

## General

### Reporting of clinical trials: missing data and effect on meta-analyses

The January 7, 2012 issue of the *BMJ* includes six papers about the reporting, misreporting, or non-reporting of clinical trials.

Forty-two meta-analyses of drug trials (nine drugs, six drug classes, 41 efficacy outcomes, one harm outcome) were re-analysed after the inclusion of previously unpublished data obtained from the US Food and Drug Administration (FDA). The reanalyses showed less drug efficacy in 19 cases, greater drug efficacy in 19, and unchanged drug efficacy in three. The absence of unpublished data from drug trial meta-analyses may affect the conclusion in either direction.

In 2005, prior registration of all trials became a condition for later publication. A study of 635 trials funded by the US National Institutes of Health and registered within ClinicalTrials.gov has shown that the results of many trials are not published promptly. Only 294 (46%) were published in a Medline-index peer-reviewed biomedical journal within 30 months of trial completion. After a median follow-up of 51 months 432 (68%) had been published and the median time to publication was 23 months. There is some evidence, though, that things are improving since the proportion of trials published within 30 months of study completion was 36% for trials completed before 2007 and 54% for trials completed in 2007 or 2008.

The US FDA amendments Act of 2007 makes it necessary to publish a results summary on ClinicalTrials.gov but the law is not being complied with. Of 738 trials completed in 2009 and subject to mandatory reporting, only 163 (22%) had reported results within a year. Among trials not subject to mandatory reporting the number reported was even less (76/727; 10%). Trials funded by industry were more likely to have been reported (40% vs 9%), as were later phase studies.

Meta-analyses using individual patient data may be subject to biases in publication, availability, and selection and these may falsely increase the impression of positive treatment effects. A review of 31 recent meta-analyses of drug trials showed that only nine included individual patient data from 'grey literature' (such as unpublished studies)

in the primary meta analysis and only 10 (32%) discussed the potential for publication bias. In 16 of the 31 meta-analyses not all of the individual patient data requested had been provided but only 11 of the 16 mentioned this as a potential problem and only six discussed how the trial conclusion could be affected by absent data. In nine of the 231 meta-analyses the identification of relevant trials was either not explained or based on a selective, non-systematic approach, raising the possibility of reviewer selection bias. The potential for all of these biases is a cause of concern about the reliability of some meta-analyses.

Even use of Medline may have its problems. Between 1994 and 2006 the Cochrane Collaboration and the US National Library of Medicine collaborated to 'retag' records of randomised controlled trials that were not indexed with RCT [pt]. It has been found that, since the retagging project ended in 2006, anybody relying on RCT[pt] to search for randomised controlled trial data may miss important evidence. It is estimated that at least 3000 records describing randomised controlled trials but not indexed as such may have been entered into Medline between 2006 and 2011. Use of validated search strategies is essential.

Finally, three types of reporting have been examined and two of them have been found to be potentially inadequate. Reports in trial results registries and in journals may provide insufficient information for complete evaluation of the studies. Of 268 studies examined, details were published in journals for 72%, in registry reports for 29%, and in study reports submitted to regulatory authorities for 38%. The highest quality of reporting was in study reports for regulatory authorities where complete information was provided for 90% of items considered necessary. By contrast journal publications and registry reports provided complete information for only 46% and 51% of items respectively.

Changes are needed in the functioning and monitoring of systems for the reporting of clinical trials. Concealment of data must be regarded as serious professional misconduct subject to disciplinary action by professional organisations.

Hart B et al. Effect of reporting bias on meta-analysis of drug trials: reanalysis of meta-analyses. *BMJ* 2012; 344 (Jan7): 13 (d7202); Ross JS et al. Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis. *Ibid*: 14 (d7292); Prayle AP et al. Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study. *Ibid*: 15 (d7373); Ahmed I et al. Assessment of

publication bias, selection bias, and unavailable data in meta-analyses using individual participant data: a database survey. *Ibid*: 16 (d7762); Wieland LS et al. Understanding why evidence from randomised clinical trials may not be retrieved from Medline: comparison of indexed and non-indexed records. *Ibid*: 17 (d7501); Wieseler B et al. Impact of document type on reporting quality of clinical drug trials: a comparison of registry reports, clinical study reports, and journal publications. *Ibid*: 18 (d8141); Chan A-W. Out of sight-but not out of mind: how to search for unpublished clinical trial evidence. *Ibid*: 19-22 (d8013) (research methods and reporting); Lehman R, Loder E. Missing clinical trial data. *Ibid*; 7-8 (d8158) (editorial).

