

General

Nucleic acid testing of donated blood

The risk of transmission of hepatitis B virus (HBV) in donated blood is currently guarded against by screening for hepatitis B surface antigen (HBsAg) and for antibodies against hepatitis B core antigen (anti-HBc). This testing, however, does not cover the possibility of infective virus in blood taken between infection and seroconversion in the donor. The value of nucleic acid testing (triplex assay for hepatitis C virus (HCV) RNA, HBV DNA and human immunodeficiency virus (HIV) RNA) has been assessed in a study of 3.7 million American Red Cross blood donations.

Samples that proved HBV-DNA-positive but HBsAg and anti-HBc negative were further evaluated. Nine donations (1 in 410540 donations) were HBV DNA positive, of which six were from donors who had been given the HBV vaccine and had developed subclinical HBV infection that resolved. Four of the nine HBV DNA positive donors had probably been infected by a sexual partner with chronic HBV infection. Two of the three unvaccinated donors developed clinically significant liver injury. The HBV genotype in all three unvaccinated donors was A2 and in the six vaccinated donors it was C2, A2, F1, and B2 in one each and two donors had sequences representing both D and A2. (The vaccine contains A2 genotype virus.) In 75 samples from seronegative donors that were reactive on nucleic acid testing there were 26 confirmed infections: 9HBV, 15 HCV, and 2 HIV.

The triplex nucleic acid testing detected potentially infectious HBV, HCV, and HIV during the window period between infection and seroconversion.

Stramer SL et al. Nucleic acid testing to detect HBV infection in blood donors. *NEJM* 2011; 364: 236–47.

Recombinant tissue plasminogen activator to prevent dialysis catheter blockage or infection

Around half of all haemodialysis catheters fail within a year. Most of the failures are due to thrombosis. Infection is also a major cause of adverse outcomes. The solution left in the catheter after dialysis (the catheter locking solution) is usually heparin. Recombinant tissue plasminogen activator (rt-PA) has been suggested as an alternative catheter locking solu-

tion but the evidence in its favour has been sparse. Now a multicentre trial at 11 Canadian centres has shown better results with rt-PA substituted for heparin on one out of three occasions during the week.

A total of 225 patients on long-term haemodialysis via a central venous catheter were randomised within 2 weeks of catheter insertion to catheter locking with heparin (5000 U per ml) on each of three sessions per week or with rt-PA (1 mg in each lumen) at the second session each week and heparin on the first and third sessions. The rate of catheter malfunction over 6 months was 40/115 (35%) in the heparin-only group and 22/110 (20%) in the rt-PA group, a significant 91% greater risk in the heparin-only group. Catheter-related bacteraemia occurred in 13% vs 4.5% (1.37 vs 0.40 episodes per 1000 patient-days), a significant difference. The risk of bacteraemia from any cause was three times greater in the heparin-only group. Adverse events including bleeding, occurred at similar rates in the two groups.

Substituting rt-PA for heparin as a catheter locking solution in one of three sessions each week reduced the risks of central venous catheter malfunction and bacteraemia.

Hemmelgarn BR et al. Prevention of dialysis catheter malfunction with recombinant tissue plasminogen activator. *NEJM* 2011; 364: 303–12, Winkelmayer WC. Tackling the Achilles' heel of haemodialysis. *Ibid*: 372–4 (editorial).

Worldwide trends in BMI since 1980

Several studies have shown rising population levels of body mass index (BMI) in recent years. Now a systematic review of health examination surveys and epidemiological studies between 1980 and 2008 has included 199 countries and territories, with 960 country-years of data and 9.1 million participants aged at least 20 years. This is one of three analyses (on BMI, blood pressure, and cholesterol levels) published in the *Lancet* of 12 February 2011.

Over the years of the study mean BMI worldwide increased by 0.4 kg/m² in men and by 0.5 kg/m² in women. National changes in BMI among women included non-significant decreases in 19 countries and increases of >2.0 kg/m² in nine countries in Oceania. Among males BMI increased in all but nine countries. The highest BMIs in 2008 were in countries in Oceania, reaching 34.5 kg/m² in men (35 kg/m² in Nauru). Low BMIs were recorded in some countries in

sub-Saharan Africa and East, South, and South-east Asia. The lowest mean male BMI was in the Democratic Republic of the Congo (20 kg/m²) and the lowest female BMI in Bangladesh (21.5 kg/m²). Among high-income countries mean BMI was highest in the USA. Worldwide in 2008 about 205 million men and 297 million women were obese.

Most countries need strategies to control obesity. Finucane MM et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants.

Lancet 2011; 377: 557–67; The *Lancet*. An epidemic of risk factors for cardiovascular disease. *Ibid*: 527 (editorial); Anand SS, Yusuf S. Stemming the global tsunami of cardiovascular disease. *Ibid*: 529–32 (comment).

