

General

Upper-GI bleeding risk with different NSAIDs: systematic review

The nonsteroidal anti-inflammatory drugs (NSAIDs) consist of the traditional, non-selective NSAIDs and the selective inhibitors of cyclo-oxygenase (COX) 2 (coxibs). The relative upper gastrointestinal (upper-GI) safety of the various individual NSAIDs has been assessed in a systematic review.

The review included nine studies: four case-control studies, three nested case-control studies, and two cohort studies. Compared with controls, the relative risk of upper-GI bleeding or perforation was 4.5 for traditional NSAIDs and 1.8 for coxibs. For individual drugs the relative risks were: ketorolac 14.5, piroxicam 9.9, naproxen 5.6, ketoprofen 5.6, indomethacin 5.4, meloxicam 4.2, diclofenac 4.0, ibuprofen 2.7, rofecoxib 2.1, aceclofenac 1.4, and celecoxib 1.4. The risk was not correlated significantly with degree of COX-1 inhibition but strong inhibition of both COX-1 and COX-2 was associated with higher risk. Higher risk was also related to long half-life and slow-release formulation.

Individual NSAIDs vary in their upper-GI safety. Long plasma half-life, slow-release formulation, and profound and coincident inhibition of both COX-1 and COX-2 are associated with higher risk.

Massó González EL et al. Variability among non-steroidal anti-inflammatory drugs in risk of upper gastrointestinal bleeding. *Arthritis and Rheumatism* 2010; 62: 1592–1601; Solomon DH. Strategies for making analgesia safer: the role of comparative effectiveness research. *Ibid*: 1568–70 (editorial).

Blood pressure control in chronic kidney disease

In almost a third of people who develop end-stage renal disease (ESRD) in the USA the disease is attributable to hypertension. The incidence of hypertension-related chronic kidney disease and ESRD is particularly high among black people. It is not known whether intensive blood pressure control slows the progression of the renal disease. A US multicentre trial confined to black patients has shown little benefit from intensive blood pressure control.

A total of 1094 black patients with hypertensive chronic kidney disease were randomised to intensive blood pressure control (target mean arterial pressure 92 mmHg or less, equivalent to <130/80 mmHg) or standard blood

pressure control (target mean arterial pressure 102–107 mmHg, corresponding to <140/90 mmHg). During a trial phase lasting 3 years mean blood pressure was 130/78 mmHg (intensive) vs 141/86 mmHg (standard). In a subsequent cohort phase of up to 7 years mean blood pressures were 131/78 and 134/78 in the two groups. The primary outcome (progression of chronic kidney disease with doubling of serum creatinine, diagnosis of ESRD, or death) occurred at a rate of 7.3 per 100 person-years in the intensive-control group and 7.5 per 100 person-years in the standard control group, a nonsignificant difference. There was, however, a significant effect of intensive control among patients with a baseline protein:creatinine ratio >0.22 among whom the primary outcome occurred at a rate of 13.8 per 100 person-years in the intensive-control group and 19.0 per 100 person-years in the standard-control group.

Overall intensive blood-pressure control as achieved in this trial did not slow the progression of hypertensive chronic kidney disease in black people. Among patients with a high urinary protein excretion at baseline, however, the intensive-control group did better.

Appel LJ et al. Intensive blood-pressure control in hypertensive chronic kidney disease. *NEJM* 2010; 363: 918–29; Ingelfinger JR. Hypertension control in African-American patients with chronic kidney disease. *Ibid*: 974–6 (editorial).

Ophthalmology

Smoking and ocular inflammation

Ocular inflammatory disease includes uveitis, scleritis and inflammation of the ocular surface. Researchers in Baltimore, USA have shown that smoking aggravates ocular inflammation.

Their retrospective cohort study included 2676 patients with active ocular inflammation. Current smokers made up 20% of the cohort. At presentation with ocular inflammation current smokers were more likely to have bilateral disease and poorer visual acuity compared with non-smokers or previous smokers. The time to disease quiescence was not affected by smoking but the time to recurrence of ocular inflammation was significantly shorter for current smokers (7.8 months) than for non-smokers (9.4 months) or previous smokers (10.7 months). Compared with non-smokers the risk of recurrence was

increased by 19% among current smokers and by 11% among previous smokers. Patients with ocular inflammation should be counselled to stop smoking.

Galor A et al. Adverse effects of smoking on patients with ocular inflammation. *British Journal of Ophthalmology* 2010; 94: 848–53; Cunningham ET. Exogenous factors influencing endogenous inflammation: what can patients do to improve control of their own uveitis? *Ibid*: 813–4 (editorial).

