SHORT CUTS

ALL YOU NEED TO READ IN THE OTHER GENERAL JOURNALS

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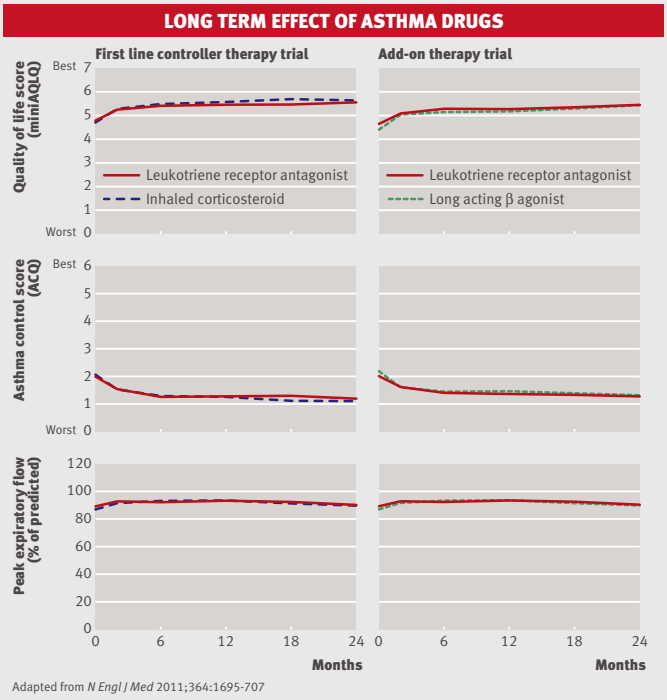
"High salt intake increases blood pressure and contributes to the western epidemic of cardiovascular disease, right? Wrong. As measured by sodium excretion, salt makes hardly any difference to systolic BP and none to diastolic"
Richard Lehman's journal blog at www.bmj.com/blogs

Real world trials challenge asthma guidelines



Adapted from *N Engl J Med* 2011;364:1695-707

Randomised trials tell us that established treatments for asthma relieve symptoms and improve lung function for selected people treated under ideal conditions. But they tell us next to nothing about the real world effectiveness of asthma treatments for the heterogeneous group of people who come through the doors of primary care doctors every day. Two new pragmatic trials from the UK go some way to bridging the gap by including diverse patients, treated by their usual doctor, in their usual clinic.

Both trials aimed to improve long term quality of life. The first compared an oral leukotriene receptor antagonist (usually montelukast) with an inhaled corticosteroid (usually beclometasone) as first line treatment for adults needing regular control for their asthma. The second compared an oral leukotriene receptor antagonist (again, usually montelukast) with a long acting β adrenoceptor agonist (usually salmeterol) for adults poorly controlled by inhaled glucocorticoids alone. Both trials found little to choose between the two treatments after two months, or two years. Comparator groups reported improvements in quality of life and asthma control that were essentially equivalent, although not always in the strict statistical sense specified in the protocol. Both trials included mostly adults aged 16-80 (n=306 and n=352). More than half were current or former smokers.

These trials challenge current guidelines, says an editorial (p 1769). Leukotriene receptor antagonists seem to compare more favourably with inhaled treatments in the real world than they do in traditional trials—possibly because people are better at taking pills than they are at using inhalers. Adherence rates were 65% and 74% for the two groups assigned a leukotriene inhibitor, compared with just 41% and 46% for controls assigned an inhaled treatment.
N Engl J Med 2011;364:1695-707

Head to head comparisons are missing from half of new drug approvals

Doctors prescribing a new drug need to know how it compares with established alternatives. Regulators approving new drugs for market don't always insist on head to head trials, however, so comparative effectiveness data can be hard to find in the crucial few years after the launch of a new drug. Preapproval documentation submitted to regulators is a potential source of information, although it was patchy in one recent study from the US.

Researchers analysed packages of documents submitted to the Food and Drug Administration for new drug approvals between 2000 and 2010. Just over half the packages (100/197) contained one or more studies that compared the new drug with an active alternative. The regulator's decision was based on comparative efficacy data for just 59 out of 197 drugs.

