005)\textsuperscript{w2}</td>
<td>Metformin monotherapy (n=208)</td>
<td>Sulfonylurea monotherapy (n=773)</td>
<td>All cause mortality at 1 year</td>
<td>29/200</td>
<td>0.43 (0.29 to 0.65)</td>
<td>0.66 (0.44 to 0.97)</td>
<td>Metformin was associated with reduced all cause mortality and a trend towards reduced risk of all cause hospital admission</td>
</tr>
<tr>
<td>Eurich et al (2005)\textsuperscript{w2}</td>
<td>Metformin and sulfonylurea combination therapy (n=852)</td>
<td>Sulfonylurea monotherapy (n=773)</td>
<td>All cause mortality at 1 year</td>
<td>97/200</td>
<td>0.34 (0.26 to 0.44)</td>
<td>0.54 (0.42 to 0.70)</td>
<td>Metformin plus sulfonylurea was associated with reduced all cause mortality and a trend towards reduced risk of all cause hospital admission. Metformin was not associated with an increased risk of lactic acidosis</td>
</tr>
</tbody>
</table>
Inzucchi et al (2005)²³
TZD (n=255)  Sulfonylurea, non-sulfonylurea secretagogues, alpha glucosidase inhibitors, insulin (n=2184)  All cause mortality at 1 year 92/768  0.60 (0.54 to 0.65)  1.04 (0.83 to 1.31)  Readmission for heart failure at 1 year 139/1083  1.22 (0.94 to 1.58)  1.15 (0.97 to 1.38)
Masoudi et al 2005²⁴ ³¹
TZD (n=2226)  Sulfonylurea, non-sulfonylurea secretagogues, alpha glucosidase inhibitors, insulin (n=12 069)  All cause mortality at 1 year 670/4345  0.77 (0.69 to 0.84)  0.87 (0.80 to 0.94)  All cause hospital admission at 1 year 1660/8702  1.14 (1.26 to 1.02)  1.04 (0.99 to 1.10)  Readmission for heart failure at 1 year 1505/7821  1.13 (1.03 to 1.25)  1.06 (1.00 to 1.12)
Dargie et al (2007)²⁷ ³⁷
TZD (n=110)  Placebo (n=114)  All cause mortality at 1 year 8/5  1.71 (0.55 to 5.34)  1.50 (0.49 to 4.59)  Readmission for heart failure at 1 year 5/4  1.31 (0.34 to 4.99)  Relative risk 1.30 (0.35 to 4.82) (no adjustment for trial design)
Aguilar et al (2007)²⁸ ³⁸
TZD (n=818)  Sulfonylurea, non-sulfonylurea secretagogues, alpha glucosidase inhibitors, insulin (n=4700)  All cause mortality at 2 years 168/1192  0.76 (0.63 to 0.91)  0.98 (0.81 to 1.17)  Hospital admission for heart failure at 2 years 134/741  1.05 (0.86 to 1.28)  1.00 (0.81 to 1.24)
Masoudi et al (2005)²³
Sulfonylurea  (n=8145)  Non-sulfonylurea secretagogues, alpha glucosidase inhibitors, metformin, TZDs, insulin (n=8272)  All cause mortality at 1 year 2679/2849  0.93 (0.87 to 1.00)  0.99 (0.91 to 1.08)  Sulfonylurea was not associated with increased risk of mortality

TZD, thiazolidinedione.

Angiotensin converting enzyme inhibitor, or myocardial infarction) and mortality (1.38, 1.06 to 1.80; table 1).

The effect of insulin was also evaluated in the CHARM (candesartan in heart failure: assessment of reduction in mortality and morbidity) study [box].²² ²⁴ Although insulin was not directly compared with other antidiabetic drugs in adjusted analyses, unadjusted risk ratios calculated from the raw data presented in the paper suggest that treatment with insulin is associated with an increased risk of all cause mortality (risk ratio 1.25, 1.03 to 1.51) and death from cardiovascular disease or hospital admission for heart failure (1.55, 1.29 to 1.86) compared with other treatments in patients with diabetes [table 1].²² ²⁴

Outcomes with insulin were also assessed in 554 consecutive patients referred to a university medical centre for management of heart failure [box].²³ Of these patients, 132 (24%) had diabetes and were prospectively followed for 11.7 months. Although insulin and non-insulin treatments were not directly compared in patients with diabetes, extrapolation from the raw data suggests an unadjusted risk ratio for all cause mortality of 3.42 (1.40 to 8.37) at one year and 2.20 (0.96 to 5.03) at two years [table 1] for patients with diabetes treated with insulin compared with those not treated with insulin.

The effects of insulin on mortality were also evaluated in a retrospective cohort study of 16 417 Medicare beneficiaries with diabetes who were discharged from hospital with a primary diagnosis of heart failure [box].²¹ Unlike previous studies, this study found no association between the use of insulin and mortality adjusted hazard ratio 0.96; 0.88 to 1.05) compared with patients receiving metformin, thiazolidinediones, sulfonylureas, non-sulfonylurea insulin secretagogues, or alpha glucosidase inhibitors [table 1].²¹

Oral antidiabetic agents

**Metformin**

Outcomes with metformin were evaluated in a retrospective cohort study of Medicare beneficiaries with diabetes discharged after hospital admission for acute myocardial infarction [box].²⁵ ²⁶ Subgroup analysis of the patients with diabetes and moderate to severe impaired left ventricular systolic function (n=2875) suggested that after multivariate adjustment treatment with metformin was not associated with any risk of all cause mortality at one year compared with patients receiving sulfonylureas, non-sulfonylurea insulin secretagogues, alpha glucosidase inhibitors, and insulin (n=406; 0.92, 0.72 to 1.18; table 1).²⁵ ²⁶

The study of Medicare beneficiaries with diabetes discharged with a primary diagnosis of heart failure also evaluated the effect of metformin on all cause mortality at one year [box].²⁵ After multivariate adjustment, compared with patients not receiving insulin sensitisers (that is, receiving sulfonylureas, non-sulfonylurea insulin secretagogues, alpha glucosidase inhibitors, or insulin) (n=12 069), all cause mortality was significantly lower in patients treated with metformin (n=1861; 0.86, 0.78 to 0.97), as well as in patients treated both with metformin and thiazolidinediones (n=261; 0.76, 0.58 to 0.99; table 1). In addition, no difference was seen in the risk for all cause hospital readmissions for patients receiving metformin (0.94, 0.89 to
Table 2 | Results of test for statistical heterogeneity

<table>
<thead>
<tr>
<th>Anti-diabetic drug</th>
<th>No of studies</th>
<th>Outcome assessed</th>
<th>P value for heterogeneity</th>
<th>I² statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>All cause mortality</td>
<td>0.03</td>
<td>67.2%</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>All cause hospital admission</td>
<td>Not determined</td>
<td>Not determined</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>All cause mortality</td>
<td>0.10</td>
<td>52.3%</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>All cause hospital admission</td>
<td>Not determined</td>
<td>Not determined</td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>All cause mortality at 1 year</td>
<td>&lt;0.001</td>
<td>83.5%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>All cause hospital admission at 1 year</td>
<td>0.26</td>
<td>20.9%</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>All cause mortality at 1 year</td>
<td>&lt;0.001</td>
<td>96.4%</td>
</tr>
</tbody>
</table>

Thiazolidinediones

In the previous Medicare study of patients with diabetes discharged after hospital admission for acute myocardial infarctionw3 after multivariate adjustment, the risk of all cause mortality at one year was no different for patients who received thiazolidinediones (n=269) than for patients treated with sulfonylureas, non-sulfonylurea insulin secretagogues, alpha glucosidase inhibitors, or insulin (1.04, 0.83 to 1.31; table 1). There was a trend, however, towards an increased risk of readmission for heart failure associated with thiazolidinediones (n=255; 1.15, 0.97 to 1.38).w3

In the second Medicare study of patients with diabetes discharged with a primary diagnosis of heart failure, after multivariate adjustment as above (n=12 069), all cause mortality at one year was significantly lower for patients treated with thiazolidinediones (n=2226; 0.87, 0.80 to 0.94; table 1).w3 This study also found no difference in the risk for all cause hospital readmissions for patients receiving thiazolidinediones (1.04, 0.99 to 1.10). However, a small increased risk of readmission for heart failure was seen in patients receiving thiazolidinediones (1.06, 1.00 to 1.12).

In a retrospective analysis using administrative records, another study compared metformin alone, or combined with sulfonylurea, to sulfonylurea monotherapy in 1833 patients with newly treated diabetes and incident heart failure. After multivariate adjustment, all cause mortality was significantly lower with metformin monotherapy (0.66, 0.44 to 0.97 at one year; 0.70, 0.54 to 0.91 after 2.5 years), or with combined treatment with metformin-sulfonylurea (0.54, 0.42 to 0.70 at one year; 0.61, 0.52 to 0.72 after 2.5 years; table 1). A reduction in the composite outcome of all cause mortality or hospital admission was also seen at the end of follow-up for the metformin monotherapy group (0.83, 0.70 to 0.99) and for combination therapy (0.86, 0.77 to 0.96; table 1).

In the second Medicare study evaluating the effect of metformin on all cause hospital admission at one year were of good methodological quality (box) and yielded similar effect estimates.w1,w2 The pooled effect suggests that treatment with metformin may be associated with reduced all cause hospital admission at one year compared to other treatments (pooled odds ratio 0.85, 0.76 to 0.95; I²=21%; P=0.004; fig 2).

Both of the studies assessing the effect of metformin on all cause hospital admission at one year were of good methodological quality (box) and yielded similar effect estimates.w1,w2 The pooled effect suggests that treatment with metformin may be associated with reduced all cause hospital admission at one year compared to other treatments (pooled odds ratio 0.85, 0.76 to 0.95; I²=21%; P=0.004; fig 2).

1.01) and a lower risk was seen in patients treated with both metformin and thiazolidinediones (0.82, 0.69 to 0.96; table 1). A lower risk was also seen for metformin users with respect to readmissions related to heart failure (0.92, 0.86 to 0.99) and a trend towards reduction in patients receiving both metformin and thiazolidinediones (0.85, 0.71 to 1.01).

In a retrospective cohort study of ambulatory patients followed through Veteran Affairs medical centres (box), after multivariate adjustment no differences were seen in all cause mortality at two years (n=814; 0.98, 0.81 to 1.17) or in hospital admission for heart failure (1.00, 0.81 to 1.24; table 1) in patients treated with thiazolidinediones compared with those not receiving insulin sensitisers (n=4700). However, in patients not receiving insulin, thiazolidinediones (n=381) were associated with an increased risk of hospital admission for heart failure compared with those not receiving insulin sensitisers (n=2217; 1.62, 1.15 to 2.29).w8

The only randomised controlled trial evaluated the addition of rosiglitazone (n=110) or placebo (n=114) to existing antidiabetic agents in patients with New York Heart Association class I or II disease (box).w7 Although not a specific end point of the study, after 52 weeks of treatment (compared with placebo) there was a trend towards an increased risk of all cause mortality for rosiglitazone (hazard ratio 1.50, 0.49 to 4.59) and in the proportion of patients with hospital admission for heart failure (relative risk 1.30, 0.35 to 4.82; table 2). A trend towards an increased in all cause mortality or worsening heart failure was also seen (hazard ratio 1.28, 0.51 to 3.21).

The pooled effect of the four studies which assessed the effect of thiazolidinediones on all cause mortalityw1,w3,w7,w8 suggests that treatment with thiazolidinediones may be associated with reduced all cause mortality compared with other treatments (pooled odds ratio 0.83, 0.71 to 0.97; I²=52%; P=0.10), although moderate heterogeneity was observed (fig 3). Similarly, the pooled effect on hospital admission for heart failure suggests that thiazolidinediones may be associated with an increased risk of such admission compared with other treatments (1.13; 1.04 to 1.22; P=0%; P=0.004; fig 4).w1,w3,w7,w8 All studies evaluating
treatment with thiazolidinediones were of good methodological quality (box). For all cause mortality, although the size and direction of effect estimates varied among studies, we found no consistent pattern of effect in relation to study quality. Similar effect estimates were seen for all studies regardless of quality with respect to hospital admission for heart failure.

**Sulfonylureas**

Few studies formally evaluated treatment with sulfonylureas as an independent exposure group. In the studies evaluating other oral treatments, however, sulfonylureas were used in about 55% of all patients in the main comparator groups (n=11 000). As a result, treatment with sulfonylurea was well represented in all of the studies evaluating oral antidiabetic agents included in our review.

Apart from the effect of sulfonylureas relative to metformin use already mentioned, only one other study looked at sulfonylureas. After multivariate analysis, no increased risk of mortality at one year was seen for patients receiving sulfonylureas compared with patients receiving other insulin secretagogues, alpha glucosidase inhibitors, metformin, thiazolidinediones, or insulin (0.99; 0.91 to 1.08).

**DISCUSSION**

Heart failure is a common comorbidity in patients with diabetes. Despite the high morbidity and mortality associated with the disease, our systematic review found few studies that formally compared antidiabetic drugs in this important population. Although several studies have evaluated the incidence of heart failure associated with the use of various antidiabetic agents, our review focused solely on the impact of such treatments in people with comorbid heart failure and diabetes. Of the eight studies included in this review, most studies were observational and there was only one randomised controlled trial, which was not designed to evaluate clinical outcomes. All studies were published in the past two years, and focused on use of insulin, thiazolidinediones, or metformin.

**Insulin**

In the four studies that specifically evaluated the use of insulin treatment, three suggested an increase in mortality, and one reported no association with mortality. Statistical heterogeneity precluded formal meta-analysis. Importantly, in two of the studies reporting increased mortality, there was no multivariate adjustment for the comparison between insulin and non-insulin treatments in patients with diabetes. Furthermore, none of the studies randomised patients to insulin or non-insulin treatment. As a result, it is difficult to tell whether this is a true adverse effect of insulin or whether it is simply confounding by indication. Treatment with insulin in these studies may well have been a marker for more advanced diabetes or vascular disease (or both). Thus, treatment with insulin may not, in itself, be associated with an increase in adverse effects in this population. Indeed, in one study that adjusted extensively for clinically important variables and compared insulin with other antidiabetic agents, insulin was not associated with an increased risk of mortality.

**Metformin**

Historically, metformin has been considered absolutely contraindicated in patients with heart failure who need drug treatment because of concerns about lactic acidosis. Recently, however, the US Food and Drug Administration has removed the heart failure contraindication from the packaging of metformin (Glucophage and Glucophage XR), although a strong warning for the cautious use of metformin in this population still exists. The true prevalence of metformin use in patients with heart failure is not known, but published studies suggest 10-25% of patients receiving metformin have comorbid heart failure. Despite the concerns, our analysis revealed that treatment with metformin may be associated with lower mortality rates, although statistical heterogeneity precluded formal meta-analysis. Furthermore, no study found an increase in adverse events with metformin and the results of both studies that evaluated all cause hospital admissions in metformin users suggested that this drug is associated with a lower rate of all cause hospital admission than other antidiabetic drugs.

**Thiazolidinediones**

Thiazolidinediones are also relatively contraindicated in patients with New York Heart Association class III or IV disease because of concerns about fluid retention, which may worsen symptoms of heart failure. Yet, the pooled effects for mortality suggest that thiazolidinediones may be associated with reduced mortality, although the results should be interpreted cautiously as moderate statistical heterogeneity was present. The only randomised controlled trial showed a trend towards an increased risk of mortality with thiazolidinediones; however, the study was not specifically designed to assess clinical outcomes and 62 (28%) patients withdrew from the study. As a result, the study was underpowered to detect any differences in
clinical outcomes between treatment groups. Data from one of the two large observational studies suggest that thiazolidinediones may be associated with lower mortality, whereas this was not seen in the other study.\(^w1\) This discrepancy may be related to the lower severity of illness in the patients in the second study, the under-representation of female patients, or differences in the use of combination treatment between study groups.\(^w8\)

All studies except for one reported higher numbers of hospital admissions related to heart failure for patients receiving thiazolidinediones\(^w1\) \(w7\) \(w8\); this risk was confirmed by formal pooling of the data. This is consistent with evidence from randomised controlled trials, including the recently published interim analysis of the RECORD (rosiglitazone evaluated for cardiovascular outcomes and regulation of glycaemia in diabetes) study, which has consistently shown increased fluid retention and admission for heart failure in patients without pre-existing heart failure who use thiazolidinediones.\(^26\)\(^27\)\(^32\)\(^34\) Recently, the US Food and Drug Administration has changed the package labels for thiazolidinediones to include a “black box” warning emphasising that these drugs may cause or exacerbate heart failure in certain patients. Furthermore, given the recent controversy over the use of thiazolidinediones and increased risk of myocardial infarction,\(^35\) the overall impact on health remains uncertain.\(^36\)

Although the lower mortality rates associated with use of metformin or thiazolidinediones are consistent with those seen in randomised controlled trials of insulin sensitiser in other populations with diabetes,\(^26\)\(^32\)\(^37\) none of the three included studies were randomised controlled trials. Although a wide range of demographic factors and patient characteristics were adjusted for in the studies, the study groups may have differed in severity of diabetes, heart failure, or other cardiovascular risk factors. Specifically, because of the commonly perceived risks of insulin sensitiser, these drugs may have been used preferentially in patients thought to be at lower risk than those given other treatments. Thus, the benefits of metformin and thiazolidinediones on mortality may be due to selection bias in these studies. Furthermore, only one study specifically evaluated the effects of oral antidiabetic agents as monotherapy.\(^w2\) Contamination of comparison groups as a result of the use of multiple antidiabetic drugs is a possibility in the other two studies.\(^w1\)\(^w3\)

### Sulfonylureas

Only two studies specifically evaluated sulfonylureas as an independent exposure.\(^w1\)\(^w2\) One study found that sulfonylurea monotherapy may be associated with worse outcomes,\(^w2\) whereas the other did not.\(^w1\) The discrepancy may partly be due to the comparator groups used in the studies. The first study compared sulfonylurea monotherapy with metformin, which has been shown to be beneficial in all similar studies, while the second compared sulfonylurea exposure (alone or in combination) with treatments that did not specifically include metformin. In the first study, it is not clear whether the risk estimates were a result of an adverse effect of sulfonylureas, a beneficial effect of metformin, or confounding by indication. Although these results are consistent with other studies evaluating sulfonylureas,\(^37\)\(^40\) a recent meta-analysis has indicated that these drugs are not associated with an increase in cardiovascular events.\(^41\) Given the current controversy surrounding the use of sulfonylureas in patients with pre-existing cardiovascular disease,\(^42\) more research is needed to determine the true impact of these drugs in people with diabetes and heart failure.

