

General

Radiographic features and pain in knee arthritis

It is often claimed that there is little relationship between the radiographic features of osteoarthritis of the knee and the pain experienced by the patient. Features peculiar to the individual patient (genetic, psychological, social, and cultural) may confound studies of this relationship. Researchers in the USA have tried to overcome this problem by studying patients with unilateral knee pain and comparing the two knees.

Patients were studied from two cohorts, the Multicenter Osteoarthritis (MOST) study in Iowa and Alabama (696 patients), and the Framingham Osteoarthritis study in Massachusetts (336). Knee X-rays were scored for Kellgren and Lawrence grade (0–4), maximal osteophyte grade (0–3), and maximal joint space narrowing grade (0–3). A Kellgren and Lawrence grading of 4 increased the likelihood of pain, compared with a grading of 0, by a factor of 151 in MOST and 73 in Framingham. Pain was more strongly associated with joint space narrowing than with osteophytes.

When personal factors are controlled for there is a strong relationship between the radiographic features of knee osteoarthritis and knee pain.

Neogi T et al. Association between radiographic features of knee osteoarthritis and pain: results from two cohort studies. *BMJ* 2009; 339: 498–501; Pineus T, Block JA. Pain and radiographic damage in osteoarthritis. *Ibid*: 469–70.

Steroids for sore throat

There is pressure to avoid antibiotic treatment for upper respiratory tract infections, including sore throats. It has been suggested steroid treatment might give symptomatic relief. Now a systematic review and meta-analysis has given some support to the use of steroids in addition to antibiotics and analgesics.

The review included eight trials with a total of 743 patients; 369 children and 374 adults. Group A β -haemolytic streptococcus was recovered from 330 patients (44%) and 348 (47%) had exudative sore throat. Steroids given with antibiotics and analgesics increased the rate of complete resolution at 24 hours more than three-fold, and at 48 hours 1.7-fold. The average time to pain relief was reduced by >6 hours.

Steroids added to antibiotics and

analgesics speeded up recovery. The effects of steroids without antibiotics are not known and neither is the risk of rare complications.

Hayward G et al. Corticosteroids for pain relief in sore throat: systematic review and meta-analysis. *BMJ* 2009; 339: 488–90; Little P. Sore throat in primary care. *Ibid*: 467–8 (editorial).

Etomidate vs ketamine for emergency intubation

Etomidate is a sedative used for emergency endotracheal intubation but it can cause reversible adrenal insufficiency by inhibiting 11 β -hydroxylase. French researchers have now shown that ketamine is a safe and effective alternative.

A total of 655 patients needing emergency intubation outside hospital, in emergency departments, or in intensive care units were randomised to etomidate 0.3 mg/kg or ketamine 2 mg/kg. They were then given succinylcholine and sedation was maintained with midazolam plus either fentanyl or sufentanil. The analysis included 469 patients. On the sequential organ failure assessment (SOFA) score of 0–24 assessed during the first 3 days in intensive care there was no significant difference between the groups (etomidate 10.3; ketamine 9.6). Ease of intubation was similar in the two groups. There were no significant differences in 28-day mortality or other clinical end points. Adrenal axis function was assessed in 232 patients and adrenal insufficiency was diagnosed in 86% in the etomidate group compared with 48% in the ketamine group.

These researchers conclude that ketamine is a valid alternative to etomidate for emergency intubation. It might be particularly useful for patients with sepsis.

Jabre P et al. Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial. *Lancet* 2009; 374: 293–300; Wenzel V, Lindner KH. Best pharmacological practice in prehospital intubation. *Ibid*: 267–8 (comment).

AIDS

Efavirenz-based vs raltegravir-based combination therapy

Raltegravir is a new HIV-1 integrase inhibitor that prevents proviral DNA-strand transfer and is active against strains of virus resistant to other antiretroviral drugs. Now raltegravir has been shown to be a valid alternative to efavirenz for combi-

nation therapy in treatment-naïve adults.

A total of 566 treatment-naïve patients were randomised at 67 centres in 14 countries to raltegravir 400 mg twice daily or efavirenz 600 mg once daily, each together with tenofovir and emtricitabine. All patients had HIV-1 infection, viral RNA >5000 copies per ml, and no baseline resistance to efavirenz, tenofovir, or emtricitabine. The primary endpoint (viral RNA <50 copies per ml at week 48) was reached by 86% (raltegravir) vs 82% (efavirenz), a non-significant difference. The time to achieve viral suppression was significantly shorter, and drug-related adverse events less frequent, with raltegravir.

Raltegravir-based treatment was rapidly effective and non-inferior to efavirenz-based treatment at week 48.

