General

Cost of doctor emigration for African countries

The overall costs of the emigration of doctors from developing countries is thought to be high but has not been measured. Now an attempt has been made to assess the financial losses experienced by nine countries in sub-Saharan Africa (Ethiopia, Kenya, Malawi, Nigeria, South Africa, Tanzania, Uganda, Zambia, and Zimbabwe) when the doctors they have trained have gone to work in Australia, Canada, the UK, or the USA.

Publicly available data were analysed to estimate the cost to the home country of the primary and secondary education and medical school education of a doctor, the cost of emigrant doctors currently working in the high-income countries, and the savings involved for the recipient countries. The estimated government-subsidised cost of a doctor's education ranged from US$21 000 to US$58 700. The overall estimated loss of returns from investment for all doctors currently working in the high-income countries was US$2.17 billion (US$1.41–13.53 billion). Among the nine African countries the estimated costs ranged from US$2.16 million in Malawi to US$1.41 billion in South Africa. The largest benefits were experience by the UK (US$2.7 billion) and the USA (US$846 million).

Australia, Canada, the UK, and the USA gain significant financial benefit by recruiting doctors from Africa.

Mills EJ et al. The financial cost of doctors emigrating from sub-Saharan Africa: human capital analysis. *BMJ* 2011; 343: 1191 (d7031); Buchan J. The financial cost of physician emigration from sub-Saharan Africa. Ibid: 1184 (d6817) (editorial).

Obstructive sleep apnoea: CPAP may be effective treatment for associated metabolic syndrome

The prevalence of obstructive sleep apnoea was estimated to be 24% in men and 9% in women in a US study, and 14% in a study in India. The prevalence of the metabolic syndrome has been reported to be 74–85% with obstructive sleep apnoea and 37–41% with non-obstructive sleep apnoea. Trials of the effects of treatment with CPAP on the metabolic syndrome in patients with obstructive sleep apnoea have given varying results. Now a trial in New Delhi, India has shown that CPAP in these patients may lower blood pressure and improve the metabolic abnormalities.

In a randomised crossover trial, 86 patients with moderate or severe obstructive sleep apnoea were randomised to CPAP or sham CPAP for 3 months, then 1 month without intervention (washout), then 3 months of the other intervention. At baseline 75 patients (87%) had the metabolic syndrome according to national US criteria, with Asian cut off values for abdominal obesity. Compared with the sham CPAP, CPAP significantly reduced systolic blood pressure by 3.9 mmHg, diastolic blood pressure by 2.5 mmHg, serum total cholesterol by 0.34 mmol/L, non-high density lipoprotein cholesterol by 0.34 mmol/L, LDL cholesterol by 0.25 mmol/L, triglycerides by 0.21 mmol/L, and glycated haemoglobin by 0.2 percentage points. After the CPAP period 14 of 71 patients with the metabolic syndrome (20%) no longer had the metabolic syndrome as defined but three of the 15 (20%) patients who did not have the syndrome at baseline developed it during CPAP. During sham CPAP 5 of 70 patients with the metabolic syndrome (7%) lost the features of the syndrome but 4 of the remaining 16 (25%) developed it.

Among patients with obstructive sleep apnoea 20% of those with the metabolic syndrome showed reversal during 3 months of CPAP but 20% of those without the syndrome developed it for the first time. During sham CPAP 7% of those with the syndrome showed reversal and 25% of those initially without it developed it. Thus the total number of patients with the metabolic syndrome decreased by 11 during CPAP and by one during sham CPAP. In patients with moderate to severe obstructive sleep apnoea CPAP may ameliorate or reverse the features of the metabolic syndrome but it does not prevent them appearing for the first time in some patients. During sham CPAP almost equal numbers (5 vs 4) lost and developed the metabolic syndrome. During CPAP 14 patients lost the metabolic syndrome and three gained it.

Sharma SK et al. CPAP for the metabolic syndrome in patients with obstructive sleep apnoea. *NEJM* 2011; 365: 2277–86.

