General

Pulmonary hypertension in adults with sickle cell disease

The prevalence of pulmonary hypertension in adults with sickle-cell disease has been estimated at up to 30% in studies based on Doppler echocardiography. This method, however, is likely to overestimate the prevalence. Researchers in France have used right heart catheterisation to confirm or dismiss a diagnosis of pulmonary hypertension suggested by Doppler echocardiography in adults with sickle-cell disease.

A total of 398 patients with sickle cell disease (mean age 34 years, 60% women) underwent echocardiography and pulmonary hypertension was suspected in 109 (27%) on the basis of a tricuspid valve regurgitant jet velocity of 2.5 m/sec or greater. Ninety-six of the 109 underwent right heart catheterisation with demonstration of pulmonary hypertension (mean pulmonary artery pressure 25 mmHg or greater) in 24 (25% of those catheterised, 6% of the total cohort). Thus the positive predictive value of echocardiography for the detection of pulmonary hypertension was 25%. The pulmonary hypertension was demonstrated to be precapillary in type in 11 patients (41%). Confirmed pulmonary hypertension was associated with older age, poorer functional capacity, and higher levels of N-terminal pro-brain natriuretic peptide. Patients with pulmonary hypertension diagnosed by echocardiography but not confirmed at right heart catheterisation had similar clinical characteristics to patients with normal echocardiography findings.

Among adults with sickle cell disease attending referral centres in France, echocardiography suggested pulmonary hypertension in 27%, but only 6% had pulmonary hypertension on right heart catheterisation.

Parent F et al. A haemodynamic study of pulmonary hypertension in sickle cell disease. *NEJM* 2011; 365: 44–53.

Low-sodium diet to control proteinuria

In patients with proteinuria, treatment with either ACE inhibitors or angiotensin receptor blockers (ARBs) alone often fails to reduce proteinuria sufficiently. Treatment with both drug types (dual blockade) usually produces only a small further reduction in proteinuria. Researchers in the Netherlands have shown that adding a low-sodium diet to ACE inhibitor therapy reduces proteinuria considerably.

A total of 52 patients with non-diabetic nephropathy entered a crossover trial in three centres in which they had four 6-week periods in which they took, in random order, an ARB with a normal diet, an ARB with a low-sodium diet, placebo with a normal diet, or placebo with a low-sodium diet, all in addition to an ACE inhibitor. The ARB was valsartan 320 mg/day, the ACE inhibitor, lisinopril 40 mg/day. The normal diet contained about 184 mmol of sodium/day and the low-sodium diet about 106 mmol of sodium/day. Mean residual proteinuria (target 1.00 g/day or less) was 1.68 g/day on ACE inhibitor plus placebo plus normal diet, 1.44 g/day on ACE inhibitor plus ARB plus normal diet, 0.85 g/day on ACE inhibitor, plus placebo plus low-sodium diet, and 0.67 g/day on ACE inhibitor plus ARB plus low-sodium diet. Adding a low-sodium diet to an ACE inhibitor reduced proteinuria significantly more than adding an ARB. Mean systolic blood pressure was134 mmHg with an ACE inhibitor alone 131 mmHg after adding an ARB, 123 mmHG after adding a low-sodium diet, and121 mmHg after adding both.

Adding both a low-sodium diet and an ARB did not have a significantly greater effect than just adding a low-sodium diet. Seven patients suffered from orthostatic hypotension on the low-sodium diet but only two needed to change their treatment.

Slagman MCJ et al. Moderate dietary sodium restriction added to angiotensin converting enzyme inhibition compared with dual blockade in lowering proteinuria and blood pressure: randomised controlled trial. *BMJ* 2011; 343: 298 (d4366).

Adequate pain management reduces agitation in patients with dementia

Both pain and agitation are common among people with dementia. A study in Norway has shown that good pain management reduces agitation and aggression.

A total of 60 clusters (independent nursing home units) in 18 nursing homes were randomised to intervention (a stepwise protocol for pain treatment) or control groups. Thirty-three clusters (175 patients with moderate to severe dementia) were randomised to intervention and 27 (177 patients) to usual care (controls) for 8 weeks with follow-up for another 4 weeks. In the intervention group, compared with the control group, agitation measured using the Cohen-Mansfield agitation inventory was reduced by an average of 17%. (Trials of risperidone for agitation have reported 3–18% reductions). There were also significant reductions in overall neuropsychiatric symptoms and in pain scores.

