

General

Dalteparin vs unfractionated heparin on ICU

Critically ill patients are at increased risk of venous thromboembolism (VTE). Present evidence suggests that both unfractionated and low-molecular-weight heparin are effective prophylaxis but it is not known whether one kind of heparin is better than the other. Dalteparin (low-molecular-weight heparin) has been compared with unfractionated heparin in a study in 67 intensive care units (ICUs) in six countries.

A total of 3764 ICU patients were randomised to dalteparin (5000IU once daily s.c.) or unfractionated heparin (5000IU twice daily) with appropriate placebos. The rates of proximal leg deep vein thrombosis (DVT) were 5.1% (dalteparin) vs 5.8% (unfractionated heparin), a nonsignificant difference. The risk of pulmonary embolism was significantly lower in the dalteparin group (1.3% vs 2.3%). The rates of major bleeding and of death in hospital were similar in the two groups. Fewer patients on dalteparin had heparin-induced thrombocytopenia.

Compared with unfractionated heparin, dalteparin did not reduce the risk of DVT in ICU patients but it was associated with a lower risk of pulmonary embolus.

The PROTECT investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group. *NEJM* 2011; 364: 1305–14.

BMI in adolescence and risks of later type 2 diabetes or coronary disease

Obesity in adults is associated with increased risks of diabetes and coronary disease. Whether obesity starting in childhood is associated with greater risks is uncertain. A study in Israel has provided data from adolescence into adulthood.

A total of 37 674 men in the Israeli army were examined from the age of 17. Mean total follow-up was for 17.4 years during which 1173 men developed type 2 diabetes and 327 coronary disease. After adjustment for age, family history of diabetes, blood pressure, physical activity, fasting blood glucose, and triglyceride level the risk of later type 2 diabetes was significantly increased in participants with an adolescent BMI within the top 30% (BMI 22.35–>25.07). The increase in risk (compared with the first decile for BMI) was 47% in the eight decile, 79%

in the ninth, and 176% in the tenth. For angiographically proved coronary disease the increase in risk (compared with the first BMI decile) rose from 71% in the second decile (BMI 18.12% to 19.00) to 585% in the tenth (BMI 25.07–35.99). Adjustment for BMI in adulthood eliminated the increased risk for diabetes associated with a higher BMI in adolescence but not the increased risk for coronary disease.

An increased risk of diabetes after adjustments was associated only with a high adult BMI whereas an increased risk of coronary disease was associated with increases in both adult and adolescent BMI. Increased risk of adult type 2 diabetes is mainly associated with raised BMI near to the time of diagnosis of diabetes. Increased risk of coronary disease is associated with raised BMI in both adolescence and adulthood. The processes relating increased weight to diabetes may be quicker than those relating increased weight to coronary disease.

Tirosh A et al. Adolescent BMI trajectory and risk of diabetes versus coronary disease. *NEJM* 2011; 364: 1315–25.

AIDS

Risk of triple-class virological failure in children with HIV infection

Until recently the recommended point of initiation of treatment for children with HIV infection was dependent on CD4 count or percentage. Now, guidelines recommend starting antiretroviral therapy (ART) in early infancy. Children need to maintain HIV suppression for longer than adults. Data from 14 European cohorts have been analysed to assess the risks of triple-class virological failure in children.

Triple-class virological failure was defined as virological failure to at least two nucleotide or nucleoside reverse transcriptase inhibitors (NRTIs), one non-NRTI (NNRTI), and one protease inhibitor. The study included 1007 children aged <16 years who had been infected with HIV perinatally and started ART with at least three drugs in 1998–2008. Follow-up was for an average of 4.2 years. A quarter of these children (24%) were exposed to triple-class ART and 10% of the total had triple-class virological failure. Viral load remained above 500 copies per ml in 29 of the 105 children with triple class virological failure. The incidence of virological failure in-

creased with time and was 12% in the first 5 years of treatment. The risk also increased with greater age at the start of treatment. Treatment with NRTIs and either an NNRTI or a ritonavir-boosted protease inhibitor was associated with a greater failure rate than in adults with heterosexually transmitted HIV infection.