Mobile phones and brain tumours: negative study

Studies of a possible relationship between brain tumours and mobile phone use have led to inconclusive results. Now a study in Denmark has shown no connection.

The study included people born in Denmark after 1925 and at least 30 years old. The study group were 358 403 people who had a mobile phone subscription prior to 1995 and the control group were people who did not. Follow-up was from 1990 to 2007 and cases of central nervous system (CNS) tumours were identified from the Danish Cancer Register. There were no significant differences between the two groups as regards incidence of CNS tumours, either overall or considering only long-term (>10 years) subscribers. This applied to men and women and for gliomas and meningiomas. Male, long-term subscribers were not at increased risk of temporal lobe gliomas (highest energy dose from a mobile dose is in the temporal lobe).

This study provides no evidence of an association between mobile phone use and CNS tumours.

Frei P et al. Use of mobile phones and risk of brain tumours: update of Danish cohort study. *BMJ* 2011; 343: 946 (d6387); Ahlbom A, Feychting M. Mobile telephones and brain tumours. Ibid: 914–5 (d6605) (editorial).

Tropical

Malaria vaccine success

Despite reductions in malaria morbidity and mortality with control measures there is still a great need for an effective malaria vaccine. The RTS,S vaccine has shown promise in preliminary trials. It is given with an adjuvant system (AS01 or AS02) and it targets the circumsprozoite protein. The initial results of a stage 3 trial in seven African countries have been reported.

The trial included a total of 15 460 children in two age groups (6537 aged 6–12 weeks and 8923 aged 5–17 months). They were randomised (2:1) to RTS, S/AS01 vaccine (three doses at monthly intervals) or a control vaccine (meningococcal group C conjugate vaccine for the younger group and rabies vaccine for the older). This report is largely confined to the first 6000 children in the older group followed for at least 12 months after the last dose. In this cohort of 6000 children the incidence of clinical malaria was 0.32 episodes per child (RTS,S/AS01) vs 0.55 episodes per child-year (controls) giving a vaccine efficacy of 50.4% (intention to treat) or 55.8% (per protocol). Against severe malaria the corresponding figures were 45.1% or 47.3%. In the older and younger age groups combined the vaccine efficacy (per protocol) against severe malaria was 34.8% after an average follow-up of 11

months. There was no excess of severe adverse events in the malaria vaccine group. The rate of generalised convulsive seizures in the older age group after receiving RTS,S/AS01 was 1.04 per 1000 doses. The full results of this trial will not be available until 2014. It is anticipated that the vaccine could be recommended for use in some African countries by 2015.

The RTS,S Clinical Trials Partnership. First results of phase 3 trial of RTS,S/AS01 malaria vaccine in African children. *NEJM* 2011; 365: 1863–75; White NJ. A vaccine for malaria. Ibid: 1926–7 (editorial).

AIDS

Avahan, an HIV-prevention initiative in India

Avahan is a privately funded HIV-prevention initiative founded in India in 2003 with a funding of US$258 million initially and an extra US$80 million in 2009. It is intended to merge it with the Indian government HIV prevention programme in 2013. Avahan is aimed at four large states in south India and two small states in the north east (total population 300 million). Prevention efforts are concentrated on high-risk groups such as female sex works, their clients and partners, men who have sex with men, injecting drug users, and truck drivers. They include peer outreach for safe-sex counselling, treatment for sexually transmitted infections, distribution of free condoms, needle and syringe exchange, and community organisation. An assessment of the population effect of Avahan in 2003–2008 has been reported.

In the six affected states 80 of 131 districts received Avahan funding. Increased funding in relation to initial HIV prevalence (grant per HIV population) was associated with a significant lowering of HIV prevalence in three of the six states. It was estimated that overall, Avahan prevented around 100 200 HIV infections during the period of study.

Well-planned and funded HIV-prevention initiatives may be effective in developing countries.