Adequate management of pain should be a priority for patients with dementia and would reduce the prescribing of psychotropic drugs.

Husebo BS et al. Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomised trial. *BMJ* 2011; 343: 193 (d 4065); Rosenberg PB, Lyketsos CG. Treating agitation in dementia. Ibid: 164–5 (d3913) (comment).

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Parent F et al. A haemodynamic study of pulmonary hypertension in sickle cell disease. *NEJM* 2011; 365: 44–53.

AIDS

Early treatment to prevent HIV-1 transmission

The point at which antiretroviral therapy should be started for HIV-1-infected patients has been debated for some years. Evidence has accumulated that early combined antiretroviral therapy reduces transmission rates and clinical events. Now a trial in sub-Saharan Africa, South America, Asia, and the USA has illustrated the benefits of early treatment.

The trial included 1763 couples in nine countries who were discordant for HIV-positivity. The HIV-positive partners had not previously received antiretroviral therapy and had CD4 counts of 350–550 cells per cu.mm. Randomisation was to early (immediate) antiretroviral therapy or delayed therapy (after a fall in CD4 count or the onset of symptoms). Almost all of the couples (97%) were heterosexual and 94% were married, half of infected partners were men and half women. After a median follow-up of 1.7 years (3152 person–years) there had been 39 HIV-1 transmissions, of which 28 were linked virologically to the infected partner. Among the 28 linked transmissions, 27 occurred in the delayed therapy group, a highly significant 96% risk reduction in the early therapy group compared with the delayed therapy group. Clinical endpoints (pulmonary tuberculosis, severe bacterial infection, WHO stage 4 events, or death) were reached by 40 (early) vs 65 (delayed), a significant relative reduction of 41% in the early-therapy group. The rates of other adverse events were the same in the two groups.

Early antiretroviral therapy reduced the within-couple risk of HIV-1 transmission and the rate of clinical endpoints. These results give extra support the use of antiretroviral therapy as a public health measure to reduce HIV-1 spread.

Cohen MS et al. Prevention of HIV-1 infection with early antiretroviral therapy. *NEJM* 2011; 365: 493–505; Hammer SM. Antiretroviral treatment as prevention. Ibid: 561–2 (editorial).

Rilpivirine versus efavirenz for first-line treatment of HIV infection – 1

Efavirenz-based regimens are recommended for first-line treatment of HIV-1 infection but efavirenz is associated with neurological and psychiatric adverse reactions, rashes, teratogenicity, and increased levels of LDL cholesterol and triglycerides. Preliminary trials have shown that the new non-nucleoside reverse transcriptase inhibitor (NNRTI), rilpivirine has similar effectiveness to efavirenz with fewer adverse effects. The two drugs have been compared in a 96-week phase 3 trial at 98 centres in 21 countries on five continents.

A total of 680 treatment-naive adults with a plasma HIV-1 load of at least 5000 copies per ml and viral sensitivity to background nucleoside or nucleotide reverse transcriptase inhibitors (N[t]RTIs) were randomised to oral rilpivirine or efavirenz, together with two other investigator-selected N[t]RTIs. The response rate was 86% (rilpivirine) vs 82% (efavirenz), showing non-inferiority of rilpivirine. CD4 counts increased similarly in the two groups. Virological failure occurred in 7% vs 5% and treatment was discontinued because of adverse events in 4% vs 7%. Grade 2-4 treatment-related adverse events occurred in 16% vs 31% and rash, dizziness, and increases in blood lipids were all significantly more common with efavirenz.

Rilpivirine compares favourably with efavirenz for the first-line treatment of HIV-1 infection.

Cohen CJ et al. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. *Lancet* 2011; 378: 229-37; Schrijvers R et al. Rilpivirine: a step forward in tailored HIV treatment. Ibid: 201–3 (comment).

Rilpivirine versus efavirenz for first-line treatment of HIV infection – 2

Another trial of rilpivirine vs efavirenz at 112 centres in 21 countries has given results similar to those of the trial referred to above.