Paediatrics

Assessing risk of respiratory complications in paediatric surgery

Respiratory events cause almost one in three perioperative cardiac arrests in children. A study in Perth, Australia has pointed the way towards predicting and preventing some of these events.

The study included all 10496 children given a general anaesthetic at the Princess Margaret Hospital for Children in Perth during the 1-year period, Feb 1, 2007 to Jan 31, 2008. Anaesthetists completed a questionnaire based on the International Study Group for Asthma and Allergies in Childhood (ISAAC) questionnaire. A total of 9297 questionnaires were analysed.

Children were regarded as having a positive respiratory history if they had had a nocturnal dry cough, wheezing during exercise, more than three episodes of wheezing in the last 12 months, or present or past eczema. Such a history increased the risk of perioperative bronchospasm eight-fold, laryngospasm four-fold, and perioperative cough, desaturation, or airway obstruction three-fold. An upper respiratory tract infection, current or in the last 2 weeks, doubled the risk of perioperative respiratory events whereas such an infection occurring 2–4 weeks before the anaesthetic was associated with a significant 34% reduction in risk. A family history of two members with asthma or atopy, or who smoked was associated with a significant increase in risk. Other factors associated with increased risk were inhalational induction of anaesthesia, intravenous maintenance of anaesthesia, anaesthesia by a registrar rather than a specialist paediatric anaesthetist, and tracheal intubation. Children at high risk could be identified and anaesthetic management tailored to the needs of the patient.

Von Ungern-Sternberg BS et al. Risk assessment for respiratory complications in paediatric anaesthesia: a prospective cohort study. *Lancet* 2010; 376: 773–83; Lerman J. Perioperative respiratory complications in children. *Ibid*: 745–6 (comment).

Inhaled nitric oxide to prevent bronchopulmonary dysplasia: negative trial

There is evidence from animal studies that bronchopulmonary dysplasia (BPD) in premature infants is a result of altered pulmonary vasculature and reduced vascular endothelial growth factor and that inhaled nitric oxide might prevent some of the change. Now a multicentre, international trial of nitric oxide for the prevention of BPD has given disappointing results.

The trial, at 36 centres in nine European countries, included 800 infants (gestational age at birth 24–28 weeks, birthweight 500g or greater) who needed treatment for respiratory distress syndrome on the first day of life. Randomisation was to inhaled nitric oxide or placebo (nitrogen) for 7–21 days. The rates of survival without BPD, (nitric oxide 65%, placebo 66%) survival to 36 weeks postmenstrual age (86% vs 90%), and development of BPD (24% vs 27%) were similar in the two groups.

The prophylactic use of inhaled nitric oxide did not benefit these infants. The writers of a Comment article point out that some trials have given positive results and the effectiveness of nitric oxide may depend on dose, timing, severity of RDS, and race. More work is needed.

Mercier J-C et al. Inhaled nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial. *Lancet* 2010; 376: 346–54; Sosenko IR, Bancalari E. NO for pre-term infants at risk of bronchopulmonary dysplasia. *Ibid*: 308–10 (comment).

Pentavalent rotavirus vaccine in Africa and Asia

Diarrhoea kills about 1.3 million children under the age of 5 years each year and over 60% of these deaths occur in Africa. About 40% of severe diarrhoea is attributable to rotavirus infection. New rotavirus vaccines have proved effective and safe in developed countries but data from developing countries are needed. Now reports from sub-Saharan Africa and from Asia have shown that the pentavalent vaccine (RotaTeq) is effective and safe.

In Ghana, Kenya, and Mali, a total of 5468 infants were randomised to RotaTeq or placebo as three oral doses at 6, 10, and 14 weeks of age. The incidence of severe rotavirus gastroenteritis was 79 cases in 2610.6 person-years in the vaccine group and 129 cases in 2585.9 person-years in the placebo group, giving a vaccine efficacy against severe rotavirus gastroenteritis of 39.3%. Median

follow-up was 527 days. The rate of serious adverse events was similar in the two groups (vaccine 1.5%, placebo 1.7%).

In Bangladesh and Vietnam a similar trial included 2036 infants. Median follow-up was for 498 days. Severe rotavirus gastroenteritis occurred in 38 children in >1197 person-years in the vaccine group and in 71 children in >1156 person-years in the placebo group, giving a vaccine efficacy against severe rotavirus diarrhoea of 48.3%. Serious adverse events occurred in 2.5% (vaccine) versus 2.0% (placebo).

The pentavalent oral rotavirus vaccine was effective and safe in sub-Saharan Africa and in Asia. These results support WHO recommendations for global use of rotavirus vaccine.