Strategies to limit virological failure in children who will need lifelong ART include early detection of nonresponse to treatment, strategies to maintain treatment adherence, especially in patients starting ART at age 13 years or older, and simplification of ART.

The Pursuing Later Treatment-Options II (PLATOII) project team for the Collaboration of Observational HIV epidemiological research Europe (COHERE). Risk of triple-class virological failure in children with HIV: a retrospective cohort study. *Lancet* 2011; 377: 1580–7; Calmy AL, Ford N. Improving treatment outcome for children with HIV. *Ibid*: 1546–8 comment.

Extended antituberculosis prophylaxis for HIV-infected adults in Botswana

Prophylaxis with isoniazid reduces the risk of tuberculosis in people with HIV and a positive tuberculin skin test. WHO has recommended a 6-month course of isoniazid for HIV-infected people with a positive skin test, but the skin test can be omitted if the prevalence of latent tuberculosis exceeds 30% and tuberculin skin testing is not feasible. In Botswana the 6-month course is given without skin testing. Now a trial in Botswana has shown that a 36-month course is more effective, especially in tuberculin-positive patients.

A total of 1995 adults with HIV infection received 6 months of isoniazid and were then randomised to another 30 months of isoniazid or placebo. All patients received antiretroviral therapy when their CD4 count fell below 200 cells per μ L. The incidence of tuberculosis was 34/989 (3.4%) in the 6-month isoniazid group and 20/1006 (2.0%) in the 36-month isoniazid group, giving incidences of 1.26% vs 0.72% per year, a significant 43% reduction in the 36-month group. The incidence of tuberculosis in the 6-month group increased rapidly about 200 days after stopping isoniazid. Treatment with isoniazid for 36 months reduced the risk of tuberculosis significantly by 74% in patients with a positive tuberculin skin test but there was a nonsignificant 25% reduction in patients with a negative skin test. At the end of the study 47% of patients had begun antiretroviral therapy. Antiretroviral therapy for 360 days halved the inci-

dence of tuberculosis. Mortality and the rate of severe adverse events were similar in the 6-month and 36-month isoniazid groups.

Prophylactic isoniazid for 36 months rather than 6 months significantly reduced the risk of tuberculosis in tuberculin-positive, but not in tuberculin-negative, patients with HIV infection.

Samandari T et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. *Lancet* 2011; 377: 1588–98; Dodd LE, Wilkinson RJ. Isoniazid preventive therapy in HIV infection. *Ibid*: 1548–50 (comment).

Obs & Gyn

Prediction of pre-eclampsia

A study in New Zealand, Australia, the UK, and Ireland has led to a prototype algorithm for the prediction of pre-eclampsia in healthy nulliparous women.

A total of 3572 healthy nulliparous women with a singleton pregnancy were included in the prospective cohort study. Clinical data were collected at 14–16 weeks gestation and fetal biometry and Doppler studies of the umbilical and uterine arteries were performed at 19–21 weeks. Pre-eclampsia developed in 186 women (5.3%), including 1.3% with preterm pre-eclampsia. An algorithm based on combinations of clinical risk factors was derived and women were selected for specialist referral on the basis of the algorithm. Among those selected for referral 21% developed pre-eclampsia. Compared with women not referred, those referred were five times more likely to develop pre-eclampsia and 12 times more likely to develop preterm pre-eclampsia.

The prediction algorithm was modestly successful but better than current risk prediction in practice. More work is needed to provide external validation of the algorithm in other populations and specific algorithms for subtypes of pre-eclampsia such as preterm and term pre-eclampsia.