Lennox JL et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naïve patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet* 2009; 374: 796–806; Emery S, Winston A. Raltegravir: a new choice in HIV and new chances for research. *Ibid*: 764–6 (comment).

Circumcision of HIV-infected men to prevent infection of female partners – negative trial

Circumcision of HIV-negative men in high HIV-prevalence areas reduces their risk of acquiring HIV infection. Preliminary studies have suggested that circumcision may reduce the risk of transmission of HIV infection from HIV-positive men to their partners. Now a trial in Uganda has produced negative results.

A total of 922 uncircumcised HIV-infected men aged 15–49 and with CD4-cell counts of at least 350 cells per μ L were randomised to immediate circumcision (intervention group) or circumcision delayed for 12 months (control group). HIV-negative female partners (163) of these men were followed at 6, 12, and 24 months. During follow-up the rate of HIV infection was 18% among partners of men in the intervention group and 12% among the partners of men in the control group. The cumulative probability of infection at 24 months was 21.7% (intervention) vs 13.4% (control) a non-significant difference.

Circumcision of HIV-infected men did not prevent transmission to their female partners.

Wawer MJ et al. Circumcision in HIV-infected men and its effect on HIV transmission to female partners in Rakai, Uganda: a randomised controlled trial. *Lancet* 2009; 374: 229–37; Baeten JM et al. Male circumcision and HIV risks and benefits for women. *Ibid*: 182–4 (comment).

Paediatrics

Integrated management of childhood illness strategy in Bangladesh

WHO and UNICEF introduced the Integrated Management of Childhood Illness (IMCI) strategy in the mid-1990s with the aim of reducing mortality from diarrhoea, pneumonia, malaria, measles, and malnutrition in children under the age of 5 years. Results have already been published from Brazil, Peru, Uganda, and Tanzania. Now final results have been reported from Bangladesh.

In a cluster-randomised trial, ten government health facility areas were assigned to IMCI and ten to usual services. IMCI had three components; health-worker training, health-systems improvements, and family and community activities. The rate of reduction in mortality among children <5 years old was similar in the two groups (IMCI 8.6% per year vs controls 7.85% per year). In IMCI areas there were improvements in health-worker skills, health-system support, and family and community practices, resulting in increased care-seeking for illnesses. More children <6 months old were exclusively breast fed (76% vs 65%) and the prevalence of stunting among children aged 24–59 months fell more quickly in IMCI areas.

IMCI resulted in improvements in input, output, and outcome indicators but did not improve mortality during the time of assessment.

Arifeen SE et al. Effect of the Integrated Management of Childhood Illness strategy on childhood mortality and nutrition in a rural area of Bangladesh: a cluster randomised trial. *Lancet* 2009; 374: 393–403; Duke T. Child survival and IMCI: in need of sustained global support. *Ibid*: 361–2 (comment).

First postnatal home visit: within 48 hours

In developing countries, home visits by trained community health workers in the neonatal period reduce perinatal and neonatal mortality. Now further analysis of data from a 2004–2005 trial in Bangladesh has shown that the first visit must be within the first 2 days to be effective.

The study included 9211 live births. Among infants who survived the first day, a visit on the first day reduced neonatal mortality by 67% compared with no visit. Among infants who survived the first 2 days a visit on the second day reduced neonatal mortality by 64%. Later visits did not reduce neonatal mortality.

In developing countries home visits should be within 2 days of birth.

Baqui AH et al. Effect of timing of first postnatal care home visit on neonatal mortality in Bangladesh: a prospective cohort study. *BMJ* 2009; 339: 445–8.

Quinine vs artemether-lumefantrine in Ugandan children

In a trial in Kampala, Uganda, the artemether-lumefantrine combination (A-L) was better than quinine (Q) for the treatment of young children with uncomplicated falciparum malaria.

A total of 175 children aged 6–59 months were randomised to one or the other treatment. Parasitological cure rates at 28 days were 96% (A-L) and 64% (Q) a highly significant difference. The risk of treatment failure was 4.1% vs 35.3%.

Artemether-lumefantrine was significantly more effective than quinine.

Achan J et al. Effectiveness of quinine versus artemether-lumefantrine for treating uncomplicated falciparum malaria in Ugandan children: randomised trial. *BMJ* 2009; 339: 283 (pico).

Obs & Gyn

HPV, cervical screening, and cervical abnormalities

Much of the 8 August 2009 issue of the *BMJ* is devoted to issues around the detection and management of cervical abnormalities

In Costa Rica, 2282 women were tested for HPV at baseline and again after 9–21 months and followed up for 5–7 years. The 3-year cumulative incidence of cervical intraepithelial neoplasia grade II + (CIN II+) was 17% among women with two positive tests. With two positive tests for HPV16 the 3-year cumulative incidence was 40%. Among women with two negative tests the 3-year cumulative incidence of cervical intraepithelial neoplasia was 0.5%.