### Limitations

Inherent to any systematic review is the potential for publication or selection bias. Studies that may have evaluated the use of antidiabetic agents in patients with heart failure as part of a stratified or secondary analysis may not have been identified using standard search strategies. However, manual searches and contact with primary authors of the included studies provided no extra articles. Any relevant articles are therefore unlikely to have been missed. Secondly, the included studies were mainly observational and only one study randomised patients to different antidiabetic drugs. As a result, the effects of unmeasured confounding variables could not be fully explored and this may be a limitation of most of the reported studies.

### Conclusions

Our results suggest that of the current antidiabetic agents, metformin is the only one not associated with any measurable harm in people with diabetes and heart failure and is associated with reduced mortality. Given the large number of people affected with diabetes and heart failure and the fact that this population is expected to increase rapidly, evidence on how to optimally control glycaemic levels in this population is urgently needed. It is therefore imperative that research be undertaken to determine the optimal approach for glycaemic control in patients with heart failure. Ideally, this research should be a randomised controlled trial which includes the use of metformin or thiazolidinedione in patients with heart failure and...
Details of the eight included studies of antidiabetic agents for treating diabetes with heart failure

**Murcia et al (2004)**

**Design**—Post hoc subgroup analysis of randomised controlled trial (SAVE; n=696)

Inclusion criteria—Diabetes, between 21 and 80 years of age, left ventricular ejection fraction ≤40% after myocardial infarction

Exclusion criteria—Contraindication to angiotensin converting enzyme inhibitors or need to treat heart failure or hypertension, creatinine >221 mmol/l; unstable illness; active ischaemia

**Agents evaluated**—Insulin

**Method of analysis**—Multivariate Cox proportional hazards regression

**Covariates included in analysis**—Age, sex, left ventricular ejection fraction, previous myocardial infarction, Killip class ≥II, thrombotic treatment, use of β blockers, and captopril assignment

Duration—Mean 3.5 years

**Methodological quality checklist score**—44%

**Potential limitations and threats to validity**—Selection bias (data derived from randomised controlled trial in patients after myocardial infarction). Uncertain drug exposure (drug use defined at start of trial, exposure to drug throughout follow-up uncertain). Confounding by severity of diabetes (no data on glucose control, duration of diabetes). Limited adjustment for clinical data. No data on type of oral antidiabetic agents used

**Pocock et al (2006)**

**Design**—Post hoc subgroup analysis of randomised controlled trial (CHARM (n=2160))

Inclusion criteria—18 years or older, symptomatic heart failure (New York Heart Association class II-IV) of at least four weeks’ duration

Exclusion criteria—Creatinine ≥265 μmol/l, K+ ≥5.5 mmol/l, bilateral renal stenosis, symptomatic hypotension, women of childbearing potential not receiving contraceptives, critical aortic or mitral stenosis, myocardial infarction, stroke or open heart surgery in the previous four weeks, use of angiotensin receptor blockers in previous two weeks, any non-cardiac disease likely to limit survival to two years

**Agents evaluated**—Insulin

**Method of analysis**—Univariate

**Covariates included in analysis**—No covariate adjustment

Duration—Median 37.7 months

**Methodological quality checklist score**—41%

**Potential limitations and threats to validity**—Confounding by severity of diabetes (no data on glucose control, duration of diabetes). No data on type of oral antidiabetic agents used. Uncertain exposure (criteria used to define ‘insulin use’ not stated; no data on duration of drug use; exposure to drug throughout follow-up uncertain). Selection bias (data derived from randomised controlled trial). No adjusted results comparing insulin with other treatments in patients with diabetes

**Smooke et al (2005)**

**Design**—Prospective cohort study (n=132)

Inclusion criteria—Consecutive patients referred to specialty clinic to manage heart failure or evaluate them for a heart transplant because of systolic dysfunction (left ventricular ejection fraction <40%) from 1 January 2000 to 30 January 2003

Exclusion criteria—No exclusions reported

**Agents evaluated**—Insulin

**Method of analysis**—Univariate

**Covariates included in analysis**—No covariate adjustment

Duration—Mean 11.7 months

**Methodological quality checklist score**—63%

**Potential limitations and threats to validity**—Small sample size initially and 15% lost to follow-up (few patients left to evaluate for two year outcome). Uncertain exposure (no data on duration of drug use; exposure to drug throughout follow-up uncertain). Significant baseline differences (incomplete adjustment because of small sample size). No adjusted results comparing insulin and non-insulin treatments in patients with diabetes. Short duration of follow-up (mean 11.7 months). Results limited to a select population of patients (advanced heart failure patients only)

**Masoudi et al (2005)**

**Design**—Retrospective cohort study (n=16417)

Inclusion criteria—Patients with diabetes receiving antidiabetic agents upon discharge with a principal discharge diagnosis of heart failure

Exclusion criteria—Over 65 years of age, died during hospital admission, unknown date of death, unknown readmission data, discharge to a hospice, no drug treatment for diabetes at discharge

**Agents evaluated**—Insulin, metformin, thiazolidinediones, sulfonylurea

**Method of analysis**—Stepwise multivariate Cox proportional hazards regression

**Covariates included in analysis**—Demographics (age, sex, race); cardiac history (history of myocardial infarction, hypertension, coronary artery disease, percutaneous transluminal coronary angioplasty; non-cardiovascular history (admission source, mobility, cerebral vascular accident, chronic pulmonary disease, urinary incontinence, dementia); clinical characteristics at admission (systolic blood pressure, respiratory rate, heart failure, Na+, glucose, blood urea nitrogen test, creatinine, white blood cell count, haematocrit); hospital course (atrial fibrillation, heart failure or pulmonary oedema on admission, cardiac catheterisation, percutaneous transluminal coronary angioplasty, coronary artery bypass surgery, complications of diabetes); discharge prescriptions; severity of diabetes; sampling time frame

Duration—Not reported

**Methodological quality checklist score**—50%

**Potential limitations and threats to validity**—Uncertain exposure (cohort created on the basis of drug prescribed at discharge; exposure to drug throughout follow-up uncertain). Short duration of follow-up (outcomes at one year). Results limited to a select population of patients (>65 years of age)

**Inzucchi et al (2005)**

**Design**—Retrospective cohort study (n=2875)

Inclusion criteria—Patients with diabetes receiving antidiabetic agents upon discharge from hospital for myocardial infarction

Exclusion criteria—Unconfirmed myocardial infarction, long term haemodialysis, over 65 years of age, died during hospital stay, unknown date of death, unknown readmission data, discharge to a hospice, transferred to another hospital, left against medical advice, no drug treatment for diabetes at discharge

**Agents evaluated**—Metformin, thiazolidinediones

**Method of analysis**—Stepwise multivariate Cox proportional hazards regression

**Covariates included in analysis**—Potential covariates included demographics (age, sex, race); cardiac history (history of heart failure, myocardial infarction, hypertension, revascularisation); non-cardiovascular history (admission source, mobility, cerebral vascular accident, chronic pulmonary disease, urinary incontinence, dementia) clinical characteristics at admission (systolic blood pressure, respiratory rate, heart failure, Na+, glucose, blood urea nitrogen test, creatinine, white blood cell count, haematocrit); hospital course (atrial fibrillation, heart failure or pulmonary oedema on admission, cardiac catheterisation, percutaneous transluminal coronary angioplasty, coronary artery bypass surgery, complications of diabetes); discharge prescriptions; severity of diabetes; sampling time frame; patient clustering by hospital

Duration—Not reported

**Methodological quality checklist score**—47%
Potential limitations and threats to validity—Selection bias (over 65 years of age, after myocardial infarction only). Small sample size (few subjects in left ventricular dysfunction subgroup). Uncertain exposure (cohort created on the basis of on drugs prescribed at discharge; exposure to drug throughout follow-up uncertain). Short duration of follow-up (outcomes at one year)

Eurich et al (2005)²

Design—Retrospective cohort study (n=1833)

Inclusion criteria—New users of oral antidiabetic agents with incident onset heart failure

Exclusion criteria—Insulin use, prevalent heart failure (diagnosis of heart failure before starting oral antidiabetic agents)

Agents evaluated—Metformin, sulfonylurea

Method of analysis—Multivariate Cox proportional hazards regression

Covariates included in analysis—Age, sex, modified chronic disease score, prescription drugs affecting outcomes in people with diabetes or heart failure (or both), total number of visits to doctor before diagnosis of heart failure, propensity score (not included in final models)

Duration—Mean 2.5 years

Methodological quality checklist score—50%

Potential limitations and threats to validity—Selection bias (uncertain diagnostic accuracy of heart failure in doctor’s service file; insulin users excluded). Uncertain exposure (cohort created based on a single prescription for antidiabetic drugs; exposure to drug through follow-up uncertain; combination therapy not necessarily concurrent therapy). Confounding by severity of diabetes or heart failure (no clinical data or functional status). Small sample size (only 208 in metformin monotherapy cohort)

Dargie et al (2007)⁷

Design—Randomised controlled trial (n=224)

Inclusion criteria—Fasting blood glucose ≥7 mmol/l, stable New York Heart Association class I/II, left ventricular ejection fraction ≤45%, treatment with angiotensin converting enzyme inhibitors or angiotensin receptor blockers and diuretic if New York Heart Association class II

Exclusion criteria—Body mass index more than 35, creatinine clearance <40 ml/min, hepatic disease, anaemia

Agents evaluated—Thiazolidinediones

Method of analysis—Cox proportional hazards regression

Covariates included in analysis—None

Duration—One year

Methodological quality checklist score—66%

Potential limitations and threats to validity—Baseline characteristics were not fully matched between placebo and treatment group. Small sample size and few clinical events (inadequate power to detect clinical differences). High withdrawal rate (28%)

Aguilar et al (2007)⁸

Design—Retrospective cohort study (n=7147)

Inclusion criteria—Patients of the Veterans Association external peer review programme who had diabetes and were prescribed hypoglycaemic drugs

Exclusion criteria—Treatment with metformin in control group

Agents evaluated—Thiazolidinediones

Method of analysis—Stepwise multivariate Cox proportional hazards regression

Covariates included in analysis—Age, sex, body mass index, left ventricular ejection fraction, glomerular filtration rate, haemoglobin, hypertension, myocardial infarction, cancer, chronic obstructive pulmonary disease, peripheral vascular disease, psychiatric disorders, liver disease, rheumatic disease, medical school affiliation, other antidiabetic drugs

Duration—Not reported

Methodological quality checklist score—50%

Potential limitations and threats to validity—Selection bias (metformin users excluded from control group but not treatment group). Uncertain exposure (cohort created on the basis of 120 day window around index outpatient visit; exposure to drug throughout follow-up uncertain). Short duration of follow-up (outcomes at two years)

Contributors: DTE, FAM, DFB, SRM, RTT, and JA helped plan and design the study. DTE, DFB, JV, and JA collected the data. DTE conducted the statistical analyses. All authors had access to the data and helped interpret the data. DTE wrote the first draft of the paper. All authors reviewed and revised the paper for important intellectual content and approved the version. DTE led the study, is lead author, and is guarantor.

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Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review

Dean T Eurich, research associate,1 Finlay A McAlister, associate professor,2 David F Blackburn, assistant professor,3 Sumit R Majumdar, associate professor,2 Ross T Tsuyuki, professor,4 Janice Varney, librarian,1 Jeffrey A Johnson, professor5

ABSTRACT

Objective To review the literature on the association between antidiabetic agents and morbidity and mortality in people with heart failure and diabetes.

Design Systematic review and meta-analysis of controlled studies (randomised trials or cohort studies) evaluating antidiabetic agents and outcomes (death and admission to hospital) in patients with heart failure and diabetes.

Data sources Electronic databases, manual reference search, and contact with investigators.

Review methods Two reviewers independently extracted data. Risk estimates for specific treatments were abstracted and pooled estimates derived by meta-analysis where appropriate.

Results Eight studies were included. Three of four studies found that insulin use was associated with increased risk for all cause mortality (odds ratio 1.25, 95% confidence interval 1.03 to 1.51; 3.42, 1.40 to 8.37 in studies that did not adjust for diet and antidiabetic drugs; hazard ratio 1.66, 1.20 to 2.31; 0.96, 0.88 to 1.05 in the studies that did). Metformin was associated with significantly reduced all cause mortality in two studies (hazard ratio 0.86, 0.78 to 0.97 compared with other antidiabetic drugs and insulin; 0.70, 0.54 to 0.91 compared with sulfonylureas); a similar trend was seen in a third. Metformin was not associated with increased hospital admission for any cause or for heart failure specifically. In four studies, use of thiazolidinediones was associated with reduced all cause mortality (pooled odds ratio 0.83, 0.71 to 0.97, I²=52%, P=0.02). Thiazolidinediones were associated with increased risk of hospital admission for heart failure (pooled odds ratio 1.13 (1.04 to 1.22), I²=0%, P=0.004). The two studies of sulfonylureas had conflicting results, probably because of differences in comparator treatments. Important limitations were noted in all studies.

Conclusion Metformin was the only antidiabetic agent not associated with harm in patients with heart failure and diabetes. It was associated with reduced all cause mortality in two of the three studies.

INTRODUCTION

Worldwide, more than 171 million people have diabetes, and its prevalence is expected to double by 2030.1 People with diabetes are at increased risk of developing heart failure;2,3 with the relative risk increasing by 10-15% per unit increase in glycated haemoglobin.4-7 Conversely, heart failure is present in 25-40% of all adults with diabetes.2,6-12 Moreover, people with heart failure have worse outcomes if they also have diabetes,13-15 and it has been suggested that any level of hyperglycaemia is associated with increased rates of hospital admission, even in patients without manifest diabetes.6

How best to achieve glycaemic control in patients with diabetes and heart failure is therefore an important clinical question. Many antidiabetic drugs are now available to control hyperglycaemia. However, their role in managing diabetes in patients with heart failure is uncertain,17 and considerable controversy exists about the overall effect of antidiabetic agents on outcomes in people with comorbid diabetes and heart failure.3,6-8 Even the level of optimal glucose control in patients with diabetes and heart failure remains uncertain, and some evidence suggests that tight glycaemic control (glycated haemoglobin ≤7%) may be associated with worse survival than less tight control in patients with heart failure, irrespective of the agent used.18 As a result, outcomes are possibly affected not only by the choice of antidiabetic agent, but also by the degree of glycaemic control achieved with the agent.

Because of the lack of evidence around these matters, current recommendations are based on pathophysiological rationale, clinical experience, and expert consensus. A better understanding of the effects of antidiabetic agents on the health of people with heart failure and diabetes is needed.17 Thus, we conducted a systematic review to examine the relation between antidiabetic treatment and outcomes in people with heart failure and diabetes.

METHODS

week of 16 July 2007 for studies with contemporaneous comparison groups (such as randomised controlled trials or cohort studies) that evaluated the association between antidiabetic agents and clinical outcomes of hospital admission or mortality (or both) in patients with diabetes and heart failure (appendix on www.achord.ca). In addition, we also manually searched reference lists from original studies and review articles and contacted experts and authors of included studies. The search was not restricted by language or quality of study. We did not assess the risk of developing heart failure associated with antidiabetic drugs.

Two reviewers (DTE and DFB) independently identified relevant citations and included them if they described original research, included subjects with both diabetes and heart failure, evaluated the effects of antidiabetic agents on health outcomes (mortality, all cause hospital admission, and hospital admission for heart failure), and included a contemporaneous control group for comparison. Discrepancies were resolved by consensus after review by a third investigator (JAJ). All data were extracted and DTE and DFB independently assessed the methodological quality of included studies using a validated quality checklist. The maximum score on the quality checklist is 32, with a score of 12 (38%) or greater considered to be acceptable quality.

**Statistical analysis**
To summarise the effects of antidiabetic drugs on outcomes of interest (all cause mortality or hospital admission), we abstracted the risk estimates and 95% confidence intervals from each study. For studies with insufficient information, we contacted the primary study authors to acquire and verify data where possible. If appropriate, we then pooled data across studies using random effects models if excessive statistical heterogeneity did not exist (measured using the $I^2$ statistic and defined a priori as $P \leq 0.10$ or $I^2 \geq 50\%$). We used Cochrane Review Manager 4.2 for all analyses.

**RESULTS**
Our search yielded 10 091 citations, and eight studies met our inclusion criteria—one randomised controlled trial, two post hoc subgroup analyses from randomised trials, four retrospective cohort studies, and one prospective cohort study (fig 1). Interobserver agreement was $k=0.84$ for study inclusion.

Of the eight studies, three had more than two comparison groups. As a result, four studies evaluated the effect of insulin treatment in patients with heart failure (n=9104), three examined metformin (n=3327), four evaluated thiazolidinediones (n=3409), and two studies (n=8918) compared sulfonylureas with other agents. No studies specifically evaluated the effects of alpha glucosidase inhibitors (such as acarbose and meglitil) or non-sulfonylurea insulin secretagogues (such as repaglinide and nateglinide) in patients with heart failure. The box and table 1 summarise the eight studies and their key findings. Overall, the studies were of acceptable quality, with a methodological quality score ranging from 13 (41%) to 22 (69%) (box); the median quality score was 16 (50%).