This trial included 690 treatment-naive HIV-1-infected adults with a pretreatment viral load of at least 5000 copies per ml and viral sensitivity to all study drugs. Randomisation was to rilpivirine or efavirenz, each with tenofovir-disoproxil-fumarate and emtricitabine. A response at week 48 was confirmed in 83% of each group, confirming non-inferiority of rilpivirine. Virological failure occurred in 13% (rilpivirine) vs 6% (efavirenz). Grade 2–4 adverse events occurred in 16% vs 31%, and 2% vs 8% therefore discontinued treatment. Rash, dizziness, abnormal dreams or nightmares, and increases in plasma lipids were more common with efavirenz.

The two drugs had similar efficacy but rilpivirine was associated with more virological failures. Efavirenz was associated with more adverse events.

Molina J-M et al. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. *Lancet* 2011; 378: 238–46; Schrijvers R et al. Rilpivirine: a step forward in tailored HIV treatment. Ibid: 201–3.

HIV incidence: effect of concurrent sexual partnerships

About two-thirds of all people with HIV infection live in sub-Saharan Africa. One of the factors that has been thought to be important in sustaining the HIV epidemic in Africa is concurrent sexual partnerships. Now a study in South Africa has shown that the lifetime number of sexual partners is more important than concurrency in determining a woman's risk of HIV infection in a high-prevalence population.

Data from a surveillance site in KwaZulu-Natal were used to estimate the geographical variation in reported concurrent and lifetime partners of 2153 sexually active men aged 15–55 years across the study area. A total of 7284 HIV-negative women aged 15 years or older in the same population were followed up and their risk of becoming infected with HIV was correlated with the sexual behaviour profiles of men in the local community. Over a follow-up period of 5 years there were 693 new HIV infections in these women (3.6 cases per 100 person–years). Among the sexually active men the point-prevalence of partnership concurrence varied in different communities between 4.0% and 76.3% and the mean number of lifetime sexual partners varied between 3.4 and 12.9. After adjustment for individual sexual behaviour and demographic, socioeconomic, and environmental factors associated with HIV acquisition, the risk of HIV infection in women was directly related to the mean lifetime number of sexual partners of the local men but not to the local partnership concurrency rate.

The risk of HIV infection in a high HIV prevalence region was related to the average lifetime number of sexual partners

reported by the local men but not to the local rate of concurrency. Educational campaigns should concentrate on reducing multiple lifetime partnerships rather than concurrency.

Tanser F et al. Effect of concurrent sexual partnerships on rate of new HIV infections in a high-prevalence, rural South African population: a cohort study. *Lancet* 2011; 378: 247–55; Padian NS, Manian S. The concurrency debate: time to put it to rest. Ibid; 203–4 (comment).

HIV transmission in Malawi: role of acute and early infection

Acute HIV infection refers to the period between being infected and becoming antibody positive. In acute and early infections there is rapid viral replication, intense immune response, and a high risk of transmission. US workers have developed a mathematical model to describe the effect of early infection on community HIV incidence in Lilongwe, Malawi and to predict the effect of preventative interventions aimed at early or chronic infection, or both.

The model was based on data from Lilongwe antenatal clinics in 1987–2005. It was estimated that 38.4% of HIV transmissions were due to sexual contact with somebody with an early HIV infection. Interventions aimed only at early infection would reduce HIV prevalence substantially but would not eliminate HIV in the community, even with 100% coverage. Interventions aimed only at chronic HIV infections would reduce HIV prevalence but would eliminate HIV only at 95–99% coverage. For the greatest effect interventions aimed at chronic infections would need to be combined with interventions aimed at people with early HIV infections.

For the best results interventions aiming at the elimination of HIV from a community should target both chronic and early infections.

Powers KA et al. The role of acute and early HIV infection in the spread of HIV and implications for transmission prevention strategies in Lilongwe, Malawi: a modelling study. *Lancet* 2011; 378: 256–68; Cohen T, Corbett EL. Test and treat in HIV: success could depend on rapid detection. Ibid: 204–6 (comment).

Paediatrics

Promoting breast feeding in Africa

Increasing breast feeding rates is probably the most effective way of saving the lives of young children in developing countries: it is estimated that it could prevent some 22 million disability adjusted life years (DALYs). The WHO recommendation is for 6 months of exclusive breast feeding (EBF). There have been few trials of the effectiveness of EBF promotion in sub-Saharan Africa. Now a trial in Burkina Faso, Uganda, and South Africa has shown that individual home-based EBF peer counselling can increase the prevalence of EBF.

