General

Contribution of physical inactivity to disease burden and mortality

Exercise reduces the risk of many non-communicable disease including coronary disease, type 2 diabetes, and cancer of breast and colon. An analysis of published studies has provided data about the contribution of inactivity to the worldwide burden of disease and mortality.

For coronary disease, physical inactivity was estimated to cause 5.8% of the worldwide burden, ranging from 3.2% in southeast Asia to 7.8% in Latin America and the Caribbean, with figures of 6.2% in North America, 5.5% in Europe, and 5.8% in the Western Pacific. The individual countries in which physical inactivity contributed most to coronary disease were Malta and the Cook Islands (population attributable fraction (PAF) 11.9%), and Swaziland and Saudi Arabia (11.4%). The lowest PAF values were in Bangladesh (0.8%) and Mozambique (1.2%). In Africa, the values ranged from 1.2% in Mozambique to 11.4% in Swaziland. For type 2 diabetes, the worldwide PAF was 7%, ranging from 3.9% in Southeast Asia to 9.6% in the eastern Mediterranean. For breast cancer the median was 10% (from 5.6% in Southeast Asia to 14.1% in the eastern Mediterranean); for colon cancer 10% (from 5.7% in Southeast Asia to 13.8% in the eastern Mediterranean). The contribution of physical inactivity to all-cause mortality worldwide was 9.4% (from 5.1% in Southeast Asia to 12.5% in the eastern Mediterranean). It is estimated that inactivity causes 5.3 million premature deaths each year and a 25% reduction in physical inactivity would avert 1.3 million such deaths each year.

Physical inactivity is a major contributor to ill health worldwide, equivalent in effect to smoking.

Lee I-M et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet* 2012; 380: 219–29; Wen CP, Wu X. Stressing harms of physical inactivity to promote exercise. Ibid: 192–3 (comment).

Dangers of hydroxyethyl starch 130/0.4 in severe sepsis

Guidelines suggest using either colloid or crystalloid solutions for fluid resuscitation in severe sepsis. Trials of high molecular weight hydroxyethyl starch showed an increase in risk of acute renal failure, but the preparation used in those trials has been replaced by HES 130/0.4, a hydroxyethyl starch solution with a lower molecular weight and a lower ratio of hydroxyethyl groups to glucose molecules. Now a trial in Denmark, Norway, Finland, and Iceland has shown that HES 130/0.4 is associated with greater risk of renal replacement therapy and death within 90 days compared with Ringer's acetate.

A total of 798 adults with severe sepsis were randomised to fluid resuscitation in the ICU with 6% HES 130/0.4 or Ringer's acetate at a rate of 33 ml/kg of ideal body weight per day and included in the analysis. At 90 days, mortality was significantly 17% higher in the HES 130/0.4 group (51% vs 43%). One patient in each group developed end-stage renal failure but renal replacement therapy was needed by 22% vs 16%, a significant 35% increase in the HES 130/0.4 group.

Compared with Ringer's acetate, use of HES 130/0.4 was associated with increased need for renal replacement therapy and increased 90-day mortality when used for fluid resuscitation in patients with severe sepsis.

Perner A et al. Hydroxyethyl starch 130/0.4 versus Ringer's acetate in severe sepsis. *NEJM* 2012; 367: 124–34.

Reconstructive surgery for female genital mutilation

In the last 10 years female genital mutilation (FMG) has been suffered by 130-140 million girls worldwide, including 92 million in Africa. Now surgeons in France have reported the results of reconstructive surgery on 2938 women between 1998 and 2009. The mean age at FMG was 6.1 years and the mutilative procedures had been performed mainly in Mali, Senegal, and the Ivory Coast, but 564 had been done in France.

Reasons given for requesting reconstructive surgery were recovery of identity (99%), improvement in sex life (81%), and pain reduction (29%). Only 866 women (29%) attended for 1-year follow-up but most of them reported improvement in pain and sexual satisfaction.

Women may benefit from reconstructive surgery after FMG. A multidisciplinary approach is needed to deal with nonsurgical issues.

Foldès P et al. Reconstructive surgery after female genital mutilation: a prospective cohort study. *Lancet* 2012; 380: 134–41; Abdulcadir J et al. Reconstructive surgery for female genital mutilation. Ibid: 90–2 (comment).

Tropical

Financing of healthcare in Ghana, South Africa, and Tanzania

An important aim of many developing countries, encouraged by world health organisations, is the provision of universal and equal health coverage for all people, according to ability to pay and health needs. Different approaches to healthcare financing and equity in access are debated but there has been little published evidence. Now data from Ghana, South Africa, and Tanzania have been reported.