A UK case-control study has shown that the effectiveness of cervical screening varies with age. There were 4012 cases of cervical cancer and 7889 matched controls. Cytological screening at age 52–54 reduced the risk of cervical cancer over the next 3–5 years by 74%. Screening at age 30–37 reduced the risk by 43–60% but screening at age 20–24 did not reduce the risk significantly.

In another multicentre UK study, a total of 4439 women aged 20–59 with borderline nuclear abnormalities or mild dyskaryosis on cervical cytology were

randomised to cervical surveillance or immediate colposcopy. Immediate colposcopy gave no clear benefit and may have caused harm. The cumulative incidence of CIN II+ was 79/1000 person-years (colposcopy) vs 58/1000 person-years (cytological surveillance). The difference was less but still significant for CIN III+. More women in the colposcopy group complained of side-effects.

The same group of researchers (TOMBOLA group) included 1983 women with similar abnormalities on cytology in a trial comparing punch biopsy and selective recall for treatment with immediate large loop excision. They concluded that punch biopsy was as effective and resulted in less overtreatment and fewer adverse effects.

In a cost-effectiveness study three options (cytological surveillance, colposcopy and biopsy with recall as necessary, and colposcopy with immediate treatment based on colposcopic appearance) for women with low-grade cervical cytological abnormalities were compared. The costs were similar for the three options.

Castle PE et al. Short term persistence of human papillomavirus and risk of cervical precancer and cancer: population based cohort study. *BMJ* 2009; 339: 327 (pico); Sasieni P et al. Effectiveness of cervical screening with age: population based case-control study of prospectively recorded data. *Ibid*: 328 (pico); Ronco G et al. Cervical screening according to age and HPV status. *Ibid*: 306–7 (editorial); TOMBOLA group. Cytological surveillance compared with immediate referral for colposcopy in management of women with low-grade cervical abnormalities: multicentre randomised controlled trial. *Ibid*: 329 (pico); TOMBOLA group. Biopsy and selective recall compared with immediate large loop excision in management of women with low-grade abnormal cervical cytology referred for colposcopy: multicentre randomised controlled trial. *Ibid*: 330 (pico); TOMBOLA group. Options for managing low-grade cervical abnormalities detected at screening – cost effectiveness study. *Ibid*: 331 (pico); Franco EL. Managing low grade and borderline cervical abnormalities. *Ibid*: 305–6 (editorial).

Tropical

Malarial resistance to artemisinin

The current WHO recommendation for first-line treatment of uncomplicated falciparum malaria in endemic areas is an artemisinin-based combination. There has been concern, however, that drug resistance may have emerged on the border of Thailand and Cambodia. Now studies at two sites, in western Cambodia and north-western Thailand have confirmed reduced susceptibility of *Plasmodium falciparum* to artesunate in western Cambodia.

At each site 40 patients were randomised to either oral artesunate 2 mg/kg daily for 7 days or oral artesunate 4 mg/kg for 3 days plus oral mefloquine 15 mg/kg on day 3 and 10 mg/kg on day 4. Median parasite clearance times were 84 hours in Cambodia and 48 hours in Thailand. Recrudescence confirmed by PCR occurred on artesunate monotherapy in 30% (Cambodia) and 10% (Thailand). On artesunate-mefloquine the corresponding figures were 5% and 5%. The differences in parasitological responses were not explained by age, drug pharmacokinetics, invitro sensitivity tests, or putative molecular correlates of *P falciparum* drug resistance. Adverse events were mild and similar in the two treatment groups.

P falciparum in western Cambodia is less susceptible to artesunate than is *P falciparum* in northwestern Thailand. This is shown by slower parasite clearance in vivo without reduced susceptibility on conventional in vitro testing. It is important to introduce measures to contain the spread of drug resistance.

Dondorp AM et al. Artemisinin resistance in *Plasmodium falciparum* malaria. *NEJM* 2009; 361: 455–67; Campbell CC. Malaria control-addressing challenges to ambitious goals. *Ibid*: 522–3 (editorial).

Sporozoite inoculation to promote immunity to malaria

There is currently some optimism about the development of a malaria vaccine. The RTS,S vaccine based on the circumsporozoite protein is at the phase 3 field trial stage but other approaches to vaccine development are proceeding. Irradiated sporozoites can invade the liver but do not mature fully and do not progress to the pathogenic blood stage. This could form the basis for a whole-parasite vaccine were it not for the fact that at least 1000 bites from irradiated mosquitoes over at least five sessions would be needed. Now a study on Dutch volunteers has supported the concept of a whole-parasite vaccine.