A total of 82 communities were randomised to intervention or control groups. Intervention consisted of home visits by peer counsellors with a 1-week training, one antenatal visit and four postnatal. In all, 2579 mother-infant pairs were included. At age 12 weeks, the EBF rates in the intervention vs control groups were 79% vs 35% in Burkina Faso, 82% vs 44% in Uganda, and 10% vs 6% in South Africa. At 24 weeks the respective EBF rates were 73% vs 22%. 55% vs 15%, and 2% vs <1%. The 12- and 24-day EBF rates were all significantly higher in the intervention groups. [The use of infant formula milks has been promoted in South Africa as part of campaigns against malnutrition and against HIV.] The prevalence of diarrhoea at ages 12 and 24 weeks did not differ significantly in the two groups in any country.

Individual, home-based, peer counselling increased EBF rates at 12 and 24 weeks but did not reduce the prevalence of diarrhoea. Promotion of breast feeding is an important public health strategy.

Tylleskär T et al. Exclusive breastfeeding promotion by peer counsellors in sub-Saharan Africa (PROMISE-EBF): a cluster-randomised trial. *Lancet* 2011; 378: 420–7; Bhutta ZA, Labbock M. Scaling up breastfeeding in developing countries. Ibid: 378–80 (comment).

Tropical

Text messaging and malaria treatment

There are over 5 billion mobile phone users around the world and text messaging has been shown to improve patient adherence to treatments. Now a study in Kenya has shown that text-messages sent to health workers may increase compliance with malaria treatment guidelines.

The study was carried out at 107 rural health facilities in 11 districts of coastal and western Kenya between March 6 2009 and May 31 2010. Facilities were randomised to intervention or control groups. In the intervention group all the health workers involved in outpatient consultations received two messages each day, Monday to Friday, about the detection and management of malaria in children, for 6 months. No text-messages were sent to health workers in the control group. Case management was assessed for 1157 intervention-group children and 1112 control-group children who needed treatment. Correct management with artemether-lumefantrine improved by 24 percentage points, in the intervention group compared with the control group, immediately after the intervention and by 25 percentage points 6 months later.

Text-messaging may improve the performance of health workers managing malaria in developing countries.

Zurovac D et al. The effect of mobile phone text-message reminders on Kenyan health workers' adherence to malaria treatment guidelines: a cluster randomised trial. *Lancet* 2011; 378: 795–803; Moonen B, Cohen JM. Text messaging to improve adherence to malaria guidelines. Ibid: 750–2 (comment).

Infection

Hepatitis B and C epidemiology in injecting drug users worldwide

There are an estimated 16 million injecting drug users (IDUs) around the world. Much of the danger of this practice is related to the transmission of HIV and of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections with the consequent risks of hepatic cirrhosis and liver cancer. More epidemiological data about the prevalence of HBV and HCV infections in IDUs and national, regional, and global data have now been reported.

Data have been gathered from peer-reviewed databases and other sources. A total of 4386 peer-reviewed and 1019 grey literature sources were assessed and 1125 sources were reviewed in full. Anti-HCV antibodies (anti-HCV) and anti-HBV antibodies (anti-HBc) were taken to indicate exposure to HCV and HBV respectively and HBV surface antigen (HBs Ag) as indicating current infection with HBV. Data from 77 countries were analysed. The prevalence of anti-HCV among IDUs was estimated at 60–80% in 25 countries and >80% in 12 countries. About 10 million IDUs worldwide might be anti-HCV positive, the greatest

numbers being in China (1.6 million), the USA (1.5 million), and Russia (1.3 million). Data from 59 countries suggested HBsAg prevalences among IDUs of 5–10% in 21 countries and >10% in ten countries. Around the world it is estimated that 6.4 million IDUs are anti-HBc positive and 1.2 million are HBsAg positive.

More IDUs are infected with HCV than with HIV. More, and more accurate, data are needed to inform efforts at prevention and treatment of HCV and HBV infections. A Lancet commentator draws attention to the widespread abuse of the human rights of IDUs.