Ng M et al. Assessment of population-level effect of Avahan, an HIV –prevention initiative in India. *Lancet* 2011; 378: 1643–52; Boerma T, de Zoysa I. Beyond accountability: learning from large-scale evaluations. Ibid: 1610–2 (comment).

HIV in Uganda: value of viral load and CD4 cell count testing

CD4 cell count monitoring may benefit patients receiving antiretroviral therapy (ART) in sub-Saharan Africa. Whether the addition of viral load testing provides additional benefit is not known. Now a study in Uganda has suggested that it does not.

A total of 1094 HIV-infected adults with a CD4 count of <250 x 106 cells/L or WHO stage 3 or 4 disease were treated with ART and randomised to three groups for monitoring; clinical monitoring plus quarterly CD4 counts and viral loads (CM + CD4 + VL), clinical monitoring plus CD4 counts (CM + CD4), or clinical monitoring alone (CM). The median CD4 count at baseline was 129 cells x 106/L. Average follow-up was 3 years. The rate of new serious morbidity or death was 4.8 events per 100 person-years (CM + CD4 + VL), 6.0 events per 100 person-years (CM + CD4), and 7.6 events per 100 person-years (CM). Patients in the CM alone group did significantly worse than patients in either of the other two groups but there was no significant difference between the CM + CD4 + VL group and the CM + CD4 group.

Adding quarterly CD4 counts to clinical monitoring improved outcomes but the further addition of viral load testing did not further improve outcomes. In an assessment of cost-effectiveness, the addition of CD4 counting to clinical monitoring cost £109 per disability adjusted life-year (DALY) averted and the further addition of viral load testing cost a further £3132 per additional DALY averted. By WHO standards CD4 testing was very cost-effective but adding viral load testing was not cost-effective.

Mermin J et al. Utility of routine viral loads, CD4 cell count, and clinical monitoring among adults with HIV receiving antiretroviral therapy in Uganda: randomised trial. *BMJ* 2011; 343: 1134 (d6792); Kahn JG et al. CD4 cell count and viral load monitoring in patients undergoing antiretroviral therapy in Uganda: cost-effectiveness study. Ibid: 1135 (d6884); Del Rio C, Armstrong W. Antiretroviral therapy programmes in resource limited settings. Ibid: 1127 (d6853) (editorial).

Paediatrics

Influenza in children worldwide

Acute lower respiratory infections (ALRI) were the cause of 1.56 million deaths in young children in 2008. The most common pathogen is respiratory syncytial virus, accounting for 22% of ALRI episodes in young children. It has been suspected that seasonal influenza viruses cause many childhood episodes of ALRI but, until now, there have been no estimates of the global burden of disease from this cause. Now the available data have been analysed in a systematic review and meta-analysis of 43 studies.

Data were obtained from studies published between Jan 1, 1995 and Oct 31, 2010 and 16 unpublished population-based studies. The 43 studies included about 8 million children younger than 5 years. It was estimated that in 2008 about 13% of all cases of ALRI, and 7% of cases of severe ALRI, in young children were caused by influenza viruses. Around the world there were 90 million new cases of influenza in this age group, 20 million cases of ALRI due to influenza, and 1 million cases of severe ALRI from this cause. The estimated number of deaths from ALRI due to influenza viruses in children <5 years old in 2008 was between 28 000 and 111 500 with almost all (99%) of these deaths occurring in developing countries.

Influenza is a common cause of ALRI in young children worldwide.

Nair H et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. *Lancet* 2011; 378: 1917–30; Zambon M. Assessment of the burden of influenza in children. Ibid: 1897–8 (comment).

Speed of intravenous rehydration for children

A recent trial in sub-Saharan Africa showed that rapid bolus intravenous fluid administration was potentially lethal for children with dehydration, fever, and poor peripheral perfusion. Now a study in Toronto, Canada has shown no advantage from rapid rehydration compared with standard rehydration.