Fifteen volunteers who had never had malaria and had not lived in an endemic area were treated with chloroquine. (Chloroquine kills blood-stage but not pre-erythrocytic *Plasmodium falciparum*.) Ten subjects (the vaccine group) were exposed to bites from mosquitoes infected with chloroquine-sensitive *P falciparum* and five (controls) were exposed to uninfected mosquitoes. One month after stopping chloroquine all 15 subjects were exposed to five infected mosquitoes. Patent (microscopical) parasitae-

mia developed in all five controls but in none of the vaccine group. There were no serious adverse events. Protection was linked to the induction of parasite-specific pluripotent effector memory T cells that produced interferon γ , tumour necrosis factor α , and interleukin-2.

This is not a practical vaccine strategy but it points the way to further developments.

Roestenberg M et al. Protection against a malaria challenge by sporozoite inoculation. *NEJM* 2009; 361: 468–77; Campbell CC. Malaria controls - addressing challenges to ambitious goals. *Ibid*: 522–3 (editorial).

Gastrology

Treatment of chronic hepatitis C

Current treatment for chronic hepatitis C is with ribavirin and either peginterferon alfa-2b or peginterferon alfa-2a. Standard and low-dose peginterferon alfa-2b and peginterferon alfa-2a (all with ribavirin) have been compared in a large US multicentre trial.

A total of 3070 patients with previously untreated chronic HCV genotype 1 infection were randomised to three 48-week treatment options: peginterferon alfa-2b 1.5 $\mu\text{g}/\text{kg}/\text{week}$ (standard dose), peginterferon alfa-2b 1.0 $\mu\text{g}/\text{kg}/\text{week}$ (low dose) or peginterferon alfa-2a 180 $\mu\text{g}/\text{week}$, all with daily ribavirin. Sustained virological response was achieved in 39.8% (standard dose peginterferon alfa-2b), 38.0% (low-dose), and 40.9% (peginterferon alfa-2a) – non-significant differences. Relapse rates were 23.5%, 20.0%, and 31.5% respectively. The safety profile was similar in the three groups. A sustained virological response was achieved in 86.2% of patients with undetectable HCV RNA at 4 weeks and 78.7% of those with undetectable levels at 12 weeks.

The results were similar for the three treatment regimens.

McHutchison JG et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *NEJM* 2009; 361: 580–93.

Laparoscopic fundoplication vs medical management for gastro-oesophageal reflux disease: cost-effectiveness

The REFLUX trial, reported in 2008, compared laparoscopic surgery with medical management in patients with

gastro-oesophageal reflux disease (GORD). Now data from that study have been used to assess cost-effectiveness in 45-year-old men using a mathematical model. The incremental cost-effectiveness ratio of surgery was £2648 per quality-adjusted life year (QALY). The probability that surgery is cost-effective was 0.94 at a threshold incremental cost-effectiveness ratio of £20000.

Laparoscopic surgery is cost-effective if clinical benefit persists in the medium to long term.

Epstein D et al. Laparoscopic fundoplication compared with medical management for gastro-oesophageal reflux disease: cost effectiveness study. *BMJ* 2009; 339: 152–5; Ford AC, Moayyedi P. Treatment of chronic gastro-oesophageal reflux disease. *Ibid*: 118–9 (editorial).

Infection

Swine 'flu in pregnancy

Influenza is more severe in pregnant than in non-pregnant women. Data about the severity of infection in pregnant women during the current pandemic of infection with H1N1 2009 influenza virus ('swine 'flu') have been reported from the US CDC.

Between April 15 and May 18 2009, a total of 34 confirmed or probable cases of pandemic H1N1 infection were reported from 13 states. Eleven women (32%) were admitted to hospital. The estimated rate of admission was 0.32 per 100000 pregnant women and 0.076 per 100000 in the general population, a significant difference. Between April 15 and June 16, six deaths from H1N1 infection were reported in pregnant women. The women died of pneumonia and acute respiratory distress syndrome. During this period there were 45 deaths in all from this infection.

Pregnant women are at increased risk of severe H1N1 infection and should be treated promptly with anti-influenza drugs.

Jamieson DJ et al. H1 N1 2009 influenza virus infection during pregnancy in the USA. *Lancet* 2009; 374: 451–8; Mangtani P et al. Pandemic H1N1 infection in pregnant women in the USA. *Ibid*: 429–30 (comment).

Severe respiratory disease from swine flu in Mexico

Two successive papers in the *New England Journal of Medicine* have described the features of swine-origin influenza A (H1N1) infection (swine flu,

S-OIV infection) in Mexico.