In all three countries overall, healthcare financing and direct taxes were progressive (higher income groups contributing a greater proportion of their income). Indirect taxation was regressive in South Africa but progressive in Ghana and Tanzania. Out-of-pocket payments were regressive in all three countries. In Ghana and Tanzania, health insurance contributions by people outside the formal sector were regressive. In all three countries, the illness burden was greater among the poor but the distribution of service benefits favoured the rich. Access to health services was unequal

Barriers to health service access for the poor need to be addressed.

Mills A et al. Equity in financing and use of health care in Ghana, South Africa, and Tanzania: implications for paths to universal coverage. *Lancet* 2012; 380: 126–33; Gwatkin DR. Paying for health care: moving beyond the user-free debate. Ibid: 88–90 (comment).

AIDS

ART given by nurses in South Africa

In order to increase access to antiretroviral therapy (ART) in Africa, tasks have been delegated to healthcare workers other than doctors (task shifting). Incomplete evidence suggests that task shifting is effective. Now a large study in South Africa has confirmed the effectiveness of the STRETCH programme (Streamlining Tasks and Roles to Expand Treatment and Care for HIV). In this programme nurses are trained to take responsibility for the initiation and maintenance (represcribing) of ART.

A total of 31 primary care ART clinics were cluster-randomised to STRETCH or standard care (controls). Cohort 1 (9252 patients) consisted of patients aged 16 years or older with CD4 counts

of 350 cells per µL or less and not on ART. Cohort 2 (6231 patients) consisted of patients aged 16 years or older who had been on ART for at least 6 months. Median follow-up was 16.3 months in cohort 1 and 18.0 months in cohort 2. In cohort 1, mortality was similar in the two groups (20% with STRETCH vs 19% in controls), as was survival time. STRETCH was associated with a slightly lower mortality than in controls in patients with a CD4 count of 201-350 cells per µL but among patients with lower CD4 counts mortality was essentially the same in the two groups. In cohort 2 viral load suppression at 12 months after enrolment was achieved by 71% of patients in the STRETCH group and 70% in the control group.

Training nurses to initiate and maintain ART was successful.

Fairall L et al. Task shifting of antiretroviral treatment from doctors to primary-care nurses in South Africa (STRETCH): a pragmatic, parallel, cluster-randomised trial. *Lancet* 2012; 380: 889–98; Boyd M, Mohapi L. STRETCHing delivery of HIV health services. Ibid: 865–7 (comment).

Antiretroviral prophylaxis for HIV-1-negative partner of HIV-1 discordant couples

A study at nine centres in Kenya and Uganda has shown that antiretroviral prophylaxis given to the HIV-1 negative partner of an HIV-1-serodiscordant couple may prevent acquisition of the infection.

The trial included a total of 4747 serodiscordant heterosexual couples. The seronegative partners were randomised to tenofovir disoproxil fumarate (TDF) 300 mg daily, the same dose of TDF plus emtricitabine 200 mg daily (TDF-FTC), or placebo and followed up monthly for up to 36 months. The seropositive partners were not eligible for antiretroviral treatment on enrolment but were referred for treatment if they became eligible. During the study, 82 seronegative partners became seropositive: 17 in the TDF group, 13 in the TDF-FTC group, and 52 in the placebo group, giving incidence rates of 0.65, 0.50, and 1.99 per 100 person–years respectively. Both treatments were significantly better than placebo in both men and women but there was no significant difference between TDF and TDF-FTC. Adverse event rates were similar in the three groups.

Both TDF and TDF-FTC were effective prophylaxis for the seronegative partner of HIV-1 serodiscordant heterosexual couples.

Baeten JM et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *NEJM* 2012; 367: 399–410; Cohen MS, Baden LR. Preexposure prophylaxis for HIV-where do we go from here: Ibid: 459–61 (editorial); Abdool Karim SS et al. Pre-exposure prophylaxis for HIV prevention. Ibid: 462–5 (clinical decisions).

Antiretroviral prophylaxis for women at increased risk: negative trial

A study in Kenya, South Africa, and Tanzania has assessed the prophylactic use of combined tenofovir disoproxil fumarate and emtricitabine (TDF-FTC) in women at increased risk of HIV-1 infection, with negative results.

The trial included 2120 sexually active HIV-negative women aged 18–35 years. Randomisation was to TDF-FTC or placebo once daily for 52 weeks and follow-up was every 4 weeks for 60 weeks. HIV infection occurred in 33 women in the prophylaxis group and 35 in the placebo group (incidence 4.7 vs 5.0 per 100 person–years, a nonsignificant difference). Prophylaxis was associated with higher rates of nausea, vomiting, and raised alanine amino-transferase levels. Drug discontinuation for kidney or liver function abnormalities was significantly more frequent in the TDF-FTC group (4.7% vs 3.0%). Plasma drug level testing suggested that drug adherence was low.