North RA et al. Clinical risk prediction for pre-eclampsia in nulliparous women: development of model in international prospective cohort. *BMJ* 2011; 342: 909 (d1875); Magee LA, Von Dadelszen P. Clinical risk prediction of pre-eclampsia. *Ibid*: 884–5 (d1863).

Payment for performance for maternal and child health service facilities in Rwanda

Most developing countries are unlikely

to reach Millennium Development Goals 4 and 5 concerning under-5s and maternal mortality. In Rwanda, a payment for performance (P4P) scheme for maternal and child health service facilities has been introduced and monitored.

The national P4P scheme in Rwanda was introduced in 2005 with payments made directly to primary health centres to be used at the discretion of each facility. In a randomised trial a total of 166 facilities were randomised to immediate PP4 (intervention group) or to continue with input-based funding for another 23 months (control group). In an attempt to distinguish between the effects of incentives and those of increased resources the control facilities were given extra money to match the amounts received as performance payments by the intervention facilities. The intervention was associated with a 23% increase in institutional deliveries, a 56% increase in preventive care clinic visits by children aged 0–23 months, and a 132% increase in such visits by children aged 24–59 months. There were no increases in the number of women having four prenatal care visits or in the number of children completing immunisation schedules. Prenatal care quality improved in the intervention group.

These researchers conclude that P4P may improve the use and quality of maternal and child health services.

Basinga P et al. Effect on maternal and child health services in Rwanda of payment to primary health-care providers for performance: an impact evaluation. *Lancet* 2011; 377: 1421–8; Montagu D, Yamey G. Pay-for-performance and the Millennium Development Goals. *Ibid*: 1383–5 (comment).

Early medical abortion provided by doctors or nurses/auxiliary nurse midwives in Nepal

It is estimated that around the world about 22 million pregnancies are terminated unsafely each year, nearly all in developing countries. Medical abortion is safer than surgical but its use is restricted because national regulations usually insist on it being provided by a doctor. Now a study in Nepal has shown that medical abortion can be provided safely by midlevel healthcare providers.

A total of 1077 women <63 days pregnant and living <90 minutes journey from the study clinic were randomised in five rural districts of Nepal to medical abortion (mifepristone 200mg orally followed after 2 days by misoprostol 800µg vaginally) provided by a doctor or mid-level provider (government-trained cer-

tified nurse or auxiliary nurse midwife). They were followed-up after 10–14 days. The abortions were complete in 97.3% (midlevel providers) and 96.1% (doctors). Failed abortion was recorded in none of the mid-level provider group and in 1% of the doctor provider group.

Medical abortion by mid-level providers at up to 9 weeks gestation was as safe and effective as that provided by doctors. Where legal, the provision of medical abortion by midlevel providers could extend safe abortion to many more women.

Warriner IK et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomised controlled equivalence trial in Nepal. *Lancet* 2011; 377: 1155–61; Chong Y-S, Tan E-K. Mid level health-care providers key to MDG5. *Ibid*: 1127–8 (comment).

Paediatrics

Stillbirths worldwide, 1995–2009

Two reports published in 2006 gave estimates of the global total of stillbirths in 2000 of 3.3 million and 3.2 million. Now more reliable estimates have been reported for the period 1995–2009.

Stillbirth was defined as fetal death in the third trimester (at least 1000g birthweight or 28 completed weeks of gestation). Data sources included vital registration data, nationally representative surveys, published and unpublished studies, and national data identified through a WHO country consultation process. Data from 193 countries were analysed. The estimated global number of stillbirths was 2.64 million (2.14 million to 3.82 million) in 2009, a fall from 3.03 million (2.37 million to 4.19 million) in 1995. The stillbirth rate was 22.1 per 1000 births in 1995 and 18.9 per 1000 births in 2009, a decrease of 14.5%. More than three-quarters of all stillbirths (76%) in 2009 were in south Asia and sub-Saharan Africa.

The stillbirth rate globally decreased by 14.5% in a 15-year period 1995–2009. This rate of reduction is less than those for maternal mortality or for under-5s mortality. Better stillbirth data are needed.