Armah GE et al. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in sub-Saharan Africa: a randomised, double-blind, placebo-controlled trial. *Lancet* 2010; 376: 606–14; Zaman K et al. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in Asia: a randomised, double-blind, placebo-controlled trial. *Ibid*: 615–23; Nelson EAS, Glass RJ. Rotavirus: realising the potential of a promising vaccine. *Ibid*: 568–70 (comment).

Psychology

Rimonabant to prevent cardiovascular events: trial stopped because of neuropsychiatric complications

Rimonabant is a selective cannabinoid-1 receptor antagonist that causes weight loss and improves several cardiovascular risk factors. Now an international trial of rimonabant to prevent cardiovascular events has been stopped early because of an increase in neuropsychiatric problems on treatment.

A total of 18695 patients with, or at increased risk of, vascular disease were randomised at 974 centres in 42 countries to rimonabant 20mg daily or placebo. The trial was discontinued after a mean follow-up of 14 months because of concerns about an increased risk of suicide in patients on rimonabant. At that time the composite primary endpoint of cardiovascular death, myocardial infarction, or stroke had occurred in 3.8% (rimonabant) and 4.0% (placebo). In the rimonabant group there were significant increases in gastrointestinal events (33% vs 22%), neuropsychiatric events (32% vs 21%), and serious psychiatric events (2.5% vs 1.3%). Suicide occurred in four patients in the rimonabant group and one in the placebo group and attempted

suicide in nine versus five. Depression, anxiety, and insomnia were all more common in the rimonabant group.

Rimonabant treatment was associated with increased risk of neuropsychiatric problems. Marketing authorisation for the drug was withdrawn in 2008.

Topol EJ et al. Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial. *Lancet* 2010; 376: 517–23; Boekholdt SM, Peters RJG. Rimonabant: obituary for a wonder drug. *Ibid*: 489–90 (comment).

Antiepileptic drugs and suicide risk

Among people with psychiatric disorders epilepsy is associated with increased suicide risk and among people with epilepsy there is an increased risk of developing a psychiatric disorder. Depression is common in severe epilepsy and known risk factors for suicide include early onset of epilepsy, psychiatric illness, temporal lobe epilepsy, and inadequate neurological supervision. A meta-analysis of clinical trials in 2008 resulted in the issuing of a safety warning about antiepileptic drugs and suicidality (suicidal behaviour or ideation) by the US Food and Drug Administration (FDA). A UK study has provided further clarification of the link between antiepileptic drugs and suicide-related events (completed or attempted suicide).

Data were obtained from The Health Improvement Network (THIN), a general practice database with 6.7 million patients representative of the UK population. The study cohort included 5 130 795 patients. The incidence of suicide-related events was 15.0 per 100 000 person-years among patients without epilepsy, depression, or bipolar disorder and not taking antiepileptic drugs. It was 38.2 per 100 000 person years among patients with epilepsy not taking antiepileptic drugs and 48.2 per 100 000 person-years among patients with epilepsy taking antiepileptic drugs. After statistical adjustments antiepileptic drug therapy was not associated with increased risk of suicide-related events among people with either epilepsy or bipolar disorder. This risk was, however, increased significantly in association with antiepileptic drug treatment among patients with depression (odds ratio 1.65) and patients without depression, epilepsy, or bipolar disorder (odds ratio 2.57).

The risk of suicide related events was not increased by the use of antiepileptic drugs among patients with epilepsy but it was increased by use of these drugs among patients with depression and

among patients without epilepsy, depression, or bipolar disorder.

Arana A et al. Suicide-related events in patients treated with antiepileptic drugs. *NEJM* 2010; 363: 542–51.

Continuing maintenance treatment after first episode of psychosis

Maintenance treatment is given after a first episode of psychosis but there is little evidence to decide how long it should be continued. A trial in Hong Kong has suggested that it should be continued for more than a year.

The trial included 178 patients who had had at least a year of maintenance antipsychotic drug treatment after a first episode of non-affective psychosis, had had no relapses, and were free of psychotic symptoms. Randomisation was to continued maintenance treatment with quetiapine 400mg daily or placebo, for 12 months. The rate of relapse during the trial was 27/89 (30.3%) in the quetiapine group and 56/89 (62.9%) in the placebo group. When patients who relapsed within 60 days of randomisation were excluded the relapse rates were 32% vs 75%. Adverse effects of quetiapine included sleepiness, reduced salivation, and constipation.

Stopping antipsychotic maintenance after 1 year is associated with increased risk of relapse.