Prophylaxis with TDF-FTC was not effective in this study but rates of adherence were probably low.

Van Damme L et al. Preexposure prophylaxis for HIV infection among African women. *NEJM* 2012; 367: 411–22; Cohen MS, Baden LR. Preexposure prophylaxis for HIV – where do we go from here? Ibid: 459–61 (editorial); Abdool Karim SS et al. Pre exposure prophylaxis for HIV prevention. Ibid: 462–5 (clinical decisions).

Antiretroviral prophylaxis for sexually active people in Uganda

In Uganda in 2008, around 40% of people aged 30–44 years were HIV-positive. A study of prophylaxis with combined tenofovir disoproxil fumarate and emtricitabine (TDF-FTC) has shown it to be effective.

A total of 1219 sexually active, HIV-negative, heterosexual men and women were randomised to TDF-FTC or placebo and followed up for up to 3.7 years (median 1.1 years). The study was ended early because of low retention and logistical problems. HIV infection occurred in 9 subjects in the prophylaxis group and 24 in the placebo group (incidence 1.2 vs 3.1 per 100 person–years; efficacy of TDF-FTC, 62%).

In this study prophylactic TDF-FTC was effective. The reasons for the differing results in the three studies in this issue of NEJM are unclear.

Thigpen MXC et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *NEJM* 2012; 367: 423–34; Cohen MS, Baden LR. Preexposure prophylaxis for HIV – where do we go from here? Ibid: 459–61 (editorial); Abdool Karim SS et al. Preexposure prophylaxis for HIV prevention. Ibid: 462–5 (clinical decisions).

HIV-2 infection inhibits progression of HIV-1 disease

HIV-1 infection occurs worldwide but HIV-2 infection occurs almost exclusively in West Africa. HIV-2 causes a less aggressive disease with only 20–30% of those infected progressing to AIDS. In West Africa, up to 3% of people are infected with both HIV-1 and HIV-2. Evidence has suggested that the dual infection may be less progressive than infection with HIV-1 alone. Now a study in Guinea-Bissau has confirmed this suggestion.

The prospective study included 98% of the Guinea-Bisau police force between 1990 and 2007. After enrolment, 223 people (187 men and 36 women) were infected with HIV. Among these 161 men and 30 women were infected with HIV-1 only and 26 men and 6 women were infected with both HIV-1 and HIV-2. The median time to AIDS was 104 months (dual infection) versus 68 months (HIV-1 only), a significant difference. Dual infection was associated with higher CD4+ T-cell counts and slower increase in CD8+T-cell counts. The longest time to AIDS and highest CD4+ T-cell counts were in patients whose HIV-2 infection preceded HIV-1 infection.

Dual infection with HIV-1 and HIV-2 is associated with less severe disease than HIV-1 infection alone, especially when infection with HIV-2 is first.

Esbjörnsson J et al. Inhibition of HIV-1 disease progression by contemporaneous HIV-2 infection. *NEJM* 2012; 367: 224–32.

Paediatrics

Progress on stunting and underweight in 141 developing countries

Millennium Development Goal 1 includes a targeted 50% reduction in underweight among children under the age of 5 years between 1990 and 2015. Progress towards the goal has been assessed with data from 141 developing countries.

Mean height-for-age Z score (HAZ) increased from -1.86 in 1985 to -1;16 in 2011 and mean weight-for-age Z score (WAZ) increased from -1.31 to -0.84. During the same period the prevalence

of moderate or severe stunting fell from 47.2% to 29.9% and of underweight from 30.1% to 16.5%. In sub-Saharan Africa the measurements got worse until the late 1990s and then improved. The largest absolute improvements were in Asia and the largest relative improvements in southern and tropical Latin America. In 2011 there were still 314 million stunted children and 258 million underweight children in these countries.

It is concluded that the likelihood of meeting the MDG1 target is <5% for developing countries as a whole but there is a 50–100% chance in 61 of the 141 countries. Further progress is dependent on economic growth and better nutritional and primary medical care for the poor.

Stevens GA et al. Trends in mild, moderate, and severe stunting and underweight, and progress towards MDG1 in 141 developing countries: a systematic analysis of population representative data. *Lancet* 2012; 380: 824–34; Gorden-Larsen P, Jones-Smith J. Challenges in ameliorating hunger while preventing obesity. Ibid: 787–9 (comment).