Cousens S et al. National, regional, and worldwide estimates of stillbirth rates in 2009 with trends since 1995: a systematic analysis. *Lancet* 2011; 377: 1319–30; Walker N. Plausible estimates of stillbirth rates. *Ibid*: 1292–4 (comment).

Omalizumab for inner city children with asthma

People who live in inner cities are likely

to be exposed to multiple allergens and more likely than country dwellers to develop allergic sensitisation. The humanised monoclonal anti-Ig E antibody, omalizumab has been shown to be effective in people with asthma. Researchers in the USA have shown that omalizumab may be effective when added to standard treatment for inner city children and young adults with persistent asthma.

In eight US cities, a total of 419 inner-city children, adolescents, and young adults with persistent asthma were randomised to s.c. olizumab or placebo every 2 or 4 weeks for 60 weeks in addition to standard treatment. In the olizumab group, compared with the placebo group, there was a significant 25% reduction in the number of days with asthma symptoms in each 2-week period during the first 48 weeks of the trial. The proportion of patients with at least one exacerbation, the need for inhaled steroid and long-acting beta agonists, and the seasonal increase in asthma symptoms (in spring and autumn) were all reduced in the olizumab group. Adverse events were more frequent in the placebo group.

Adding olizumab to standard therapy may be beneficial for some inner city children and young adults with persistent asthma.

Busse WW et al. Randomized trial of omalizumab (Anti-IgE) for asthma in inner-city children. *NEJM* 2011; 364: 1005–15.

Antenatal steroid at 34–36 weeks to prevent neonatal respiratory disorders: negative trial

For infants born before 34 weeks gestation antenatal steroid given to the mother is safe and effective in reducing the risk of respiratory distress syndrome (RDS). Now a study in Brazil has shown that this treatment given at 34–36 weeks is not effective.

The study included 320 women at risk of imminent delivery at 34–36 weeks gestation. Randomisation was to betamethasone 12 mg i.m. or placebo, for two consecutive days. The risk of RDS was low: it developed in only two infants in the steroid group and one in the placebo group (1.4% vs 0.8%). Transient tachypnoea of the newborn occurred in 34 (25%) vs 29 (22%),

Antenatal steroid treatment was not effective at 34–36 weeks gestation.

Porto AMF et al. Effectiveness of antenatal corticosteroids in reducing respiratory disorders in late preterm infants: randomised clinical trial. *BMJ* 2011; 342: 858 (d1696); Roberts D. Antenatal corticosteroids in late preterm infants. *Ibid*: 833–4 (d1614).

Tropical

Co-trimoxazole to protect the infants of HIV-infected mothers from malaria

Observational studies of co-trimoxazole prophylaxis have suggested that it might be effective against malaria.

A randomised trial in Uganda has confirmed that prophylactic co-trimoxazole given to the HIV-negative infants of HIV-positive mothers has a protective effect against malaria. The trial, in a rural area of high malaria transmission intensity, included 203 breastfeeding infants of HIV-infected mothers. Co-trimoxazole was given to the infants from the time of enrolment until they stopped breastfeeding. PCR testing for HIV DNA then showed that 185 infants were HIV-negative and these infants were then randomised to stop co-trimoxazole or continue it to the age of 2 years. From the time of randomisation to age 2 years the incidence of malaria was 3.24 episodes per person-year in the continuing co-trimoxazole group and 5.57 episodes per person-year in the stop co-trimoxazole group, a significant 39% difference. The rates of complicated malaria, diarrhoea, pneumonia, adverse events, hospital admission, and death were similar in the two groups.

Co-trimoxazole prophylaxis reduced the risk of malaria among the HIV-negative infants of HIV-positive mothers.

Sandison TG et al. Protective efficacy of co-trimoxazole prophylaxis against malaria in HIV exposed children in rural Uganda: a randomised clinical trial. *BMJ* 2011; 342: 809 (d1617).