Table 2 summarises the statistical heterogeneity of the studies. A formal meta-analysis was not performed for the effects of insulin or metformin on all cause mortality because of significant statistical heterogeneity. With respect to hospital admission, meta-analyses could only be interpreted for the effects of metformin on all cause hospital admission and thiazolidinediones on hospital admission for heart failure (table 2).

**Insulin**
Outcomes with insulin were evaluated in a subgroup analysis of 496 patients with diabetes and left ventricular dysfunction (ejection fraction <40% after acute myocardial infarction) from the survival and ventricular enlargement (SAVE) trial (box). After multivariate adjustment, compared with 328 patients not treated with insulin (but treated with diet, sulfonylurea, or metformin), the 168 patients treated with insulin had significantly increased risk of all cause mortality (adjusted hazard ratio 1.66, 95% confidence interval 1.20 to 2.31), and cardiovascular morbidity (hospital admission for heart failure or prescription of an open label

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**Fig 1 | QUOROM diagram of systematic search**

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Table 1 Results of studies assessing antidiabetic agents in the treatment of diabetes in patients with heart failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Study agent (n)</th>
<th>Comparator (n)</th>
<th>Outcome</th>
<th>Crude events (n) (treatment/controls)</th>
<th>Unadjusted risk estimates (95% CI)</th>
<th>Adjusted risk estimates (95% CI)</th>
<th>Key findings</th>
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<td>Murcia et al (2004)w1</td>
<td>Insulin (n=168)</td>
<td>Diet, sulfonylurea, metformin (n=328)</td>
<td>All cause mortality</td>
<td>69/86; 98/150</td>
<td>1.96 (1.33 to 2.90); 1.66 (1.20 to 2.31)</td>
<td>1.86 (1.35 to 2.62); 1.54 (1.13 to 2.11)</td>
<td>Patients with diabetes who survive a myocardial infarction with left ventricular dysfunction are at increased risk of subsequent mortality or cardiovascular events. Patients treated with insulin are at higher risk than those given other antidiabetic agents</td>
</tr>
<tr>
<td>Pocock et al (2006)w4</td>
<td>Insulin (n=706)</td>
<td>Diet, sulfonylurea, metformin, thiazolidinediones (n=1454)</td>
<td>All cause mortality</td>
<td>245/435; 367/598</td>
<td>1.25 (1.03 to 1.51); 1.55 (1.29 to 1.86)</td>
<td>No adjusted estimate; No adjusted estimate</td>
<td>In patients with systolic dysfunction and with preserved systolic function, the presence of diabetes and diabetes treated with insulin was highly prognostic of all cause mortality, death from cardiovascular disease, or hospital admission for heart failure</td>
</tr>
<tr>
<td>Smooke et al (2006)w5</td>
<td>Insulin (n=43)</td>
<td>Diet, sulfonylurea, metformin, thiazolidinediones (n=89)</td>
<td>All cause mortality at 1 year</td>
<td>13/10; 14/16</td>
<td>3.42 (1.40 to 8.37); 2.20 (0.96 to 5.03)</td>
<td>No adjusted estimate; No adjusted estimate</td>
<td>Insulin was associated with a pronounced increase in mortality. No increased risk of mortality was seen for non-insulin treated diabetes</td>
</tr>
<tr>
<td>Masoudi et al (2005)w1</td>
<td>Insulin (n=8187)</td>
<td>Sulfonylurea, non-sulfonylurea secretagogues, alpha glucosidase inhibitors, metformin, TZDs (n=8230)</td>
<td>All cause mortality at 1 year</td>
<td>2891/2637; 1265/8702</td>
<td>0.55 (0.43 to 0.70); 0.82 (0.74 to 0.91)</td>
<td>0.92 (0.72 to 1.18); 0.94 (0.89 to 1.01)</td>
<td>Insulin was not associated with an increased risk of mortality</td>
</tr>
<tr>
<td>Inzucchi et al (2005)w3</td>
<td>Metformin (n=406)</td>
<td>Sulfonylurea, non-sulfonylurea secretagogues, alpha glucosidase inhibitors, metformin, TZDs (n=2184)</td>
<td>All cause mortality at 1 year</td>
<td>93/768; 460/4345</td>
<td>0.58 (0.52 to 0.65); 0.58 (0.52 to 0.65)</td>
<td>0.86 (0.78 to 0.97); 0.86 (0.78 to 0.97)</td>
<td>In the subgroup of patients with left ventricular dysfunction, metformin did not increase the risk of mortality</td>
</tr>
<tr>
<td>Masoudi et al (2005)w1</td>
<td>Metformin (n=1861)</td>
<td>Sulfonylurea, non-sulfonylurea secretagogues, alpha glucosidase inhibitors, metformin, TZDs (n=12 069)</td>
<td>All cause mortality at 1 year</td>
<td>460/4345; 1265/8702</td>
<td>0.65 (0.59 to 0.71); 0.82 (0.74 to 0.91)</td>
<td>0.86 (0.78 to 0.97); 0.94 (0.89 to 1.01)</td>
<td>Metformin was associated with reduced mortality, all cause hospital admission, and heart failure related hospital admission. Metformin did not increase the risk for hospital admission for lactic acidosis</td>
</tr>
<tr>
<td>Eurich et al (2005)w2</td>
<td>Metformin monotherapy (n=208)</td>
<td>Sulfonylurea monotherapy (n=773)</td>
<td>All cause mortality at 1 year</td>
<td>29/200; 1091/7821</td>
<td>0.43 (0.29 to 0.65); 0.52 (0.57 to 0.48)</td>
<td>0.66 (0.44 to 0.97); 0.92 (0.86 to 0.99)</td>
<td>Metformin was associated with reduced all cause mortality and a trend towards reduced risk of all cause hospital admission</td>
</tr>
<tr>
<td>Eurich et al (2005)w2</td>
<td>Metformin and sulfonylurea combination therapy (n=852)</td>
<td>Sulfonylurea monotherapy (n=773)</td>
<td>All cause mortality at 1 year</td>
<td>97/200; 102/406</td>
<td>0.34 (0.26 to 0.44); 0.87 (0.64 to 1.18)</td>
<td>0.54 (0.42 to 0.70); 0.84 (0.67 to 1.04)</td>
<td>Metformin plus sulfonylurea was associated with reduced all cause mortality and a trend towards reduced risk of all cause hospital admission. Metformin was not associated with an increased risk of lactic acidosis</td>
</tr>
</tbody>
</table>
**TZD, thiazolidinedione.**

<table>
<thead>
<tr>
<th><strong>Inzucchi et al (2005)</strong></th>
<th><strong>TZD (n=255)</strong></th>
<th>Sulfonyleurea, non-sulfonylurea secretagogues, alpha glucosidase inhibitors, insulin (n=2184)</th>
<th>All cause mortality at 1 year</th>
<th>92/768</th>
<th>0.60 (0.54 to 0.65)</th>
<th>1.04 (0.83 to 1.31)</th>
<th>Readmission for heart failure at 1 year</th>
<th>139/1083</th>
<th>1.22 (0.94 to 1.58)</th>
<th>1.15 (0.97 to 1.38)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Masoudi et al 2005</strong></th>
<th><strong>TZD (n=2226)</strong></th>
<th>Sulfonyleurea, non-sulfonylurea secretagogues, alpha glucosidase inhibitors, insulin (n=12 069)</th>
<th>All cause mortality at 1 year</th>
<th>670/4345</th>
<th>0.77 (0.69 to 0.84)</th>
<th>0.87 (0.80 to 0.94)</th>
<th>All cause hospital admission at 1 year</th>
<th>1660/8702</th>
<th>1.14 (1.26 to 1.02)</th>
<th>1.04 (0.99 to 1.10)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Dargie et al (2007)</strong></th>
<th><strong>TZD (n=110)</strong></th>
<th>Placebo (n=114)</th>
<th>All cause mortality at 1 year</th>
<th>8/5</th>
<th>1.71 (0.55 to 5.34)</th>
<th>1.50 (0.49 to 4.59)</th>
<th>Readmission for heart failure at 1 year</th>
<th>5/4</th>
<th>1.31 (0.34 to 4.99)</th>
<th>Relative risk 1.30 (0.35 to 4.82) (no adjustment because of trial design)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Aguilar et al (2007)</strong></th>
<th><strong>TZD (n=818)</strong></th>
<th>Sulfonyleurea, non-sulfonylurea secretagogues, alpha glucosidase inhibitors, insulin (n=4700)</th>
<th>All cause mortality at 2 years</th>
<th>168/1192</th>
<th>0.76 (0.63 to 0.91)</th>
<th>0.98 (0.81 to 1.17)</th>
<th>Hospital admission for heart failure at 2 years</th>
<th>134/741</th>
<th>1.05 (0.86 to 1.28)</th>
<th>1.00 (0.81 to 1.24)</th>
</tr>
</thead>
</table>

| **Masoudi et al (2005)** | **Sulfonyleurea (n=8145)** | Non-sulfonylurea secretagogues, alpha glucosidase inhibitors, metformin, TZDs, insulin (n=8272) | All cause mortality at 1 year | 2679/2849 | 0.93 (0.87 to 1.00) | 0.99 (0.91 to 1.08) | Sulfonyleurea was not associated with increase risk of mortality |
|------------------------|-----------------|-----------------|---------------------------------|-----|-------------------|------------------|--------------------------------------|-----|-------------------|------------------|

TZD, thiazolidinedione.

angiotensin converting enzyme inhibitor, or myocardial infarction) and mortality (1.38, 1.06 to 1.80; table 1).

The effect of insulin was also evaluated in the CHARM (candesartan in heart failure: assessment of reduction in mortality and morbidity) study (box).23 w4 Although insulin was not directly compared with other antidiabetic drugs in adjusted analyses, unadjusted risk ratios calculated from the raw data presented in the paper suggest that treatment with insulin is associated with an increased risk of all cause mortality (risk ratio 1.25, 1.03 to 1.51) and death from cardiovascular disease or hospital admission for heart failure (1.55, 1.29 to 1.86) compared with other treatments in patients with diabetes (table 1).23 w4

Outcomes with insulin were also assessed in 554 consecutive patients referred to a university medical centre for management of heart failure (box).w6 Of these patients, 132 (24%) had diabetes and were prospectively followed for 11.7 months. Although insulin and non-insulin treatments were not directly compared in patients with diabetes, extrapolation from the raw data suggests an unadjusted risk ratio for all cause mortality of 3.42 (1.40 to 8.37) at one year and 2.20 (0.96 to 5.03) at two years (table 1) for patients with diabetes treated with insulin compared with those not treated with insulin.

The effects of insulin on mortality were also evaluated in a retrospective cohort study of 16 417 Medicare beneficiaries with diabetes who were discharged from hospital with a primary diagnosis of heart failure (box).w1 Unlike previous studies, this study found no association between the use of insulin and mortality adjusted hazard ratio 0.96; 0.88 to 1.05) compared with patients receiving metformin, thiazolidinediones, sulfonylureas, non-sulfonylurea insulin secretagogues, or alpha glucosidase inhibitors (table 1).w1

**Oral antidiabetic agents**

**Metformin**

Outcomes with metformin were evaluated in a retrospective cohort study of Medicare beneficiaries with diabetes discharged after hospital admission for acute myocardial infarction (box).w5 Subgroup analysis of the patients with diabetes and moderate to severe impaired left ventricular systolic function (n=2875) suggested that after multivariate adjustment treatment with metformin was not associated with any risk of all cause mortality at one year compared with patients receiving sulfonylureas, non-sulfonylurea insulin secretagogues, alpha glucosidase inhibitors, and insulin (n=406; 0.92, 0.72 to 1.18; table 1).w5

The study of Medicare beneficiaries with diabetes discharged with a primary diagnosis of heart failure also evaluated the effect of metformin on all cause mortality at one year (box).w7 After multivariate adjustment, compared with patients not receiving insulin sensitisers (that is, receiving sulfonylureas, non-sulfonylurea insulin secretagogues, alpha glucosidase inhibitors, or insulin) (n=12 069), all cause mortality was significantly lower in patients treated with metformin (n=1861; 0.86, 0.78 to 0.97), as well as in patients treated both with metformin and thiazolidinediones (n=261; 0.76, 0.58 to 0.99; table 1). In addition, no difference was seen in the risk for all cause hospital readmissions for patients receiving metformin (0.94, 0.89 to
Thiazolidinediones

In the previous Medicare study of patients with diabetes discharged after hospital admission for acute myocardial infarction, all after multivariate adjustment, the risk of all cause mortality at one year was no different for patients who received thiazolidinediones (n=255) than for patients treated with sulfonylureas, non-sulfonylurea insulin secretagogues, alpha glucosidase inhibitors, or insulin (1.04, 0.83 to 1.31; table 1). There was a trend, however, towards an increased risk of readmission for heart failure associated with thiazolidinediones (n=255; 1.15, 0.97 to 1.38).

In the second Medicare study of patients with diabetes discharged with a primary diagnosis of heart failure, after multivariate adjustment as above (n=12 069), all cause mortality at one year was significantly lower for patients treated with thiazolidinediones (n=2226; 0.87, 0.80 to 0.94; table 1). This study also found no difference in the risk for all cause hospital readmissions for patients receiving thiazolidinediones (1.04, 0.99 to 1.10). However, a small increased risk of readmission for heart failure was seen in patients receiving thiazolidinediones (1.06, 1.00 to 1.12).

In a retrospective cohort study of ambulatory patients followed through Veteran Affairs medical centres (box), after multivariate adjustment no differences were seen in all cause mortality at two years (n=814; 0.98, 0.81 to 1.17) or in hospital admission for heart failure (1.00, 0.81 to 1.24; table 1) in patients treated with thiazolidinediones compared with those not receiving insulin sensitisers (n=4700). However, in patients not receiving insulin, thiazolidinediones (n=381) were associated with an increased risk of hospital admission for heart failure compared with those not receiving insulin sensitisers (n=2217; 1.62, 1.15 to 2.29).

The only randomised controlled trial evaluated the addition of rosiglitazone (n=110) or placebo (n=114) to existing antidiabetic agents in patients with New York Heart Association class I or II disease (box). Although not a specific end point of the study, after 52 weeks of treatment (compared with placebo) there was a trend towards an increased risk of all cause mortality for rosiglitazone (hazard ratio 1.50, 0.49 to 4.59) and in the proportion of patients with hospital admission for heart failure (relative risk 1.30, 0.35 to 4.82; table 2). A trend towards an increase in all cause mortality or worsening heart failure was also seen (hazard ratio 1.28, 0.51 to 3.21).

The pooled effect of the four studies which assessed the effect of thiazolidinediones on all cause mortality suggests that treatment with thiazolidinediones may be associated with reduced all cause mortality compared with other treatments (pooled odds ratio 0.83, 0.71 to 0.97; P=0.02; I²=20.9%)

### Table 2 Results of test for statistical heterogeneity

<table>
<thead>
<tr>
<th>Antidiabetic drug</th>
<th>No of studies</th>
<th>Outcome assessed</th>
<th>P value for heterogeneity</th>
<th>I² statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>All cause mortality</td>
<td>0.03</td>
<td>67.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not determined</td>
<td>Not determined</td>
<td></td>
</tr>
<tr>
<td><strong>Thiazolidinediones</strong></td>
<td>4</td>
<td>All cause hospital admission</td>
<td>0.10</td>
<td>52.3%</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>All cause hospital admission</td>
<td>Not determined</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Heart failure related hospital admission</td>
<td>0.82</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Metformin</strong></td>
<td>3</td>
<td>All cause mortality at 1 year</td>
<td>&lt;0.001</td>
<td>83.5%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>All cause hospital admission at 1 year</td>
<td>0.26</td>
<td>20.9%</td>
</tr>
<tr>
<td><strong>Sulfonylurea</strong></td>
<td>2</td>
<td>All cause mortality at 1 year</td>
<td>&lt;0.001</td>
<td>96.4%</td>
</tr>
</tbody>
</table>

The pooled effect of the four studies which assessed the effect of thiazolidinediones on all cause mortality suggests that treatment with thiazolidinediones may be associated with reduced all cause mortality compared with other treatments (pooled odds ratio 0.83, 0.71 to 0.97; P=0.02; I²=20.9%), although moderate heterogeneity was observed (fig 3). Similarly, the pooled effect on hospital admission for heart failure suggests that thiazolidinediones may be associated with an increased risk of such admission compared with other treatments (1.13; 1.04 to 1.22; P=0.004; I²=52%; fig 4).