Alcohol and cardiovascular health

Two successive papers in the *BMJ* have reported systematic reviews and meta-analyses of evidence about alcohol consumption and cardiovascular disease. The first paper concerns alcohol and cardiovascular disease outcomes and is based on 84 studies. Pooled data showed significant reductions, in drinkers compared with non-drinkers, of 25% for cardiovascular disease mortality, 29% for incident coronary disease, and 25% for coronary disease mortality. Drinking had no significant effect on stroke. The lowest risk of coronary disease was with one or two drinks per day.

The second paper deals with the effects of alcohol on biological markers for coronary disease and is based on 44 interventional studies. Moderate alcohol consumption was associated with significant increases in levels of HDL cholesterol and adiponectin and decreased levels of fibrinogen. The increase in HDL level was directly related to the amount of alcohol taken.

Light or moderate drinking of alcohol may protect against coronary disease. The Practice section of the *BMJ* includes a summary of guidance on the diagnosis, assessment, and management of harmful drinking.

Ronksley PE et al. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. *BMJ* 2011; 342: 479 (d671); Brien SE et al. Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies. *Ibid*: 480 (d636); Coltart CEM, Gilmore IT. Minimal alcohol pricing in England. *Ibid*: 449–50 (d1063) (editorial); Pilling S et al. Diagnosis, assessment, and management of harmful drinking and alcohol dependence: summary of NICE guidance. *Ibid*: 490–2 (d700) (Practice).

Worldwide trends in systolic blood pressure since 1980

Worldwide trends in systolic blood pressure (SBP) between 1980 and 2008 have been estimated in 199 countries and territories (786 country-years 5.4 million people aged at least 25 years).

The age-standardised mean SBP worldwide in 2008 was 128.1 mmHg in men and 124.4 mmHg in women. Over the period of the study SBP tended to decrease in high-income countries and to increase in low- or middle-income countries. Worldwide, SBP decreased by 0.8 mmHg per decade in men and by 1.0 mmHg per decade in women. SBP in women fell by at least 3.5 mmHg per decade in Western Europe and Australasia but increased in west Africa. SBP in men fell by 2.8 mmHg per decade in the USA and Canada and by 2.0 mmHg per decade in Australia and Western Europe. In Oceania, East Africa, and South and South-east Asia, SBP increased in both sexes, by 0.8–1.6 mmHg per decade in men and 1.0–2.7 mmHg per decade in women. The highest SBPs in women were in some east and West African countries (mean SBP 135 mmHg or higher) and in men in the Baltic and East and West Africa (mean 138 mmHg or higher). In high-income regions the highest SBPs in both sexes were in Western Europe.

Average SBPs have fallen slightly worldwide with the greatest decreases in high-income countries. Strategies for SBP reduction need to be aimed at low- or middle-income countries.

Danaei G et al. National regional, and global trends in systolic blood pressure since 1980: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5.4 million participants. *Lancet* 2011; 377: 568-77; The Lancet. An epidemic of risk factors for cardiovascular disease. *Ibid*: 527 (editorial); Anand SS, Yusuf S. Stemming the global tsunami of cardiovascular disease. *Ibid*: 529-32 (comment).

Infection

HPV vaccination in males

Males contract genital papillomavirus (HPV) infections as frequently as females and the infections may lead to anogenital condylomata acuminata and cancers of the penis, anus, and oropharynx. Females, however, are more likely to become seropositive and to have higher antibody titres. The quadrivalent vaccine (HPV types 6, 11, 16, and 18) has been tested in boys and young men in an international study.

The randomised, placebo-controlled trial, at 71 sites in 18 countries included 4065 healthy males aged 16–26 years, among whom 602 had sex with men. Randomisation was to the quadrivalent vaccine or placebo at baseline, month 2, and month 6. In subjects who received the vaccine and returned for follow-up and may have been seropositive or seronegative at baseline (the intention to treat population) the vaccine efficacy was 60% against external genital lesions and 66% against lesions related to HPV-6, 11, 16, or 18. In the per-protocol population (seronegative at baseline, PCR-negative for swab and biopsy specimens from baseline to month 7 for the vaccine HPV types, and no protocol violations) the efficacy against vaccine HPV-type lesions was 90%. The efficacy against persistent infection with vaccine HPV types was 48% in the intention-to-treat population and 86% in the per-protocol population. The efficacy against detection of related DNA at any time was 27% vs 45% respectively. Pain at the injection site occurred in 57% of vaccine recipients and 51% among placebo recipients.