Between March 24 and April 29, 2009 a total of 2155 cases of severe pneumonia with 821 admissions to hospital and 100 deaths were reported. Of 8817 nasopharyngeal specimens, 2582 were positive for S-OIV. Older people were less likely to be affected than in previous influenza epidemics. Most deaths (87%) and cases of severe pneumonia (71%) were in people aged 5–59 years whereas in previous epidemics the corresponding proportions have been 17% and 32%. This age distribution suggested some immunity in older people, possibly because of exposure in previous pandemics such as the one in 1957. At the national hospital for respiratory diseases in Mexico City, 98 people were admitted with acute respiratory illness and 18 of these had pneumonia and S-OIV infection. Five of these 18 patients were aged 15 years or younger, 11 were between 15 and 50 years old, and only two were older than 50 years. Eight had pre-existing medical conditions. All 18 had fever, cough, dyspnoea or respiratory distress, bilateral patchy pneumonia, and increased serum lactate dehydrogenase levels. Twelve received mechanical ventilation and seven died. Twenty-two healthcare workers developed a mild or moderate influenza-like illness within 7 days of contact with these patients.

In March and April 2009 swine flu in Mexico affected a younger population than in previous influenza epidemics. Some patients had severe respiratory illness, including some young or middle-aged people who had previously been healthy. Seven of 18 severe cases died. Secondary infections in healthcare workers were not severe.

Chowell G et al. Severe respiratory disease concurrent with the circulation of H1N1 influenza. *NEJM* 2009; 361: 674–9; Perez-Padilla R et al. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. *Ibid*: 680–9.

Typhoid vaccine effectiveness

Most of the up to 600 000 deaths a year from typhoid fever occur in developing countries. The injectable Vi polysaccharide typhoid vaccine is cheap and could be used in developing countries but there are doubts about its effectiveness in young children and its ability to confer herd immunity. Now a study in Kolkata, India has provided reassurances on these scores.

A total of 37 673 people in the slums of Kolkata were randomised by cluster

(80 clusters) to i.m. Vi vaccine or hepatitis A vaccine (controls). Coverage was around 60% for each group. Typhoid fever occurred over a 2-year follow-up in 1.8 per 1000 (Vi vaccine) vs 5.1 per 1000 (controls). The protective effectiveness of the Vi vaccine was 61% overall: 80% among children aged 2–4 years, 56% among children aged 5–15 years, and 46% among subjects aged 16 years or older. There was 44% protection for unvaccinated people living in Vi vaccine clusters. There were no serious adverse events.

The Vi vaccine was protective for young children and provided herd immunity. Of the two typhoid vaccines available the Vi vaccine is given as a single i.m. dose and the Ty21a vaccine is given as three oral doses. The Vi vaccine provides no protection against paratyphoid and the oral vaccine protects against paratyphoid B but not paratyphoid A.

More use should be made of typhoid vaccines.

Sur D et al. A cluster-randomized effectiveness trial of Vi typhoid vaccine in India. *NEJM* 2009; 361: 335–44; Levine MM. Typhoid vaccines ready for implementation. *Ibid*: 403–5 (editorial).

Pulmonary

Roflumilast for COPD

Treatment of chronic obstructive pulmonary disease (COPD) is often with inhaled bronchodilators with or without inhaled steroid. Roflumilast is an inhibitor of phosphodiesterase-4 (PDE4) that reduces airway inflammation. Initial studies have suggested that roflumilast may reduce exacerbations in selected patients with COPD. Now a combined analysis of two identical international studies has shown that roflumilast has a beneficial effect.

A total of 3091 patients with severe COPD were randomised to oral roflumilast 500 µg daily or placebo, for 52 weeks. Prebronchodilator FEV1 increased by 48 ml with roflumilast compared with placebo, a highly significant difference. Moderate or severe exacerbations were reduced from a rate of 1.37 per year with placebo to 1.14 per year with roflumilast, also a highly significant difference. Adverse events, mainly diarrhoea, nausea, and headache, were more frequent in the roflumilast group.

Roflumilast had a beneficial effect. It is suggested that future research should

be aimed at defining subgroups of patients likely to respond to roflumilast.

In two other trials similar to the two described above patients were concomitantly treated with a long-acting inhaled bronchodilator (salmeterol in one trial and tiotropium in the other). In all, 1676 patients entered the two trials and were randomised to roflumilast or placebo. Compared with the placebo groups, the improvement in prebronchodilator FEV1 with roflumilast was 49 ml in those also taking salmeterol and 80 ml in those also taking tiotropium. Adverse events were similar to those in the first two trials.