### At what age does cognitive decline begin?

There is uncertainty about the age at which cognitive decline begins in the population. Much of the evidence is based on cross-sectional data that may not be reliable for this purpose. The Whitehall II prospective cohort study began in 1985-1988 and included 10308 civil servants in London. Cognitive testing began in 1997-1999 when there were 9250 people still in the study. Cognitive testing (memory, reasoning, vocabulary, phonemic and semantic fluency) was performed on 7390 people aged 45-70 at the start of 10 years of follow-up. Testing was done three times, in 1997-1999, 2002-2004, and 2007-2009. Over a period of 10 years there was significant decline in test scores for all modalities except vocabulary and this decline occurred in all age groups including those aged 45-49 at the first testing session. Decline was greater at older ages.

The belief that cognitive decline does not occur until after the age of 60 was derived mainly from evidence based on cross-sectional studies. This longitudinal study shows that cognitive decline may begin in the late 40s or even earlier.

Singh-Manoux A et al. Timing of onset of cognitive decline: results from Whitehall II prospective cohort study. *BMJ* 2012; 344 (Jan 21): 18 (2011); 343: d7622); Grodstein F. How early can cognitive decline be detected? *Ibid*: 10 (d7652) (editorial).

### Management of diabetes and hypertension by rural healthcare workers in Iran

In high-income countries the incidence of cardiovascular and some other non-communicable diseases has decreased after population aging has been accounted for. Dietary and lifestyle interventions, decrease in smoking, and better control of blood pressure and cholesterol levels may have played a considerable part. The prevalence of cardiovascular risk factors has changed little, however, in low- and middle-income countries. Little is known

about optimal method of providing primary care, especially in rural areas, and its influence on non-communicable disease in poorer countries. A rural primary care system in Iran, the Behvarz system, has been assessed.

In the Behvarz system, rural primary care is provided by community health workers, who are community members who, having been educated to at least a primary level, are given 2 years of medical education after passing an entrance examination. Survey and census data for 2005 and 2006 were used to assess the contribution of Behvarz workers (BW) to diabetes and hypertension control.

From the Non-Communicable Disease Surveillance Survey (NCDSS) of 2005 data for systolic blood pressure (SBP) were available for 64 694 adults (11 521 in rural areas) and for fasting plasma glucose (FPG) for 50 202 (9 337 in rural areas). Overall, 39% of people with diabetes and 36% with hypertension were receiving treatment (more likely in women and in urban areas). On average, treatment in rural areas lowered FPG by 1.34 mmol/L and SBP by 2.5 mmHg. In urban areas the corresponding reductions were 0.21 mmol/L and 3.8 mmHg. A single additional BW per 1000 adults was associated with a significant 0.09 mmol/L lowering of district-level average FPG but did not reduce SBP significantly.

These researchers conclude that primary care systems with trained community health-care workers and well-established guidelines can be effective in non-communicable disease prevention and management.

Farzadfar F et al. Effectiveness of diabetes and hypertension management by rural primary health-care workers (Behvarz workers) in Iran: a nationally representative observational study. *Lancet* 2012; 379: 45–54; Habibzadeh F. The control of non-communicable diseases in Iran. *Ibid*: 6–7 (comment).

### Autoimmune disorders and pulmonary embolism

In the USA, the incidence of acute pulmonary embolism is about 1 in a thousand people per year and mortality within 3 months is >15%, similar to that of myocardial infarction. Autoimmune disorders such as inflammatory bowel disease, Behçet's syndrome, rheumatoid arthritis, celiac disease, type-1 diabetes, systemic lupus erythematosus, hyperthyroidism, and Wegener's granulomatosis have been associated with increased risk of venous thromboembolism. Data from Swedish national registries have been used to assess the risk of pulmonary

embolism in people with autoimmune disorders.

Between 1964 and 2008 a total of 535 538 people were admitted to hospital with one of 33 autoimmune disorders. The risk of pulmonary embolism in the first year after hospital admission for an autoimmune disorder was 6.38%. Each of the 33 disorders was associated with significantly increased risk of pulmonary embolism during the year after admission. The risk was highest with polymyositis or dermatomyositis (standardised incidence ratio, 16.44), polyarteritis nodosa (13.26), immune thrombocytopenia purpura (10.79), ulcerative colitis (10.26), and systemic lupus erythematosus (10.23). The risks decreased with time but were increased in both sexes and at all ages.

The risk of pulmonary embolism is increased after hospital admission for an autoimmune disorder, particularly in the first year. These disorders should be regarded as hypercoagulability disorders. Prophylaxis might be indicated in some cases.

Zöller B et al. Risk of pulmonary embolism in patients with autoimmune disorder: a nationwide follow-up study from Sweden. *Lancet* 2012; 379: 244–9; Sanjeevi CB. Autoimmune diseases and risk of pulmonary embolism. *Ibid*: 200–1 (comment).