Chen EYH et al. Maintenance treatment with quetiapine versus discontinuation after one year of treatment in patients with remitted first episode psychosis: randomised controlled trial. *BMJ* 2010; 341: 435 (c4024); Craig JC et al. How long should treatments be continued? *Ibid*: 409–10 (c4102) (editorial).

Obs & Gyn

Optimum pregnancy interval after miscarriage in first pregnancy

There is little evidence to guide women who have had a miscarriage in their first pregnancy and wish to know when they should best attempt a second pregnancy. Data from Scottish hospital discharge records have provided an answer. The data included 30937 women who between 1991 and 2000 had had a miscarriage in their first pregnancy and had subsequently become pregnant for a second time.

Compared with an interpregnancy interval of 6–12 months women who conceived again within 6 months were significantly 34% less likely have another miscarriage. At greater inter-pregnancy

intervals the miscarriage risk remained fairly constant. The risks of ectopic pregnancy, termination, and stillbirth were also lower at an interpregnancy interval of <6 months compared with one of 6–12 months. The risk of termination increased with increasing interpregnancy interval up to and beyond 24 months. A long interpregnancy interval was associated with a doubling of the risk of ectopic pregnancy compared with a 6–12 month interval.

Women who conceived again within 6 months had the best pregnancy outcomes.

Love ER et al. Effect of interpregnancy interval on outcomes of pregnancy after miscarriage: retrospective analysis of hospital episode statistics in Scotland. *BMJ* 2010; 341: 437 (c3967); Shelley J. Miscarriage and time to next pregnancy. *Ibid*: 410–11 (c4181) (editorial).

Four-year efficacy of HPV vaccine against low-grade anogenital lesions

Little is known about effects of quadrivalent human papillomavirus (HPV) vaccine on the total burden of low-grade anogenital lesions. An international study has provided some answers.

A total of 17622 women aged 16–26 years were randomised in 24 countries and territories to quadrivalent (serotypes 6, 11, 16, and 18) HPV vaccine or placebo, in three doses at day 1, month 2, and month 6. Follow-up was for 4 years. Vaccine efficacy against lesions attributable to vaccine HPV types was 96% for cervical intraepithelial neoplasia grade I, 100% for both vulvar and vaginal intraepithelial neoplasia grade I, and 99% for condyloma. Vaccine efficacy against all lesions (regardless of HPV type) in the largely HPV naïve population was 30%, 48%, and 33% for the above lesions respectively.

The quadrivalent vaccine provides good protection for up to 4 years against vaccine-serotype-associated lesions.

The *FUTURE VII* Study Group. Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomised controlled trial. *BMJ* 2010; 341: 239 (c3493).

Patient satisfaction with treatments for menorrhagia

A systematic review and meta-analysis has addressed the question of patient satisfaction with different treatments for heavy menstrual bleeding.

Data were analysed from 17 trials (2814 women) of hysterectomy, first- and

second-generation endometrial destruction techniques, or the levonorgestrel releasing intrauterine system (Mirena) for the treatment of heavy menstrual bleeding. At 12 months, rates of patient dissatisfaction were 13% after first generation hysteroscopic techniques and 5% after hysterectomy despite longer hospital stays after hysterectomy. First and second generation techniques gave similar rates of unsatisfactory outcome but recovery was quicker after second-generation procedures. Second-generation techniques may have produced more unsatisfactory outcomes than hysterectomy. Outcomes after Mirena also seemed to be worse than after hysterectomy.

Hysterectomy seems to produce less patient dissatisfaction than newer techniques for the treatment of heavy periods. Nevertheless, a *BMJ* editorialist insists that most women would be well advised to try a less radical treatment initially.

Middleton LJ et al. Hysterectomy, endometrial destruction, and levonorgestrel releasing intrauterine system (Mirena) for heavy menstrual bleeding: systematic review and meta-analysis of data from individual patients. *BMJ* 2010; 341: 379 (c 3929); Clarke J. Treatment of heavy menstrual bleeding. *Ibid*: 353–4 (c 3771) (editorial).

AIDS

Prognosis on ART in sub-Saharan Africa: prognostic models

The prognosis for patients with HIV infection treated with antiretroviral therapy (ART) in developed countries is well established but much less is known about the prognosis in developing countries. Now prognostic models have been developed for patients in sub-Saharan Africa.

Data were analysed for patients in Côte d'Ivoire, South Africa, and Malawi beginning ART in 2004–2007. Two prognostic models were derived, one based on CD4 cell count, clinical stage, body-weight, age, and sex (CD4 model) and one in which total lymphocyte count and severity of anaemia replaced CD4 cell count (lymphocyte/Hb model). The study included 11153 patients and 912 (8.2%) died during the first year of ART. The median CD4 cell count at the start of ART was 117 cells per μ L among those who survived the first year and 50 cells per μ L among those who did not. The risk of death was increased with age >40, male sex, advanced clinical stage, lower CD4 cell count, low body weight, low total

lymphocyte count, and severe anaemia. The probability of death in the first year of ART ranged from 0.9% to 52.5% with the CD4 model and from 0.9% to 59.6% with the lymphocyte/Hb model. Both models were accurate predictors of early mortality.