Violence against handicapped children

Child abuse is common. It is estimated that in 2001 some 53 000 children were murdered and 223 million were sexually abused. About 5% of children (3% in high-income countries and up to 6% in low- or middle-income countries) have moderate or severe disability. It is known that adults with disability are particularly vulnerable to violence and suspected that the same applies to children with disability. A systematic review and meta-analysis of observational studies of violence in disabled children has confirmed this susceptibility whilst criticising the quality of current evidence.

The analysis included 17 studies. The prevalence of violence of any kind against children with any disability was 26.7%; for physical violence it was 20.4%; and for sexual violence 13.7%. Compared with other children, children with a disability were almost four times more likely to suffer violence of any kind, more than three times more likely to suffer physical violence, and almost three times more likely to suffer sexual violence.

The analysis confirms the increased prevalence of violence in disabled children compared with other children but much more needs to be known about risk factors and means of prevention.

Jones L et al. Prevalence and risk of violence against children with disabilities: a systematic review and meta-analysis of observational studies. *Lancet* 2012; 380: 899–907; Lund EM, Vaughn-Jensen JE. Victimisation of children with disabilities. Ibid: 867–9 (comment).

Respiratory rate corrected for age and temperature in diagnosis of lower respiratory infection in children

Respiratory rate is important in the diagnosis of lower respiratory tract infection in children but it may be affected by age and body temperature. Data from a single children's emergency department in the Netherlands have been used to derive age and temperature dependent reference values for respiratory rate in febrile children.

The derivation population consisted of 1555 children under the age of 16 years. Centile charts for respiratory rate were constructed for children of different ages and body temperatures. A validation population of 671 children was used to compare respiratory rate and temperature values for children of different ages with pneumonia, other lower respiratory infections, and non-lower respiratory infections. Overall, respiratory rate increased by 2.2 breaths per minute with every 1°C rise in body temperature. Respiratory rate values above the 97th centile on the new age and temperature dependent charts were more useful in the diagnosis of lower respiratory tract infection than was use of existing respiratory rate thresholds but could not discriminate between pneumonia and other lower respiratory tract infections. They gave a specificity of 0.94 and a positive likelihood ratio of 3.66. In infancy the 97th centile value for respiratory rate was 69 breaths/min with a temperature of 37.0 to 37.9°C and 75 breaths/min with a temperature of 39.0 to 39.9°C. At ages 5 to 16 years the corresponding values were 36 and 44 breaths/min.

Centile charts for respiratory rate taking into account age and body temperature may be useful in the diagnosis of lower respiratory tract infection in children. The data should be used only to add strength to diagnosis of lower respiratory infection and not to dismiss it.

Nijman RG et al. Derivation and validation of age and temperature specific reference values and centile charts to predict lower respiratory tract infection in children with fever: prospective observational study. *BMJ* 2012; 345: (July 28): 15 (e4224): Kilonback A. Assessing respiratory rate for children with fever. Ibid: 8 (e4249).

Obs & Gyn

Effect of contraception on maternal mortality rates

The Safe Motherhood Initiative begun in 1987 has four strategies to reduce maternal mortality: family planning, antenatal care, safe delivery, and postnatal care. Now the effects of contraceptive use on maternal mortality worldwide have been estimated from three international databases.

Data were analysed from 172 countries for 2008. The number of deaths from maternal causes in 2008 was estimated at 342 203 (data from 172 countries). The estimated number of maternal deaths averted by contraception was 272 040, a 44% reduction of the potential total. It was also estimated that expansion of contraceptive use could avert another 104 000 maternal deaths each year. The number of deaths averted increased with increased contraceptive use. In countries with high (>65%) contraceptive use almost 60% of potential maternal deaths were averted whereas in sub-Saharan Africa (22% contraceptive use) only 32% of potential maternal deaths were averted.

Increased use of contraception could prevent many maternal deaths in developing countries.

Ahmed S et al. Maternal deaths averted by contraceptive use: an analysis of 172 countries. *Lancet* 2012; 380: 111–25; Gilmore K, Gebreyesus TA. What will it take to eliminate preventable maternal deaths? Ibid: 87–8 (comment).

Urinary protein-to-creatinine or albumin-to-creatinine ratio to detect significant proteinuria in pregnancy

A systematic review and met-analysis has addressed the use of spot urine protein-to-creatinine or albumin-to-creatinine ratio to detect significant proteinuria in pregnancy in the diagnosis of pre-eclampsia.

The analysis included 20 studies (2978 women). Threshold values for protein-to-creatinine ratio ranged from 0.13 to 0.5 with sensitivity values between 0.65 and 0.89 and specificity of 0.63 to 0.87 for the detection of 24-hour urinary protein >0.3 g/day. The optimum threshold values for protein-to-creatinine ratio appeared to be 0.30–0.35. There was insufficient evidence about the use of albumin-to-creatinine ratio. One study suggested that a value of >2 mg/mmol was associated with a sensitivity and a specificity both of 0.94. There is insufficient evidence about the use of either test to predict adverse pregnancy outcome.