Surgery

Prediction rule for walking after spinal injury

After spinal cord injury it is important to try to predict whether the patient will walk or not in order to guide counselling and rehabilitation.

Data from 19 European spinal centres have been analysed to derive a clinical prediction rule for ambulation. The data included 1442 patients with traumatic spinal injury. Clinical examination was recorded within 15 days of the injury and 492 patients had outcome data recorded. The clinical prediction rule was based on age and neurological variables (age <65 or 65 and over, motor scores of the quadriceps femoris (L3) and gas-

trosoleus (S1) muscles, and light touch sensation at dermatomes L3 and S1). An equation was derived and a graph drawn relating the prediction rule score (-10 to +40) from these variables to the probability of independent walking at 1 year. The prediction rule score showed excellent discrimination in distinguishing between independent walkers, dependent walkers, and non-walkers. Temporal validation in 99 patients confirmed this discriminating ability.

The clinical prediction rule can be used to give an early prognosis about walking at 1 year after traumatic spinal cord injury.

Von Middendorp JJ et al. A clinical prediction rule for ambulation outcomes after traumatic spinal cord injury: a longitudinal cohort study. *Lancet* 2011; 377: 1004–10; El Masri(y) WS, Kumar N. Traumatic spinal cord injuries. *Ibid*: 972–4 (comment).

Antibiotics vs surgery for acute appendicitis

Local or generalised peritonitis occurs in about 20% of cases of acute appendicitis. Appendicectomy is still the most common treatment for acute appendicitis but evidence has accumulated that antibiotic treatment without surgery may be effective. Surgery may lead to complication in the short term and in the long term to intestinal obstruction from adhesions.

Researchers in France have compared appendicectomy with antibiotic treatment in a noninferiority trial. A total of 239 patients with a diagnosis of uncomplicated acute appendicitis after CT scan were randomised at six centres to amoxicillin plus clavulanic acid given orally (or intravenously in the presence of nausea and vomiting) or to emergency appendicectomy. Peritonitis occurred within 30 days in 8% (antibiotics) vs 2% (surgery), a significant difference. Peritonitis was found at operation in 18% of the surgery group despite a normal preoperative CT scan. In the antibiotic group, 12% had an appendicectomy within 30 days and another 29% over the subsequent 11 months.

Appendicectomy gave better results than antibiotic treatment (antibiotic treatment was not noninferior). Better use of CT scanning might identify patients suitable for antibiotic treatment. A *Lancet* commentator criticises the trial because of the choice of antibiotic and of noninferiority margin. A wider margin might have demonstrated noninferiority.

Vons C et al. Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label non-inferiority, randomised controlled trial. *Lancet* 2011; 377: 1573–9; Mason RJ. Appendicitis: is surgery the best option. *Ibid*: 1545–6.

Infection

Xpert MTB/RIF testing for tuberculosis in resource-poor health facilities

Smear microscopy detects only about 28% of cases of tuberculosis. A rapid diagnostic test would be very valuable, especially in areas with a high prevalence of HIV infection. A new real-time PCR assay (Xpert-MTB/RIF) detects *Mycobacterium tuberculosis* and also detects rifampicin resistance. In a study in reference laboratories this test detected 92% of cases of tuberculosis, including 73% of patients with smear-negative disease. Now it has been shown to be effective in resource-poor countries.

The study included 6648 adults with suspected tuberculosis or multidrug-resistant tuberculosis in South Africa, Peru, India, Azerbaijan, the Philippines, and Uganda. Of 1033 culture-confirmed cases of tuberculosis the MTB/RIF test detected 933 (90.3%) whereas microscopy detected 699 (67.1%). The MTB/RIF test was 77% sensitive in smear-negative, culture-positive patients and 99% specific. For rifampicin resistance it was 94% sensitive and 98% specific. Co-infection with HIV significantly decreased the sensitivity of microscopy but not of the MTB/RIF test. Results were available within 1 day with the MTB/RIF test, within 2 days with microscopy, and within 58 days with culture. For smear-negative tuberculosis the MTB/RIF test reduced the median time to treatment from 56 days to 5 days. Results were indeterminate for 2.4% of MTB/RIF tests and 4.6% of cultures.