The vaccine is effective in sexually active boys and young men. Whether routine HPV immunisation for both sexes would be cost-effective is still debated, and may change, but the US Advisory Committee on Immunization practices has decided against recommending it for the time being.

Giuliano A R et al. Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. *NEJM* 2011; 364: 401-11; Kim JJ. Weighing the benefits and costs of HPV vaccination of young men. *Ibid*: 393-5 (perspective).

Treatment of *Clostridium difficile* infection: fidaxomicin versus vancomycin

The incidence and severity of *Clostridium difficile* infection has increased in the USA and elsewhere. Much of this increase in the USA has been due to the emergence of a strain of *C difficile* known variously as North American Pulsed Field type 1 (NAP1), restriction endonuclease analysis (REA) type BI, or polymerase-chain-reaction ribotype 027, (the NAP1/BI/027 strain). Fidaxomicin (previously known as OPT-80) is a macrocyclic antibiotic that is eight times more active in vitro than vancomycin against *C difficile*, including the NAP1/BI/027 strain. Now a trial in the USA and Canada has shown fidaxomicin to be at least as effective as vancomycin in the treatment of *C difficile* infection.

A total of 629 adults with *C difficile* infection, acute symptoms, and a positive stool toxin test were randomised to fidaxomicin 200 mg twice daily or vancomycin 125 mg four times daily, orally for 10 days. The analysis included 548 patients. In the modified intention-to-treat analysis the clinical cure rates were 88.2% (fidaxomicin) vs 85.8% (vancomycin). In the per-protocol analysis these rates were 92.1% vs 89.8%. Thus fidaxomicin was noninferior to vancomycin. Recurrent *C difficile* infection occurred in 15.4% vs 25.3% (modified intention-to-treat) and 13.3% vs 24.0% (per-protocol). Among patients with the NAP1/BI/027 strain the recurrence rate was about 24% with either antibiotic. Among patients infected with other strains the recurrence rate was 7.8% (fidaxomicin) vs 25.5% (vancomycin). Adverse events were similar with the two antibiotics.

Fidaxomicin was noninferior to vancomycin in rates of clinical cure and was associated with less risk of recurrence of infection with non-NAP1/BI/027 strains.

Louie TJ et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *NEJM* 2011; 364: 422-31; DuPont HL. The search for effective treatment of *Clostridium difficile* infection. *Ibid*: 473-5 (editorial).

Blood test for vCJD

Variant Creutzfeldt-Jakob disease (vCJD) in humans is a result of exposure to bovine spongiform encephalopathy (BSE) in cattle. The asymptomatic incubation period of vCJD is very long (up to 50 years or more) and therefore the number of people incubating the disease and the population risk of infection are difficult to assess. Now researchers in London, England have assessed a blood test for vCJD prion infection.

The test depends on a solid-state binding matrix that captures and concentrates the disease-associated prion proteins. This leads to direct immunodetection of surface-bound material. A total of 190 blood samples were tested: 21 from patients with vCJD, 27 with sporadic CJD, 42 with other neurological diseases, and 100 normal controls. The assay was highly sensitive for distinguishing between vCJD prion-infected and normal brain tissue. Fifteen of the 190 blood samples were positive for vCJD and all 15 samples proved to be from patients with vCJD, giving a vCJD assay sensitivity of 71.4% and a specificity of 100%.

The test is able to detect vCJD in symptomatic patients. It is hoped that it can be developed to detect asymptomatic vCJD

infection and as a blood-screening test but much more work will have to be done before these aims are realised.

Edgeworth JA et al. Detection of prion infection in variant Creutzfeldt-Jakob disease: a blood-based assay. *Lancet* 2011; 377: 487–93; Gregori L. A prototype assay to detect vCJD-infected blood. *Ibid*: 444–6.

Gastrology

Quadruple therapy for eradication of *Helicobacter pylori*

Some 25–50% of people in developed countries and up to 80% in developing countries are infected with *Helicobacter pylori*. Standard treatment is with omeprazole, amoxicillin, and clarithromycin. Bismuth may be added in regions with high rates of resistance to clarithromycin or metronidazole. Rates of antimicrobial resistance have increased in recent years and a reassessment of *H pylori* eradication therapy has become necessary. Quadruple therapy has been compared with standard therapy in a multinational European trial.

A total of 440 adults with *H pylori* infection were randomised to 10 days of omeprazole plus a 3-in-1 capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline (quadruple therapy) or 7 days of omeprazole, amoxicillin, and clarithromycin (standard therapy). In a per-protocol population quadruple therapy was shown to be noninferior to standard therapy. In the intention-to-treat population the eradication rates were 80% (quadruple therapy) vs 55% (standard therapy) proving the superiority of quadruple therapy. The safety profiles were similar for both treatments.

These researchers propose that quadruple therapy should be considered for first-line treatment.