## Tropical

### Mass azithromycin treatment for trachoma: once or twice a year?

Mass treatment with azithromycin is effective in trachoma hyperendemic communities. WHO recommends three annual mass treatments before reassessment in districts with clinically active trachoma in 10% or more of children aged 1–9 years. It is not known whether more frequent mass treatments (twice a year) would be more effective. A cluster-randomised trial has been reported from a hyperendemic region of Ethiopia.

Twenty-four sub-districts in northern Ethiopia were randomised to treatment of all residents of all ages with azithromycin (20 mg/kg for children, 1 g for residents >15 years old) either once or twice a year. Infants, pregnant women, people allergic to azithromycin, and people who refused azithromycin were offered a 6-month course of topical 1% tetracycline ointment as an alternative. More than 80% of children aged 0–9 years were treated at each study visit. In the annual treatment districts the prevalence of *C. trachomatis* infection among

children aged 0–9 years fell from 42% at baseline to 2% at 42 months. In the twice-yearly treatment districts the decrease was from 38% to 3%. There was no significant difference in ocular chlamydial infection rates between the two groups at 18, 30, and 42 months. The mean elimination time was 7.5 months shorter in the twice-yearly group.

Annual and twice-yearly treatments were equally effective but elimination of the infection was quicker with twice-yearly treatment.

Gebre T et al. Comparison of annual versus twice-yearly mass azithromycin treatment for hyperendemic trachoma in Ethiopia: a cluster-randomised trial. *Lancet* 2012; 379: 143–51. Gower EW. Solving the trachoma elimination puzzle, one piece at a time. *Ibid*: 102–3 (comment).

## Gastrology

### New drugs for chronic hepatitis C genotype 1

Treatment of chronic hepatitis C virus (HCV) infection with peginterferon alpha and ribavirin for 48 weeks achieves a sustained virological response at 24 weeks after stopping treatment in 40–50% of patients. Adding a protease inhibitor to treatment for nonresponders after 12 weeks of treatment produces a sustained virological response in 14–33%. Now a multicentre phase 2 study in the USA has shown that use of two new antiviral agents may improve results. Daclatasvir is an HCV NS5A replication complex inhibitor and asunaprevir is an HCV NS3 protease inhibitor.

The trial included 21 patients with chronic HCV genotype 1 infection unresponsive to treatment with peginterferon and ribavirin for 12 weeks. Randomisation was to daclatasvir plus asunaprevir with (DAPR) or without (DA) peginterferon plus ribavirin. In the DA group 4 of 11 patients achieved a sustained virological response at 12 and 24 weeks after treatment. In the DAPR group all 10 patients had a sustained virological response at 12 weeks and nine at 24 weeks. In the DA group six patients had viral breakthrough on treatment and in all six cases there were resistance mutations to both daclatasvir and asunaprevir. Diarrhoea was common in both groups and six patients had transient rises in alanine aminotransferase levels.

Adding daclatasvir and asunaprevir to peginterferon and ribavirin achieved sustained virological response in patients who had not responded initially to

peginterferon and ribavirin alone.

Lok AS et al. Preliminary study of two antiviral agents for hepatitis C genotype 1. *NEJM* 2012; 366: 216–24; Chung RT. A watershed moment in the treatment of hepatitis C. *Ibid*: 273–5 (editorial).

### Non-alcoholic fatty liver disease in the USA: no increase in mortality

The prevalence of obesity has increased rapidly around the world and with it that of non-alcoholic fatty liver disease (NAFLD). The diagnosis of NAFLD depends on ultrasound scanning of the liver (increased echogenicity) and increased levels of liver enzymes. Disease severity ranges from simple steatosis with little or no increase in mortality to non-alcoholic steatohepatitis with increased risk of cardiovascular and potentially fatal liver disease. Now US workers have sprung a surprise by reporting a cohort study showing no increase in mortality in patients with either simple hepatic steatosis or non-alcoholic steatohepatitis.

They analysed data from the third National Health and Nutrition Examination Survey (NHANES III) cohort of 1988–1994. Cohort members were aged 20–74 and median follow-up was for 14.5 years. NAFLD was categorised as simple steatosis (moderate to severe hepatic steatosis with normal liver enzyme levels) or non-alcoholic steatohepatitis (with raised liver enzyme levels, no hepatitis B or C antibodies, and no iron overload). The overall prevalence of NAFLD in this cohort was 19.5%, 16.4% without and 3.1% with steatohepatitis. NAFLD was associated with older age, male sex, Mexican-American ethnicity, poor education, sedentary lifestyle, increased waist circumference, diabetes, hypercholesterolaemia, hypertension, cardiovascular disease, low-to-moderate alcohol consumption, and current non-smoking. At the end of the follow-up, all cause mortality was 22%. Cause-specific mortalities were 10.9% (cardiovascular), 6.0% (cancer), and 0.5% (liver disease). There were no significant differences in overall or disease-specific mortality between people without hepatic steatosis and people with either simple non-alcoholic hepatic steatosis or non-alcoholic hepatic steatohepatitis.