The MTB/RIF test is suitable for use in low-resource countries and could improve the results of treatment.

Boehme CC et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert/MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. *Lancet* 2011; 377: 1495–1505, Kranzer K. Improving tuberculosis diagnostics and treatment. *Ibid*: 1467–8.

Inactivated yellow fever vaccine

The current vaccine against yellow fever (17D) is a live attenuated vaccine first produced 75 years ago. It may produce a life-threatening disease similar to yellow fever and may also cause encephalitis and anaphylaxis. A new inactivated cell-culture vaccine (XRX-001) has been assessed in Kansas City, USA.

Sixty healthy people aged 18–49 years were randomised to (2:2:1) to two

doses of XRX-100 21 days apart at a dose of either 0.48 or 4.8 µg of antigen per injection, or placebo. All of the participants receiving the 4.8 µg dose and 88% of those receiving the 0.48 µg dose developed neutralising antibodies. Antibody levels increased by day 10 after the second injection when levels were significantly higher in the group receiving the higher dose (geometric mean titre, 146 vs 39). Mild pain, tenderness, and, occasionally, itching at the injection site occurred more frequently in the vaccine group than in the placebo group.

The new vaccine may be safer than the current vaccine.

Monath TP et al. A inactivated cell-culture vaccine against yellow fever. *NEJM* 2011; 364: 1326–33.

Diabetes

Cardiovascular effects of rosiglitazone vs pioglitazone

The thiazolidinediones, rosiglitazone and pioglitazone, both have cardiac adverse effects. A systemic review and meta-analysis of published studies has been carried out to compare the two drugs.

The analysis included 16 studies (810 000 patients treated with a thiazolidinedione for type 2 diabetes) in North America, the UK, and Taiwan. The average age of participants was >60 years. Compared with pioglitazone, rosiglitazone was associated with significant increases of 16% in myocardial infarction, 22% in congestive heart failure, and 14% in mortality. For every 100 000 patients treated with rosiglitazone rather than pioglitazone there would be 170 extra myocardial infarctions, 649 extra cases of heart failure, and 431 extra deaths.

The cardiovascular risks of rosiglitazone are greater than those of pioglitazone.

Loke YK et al. Comparative cardiovascular effects of thiazolidinediones: systematic review and meta-analysis of observational studies. *BMJ* 2011 342: 692 (d1309); Montori VM, Shah ND. What have we learnt from the rosiglitazone saga? *Ibid*: 666 (d1354) (editorial).

Overnight closed loop insulin delivery in adults

Overnight closed-loop delivery of insulin has been successful in children and adolescents with type 1 diabetes but there are few data about its use in adults. Now two sequential, open-label ran-

domised controlled crossover studies in adults have been reported together.

The two studies had 24 participants with type 1 diabetes. Twelve were studied after an average meal ('eating in') and 12 after a larger meal with wine ('eating out'). During experimental nights closed-loop delivery of insulin was used overnight with glucose sensor measurements fed into a computer algorithm that determined infusion rates at 15 minute intervals. A nurse adjusted the insulin pump delivery rates using the computer information. During control nights conventional insulin pump settings were used. Overall, closed-loop delivery increased the time plasma glucose levels were in the target range (3.91–8.0 mmol/L) by a significant 22% (15% on 'eating in' nights and 28% on 'eating out' nights). It reduced hypoglycaemia (plasma glucose 3.9 mmol/L or less) times significantly by 3% and abolished plasma glucose levels <3.0 mmol/L after midnight.