---

1. Test for overall effect: z=2.87, P=0.004
2. BMJ | ONLINE FIRST | bmj.com
3. Total (95% CI) 2921 12 842
4. Total events: 1802 (treatment), 9108 (control)
5. Test for heterogeneity: \( \chi^2=1.26 \), df=1, P=0.26, I²=20.9%
6. Test for overall effect: z=2.87, P=0.004
7. Thiazolidinediones
8. In the previous Medicare study of patients with diabetes discharged after hospital admission for acute myocardial infarction, all after multivariate adjustment, the risk of all cause mortality at one year was no different for patients who received thiazolidinediones (n=255) than for patients treated with sulfonylureas, non-sulfonylurea insulin secretagogues, alpha glucosidase inhibitors, or insulin (1.04, 0.83 to 1.31; table 1). There was a trend, however, towards an increased risk of readmission for heart failure associated with thiazolidinediones (n=255; 1.15, 0.97 to 1.38).
9. In the second Medicare study of patients with diabetes discharged with a primary diagnosis of heart failure, after multivariate adjustment as above (n=12 069), all cause mortality at one year was significantly lower for patients treated with thiazolidinediones (n=2226; 0.87, 0.80 to 0.94; table 1). This study also found no difference in the risk for all cause hospital readmissions for patients receiving thiazolidinediones (1.04, 0.99 to 1.10). However, a small increased risk of readmission for heart failure was seen in patients receiving thiazolidinediones (1.06, 1.00 to 1.12).
10. In a retrospective analysis using administrative records, another study compared metformin alone, or combined with sulfonylurea, to sulfonylurea monotherapy in 1833 patients with newly treated diabetes and incident heart failure (box). After multivariate adjustment, all cause mortality was significantly lower with metformin monotherapy (0.66, 0.44 to 0.97 at one year; 0.70, 0.54 to 0.91 after 2.5 years), or with combined treatment with metformin-sulfonylurea (0.54, 0.42 to 0.70 at one year; 0.61, 0.52 to 0.72 after 2.5 years; table 1). A reduction in the composite outcome of all cause mortality or hospital admission was also seen at the end of follow-up for the metformin monotherapy group (0.83, 0.70 to 0.99) and for combination therapy (0.86, 0.77 to 0.96; table 1).
11. Both of the studies assessing the effect of metformin on all cause hospital admission at one year were of good methodological quality (box) and yielded similar effect estimates. The pooled effect suggests that treatment with metformin may be associated with reduced all cause hospital admission at one year compared to other treatments (pooled odds ratio 0.85, 0.76 to 0.95; P=0.004; fig 2).
12. The only randomised controlled trial evaluated the addition of rosiglitazone (n=110) or placebo (n=114) to existing antidiabetic agents in patients with New York Heart Association class I or II disease (box). Although not a specific end point of the study, after 52 weeks of treatment (compared with placebo) there was a trend towards an increased risk of all cause mortality for rosiglitazone (hazard ratio 1.50, 0.49 to 4.59) and in the proportion of patients with hospital admission for heart failure (relative risk 1.30, 0.35 to 4.82; table 2). A trend towards an increase in all cause mortality or worsening heart failure was also seen (hazard ratio 1.28, 0.51 to 3.21).
13. The pooled effect of the four studies which assessed the effect of thiazolidinediones on all cause mortality suggests that treatment with thiazolidinediones may be associated with reduced all cause mortality compared with other treatments (pooled odds ratio 0.83, 0.71 to 0.97; P=0.02; I²=20.9%) although moderate heterogeneity was observed (fig 3). Similarly, the pooled effect on hospital admission for heart failure suggests that thiazolidinediones may be associated with an increased risk of such admission compared with other treatments (1.13; 1.04 to 1.22; P=0.004; I²=52%; fig 4).
treatment with thiazolidinediones were of good methodological quality (box). For all cause mortality, although the size and direction of effect estimates varied among studies, we found no consistent pattern of effect in relation to study quality. Similar effect estimates were seen for all studies regardless of quality with respect to hospital admission for heart failure.

**Sulfonylureas**

Few studies formally evaluated treatment with sulfonylureas as an independent exposure group. In the studies evaluating other oral treatments, however, sulfonylureas were used in about 55% of all patients in the main comparator groups (n=11 000). As a result, treatment with sulfonylurea was well represented in all of the studies evaluating oral antidiabetic agents included in our review.

Apart from the effect of sulfonylureas relative to metformin use already mentioned, only one other study looked at sulfonylureas. After multivariate analysis, no increased risk of mortality at one year was seen for patients receiving sulfonylureas compared with patients receiving other insulin secretagogues, alpha glucosidase inhibitors, metformin, thiazolidinediones, or insulin (0.99; 0.91 to 1.08).

**DISCUSSION**

Heart failure is a common comorbidity in patients with diabetes. Despite the high morbidity and mortality associated with the disease, our systematic review found few studies that formally compared antidiabetic drugs in this important population. Although several studies have evaluated the incidence of heart failure associated with the use of various antidiabetic agents, our review focused solely on the impact of such treatments in people with comorbid heart failure and diabetes. Of the eight studies included in this review, most studies were observational and there was only one randomised controlled trial, which was not designed to evaluate clinical outcomes. All studies were published in the past two years, and focused on use of insulin, thiazolidinediones, or metformin.

**Insulin**

In the four studies that specifically evaluated the use of insulin treatment, three suggested an increase in mortality, and one reported no association with mortality. Statistical heterogeneity precluded formal meta-analysis. Importantly, in two of the studies reporting increased mortality, there was no multivariate adjustment for the comparison between insulin and non-insulin treatments in patients with diabetes. Furthermore, none of the studies randomised patients to insulin or non-insulin treatment. As a result, it is difficult to tell whether this is a true adverse effect of insulin or whether it is simply confounding by indication. Treatment with insulin in these studies may well have been a marker for more advanced diabetes or vascular disease (or both). Thus, treatment with insulin may not, in itself, be associated with an increase in adverse effects in this population. Indeed, in one study that adjusted extensively for clinically important variables and compared insulin with other antidiabetic agents, insulin was not associated with an increased risk of mortality.

**Metformin**

Historically, metformin has been considered absolutely contraindicated in patients with heart failure who need drug treatment because of concerns about lactic acidosis. Recently, however, the US Food and Drug Administration has removed the heart failure contraindication from the packaging of metformin (Glucophage and Glucophage XR), although a strong warning for the cautious use of metformin in this population still exists. The true prevalence of metformin use in patients with heart failure is not known, but published studies suggest 10-25% of patients receiving metformin have comorbid heart failure. Despite the concerns, our analysis revealed that treatment with metformin may be associated with lower mortality rates, although statistical heterogeneity precluded formal meta-analysis. Furthermore, no study found an increase in adverse events with metformin and the results of both studies that evaluated all cause hospital admissions in metformin users suggested that this drug is associated with a lower rate of all cause hospital admission than other antidiabetic drugs.

**Thiazolidinediones**

Thiazolidinediones are also relatively contraindicated in patients with New York Heart Association class III or IV disease because of concerns about fluid retention, which may worsen symptoms of heart failure. Yet, the pooled effects for mortality suggest that thiazolidinediones may be associated with reduced mortality, although the results should be interpreted cautiously as moderate statistical heterogeneity was present. The only randomised controlled trial showed a trend towards an increased risk of mortality with thiazolidinediones; however, the study was not specifically designed to assess clinical outcomes and 62 (28%) patients withdrew from the study. As a result, the study was underpowered to detect any differences in...
clinical outcomes between treatment groups. Data from one of the two large observational studies suggest that thiazolidinediones may be associated with lower mortality, whereas this was not seen in the other study.\(^1\)\(^8\) This discrepancy may be related to the lower severity of illness in the patients in the second study, the under-representation of female patients, or differences in the use of combination treatment between study groups.\(^8\)

All studies except for one reported higher numbers of hospital admissions related to heart failure for patients receiving thiazolidinediones\(^1\)\(^3\)\(^7\)\(^8\); this risk was confirmed by formal pooling of the data. This is consistent with evidence from randomised controlled trials, including the recently published interim analysis of the RECORD (rosiglitazone evaluated for cardiac outcomes and regulation of glycaemia in diabetes) study, which has consistently shown increased fluid retention and admission for heart failure in patients without pre-existing heart failure who use thiazolidinediones.\(^2\)\(^6\)\(^32\)\(^34\) Recently, the US Food and Drug Administration has changed the package labels for thiazolidinediones to include a “black box” warning emphasising that these drugs may cause or exacerbate heart failure in certain patients. Furthermore, given the recent controversy over the use of thiazolidinediones and increased risk of myocardial infarction,\(^35\) the overall impact on health remains uncertain.\(^36\)

Although the lower mortality rates associated with use of metformin or thiazolidinediones are consistent with those seen in randomised controlled trials of insulin sensitizers in other populations with diabetes,\(^2\)\(^6\)\(^32\)\(^37\) none of the three included studies were randomised controlled trials. Although a wide range of demographic factors and patient characteristics were adjusted for in the studies, the study groups may have differed in severity of diabetes, heart failure, or other cardiovascular risk factors. Specifically, because of the commonly perceived risks of insulin sensitizers, these drugs may have been used preferentially in patients thought to be at lower risk than those given other treatments. Thus, the benefits of metformin and thiazolidinediones on mortality may be due to selection bias in these studies. Furthermore, only one study specifically evaluated the effects of oral antidiabetic agents as monotherapy.\(^1\)\(^8\) Contamination of comparison groups as a result of the use of multiple antidiabetic drugs is a possibility in the other two studies.\(^1\)\(^3\)\(^8\)

### Sulfonylureas

Only two studies specifically evaluated sulfonylureas as an independent exposure.\(^1\)\(^7\)\(^8\) One study found that sulfonylurea monotherapy may be associated with worse outcomes,\(^1\) whereas the other did not.\(^1\)

The discrepancy may partly be due to the comparator groups used in the studies. The first study compared sulfonylurea monotherapy with metformin, which has been shown to be beneficial in all similar studies, while the second compared sulfonylurea exposure (alone or in combination) with treatments that did not specifically include metformin. In the first study, it is not clear whether the risk estimates were a result of an adverse effect of sulfonylureas, a beneficial effect of metformin, or confounding by indication. Although these results are consistent with other studies evaluating sulfonylureas,\(^37\)\(^40\) a recent meta-analysis has indicated that these drugs are not associated with an increase in cardiovascular events.\(^41\) Given the current controversy surrounding the use of sulfonylureas in patients with pre-existing cardiovascular disease,\(^42\) more research is needed to determine the true impact of these drugs in people with diabetes and heart failure.

### Limitations

Inherent to any systematic review is the potential for publication or selection bias. Studies that may have evaluated the use of antidiabetic agents in patients with heart failure as part of a stratified or secondary analysis may not have been identified using standard search strategies. However, manual searches and contact with primary authors of the included studies provided no extra articles. Any relevant articles are therefore unlikely to have been missed. Secondly, the included studies were mainly observational and only one study randomised patients to different antidiabetic drugs. As a result, the effects of unmeasured confounding variables could not be fully explored and this may be a limitation of most of the reported studies.

### Conclusions

Our results suggest that of the current antidiabetic agents, metformin is the only one not associated with any measurable harm in people with diabetes and heart failure and is associated with reduced mortality. Given the large number of people affected with diabetes and heart failure and the fact that this population is expected to increase rapidly, evidence on how to optimally control glycaemic levels in this population is urgently needed. It is therefore imperative that research be undertaken to determine the optimal approach for glycaemic control in patients with heart failure. Ideally, this research should be a randomised controlled trial which includes the use of metformin or thiazolidinedione in patients with heart failure and...
Details of the eight included studies of antidiabetic agents for treating diabetes with heart failure

Design—Post hoc subgroup analysis of randomised controlled trial (SAVE; n=696)
Inclusion criteria—Diabetes, between 21 and 80 years of age, left ventricular ejection fraction <40% after myocardial infarction
Exclusion criteria—Contraindication to angiotensin converting enzyme inhibitors or need to treat heart failure or hypertension, creatinine >221 mmol/l; unstable illness; active ischaemia
Agents evaluated—Insulin
Method of analysis—Multivariate Cox proportional hazards regression
Covariates included in analysis—Age, sex, left ventricular ejection fraction, previous myocardial infarction, Killip class ≥II, thrombolytic treatment, use of β blockers, and captopril assignment
Duration—Mean 3.5 years
Methodological quality checklist score—44%
Potential limitations and threats to validity—Selection bias (data derived from randomised controlled trial in patients after myocardial infarction). Uncertain drug exposure (drug use defined at start of trial, exposure to drug throughout follow-up uncertain). Confounding by severity of diabetes (no data on glucose control, duration of diabetes). Limited adjustment for clinical data. No data on type of oral antidiabetic agents used

Pocock et al (2006)w4
Design—Post hoc subgroup analysis of randomised controlled trial (CHARM (n=2160))
Inclusion criteria—18 years or older, symptomatic heart failure (New York Heart Association class II-IV) of at least four weeks’ duration
Exclusion criteria—Creatinine ≥265 µmol/l, K+ ≥5.5 mmol/l, bilateral renal stenosis, symptomatic hypotension, women of childbearing potential not receiving contraceptives, critical aortic or mitral stenosis, myocardial infarction, stroke or open heart surgery in the previous four weeks, use of angiotensin receptor blockers in previous two weeks, any non-cardiac disease likely to limit survival to two years
Agents evaluated—Insulin
Method of analysis—Univariate
Covariates included in analysis—No covariate adjustment
Duration—Median 37.7 months
Methodological quality checklist score—41%
Potential limitations and threats to validity—Confounding by severity of diabetes (no data on glucose control, duration of diabetes). No data on type of oral antidiabetic agents used. Uncertain exposure (criteria used to define ‘insulin use’ not stated; no data on duration of drug use; exposure to drug throughout follow-up uncertain). Selection bias (data derived from randomised controlled trial). No adjusted results comparing insulin with other treatments in patients with diabetes

Smooke et al (2005)w5
Design—Prospective cohort study (n=132)
Inclusion criteria—Consecutive patients referred to specialty clinic to manage heart failure or evaluate them for a heart transplant because of systolic dysfunction (left ventricular ejection fraction <40%) from 1 January 2000 to 30 January 2003
Exclusion criteria—No exclusions reported
Agents evaluated—Insulin
Method of analysis—Univariate
Covariates included in analysis—No covariate adjustment
Duration—Mean 11.7 months
Methodological quality checklist score—63%
Potential limitations and threats to validity—Small sample size initially and 15% lost to follow-up (few patients left to evaluate for two year outcome). Uncertain exposure (no data on duration of drug use; exposure to drug throughout follow-up uncertain). Significant baseline differences (incomplete adjustment because of small sample size). No adjusted results comparing insulin and non-insulin treatments in patients with diabetes. Short duration of follow-up (mean 11.7 months). Results limited to a select population of patients (advanced heart failure patients only)

Masoudi et al (2005)w7
Design—Retrospective cohort study (n=16 417)
Inclusion criteria—Patients with diabetes receiving antidiabetic agents upon discharge with a principal discharge diagnosis of heart failure
Exclusion criteria—Over 65 years of age, died during hospital admission, unknown date of death, unknown readmission data, discharge to a hospice, no drug treatment for diabetes at discharge
Agents evaluated—Insulin, metformin, thiazolidinediones, sulfonylurea
Method of analysis—Stepwise multivariate Cox proportional hazards regression
Covariates included in analysis—Demographics (age, sex, race); cardiac history (history of myocardial infarction, hypertension, coronary artery disease, percutaneous transluminal coronary angioplasty; non-cardiovascular history (admission source, mobility, cerebral vascular accident, chronic pulmonary disease, urinary incontinence, dementia); clinical characteristics at admission (systolic blood pressure, respiratory rate, heart failure, Na+, glucose, blood urea nitrogen test, creatinine, white blood cell count, haematocrit); hospital course (atrial fibrillation, heart failure or pulmonary oedema on admission, cardiac catheterisation, percutaneous transluminal coronary angioplasty, coronary artery bypass surgery, complications of diabetes); discharge prescriptions; severity of diabetes; sampling time frame
Duration—Not reported
Methodological quality checklist score—50%
Potential limitations and threats to validity—Uncertain exposure (cohort created on the basis of drug prescribed at discharge; exposure to drug throughout follow-up uncertain). Short duration of follow-up (outcomes at one year). Results limited to a select population of patients (>65 years of age)

Inzucchi et al (2005)w3
Design—Retrospective cohort study (n=2875)
Inclusion criteria—Patients with diabetes receiving antidiabetic agents upon discharge from hospital for myocardial infarction
Exclusion criteria—Unconfirmed myocardial infarction, long term haemodialysis, over 65 years of age, died during hospital stay, unknown date of death, unknown readmission data, discharge to a hospice, transferred to another hospital, left against medical advice, no drug treatment for diabetes at discharge
Agents evaluated—Metformin, thiazolidinediones
Method of analysis—Stepwise multivariate Cox proportional hazards regression
Covariates included in analysis—Potential covariates included demographics (age, sex, race); cardiac history (history of heart failure, myocardial infarction, hypertension, revascularisation); non-cardiovascular history (admission source, mobility, cerebral vascular accident, chronic pulmonary disease, urinary incontinence, dementia); clinical characteristics at admission (systolic blood pressure, respiratory rate, heart failure, Na+, glucose, blood urea nitrogen test, creatinine, white blood cell count, haematocrit); hospital course (atrial fibrillation, heart failure or pulmonary oedema on admission, cardiac catheterisation, percutaneous transluminal coronary angioplasty, coronary artery bypass surgery, complications of diabetes); discharge prescriptions; severity of diabetes; sampling time frame; patient clustering by hospital
Duration—Not reported
Methodological quality checklist score—47%
Potential limitations and threats to validity—Selection bias (over 65 years of age, after myocardial infarction only). Small sample size (few subjects in left ventricular dysfunction subgroup). Uncertain exposure (cohort created in left ventricular dysfunction subgroup). Short duration of follow-up (outcomes at one year).