This study did not show increased mortality with non-alcoholic liver disease, either simple steatosis or steatohepatitis. *BMJ* editorialists point out that some cohort members may not have been diagnosed as having NAFLD at baseline but may have developed it later and died of it, causing the mortality from

this cause to be underestimated. Cases may also have been misclassified in the absence of liver biopsy. They suggest that the results should be interpreted with caution. Future studies should attempt to distinguish more reliably between simple steatosis and steatohepatitis.

Lazo M et al. Non-alcoholic fatty liver disease and mortality among US adults: prospective cohort study. *BMJ* 2011; 343: 1245 (d6891); Jepsen P, Grønbaek H. Prognosis and staging of non-alcoholic fatty liver disease. *Ibid*: 1236 (d7302)

## Infection

### Herpes simplex vaccine

Herpes simplex viruses 1 and 2 (HSV-1 and HSV-2) both cause genital infections and HSV-1 infections are increasingly prevalent. Transmission from mother to newborn infant may cause severe disease. Trials of an HSV-2 glycoprotein D-based subunit (gD-2) vaccine have shown around 75% efficacy against HSV-2 disease among women seronegative for both HSV-1 and HSV-2 antibodies. Now a trial in the USA and Canada has surprisingly shown efficacy against HSV-1 genital disease but not HSV-2 disease.

The trial included 8323 women aged 18–30 years who were doubly seronegative (HSV-1 and HSV-2). Randomisation was to the HSV-2 glycoprotein D vaccine with alum and 3-0-deacylated monophosphoryl lipid A as an adjuvant or hepatitis A vaccine, at months 0, 1, and 6. The HSV-2 vaccine induced ELISA and neutralising antibodies to HSV-2. The vaccine efficacy was only 20% against any genital herpes simplex infection but 58% against HSV-1 genital disease. Against HSV-1, infection with or without disease, efficacy was 35%. There was no efficacy (-8%) against HSV-2 infection.

The HSV-2 vaccine was effective against HSV-1 genital disease but not against HSV-2 infection; the reasons are unexplained. An HSV vaccine suitable for general use is not yet available.

Belshe RB et al. Efficacy results of a trial of a herpes simplex vaccine. *NEJM* 2012; 366: 34–43.

### Vaccine against norovirus infection

Noroviruses are a cause of both epidemic and sporadic acute gastroenteritis. The viruses have not been grown in culture, making the development of a vaccine difficult. Norwalk virus, the cause of a school outbreak in 1968, is the best-studied norovirus and susceptibility to

it is genetically controlled. A vaccine consisting of norovirus-like particles (VLPs) has been tested on volunteers in the USA.

Ninety-eight healthy people aged 18–50 years were randomised to intranasal administration of the VLP vaccine, with chitosan and monophosphoryl lipid A adjuvants, or placebo, in two doses 3 weeks apart. All participants had a functional FUT2 gene and were therefore susceptible to Norwalk virus infection. Three weeks after the second dose they were challenged with oral Norwalk virus. A virus-specific IgA seroresponse occurred in 70% of vaccine recipients. Norwalk virus gastroenteritis occurred after challenge in 37% in the vaccine group and 69% of the placebo group and Norwalk virus infection in 82% vs 61%. There was no excess of adverse events in the vaccine group.

The norovirus VLP vaccine was protective and safe. More work is needed to produce a norovirus vaccine for clinical use, probably involving a multivalent vaccine against both GI and GII strains.

Atmar RL et al. Norovirus vaccine against experimental human Norwalk virus illness. *NEJM* 2011; 365: 2178–87.

## AIDS

### Extended nevirapine for breast-feeding infants of HIV-infected mothers

Although breastfeeding is essential in sub-Saharan Africa for the infant's nutrition and protection from infection, prolonged breastfeeding may lead to mother-to-child transmission of HIV-1. Antiretroviral therapy is given to protect against antenatal and intrapartum HIV transmission but prolonged prophylaxis during breastfeeding has been difficult to achieve in many countries. Now successful prophylaxis during breastfeeding has been reported from South Africa, Tanzania, Uganda, and Zimbabwe.

The study included 1527 breastfeeding infants of HIV-1-positive mothers. The infants received oral nevirapine suspension for the first 6 weeks. Those who were HIV-negative at 6 weeks were then randomised to continued nevirapine, or placebo, until the age of 6 months or until stopping breastfeeding. Between the ages of 6 weeks and 6 months HIV-1 infection was acquired by 1.1% in the extended nevirapine group and 2.4% in the placebo group, a significant 54%

improvement with extended nevirapine. At 6 months of age, mortality, combined mortality and HIV-1 infection, and severe adverse event rates, were similar in the two groups.