So some data are available, some of the time. The researchers weren't able to say whether the head to head studies found on the FDA's website were good enough to be useful to doctors, other prescribers, or decision makers in charge of formularies. But they do think the source has potential and should be more accessible and easier to use. They would also like to see more comparative studies before drugs are approved. The findings of this US analysis are broadly in line with a study of approval decisions made by the European regulator between 1999 and 2005.
JAMA 2011;305:1786-9

Bisphosphonates linked to atypical fractures of the femoral shaft

Bisphosphonates help prevent osteoporotic fractures in older women, although some observers have noticed an association between these drugs and an excess of rare atypical fractures, such as stress fractures of the femoral shaft. Swedish researchers recently confirmed the association in two population based analyses, but they also report that the absolute risk of an atypical fracture remains very low.

They found just 59 atypical fractures among 12 777 older women who had a fracture of the femur in 2008. Bisphosphonates were implicated in five (95% CI four to seven) extra cases per 10 000 person years, or one extra atypical fracture for every 2000 women treated for one year.

In a case-control analysis, 46 of the 59 women with atypical fractures used or had used bisphosphonates, compared with 26 out of 263 carefully selected control women with other fractures of the femoral shaft (adjusted odds ratio 33.3, 14.3 to 77.8). The difference was unrelated to age, frailty, coexisting illnesses, or use of other drugs including glucocorticoids.

The researchers used two observational designs and three national registries to try to quantify an association that had emerged anecdotally from case reports. The results shouldn't deter women from taking bisphosphonates, they write. These analyses can't establish cause and effect, and even if bisphosphonates do cause a few extra atypical fractures (still a big if), we know they prevent many more fractures overall.
N Engl J Med 2011;364:1728-37

New data from an old trial still favours radical prostatectomy

In 1989, Scandinavian researchers launched a trial comparing radical prostatectomy with watchful waiting for men with early prostate cancer. In 2008, they reported that prostatectomy was associated with better survival over nine years of follow-up. It

is still associated with significantly better survival 15 years after randomisation, according to the latest estimates (cumulative incidence of death from all causes 46.1% (95% CI 40.8 to 52.0) *v* 52.7% (47.4 to 58.6); relative risk 0.75 (0.61 to 0.92)). Men who had a radical prostatectomy were less likely to die from prostate cancer than controls offered watchful waiting (0.62 (0.44 to 0.87)) and less likely to develop distant metastases. The benefits of radical surgery looked greatest for men under 65 and were evident even for those with the lowest risk tumours. Half the men given radical surgery were impotent afterwards, and a third reported urinary incontinence.

An editorial (p 1770) welcomes the trial's long term results but cautions that they come from an era before widespread screening with prostate specific antigen. Almost all the participants in the Scandinavian trial had symptoms of prostate cancer and 88% had palpable tumours at diagnosis. Most cancers (at least in the US) are now identified through screening, not symptoms, and only half are palpable at diagnosis. Smarter surveillance protocols, more sophisticated surgery, and extras such as radiation and antiandrogen treatment have also changed the therapeutic landscape for early prostate cancer since this trial began. Newer trials comparing intervention with observation are already under way, says the editorial. At least one is confined to early cancers identified through screening.

N Engl J Med 2011;364:1708-17

Erythropoietin for heart attacks falls at the first hurdle

Experiments in animals led researchers to evaluate erythropoietin as a treatment for myocardial infarction, with the hope that it might reduce infarct size if given soon after an early and successful percutaneous coronary intervention. Results from the first phase II trial were disappointing, however, and at least one commentator thinks they spell the end for this particular line of inquiry (p 1908).

Epoetin alfa made no overall difference to infarct size in the short or medium term compared with a placebo, and it may even have increased infarct size in patients over 70 years. Safety analyses reported a significant excess of serious adverse events in the erythropoietin group (20% (25/125) *v* 10.3% (10/97); p=0.05). Adults given erythropoietin were significantly more likely than controls to die or to have a further myocardial infarction, stroke, or stent thrombosis (5/125 *v* 0/97; p=0.04).

The animal experiments looked fairly convincing and testing erythropoietin in humans was a reasonable next step, says the commentator. But testing should probably stop here. Erythropoietin has a troublesome safety record in other clinical areas and has been linked to thromboses and ischaemic events when used to treat anaemia. Researchers should now look elsewhere for agents to help limit the size of infarcts. They may have to test them outside the US, he writes. Trials are no longer welcome where they might delay rapid access to percutaneous coronary intervention, even for a few minutes. These researchers took three years to recruit 222 patients from 22 sites in the US.