Nelson PK et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet* 2011; 378: 571–83; Amon JJ. Hepatitis in drug users: time for attention, time for action. Ibid: 543–4(comment).

Salmonella Typhimurium from peanut products in the USA

Foodborne disease surveillance in the USA is done by PulseNet, the national molecular subtyping network for foodborne diseases. In November 2008 a cluster of 35 Salmonella Typhimurium isolates was detected in 16 states and later that month a second cluster of 27 isolates in 14 states was recognised. The isolates in the two clusters had related pulsed-field gel electrophoresis patterns previously unknown to PulseNet. Between September 2008 and April 2009, 714 cases were identified in 46 states. Among these cases, 166 (23%) were admitted to hospital and 9 (1%) died. In the first of two independent studies illness was associated with peanut butter, peanut butter-containing products, or frozen chicken products. Investigations of focal clusters and single cases associated with nine institutions pointed the blame at a single brand of peanut butter. In the second study illness was associated with eating peanut butter outside the home and two brands of peanut butter crackers both made from the brand of peanut butter implicated in the first study. The responsible strain of Salmonella Typhimurium was isolated from this brand of peanut butter, one brand of peanut butter crackers, and 15 other products. A total of 3918 peanut butter-containing products were recalled between January 10 and April 29, 2009 and the financial loss in peanut sales was estimated at a billion dollars.

A nationwide outbreak of Salmonella Typhimurium infection in the USA was traced to peanut butter and peanut butter products.

Cavallaro E et al. Salmonella Typhimurium infections associated with peanut products. *NEJM* 2011; 365: 601–10.

Gastrology

Linaclotide for chronic constipation

Linaclotide is a synthetic peptide structurally related to the endogenous guanylin peptide family. It activates the guanylate cyclase C receptor on the surface of intestinal epithelium, increasing both intracellular and extracellular levels of cyclic guanosine monophosphate (c GMP). This causes activation of the cystic fibrosis transmembrane conductance regulator, with increased secretion of chloride and bicarbonate into the intestinal lumen, increased luminal fluid secretion, and more rapid intestinal transit. Two trials, reported together, have shown that treatment with linaclotide might be effective in chronic constipation.

The two trials included a total of 1276 adults with chronic constipation (<3 spontaneous bowel movements per week plus other symptoms of constipation) at 212 centres in the USA and Canada. Randomisation was to linaclotide 145 µg, linaclotide 290 µg, or placebo, daily for 12 weeks. The primary endpoint was three or more complete spontaneous bowel movements (CSBMs) per week with an increase of at least one CSBM from baseline during at least 9 of the 12 weeks. In the two trials separately this endpoint was reached by 21.2% and 16.0% on linaclotide 145 µg daily, 19.4% and 21.3% on linaclotide 290 µg daily, and 3.3% and 6.0% on placebo, significantly better for either dose than for placebo in each trial. Linaclotide was also superior to placebo for other end points such as stool consistency, straining, abdominal discomfort or bloating, severity of constipation, and treatment satisfaction. Diarrhoea leading to treatment discontinuation occurred in 4.2% of patients on linaclotide; otherwise adverse events were similar in all groups.

Linaclotide shows promise as a treatment for chronic constipation but more data are needed.

Lembo AJ et al. Two randomised trials of linaclotide for chronic constipation. *NEJM* 2011; 365: 527–36.

Treatment of *H pylori* infection in Latin America

Most people become infected with *Helicobacter pylori* and it is thought to be the cause of 60% of gastric cancers. Almost all deaths from gastric cancer occur in east Asia and Latin America. *H pylori* is also the main cause of peptic ulcer disease. If successful, population-wide *H pylori* eradication programmes would prevent many deaths and much morbidity. In a trial in Latin America standard 14-day triple-drug therapy has been compared with 5-day concomitant and 10-day sequential four-drug regimens.

The trial, in Chile, Colombia, Costa Rica, Honduras, Nicaragua, and Mexico (2 sites), included 1463 patients aged 21–65 with a positive H pylori urea breath test. Randomisation was to one of three regimens: standard therapy (lansoprazole, amoxicillin, and clarithromycin for 14 days), concomitant therapy (lansoprazole, amoxicillin, clarithromycin, and metronidazole for 5 days), or sequential therapy (lansoprazole and amoxicillin for 5 days followed by lansoprazole, clarithromycin, and metronidazole for 5 days). The rates of eradication were 82.2% (standard therapy), 73.6% (concomitant therapy), and 76.5% (sequential therapy). Neither of the four-drug regimens was significantly better than standard therapy at any of the sites.