Extended nevirapine prophylaxis given to the breastfeeding infant is effective for at least 6 months. It should be used along with other provisions such as routine HIV screening in pregnancy, and antiretroviral interventions during pregnancy, labour, and delivery.

Coovadia HM et al. Efficacy and safety of an extended nevirapine regimen in infant children of breastfeeding mothers with HIV-1 infection for prevention of postnatal HIV-1 transmission (HPTN 046): a randomised, double-blind, placebo-controlled trial. *Lancet* 2012; 379: 221–8.

## Psychiatry

### Self-harm in adolescents and young adults

A population-based, cohort study in the state of Victoria, Australia has provided needed information about the natural history of nonfatal self-harm in adolescence and early adulthood.

A total of 1943 unselected adolescents from 44 schools entered the study between August 1992 and January 2008. Follow-up was in seven waves from a mean age of 15.9 years to a mean age of 29.0 years. Throughout adolescence, 8% of subjects (10% of girls and 6% of boys) reported self-harm but the rate fell during adolescence, from 6.5% to 2.5% (girls) and from 3.6% to 0.3% (boys) between mean ages of 15.9 years and 17.4 years. Self-harm with suicidal intent was reported by 1.4% of adolescent girls and 0.2% of adolescent boys. The most common types of self-harm in adolescence were cuts or burns, poison or overdose, self-battery, and 'risk taking'. Among young adults the rates of self-harm fell from 2.2% to 0.3% (women) and from 1.1% to 0.8% (men) between mean ages of 20.7 years and 29.0 years. Self-harm with suicidal intent was reported by 0.6% of both sexes. The modes of self-harm were similar to those in adolescence. Adolescent self-harm was associated with symptoms of depression and anxiety, antisocial behaviour, high-risk use of alcohol, cannabis use, and cigarette smoking. Adolescents with symptoms of depression and anxiety were six times more likely than adolescents without these symptoms to harm themselves as young adults.

Detecting and treating depression

and anxiety in adolescents could prevent some young adult suicides but most adolescents who harm themselves do not go on to do so as young adults.

Moran P et al. The natural history of self-harm from adolescence to young adulthood: a population-based cohort study. *Lancet* 2012; 379: 236–43; Hawton K, O'Connor R. Self-harm in adolescence and future mental health. *Ibid*: 198–9 (comment).

## Obs & Gyn

### Hydatidiform mole, hCG concentrations, and chemotherapy

In the UK, hydatidiform moles constitute between 1 and 3 of every 1000 pregnancies but they are more common in east Asia. They are more common in younger (<16 years) and older (>45 years) women. Molar pregnancies present with vaginal bleeding in the first trimester and levels of human chorionic gonadotropin (hCG) in serum and urine are raised. Following dilatation and curettage hCG levels return to normal in about 92% of cases. Malignant transformation occurs in about 15% of cases after complete hydatidiform mole and 0.5–1% after partial hydatidiform mole. Chemotherapy, usually with methotrexate or dactinomycin, is then necessary. All women with a hydatidiform mole in the UK are referred for hCG monitoring and surveillance to one of three national centres in Dundee, Sheffield, and London. Post-mole gestational trophoblastic neoplasia is suspected when hCG levels plateau or increase or remain raised at 6 months though falling. Evidence suggests, however, than an increased but falling hCG level at 6 months after uterine evacuation may not necessarily necessitate chemotherapy. A retrospective study at a single hospital in London, England has added support to this suggestion.

The study included 13960 women with a diagnosis of hydatidiform mole between January 1993 and May, 2008. Among these women, 76 (<1%) had persistently high (>5IU/L) hCG levels at 6 months. Sixty-six of these patients continued under surveillance and hCG levels returned to normal without chemotherapy in 65 (98%). The one patient whose hCG levels remained high had chronic renal failure as a cause of the high levels and remained otherwise well. Ten patients received chemotherapy and hCG levels returned to normal in eight of them (80%). The remaining two patients had persistent slightly high (6–11 IU/L)

levels but there were no associated clinical problems off treatment. There were no deaths and outcomes were similar with or without chemotherapy.

These researchers conclude that a policy of continued surveillance without chemotherapy seems acceptable for patients with raised (not very high) but falling hCG levels at 6 months after evacuation of a hydatidiform mole.

Agarwal R et al. Chemotherapy and human chorionic gonadotropin concentrations 6 months after uterine evacuation of molar pregnancy: a retrospective cohort study. *Lancet* 2012; 379: 130–5; Cheung ANY, Chan KKL. Perplexing hCG profile after evacuation of hydatidiform mole. *Ibid*: 98–100 (comment).