These prognostic models should be useful in sub-Saharan Africa.

May M et al. Prognosis of patients with HIV-1 infection starting antiretroviral therapy in sub-Saharan Africa: a collaborative analysis of scale-up programmes. *Lancet* 2010; 376: 449–57; Koole O, Colebunders R. ART in low-resource settings: how to do more with less. *Ibid*: 396–8 (comment).

The AIDS epidemic and care of the elderly in Africa

A multinational study has brought to light the adverse effect of the AIDS epidemic on the care of elderly people in Africa.

Data for 1991–2006 were analysed about 123 176 people aged >60 years in 22 African countries that together encompassed 20% of the sub-Saharan population. Each increase in a country's annual AIDS mortality of 1 per 1000 population was associated with a 1.5% increase in the proportion of older people living alone and an 0.4% increase in the proportion of older people living only with children <10 years old. Increased AIDS mortality was also associated with more older people living in households with fewer adults aged 18–59 years. It was calculated that in 2006 the AIDS epidemic was associated with between 582 200 and 917 000 elderly people living alone and between 141 000 and 323 100 being responsible for the care of young children in these 22 countries.

The AIDS epidemic in Africa has led to many elderly people living alone and to many others having to care for young children.

Kautz T et al. AIDS and declining support for dependent elderly people in Africa: retrospective analysis using demographic and health surveys. *BMJ* 2010; 341: 136 (340: c2841).

HAART coverage, population viral load, and incidence of HIV infection

There is good evidence that highly active antiretroviral therapy (HAART) reduces the risk of HIV transmission. Now a study in British Columbia, Canada has confirmed a strong association at a population level between increasing HAART coverage, decreased viral load, and reduced incidence of HIV infection.

Data were obtained from population-based registries. The number of people

being treated with HAART was 837 in 1996 and 5413 in 2009; during the same period the number of new HIV diagnoses fell from 702 to 338 per year. For every additional 100 patients on HAART there were 3% fewer new HIV cases and for 1 log₁₀ reduction in viral load there was a 14% reduction in new cases.

Increased HAART coverage and reduced population viral load are associated with reduced incidence of HIV infection within the community.

Montaner JSG et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. *Lancet* 2010; 376: 532–9; Maggiolo F, Leone S. Is HAART modifying the HIV epidemic? *Ibid*: 492–3 (comment).

Cardiology

Cardiovascular risk with sibutramine for obesity

Sibutramine is a norepinephrine and serotonin reuptake inhibitor that reduces appetite and increases energy expenditure. It may also increase blood pressure and/or heart rate. Now a large international trial has shown that, in patients with pre-existing cardiovascular disease, long-term treatment with sibutramine increases cardiovascular risk.

A total of 10744 overweight or obese patients aged at least 55 years and with pre-existing cardiovascular disease, type 2 diabetes, or both entered a weight-management programme and received sibutramine for 6 weeks. They were then randomised to sibutramine 10mg/day or placebo. During the 6-weeks lead-in period mean weight loss was 2.6kg. In the 12 months after randomisation there was a mean further weight loss of 1.7kg in the sibutramine group and a mean weight gain of 0.7kg in the placebo group. Mean blood pressure fell in both groups, to a greater extent in the placebo group. The primary outcome (nonfatal myocardial infarction, nonfatal stroke, resuscitation for cardiac arrest, or cardiovascular death) was reached by 11.4% (sibutramine) vs 10.0% (placebo), a significant difference. Sibutramine increased the risks of nonfatal myocardial infarction and nonfatal stroke significantly by 28% and 36% respectively (4.2% vs 3.2% and 2.6% vs 1.9% in the sibutramine and placebo groups). Overall and cardiovascular mortalities were not increased significantly by sibutramine.

Among high-cardiovascular-risk patients

sibutramine increased the risks of nonfatal myocardial infarction and nonfatal stroke. Sibutramine should not be used for patients with cardiovascular disease. *New England Journal of Medicine* editorialists write that it is difficult to justify keeping sibutramine on the market.

James WPT et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. *NEJM* 2010; 363: 905–17; Curfman GD et al. Sibutramine – another flawed diet pill. *Ibid*: 972–4 (editorial).