Malfertheiner P et al. *Helicobacter pylori* eradication with a capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline given with omeprazole versus clarithromycin-based triple therapy: a randomised, open-label, non-inferiority, phase 3 trial. *Lancet* 2011; 377: 905–13; Lee BH, Kim N. Quadruple or triple therapy to eradicate *H pylori*. *Ibid*: 877–8 (comment).

Peginterferon plus adefovir for hepatitis B/hepatitis delta

Hepatitis delta virus (HDV) is only pathogenic when there is coinfection with hepatitis B virus (HBV). Long-term carriers of HBV who become infected with HDV are at risk of fulminant acute

hepatitis or severe chronic hepatitis leading to cirrhosis and hepatocellular carcinoma. No treatment is approved at present for HDV infection. Now workers in Germany, Turkey, and Greece have reported a trial of peginterferon plus adefovir versus either drug alone.

A total of 90 patients with HDV infection were randomised to peginterferon alfa-2a 180 µg weekly plus adefovir 10mg daily, peginterferon alone, or adefovir alone, all for 48 weeks, with follow-up for another 24 weeks. The primary endpoint (normal alanine aminotransferase levels and clearance of HDV RNA at 48 weeks) was reached by two patients in the combined treatment group and two in the peginterferon-only group, but none in the adefovir-only group. Negative HDV RNA testing was achieved in 23%, 24%, and 0%, respectively. The effectiveness in the first two groups was sustained 24 weeks after the end of treatment, with negative HDV RNA testing in 28% of the two groups combined. HBsAg levels decreased by >1 log₁₀ IU per ml between baseline and week 48 in 10 patients, 2, and 0, in the three groups, respectively.

Treatment with peginterferon alfa-2a for 48 weeks was effective in almost 25% of patients whether or not adefovir was added. Adefovir alone was not effective.

Wedemeyer H et al. Peginterferon plus adefovir versus either drug alone for hepatitis delta. *NEJM* 2011; 364: 322–31.

Tropical

Short-course multidrug treatment for visceral leishmaniasis in India

Around the world, the most frequently used treatment for visceral leishmaniasis is with pentavalent antimonials. In the state of Bihar, India, however, amphotericin B is standard treatment because resistance to the pentavalent antimonials has developed. Now a study at two sites in Bihar has shown that combination drug treatments are effective and safe.

A total of 634 patients aged 5–60 years with parasitologically confirmed visceral leishmaniasis were randomised to standard treatment (amphotericin B 1/kg/mg by infusion on alternate days for 30 days) or three other options: single injection of liposomal amphotericin B 5mg/kg and 7 days of oral miltefosine 50mg; single-dose liposomal amphotericin B and 10 days of i.m. paromomycin 11 mg/kg, or 10 days each of miltefosine and paro-

momycin. The 6-month cure rates were 93% (amphotericin B), 97.5% (liposomal amphotericin B and miltefosine), 97.5% (liposomal amphotericin B and paromomycin, and 98.7% (miltefosine and paromomycin). Each of the combination treatments was noninferior to standard treatment and associated with fewer adverse events.

Combination treatments for visceral leishmaniasis are effective and safe. Because they involve shorter durations of treatment they should encourage adherence and might reduce the risk of drug resistance. *Lancet* commentators point out that more effective drug treatment will only be effective in public health terms if accompanied by vector control, rapid diagnosis and treatment, and effective monitoring and evaluation.

Sundar S et al. Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomised controlled trial. *Lancet* 2011; 377: 477–86; Van Griensven J, Boelaert M. Combination therapy for visceral leishmaniasis. *Ibid*: 443–4 (comment).

Paediatrics

Training birth attendants in Zambia reduces neonatal mortality

In developing countries reductions in neonatal mortality have been more difficult to achieve than reductions in mortality in children aged 1–59 months.

Neonatal deaths constitute >40% of under-5s mortality and around 75% of neonatal deaths are in the first week of life. Now a study in rural Zambia has shown that training traditional birth attendants in neonatal resuscitation and administration of antibiotics almost halved neonatal mortality. The study was carried out in a large, sparsely populated district with no hospital and no resident doctors. There were 12 government supported rural health centres staffed by nurse midwives or clinical officers. Traditional birth attendants were randomised to intervention or control groups. Before the study all traditional birth attendants had received training in basic newborn care. They used clean delivery kits and referred high-risk pregnancies for delivery at a health centre. The intervention group of birth attendants participated in two 1-week training courses when they were instructed in neonatal resuscitation, avoidance of hypothermia, and use of single dose amoxicillin for infected infants, with facilitated referral to a health centre. Control birth attendants

continued with usual care. During the study 3559 infants were delivered by 127 traditional birth attendants. Reliable information was available for 3497 deliveries. The number of stillbirths and neonatal deaths per 1000 deliveries was 42.0 in the intervention group and 58.2 in the control group, a significant 28% reduction in the intervention group. Neonatal mortality was 22.8 vs 40.2 per 1000 live births, a significant 45% reduction. The intervention prevented one neonatal death for every 56 births. There was a 60% reduction in infant deaths in the first 24 hours (7.8 vs 19.9 deaths per 1000 live births) and an 81% reduction in deaths from birth asphyxia in the first 2 days. Rates of stillbirth and neonatal death from infection were similar in the two groups.