### Effectiveness of trained traditional birth attendants

Traditional birth attendants are in charge at many births in developing countries and giving them extra training and resources can improve obstetric and neonatal outcomes. A meta-analysis of six randomised controlled trials and seven non-randomised studies has confirmed that training these workers results in improved results.

A total of 138549 patients were included in the randomised trials that assessed the effects of training and support for traditional birth attendants. Meta-analysis showed significant reductions of 24% in perinatal mortality and 21% in neonatal mortality after such training and support. The non-randomised trials included 72225 patients. Meta-analysis showed significant reductions of 30% in perinatal mortality and 39% in neonatal mortality. Meta-analysis of six studies of maternal mortality showed a non-significant reduction of 20% after training and support of traditional birth attendants.

Training and support of traditional birth attendants in developing countries improves outcomes according to the type and extent of training and support provided. Perinatal, neonatal, and maternal mortalities may all be improved.

Wilson A et al. Effectiveness of strategies incorporating training and support of traditional birth attendants on perinatal and maternal mortality: meta-analysis. *BMJ* 2012; 344 (Jan21): 16 (2011); 343: d7102; Hodnett E. Traditional birth attendants are an effective resource. *Ibid*: 9 (e365) (editorial).

## Pulmonary

### I.V. $\beta$ -2 agonist in ARDS – unsafe

Acute respiratory distress syndrome (ARDS) has a mortality of around 50% with persisting morbidity in survivors.  $\beta$ 2

agonists have several pharmacological effects that might be beneficial in ARDS, in particular in maintaining alveolar-capillary integrity and reducing the risk of alveolar flooding. In a trial reported in 2006, 7 days of i.v. salbutamol reduced extravascular lung water and plateau airway pressure. Now a UK trial has shown increased mortality at 28 days with salbutamol treatment.

At 46 intensive care units between December 2006 and March 2010 a total of 326 intubated and mechanically ventilated adults were randomised within 72 hours of ARDS onset to i.v. infusion of Salbutamol (15 µg per kg ideal body-weight per hour) or placebo infusion, for up to 7 days. Recruitment was stopped early because of poor results in the salbutamol group. Mortality at 28 days was 34% (salbutamol) vs 23% (placebo), a significant 47% increase in risk with salbutamol.

These researchers conclude that routine use of β-2 agonist treatment in ventilated patients with ARDS cannot be recommended.

Smith FG et al. Effect of intravenous β-2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, randomised controlled trial. *Lancet* 2012; 379: 229–35; Thomspon BT. β-agonists for ARDS: the dark side of adrenergic stimulation? *Ibid*: 196–8 (comment).

## Cardiology

### Stroke risk with sub-clinical atrial fibrillation

About 15% of strokes are attributed to known atrial fibrillation (AF) but AF may be asymptomatic and undetected. In about 25% of cases of ischaemic stroke the cause remains unknown. The results of a multinational study have suggested that in some of these cases the cause may be undetected AF.

The study, in 23 countries, included 2580 patients aged 65 years or older with hypertension and no history of AF. They had all recently received an implanted pacemaker or defibrillator. Patients were monitored for 3 months for episodes of subclinical atrial tachyarrhythmia (atrial rate >190 beats per minute for >6 minutes) indicative of AF. Mean follow-up was for 2.5 years. At 3 months subclinical atrial tachycardia had occurred in 261 patients (10%). The occurrence of subclinical atrial tachyarrhythmia was associated with a 5.6-fold increase in risk of clinical AF and a 2.5-

fold increase in risk of ischaemic stroke or systemic embolism. Fifty-one patients had an ischaemic stroke or systemic embolism and 11 of them had had subclinical atrial tachyarrhythmia on monitoring in the first 3 months. None had had clinical AF during that time. The population attributable risk of stroke or systemic embolism associated with subclinical atrial tachyarrhythmia was 13%.

Subclinical AF may explain many strokes of which the cause is not apparent. Healey JS et al. Subclinical atrial fibrillation and the risk of stroke. *NEJM* 2012; 366: 120–9; Lamas G. How much atrial fibrillation is too much atrial fibrillation? *Ibid*: 178–80 (editorial).

### Cardiac arrest in marathons

Long-distance races have become more popular. In the last decade participation in marathons and half-marathons in the USA has doubled from 1 million to 2 million participants. The occurrence of sudden death among the competitors has attracted media attention. Now a US study has shown a cardiac arrest rate of 0.54 per 100 000 runners.