Eurich et al (2005)\textsuperscript{a}

Design—Retrospective cohort study (n=1833)

Inclusion criteria—New users of oral antidiabetic agents with incident onset heart failure

Exclusion criteria—Insulin use, prevalent heart failure (diagnosis of heart failure before starting oral antidiabetic agents)

Agents evaluated—Metformin, sulfonylurea

Method of analysis—Multivariate Cox proportional hazards regression

Covariates included in analysis—Age, sex, modified chronic disease score, prescription drugs affecting outcomes in people with diabetes or heart failure (or both), total number of visits to doctor before diagnosis of heart failure, propensity score (not included in final models)

Duration—Mean 2.5 years

Methodological quality checklist score—50%

Potential limitations and threats to validity—Selection bias (uncertain diagnostic accuracy of heart failure in doctor’s service file; insulin users excluded). Uncertain exposure (cohort created on a single prescription for antidiabetic drugs; exposure to drug through follow-up uncertain; combination therapy not necessarily concurrent therapy). Confounding by severity of diabetes or heart failure (no clinical data or functional status). Small sample size (only 208 in metformin monotherapy cohort)

Dargie et al (2007)\textsuperscript{a}

Design—Randomized controlled trial (n=224)

Inclusion criteria—Fasting blood glucose ≥7 mmol/l, stable New York Heart Association class I/II, left ventricular ejection fraction ≤45%, treatment with angiotensin converting enzyme inhibitors or angiotensin receptor blockers and diuretic if New York Heart Association class II

Exclusion criteria—Body mass index more than 35, creatinine clearance ≤40 ml/min, hepatic disease, anaemia

Agents evaluated—Thiazolidinediones

Method of analysis—Cox proportional hazards regression

Covariates included in analysis—None

Duration—One year

Methodological quality checklist score—66%

Potential limitations and threats to validity—Baseline characteristics were not fully matched between placebo and treatment group. Small sample size and few clinical events (inadequate power to detect clinical differences). High withdrawal rate (28%)

Aguilar et al (2007)\textsuperscript{a}

Design—Retrospective cohort study (n=7147)

Inclusion criteria—Patients of the Veterans Associationexternal peer review programme who had diabetes and were prescribed hypoglycaemic drugs

Exclusion criteria—Treatment with metformin in control group

Agents evaluated—Thiazolidinediones

Method of analysis—Stepwise multivariate Cox proportional hazards regression

Covariates included in analysis—Age, sex, body mass index, left ventricular ejection fraction, glomerular filtration rate, haemoglobin, hypertensive medication, age, race, previous diabetic complications, atrial fibrillation, heart failure related drugs, previous hospital admission for heart failure, hyperglycaemia, anaemia, chronic obstructive pulmonary disease, peripheral vascular disease, psychiatric disorders, liver disease, rheumatic disease, medical school affiliation, other antidiabetic drugs

Duration—Not reported

Methodological quality checklist score—50%

Potential limitations and threats to validity—Selection bias (metformin users excluded from control group but not treatment group). Uncertain exposure (cohort created on the basis of 120 day window around index outpatient visit; exposure to drug throughout follow-up uncertain). Short duration of follow-up (outcomes at two years)

Contributors: DTE, FAM, DFB, SRM, RTT, and JA helped plan and design the study. DTE, DFB, JV, and JA collected the data. DTE conducted the statistical analyses. All authors had access to the data and helped interpret the data. DTE wrote the first draft of the paper. All authors reviewed and revised the paper for important intellectual content and approved the version. DTE led the study, is lead author, and is guarantor.

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Perennial rhinitis

Hesham A Saleh,1 Stephen R Durham2

Perennial rhinitis can be defined clinically as an inflammatory condition of the nose characterised by nasal obstruction, sneezing, itching, or rhinorrhoea, occurring for an hour or more on most days throughout the year. Rhinitis is commonly managed by both primary and secondary care physicians. Although most cases can be diagnosed and treated in primary care, referral to secondary care is often necessary when patients do not respond to treatment or other diagnoses are suspected.

A recent large scale, cross sectional study in six western European countries found that the overall prevalence of rhinitis was 23%. The study also showed that the condition is often undiagnosed, as 45% of patients with investigator confirmed allergic rhinitis had not previously received a diagnosis from their physicians. A published review of previous population based studies showed that, as with asthma, both seasonal and perennial rhinitis seem to be increasing.

How is perennial rhinitis classified?

Allergic rhinitis

Perennial allergic rhinitis can be more difficult to diagnose than seasonal allergy, particularly if the patient presents with secondary symptoms of sinusitis and a “permanent cold.” The most common allergens to account for perennial allergy symptoms is the house dust mite (Dermatophagoides pteronyssinus). Other common causes are animals, particularly cats, dogs, and horses. In some parts of the world “typical” seasonal allergens are perennial in nature. Equally, symptoms of perennial rhinitis may not be present all year round.

For these reasons a new classification has been put forward in the document on allergic rhinitis and its impact on asthma (ARIA). This subdivides allergic rhinitis in relation to the duration of symptoms into “intermittent” and “persistent.” The severity of allergic rhinitis is also classified as “mild” or “moderate-severe” (fig 1). Recent cross sectional studies showed that a large number of patients classified by their doctor as having seasonal symptoms did in fact have persistent rhinitis, whereas many classified as having perennial rhinitis actually had intermittent rhinitis. Patients with persistent rhinitis had more severe symptoms and higher rate of self awareness and previous diagnosis of rhinitis; they were also clearly distinct in their sensitisation pattern and drug use. This supports the validity of the classification and is expected to simplify management decisions by allowing them to be tailored to the individual patient.

Non-allergic rhinitis

Patients with non-allergic rhinitis present with perennial or persistent symptoms, which can occasionally be attributed to certain factors; however, in a large number of patients no specific triggers can be found and the condition is termed “idiopathic rhinitis.” To date, no precise data are available on the prevalence of non-allergic rhinitis, but it is considered to be less common than allergic rhinitis. Table 1 lists various types of non-allergic rhinitis with their causes and characteristics.

What is the differential diagnosis?

Structural abnormalities of the nose include deviation of the nose or septum, enlarged middle and inferior turbinates, adenoidal hypertrophy (particularly in children; rare in adults), and choanal atresia. Chronic rhinosinusitis is secondary to obstruction of the ostiomeatal complex, whether structural or secondary to an inflammatory condition. This is the area lying between the middle and inferior turbinates and the natural ostium of the maxillary sinus where the maxillary, anterior ethmoidal, and frontal sinuses drain.

Nasal polyps result from inflammation of the mucosal lining of the sinuses; the lining prolapses down, particularly from the anterior ethmoidal sinuses, through the middle meatus to obstruct the nasal airway (fig 2). Allergy does not seem to be an important factor. Nasal polyps in children are rare and are almost invariably associated with cystic fibrosis. In adults, a strong association exists between

Box 1 | Taking a history

- Listen to patient’s account of symptoms
- How long has the condition been present?
- Impact on lifestyle: how frequent and severe is it? Does it affect work, school, leisure time, sleep?
- Seasonal or perennial?
- Trigger factors: allergic or non-allergic?
- Exposure to allergens through occupation or hobbies?
- Allergens in the home
- Does patient have history of asthma, eczema, rhinitis?
- Drug or food induced?
- Family history
- Treatment: compliance, efficacy, side effects
- What is the main symptom?
nasal polyps, asthma, and sensitivity to aspirin (Samter’s triad). Granulomatous rhinitis may be associated with Wegener’s granulomatosis and sarcoidosis (fig 3).

Leaking of cerebrospinal fluid will present with watery rhinorrhoea, often unilateral. It is usually associated with trauma (including surgical trauma) or neoplasia, but spontaneous leaking may occur. Nasal neoplasms are rare; the diagnosis should be considered in patients with unilateral symptoms of nasal obstruction, pain, or bleeding.

**How is the diagnosis made?**

The diagnosis is made on history and examination and is supported by skin prick testing. Taking a history need not be time consuming. A glance at the classification and differential diagnosis will suggest the most important questions (box 1). Rare, sinister causes of rhinitis need to be excluded. Unilateral symptoms should always be regarded with suspicion, particularly if associated with symptoms of increasing nasal obstruction, blood stained nasal discharge, or facial pain.9

Ear, nose, and throat surgeons examine the nose with a head mirror or headlight and a nasal speculum, supplemented by rigid or flexible nasendoscopy. In general practice, the nose can be examined with an auriscope fitted with the largest speculum. A large, swollen, oedematous inferior or middle turbinate can easily be confused with a polyp; polyps, however, unlike turbinates, are usually pale grey, translucent, and mobile and lack any sensation on gentle probing (fig 4).

**What investigations are needed?**

**Skin prick test**

Most cases of perennial allergic and non-allergic rhinitis need no specific investigations other than skin prick testing. Evidence from controlled trials shows the high sensitivity and specificity of skin tests.10 These provide supportive information for the history to diagnose specific allergies and, when negative, largely exclude IgE mediated disease. They are also important if avoidance measures are to be considered. When skin prick tests are not available or the patient is taking antihistamines or has dermatographism, total and allergen specific IgE concentrations in the blood may be determined (radio-allergosorbent test—RAST—or enzyme linked immunosorbent assay—ELISA).

**Other tests**

If the history or examination suggests that other factors need to be excluded, the patient may need a variety of investigations, depending on the history and clinical findings. These are usually done in secondary care.

**Blood tests**

In chronic rhinosinusitis, full blood count and differential, including an eosinophil count, may be useful and immunoglobulin concentrations should be checked. If in doubt and infective rhinitis is suspected, specific IgG antibodies to tetanus and pneumococcus can be measured; if these are low, the measurements can be repeated six weeks after specific vaccination with tetanus or pneumovax.

**Erythrocyte sedimentation rate**

Erythrocyte sedimentation rate is indicated if rhinitis as a presenting feature of vasculitis such as Churg-Strauss syndrome is suspected. Blood tests for antineutrophil cytoplasmic antibody or angiotensin converting enzyme may be indicated if Wegener’s granulomatosis or nasal sarcoidosis is suspected. It is also important to consider whether the patient may be HIV positive or be...
compromised by treatment with immunosuppressant drugs that predispose to infective rhinitis.

**Imaging**

Computed tomography scanning of the sinuses is indicated when medical treatment has failed, the diagnosis of chronic rhinosinusitis is suspected and could not be confirmed on history and examination, or neoplasia is suspected. Evidence shows that plain radiographs of the sinuses can be misleading, and computed tomography of the sinuses in the coronal plane has become the standard international imaging method. Good quality cross sectional studies show that some mucosal thickening is often present on computed tomography scans of patients with allergic rhinitis, but the diagnosis of chronic rhinosinusitis is asserted when obstruction of the ostiomeatal complex is present.

**Further tests**

Further tests are considered to exclude rarer conditions and are usually done in highly specialised centres, where some of them are mainly used for research purposes. Nasal inspiratory peak flow can be measured with a modified peak flow meter. This test is easy and inexpensive to do, but forced inspiration may be associated with vestibular collapse. Rhinomanometry records resistance in the nasal airway by measuring nasal airflow with a face mask and pneumotachograph, and pressure gradient from the front to the back of the nose with a manometer. Acoustic rhinometry measures the cross sectional area of the nasal cavity and is much easier to do.

Nasal allergen challenge is occasionally indicated when a strong history exists in the face of negative skin prick test or radio-allergosorbent test. Patients with suspected occupational rhinitis due to a sensitizer in the workplace may need an occupational type provocation in which simulated exposure to the suspected agent is reproduced in an isolation cubicle. Assessment of nasal mucociliary clearance is indicated when ciliary dyskinesia is suspected. This is assessed simply by measuring the time taken for the patient to detect a sweet taste after a 0.5 mm particle of saccharin is placed on the mucosa of the inferior turbinate. If the test result is abnormal, further

### Table 1 | Types of non-allergic rhinitis

<table>
<thead>
<tr>
<th>Type</th>
<th>Causes</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic rhinitis</td>
<td>Unknown</td>
<td>Rhinitis with sensitivity to strong smells and changes in temperature</td>
</tr>
<tr>
<td>Infective rhinitis</td>
<td>Acute or chronic infections</td>
<td>Chronic infection may result from host defence deficiency or a local problem (for example, primary ciliary dyskinesia)</td>
</tr>
<tr>
<td>Occupational rhinitis</td>
<td>Organic or chemical agents at place of work</td>
<td>Symptoms are absent during weekends and holidays; affects farmers, laboratory workers, hairdressers, and so on</td>
</tr>
<tr>
<td>Non-allergic rhinitis with eosinophilia syndrome (NARES)</td>
<td>Unknown</td>
<td>Nasal eosinophilia; more common in young women</td>
</tr>
<tr>
<td>Hormonal rhinitis</td>
<td>Hormonal effects on nasal mucosa and its neurovasculature</td>
<td>Occurs with pregnancy, puberty, hypothyroidism, and acromegaly</td>
</tr>
<tr>
<td>Drug induced rhinitis</td>
<td>Systemic drug effects</td>
<td>Common with β blockers, chlorpromazine, oral contraceptives, and aspirin</td>
</tr>
<tr>
<td>Food induced rhinitis</td>
<td>Non-allergic reactions to food colourings and preservatives or &quot;IgE hypersensitivity to certain food products&quot;</td>
<td>Rhinitis due to food allergy is always associated with systemic manifestations (such as oral and gastrointestinal symptoms)</td>
</tr>
<tr>
<td>Atrophic rhinitis</td>
<td>Primary or secondary to radical surgery, infections, irradiation, or trauma</td>
<td>Nasal crusting and congestion despite having wide nasal passages</td>
</tr>
<tr>
<td>Gastro-oesophageal reflux</td>
<td>Direct irritation to nasal mucosa</td>
<td>Particularly affects children</td>
</tr>
</tbody>
</table>

**Box 3 | Surgical treatment (evidence levels 3 and 4)**

- The first line of treatment for allergic or non-allergic perennial rhinitis is medical
- When drugs fail and a structural abnormality exists, surgery may be indicated
- Surgical reduction of the inferior turbinates or correction of a deviated nasal septum or nose may be needed to improve the airway or at least to improve access for topical medical treatment
- Surgery continues to have a major role in the management of nasal polyps and sinusitis when these conditions fail to respond to medical treatment
- The management of nasal polyps and sinusitis has improved with the introduction of minimally invasive endoscopic sinus surgery
assessment of ciliary function is done in specialist rhinology clinics and involves taking a brushing of the nasal mucosa overlying the inferior turbinate and measuring the frequency of the beating cilia detected with a microscope attached to a photometric cell (normal range 12-15 Hz). Exhaled nasal nitric oxide is a sensitive marker of inflammation and can be measured through a face mask. This is currently used primarily in research trials but is diagnostic of primary ciliary dyskinesia in patients without severe nasal obstruction.

Swabs, smears, and biopsies
With infective symptoms, swabs for culture and sensitivity may be useful; nasal smears for cytology may show high concentrations of eosinophils; and biopsies for histology may be indicated when investigating granulomatous conditions or neoplastic disease. Olfactory thresholds can be assessed by the readily available “scratch and sniff” tests that use cards impregnated with microencapsulated odorants.

How is perennial rhinitis treated?
A stepwise approach according to the severity of symptoms, based on the available randomised trials, has been adopted by ARIA (fig 5). Main lines of treatment are allergy avoidance, antihistamines, and topical steroids. Patients with non-allergic rhinitis are more difficult to treat, but many respond to topical steroids. If a particular factor for non-allergic rhinitis has been identified (such as a drug), symptoms can usually be eliminated by its exclusion. Patients may need long term or permanent treatment. Long term prognosis is not well documented, but patients with perennial rhinitis are generally thought to improve over time.

Allergen avoidance
Perennial allergic rhinitis is commonly associated with allergy to house dust mite. The routine implementation of mite avoidance measures has been questioned in a recent Cochrane systematic review. However, whether effective reduction of mite levels was achieved in many studies was not clear. Two studies in adults—one in perennial rhinitis and one in bronchial asthma—showed that a single intervention with mite proof bed covers was unsuccessful, and clearly such measures should not be recommended in isolation. Multiple avoidance measures are still thought to be effective and should in our opinion be recommended.

Patients who are found to be allergic to furred animals should reduce their exposure as much as possible and be discouraged from having pets in the home, although psychosocial consequences often have to be considered. Occupational allergy requires prompt recognition and avoidance of the offending agent if long term consequences are to be avoided.

Medical treatment
Table 2 shows the comparative effectiveness of drugs for allergic rhinitis. A recent review of randomised controlled trials confirmed the efficacy of antihistamines in persistent allergic rhinitis. Most patients will attain good control on intranasal steroids, and a large body of data shows that they are effective for all symptoms of allergic perennial rhinitis, including nasal obstruction, itching, sneezing, and watery rhinorrhoea. Modern intranasal steroids are safe for long term use in adults when used within the recommended dosage. In children, they should be used at the lowest dose that controls symptoms, particularly when used concurrently with other inhaled or intranasal steroids. Occasionally, intranasal steroids may be associated with dryness, crusts, crust, or slight bleeding, which if recurrent may necessitate withdrawal of treatment.

The chromone sodium cromoglycate is less effective than antihistamines and corticosteroids and needs

Table 2 | Comparative effects of various agents on rhinitis associated symptoms (from consensus statement)\textsuperscript{17}

<table>
<thead>
<tr>
<th>H\textsubscript{2} antihistamines:</th>
<th>Sneezing</th>
<th>Rhinorrhoea</th>
<th>Nasal obstruction</th>
<th>Nasal itch</th>
<th>Eye symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Intranasal</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Intraocular</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+++</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Cromoglycates:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intranasal</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Intraocular</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Antileukotrienes</td>
<td>0</td>
<td>+</td>
<td>++</td>
<td>0</td>
<td>++</td>
</tr>
</tbody>
</table>

**SOURCES AND SELECTION CRITERIA**

We searched Medline by using the keywords “rhinitis,” “perennial rhinitis,” “persistent rhinitis,” “diagnosis,” and “management.” We also searched the Cochrane Database of Systematic Reviews with the keywords “rhinitis,” “perennial rhinitis,” and “persistent rhinitis.” We also consulted personal archives and documents on the subject.
What to exclude (differential diagnosis)

- Structural abnormalities that cause nasal obstruction such as deviation of the septum, enlarged middle and inferior turbinates, adenoidal hypertrophy (particularly in children; rare in adults), and choanal atresia
- Chronic rhinosinusitis, in which patients may have purulent anterior or posterior discharge, sinus pressure or pain, and nasal obstruction or congestion
- Nasal polyps, which can be characterised by severe nasal obstruction, loss of sense of smell, and greyish insensitive swellings on nasal examination
- Rarely, granulomatous rhinitis may be associated with Wegener’s granulomatosis and sarcoidosis
- Leaking of cerebrospinal fluid, either secondary to trauma or spontaneous, will present with watery rhinorrhea, often unilateral

When to refer to a specialist

- If the diagnosis is in doubt
- If medical treatment of rhinitis was not successful
- If the patient has unilateral symptoms of nasal obstruction, pain, or bleeding
- If the patient has a suspected structural abnormality, nasal polyps, granulomas, or cerebrospinal fluid leak—in the case of chronic rhinosinusitis, medical treatment should be tried first
SUMMARY POINTS

Perennial allergic rhinitis is a common condition in general practice
The most common allergen is the house dust mite, followed by cats and dogs.
Diagnosis is through history and skin prick testing
Patients with unilateral symptoms, especially if they have pain or bleeding, should be referred to an ear, nose, and throat specialist.
Avoidance measures should be taken where appropriate.
Medical treatment, mainly with antihistamines, topical corticosteroids, or both, is usually highly effective.
Immunotherapy is reserved for severe cases in which avoidance measures and medical treatment are either not effective or not tolerated.
Surgery is reserved for certain patients who have structural abnormalities.