Calverley PMA et al. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet* 2009; 374: 685–94; Fabbri LM et al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with long-acting bronchodilators: two randomised clinical trials. *Ibid*: 695–703; *The Lancet. COPD - more than just tobacco smoke*. *Ibid*: 663 (editorial); O'Byrne PM, Gauvreau G. Phosphodiesterase-4 inhibition in COPD. *Ibid* 665–7 (comment).

Assessing prognosis in COPD

The BODE (Body mass index, airway Obstruction, Dyspnoea, and Exercise capacity) index was described in 2004 as a prognostic index for patients with chronic obstructive pulmonary disease (COPD). Now data from Swiss and Spanish cohorts have been used to update the index.

The BODE index under-predicted 3-year mortality by 36% in the Swiss cohort and over-predicted mortality by 39% in the Spanish cohort. The BODE index was therefore updated using the Swiss data and validated in the Spanish cohort. A simple index for use in general practice was also developed (the ADO [Age, Dyspnoea, and airway Obstruction]) index. Both the updated BODE and ADO index gave accurate predictions of mortality in the Spanish cohort.

The new indices may aid assessment of prognosis in patients with COPD.

Puhan MA et al. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease; the updated BODE index and the ADO index. *Lancet* 2009; 374: 704–11; Schunemann H. From BODE to ADO to outcomes in multimorbid COPD patients. *Ibid*: 667–8 (comment).

No increase in pneumonia in COPD patients treated with budesonide

Several studies and a meta-analysis have suggested that use of inhaled steroid for patients with COPD might increase the risk of pneumonia. Now a meta-analysis of individual patient data

from seven large trials has shown no increased risk of pneumonia.

The analysis included 7042 patients; 3801 on inhaled budesonide and 3241 on control treatment. The risk of pneumonia was 3% in each group. Serious pneumonia occurred in 1% vs 2%, a non-significant difference. Time to pneumonia was similar in the two groups. Pneumonia was associated with increasing age and decreasing FEV1.

Treatment with budesonide appears to be safe for COPD patients.

Sin DD et al. Budesonide and the risk of pneumonia: a meta-analysis of individual patient data. *Lancet* 2009; 373: 712–9; Welte T. Inhaled corticosteroids in COPD and the risk of pneumonia. *Ibid*: 668–70

Cardiology

Tighter blood pressure control

The desirable strictness of control of systolic blood pressure in patients with hypertension is debated. A study at 44 centres in Italy has given support to the adoption of a lower target blood pressure.

A total of 1111 patients with a systolic blood pressure of at least 150mmHg and without diabetes were randomised to a target blood pressure of <130mmHg (tight control) or <140mmHg (usual control). Over an average follow-up of 2 years there were significantly greater reductions in both systolic and diastolic pressures in the tight-control group (mean reductions 27.3/10.4mmHg vs 23.5/8.9mmHg). Left ventricular hypertrophy on ECG at 2 years was recorded in 11.4% (tight) vs 17.0% (usual). The composite outcome of multiple cardiovascular endpoints was reached in 4.8% vs 9.4%.

A lower target systolic pressure than is often recommended may give better outcomes for non-diabetic patients with hypertension.

Verdecchia P et al. Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial. *Lancet* 2009; 374: 525–33; *The Lancet. Heart disease: breaking down barriers*. *Ibid*: 301 (editorial); Carlberg B. Time to lower treatment BP targets for hypertension? *Ibid*: 503–4 (comment).

Percutaneous closure of left atrial appendage to prevent stroke in atrial fibrillation

The risk of stroke among people with atrial fibrillation (AF) not taking anticoagulants is about 5% per year, increasing from 1.5% at ages 50–59 to 24% at

ages 80–89. Warfarin treatment is recommended but many patients are intolerant of it and the therapeutic range is often not achieved. Since the source of emboli is clots in the left atrial appendage (LAA) in >90% of patients without valvular heart disease closure of the LAA might be an alternative to long-term anticoagulant therapy. Now an international trial has provided support for the use of a percutaneously placed device for closure of the LAA.

A total of 707 patients with non-valvular AF were randomised 2:1 to insertion of the device and subsequent discontinuation of warfarin or treatment with warfarin (target ICR 2.0–3.0). The device used was a self-expanding frame structure with fixation bars and a permeable cover (the WATCHMAN device). It was inserted trans-septally via a catheter under fluoroscopic and transoesophageal echocardiographic guidance. After 1065 patient-years of follow-up the composite endpoint of stroke, cardiovascular death, or systemic embolism occurred in 3.0 per 100 patient-years in the intervention group and 4.9 per 100 patient-years in the control group. The probability that the intervention was non-inferior was >99.9%. There were more adverse events (including major bleeding, pericardial effusion, and device embolisation) in the intervention group (10.2% vs 6.8% after 2 years).