The study included 10.9 million runners who took part in marathon or half-marathon races between January 1, 2000 and May 31, 2010. There were 59 cases of cardiac arrest (51 men, 8 women, mean age 42 years), 0.54 per 100 000 participants (1.01 per 100 000 in marathons, 0.27 per 100 000 in half-marathons, a significant difference). Men were at greater risk than women (0.90 vs 0.16 per 100 000). The risk to male marathon runners increased during the later years of the study (0.71 per 100 000 in 2000–2004 and 2.03 per 100 000 in 2005–2010). Cardiac arrest was fatal in 71% of cases. Among 31 cases with adequate data the strongest factors predicting survival after cardiac arrest were cardiopulmonary resuscitation by bystanders and a diagnosis other than hypertrophic cardiomyopathy. The most common underlying cases of cardiac arrest were hypertrophic cardiomyopathy and ischaemic heart disease.

Cardiac arrest occurred at an overall rate of 0.54 per 100 000 runners. It was more likely in marathons rather than half-marathons and in men rather than women. The most common underlying causes were hypertrophic cardiomyopathy and coronary disease. The rate of cardiac arrest has increased in male marathon runners, possibly because more at-risk men have been tempted to participate.

Kim JH et al. Cardiac arrest during long-distance running races. *NEJM* 2012; 366: 130–40.

### Lifetime cardiovascular risks

People who are considered to be at low risk of cardiovascular disease in the short term (10 years) may be at considerable lifetime risk. Lifetime risks have been estimated by pooling data from US studies over the past 50 years.

A met-analysis included 18 cohort studies with a total of 257 384 men and women and risk factors assessed at ages 45, 55, 65, and 75. At age 55 the estimated risk of death from cardiovascular disease up to the age of 80 was 4.7% for men and 6.4% for women among people with a good risk-factor profile (total cholesterol <4.7 mmol/L, blood pressure <120/80 mmHg, non-smoking, no diabetes). Among people with two or more major risk factors the corresponding estimates were 29.6% for men and 20.5% for women. The difference in risk between the two risk factor groups among men was 3.6% vs 37.5% for coronary death or myocardial infarction, and 2.4% vs 8.3% for stroke. Among women the differences were <1% vs 18.3% for coronary death or myocardial infarction, and 5.3% vs 10.7% for stroke. Race and birth cohort made little difference to the trends within risk-factor strata.

Risk-factor profiles can distinguish between very different lifetime cardiovascular risks.

Berry JD et al. Lifetime risks of cardiovascular disease. *NEJM* 2012; 366: 321–9.

## Neurology

### Cortical demyelinating lesions in early multiple sclerosis

Cortical lesions in multiple sclerosis (MS) are associated with cognitive deterioration and disease progression. They are of three types: lesions extending into the cortex from the white matter (leukocortical), lesions extending radially from cortical microvessels (intracortical), and lesions extending into the cortex from the pia mater (subpial). A neuropathological study of 138 patients has been reported.

Each of the patients had had a brain biopsy and cortical tissue was obtained in passing during biopsy of white matter lesions. Most had been suspected of having a tumour and biopsy had been done stereoscopically within days or weeks of presentation. Cortical demyelination was found in 53 patients (38% of the total) and 25 of these (47%) had definite MS. Of the 85 patients without cortical demyelination, 33 (39%) had definite MS.

CD3+ T-cell infiltrates were present in 82% of examined lesions and macrophage-associated demyelination in 41%. Among patients with enough meningeal tissue to study, meningeal inflammation was found adjacent to cortical demyelination.

Among patients with early MS, cortical demyelinating lesions were frequent, inflammatory, and strongly associated with meningeal inflammation. Cortical neuronal loss may be directly associated with inflammatory demyelination and suppression of this inflammation could be neuroprotective in both grey and white matter.

Lucchinetti CF et al. Inflammatory cortical demyelination in early multiple sclerosis. *NEJM* 2011; 365: 2188-97; Calabresi PS. Inflammation in multiple sclerosis – sorting out the gray matter. *Ibid*: 2231-3 (editorial).

### EEG to detect awareness in vegetative state patients

When assessed in detail up to 43% of patients with a diagnosis of vegetative state show some signs of consciousness. Use of functional MRI (fMRI) may demonstrate awareness but it is not generally available. Now a study at two hospitals, in England and Belgium, has shown that an EEG-based assessment might demonstrate ability to understand commands.

The study included a total of 16 patients with a clinical diagnosis of vegetative state (Coma Recovery Scale-Revised definition) and 12 healthy controls. EEG recordings show reductions in power of  $\mu$  and  $\beta$  frequency bands over the appropriate areas of the motor cortex on imagining movements of body parts. Sometimes there are increases in contralateral areas of the motor cortex or surrounding the reduced-power areas. Subjects were asked to respond to a beep by imagining making a tight fist with their right hand on four to eight occasions and by imagining wiggling the toes on both feet on four to eight other occasions. Controls were asked to listen to the task but not to follow it. Appropriate responses were detected by EEG in three of the 16 patients. Two of five post-traumatic patients, and one of 11 patients with non-traumatic brain injury, responded.