Contributors: HAS collected the data and wrote the first draft. SRD revised and added to the manuscript and provided further references. HAS is the guarantor.

Competing interests: None declared.

Provenance and peer review: Commissioned; externally peer reviewed.

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Life class lives again

The teachers at Homerton School of Art were worried that their students could draw still life, but not movement. They made a film with five nude models, always on the move, while the students made drawings on paper arranged on the floor. As a visiting lecturer at Bradford College of Art, I was invited to see the film, and my thoughts turned to my own students—making one or two drawings in a two hour practical and completing them from a textbook at home.

Next practical I gave my students paper, pencils, and a board to draw on—and released 13 frogs from a box. The rules were simple: each student had to choose a frog and follow it, making as many drawings as possible. They made a film with five nude models, always on the move, while the students made drawings on paper arranged on the floor. As a visiting lecturer at Bradford College of Art, I was invited to see the film, and my thoughts turned to my own students—making one or two drawings in a two hour practical and completing them from a textbook at home. The running, jumping and standing still game.

Next year we visited Moscow for a microbiological conference, taking a translation of his book to Kornei Chukovsky, the great Russian man of letters. Only on the last afternoon did we manage to reach his house in the writers’ village. Sitting with him on a tree trunk in his children’s garden theatre, my wife told him of my frogs. Turning to me, he said, “They don’t let you teach that anywhere, do they?”

“No,” I said, “but how did you know?”

“It’s the same everywhere,” he replied.

Several years later, at dinner at a conference on teaching, I remarked that in science one received requests for reprints and other scientists cited one’s work, but no one had ever written to me for a paper about teaching. “Did anyone ever read what I had written?” I asked, citing my frog paper.

Someone further down the table answered, “Yes, that paper changed my life.”

H V Wyatt
visiting lecturer in philosophy, University of Leeds, Leeds nruwhv@leeds.ac.uk
Metformin, heart failure, and lactic acidosis: is metformin absolutely contraindicated?

A A Tahrani, G I Varughese, J H Scarpello, F W F Hanna

Many patients with type 2 diabetes are denied treatment with metformin because of “contraindications” such as cardiac failure, which may not be absolute contraindications.

Metformin first became available in the United Kingdom in 1957 but was first prescribed in the United States only in 1995. The mechanism of action has been extensively reviewed. The UK prospective diabetes study showed that metformin was associated with a lower mortality from cardiovascular disease than sulphonylureas or insulin in obese patients with type 2 diabetes mellitus. It was also associated with reduced all cause mortality, which was not seen in patients with equally well controlled blood glucose treated with sulphonylureas or insulin.

Despite the evidence base for the benefits of metformin, concerns remain about its side effects and especially the perceived risk of lactic acidosis in the presence of renal, hepatic, respiratory, or cardiac failure. Perhaps as a result of this, many suitable patients with type 2 diabetes are denied metformin treatment. The box summarises the current contraindications to metformin use. In this article we review the evidence for the use of metformin in the presence of stated contraindications and especially for patients with heart failure.

Data sources

We searched Medline with the following terms: metformin, phenformin, biguanides, biguanide, lactic acidosis, lactic acid, heart failure, cardiac failure, congestive cardiac failure, left ventricular impairment, metformin contraindications, renal impairment, renal failure, diabetes, type 2 diabetes, non-insulin dependent diabetes, and combinations of these terms. In addition, we consulted the Cochrane systematic reviews.

Metformin and risk of lactic acidosis: what evidence?

The perceived risk of developing lactic acidosis with metformin is high, particularly in the United States. An increasing body of evidence challenges the so called “contraindications” to metformin. Most of the evidence for the association between metformin and lactic acidosis is historical data for phenformin (withdrawn in 1977). Metformin is less likely than phenformin to cause lactic acidosis. Phenformin related lactic acidosis had an estimated incidence of 0.25 per 1000 patient years compared with an estimated incidence of 0-0.09 case per 1000 patient years with metformin. This difference in the incidence of lactic acidosis between metformin and phenformin could be due to more...
stringent contraindications applied after the experience with phenformin. However, despite increased disregard of contraindications to metformin, as discussed below, the incidence of lactic acidosis has not increased.

Metformin and phenformin have different pharmacological characteristics that could explain the much lower incidence of lactic acidosis associated with metformin. Table 1 summarises some of these differences.

Evidence from case reports
Most case reports of lactic acidosis in people taking metformin have failed to provide adequate information to permit assessment of causation, including lactic acid concentrations and pH. In a review of published case reports, Stades et al showed that plasma concentrations of metformin were not related to increased lactic acid concentration. In addition, increased concentrations of neither lactic acid nor metformin were associated with increased mortality risk. In contrast, acute cardiovascular events, liver cirrhosis, and sepsis were all associated with an increased mortality risk. Interestingly, all but one of the cases in this review had at least one risk factor (renal failure, cardiovascular events, pulmonary failure, hepatic failure, alcohol excess, or sepsis) for the development of lactic acidosis independent of metformin use. Most of the patients developed lactic acidosis in the presence of acute or worsening renal failure. Creatinine concentrations, however, did not correlate with lactic acid concentrations, metformin concentrations, or mortality.

Similar results were described by Lalau et al, who showed that neither lactate nor metformin concentrations were prognostically related to mortality and that death seemed to be related to other hypoxic disease or underlying ill health. The median lactate concentrations were similar in patients who survived and those who died. In addition, the median plasma metformin concentration was three times higher in patients who survived, which suggests that accumulation of metformin may not be as important in lactic acidosis as has been thought. The lack of a relation between lactic acid/metformin concentrations and mortality and the absence of an association between metformin concentration and lactic acid concentration suggest that the association between lactic acidosis and metformin is coincidental, although causality cannot be ruled out completely.

Epidemiological data
Brown et al collected 41,426 person years of data for patients with type 2 diabetes in the era before the introduction of metformin and found a rate of 0.097-0.169 events of lactic acidosis per 1000 person years of follow-up. Use of metformin was associated with a 59% lower rate of lactic acidosis. The lack of a relation between metformin use and lactic acidosis in patients with type 2 diabetes in the era before the introduction of metformin is consistent with an observational study of 15,000 patients with type 2 diabetes followed up for 15 years in the UK. The authors showed that use of sulfonylureas was associated with a 2.2-fold increase in risk of lactic acidosis compared with use of metformin, which supports the hypothesis that the use of metformin is protective against lactic acidosis.

Table 2 | Summary of studies documenting non-adherence to standard contraindications/precautions to metformin and number of cases of lactic acidosis

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients taking metformin</th>
<th>Percentage with contraindications (≥1)</th>
<th>Contraindications</th>
<th>Lactic acidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rakovac et al 2005 [12]</td>
<td>4401</td>
<td>18.9</td>
<td>Alcohol consumption (250 g/week), renal impairment, and heart failure needing drug treatment</td>
<td>NA</td>
</tr>
<tr>
<td>Calabrese et al 2002 [13]</td>
<td>204</td>
<td>44</td>
<td>Renal dysfunction (serum creatinine &gt;133 µmol/l in men and &gt;124 µmol/l in women), congestive heart failure needing drug treatment, acute or chronic metabolic acidosis, intravascular iodinated contrast material, age &gt;80 years (unless measurement of creatinine clearance shows that renal function is not reduced), hepatic disease, concomitant cationic drug use, presence of any condition associated with hypoxaemia (such as chronic obstructive pulmonary disease and acute myocardial infarction), dehydration, sepsis, excessive alcohol intake, and after any surgery until patient’s oral intake is resumed and renal function is deemed normal</td>
<td>0</td>
</tr>
<tr>
<td>Horlen et al 2002 [14]</td>
<td>100</td>
<td>22</td>
<td>Documented heart failure, renal dysfunction (serum creatinine &gt;132.6 µmol/l in men and &gt;123 µmol/l in women)</td>
<td>0</td>
</tr>
<tr>
<td>Emslie-Smith et al 2002 [15]</td>
<td>1847</td>
<td>24.5</td>
<td>Acute myocardial infarction, cardiac failure, renal impairment, or chronic renal disease</td>
<td>1</td>
</tr>
<tr>
<td>Holstein et al 1999 [16]</td>
<td>308</td>
<td>73</td>
<td>Renal impairment (creatinine clearance &lt;60 ml/min), hepatic impairment, chronic respiratory failure, heart failure (ejection fraction &lt;50%, lung congestion on radiograph), advanced coronary heart disease conditions, chronic alcohol misuse, severe infections, pregnancy/breastfeeding, intravenous administration of contrast agents, and operations under general anaesthesia</td>
<td>0</td>
</tr>
<tr>
<td>Yap et al 1998 [17]</td>
<td>70</td>
<td>94</td>
<td>Insulin dependent diabetes, hypersensitivity, impaired renal function, cardiovascular disease, conditions associated with hypoxia, serious liver dysfunction, excessive alcohol intake, concomitant use of diuretics, acute intercurrent illness, elderly, children, dehydration, serious infection, trauma, use of contrast</td>
<td>NA</td>
</tr>
<tr>
<td>Sulkin et al 1997 [18]</td>
<td>89</td>
<td>54</td>
<td>Renal impairment, cardiac failure, chronic liver disease, ischaemic heart disease, clinical proteinuria, peripheral vascular disease, and pulmonary disease</td>
<td>0</td>
</tr>
</tbody>
</table>

NA = not available.
years. This rate of lactic acidosis events is similar to that reported in patients with type 2 diabetes taking metformin, which raises the possibility that the incidence of lactic acidosis in metformin treated patients might be related to type 2 diabetes rather than metformin treatment itself. A Cochrane review of 206 comparative trials and cohort studies in patients with type 2 diabetes who were treated with metformin and had no contraindications to its use, found no evidence of increased risk of developing fatal or non-fatal lactic acidosis in the subgroup of metformin treated patients. It also found no difference in lactate concentrations between patients treated with metformin or with non-biguanide drugs.

Disregard of contraindications
Several reports found that physicians have increasingly ignored contraindications to prescribing metformin and yet the incidence of lactic acidosis has remained very low (table 2). In a population based study in Scotland between January 1993 and June 1995, found that 24.5% of patients receiving metformin had contraindications to its use, including acute myocardial infarction, cardiac failure, renal impairment, or chronic renal disease. Despite this, only one episode of lactic acidosis occurred in 4600 patient years, and this was in a 72 year old patient with acute myocardial infarction complicated by acute renal failure. A cross sectional analysis, by Holstein et al, of 308 consecutive type 2 diabetes patients treated with metformin from 1 January 1995 to 31 May 1998 found that 73% of these patients had at least one contraindication to the use of metformin. None the less, no cases of lactic acidosis were seen. Contraindications in the study by Holstein et al included renal impairment (creatinine clearance <60 ml/min), hepatic impairment, chronic respiratory failure, heart failure (ejection fraction <50%, lung congestion on radiograph), advanced coronary heart disease conditions, chronic alcohol misuse, severe infections, pregnancy or breast feeding, intravenous administration of contrast agents, and operations under general anaesthesia. Of note, none of the patients in the UK prospective diabetes study developed lactic acidosis. The study protocol, however, would have ensured that metformin was not used in patients with contraindications.

Table 2 summarises the studies that have shown increased disregard of contraindications to metformin and the contraindications used in each study. However, these studies are observational, so confounding factors, particularly confounding by indication, affecting the outcome could not be excluded. In addition, the percentage of patients taking metformin who have at least one contraindication varies considerably. The evidence from these reports reinforces the viewpoint that metformin is an extremely rare cause of lactic acidosis in patients with type 2 diabetes, even in the presence of contraindications including renal, hepatic, and cardiac failure.

Cardiac failure and metformin
Patients with type 2 diabetes are at an increased risk of developing congestive cardiac failure compared with patients without diabetes. In one study by Nichols et al, the incidence of developing cardiac failure among patients with type 2 diabetes was 30.9 cases per 1000 person years compared with 12.4 cases per 1000 person years in patients without diabetes, a relative risk of 2.5. The difference between the rates of cardiac failure was even greater among the younger age groups. In the same study, age, ischaemic heart disease, poorer glycaemic control, and greater body mass index were predictors of the development of cardiac failure. The UK prospective diabetes study estimated the incidence of cardiac failure in patients with type 2 diabetes to be 2.3-11.9 per 1000 person years. Diabetes is also an independent predictor of mortality in patients admitted to hospital with cardiac failure. This risk is particularly high in women.

Cardiac failure is usually considered to be a contraindication to metformin treatment and is withheld from large numbers of patients with type 2 diabetes and coexistent cardiac failure. More recent studies suggest that metformin may not be absolutely contraindicated and could be beneficial in such patients. It improves glycaemic control and has a favourable effect on other cardiovascular risk factors, including lipids. The UK prospective diabetes study has shown that it reduces mortality and macrovascular end points in patients with type 2 diabetes, although these patients did not have heart failure.

Table 3 | Adjusted odds ratios (95% confidence intervals) from an observational population study by Johnson et al and adjusted hazard ratios (95% confidence intervals) from observational studies in patients with cardiac failure by Eurich et al and Masoudi et al

<table>
<thead>
<tr>
<th>Study</th>
<th>All cause mortality</th>
<th>All cause hospital admissions</th>
<th>Cardiovascular disease deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metformin</td>
<td>Sulphonylurea</td>
<td>Metformin plus sulphonylurea</td>
</tr>
<tr>
<td>Johnson et al 2002</td>
<td>0.60 (0.49 to 0.74)</td>
<td>1</td>
<td>0.66 (0.58 to 0.75)</td>
</tr>
<tr>
<td>Eurich et al 2005</td>
<td>0.70 (0.54 to 0.91)</td>
<td>1</td>
<td>0.61 (0.52 to 0.72)</td>
</tr>
<tr>
<td>Masoudi et al 2005</td>
<td>0.86 (0.78 to 0.97)</td>
<td>0.99 (0.91 to 1.08)</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA=not applicable.
Canadian cardiac failure data
In a more recent study using the same database, Eurich et al compared the clinical outcomes of patients with type 2 diabetes who were known to have cardiac failure and were on metformin alone, sulphonylurea alone, or combination treatment. They identified 2793 patients with type 2 diabetes who were treated with oral hypoglycaemic agents and had a hospital admission with heart failure between 1991 and 1996. Patients who were on insulin or had had heart failure for more than three years before starting oral hypoglycaemic agents were excluded, and 1833 patients were eligible for the study. Patients were followed up for a period of between one and nine years, and the primary outcome was all cause mortality at one year (short term) and at the end of follow-up (long term). Secondary outcomes were all cause hospital admissions at one year and long term. The researchers also evaluated the effects of oral hypoglycaemic agents on composite outcomes, including all cause hospital admission and all cause mortality. At one year, compared with the 200 (26%) deaths in the sulphonylurea monotherapy group, 29 (14%) deaths occurred in the metformin monotherapy group (unadjusted hazard ratio 0.52, 95% confidence interval 0.35 to 0.76) and 97 (11%) deaths (unadjusted hazard ratio 0.41, 0.32 to 0.52) in the metformin-sulphonylurea combination group. After controlling for age, sex, drugs known to affect outcomes of heart failure, and total physician visits before diagnosis of heart failure, the authors found that metformin alone (adjusted hazard ratio 0.66, 0.44 to 0.97) or in combination with other agents (0.54, 0.42 to 0.70) was associated with reduced one year all cause mortality compared with sulphonylurea monotherapy in patients with heart failure. The long term mortality and morbidity in patients treated with metformin, alone or in combination with other antidiabetic agents, was lower than that observed for patients treated with sulphonylurea only (52% for sulphonylurea monotherapy v 33% for metformin monotherapy v 31% for combination treatment). Table 3 summarises the long term outcomes of this study, including hazard ratios and 95% confidence intervals. The all cause hospitalisation was significantly lower in the metformin monotherapy group compared with sulphonylurea monotherapy or combination treatment both at one year and long term. Similar to the previous study by Johnson et al, one of the main limitations is that this study is observational and based on a database, which means that drug prescription may not reflect exposure and that confounding by indication could not be ruled out. Another important limitation is that the investigators did not have any information about the severity of heart failure and the presence or absence of renal failure. The latter is particularly important, as renal failure is an independent predictor of poor prognosis in heart failure. If the metformin group had less renal failure, this would affect the validity of the results. This is unlikely, however, as renal dysfunction is very common in patients with heart failure, so a considerable proportion of patients in all groups are likely to have renal impairment.

US cardiac failure data
Masoudi et al found similar results. They evaluated the impact of insulin sensitisers (metformin or thiazolidinediones) on outcomes in patients with type 2 diabetes and cardiac failure. Crude one year mortality was lower among patients treated with a thiazolidinedione (30.1%) or metformin (24.7%) compared with patients treated without insulin sensitising drugs (36.0%; P=0.0001 for both comparisons). Treatment with thiazolidinedione (hazard ratio 0.87, 0.80 to 0.94) or metformin (0.86, 0.78 to 0.97) was associated with significantly lower risks of death. No significant association was found between treatment with sulphonylurea (0.99, 0.91 to 1.08) or insulin (0.96, 0.88 to 1.05) and mortality. Admissions for all causes did not differ with either insulin sensitiser, although the risk of readmission for heart failure was higher in those receiving thiazolidinedione (1.06, 1.00 to 1.09) and lower with metformin treatment (0.92, 0.92 to 0.99). The study was an observational retrospective cohort, so the results should be interpreted with caution. Although the authors made adjustments for a
SUMMARY POINTS

Treatment with metformin is not associated with an increased risk of lactic acidosis among patients with type 2 diabetes mellitus who have no cardiac, renal, or liver failure. Despite increasing disregard of contraindications to metformin by physicians, the incidence of lactic acidosis has not increased, so metformin may be safe even in patients with “contraindications”.