In these pump-treatment-accustomed adults closed loop delivery improved overnight glucose control and eliminated post midnight glucose levels <3.0 mmol/L. Further development of 'artificial pancreas' systems is needed and expected.

Hovorka R et al. Overnight closed loop insulin delivery (artificial pancreas) in adults with type 1 diabetes: crossover randomised controlled studies. *BMJ* 2011; 342: 906 (d1855); Kovatchev B. Closed loop control for type 1 diabetes. *Ibid*: 883–4 (d1911) (editorial).

Pioglitazone to prevent diabetes in patients with impaired glucose tolerance

Interventions that delay the onset of type 2 diabetes in people with impaired glucose tolerance (IGT) include lifestyle modification, use of drugs such as metformin, thiazolidinediones, or acarbose, and bariatric surgery. Of the thiazolidinediones, troglitazone is no longer available and the use of rosiglitazone is restricted because of concerns about cardiovascular safety.

Now a multicentre US trial has shown that treatment with pioglitazone reduces the risk of conversion from impaired glucose tolerance to type 2 diabetes. A total of 602 patients aged 18 years or older with IGT and a BMI of 25 or greater were randomised to pioglitazone or placebo. The annual incidence of type 2 diabetes was 2.1% (pioglitazone) vs 7.6% (placebo), a highly significant 72% risk reduction with pioglitazone. Glucose tolerance reverted to normal in 48% vs 28%. Treatment with pioglitazone was

associated with significant reductions in fasting glucose, 2-hour glucose, and glycosylated haemoglobin levels compared with placebo treatment.

Pioglitazone treatment was also associated with a reduction in blood pressure and in carotid intima-media thickening, and an increase in HDL cholesterol levels. Weight gain was greater with pioglitazone and oedema was more frequent.

Pioglitazone reduced the risk of type 2 diabetes among people with IGT but was associated with increased risk of weight gain and oedema.

DeFronzo RA et al. Pioglitazone for diabetes prevention in impaired glucose tolerance. *NEJM* 2011; 354: 1104–15.

Cardiology

Two-year outcomes of drug-eluting stents trial

The RESOLUTE All Comers trial, published in 2010, compared two new generation drug-eluting coronary stents and showed that the Resolute zotarolimus-eluting stent was noninferior to the Xience V everolimus-eluting stent for the endpoint of target lesion failure at 1 year. Now the 2-year clinical outcomes have been reported.

A total of 2292 patients were randomised to one or the other stent. At 2 years the rate of the patient-related outcome (death, myocardial infarction, or any revascularisation) was 20.6% in the zotarolimus group and 20.5% in the everolimus group. The rates of the stent-related outcome (cardiac death, target vessel myocardial infarction, or ischaemia-driven target vessel revascularisation) at 2 years were 11.2 vs 10.7%. Three patients (0.3%) in each group had very late (>1 year) stent thrombosis.

The outcomes with the two stents were similar at 2 years.

Silber S et al. Unrestricted randomised use of two new generation drug-eluting coronary stents: 2-year patient-related stent-related outcomes from the RESOLUTE All Comers trial. *Lancet* 2011; 377: 1241–7; Lassen JF. Long-term safety and efficacy of drug-eluting stents. *Ibid*: 1213–4 (comment).

Angiotensin-receptor blockers: no increased risk of myocardial infarction

After a trial of the angiotensin receptor blocker (ARB), valsartan for hypertension it was suggested that ARBs might increase the risk of myocardial infarction. Now a meta-analysis of data from

37 randomised trials (147 020 patients, 485 166 patient-years of follow-up) has refuted the suggestion.

The data showed a nonsignificant 1% decrease in risk of myocardial infarction with ARB treatment compared with controls (placebo or active treatment). There were also no increases in risk of death from any cause, death from cardiovascular causes, or angina. There was no evidence of even a relative 5.0–7.5% (absolute 0.3%) increase in risk of myocardial infarction. There was also no evidence that ARBs protected against myocardial infarction. There was, however, evidence that ARB treatment reduced the relative risks of stroke, heart failure, or new onset diabetes, by about 10% on average in each case.