Training in neonatal resuscitation for traditional birth attendants could save many lives.

Gill CJ et al. Effect of training traditional birth attendants on neonatal mortality (Lufwanyama Neonatal Survival Project): randomised controlled study. *BMJ* 2011; 342: 373 (d346).

Intravitreal bevacizumab for stage 3+ retinopathy of prematurity

Retinopathy of prematurity (ROP) is characterised by new-vessel growth in the retina with consequent macular dragging and retinal detachment. It is a major cause of childhood blindness in both developing and developed countries. Retinal vascularisation spreads during gestation from the area of the optic disc to the periphery of the retina. Three zones of retinopathy are defined: zone 1 is a circle extending from the optic disc to twice the distance between the centre of the disc and the centre of the macula; zone 2 extends from zone 1 to the periphery of the nasal retina; zone 2 posterior extends for three times the distance between the centre of the disc and the centre of the macula; zone 3 is the rest of the retina, mainly on the temporal side.

Retinopathy in zone 1 is the most serious. In the early stages of development of ROP, levels of vascular endothelial growth factor (VEGF) are low but they are increased later. In a multicentre US trial the anti-VEGF agent, bevacizumab, given intravitreally, has been compared with laser therapy for stage 3+ ROP. A total of 150 infants of around 24 weeks gestational age with zone I or zone II posterior stage 3+ ROP were randomised at 15 centres to intravitreal bevacizumab or conventional laser therapy, to both eyes. One hundred and forty three (143) infants survived to 54 weeks postmenstrual age.

ROP recurred in four infants (6/140 eyes, 4%) in the bevacizumab group and 19 infants (32/146 eyes, 22%) in the laser group. Among infants with zone 1 disease, the rate of recurrence was significantly lower in the bevacizumab group (6%) of infants than in the laser group (42%). Among infants with zone II posterior disease the rate of recurrence was 5% vs 12%, a nonsignificant difference.

Compared with conventional laser therapy, treatment with intravitreal bevacizumab was more beneficial for zone 1, but not zone II, ROP.

Mintz-Hittner HA et al. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *NEJM* 2011; 364: 603-15; Reynolds JD. Bevacizumab for retinopathy of prematurity. *Ibid*: 677-8 (editorial).

Obs & Gyn

Treatment of periodontal disease in pregnancy: no effect on risk of preterm birth

There is evidence that periodontal disease in pregnancy increases the risk of preterm birth: a 2005 meta-analysis showed a 2.8-fold increase in risk. A meta-analysis published in 2009 showed a reduction in this risk with treatment of periodontal disease (scaling and root planing) in pregnancy but the studies included have been criticised for low methodological quality. Now an up-to-date meta-analysis has shown no risk reduction with such treatment.

The meta-analysis included 11 studies (6558 women) with 5 of the studies considered to be of high-methodological quality. The low-quality trials showed apparent benefit but the high-quality trials did not. In the high-quality trials treatment of periodontal disease was associated with a non-significant 15% increase in preterm delivery whereas the low-quality trials showed a significant 48% decrease. Taking all 11 trials together there was a non-significant 7% reduction in risk. Data from the high quality trials showed no significant reductions in rates of low birthweight, spontaneous abortion, or stillbirth, or overall adverse pregnancy outcomes with periodontal disease treatment.

Treatment of periodontal disease in pregnancy does not reduce the risk of preterm birth.

Polyzos NP et al. Obstetric outcomes after treatment of periodontal disease during pregnancy: systematic review and meta-analysis. *BMJ* 2011; 342: 91 (2010; 341: c7017); Macones G. Treatment of periodontal disease in pregnancy. *Ibid*: 59-60 (2010; 341: c7090).

Community interventions to improve perinatal and newborn care in rural Pakistan

Mortality in children under the age of 5 years in Pakistan is 94 per 1000 live births and more than half (57%) of these deaths occur in neonates, usually early in the neonatal period. Neonatal mortality is higher in rural areas than in towns and the proportion of children born at home is 74% in rural areas and 43% in urban areas. Traditional, usually untrained, birth attendants (Dais) conduct half of these births. Lady health workers (LHWs) who have at least 8 years of schooling and 15 months of healthcare training provide much of domestic health care including antenatal care, family planning, growth monitoring, and immunisations. Now a cluster-randomised trial of a community-based intervention package delivered through LHWs working with traditional birth attendants and community health committees has been reported.