Urinary protein-to-creatinine ratio may be useful in the diagnosis of pre-eclampsia but there is insufficient evidence about the use of albumin-to-creatinine ratio for this purpose or about the use of

either test to predict adverse pregnancy outcome.

Morris RK et al. Diagnostic accuracy of spot urinary protein and albumin to creatinine ratios for detection of significant proteinuria or adverse pregnancy outcome in patients with suspected pre-eclampsia: systematic review and meta-analysis. *BMJ* 2012; 345: (July 21): 14 (e4342).

Oncology

Localised prostate cancer: radical prostatectomy versus 'wait and see'

The management of localised prostate cancer detected as a result of PSA screening remains controversial. Available data are from trials conducted before PSA screening became widespread. Now a multicentre US trial has added support to a policy of observation.

Between November 1994 and January 2002 a total of 731 men with localised prostate cancer were randomised at 52 centres to radical prostatectomy or regular follow-up without surgery. After an average follow-up of 10 years overall mortality was 47.0% (radical prostatectomy) vs 49.9% (observation), a nonsignificant difference. Death from prostate cancer or treatment occurred in 5.8% vs 8.4%, also a nonsignificant difference. The effect of treatment on mortality rates was not affected by age, race, comorbidity, performance status, or tumour histology. Radical prostatectomy was associated with significantly reduced overall mortality among men with a PSA level >10§ng/ml and possibly among men with intermediate-or high-risk tumours. In the radical prostatectomy group 21.4% had at least one adverse event within 30 days of operation.

Radical prostatectomy did not reduce all-cause or prostate-cancer-specific mortality after at least 12 years of follow-up.

Wilt TJ et al. Radical prostatectomy versus observation for localized prostate cancer. *NEJM* 2012; 367: 203–13; Thompson IM, Tangen CM. Prostate cancer – uncertainty and a way forward. Ibid: 270–1 (editorial).

Dabrafenib for BRAF-mutated metastatic melanoma

The V600E BRAF mutation is present in 40–45% of melanomas. Vemurafenib, an inhibitor of mutated BRAF, has been approved by US and European regulatory bodies for the treatment of BRAF-mutated melanoma. Dabrafenib is a selective inhibitor of BRAFV600E kinase. A multinational trial has shown dabrafenib to be beneficial in patients with metastatic melanoma with a BRAFV600E mutation.

A total of 250 patients were randomised (3:1) to dabrafenib or chemotherapy with dacarbazine. Median progression-free survival was 5.1 months (dabrafenib) vs 2.7 months (dacarbazine), a significant difference. The rate of toxicity (grade 2 or higher treatment-related adverse events) was 53% vs 44%. Grade 3–4 adverse events were uncommon in both groups.

Dabrafenib was associated with a significant increase in progression-free survival compared with dacarbazine.

Hauschild a et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet* 2012; 380: 358–65; Margolin K. BRAF inhibition and beyond in advanced melanoma. Ibid: 320–2 (comment).

Cardiology

Statins for everybody?

Statins are effective in reducing cardiovascular risk. A new meta-analysis has shown that they are probably beneficial, even for people at low risk.

The meta-analysis included individual participant data from 22 trials of statin vs control (134 537 people) and five trials comparing high vs low dose statin. Major vascular risk over 5 years was categorised as <5%, 5–<10%, 10–<20%, 20–<30%, or 30% or greater on control therapy. Each 1.0 mmol/L reduction in LDL cholesterol level was associated with a significant 21% reduction in risk of major cardiovascular events largely irrespective of age, sex, baseline LDL cholesterol level, or previous cardiovascular history. The proportional reduction in risk was similar for high-risk and low-risk participants. There were significant risk reductions for major coronary events of 43% and 39% for each 1.0 mmol /L reduction in LDL cholesterol in the two lowest risk categories. The relative reduction in risk of stroke was a significant 24% in the two lowest risk categories. For primary prevention there were relative reductions of 15% and 9% in vascular and all-cause mortality rates. Statin therapy was not associated with increased cancer incidence or mortality or increased mortality from other non-vascular causes.

Statins are effective for primary prevention even in low-risk people. The extent to which statin prophylaxis should be extended will be debated.

Cholesterol Treatment Trialists' (CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012; 380: 581–90; Watts GF, Ooi EM. Balancing the cardiometabolic benefits and risks of statins. Ibid: 541–3 (comment); Ebrahim S, Casas JP. Statins for all by the age of 50 years? Ibid: 545–7 (comment).