Aspirin and clopidogrel doses in acute coronary syndromes

The optimal doses of aspirin and clopidogrel in patients with acute coronary syndromes are unclear. Two dosing strategies have been compared in an international trial.

A total of 25 086 patients with an acute coronary syndrome and planned early PCI were randomised to standard-dose clopidogrel (300mg loading dose then 75mg daily for 6 days) or double-dose clopidogrel (600mg then 150mg daily) and to high-dose aspirin (300–325 daily) or lower dose aspirin (75–100mg daily) in a 2-by-2 factorial design. All patients received clopidogrel 75mg daily on days 8 to 30 and aspirin was continued up to day 30. The primary outcome (cardiovascular death, myocardial infarction or stroke by day 30) occurred in 4.2% (double-dose clopidogrel) and 4.4% (standard dose), a non-significant difference. Major bleeding occurred in 2.5% vs 2.0%, a significant difference. Stent thrombosis was significantly less frequent (1.6% vs 2.3%) after double-dose clopidogrel. The higher and lower-dose aspirin regimens were associated with similar outcomes (primary outcome 4.2% (higher) vs 4.4% (lower), major bleeding 2.3% in both groups).

The two dosage schemes for clopidogrel and aspirin gave similar rates of the primary outcome. The double-dose clopidogrel regimen was associated with increased major bleeding and a significant reduction in stent thrombosis.

The CURRENT-OASIS 7 investigators. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *NEJM* 2010; 363: 930–42; Fuster V. Fine-tuning therapy for acute coronary syndromes. *Ibid*: 976–7 (editorial).

CPR: chest compression only?

Two successive papers in the *New England Journal of Medicine* describe trials of conventional cardiopulmonary resuscitation (CPR) with rescue breathing versus chest compression only for bystander CPR for out-of-hospital cardiac arrest in

adults. In Washington State, USA and London, England, dispatchers gave instructions to bystanders. Randomisation was to dispatcher instructions for chest compression plus rescue breathing (CB) or chest compression alone (C). A total of 1941 patients were included. The rates of survival to hospital discharge were 12.5% vs 11.5% and of survival with favourable neurological outcome 14.4% vs 11.5%. Neither of these differences was significant. There was a trend towards better results with compression alone among patients with a cardiac cause for the cardiac arrest and for patients with rhythms responsive to shock.

A similar trial in Sweden included 1276 patients. The rates of 30-day survival were 8.7% (C) vs 7.0% (CB), a non-significant difference.

The results of chest compression alone were as good as those of compression plus rescue breathing in these trials. Interrupting chest compression to perform mouth-to-mouth ventilation may simply diminish coronary flow. Conventional CPR should still be taught because it is important for cardiac arrest of pulmonary origin which is the case for most children with cardiac arrest.

Rea TD et al. CPR with chest compression alone or with rescue breathing. *NEJM* 2010; 363: 423–33; Svensson L et al. Compression-only CPR or standard CPR in out-of-hospital cardiac arrest. *Ibid*: 434–42; Weisfeldt ML. In CPR, less may be better. *Ibid*: 481–3 (editorial).

Diabetes

Diet for poorly controlled type 2 diabetes

A study in New Zealand has shown that intensive dietary advice may improve glycaemic control in patients with type 2 diabetes poorly controlled despite maximal drug treatment.

A total of 93 patients with $HbA_{1c} > 7\%$ despite optimal drug treatment and with at least two of overweight/obesity, hypertension, or dyslipidaemia were randomised to intensive dietary advice, based on the recommendations of the European Association for the Study of Diabetes, or a control group. The main dietary changes in the intervention group were a decrease in saturated fat and an increase in protein. At 6 months mean HbA_{1c} levels had fallen from 8.9% to 8.4% in the intervention group and had remained steady at 8.6% in the control group, a highly significant difference in

change. There were also significantly greater reductions in BMI and waist circumference in the intervention group.

Intensive dietary advice may benefit patients with poorly controlled type 2 diabetes.

Coppell KJ et al. Nutritional intervention in patients with type 2 diabetes who are hyperglycaemic despite optimised drug treatment – Lifestyle over and Above Drugs in Diabetes (LOADD) study: randomised controlled trial. *BMJ* 2010; 341: 237 (c3337); Clifton P. Nutrition in people with poorly controlled type 2 diabetes. *Ibid*: 209–10 (c3393) (editorial).

Intensive glycaemic control in type 2 diabetes

The ACCORD trial was a parallel-group randomised trial at 77 centres in North America in which patients with poorly controlled diabetes and at high cardiovascular risk were randomised to intensive therapy (target $HbA_{1c} < 6.0\%$) or standard therapy (target HbA_{1c} 7.0–7.9%).