Sixteen population clusters (47121 households, 23834 births) were randomised to intervention or control groups. The intervention package concentrated on antenatal care, maternal health education, clean delivery kits, facility births, immediate newborn care, danger signs, and promotion of care seeking. The control clusters received usual care. Data collectors obtained data about births, deaths, and household mother and newborn management practices every 3 months. In the intervention clusters the LHWs were able to undertake 63% of planned group sessions and to visit 24% of neonates. The stillbirth rate during the study fell to 39 per 1000 births in intervention clusters and was 49 per 1000 births in the control clusters, a highly significant difference. Neonatal mortality was also reduced significantly (43 vs 49 neonatal deaths per 1000 live births).

The intervention was associated with reductions in stillbirth and neonatal mortality rates.

Bhutta ZA et al. Improvement in perinatal and newborn care in rural Pakistan through community-based strategies: a cluster-randomised effectiveness trial. *Lancet* 2011; 377: 403-12; Coovadia H, Rollins N. Tying up loose threads in delivery of a newborn care package. *Ibid*: 361-3 (comment).

First-trimester abortion and mental illness: no connection

Some studies have suggested that mental health problems may follow an induced abortion but these studies have had methodological problems. Now a

cohort study in Denmark has shown no association between first-trimester abortion and mental health.

The population-based cohort study used Danish national registers. It included girls and women born in Denmark in 1962–1993 who had no history of inpatient mental disorder 9 months before a first childbirth or first-trimester abortion. Between 1995 and 2007, 84620 subjects had a first first-trimester abortion. The rate of first psychiatric inpatient or outpatient contact was 14.6 per 1000 person-years in the 9 months before the abortion and 15.2 per 1000 person-years in the 12 months after the abortion, a non-significant difference. Among subjects who had had a first childbirth the corresponding rates were 3.9 and 6.7 per 1000 person-years. The risk of psychiatric contact increased significantly after childbirth but not after induced abortion.

This study gives no support to the suggestion that first-trimester abortion may cause mental illness.

Munk-Olsen T et al. Induced first-trimester abortion and risk of mental disorder. *NEJM* 2011; 364: 332–9.

Diabetes

Olmesartan to delay or prevent microalbuminuria in type 2 diabetes

In patients with diabetes microalbuminuria is predictive of diabetic nephropathy and premature cardiovascular disease. A study at 262 centres in 19 countries of Europe has shown that treatment with the angiotensin-receptor blocker (ARB), olmesartan may delay the onset of microalbuminuria in patients with type 2 diabetes.

A total of 4447 patients with type 2 diabetes were randomised to olmesartan 40 mg daily or placebo for an average of 3.2 years. Additional therapy (not ACE inhibitors or ARBs) was used as necessary to achieve a blood pressure <130/80mmHg. This target was reached by 80% in the olmesartan group and 71% in the placebo group. Microalbuminuria developed in 8.2% (olmesartan) vs 9.8% (placebo) and olmesartan increased the time to onset of microalbuminuria by 23%. The risk of nonfatal cardiovascular events was nonsignificantly less in the olmesartan group (3.6% vs 4.1%) but the risk of fatal cardiovascular events was significantly greater (0.7% vs 0.1%). Among patients with pre-existing coronary disease, mortality from cardio-

vascular disease was significantly greater in the olmesartan group (2.0% vs 0.2%).

Olmesartan delayed the onset of microalbuminuria even though blood pressure control was good in both groups. The increase in fatal cardiovascular events with olmesartan among patients with known coronary disease is cause for concern.

Haller H et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *NEJM* 2011; 364: 907–17; Ingelfinger JR. Pre-emptive olmesartan for the delay or prevention of microalbuminuria in diabetes. *Ibid*: 970–1 (editorial).

Exercise, BMI, and insulin sensitivity

A study in Tasmania, Australia has confirmed a connection between exercise, BMI, and insulin sensitivity.

In the population-based cohort study 592 adults (mean age 51 years) were assessed in 2000 and again in 2005. Physical activity was measured using a pedometer and a questionnaire and food intake was assessed by questionnaire. The main outcome measures were BMI, waist-to-hip ratio, and HOMA insulin sensitivity in 2005. Over the course of the study the daily pedometer step count decreased in 65% of participants. BMI in 2005 fell by 0.08kg/m² for every 1000 steps per day increase in pedometer count between 2000 and 2005. Increased step count was also associated with reduced waist-to-hip ratio, and greater insulin sensitivity. The increase in insulin sensitivity was less after adjustment for BMI.

