SHORT CUTS

ALL YOU NEED TO READ IN THE OTHER GENERAL JOURNALS

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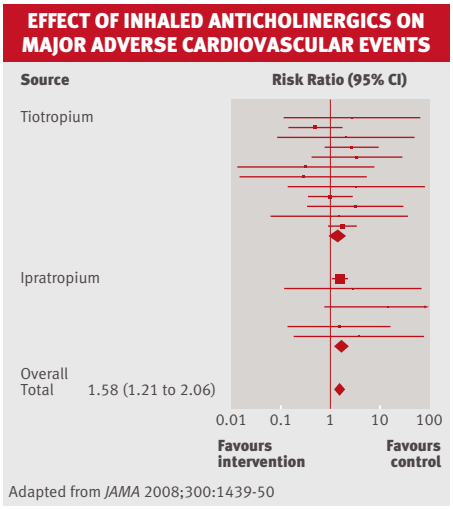
Anticholinergics linked to extra deaths and heart attacks in COPD



Adapted from *JAMA* 2008;300:1439-50

Inhaled anticholinergic drugs reduce the breathlessness associated with chronic obstructive pulmonary disease (COPD), help prevent exacerbations, and improve patients' quality of life. A meta-analysis of 17 randomised trials now reports that the two commonly used agents also increase the risk of a serious cardiovascular event, including death, by an estimated 58% (1.8% *v* 1.2% for control; relative risk 1.58, 95% CI 1.21 to 2.06). The analysis included 14 783 men and women.

Patients treated with ipratropium or tiotropium for at least a month were more likely than controls to have a heart attack (1.53, 1.05 to 2.23) and to die of cardiovascular disease (1.80, 1.17 to 2.77). The authors found one extra death from cardiovascular disease for every 40 (18 to 185) patients treated for a year and one extra heart attack for every 174 (75 to 1835) patients treated. Controls had a placebo, inhaled β agonists such as salmeterol, or a combination inhaler containing a β agonist and a corticosteroid. Anticholinergics did not increase the risk of stroke or all cause mortality in this analysis.

Patients with chronic obstructive pulmonary disease already have a high risk of cardiovascular events, say the authors. Doctors and patients must decide if the extra risk associated with these agents is an acceptable trade off for improved symptoms.

JAMA 2008;300:1439-50

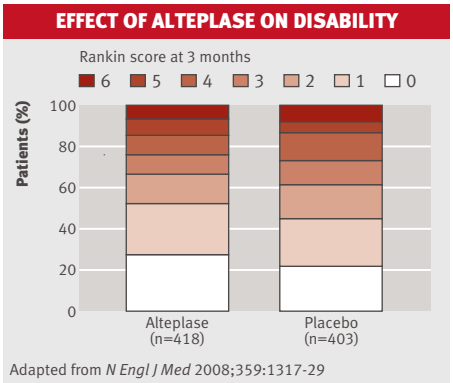
Report estimates 16 million injecting drug users worldwide, three million with HIV

Nearly 16 million (15.9 million, range 11.0-21.2 million) people worldwide are injecting drug users, according to the latest estimates. Around 3 million (0.8-6.6 million) of them are HIV positive. China, Russia, and the US have the greatest numbers of injecting drug users, partly because they are among the most populous countries in the world. The prevalence of HIV in users is more than 10% in both China and the US. The prevalence in Russia is estimated at 37%. This figure rises to over 40% in nine countries of southeast Asia, Eastern Europe, and Latin America. In Estonia, nearly three quarters (72.1%) of injecting drugs users have HIV.

These figures are no more than "best guesses" based on a systematic search of published and unpublished studies and extensive consultation with international agencies, say researchers. Little information is available from large parts of Africa, the Middle East, Latin America, and the Caribbean. Even so, it looks as though injecting drug use and HIV have both become more widespread since the last estimates in 2004. The present analysis included data from 148 countries. Prevalence estimates for injecting drug use were available from 61 countries covering more than three quarters of the world's population aged 15-64.

Lancet 2008; doi:10.1016/S0140-6736(08)61311-2

Thrombolysis works up to 4.5 hours after an ischaemic stroke



Adapted from *N Engl J Med* 2008;359:1317-29

A long awaited trial reports that patients with ischaemic stroke can benefit from thrombolytic treatment up to 4.5 hours after the start of their symptoms. Participants given alteplase 3-4.5 hours after a stroke made a significantly better recovery than those given a placebo in the same time window. They were less disabled than controls at three months (52.4% *v* 45.2% scored 0 or 1 on the modified Rankin scale; P=0.04) and had better global outcomes on a measure that combined scores of disability, neurological deficit, and independence.