Atrial fibrillation plus chronic kidney disease: risks of stroke or bleeding

Both atrial fibrillation and chronic kidney disease are associated with increased risk of stroke. Data from Danish national registries have been used to show the risks associated with both conditions combined.

Between 1997 and 2008, a total of 146 251 patients with nonvalvular atrial fibrillation were discharged from Danish hospitals and 132 372 were included in the present study, among whom 3587 (2.7%) had non-end-stage chronic kidney disease and 901 (0.7%) had end-stage kidney disease. Compared with patients with atrial fibrillation alone, those with atrial fibrillation and non-end-stage chronic kidney disease had a significant 49% increase in risk of stroke or systemic thromboembolism. Among patients with atrial fibrillation and end-stage chronic kidney disease there was an 83% increase in this risk. Warfarin treatment reduced the risk but aspirin increased it. The risk of bleeding was increased among patients with chronic kidney disease and was further increased with warfarin, or aspirin, or both.

The risk of stroke or thromboembolism in patients with atrial fibrillation is further increased in the presence of chronic kidney disease. Warfarin therapy reduced the risk but both warfarin and aspirin, singly or combined increased the risk of bleeding.

Olesen JB et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *NEJM* 2012; 367: 625–35.

Coronary CT angiography in acute chest pain

Contrast-enhanced coronary computed tomographic angiography (CCTA) is accurate for the detection of coronary lesions. CCTA has been compared with standard evaluation for the assessment of patients with suspected coronary pain in the emergency department in a US multicentre study.

The study included 1000 patients aged 47–74 years (47% women) with acute chest pain and nondiagnostic ECG findings and troponin tests. Randomisa-

tion was to CCTA or standard evaluation. Overall, 8% of patients proved to have an acute coronary syndrome. The mean length of stay in hospital was 23.2 hours (CCTA) vs 30.8 hours (controls). The proportion of patients discharged directly from the emergency department was 47% vs 12%. There were no significant differences between the groups in rate of major adverse cardiovascular events at 28 days and no undetected acute coronary syndromes. CCTA resulted in more additional testing and higher radiation exposure. The costs were similar in the two groups (US $4289 vs 4060).

Use of CCTA was associated with shorter hospital stay and more patients being discharged directly from the emergency department. It also resulted in increased testing and greater exposure to radiation. Costs were similar in the two groups. An editorialist questions whether any further testing is necessary for patients with a normal ECG and normal troponin levels and suggests that such patients should be discharged without further testing.

Hoffman U et al. Coronary CT angiography versus standard evaluation in acute chest pain. *NEJM* 2012; 367: 299–308; Redberg RF. Coronary CT angiography for acute chest pain. Ibid: 375–6 (editorial).

Diabetes

Linagliptin versus glimepiride for metformin-resistant type 2 diabetes

Many patients with type 2 diabetes treated with metformin eventually suffer from deteriorating control of blood glucose levels. A sulphonylurea is then often added but may cause hypoglycaemia and weight gain. Dipeptidyl peptidase-4 (DPP-4) inhibitors are less likely to cause hypoglycaemia and weight gain. A trial in 16 countries on four continents has confirmed that linagliptin (a DPP-4 inhibitor) was noninferior in glycaemic control and safer when compared with glimepiride (a sulphonylurea) as an addition to metformin.

A total of 1519 patients with HbA1c levels of 6.5–10.0% on metformin were randomised to take in addition linagliptin 5 mg daily or glimepiride 1–4 mg daily and included in the analysis. After 2 years, the reduction in HbA_{1c} level from a mean baseline level of 7.69% was 0.16% (linagliptin) vs 0.36% (glimepiride), a difference of 0.20%, meeting the predefined non-inferiority criterion of 0.35% or less. Significantly fewer patients in the linagliptin group had hypoglycaemia (7% vs 36%), severe hypoglycaemia (<1% vs 2%), or cardiovascular events (2% vs 3%). There was a 1.4 kg mean reduction in bodyweight with linagliptin and a 1.3 kg increase with glimepiride.

The two drugs gave similar glycaemic control but linagliptin was associated with less risk of hypoglycaemia and weight gain.

Gallwitz B et al. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. Lancet 2012; 380: 475–83; Scheen AJ, Paquot N. Gliptin versus a sulphonylurea as add-on to metformin. Ibid: 450–2 (comment).