It is concluded that use of the device might be an alternative to long-term use of warfarin. Issues around antithrombotic prophylaxis after use of the device and the reduction of periprocedural complications need to be addressed.

Holmes DR et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009; 374: 534–42; *The Lancet. Heart disease: breaking down barriers*. *Ibid*: 501 (editorial) McCabe JH et al. Left atrial appendage occlusion in non-valvular atrial fibrillation. *Ibid*: 504–6 (comment).

Albuminuria in chronic heart failure

Albuminuria is a risk factor for overall mortality, cardiovascular events, and renal failure in the general population and specifically in patients with diabetes or hypertension. Now a study in North America has shown that albuminuria is a predictor of poor prognosis in patients with chronic heart failure.

Urine albumin to creatinine ratio (UACR) was measured at baseline and subsequently in 2310 patients with New York Heart Association class II to IV heart

failure. Among these patients, 58% had a normal UACR, 30% had microalbuminuria, and 11% had macroalbuminuria. Patients with albuminuria had more cardiovascular comorbidity, worse renal function, and a higher prevalence of diabetes than those without albuminuria. The prevalence of albuminuria was high even without diabetes, hypertension, or renal dysfunction. Raised UACR was independently associated with the composite outcome of overall or cardiovascular mortality or worsening heart failure. Microalbuminuria and macroalbuminuria increased the risk of the composite outcome by 43% and 75% respectively, a highly significant increase in each case. Mortality was increased by 62% and 76% respectively. Treatment with candesartan did not reduce the risk of albuminuria.

Albuminuria is a strong and independent predictor of poor prognosis in patients with heart failure.

Jackson CE et al. Albuminuria in chronic heart failure: prevalence and prognostic importance. *Lancet* 2009; 374: 543–50; *The Lancet. Heart disease: breaking down barriers*. *Ibid*: 501 (editorial); Damman K et al. Albuminuria in heart failure: a CHARMing new risk factor? *Ibid*: 506–8 (comment).

Psychology

Diagnosis of depression in primary care

A World Health Organization (WHO) study of depression in 14 countries showed a prevalence of 14%. Some 15–60% of people with depression receive appropriate treatment. In general practice depression is often under-diagnosed but it may also be over-diagnosed. Now a meta-analysis has provided an assessment of the accuracy of diagnosis in general practice.

The analysis included 41 studies (50371 patients) of depression in general practice. Depression was correctly diagnosed in 47.3% of cases and recorded in the notes in 33.6%. From 19 studies with adequate information the weighted sensitivity was 50.1% and specificity 81.3%. At a rate of 21.9% the positive predictive value was 42.0% and the negative predictive value 85.3%. A motivated GP in an urban practice with a depression rate of 20%, on seeing 100 patients would correctly diagnose depression in 10, miss the diagnosis in 10, correctly diagnose 65 patients as not being depressed, and make an incorrect diagnosis of

depression in 15. Accuracy of diagnosis was improved by assessment over 3–12 months rather than a single consultation.

Over-diagnosis is more common than under-diagnosis.

Mitchell AJ et al. Clinical diagnosis of depression in primary care: a meta-analysis. *Lancet* 2009; 374: 609–19; *The Lancet. Movement for global mental health gains momentum*. Ibid: 587 (editorial); Tyrer P. Are general practitioners really unable to diagnose depression? Ibid: 589–90 (comment).

Antidepressants and suicidal thoughts and behaviour

Antidepressant drugs may increase the risk of suicidal thoughts and behaviour (suicidality) in children and adolescents. Whether the same applies to adults is uncertain. Now a meta-analysis has emphasised the effect of age.

The analysis included 372 trials and 99231 adults assigned to antidepressant or placebo. Among people treated for non-psychiatric conditions there was no relationship between treatment and suicidality. Among young adults (<25 years) treatment for psychiatric illness with an antidepressant rather than placebo increased the risk of suicidal behaviour or ideation by 62% and of suicidal behaviour by a factor of 2.3. At ages 25–64 there was no increase in risk of suicidal behaviour and possibly a protective effect against suicidal ideation, and at age 65 or older treatment reduced both risks.

Antidepressant treatment increases suicidality risk in people <25 years old, has little effect at ages 25–64, and is protective at 65 years or older. There may be differences between different antidepressants.

Stone M et al. Risk of suicidality in clinical trials of antidepressives in adults: analysis of proprietary data submitted to US Food and Drug Administration. *BMJ* 2009; 339: 431–4; Geddes JR et al. Risk of suicidal behaviour in adults taking antidepressants. Ibid: 411–2.