Angiotensin receptor blockers do not increase the risk of myocardial infarction.

Bangalore S et al. Angiotensin receptor blockers and risk of myocardial infarction: meta-analyses and trial sequential analyses of 147020 patients from randomised trials. *BMJ* 2011; 342: 1010 (d2234); Hobbs FDR. Angiotensin receptor blockers and cardiovascular outcomes. *Ibid*: 985–6 (d2193) (editorial).

Pulmonary

Acute respiratory distress syndrome: 5-year follow-up

Studies of outcome after acute respiratory distress syndrome (ARDS) have not gone beyond 2 years. Now 5-year data have been reported from four centres in Toronto, Canada.

One hundred and nine (109) survivors of ARDS (median age 44 years at onset of ARDS) were followed-up at 3, 6, and 12 months and 2, 3, 4, and 5 years after the acute episode. At 5 years the median 6-minute walk distance was 436m (76% of predicted). The average score on the Medical Outcomes Study 36-Item Short-Form Health Survey was 41 (mean normal for age and sex 50). Younger patients had better scores and recovered faster than older patients but neither returned to normal. Pulmonary function was normal or close to normal. Both patients and family caregivers had physical and psychological problems for up to 5 years.

Patients with ARDS may have physical and psychological problems for 5 years or more after the acute episode.

Herridge MS et al. Functional disability 5 years after acute respiratory distress syndrome. *NEJM* 2011; 364: 1293–304; Hall JB, Keress JP. The burden of functional recovery from ARDS. *Ibid*: 1358–9 (editorial).

Improved survival in cystic fibrosis

The use of nebulised recombinant human DNase may have played a large part in the improvement of survival rates among adults with cystic fibrosis and poor lung function over the last two decades.

At the Royal Brompton Hospital in London a cohort study included 276 adults with cystic fibrosis whose FEV1 was first recorded at <30% of the predicted value in 1990–2003. Among patients recruited in 1990–1991, median survival was 1.2 years but among patients recruited in 2002–2003 it was 5.3 years. Most of the improvement occurred between 1994 and 1997 and followed increasing use of nebulised recombinant human DNase. There was an increase in average body mass index at the same time.

Survival among adult patients with cystic fibrosis and poor lung function has improved since 1990 and at least some of the improvement may have been due to use of nebulised recombinant human DNase.

George PM et al. Improved survival at low lung function in cystic fibrosis: cohort study from 1990 to 2007. *BMJ* 2011; 342: 586 (d1008); Dasenbrook EC. Cystic fibrosis and survival in patients with advanced lung disease. *Ibid*: 558–9 (d726) (editorial).

Preventing exacerbations of COPD: tiotropium vs salmeterol

The use of inhaled long-acting bronchodilators is recommended for patients with moderate-to-very severe chronic obstructive pulmonary disease (COPD). Inhaled tiotropium (a long-acting anticholinergic drug) has been compared with inhaled salmeterol (long-acting β_2 agonist) in a multinational trial.

A total of 7376 patients with moderate-to-very severe COPD were randomised at 725 centres in 25 countries to inhaled tiotropium 18 μ g once daily or inhaled salmeterol 50 μ g twice daily. Compared with salmeterol, tiotropium increased the time to the first exacerbation (187 days vs 145 days, a significant 17% risk reduction). The time to the first severe exacerbation, the annual number of moderate or severe exacerbations, and the annual number of severe exacerbations were all improved significantly with tiotropium compared with salmeterol. The rate of adverse events was similar in the two groups.

Tiotropium gave better results than salmeterol.

Vogelmeier C et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *NEJM* 2011; 364: 1093–103; Wedzicha JS. Choice of bronchodilator therapy for patients with COPD. *Ibid*: 1167–8.