PTEN mutations: reduced risk of type 2 diabetes and increased risk of obesity and cancer

There are links between type 2 diabetes, obesity, and cancer. Some genetic loci that are associated with increased risk of type 2 diabetes are close to genes known to be concerned in cell-cycle regulation. The tumour-suppressor phosphatase and tensin homologue (*PTEN*) protein and lipid phosphatase is involved in both cell cycle regulation and glucose metabolism. Loss-of-function *PTEN* mutations are associated with a rare cancer-predisposition syndrome (Cowden syndrome) and *PTEN* also has a role in insulin signalling. A study of 15 patients with the Cowden syndrome in England has shown that it is associated with obesity and insulin oversensitivity.

All 15 patients had *PTEN* mutations (seven nonsense mutations, six missense mutations, and two deletions) all expected to cause loss of function. Their mean BMI was 43 (range 23–42) compared with a mean BMI of 26 (15–48) in 2097 population controls. The Cowden syndrome patients had a lower mean fasting plasma insulin level compared with 15 matched controls (29 vs 74 pmol per L), suggesting lowered insulin resistance. Tests of insulin signalling on five patients and five matched controls confirmed increased insulin sensitivity in the patients.

PTEN mutations and the Cowden syndrome are associated with increased insulin sensitivity and obesity. Lack-of-function of *PTEN* therefore causes a cancer predisposition syndrome, a tendency to obesity, and probable protection against type 2 diabetes.

Pal A et al. *PTEN* mutations as a cause of constitutive insulin sensitivity and obesity. NEJM 2012; 367: 1002–11; Smith U. PTEN - linking metabolism, cell growth, and cancer. Ibid: 1061–3 (editorial).

Pulmonary

ACE inhibitors, ARBs, and pneumonia

It has been suggested that ACE inhibitors may protect against pneumonia. A systematic review and meta-analysis has been reported.

Thirty-seven studies were included in the review. The risk of pneumonia was reduced significantly by 34% with use of Ace inhibitors compared with control treatment and by 31% compared with angiotensin receptor blockers (ARBs).

ACE inhibitors seem to protect against pneumonia but ARBs do not. It is suggested that patients might try to continue with ACE inhibitor treatment despite a mild cough but an editorialist points to faults in the design of this study and disagrees with the suggestion given the uncertainty of present evidence.

Caldeira D et al. Risk of pneumonia associated with use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers: systematic review and meta-analysis. *BMJ* 2012; 345: (Aug 4): 15 (e4260); Barnes RA. Pneumonia and ACE inhibitors – and cough. Ibid: 6 (e4566) (editorial).

Enlarged pulmonary artery and exacerbations of COPD

Severe pulmonary hypertension occurs in advanced chronic obstructive pulmonary disease and is associated with an increased frequency of exacerbations. A multicenter US study has shown that an increased pulmonary artery:aorta diameter ratio is predictive of severe exacerbations of COPD.

The study included 3464 adult smokers with GOLD stage II to IV COPD. The diameters of the pulmonary artery (PA) and aorta (A) were measured by CT scanning. Pulmonary artery enlargement was defined as a PA:A ratio >1. At the time of enrolment a severe exacerbation in the previous year was reported by 53% of patients with a PA:A ratio of >1 and 13% of patients with a lesser ratio. Pulmonary artery enlargement was associated with 3.44-fold increase in risk of severe exacerbations during the trial and a 2.8-fold increase in this risk in an external validation cohort. Overall, pulmonary artery enlargement was the single factor most strongly associated with severe exacerbations of COPD.

Pulmonary artery enlargement (PA:A ratio >1) is associated with increased risk of severe exacerbations of COPD. An editorialist points out that there are

less expensive and more practical ways of measuring PA:A ratio.

Wells JM et al. Pulmonary arterial enlargement and acute exacerbations of COPD. NEJM 2012; 367: 913–21; Stanbrook MB. The pulmonary artery in

Mepolizumab for severe eosinophilic asthma

Eosinophilic airway inflammation characterises a subgroup of patients with severe asthma. Mepolizumab is a humanised monoclonal antibody against interleukin 5 that inhibits eosinic airway inflammation and has been shown to reduce the frequency of asthma exacerbations in small studies. Now a multinational trial has been reported.

A total of 621 patients aged 12–74 years with severe eosinophilic asthma were randomised at 81 centres in 13 countries to mepolizumab at doses of 75, 250, or 750 mg, or placebo, by i.v. infusion every 4 weeks for a total of 13 infusions. The rate of clinically significant exacerbations during the trial was 1.24, 1.46, and 1.15 per patient per year in the 75, 250, and 750 groups and 2.40 per patient per year in the placebo group. There were significant reductions of 48%, 39%, and 52% in the mepolizumab groups compared with the placebo group. The treatment was well tolerated on the whole.