Increased physical activity as judged by daily step count was associated with increased insulin sensitivity over a 5-year period.

Dwyer T et al. Association of change in daily step count over five years with insulin sensitivity and adiposity: population based cohort study. *BMJ* 2011; 342: 216 (2010); 341: c7249.

Insulin degludec versus insulin glargine

Insulin degludec is an ultra-long-acting insulin that forms soluble multihexamers at the site of injection from which monomers are gradually released. This results in a flat and stable pharmacokinetic profile that might reduce the risk of hypoglycaemia. Dosing could be only three times a week, simplifying insulin treatment. A trial in Canada, India, South Africa, and the USA has compared insulin degludec once a day or three times a week with insulin glargine once a day.

The trial included 245 insulin-naïve adult patients with type 2 diabetes who

had been inadequately controlled on oral antidiabetic drugs and had glycosylated haemoglobin levels of 7.0–11.0%. Randomisation was to one of four options: insulin degludec (900nmol/ml) three times a week on Monday, Wednesday, and Friday evenings (ID3); insulin degludec (600 nmol/ml) once a day (IDA); insulin degludec (900nmol/ml) once a day (IDB) or insulin glargine (600nmol/ml) once a day (IG). All patients also received metformin. After 16 weeks levels of glycosylated haemoglobin were similar in the four groups (ID3, 7.3%; IDA, 7.4%; IDB, 7.5%; IG, 7.2%). Adverse events rates did not differ significantly between groups. Rates of hypoglycaemia were similar and low in the four groups.

Glycaemic control was similar in the four groups. Insulin degludec three times a week might provide satisfactory control.

Zinman B et al. Insulin degludec, an ultra-long-acting basal insulin, once a day or three times a week versus insulin glargine once a day in patients with type 2 diabetes: a 16-week, randomised, open-label, phase 2 trial. *Lancet* 2011; 377: 924–31; Kudva YC, Basu A. Ultra-long-acting insulins for a lifestyle-related pandemic. *Ibid*: 880–1 (comment).

Cardiology

Triggers of myocardial infarction

Known triggers of myocardial infarction include alcohol, anger, physical exertion, and use of marijuana. Air pollution may also play a part. A review of 36 studies has been reported.

The analysed studies were case-control studies (28), time series (7), and case-control (1). Thirteen triggers of acute myocardial infarction were studied and their prevalence varied from 0.2% to 100%. The time from exposure to the trigger to onset of myocardial infarction was usually between 2 and 24 hours and the odds ratios varied between 1.5 and 23.7. In order of risk to the individual the triggers were cocaine use, heavy meal, marijuana use, negative emotions, physical exertion, positive emotions, anger, sexual activity, alcohol, exposure to traffic, respiratory infections, coffee drinking, and air pollution. The triggers with the highest population attributable fractions were traffic exposure (7.4%) and physical exertion (6.2%), followed by alcohol (5.0%), coffee (5.0%), air pollution (4.8%), negative emotions (3.9%), anger (3.1%), heavy meal (2.7%), positive emotions (2.4%), sexual activity (2.2%), cocaine use (0.9%), marijuana (0.8%),

and respiratory infections (0.6%).

These researchers point in particular to the public health importance of air pollution.

Nawrot TS et al. Public health importance of triggers of myocardial infarction: a comparative risk assessment. *Lancet* 2011; 377: 732–40; Baccarelli A, Benjamin EJ. Triggers of MI for the individual and in the community. *Ibid*: 694–6 (comment).

CRP and statin therapy

A raised C-reactive protein (CRP) level is associated with cardiovascular risk. Some data have suggested that statin therapy might be less effective in the absence of raised CRP. Now a multicentre UK study has shown that the beneficial effects of statin therapy are independent of CRP levels.

In the Heart Protection Study (HPS) a total of 20536 patients at high cardiovascular risk aged 40–80 years were randomised to simvastatin 40 mg, or placebo, daily for 5 years. There was a significant 24% reduction in the incidence of vascular events after randomisation in the simvastatin group compared with the placebo group. Baseline CRP level did not affect the results. At the lowest CRP levels (<1.25 mg/L) the incidence of major vascular events was reduced by 29%. Among participants with both low CRP and low LDL cholesterol levels the reduction in risk was 27%.

The benefits of statin therapy were similar at both high and low baseline levels of CRP.

Heart Protection Study Collaborative Group. C-reactive protein concentration and the vascular benefits of statin therapy: an analysis of 20536 patients in the Heart Protection Study. *Lancet* 2011; 377: 469–76; Després J-P. CRP: star trekking the galaxy of risk markers. *Ibid*: 441–2 (comment)

Conventional CPR versus chest compression only

For cardiopulmonary resuscitation (CPR) after out-of-hospital cardiac arrest chest compression only rather than conventional CPR has been recommended for use by bystanders. Another trial, in Japan, has shown better outcomes with conventional CPR.