A total of 10251 patients entered the trial, which was stopped early because of higher mortality in the intensive therapy group, and all patients were then given standard therapy. On stopping the trial and on further follow-up outcomes were similar in the two groups as regards retinopathy, nephropathy, and neuropathy. Intensive therapy was associated with delayed onset of albuminuria, some measures of eye complications, and neuropathy.

These researchers conclude that the microvascular benefit of intensive therapy must be weighed against an increase in overall and cardiovascular mortality, increased weight gain, and a high risk of severe hypoglycaemia.

Ismail-Beigi F et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. *Klein R*. Intensive treatment of hyperglycaemia: ACCORD. *Ibid*: 391–2 (comment).

Exenatide once weekly versus sitagliptin or pioglitazone as treatment added to metformin in type 2 diabetes

Treatment of type 2 diabetes is often with metformin but additional treatment is often needed. Such additional treatments include glucagon-like peptide 1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, and the thiazolidinediones. Now these three types of drug have been compared in an international trial.

At 72 centres in the USA, India, and Mexico, a total of 514 patients with a mean HbA_{1c} level of 8.5% on metformin were randomised to take in addition in-

jected exenatide (a GLP-1 receptor agonist) 2 mg once weekly, or oral sitagliptin (a DPP-4 inhibitor) 100 mg daily, or oral pioglitazone (a thiazolidinedione) 45 mg daily, with appropriate placebos, for 26 weeks. The mean reductions in HbA_{1c} were 1.5% (exenatide), 0.9% (sitagliptin), and 1.2% (pioglitazone), significantly greater with exenatide than with either sitagliptin or pioglitazone. There was a mean weight loss of 2.3 kg with exenatide and 0.8 kg with sitagliptin, and a mean weight gain of 2.8 kg with pioglitazone. No patient in any of the groups had an episode of major hypoglycaemia. The main adverse events were nausea and diarrhoea with exenatide and sitagliptin, and upper respiratory tract infection and peripheral oedema with pioglitazone.

Weekly injections of exenatide gave better results than daily oral sitagliptin or pioglitazone.

Bergenstal RM et al. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. *Lancet* 2010; 276: 431–9; Nauck MA, Meier JJ. Individualised incretin-based treatment for type 2 diabetes. *Ibid*: 393–4 (comment).

Oncology

Immunotherapy for prostate cancer

Sipuleucel-T consists of autologous peripheral-blood mononuclear cells that have been activated by culturing them for 36–44 hours with media containing PA2024, a recombinant fusion protein consisting of a prostate antigen (prostatic acid phosphatase) fused to granulocyte-macrophage colony-stimulating factor. Trials have shown that treatment with sipuleucel-T may benefit men with metastatic, castration-resistant, prostate cancer. Now a multicentre North American trial has confirmed the benefit.

A total of 512 patients were randomised (2:1) at 75 centres in the USA and Canada to sipuleucel-T or placebo i.v. at 2-week intervals to a total of three infusions. The risk of death was reduced by 22% in the treated group, a significant reduction increasing average survival from 21.7 to 25.8 months. The probability of surviving for 36 months was increased from 23.0% to 31.7%. Time to disease progression was similar in the two groups. Antigen responses were detected in the treated group. Chills, fever, and headache were more common in the

sipuleucel-T group.

Sipuleucel-T prolonged survival in men with metastatic, castration-resistant prostate cancer.

Kantoff PW et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *NEJM* 2010; 363: 411–22; Longo DL. New therapies for castration-resistant prostate cancer. *Ibid*: 479–81 (editorial).

Treatment of early-stage Hodgkin's lymphoma

The intensity of treatment necessary for early-stage, good-prognosis Hodgkin's lymphoma is uncertain. A study in Germany, Switzerland, the Netherlands, the Czech Republic, and Austria has shown that less intensive treatment may retain effectiveness with less toxicity.

A total of 1370 patients were randomised at 329 centres to one of four groups: four cycles of chemotherapy followed by 30Gy of radiotherapy (C4, 30), four cycles of chemotherapy followed by 20Gy of radiotherapy (C4, 20), two cycles of chemotherapy followed by 30Gy of radiotherapy (C2, 30), or two cycles of chemotherapy followed by 20Gy of radiotherapy (C2, 20). There were no significant differences between the groups in rates of treatment failure or survival. Toxicity was greater in the C4, 30 group.

The lowest dose regimen was as effective as the highest dose and less toxic.

Engert A et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *NEJM* 2010; 363: 640–52.