The vast majority of case reports relating metformin to lactic acidosis report at least one other disease/illness that could result in lactic acidosis.

Use of metformin in patients with heart failure might be associated with lower mortality and morbidity, with no increase in hospital admissions and no documented increased risk of lactic acidosis.

Further studies are needed to assess the risk of lactic acidosis in patients with type 2 diabetes and traditional contraindications to metformin.

wide range of variables, including markers of severity of heart failure and comorbidities, variations in the institution and clinician who treated the patients may influence the results. Consequently, these results could reflect the influences of unmeasured confounding factors, including confounding by indication.

Conclusions

An increasing body of evidence suggests that metformin treatment alone will not result in lactic acidosis unless other contributing factors coexist. More importantly, treatment with metformin is not absolutely contraindicated in patients who have isolated heart failure, and it may be beneficial. The risk of lactic acidosis due to metformin is negligible in these patients and is unrelated to the plasma concentration of metformin. The presence of other organ failure, such as renal failure, in addition to heart failure might still pose a risk of lactic acidosis. Metformin provides a greater degree of cardiovascular protection than would be expected from its antihyperglycaemic actions alone and is the first drug of choice for the treatment of type 2 diabetes. The decision to stop or continue metformin in the presence of heart failure should be individualised to the particular patient until further evidence is available.

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Endpiece

Evil in the United States in 1834

Eating too much, and of unwholesome articles, is a national evil in the United States; and were I to add, a national disgrace, the charge would not be too severe… It is much easier to procure the means to gratify the palate, and other animal appetites, in proportion to the facilities of indulgence they enjoy. I confidently believe, that the thirteen or fourteen millions of people, inhabiting this country, eat more rash, for amusement, and fashion’s sake, and to pass away idle time, than half the inhabitants of Europe united. Unquestionably they consume a greater amount of such articles, in the proportion of five to one, than an equal number of the people of any other country I have ever visited.

Caldwell C. Thoughts on physical education. Boston: Marsh, Capen and Lyon, 1834: 51-2

Submitted by Jeremy Hugh Baron, honorary professorial lecturer, Mount Sinai School of Medicine, New York
Using a combination inhaler (budesonide plus formoterol) as rescue therapy improves asthma control

Peter J Barnes

The clinical problem
Asthma is effectively controlled in most patients with maintenance treatment. In those with moderate or severe persistent asthma, control may be achieved with an inhaled corticosteroid or a combination inhaler containing a corticosteroid and a long acting β₂ agonist. The combination inhaler is more effective, but patients still require short acting β₂ agonists such as salbutamol or terbutaline to relieve symptoms. I describe a new approach for acute exacerbation—SMART (single inhaler maintenance and reliever therapy). This uses the combination inhaler, rather than the short acting β₂ agonist, as the reliever.

The evidence for change
Using a formulation of budesonide plus formoterol (budesonide/formoterol) both as a reliever and as maintenance therapy once or twice daily is more effective in controlling asthma than conventional approaches using budesonide/formoterol, fluticasone/salmeterol, or high dose corticosteroids (budesonide or fluticasone) as the maintenance treatment with short acting β₂ agonists as relievers (table).1-5 The most striking benefits are fewer exacerbations (severe exacerbations, defined as needing of course of oral corticosteroids, are about halved) and fewer admissions to hospital. The mean number of extra puffs of budesonide/formoterol taken in the SMART studies was about one a day. The single inhaler approach with budesonide/formoterol seems to be effective in mild, moderate, and severe persistent asthma. Previous studies have shown that inhaled formoterol is even more effective than salbutamol as a rescue therapy, with an onset as fast and with similar side effects.6 However, using the budesonide/formoterol inhaler as rescue therapy is more effective than formoterol alone, indicating that the inhaled corticosteroid in the rescue inhaler also plays an important role.7 Analysis of asthma exacerbations shows a slow evolution over several days with increasing symptoms and use of rescue medication.8 Studies in unselected populations also show that, as an exacerbation develops, patients increase the dose of rescue inhalers but not usually the dose of inhaled corticosteroid.9 This new, simplified, single inhaler approach may also improve compliance.

The fluticasone/salmeterol combination inhaler is unsuitable as a rescue therapy as salmeterol has a slower onset of action than formoterol and cumulative side effects. However, other combination inhalers (with different corticosteroids plus formoterol) are now in development; a beclomethasone/formoterol inhaler is already available in Germany.

KEY POINTS
- Single inhaler therapy for asthma with combined budesonide and formoterol as maintenance therapy and as a reliever provides better control of asthma than combination inhalers or higher doses of inhaled corticosteroids as maintenance plus a short acting β₂ agonist as reliever.
- The greatest benefit is the reduction of exacerbations.
- The strategy is simple for patients to adopt.
- Overuse of rescue combination therapy does not seem to be a problem.

Barriers to change
Early experience suggests that it is helpful for patients to have two combination inhalers: one at home for maintenance therapy, the other carried for rescue therapy. An initial concern was that patients may overuse the rescue inhaler and therefore end up taking high doses of inhaled corticosteroids. This practice was not seen in the large clinical trials, presumably as the SMART strategy was more effective in controlling asthma. Patients should be advised to see their doctor if they need to use more than six additional puffs of budesonide/formoterol rescue inhaler.

How should we change our practice?
Single inhaler therapy using combined budesonide/formoterol for both maintenance and rescue therapy is more effective than conventional therapy. Eligible patients are those with moderate to severe asthma whose condition is not controlled with conventional therapy and who are using rescue inhaler therapy.

Single inhaler maintenance and reliever therapy is easy to implement as the patient merely replaces their usual rescue inhaler with the budesonide/formoterol inhaler. Maintenance budesonide/formoterol may be given twice daily for severe asthma (or once daily for moderate asthma).2 The strategy has also been shown to be effective in children aged 4-12 years but has not yet been approved by regulatory authorities for use in them.11 Single inhaler therapy is not suitable for patients who overuse their rescue inhalers or who find it difficult to recognise if their asthma is worsening.
Pleasing doctors: when it gets in the way

PERSONAL VIEW Robert Klitzman

“Y ou want your doctors to like you,” she said. “You want to be a good patient and sometimes are afraid to rock the boat.” The woman speaking to me was a physician with cancer. I was interviewing her as part of a study of doctors who had become sick with serious disease (Perspect Biol Med 2006;49:542-52). To my surprise, she and others I talked to described repeatedly how they hesitated to be aggressive or “pushy” with their own healthcare providers and instead tried to please them.

“If I trust the doctor,” another doctor with cancer told me, “he feels good. The fewer questions I ask, the happier he is and the more positive he’ll relate to me. I want him to know he’s a good guy.”

In general, people want others in social interactions to feel positively, and doctor-patient interactions are no exception. Unfortunately such behaviour can hamper open communication between patients and their providers and hence impair care.


As another physician with cancer recently told me, “When the doctor stops on rounds and says, ‘How are you doing?’ and the patient answers, ‘Poorly,’ the doctor has a long face. When the patient says, ‘Fine,’ the doctor smiles and waves hello.” These ill physicians shed light on how doctors encourage patients’ efforts to be pleasing, and patients may then be conditioned to give doctors positive feedback.

Doctors may simply be busy, overwhelmed, or eager to get through their day as quickly and efficiently as possible. Doctors may also seek to protect themselves from difficult medical or emotional interactions. But patients seek such cues from doctors that prompt or discourage discourse—and patients may respond accordingly. One doctor told me how he had often hugged patients to show support and only now, as a patient himself, realised that this gesture could unintentionally silence them—“I’m really giving them physical cues to shut up!”

Communication may be hindered by patients too. They may hesitate to talk about certain topics, especially perceived taboos such as depression, non-adherence to treatment, or sexual dysfunction. They may play down problems because of embarrassment, denial, or the wish to avoid giving what they see as “bad news” to their providers.

These complex dynamics in communication between doctors and patients are of ever growing importance in the United States and elsewhere, as managed care may limit the amount of time doctors have with many patients, and high tech treatments (as opposed to low tech human interactions) become ever more profitable and common. Being assertive and proactive may potentially help patients fight disease, but these dynamics of communication may lead to patients feeling disempowered and failing to assert themselves.

What (and how) doctors and patients decide to communicate seems to be shaped by their perceptions of how they think the other party will reply, how they wish the other party will reply, and how they think the other party wants to reply. For example, patients often tell their doctor what they think they want the doctor to hear, but they may misperceive or misunderstand their doctor’s wishes, fearing negative responses. Such assumptions can further impede care. The desire to establish trust can conflict with the imperative to disclose the whole truth. Patients face a tension between pleasing doctors and divulging disappointing news.

Yet professional training and public education do not address these issues. Indeed, the ill doctors I interviewed were generally astonished to see themselves engaged in these processes and were previously unaware of seeking positive feedback from their patients. Their surprise surprised me.

Doctors, too, often face tensions between expressing themselves and concealing their disappointment with patients. Moreover, doctors’ and patients’ desires may clash: patients may want to disclose information and prolong or extend interactions, while doctors do not. Patients’ desire to please doctors, doctors’ desire to be pleased, and doctors’ arrogance can amalgamate, further impeding discourse.

Additional factors may facilitate or impede these dynamics. Patients may think that their symptoms are too mild to mention, even though they may be important in the clinical assessment. Such dynamics have been seriously underexamined and need to be further researched to explore further how, when, and to what degree they operate. More careful consideration of these issues will be in the best interests of patients and, in the long term, doctors as well.

Robert Klitzman is associate professor of clinical psychiatry, College of Physicians and Surgeons and Mailman School of Public Health, Columbia University, New York.

rlk2@columbia.edu
Busting myths about cancer and other diseases, p517

Review of the Week

Blade runners

A new textbook on surgical complications is a timely aid for modern surgeons faced with multiple risk factors, Harold Ellis finds.

How do you judge a good surgeon? Certainly not by appearance. The only person at Westminster Hospital when I was there who looked like a surgeon—tall, distinguished, beautifully dressed, hair just greying at the sides, long tapering fingers—was the hospital barber. What you must take into account is diagnostic skill, ability to communicate, empathy with patients, research ability, and, of course, technical skill in the operating theatre. Don’t judge a surgeon by mortality figures: the better the surgeon, the stickier the patients referred to him or her. Overly cautious surgeons may never lose a patient, but a lot of “bad” patients might be denied the chance of relief through surgery.

Also important, but difficult to quantify, is how good surgeons are at avoiding complications and, if and when they occur, how good they are at spotting them and dealing with them quickly and effectively. As surgery becomes ever more sophisticated and its scope expands, so the chance of complications increases. Patients who would have been denied surgery when I retired from surgical practice in 1989—with their bad hearts or terrible chests or seemingly hopeless pathology—may now be submitted to life-saving surgery. Audits now show up complications that would not have arisen then, simply because the patient would have been deemed inoperable and would have died.

Today we know far more about the incidence of postoperative complications; and their management has become more standardised and more efficient. For example, audits such as the National Confidential Enquiry into Patient Outcomes and Deaths in England and Wales and the Scottish Audit of Surgical Mortality have provided essential information on the incidence of severe complications. Guidelines laid down by bodies such as the Association of Anaesthetists of Great Britain and Ireland and the National Institute for Health and Clinical Excellence (NICE) give important pointers to safer practice. For example, NICE advises the use of two dimensional ultrasonography as an aid to placement of central venous catheters, which reduces the likelihood of pneumothorax and other complications of this common procedure.

Any number of modern textbooks of surgery, from both sides of the Atlantic, cover diagnosis and management in splendid detail and, of course, deal with the complications of surgery. However, you can search library shelves in vain for a modern text that is devoted to the diagnosis and management of this important topic. The two editors—surgeons on the transplantation unit at Hammersmith Hospital, London—have assembled a large and international team of contributors, covering the surgical specialties as well as anaesthesiology, gastrointestinal medicine, and imaging, and also including a medical historian and a medicolegal ethicist. Its chapters cover pretty well every aspect of this broad subject.

Despite today’s sophisticated surgery and the array of modern antibiotics, hospital infection remains a serious and indeed an apparently increasing problem. We are warned in the long chapter on this topic that hospital acquired infections account for 5000 deaths a year in the United Kingdom and cost the NHS £1bn (€1.5bn; $2bn) a year. They more than double the length of the average stay in hospital and add £3000 to the cost of the average case. The book has a good account of necrotising fasciitis (although some colour photographs would have been useful). However, the two hospital acquired infections that appear so often in our newspapers—methicillin resistant Staphylococcus aureus and Clostridium difficile induced pseudomembranous enterocolitis—deserve fuller treatment in future editions.

Apart from these drawbacks the book provides surgeons with a splendid account of today’s diagnostic and therapeutic arsenal in managing surgical complications, including such wonders as imaging controlled percutaneous drainage of deeply placed fluid collections and catheter embolisation of spurring blood vessels.

As is often the case with today’s medical texts a chapter on medicolegal issues concludes this nicely produced and illustrated and easy to read book.

Harold Ellis is emeritus professor of surgery, King’s College London.
Patient safety

A colleague is stabbed a few miles from where I work. Thankfully she is alive and I hope that she will make a full recovery. Our thoughts are with her family and friends. I feel sadness and anger that these things should happen. Then predictably and selfishly I fret about my own vulnerability. Irrespective of where you work, general practice is harsher than many people believe. Medicine is often the only interface with society’s forgotten people. Family medicine is the lowest common denominator where all of society’s woes are legally dumped. Amid the debris there are medical emergencies and diagnoses to be made. I like it, but it is not for everyone.

The inner cities in particular are a distillation of debilitating ailments, heaped together in high rise concrete cages. Addiction, poverty, unemployment, and chronic mental problems—the most vulnerable people are left exposed to the elements. Violence is endemic in this environment and is seen a legitimate form of communication.

GPs are literally at the frontline. I have been threatened, had a hammer pulled on me, been shown knives, and been chased by a gang while on a house call. Instinctively and constantly I scan for those non-verbal cues of aggression—the narrowing of the eyes, the intake of breath, and the change in body stance. Long ago I learnt never to raise my voice and to steer well clear of direct confrontation. My experience is common to many GPs.

Our practice’s panic button system is only ever activated by children while I am distracted by their ill parents. The only response is a stampede of panic in the reception area. Pressing the panic button is perhaps the last thing I would consider, as this merely ups the stakes.

So how to protect us? Tougher sentencing may feel like more justice but would not deter attacks. More security may make GPs feel safer but would not prevent the determined nor the random attacker, and we would lose our greatest strength—accessibility. As doctors we have to accept the unacceptable—that we live in a violent society. No well chosen soundbite or magic pills can heal our violently sick society. We are so obsessed with the unimportant, and we are blind to the fundamental similarities and collective values that we share. The solution is simple but difficult—to put others before oneself. This is the only way to re-establish the protection that is community.

Des Spence is a general practitioner, Glasgow des2wo@yahoo.co.uk

Worrying world of eating disorder wannabes

I first heard about “wannarexia” while sitting on a bus. A group of teenage girls were dissecting each of their classmates. One girl in particular received marked censure. “She’s such a wannarexic,” said one.

The others all agreed. Forced to admit that I was out of the loop with teen jargon I turned to the internet, the bible of youth trends.

Wannarexia is a pejorative term and, says Urban Dictionary (www.urbandictionary.com), is “an imaginary disease most commonly found amongst preteen to teenage, overweight females who claim to have the eating disorder anorexia, but they do not meet the criteria.” It continues, “In fact, they do not have an eating disorder at all. Most wannarexic people feel that anorexia is a ‘quick fix’ to lose weight and that it is glamorous.”

Wannarexia is the latest word to come from the fast paced world of eating disorder terminology.

Although the internet has allowed genuine supportive communities to flourish, it has propagated subgroups. One result is the “pro-ana” and “pro-mia” craze, which sees anorexia and bulimia as lifestyle choices rather than illnesses.

Initially, many web servers took down pro-ana and pro-mia sites, but with the emergence of social networking sites they have reappeared. Facebook recently ran into trouble for refusing to remove links to pro-anorexia sites, and YouTube and MySpace have come under fire for featuring “thinspiration” videos, which show unhealthily thin girls offering tips on losing weight. One group on MySpace says: “No people trying to recover. It ruins our motivation.”

Wannarexics draw anger and derision from people with anorexia and bulimia. Community websites for genuinely anorexic and bulimic people have hit back by setting up sites offering advice to those trying to “develop anorexia,” saying that they don’t want their “warped perspectives and dangerous behaviour to affect others.” One such website, Anorexic’s Advice—so-called to target wannarexics trawling the internet for tips—features startling videos and photos of people with anorexia in an attempt to debunk the myth that it’s a glamorous disorder that makes people popular.

Videos and blogs mocking wannarexics have appeared on YouTube, with advice on how to “spot one.” They say “wannarexics” openly refer to each other as “ana” or “mia” and wear wrist bands to identify each other. Their main icon is Mary Kate Olsen, an American actress who allegedly has anorexia, generating the motivational expression “WWMKD?”—what would Mary Kate do?

One blogger offers advice on Urban Dictionary: “No treatment is possible to convince people suffering from wannarexia that they are not anorexic, unless the treatment includes brain replacement.” Another has the last word: “Wannarexics aren’t as bad as wannacutters,” she says.

Deborah Cohen is features editor, BMJ dcohen@bmj.com
The doctor writer’s handbook

Every so often a junior doctor would come to me and confess that he or she wanted to write. This was not in itself absurd: the number of doctor writers is, after all, legion.

Junior doctors afflicted with literary ambition would ask my advice. I had only three pieces of advice to give: firstly, that they should continue in the hospital for a few more years, because human nature was concentrated and distilled there as if for the express purpose of training writers; secondly, that on no account should they consort with academics of the humanities departments of any university, for to do so was the primrose path to stylistic perdition; and finally, that they should read a great deal.