The study included all bystander-witnessed cardiac arrests in Japan in 2005, 2006, and 2007. Rates of survival to 1 month were 10.3% (conventional CPR) vs 8.7% (chest compression only), a highly significant improvement of 17% (after adjustment) with conventional CPR. The corresponding rates of survival to 1 month with neurologically favourable features were 5.6% and 4.6%, a significant 17% improvement with con-

ventional CPR. Conventional CPR was more successful, particularly for younger patients, arrest of non-cardiac cause, and when the onset of CPR was delayed.

For bystander-witnessed out-of-hospital cardiac arrest conventional CPR may be better than compression-only CPR, particularly for younger patients, arrest of non-cardiac origin, and delayed resuscitation.

Ogawa T et al. Outcomes of chest compression only CPR versus conventional CPR conducted by lay people in patients with out of hospital cardiopulmonary arrest witnessed by bystanders: nationwide population based observational study. *BMJ* 2011; 342: 321 (c7106); Jacobs IG. Chest compression or conventional CPR after out of hospital cardiac arrest? *Ibid*: 290–1 (d374) (editorial).

Oncology

Denosumab for bone metastases from prostate cancer

Zoledronic acid given intravenously reduces the rate of skeletal events in men with bone metastases from castration-resistant prostate cancer. Now a multinational trial has shown better results with denosumab, a monoclonal antibody against the promoter of osteoclastic activity, RANKL.

A total of 1904 patients with castration-resistant prostate cancer and bone metastases were randomised at 342 centres in 39 countries to s.c. denosumab 120 mg plus i.v. placebo or i.v. zoledronic acid, 4 mg plus s.c. placebo, every 4 weeks. The median time to the first skeletal event (pathological fracture, radiation therapy, bone surgery, or spinal cord compression) after randomisation was 20.7 months (denosumab) vs 17.1 months (zoledronic acid), a significant 18% improvement with denosumab compared to zoledronic acid. Adverse events occurred in 97% of patients in each group and serious adverse events in 63% (denosumab) vs 60% (zoledronic acid). Hypercalcaemia was more frequent with denosumab (13% vs 6%). Jaw osteonecrosis occurred in 2% vs 1%, a nonsignificant difference.

Denosumab was better than zoledronic acid for the prevention of skeletal events. The prophylactic use of denosumab before the occurrence of metastases is under investigation.

Fizazi K et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet* 2011; 377: 813–22; Aragon-Ching JB. Unravelling the role of denosumab in prostate cancer. *Ibid*: 785–6 (comment).

Eribulin for advanced breast cancer

Eribulin mesilate is a new anticancer drug with a novel mode of action as a non-toxane inhibitor of microtubule dynamics. A multinational trial has shown that it is effective for women with advanced breast cancer resistant to other treatments.

A total of 762 women with locally recurrent or metastatic breast cancer were randomised (2:1) to eribulin mesilate (1.4 mg/m² i.v. over a 2–5 min period on days 1 and 8 of a 21-day cycle) or treatment of physician's choice. All patients had previously received between two and five chemotherapy regimens. Overall survival was 13.1 months (eribulin) vs 10.6 months (controls). Adverse events, mainly asthenia, fatigue, and neutropenia were more common in the eribulin group. Peripheral neuropathy led to discontinuation of eribulin in 5% of patients.

Eribulin increased overall survival in 5% of patients. Eribulin increased overall survival in women with advanced, treatment resistant breast cancer. women with advanced, treatment resistant breast cancer.

Cortes J et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet* 2011; 377: 914–23; Lin NU, Burstein HJ. EMBRACE, eribulin, and new realities of advanced breast cancer. *Ibid*: 878–80 (comment).

Pulmonary

Protocols to reduce ventilation duration on ICU

A systematic review and meta-analysis has shown that the use of weaning protocols could reduce the duration of mechanical ventilation for patients on intensive care units (ICUs).

The analysis included 11 randomised or quasi-randomised trials (1971 patients) comparing weaning off ventilation with or without the use of a protocol. Use of a weaning protocol reduced the total duration of ventilation by 25% on average. The duration of the weaning process was reduced by 78% and the length of stay in ICU by 10%. There was considerable variation between studies. It is pointed out that weaning protocols might not be so effective on units where good practice already prevails

Blackwood B et al. Use of weaning protocols for reducing duration of mechanical ventilation in critically ill adult patients: Cochrane systematic review and meta-analysis. *BMJ* 2011; 342: 214 (c7237).