Standard 14-day triple-drug therapy remains the best option in Latin America. Population-wide eradication programmes would be feasible.

Greenberg ER et al. 14-day triple, 5-day concomitant, and 10-day sequential therapies for Helicobacter pylori infection in seven Latin American sites: a randomised trial. *Lancet* 2011; 378: 507–14; Mazzoleni LE et al. Mass eradication of Helicobacter pylori: feasible and advisable? Ibid: 462–4 (comment)

Surgery

Preventing awareness during operation

Awareness during operation under general anaesthesia can give rise to post-traumatic stress disorder. High risk of intraoperative awareness is defined by the presence of at least one of 13 factors ranging from planned open heart surgery, to daily alcohol consumption, use of certain drugs, and low cardiac ejection fraction. Among high-risk patients the rate of intraoperative awareness is up

to 1%. In the main, two methods are used to monitor patients during operation with the aim of avoiding intraoperative awareness: monitoring of end-tidal concentration of anaesthetic agent (ETAC) and use of the bispectral index (BIS) that depends on monitoring a single frontal EEG signal producing a number ranging from 0 (no brain electrical activity) to 100 (awake), with a target range of 40–60. Researchers at three centres in the USA and Canada postulated that BIS would be better than ETAC but failed to prove it.

A total of 6041 patients with a high awareness risk were randomised to BIS or ETAC monitoring each with an audible alert if levels outside the target range were reached. Protocols also included structured education and checklists. Definite operative awareness occurred in 7/2862 (0.24%) in the BIS group and 2/2852 (0.07%) in the ETAC group, a nonsignificant difference. Definite or possible intraoperative awareness occurred in 0.66% vs 0.28%, also a nonsignificant difference. The two groups were similar as regards the amount of anaesthetic administered or the rate of major postoperative adverse outcomes.

The superiority of BIS was not established.

Avidan MS et al. Prevention of intraoperative awareness in a high-risk surgical population. *NEJM* 2011; 365: 591–600; Crosby G. General anesthesia – minding the mind during surgery. Ibid: 660–1 (editorial).

Obs & Gyn

Control of bleeding at elective caesarean section: oxytocin bolus with or without oxytocin infusion

Use of oxytocin reduces postpartum haemorrhage after vaginal delivery but the effect at caesarean section has been little studied. Now researchers in the Republic of Ireland have shown that adding oxytocin infusion to an oxytocin bolus at elective caesarean section reduced the need for additional uterotonics but did not affect the risk of major bleeding.

A total of 2069 healthy women at term with a singleton pregnancy booked for elective caesarean section were randomised to oxytocin bolus (5IU over 1 minute followed by oxytocin infusion (40 IU in 500ml 0.9% saline over 4 hours) or oxytocin bolus followed by saline infusion. Major obstetric haemorrhage occurred in 16.0% (bolus) vs 15.7% (bolus plus infusion, a nonsignificant difference. Additional uterotonics were needed by 18.4% (bolus) vs 12.2% (bolus plus infusion), a highly significant difference.

The addition of an oxytocin infusion did not reduce the risk of major obstetric haemorrhage but it did reduce the need for additional uterotonic therapy.

Sheehan SR et al. Oxytocin bolus versus oxytocin bolus and infusion for control of blood loss at elective caesarean section: double blind, placebo controlled, randomised trial. *BMJ* 2011; 343: 355 (d4661).

Oncology

Low-dose CT screening: reduces lung cancer deaths

Screening with chest X-rays with or without sputum cytology, has not reduced lung cancer mortality. Advances in computerised tomography (CT) have made low-dose CT screening feasible with acceptable levels of radiation exposure. Now a national trial of CT screening in the USA has shown that it has reduced lung-cancer mortality.