A total of 226 children >90 days old (weight 5–33 kg) presenting with gastroenteritis and mild to moderate dehydration to the emergency department of a children's hospital were treated initially with oral rehydration. When oral rehydration had failed they were randomised to rapid i.v. rehydration (0.9% saline 60 ml/kg over 1 hour) or standard i.v. rehydration (20 ml/kg over 1 hour). Clinical rehydration at 2 hours was achieved in 36% (rapid) vs 30% (standard), a nonsignificant difference. Prolonged treatment was needed by 52% vs 43% (difference nonsignificant) but the time to hospital discharge was significantly longer in the rapid rehydration group (6.3 vs 5.0 hours).

Rapid rehydration did not give better results than standard rehydration. The writer of a largely critical editorial insists that currently available evidence points, overall, to rapid rehydration being effective and safe.

Freedman SB et al. Rapid versus standard intravenous

rehydration in paediatric gastroenteritis: pragmatic blinded randomised clinical trial. *BMJ* 2011; 343: 1190 (d6976); Nager AL. Rapid intravenous rehydration in paediatric gastroenteritis. Ibid: 1183 (d7083).

Hospital-acquired bacteraemia in children in a Kenyan hospital

Although community-acquired bacteraemia is common in children in sub-Saharan Africa there are few data about hospital-acquired bacteraemia. A 7-year survey in a single hospital has been reported.

In the Kilifi District Hospital in Kenya between 16 April 2002 and 30 September 2009 there were 33 188 admissions of children up to the age of 15 years (14% aged 0–28 days, 3% 29–59 days, 25% 60 days to 1 year, and 58% over 1 year). The rate of hospital-acquired (>48 hours after admission) bacteraemia was 5.9 per 1000 admissions overall, rising during the study period by 27% per year. These researchers suspect that the increase is related to increased hospital stays because of an increasing proportion of neonates and fewer short stays with malaria. The incidence was 1.0 per 1000 days in hospital, about 40 times the local rate of community-acquired bacteraemia. Mortality was 53% for hospital-acquired bacteraemia and 24% for community-acquired bacteraemia. Survivors of hospital-acquired bacteraemia spent an extra 10 days in hospital compared with patients who did not become bacteraemic. The main infecting organisms were *Escherichia coli* and *Klebsiella pneumoniae*, each accounting for around 20% of cases. *Acinetobacter* species, *Staphylococcus aureus*, group D streptococci, and *Pseudomonas aeruginosa* each accounted for slightly less than 10% of cases and, in all, 18 bacterial pathogens were isolated. Yeasts were isolated in 5% of cases. The main pathogen in community-acquired bacteraemia was *Streptococcus pneumoniae* (29%), followed by *Staphylococcus aureus* (13%), *Acinetobacter* species (10%), and non-typhi *Salmonella* species (9%). Factors associated with hospital-acquired bacteraemia included severe malnutrition and blood transfusion in the absence of severe anaemia.

Hospital-acquired bacteraemia was uncommon in this study but carried a high mortality. The main pathogens differed from those of community-acquired bacteraemia and severe malnutrition and unnecessary blood transfusion were contributory factors.

Aiken AM et al. Risk and causes of paediatric hospital-acquired bacteraemia in Kilifi District Hospital, Kenya: a prospective cohort study. *Lancet* 2011; 378: 2021–7; Feasy N, Molyneux E. Keep it clean: hospital-acquired infections in children. Ibid: 1982–3.

Household smoke and childhood pneumonia in Guatemala

Pneumonia kills more children than any other disease and exposure to smoke in the home is a major factor increasing the risk of pneumonia. Now a study in Guatemala has given support for calls to reduce the exposure of children to smoke from home stoves that burn biomass fuels such as wood, animal dung, or crop wastes.