Mepolizumab reduces the rate of exacerbations in people with severe eosinophilic asthma.

Pavord ID et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012; 380: 651–9; Hashimoto S, Bel EH. Targeting IL-5 in severe asthma: a DREAM come true? Ibid: 626–7 (comment).

Infection

Anti-interferon γ autoimmune disease in Thailand and Taiwan

Interferon-γ, interleukin-12, and tumour necrosis factor α (TNF-α) are important in protecting against mycobacteria, fungi, and salmonella. Since 2004 there have been case reports of 25 HIV-negative adults, mostly in East Asia, with neutralising anti-interferon-γ autoantibodies and disseminated nontuberculous mycobacterial infection and other opportunistic infections simulating HIV disease. Now a study in Thailand and Taiwan has provided more data about such patients.

The study included 203 subjects in five groups: 52 patients with disseminated nontuberculous mycobacterial infection (non-TB MI), 45 patients with another opportunistic infection, with or without non-TB MI (OOI), 9 patients with disseminated tuberculosis (DTB); 49 patients with pulmonary tuberculosis (PTB), and 48 healthy controls. Plasma from the first two groups (non-TB MI and OOI) inhibited the activity of interferon-γ in normal cells. High-titre anti-interferon-γ autoantibodies were demonstrated in 81% of patients (non-TB MI), 96% (OOI), 11% (1 patient) (DTB), 2% (one patient) (PTB), and 2% (one patient) (controls). Testing for autoantibodies against 40 other cytokines revealed one patient with cryptococcal meningitis and autoantibodies against granulocyte-macrophage colony-stimulating factor but no other anticytokine-autoantibody-related infections.

Neutralising autoantibodies against interferon-γ were found in 88% of HIV-negative patients with an immunodeficiency syndrome akin to HIV-1 infection. The cause of this autoantibody production is not known.

Browne SK et al. Adult-onset immunodeficiency in Thailand and Taiwan. *NEJM* 2012; 367: 725–34.

Acute pyelonephritis in women: 7 days versus 14 days of ciprofloxacin

The optimum duration of treatment for women with acute pyelonephritis is uncertain though 14 days is often recommended. A study in Sweden has suggested that 7 days of treatment with ciprofloxacin is as effective as 14 days.

A total of 248 non-pregnant women aged 18 years or older with acute pyelonephritis were randomised at 21 infectious diseases centres in Sweden to treatment with ciprofloxacin 500 mg twice daily for 7 days or 14 days. Only 156 patients were included in the analysis. Short-term cure was achieved in 97% (7 days) vs 96% (14 days). On longer term follow-up efficacy was 93% in each group. Mucosal candida infection occurred in five patients after 14 days of treatment but in none after 7 days.

Seven days of treatment with ciprofloxacin is usually adequate for non-pregnant women with acute pyelonephritis. Shorter treatment may discourage bacterial antibiotic resistance.

Sandberg T et al. Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomised, open-label and double-blind, placebo-controlled non-inferiority study. *Lancet* 2012; 380: 484–90; Nicolle LE. Minimum antimicrobial treatment for acute pyelonephritis. Ibid: 452–3 (comment).

Neurology

Autoantibodies against potassium channel in multiple sclerosis

There is evidence that autoimmune antibodies may play a part in the pathogenesis of multiple sclerosis (MS) but the target antigens are not known. Researchers in Germany and the USA have shown that potassium channel KIR4.1 is an antibody target in some patients with MS.

Serum IgG from 11 of 19 patients with MS (58%) reacted specifically with glial cells in human brain sections. Samples from 24 patients with other neurological diseases did not show glial-specific immunoreactivity. In another experiment including serum samples from 56 patients with MS and 29 with other neurological diseases the serum from MS patients bound to membrane protein, but not to cytoplasmic proteins, more avidly than did serum from patients with other neurological diseases. A proteomic approach focusing on membrane proteins then identified the ATP-sensitive inward rectifying potassium channel KIR4.1 as the target of IgG antibodies. Serum levels of KIR4.1 antibodies were significantly higher in patients with MS than in patients with other neurological diseases or normal controls. Serum antibodies against KIR4.1 were found in 186/397 people with MS (46.9%), and none of 59 normal controls. The antibodies bound to the first extracellular loop of KIR4.1.

Some people with MS have autoantibodies against potassium channel KIR4.1 in brain glial cells. Further work is needed to define the clinical importance of these findings.

Srivastava R et al. Potassium channel KIR4.1 as an immune target in multiple sclerosis. *NEJM* 2012; 367: 115–23; Cross AH, Waubant E. Antibodies to potassium channels in multiple sclerosis. Ibid: 172–4 (editorial).

CPD Challenge

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