The trial included 53454 people aged 55–74 with a history of at least 30 pack-years of cigarette smoking and being present smokers or having stopped within the last 15 years. They were randomised to three annual screenings with low-dose CT or single-view posteroanterior chest radiography. Enrolment was from August 2002 to April 2004 and follow-up data were available to December 2009; screening was positive in 24.2% (CT) and 6.9% (chest X-ray) with false-positive rates of 96.4% and 94.5%. The true-positive rates were 645 vs 572 cases of lung cancer per 100000 person–years, a significant 13% increase in the CT group. Lung cancer mortality was 247 vs 309 deaths per 100000 person-years, a significant 20% relative reduction with CT screening. There was also a significant 6.7% reduction in all-cause mortality with CT screening compared with chest X-ray screening.

Low-dose CT screening of at-risk people has the potential to prevent many deaths from lung cancer. Both the researchers and the writer of an editorial warn against implementing screening programmes before the effects of screening, including over-diagnosis, and cost-effectiveness analyses have been fully assessed.

The National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. NEJM 2011; 365: 395–409; Sox HC. Better evidence about screening for lung cancer. Ibid: 455–7 (editorial).

Efficacy of adjuvant tamoxifen in early breast cancer

A meta-analysis of 5-year trials of adjuvant tamoxifen in early breast cancer has been reported.

The meta-analysis included 20 trials (21457 patients). Among women with oestrogen receptor (ER)-positive breast cancer, 5 years of tamoxifen treatment reduced recurrence rates by 47% in the first 4 years and by 32% in years 5–9. There was no effect after 10 years. Among women with marginally ER-positive disease the risk reduction was 33%. In ER-positive breast cancer the risk reduction from tamoxifen was largely independent of progesterone receptor status, age, nodal status, or use of chemotherapy. Breast cancer mortality was reduced by 29% during years 0–4, 34% during years 5–9, and 32% during years 10–14. Non-breast-cancer mortality was not much affected although there were small increases in deaths from thromboembolism and uterine cancer in women over the age of 55. Tamoxifen was not effective in ER-negative breast cancer.

ER status was the only recorded factor associated with reduction in risk of recurrence or death from breast cancer with tamoxifen.

Early breast cancer trialists' collaborative group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 2011; 378: 771–84; Chia SK, Wolff AC. With maturity comes confidence: EBCTCG tamoxifen update. Ibid: 747–9 (comment).

Pulmonary

Placebo effects in patients with asthma

Asthma is a good subject for the study of placebo effects because short-term responses can be measured easily. Researchers in the USA have studied lung function and subjective responses after a variety of active and non-active interventions.

The study included 46 patients with mild-to-moderate asthma and an FEV1 response to inhaled salbutamol, and 39 completed the course of investigations. There were four interventions: inhaled

salbutamol (albuterol), inhaled placebo, sham acupuncture, or control (no intervention). Using a block design, each subject received a different one of these interventions in random order on each of four visits with an interval of 3–7 days between visits. This procedure was repeated twice to a total of 12 visits per subject (three blocks, each of four visits). The average increase in FEV1 was 20% with salbutamol and around 7% with the placebo inhaler, sham acupuncture, or control groups. Subjective responses were assessed by asking subjects to assess their own improvement on a scale of 0–10 (0 = no improvement, 10 = complete improvement). The average subjective improvement was 50% (salbutamol), 45% (placebo inhaler), 46% (sham acupuncture), and 21% (controls). All three interventions were followed by significantly greater subjective improvement than in the control group.

The placebo interventions had no objective effect but subjectively assessed responses were similar with active (salbutamol) treatment and the two placebo treatments and all three were superior to no treatment (controls).

Wechsler ME et al. Active albuterol or placebo, sham acupuncture, or no intervention in asthma. *NEJM* 2011; 365: 119–26; Moerman DE. Meaningful placebos – controlling the uncontrollable. Ibid: 171–2 (editorial).

Cardiology

Risk of myocardial infarction after discontinuing aspirin

Data from a UK primary care database have confirmed that stopping aspirin prophylaxis increases the risk of myocardial infarction.

The data included 39§513 patients aged 50–84 with a first prescription for aspirin for secondary prophylaxis between 2000 and 2007. Follow-up averaged 3.2 years. There were 876 nonfatal myocardial infarctions and 346 deaths from coronary disease. Overall the incidence of nonfatal myocardial infarction or coronary disease death was 9.58 per 1000 person–years. Patients who had recently stopped taking aspirin had a significant 43% increase in this risk and distant discontinuation was associated with a nonsignificant 19% increase in risk. Among patients who recently discontinued aspirin there was a significant 63% increase in risk of nonfatal myocardial infarction but a nonsignificant 7% increase in risk of death from coronary disease.