These EEG techniques might be a useful, readily available, bedside method for detecting awareness in patients in an apparently vegetative state. *Lancet* commentators discuss the implications of these findings and conclude that they demonstrate 'something different than (sic) the presence and absence of consciousness.'

Cruse D et al. Bedside detection of awareness in the vegetative state: a cohort study. *Lancet* 2011; 378: 2088-94; Overgaard M, Overgaard R. Measurements of consciousness in the vegetative state. *Ibid*: 2052-4.

## Oncology

### Gene changes and resistance of colorectal cancer to chemotherapy

Gene alterations, both genomic and epigenetic, are common in human cancers and some of them may affect response to chemotherapy. Researchers in Germany have concentrated on the gene encoding transcription factor AP-2 epsilon (TFAP2E) and its potential downstream target, DKK4, the gene encoding Dickkopf homologue 4 protein. Tumour samples were obtained from 74 patients treated for colorectal cancer and, later, another four cohorts (total 220 patients) undergoing chemotherapy with or without radiotherapy. The expression, methylation, and function of TFAP2E was analysed in colorectal-cancer cell lines in vitro and in patients with colorectal cancer. The gene was hypermethylated in 38 of the initial 74 samples and this was associated with decreased gene expression. Cancer-cell lines with over expression of DKK4 had increased resistance to fluorouracil but not to irinotecan or oxaliplatin. In the four later cohorts hypermethylation of TFAP2E was significantly associated with resistance to chemotherapy. Hypomethylation was associated with a six-fold increase in likelihood of chemotherapy responsiveness. Epigenetic alterations in TFAP2E were independent of key regulatory cancer gene mutations, microsatellite instability, and other genes affecting fluorouracil metabolism.

Hypermethylation of TFAP2E is associated with chemotherapy resistance in patients with colorectal cancer and this resistance is mediated through DKK4. Targeting of DKK4 could potentially reverse this resistance.

Ebert MPA et al. TFAP2E-DKK4 and chemoresistance in colorectal cancer. *NEJM* 2012; 366: 44-53.

### Short-term complications of prostate biopsy

Prostate biopsy is known to cause pain, sepsis, and bleeding. A multicentre UK study has provided more data about short-term complications.

Men aged 50-69 having PSA testing and a first prostate biopsy were recruited at eight centres between February 2006 and May 2008. The study included 1147 men who completed questionnaires at

baseline and over a period of 35 days after biopsy. Moderate to severe pain immediately after the procedure was reported by 6% to 36% in the different centres. Other symptoms occurring within 35 days after biopsy included haemoejaculate (93% of sexually active subjects), haematuria (66%), haematochezia (37%), shivering (19%), and fever (18%). Most of these problems were mild and only 15 men (1.3%) needed hospital admission and 119 (10%) consulted a general practitioner or other health professional. Up to 20% of men considered repeat biopsy to be a moderate or major problem within 7 days of first biopsy. The major correlates of a negative attitude to repeat biopsy were postbiopsy pain and symptoms related to infection or bleeding. Rosario DJ et al. Short term outcomes of prostate biopsy in men tested for cancer by prostate specific antigen: prospective evaluation within ProtecT study. *BMJ* 2012; 344 (Jan 21): 19 (d7894); Djavan B, Rocco B. Optimising prostate biopsy. *Ibid*: 11 (d8201).

### Prostate cancer gene mutation

Prostate cancer may be familial but the genetic basis is unclear. Genomewide association studies have identified >30 single nucleotide polymorphisms associated with increased risk but the increase in risk from each of them has been low. An intensely studied locus has been at chromosome 17q21-22. Now a US study has identified a new variant in the gene HOXB13 that is associated with increased risk of hereditary prostate cancer.

More than 200 genes in the 17q21-22 region were screened by sequencing germline DNA from 94 unrelated patients with prostate cancer from families with familial prostate cancer linked to the 17q21-22 region. Four of these subjects had a mutation (G84E) in HOXB13 (rs138213197), a homeobox transcription factor gene important in prostate development. In these four families there were 18 men with prostate cancer and available DNA and all of them carried the mutation. This mutation was present in 72 of 5083 unrelated men of European descent with prostate cancer (1.4%) and 1 of 1401 controls without prostate cancer (0.1%), a highly significant difference. It was significantly more common in men with early-onset, familial prostate cancer (3.1%) than in men with late-onset nonfamilial prostate cancer (0.6%).

The new variant accounts for a small proportion of prostate cancers but may provide increased understanding of the disease.

Ewing CM et al. Germline mutations in HOXB13 and prostate-cancer risk. *NEJM* 2012; 366: 141-9.