In the highlands of Guatemala (2200–3000 m above sea level) nearly all households use open wood fires for cooking and heating indoors. A total of 534 households, each with a pregnant woman or young infant, were randomised to intervention (supply of a wood stove with a chimney) or control (no change) groups. The children were followed up weekly to the age of 18 months. There was a nonsignificant 16% reduction in rate of pneumonia in the intervention group. There was, however, a significant 33% reduction in severe pneumonia. The chimney stoves reduced carbon monoxide exposure by about 50% but there was a large overlap in exposure within the two groups. Overall, a 50% reduction in exposure was associated with a significant 18% reduction in pneumonia.

These results suggest that reducing indoor pollution from wood stoves does reduce the risk of pneumonia, and particularly of severe pneumonia, in young children but that the chimney stoves used in this study were not ideal for the purpose.

Smith KR et al. Effect of reduction in household air pollution on childhood pneumonia in Guatemala (RESPIRE): a randomised controlled trial. *Lancet* 2011; 378: 1717–26; Miller RL, Agerstrand CL. Targeting of household air pollution: interpretation of RESPIRE. Ibid: 1682–4 (comment).

Obs & Gyn

Patient-collected vaginal specimens for HPV testing

Evidence suggests that screening for human papillomavirus DNA (HPV DNA) is superior to cervical cytology for the detection of cervical intraepithelial neoplasia (CIN) grade 2 or worse and for combating cervical cancer. In developing countries cervical cancer in common and resources for cytology are poor and HPV testing of self-collected vaginal specimens could increase screening coverage. A trial in Mexico has shown that HPV DNA testing using self-collected specimens is feasible and might improve detection rates.

A total of 25 061 women aged 25–65 in low socioeconomic status rural areas were randomised to home self-collected HPV specimen testing or cervical cytology at a health centre. The protocol was adhered to by 20 256 women. The prevalence of HPV positivity was 9.8% and the abnormal cytology rate 0.38%. Colposcopy on women with positive results in either group detected CIN2 or worse at a rate of 117.4 per 10 000 women in the HPV group and 34.4 per 10 000 in the cytology group. HPV testing was 3.4 times more sensitive than cytology and detected 4.2 times as many invasive cancers. There were nine times as many false positives in the HPV-testing group.

HPV-testing of self-collected vaginal specimens detects many more CIN 2+ lesions or cancers at a cost of many more false–positives compared with cytology in resource-poor areas. The high sensitivity might be an advantage in areas in which women will be screened infrequently.

Lazcano-Ponce E et al. Self-collection of vaginal specimens for human papillomavirus testing in cervical cancer prevention (MARCH): a community-based randomised controlled trial. *Lancet* 2011; 378: 1868–73; Muñoz N, Herrero R. Prevention of cervical cancer in women's hands: Mexico leads the way. Ibid: 1829–31 (comment).

ACE inhibitors, hypertension, and birth defects

The use of ACE inhibitors in the first trimester of pregnancy has been associated with increased risk of birth defects. Now a US retrospective cohort study has suggested that the increased risk is due to the hypertension for which ACE inhibitors are prescribed rather than the drugs themselves.

The study in California, included 465 754 mother–infant pairs between 1995 and 2008. The rate of ACE inhibitor use in the first trimester was 0.9 per 1000 and 2.4 per 1000 mothers had used other antihypertensives in the first trimester. After statistical adjustments there was a significant increase in congenital heart defects in the infants of mothers who had taken ACE inhibitors only when compared with normotensive mothers (3.9% vs 1.6%), but not when compared with other hypertensive mothers (2.4%) or mothers who had taken other antihypertensives during the first trimester (2.6%).

These results suggest that ACE inhibitors in the first trimester are associated with the same risk of congenital heart defects as other antihypertensives and it is the hypertension itself rather than the antihypertensive drugs that increases the risk.

Li D-K et al. Maternal exposure to angiotensin converting enzyme inhibitors in the first trimester and risk of malformations in offspring: a retrospective cohort study. *BMJ* 2011; 343: 887 (d5931); Mitchell AA. Fetal risk from ACE inhibitors in the first trimester. Ibid: 857–8 (d6667) (editorial).