Patients taking low-dose aspirin for secondary prophylaxis against coronary events should not stop it unless there is a good medical reason to do so.

García Rodríguez LA et al. Discontinuation of low dose aspirin and risk of myocardial infarction: case-control study in UK primary care. *BMJ* 2011; 343: 195 (d 4094); Biondi-Zoccai G, Landoni G. Discontinuation of aspirin for secondary prevention. Ibid: 165–6 (d 3942) (editorial).

Diabetes

Diet alone or diet plus exercise in newly diagnosed type 2 diabetes

Advice about diet and exercise is usually given to patients with newly diagnosed type 2 diabetes, but whether the two together are an improvement on diet alone remains uncertain. A UK trial has shown that adding an exercise programme to dietary advice did not improve diabetes control.

The trial, at five centres in southwest England, included 593 patients with a new diagnosis of type 2 diabetes 5–8 months before trial entry. They were randomised (2:5:5) to one of three options: dietary advice and 6-monthly follow-up (controls), intensive dietary intervention with dietary consultation every 3 months and monthly nurse support (ID), or intensive dietary intervention plus a pedometer-based exercise programme (ID+E). At 6 months mean HbA_{1c} levels had risen to 6.86% from a baseline value of 6.72% in the control group but had fallen from 6.64% to 6.57% in ID group, and from 6.69% to 6.60% in the ID+E group. At 12 months the mean HbA_{1c} levels were 6.81%, 6.55%, and 6.65%. The responses were significantly better in the ID and the ID+E groups than in the control group but there was no significant difference between the ID and ID+E groups. There were similar patterns of response for body weight and insulin resistance.

Intensive dietary advice and intensive dietary advice plus exercise had similar effects on blood glucose control and other measures of diabetes control. This is not to deny the well-known benefits of exercise for everybody.

Andrews RC et al. Diet or diet plus physical activity versus usual care in patients with newly diagnosed type 2 diabetes: the Early ACTID randomised controlled trial. *Lancet* 2011; 378: 129–39; Hu FB. Diet and exercise for new-onset type 2 diabetes: Ibid: 101–2 (comment).

Prediabetes: diagnosis and risk of progression to diabetes

Prediabetes (high fasting blood glucose but not high enough to make a diagnosis of diabetes) increases the risk of developing diabetes. It has been proposed that measurement of HbA1c levels might help in the diagnosis of prediabetes. Researchers in Japan have assessed the use of impaired fasting blood glucose and/or HbA1c levels.

The study included 4670 men and 1571 women aged 24–82 who did not have diabetes and were attending for a routine health check between 1997 and 2003. Prediabetes was diagnosed with an HbA_{1c} level of 5.7–6.4%, or a fasting plasma glucose of 5.6–6.9 mmol/L, or both. Over a mean follow-up of 4.7 years this diagnosis was made for 2092 participants (33.5%). Of these, 1270 had a raised fasting plasma glucose alone, 412 had a raised HbA_{1c} alone, and 410 had raised levels for both measurements. Diabetes developed in 7% of subjects with raised HbA_{1c} alone, and 9% of those with raised fasting plasma glucose alone (a nonsignificant difference). The risk of developing diabetes was increased 6.00-fold among subjects with a raised HbA_{1c} alone, 6.16-fold among subjects with a raised fasting plasma glucose only, and 31.9-fold among subjects with both, compared with subjects with normal values at baseline. Among subjects who developed diabetes 14% had normal values at baseline, 9% had raised HbA_{1c} alone, 32% had raised fasting plasma glucose alone, and 46% had raised values for both measurements.

Screening using HbA_{1c} alone would detect 40% of people with prediabetes and screening with fasting plasma glucose alone would detect 80%. Using both tests would detect 100% by these criteria and identify more people at high cardiovascular risk.

Heianza Y et al. HbA1c 5.7-6.4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS3): a longitudinal cohort study. *Lancet* 2011; 378: 147–55; Misra A, Garg S. HbA1c and blood glucose for the diagnosis of diabetes. Ibid: 104–6 (comment).

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