Ipilimumab for metastatic melanoma

Ipilimumab is a human monoclonal antibody that promotes antitumour immunity by blocking cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), a molecule that impairs T-cell activation. Now an international trial has shown that ipilimumab is active against metastatic melanoma.

A total of 676 HLA-A*0201-positive patients with unresectable stage III or IV melanoma and progressive disease on treatment were randomised at 125 centres in 13 countries in North and South America, Europe, and Africa to ipilimumab plus glycoprotein 100 (gp100), ipilimumab alone, or gp100 alone in a 3:1:1 ratio. Median overall survival was 10 months (combination), 10.1 months (ipilimumab alone), and 6.4 months (gp100 alone), a significant difference between the ipilimumab groups and the gp100 only group. Grade 3 or 4 immune-related adverse events occurred in

10–15% of patients on ipilimumab and in 3% on gp100 alone.

Ipilimumab improved overall survival in patients with metastatic melanoma.

Hodi FS et al. Improved survival with ipilimumab in patients with metastatic melanoma. *NEJM* 2010; 363: 711–23; Hwu P. Treating cancer by targeting the immune system. *Ibid*: 779–81 (editorial).

Trastuzumab plus chemotherapy for HER2-positive gastric cancer

Some 7–34% of gastric cancers are positive for human epidermal growth factor receptor 2 (HER2, or ERBB2). Trastuzumab is a monoclonal antibody against HER2. Now an international trial has shown that chemotherapy plus trastuzumab is better than chemotherapy alone in the treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer.

At 122 centres in 24 countries in Asia, central and South America, and Europe a total of 594 patients were randomised to chemotherapy alone (capecitabine plus cisplatin or fluorouracil plus cisplatin) or chemotherapy plus trastuzumab. Median overall survival was 13.8 months (trastuzumab plus chemotherapy) vs 11.1 months (chemotherapy alone), a significant difference. Toxicity was similar in the two groups.

These researchers conclude that trastuzumab plus chemotherapy should be standard treatment for HER2-positive advanced gastric or gastro-oesophageal junction cancer. *Lancet* commentators question the cost-effectiveness of adding trastuzumab, especially in developing countries.

Bang Y-J et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER-2 positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010; 376: 687–97; Munro AJ, Niblock PG. Cancer research in the global village. *Ibid*: 659–60 (comment).

Pulmonary

Sildenafil for idiopathic pulmonary fibrosis: negative study

Sildenafil stabilises cyclic guanosine monophosphate, the second messenger of nitric oxide and causes vasodilatation in the lungs. Theoretically it should improve pulmonary ventilation-perfusion matching and gas exchange in patients with idiopathic pulmonary fibrosis. A US multicentre study has given disappointing results.

A total of 180 patients were enrolled in a two-phase study. During the first 12-week phase patients were randomised to oral sildenafil 20mg three times daily or placebo. During the second 12-week phase all patients received sildenafil. In the first phase 10% of the sildenafil group and 7% in the placebo group had an improvement in 6-minute walk distance of 20% or greater, a non-significant difference for the primary outcome. Secondary outcomes included arterial oxygenation, carbon monoxide diffusion capacity, degree of dyspnoea, and quality of life and there were small but significant improvements in the sildenafil group.

Sildenafil did not affect the primary outcome but some improvements in secondary outcomes might encourage further research.

The Idiopathic Pulmonary Fibrosis Clinical Research Network. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *NEJM* 2010; 363: 620–8.

Oxygen versus room air for refractory dyspnoea

Oxygen is often given to patients with life-threatening illness and dyspnoea but its effectiveness for patients who are not hypoxaemic is uncertain. An international study has shown that oxygen used in this way provides no more benefit than room air.

At nine sites in Australia, the USA, and the UK, a total of 239 patients with refractory dyspnoea, a life-threatening illness, and PaO₂ >7.3k Pa were randomised to oxygen or room air via a concentrator through a nasal catheter at 2L per min for 7 days (15 hours a day). Breathlessness was recorded by the patient twice daily on a 0–10 numerical rating scale. Over the course of the trial there was little difference between the groups in change in breathlessness: mean morning breathlessness fell by 0.9 points (oxygen and 0.7 points (air) and evening breathlessness by 0.3 points and 0.5 points respectively. The differences between the groups were not significant. Side-effects were similar in the two groups.

These researchers suggest that after a brief trial of oxygen in the individual patient 'less burdensome strategies' should be considered.

Abernethy AP et al. Effect of palliative oxygen versus room air in relief of breathlessness in patients with dyspnoea: a double-blind, randomised controlled trial. *Lancet* 2010; 376: 784–93; Higginson IJ. Refractory breathlessness: oxygen or room air? *Ibid*: 746–8 (comment).