Infection

Risk factors for *Clostridium difficile* infection

Known risk factors for hospital-acquired *Clostridium difficile* infection include older age, severe primary illness, previous hospital stay, use of feeding tubes, gastrointestinal surgery, and use of proton-pump inhibitors. A study in six hospitals in Canada has added to data about risk factors.

The study included a total of 4143 patients. *C difficile* infection was diagnosed in 117 patients (2.8%) and *C difficile* colonisation in 123 (3.0%). *C difficile* infection was significantly associated with older age, antibiotic use, and proton-pump inhibitor use. The factors associated with *C Difficile* colonisation were: hospital stay within the last 2 months, chemotherapy, proton-pump inhibitor use, H2 blocker use, and antibodies against toxin B. The North American PFGE type 1 (NAP1) strain of *C Difficile* was found in 63% of infected patients and 36% of colonised patients.

Older age, use of antibiotics, and use of proton-pump inhibitors are associated with increased risk of *C Difficile* infection in hospitals.

Loo VG et al. Host and pathogen factors for *Clostridium difficile* infection and colonization. *NEJM* 2011; 365: 1693–703.

Short-course isoniazid and rifapentine for latent tuberculosis

Standard treatment for latent tuberculosis is with daily isoniazid for 9 months. It is effective but the length of treatment means that many patients fail to complete the course. There are also concerns about toxicity, especially hepatic toxicity. Rifapentine is a rifampicin derivative with a long half-life and greater potency against *Mycobacterium tuberculosis*. Now a study in North America, Brazil, and Spain has shown that 3 months of rifapentine and isoniazid is as effective as 9 months of isoniazid and patients are more likely to finish the course of treatment.

A total of 7731 patients aged at least 2 years (median 35 years) at high risk of tuberculosis were randomised to directly observed rifapentine 900 mg plus isoniazid 900 mg once a week for 3 months (RI3) or self-administered isoniazid alone 300 mg daily for 9 months (I9). Over 33 months of follow-up tuberculosis developed in seven patients (0.18%) in the RI3 group and 15 (0.40 in the I9 group). The RI3 regimen was noninferior to the I9 regimen. The rate of treatment completion was significantly higher in the RI3 group (82% vs 69%). Drug discontinuation because of adverse events was significantly more common in the RI3 group (4.9% vs 3.7%) but drug-related hepatotoxicity was significantly less common (0.4% vs 2.7%).

Directly observed weekly rifapentine and isoniazid for 3 months was noninferior to 9 months of daily isoniazid alone and more likely to be complied with. Long-term safety monitoring will be needed. The duration of protection provided is not known, nor is the effect of concomitant HIV infection on treatment success.

Sterling TR et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *NEJM* 2011; 365: 2155–66; Dye C. Practical preventive therapy for tuberculosis. Ibid: 2230–1 (editorial).

Diabetes

Intensive blood glucose control for type 2 diabetes: meta-analysis

There is uncertainty about the ability of intensive blood glucose control to reduce the risks of death, macrovascular disease, or microvascular disease in people with type 2 diabetes. A systematic review and meta-analysis has suggested that intensive control does not reduce all-cause mortality but it does increase the risk of severe hypoglycaemia by about 30%.

The review included 14 trials with a total of 28 614 patients randomised to intensive or conventional control. All-cause mortality was similar in the two groups (9.6% intensive, 8.4% conventional, relative risk 1.02). Cardiovascular mortality was also similar in the two groups. There were apparently significant reductions in risk of nonfatal myocardial and microvascular disease in the intensive control group but further statistical analysis failed to confirm the significance of these findings. The risk of severe hypoglycaemia was increased by at least 30% with intensive control.

Intensive blood glucose control does not reduce all-cause mortality (or if it does, the reduction is less than 10%) and it increases the risk of severe hypoglycaemia by at least 30% (overall relative risk in this meta-analysis, 2.39).