Neurology

Encouraging physical activity after stroke: may not help

Physical activity is often recommended after stroke although its effect is uncertain. Now a trial in Denmark, China, Poland, and Estonia has shown no benefit from a programme encouraging physical activity.

A total of 314 patients who were ambulant after ischaemic stroke were randomised to intervention or control groups. The intervention consisted of a training programme encouraging physical activity with sessions before hospital

discharge and at five follow-up visits over the next 2 years. Control patients had the same number of visits but without the training programme. Physical activity as assessed with the Physical Activity Scale for the Elderly (PASE) did not differ significantly between the two groups. There were no significant differences in rates of mortality, recurrent stroke, myocardial infarction, or falls and fractures.

The programme did not increase physical activity.

Boysen G et al. ExStroke Pilot Trial of the effect of repeated instructions to improve physical activity after ischaemic stroke: a multinational randomised controlled clinical trial. *BMJ* 2009; 339: 273–6; Mead G. Exercise after stroke. Ibid: 247–8 (editorial).

Oncology

Letrozole in breast cancer

There is still uncertainty about the best ways to use tamoxifen and/or an aromatase inhibitor in the adjuvant treatment of hormone-receptor-positive early breast cancer. First results from the international BIG 1–98 study showed that letrozole (an aromatase inhibitor) alone gave better results than tamoxifen alone. Now letrozole alone (L) has been compared with tamoxifen alone (T), letrozole for 2 years then tamoxifen for 3 years (LT), and tamoxifen for 2 years then letrozole for 3 years (TL).

A total of 6182 postmenopausal women were randomised to one of the four options. After an average follow-up of 71 months there was no significant difference in disease-free survival for either LT or TL compared with L. There were more early relapses with TL compared with L. In an updated analysis of T v L monotherapy the 5-year overall survival rate was 90.9% (T) vs 91.8% (L), a non-significant 13% increase in mortality with tamoxifen. Time to distant recurrence was greater with letrozole.

Neither letrozole followed by tamoxifen nor tamoxifen followed by letrozole improved disease-free survival compared with letrozole alone. There was no significant difference in overall survival between letrozole or tamoxifen monotherapies.

The BIG 1–98 Collaborative Group. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. *NEJM* 2009; 361: 766–76.

Weight lifting for women with breast-cancer-related lymphoedema

Lymphoedema of the arm may be a chronic problem after breast cancer surgery, more often after axillary dissection

than after sentinel node biopsy. Lifting heavy objects with the affected arm is often proscribed but controlled weight lifting might be beneficial. Now researchers have confirmed this benefit.

A total of 141 patients with breast-cancer-related lymphoedema were randomised to twice weekly progressive weight lifting for 1 year or to a control group. A 'compression garment' was worn while weight lifting. The amount of limb swelling remained similar in the two groups. Lymphoedema exacerbations occurred in 14% (weight lifting) vs 29% (controls). The weight-lifting group had more improvement in lymphoedema-related symptoms and in upper and lower-body strength.

A programme of progressively increasing weight lifting had no effect on limb swelling but it did reduce symptoms and the rate of exacerbations of lymphoedema and increase muscle strength.

Schmitz KH et al. Weight lifting in women with breast-cancer-related lymphoedema. *NEJM* 2009; 361: 664–73; Demark-Wahnefried W. A weighty matter – lifting after breast cancer. Ibid: 710–1 (editorial).

Denosumab with androgen-deprivation therapy

Androgen-deprivation therapy, used in the treatment of prostate cancer, is associated with bone loss and increased risk of fracture. Denosumab is a human monoclonal antibody against the receptor activator of nuclear factor- κ B ligand that mediates the formation, function, and survival of osteoclasts and increases bone density. Researchers in North America and Europe have shown that denosumab may benefit men who are receiving androgen-deprivation therapy for prostate cancer.

A total of 1468 men on androgen-deprivation therapy for nonmetastatic prostate cancer were randomised at 156 centres to denosumab 60mg s.c. every 6 months or placebo. Bone mineral density of the lumbar spine at 2 years had increased by 5.6% in the denosumab group and decreased by 1.0% in the placebo group. The benefit of denosumab on BMD was measurable at 1 month and persisted at 36 months. BMD also increased significantly at the hip, femoral neck, and distal radius. The incidence of new vertebral fractures at 36 months was 1.5% (denosumab) vs 3.9% (placebo). Adverse event rates were similar in the two groups.

Denosumab may prevent fractures in men on androgen-deprivation therapy.

Smith MR et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *NEJM* 2009; 361: 745–55; Khosla S. Increasing options for the treatment of osteoporosis. Ibid: 818–20.