JAMA 2011;305:1863-72

Structured exercise programmes help control type 2 diabetes

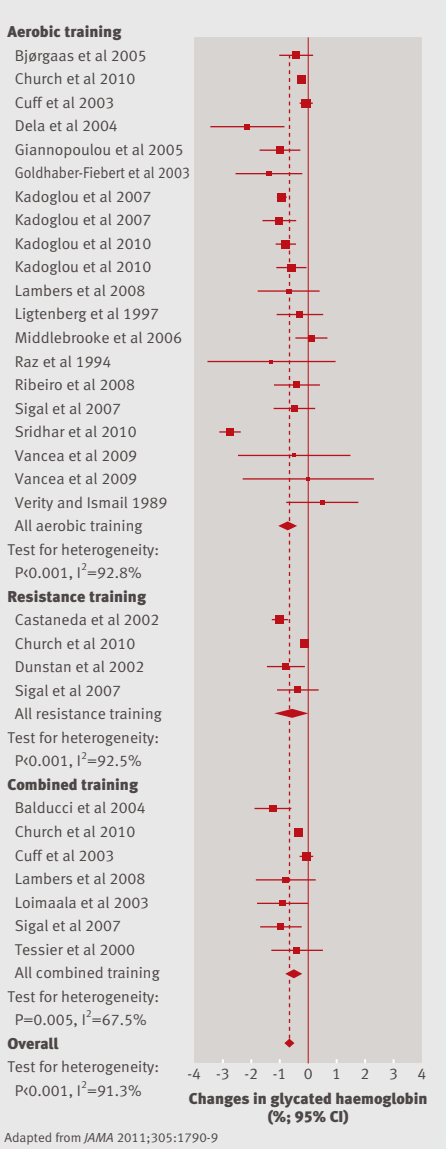
Exercise is good for adults with type 2 diabetes, and a structured supervised programme works best, according to a meta-analysis of 47 randomised trials. Aerobic exercise or resistance training alone or in combination were associated with significant reductions in glycated haemoglobin concentration compared with control interventions without exercise. The benefits looked big enough to be clinically relevant—a drop of 0.67% (95% CI −0.84% to −0.49%) for any structured training, 0.73% (−1.06% to −0.40%) for aerobic exercise, and 0.57% (−1.14% to −0.01%) for resistance training. Programmes that scheduled more than 150 minutes a week worked better than programmes that scheduled less.

The trials were heterogeneous and most had methodological shortcomings, but a linked editorial (p 1808) says the combined results are credible. Simply advising people to take more exercise didn't improve diabetic control in these analyses, although combined advice about diet and exercise reduced glycated haemoglobin concentrations by 0.58% (−0.74% to −0.43%).

Many guidelines already recommend structured exercise for people with type 2 diabetes, but insurers don't always pay for it. Perhaps they should, says the editorial. We know exercise can help prevent diabetes and help control it. We know exercise is good for serum lipids, blood pressure, cognitive function, and quality of life. Medicare (national insurance for older people in the US) funds other lifestyle interventions for diabetes, including self management programmes and nutritional therapy. The US government should now consider adding structured exercise programmes to the menu.

JAMA 2011;305:1790-9

EXERCISE TRAINING AND GLYCATED HAEMOGLOBIN CONCENTRATION



Adapted from *JAMA* 2011;305:1790-9

Doctors conflicted over funding for CME

When researchers surveyed 1347 US doctors and nurses attending continuing medical education (CME) on HIV, 88% of the 770 respondents said they were worried about bias in programmes funded by manufacturers of drugs or devices. They also thought that risk of bias went up in line with the proportion of funding provided by industry. But fewer than half the respondents (42%) were willing to pay more themselves to reduce dependence on industry. Just 17% of doctors and 15% of other health professionals wanted to eliminate industry funding from CME in the US, where commercial companies currently pay 60% of CME costs.

Respondents underestimated the true cost of hospitality such as coffee and lunch at these events (around $5 (£3; €3.5) for a coffee in Washington DC and $117 for lunch in New York) and overestimated the proportion of total costs covered by their own registration fees.

The most popular suggestion for reducing costs was a switch from preprinted to online educational materials. There was also some support (around 50%) for cheaper venues and no free lunches. Few respondents would agree to cut CME content or hours.

Arch Intern Med 2011;171:840-6

Cite this as: *BMJ* 2011;342:d2841