Hemmingsen B et al. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *BMJ* 2011; 343: 1136 (d6898).

Diabetes risk models and scores

A systematic review has assessed risk models and scores for the prediction of risk of type 2 diabetes

The review included 43 papers with details of the development and/or validation of 145 models and scores, of which 94 were assessed in detail. They had been based on data from almost 7§million people with follow-up for up to 28 years. Meta-analysis was not possible because of the heterogeneity of the data. The mean number of components per score was eight (3–14) and some, but not all, models and scores were statistically robust and had been externally validated on a different population. Seven risk scores were chosen as having a high potential for use in practice and ten mechanisms were outlined whereby the assessment of risk of type 2 diabetes might lead to improvement in outcomes.

There are many risk scores for the development of type 2 diabetes but few are used routinely. Seven risk scores were considered to be highly suitable for clinical use.

Noble D et al. Risk models and scores for type 2 diabetes: systematic review. *BMJ* 2011; 343: 1243 (d7163).

Cardiology

11-year follow-up of patients in statin trial

The short-term benefits of statin treatment for cardiovascular at-risk patients are well established but there are concerns about possible long-term problems such as increased cancer risk. Now a long-term follow-up report of one trial has shown no evidence of such risks.

In the Medical Research Council and British Heart Foundation Heart Protection Study (HPS) 20 536 patients at high cardiovascular risk were randomised to simvastatin 40§mg daily or placebo.

Mean follow-up in the trial was 5.3 years but post-trial follow-up extended mean overall follow-up to 11.0 years. In-trial follow-up showed an average reduction in LDL cholesterol level of 1.0 mmol/L and a 23% reduction in major vascular events. During post-trial follow-up statin use and serum lipid levels were similar in the two groups, and there were no further reductions in major vascular event rates. During the 11 years of total follow-up the rates of cancer incidence and mortality and of nonvascular mortality were similar in the two groups.

Statin treatment is effective and no long-term adverse effects emerged in this study. In particular, there was no increase in cancer. *Lancet* commentators conclude that concerns about the long-term safety of statin treatment for at-risk patients should be 'put to rest'.

Heart Protection Study Collaborative Group. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20§536 high-risk individuals: a randomised controlled trial. *Lancet* 2011; 378: 2013–20; Kohli P, Cannon CP. Statins and safety: can we finally be reassured? Ibid: 1980–1 (comment).

Statins and infections: no benefit

Observational studies have suggested that people on statins might be less prone to infection. Now a systematic review and meta-analysis of 11 trials has shown no protective effect of statins against infection.

The eleven trials included 30 947 patients receiving a statin or placebo. Infection was reported in 2368 subjects on statins and 2287 on placebo. Meta-analysis showed that statin treatment did not affect the risk of infection or death related to infection.

Randomised controlled trials of statin therapy vs placebo have shown no evidence that statin therapy increases the risk of infection but not all trials provided this information.

Van den Hoek HL et al. Statins and prevention of infections: systematic review and meta-analysis of data from large randomised placebo controlled trials. *BMJ* 2011; 343: 1242 (d.7281); Golomb BA. Do statins reduce the risk of infection? Ibid: 1235 (d7134)

Biodegradable versus durable polymer stents

Drug-eluting stents, compared with bare metal stents, reduce the risk of repeat revascularisation but may increase the risk of very late (>1 year) stent thrombosis. It has been suggested that this increase in risk may arise from the durable nature of the polymer used in their construction that allows polymer material to persist and stimulate an inflammatory response. Drug-eluting stents made of biodegradable polymer might avoid this risk. A multinational European trial has shown that biodegradable polymer drug-eluting stents may have an advantage over durable polymer stents.