“Yes, but what?” they would ask.

“There are two books that you should study,” I would reply. “The first is A Companion to Murder by E Spencer Shew, and the second is A Second Companion to Murder by E Spencer Shew, published in 1960 and 1961 respectively.”

This recommendation rather took my interlocutors by surprise—they had probably expected me to recommend Tolstoy or Shakespeare. But the study of the works of E Spencer Shew, who was for many years crime correspondent of the Daily Express, would be more immediately profitable, for it is a fact that, despite the lengthy subtitles of his books—A Dictionary of Death by Poison, Death by Shooting, Death by Suffocation and Drowning, Death by the Stranger’s Hand, and A Dictionary of Death by the Knife, the Dagger, the Razor; Death by the Axe, the Chopper, the Chisel; Death by the Iron File, the Marline Spike; Death by the Hammer, the Poker, the Bottle; Death by the Jemmy, the Spanner, the Tyre Lever, the Iron Bar, the Starting Handle; Death by the Sandbag, the Sash Weight; Death by the Mallet, the Half-brick, the Stick, the Stone; Death by the Fire Tongs, the Butt End of a Revolver; Death by the Metal Chair, etc—Shew was a master of concision, who could convey atmosphere and character in a few exquisitely chosen words.

Open the book anywhere and you will find little gems of concision (which is next to godliness) in the first two or three lines of an entry. Here is Dr Crippen: “Crippen, Hawley Harvey, with his bul- bous eyes, straggling moustache, choker collar, mild man- ners, indestructible air of respectability, florid wife, and mouse-like mistress, is the central figure of the one indisputable murder ‘classic’ of the twentieth century.”

There is much of medical interest in these two volumes, so that even if our literary junior doctors do not succeed in their ambitions they will not entirely have lost their time in reading them. The murder- ous doctor is there, in the person of Dr Buck Ruxton who, in his own words, could live neither with his wife nor without her but decided that the latter was the preferable alternative; so is the great forensic pathologist Sir Bernard Spilsbury; and also an unfortunate succession of GPs, whose erroneous diagnoses of epi- lepsy so assisted the Brides in the Bath murderer, George Joseph Smith, “murderer, bigamist, swindler, performer on the harp.” Never did misdiagnosis have worse consequences.

It is not only stylistic concision that one learns from E Spencer Shew but the useful lesson that, in the way of human wickedness, there is no new thing under the sun.

BETWEEN THE LINES

Theodore Dalrymple

It is not only stylistic concision that one learns from E Spencer Shew but the useful lesson that, in the way of human wickedness, there is no new thing under the sun.

MEDICAL CLASSICS

Illness as Metaphor; AIDS and its Metaphors By Susan Sontag

First published 1978 and 1988, respectively

It is not uncommon for people to write about their experience of illness. After the US writer Susan Sontag underwent chemotherapy for breast cancer, however, she took a different approach. Illness as Metaphor examines in more general than personal terms how society regards illness and being ill, in particular “the punitive or sentimental fantasies concocted about that situation.”

In a sense she still writes from her experience in focusing on descriptions of cancer (with some comparisons with tuberculosis, the disease that killed her father), though drawing examples mainly from Western literature. The result is an important and influential essay that exposes some common and detrimental myths about illness.

Sontag cites example after example from novels, essays, and medical writings to show how cancer has traditionally been associated with repression and defeat. It is seen as a shameful disease and always as inevitably fatal, even in the late 20th century, by which time treatments had improved. Such metaphors combine to create the effect that “much of the very reputation of the illness added to suffering of those who had it”—a situation not helped by the use of the word “cancer” in common parlance to mean “the epitome of evil.”

Fallacies about the emotional basis of cancer even gained some credence in medical literature, with the theory that certain personality types were prone to the disease. The militaristic language associated with cancer also riles Sontag (and many cancer patients)—from descriptions of the biological process (an invasion through the body’s defences) to treatment (“a war on cancer”). Such a view of cancer burdens patients: not only do they seem to have to shoulder some responsibility, they also have to shoulder arms against it.

Many of the myths concerning cancer arose from ignorance about its causes, an aspect Sontag discusses in her companion essay, AIDS and its Metaphors. This piece, written at the beginning of the AIDS epidemic, examines in terms similar to those used in the earlier work how the disease was being described at the time, when there was much talk of contamination, plagues, and punishment.

In both pieces Sontag writes forcefully but with wit. Her writing is always lively and provocative. There can be flaws, as with anything written in such a polemical style. Sometimes points are repeated or contradicted a few pages later. There are passages where her arguments may be weak, but even these make the reader think. For this reason—and because these two essays challenge us to question how we think and talk about illness and the effect our language has on patients—these works are a valuable read for all doctors.

James Curran is a GP locum, Glasgow.

cldcur@dircon.co.uk

Theodore Dalrymple is a writer and retired doctor

By Susan Sontag

Sontag: challenged how we talk about illness

Illness as Metaphor: On Sickness and Its Literary Representations Aids and Its Metaphors By Susan Sontag

First published 1978 and 1988, respectively
Edward Arthur Boyse

Immunologist who realised the potential of cord blood stem cells in transplants and discovered the subtypes of T cells

Around the globe at least 100 000 children born with fatal inherited blood diseases have had their lives saved by a transplant of placental blood stem cells. They owe this to Ted Boyse, who in 1989 realised that every placenta thrown in the incinerator is rich in blood stem cells that might be useful for transplantation. He then painstakingly extracted and froze, for differing lengths of time, stem cells from over 100 placentas. He found that the cells survived long periods of freezing. As it was well known that cancer chemotherapy was toxic to the haematopoietic cells of bone marrow, he postulated that children with such diseases could have their own stem cells destroyed and replaced with cord blood stem cells. With French and American collaborators, he participated in the first such transplant, in France. The patient, a child with Fanconi’s anaemia, was cured.

According to Sir Walter Bodmer, he was “one of the early pioneers of immunogenetics in the mouse. He subsequently made major contributions to understanding T lymphocyte subsets and the use of cord blood as a source of bone marrow derived stem cells. He was an original and stimulating thinker.”

Earlier, it was Boyse who discovered that not all T lymphocytes are the same, identifying the subsets now called CD4 and CD8 and recognising their killer and helper functions.

His third major achievement was to show—in mice, and later in humans—that an individual’s odour, including the smell of their urine, is determined by the genes of the major histocompatibility complex. Identical twins smell the same, as police dog handlers know. Lewis Thomas, Boyse’s chief at the Sloan-Kettering Institute in New York, postulated that sniffer dogs could be used to recognise whether a potential donor and patient were sufficiently similar in the HLA groups for a transplant to be feasible. Boyse did some experimental work on this, but the results were inconclusive and were therefore not published. He showed that mice can tell the difference in scent between relatives and strangers, preferring to mate with partners that are immunogenetically (and odorifically) unrelated. He postulated that humans have a similar instinct. This work has been less widely accepted.

Boyse was born in Worthing, the son of a church organist who was a fellow of the Royal College of Organists. In adult life he could not recall the name of his private junior school, run by two maiden ladies who kept a pair of crossed assegais [hunting spears of the Bantu tribe] over the fireplace. He left Worthing Grammar School in 1941, aged 17, to join up. He qualified as a flying instructor in the Royal Air Force, and was commended in 1943.

He was demobbed in 1946, finished his matriculation, and entered St Bartholomew’s Medical School, qualifying in 1952. After a five year series of hospital jobs, during which he got his MD, he moved in 1957 to a three year research appointment at Guy’s with Peter Gorer, who had discovered the major histocompatibility complex H2, in mice.

In 1960 he joined the brain drain to New York University Medical School. Seven years later he moved to the Sloan-Kettering Institute for Cancer Research, where, often working with Lewis Thomas, he identified and conducted seminal work on the immunogenetics of the lymphocyte surface markers CD4 and CD8, which he originally named the Ly system.

He spent 22 years at Sloan-Kettering, and for 20 of these he was also biology professor at Cornell Medical School, which was across the road.

His final career move was to Arizona University, as distinguished professor of microbiology and immunology. He officially retired in 1994 as emeritus professor but continued working. His last paper, in 2002, was on the way that mice with mammary tumours had a specific change of body odour.

Ted Boyse’s work on the types and functions of T cells underpins modern immunology. He was the first person to be a fellow of the Royal Society, the US National Academy of Sciences, and the American Academy of Arts and Sciences. His other awards included the US Cancer Research Institute award in tumour immunology (1973) and the Rockefeller and Harvard Universities’ Isaac Adler Award (1976). He published over 400 scientific papers.

Ted Boyse had a sense of fun, was passionate about his work, and was a perfectionist in all he did. He made and restored furniture to professional standards. He kept fit by running, digging his garden, and planting trees.

His health deteriorated in his last years. He leaves his wife and colleague, Judith Bard, and two children; one son predeceased him.

Caroline Richmond

James Stokes Ellis

Former professor of orthopaedic and accident surgery University of Southampton (b 1912; q Cambridge/ St Thomas' Hospital, London, 1937; FRCS, MChir), d 3 May 2007.
During the second world war Jim Ellis was in the Emergency Medical Service in Basingstoke and the Royal Army Medical Corps in Aldershot. In 1948 he was one of the first group of Nuffield travelling fellows to North America. He returned to the orthopaedic department at St Thomas’ Hospital until 1950, when he was appointed consultant to the Winchester and Southampton group of hospitals. He was professor of orthopaedic and accident surgery in 1971 until he retired in 1976. Jim was president of the orthopaedic section of the Royal Society of Medicine in 1970-1 and vice president of the British Orthopaedic Association in 1975-6. Predeceased by one child and by his wife, Monica, he leaves two children and four grandchildren.

Peter Ellis

Khaled (“Karl”) Ghattas

Former junior surgeon then artist, philosopher, and poet (b 1958; q Royal Free Hospital 1982; MSc), died from a heart attack on 12 July 2007. Khaled Ghattas (“Karl”) worked as a senior house officer in surgery in London and Chester and at the Royal National Ear, Nose, and Throat Hospital. Disenchanted with many aspects of medicine, he took an MSc in philosophy at the London School of Economics in 1989. He taught himself to paint and had several acclaimed one man and group exhibitions in London’s Cork Street, Paris, New York, and Barcelona, with work in public and private collections, including the Fitzwilliam Museum and Courtauld Institute. He was lecturer in art at Winchester, London, and Barcelona. He recently won three international poetry prizes as well as publishing his first collection. He leaves two sons and a partner, Celso.

Alan Selwyn

Gerald Godfrey

Former general practitioner Leeds (b 1914; q Leeds 1941), died from heart failure on 14 February 2007. Gerald Godfrey (“Gerry”) was a general practitioner in Meanwood and Alwoodley, Leeds, from 1945 to 1985, when he reluctantly retired, though he continued doing medical assessments for the Department of Works and Pensions for a further two years. He joined the Royal Army Medical Corps in 1942, serving mainly in Italy and North Africa with the artillery in a field ambulance station and was mentioned in dispatches. After demobilisation as an acting major Gerry returned to Leeds to start a general practice. By the time he retired his list was over 5000 patients, and he had delivered two generations of some families. Gerry also grew trees and unusual plants from seed. He leaves a wife, Audrey, and two children. S Fathe-Azam, S Fellerman, A Godfrey, C Huston

Barbara Jones

Former senior clinical medical officer in Cheshire (b 1924; q Birmingham 1947; MFCM), d 6 March 2007. Barbara worked continuously full time after qualifying, initially entering general practice in Birmingham and Manchester. She worked for 10 years as a clinical assistant at Manchester Children’s Hospital and subsequently became assistant county medical officer in Cheshire. In 1968 she was promoted to senior clinical medical officer, a post which she held until her retirement in 1989. She specialised in community child health with particular interest in developmental problems. She was also a past president of the Manchester Medical Women’s Federation. She leaves three children and nine grandchildren.

Louise Jones

Harold Gordon Mather

Former consultant physician Southmead Hospital, Bristol (b 1921; Cambridge/King’s College Hospital, London, 1946; MD, FRCP), died from cerebrovascular disease on 13 July 2007. At King’s, Gordon Mather was awarded a Rockefeller Foundation studentship to Western Reserve University, Cleveland, Ohio, where he qualified MD. On return and after house jobs he did his national service with the Royal Army Medical Corps in Singapore and Calcutta. He published several papers and gained his Cambridge MD on sarcoidosis. In 1956 he was appointed consultant physician at Southmead Hospital, where he developed cardiac services and set up the first intensive care unit in the south west. Jointly setting up a foundation to support the research of junior staff, Gordon also served on hospital management committees, chaired his hospital medical advisory committee, and was president of the Bristol division of the BMA. He leaves a wife, Betty; three sons; and eight grandchildren.

Robert Mather

Edmund Eric Richey

Former consultant anaesthetist Eme Hospital, Enniskillen (b 1930; q Queen’s University, Belfast, 1962; LAH, FFA RCSI), died from prostate cancer on 27 June 2007. Edmund Richey studied pharmacy followed by medicine, working in his father’s chemist shop on the Newtownards Road during his studies. His first consultant post was between the Royal Victoria Hospital and Whiteabbey before he became consultant in Eme Hospital in 1977. He took early retirement in 1993 to care for his wife, Anne, who died in 2005. He leaves three daughters and three granddaughters.

Ruth Richey

George Walter Scott

Former consultant physician Guy’s Hospital, London (b 1923; q Guy’s 1949; MD, FRCP), died from coronary thrombosis followed by a stroke on 17 May 2007. George Scott was a wartime medical student at Guy’s but left to enlist in the Fleet Air Arm after his brother died on active service. In 1957 he was Fulbright scholar at Johns Hopkins Hospital, Baltimore. On the staff of Guy’s since 1962, he coauthored a popular treatise on medical treatment, and with Bob Knight made regular satirical contributions to Guy’s Hospital Gazette as Ratty and Mole. George’s capacity for enjoyment was impressive: as captain of a cricket club, as part owner of a racehorse, and as a golfer and skier. When partial quadriplegia in 1990 made walking difficult, he continued to work and play golf. Latterly he cared for his wife, Brenda, who had a severe stroke in 2000 while they were visiting their son in the United States.

M G Thorne

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MINERVA

Evidence is emerging that the outcome for patients with subarachnoid haemorrhage may be poorer if they carry the APOE4 allele. In a meta-analysis of eight observational studies involving almost 700 patients, E4 carriers were more likely to have a negative outcome (death, dependency, or severe cognitive impairment) and delayed ischaemia. The apoE protein has neurotrophic and antioxidant functions (Neurology 2007;69:766-75).

A systematic review of human papillomavirus (HPV) infection and disease in women reports that for women aged 15-25 who were not previously infected with vaccine-type HPV strains, prophylactic vaccination seems to be highly effective in preventing HPV infection and precancerous cervical disease. The proof will be in the pudding, however, when data on a reduction—or otherwise—in the incidence of cervical cancer finally filter through (CMA/2007;177:469-79).

Could your hospital accommodate the four huge “Acts of Mercy” paintings that belong to the former Middlesex Hospital in London (BMJ 2007;334:820)? Their sale has been deferred for six months so that an appropriate location can be found for them—preferably in a hospital. If you’ve got a space of 3 metres by 4.80 metres for each of them, please contact Johanna Kociejowski (jkociejowski@artfund.org).

Cancer cells overexpress certain sugar molecules on their cell surface, and antibodies to these sugars can eliminate circulating tumour cells and micro-metastases in cancer patients. A study in mice has now identified a single chemical structure that incorporates adjuvants into a vaccine that produces a more powerful immune response than previously. This new structure enables the body to produce enough antibodies to recognise cancer cells. The next step is to test the vaccine for its ability to kill cancer cells (Nature Chemical Biology 2007; doi:10.1038/nchembio.2007.25).

Patients, clinical staff, and the public are being put at risk needlessly, says the Health Services Journal, because investigations into “what went wrong” when mental health patients have killed are taking years to complete, as is changing flawed systems (23 August 2007, http://tinyurl.com/yr2nl). NHS reorganisations, police inquiries, and deliberate foot dragging are blamed. The journal says there are currently 27 outstanding cases in England, and seven of the 10 strategic health authorities are yet to implement changes arising from incidents that happened three or more years ago.

Whether speed cameras in urban Spain reduce the number of road traffic injuries has been assessed (American Journal of Public Health 2007;97:1632-7). The relative risk of a road crash occurring after speed cameras were installed was 0.73 (95% confidence interval 0.63 to 0.85), compared with before installation. The protective effect was greater at weekends. In the two years of the study, an estimated 364 collisions were prevented by speed cameras, 507 fewer people were injured, and 789 fewer vehicles involved in collisions.

If women are obese before they become pregnant, are they more likely to produce babies with structural defects? The answer, according to a multicentre case-control study, is “possibly.” Maternal obesity has a weak to moderate positive association with seven of 16 categories of birth defects, but a strong inverse association with gastrochisis. Undiagnosed diabetes may be the culprit (Archives of Pediatric and Adolescent Medicine 2007;161:745-50).

The latest in a long line of tests devised to establish the existence of a superior labral tear of the shoulder joint has passed with distinction. The “passive compressive test” (American Journal of Sports Medicine 2007;35:1489-94) achieved success (confirmed by arthroscopy) in 27 of 31 patients with a positive result. Of the 30 patients with a negative result, six turned out to have a superior labral tear. The authors estimate a sensitivity of 81.8% and a specificity of 85.7%.

What’s the optimal antibiotic regimen for treating acute exacerbations of chronic bronchitis? A meta-analysis of 12 randomised controlled trials concludes that first line antibiotics (amoxicillin, trimethoprim, and doxycycline, among others) were associated with lower treatment success (but not less safety) than second line antibiotics (macrolides and second and third generation cephalosporins, among others). The authors caution readers to look at the fine print, however. The data didn’t allow for further analyses that might be relevant, such as age, impaired lung function, and the frequency of exacerbations (Chest 2007;132:447-55).