A total of 1707 patients with coronary disease (2472 lesions) were randomised to biodegradable polymer biolimus-eluting stents (BPBES) or durable polymer sirolimus-eluting stents (DPSES). After 4 years of follow-up BPBES were noninferior to DPSES. The primary endpoint (myocardial infarction, clinically-indicated target vessel revascularisation, or cardiac death) occurred in 18.7% (BPBES) vs 22.6% (DPSES), a 19% difference proving noninferiority of BPBES. There was a 38% overall reduction in stent thrombosis, a significant 80% reduction between years 1 and 4 and a nonsignificant 0.01% reduction during the first year. There was no significant reduction in primary endpoint events associated with stent thrombosis during the first year but a significant 83% reduction in such events between years 1 and 4.

BPBES were noninferior to DPSES and reduced the risk of very late stent thrombosis. It is not known whether BPBES will prove to be better than second generation drug-eluting stents.

Stefanini GG et al. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4-year follow-up of a randomised non-inferiority trial. *Lancet* 2011; 378: 1940–8; Waksman R, Maluenda G. Polymer drug-eluting stents: is the future biodegradable? Ibid: 1900–2 (comment).

Oncology

Dietary fibre and colorectal cancer

It is accepted that dietary fibre probably protects against colorectal cancer. Questions remain, however, about the types of fibre involved and the dose-response relationship. A systematic review and meta-analysis has provided some answers.

The review included prospective cohort, case-cohort, and nested case-control studies. For total dietary fibre 16 studies were analysed, for fruit fibre nine studies, for vegetable fibre nine studies, for legume fibre four studies, and for cereal fibre eight studies. The risk of colorectal was reduced by a significant 10% for each 10 g/day intake of total dietary fibre. This reduction as 7% for fruit fibre, 2% for vegetable fibre, 38% for legume fibre, and 10% for cereal fibre. The reductions were significant for cereal fibre. For whole grains three extra servings a day reduced the risk of colorectal cancer significantly by 17%.

Increased intake of total dietary fibre, cereal fibre, and whole grains reduced the risk of colorectal cancer. Fruit fibre, legume fibre, and vegetable fibre had no significant effect. A general increase in consumption of wholegrain foods and cereals could be recommended.

Aune D et al. Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies. *BMJ* 2011; 343: 1082 (d6617); Tjønneland A, Olsen A. Fibre and prevention of chronic diseases. Ibid: 1075 (d6938) (editorial).

Long-term benefits of radiotherapy after breast-conserving surgery for breast cancer: meta-analysis

A meta-analysis of 17 trials including 10 801 patients has shown the long-term benefits of radiotherapy after breast-conserving surgery for breast cancer.

Overall, radiotherapy reduced the 10-year recurrence risk from 35.0% to 19.3% and the 15-year disease-specific mortality rate from 25.2% to 21.4% (both reductions highly significant). Among the 7287 women with pathologically confirmed node-negative (pN0) disease the corresponding reductions were from 31.0% to 15.6% (10-year recurrence) and from 20.5% to 17.2% (15-year disease-specific mortality). In this group, absolute reductions in recurrence varied with age, grade, oestrogen-receptor status, tamoxifen use, and extent of surgery and these features were used to define large, intermediate, or lower recurrence risk categories. The absolute reductions in 15-year disease-specific mortality in these three subgroups were 7.8%, 1.1%, and 0.1% respectively (significant only in the first of these). Among the 1050 women with node positive (pN+) disease radiotherapy reduced 10-year recurrence risk from 63.7% to 42.5% and 15-year disease-specific mortality from 51.3% to 42.8%. Overall, for every four recurrences avoided at 10 years, one death was avoided at 15 years.

Radiotherapy after breast-conserving surgery reduces disease recurrence by about half and deaths from breast cancer by about a sixth. The absolute benefits vary and can be predicted by patient characteristics at the time of decision-making.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10801 women in 17 randomised trials. *Lancet* 2011; 378: 1707–16; Buchholz TA. Radiotherapy and survival in breast cancer. Ibid: 1680–2.