Alteplase increased the risk of intracranial haemorrhage in line with previous trials (2.4% *v* 0.2% for symptomatic bleeds, P=0.008). It had no effect on mortality (7.7% *v* 8.4%) and an independent editorial (p 1393) emphasises that the benefits of treatment substantially outweigh the risks.

These results are welcome, but health professionals should remember that thrombolytics become less effective with every passing minute after a stroke, says the editorial. This trial is not a licence to take an even more relaxed approach with patients who have had a stroke. We are already doing a poor job, with slow door to needle times denying most patients effective treatment for a devastating event. "The patients are coming in, but we are not," writes the editorialist. About a third of patients with stroke get to emergency rooms in time for thrombolytic treatment. Only one in 25 actually receives it.

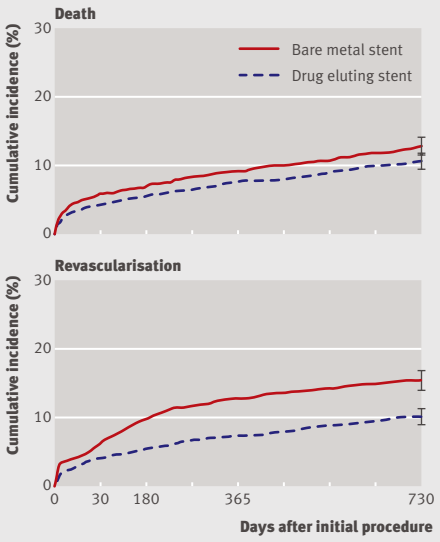
N Engl J Med 2008;359:1317-29

Drug eluting stents associated with lower mortality after heart attack

Between spring 2003 and autumn 2004, more than 7000 adults with acute myocardial infarction received intracoronary stents at hospitals in Massachusetts. A recent safety analysis found that those who received a drug eluting stent were slightly but significantly less likely to die over the next two years than those who received a bare metal stent (10.7% *v* 12.8%, P=0.02). The favourable result for drug eluting stents surprised researchers and persisted through extensive adjustment (propensity scoring) to balance the many baseline differences between people given the two kinds of stent.

Drug eluting stents looked better for people with and without ST segment elevation. They

OUTCOMES AFTER STENTING FOR ANY MYOCARDIAL INFARCTION



Adapted from *N Engl J Med* 2008;359:1330-42

were associated with fewer revascularisation procedures (9.6% *v* 14.5%, P<0.001) and reduced mortality in both groups.

Most of the 4016 patients treated with a drug eluting stent received a sirolimus eluting stent (71%). The rest had a paclitaxel eluting stent (27%) or one of each (2%).

These findings are reassuring, say the researchers but must be confirmed in a randomised trial. Despite their best efforts researchers were unable to rule out residual confounding.

N Engl J Med 2008;359:1330-42

Regional variations determine survival from out of hospital cardiac arrest

Your chances of surviving an out of hospital cardiac arrest depend very much on where you live. Citizens of Seattle had the best survival rate in one comparison of 10 sites in Canada and the US—16.3% of those treated by the emergency services survived to hospital discharge. Citizens of Alabama had the worst survival rate (3%). The incidence of out of hospital cardiac arrest (as assessed by the emergency services) also varied widely—from 71.8 per 100 000 in Ottawa to 159 per 100 000 in Dallas. Across all 10 sites, 7.9% of all treated patients and 21% of those with ventricular fibrillation survived to hospital discharge.

Regional variations in data collection and demographics—particularly poverty—may explain some of the variation, say the study's authors. But differences in the availability and organisation of emergency care could be more important.

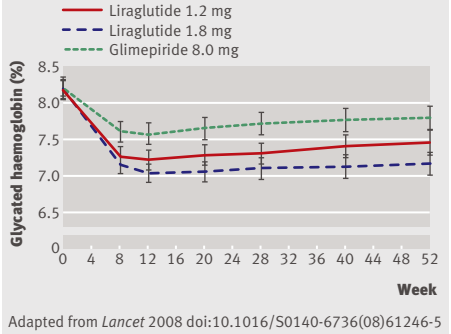
Outcomes from out of hospital cardiac arrest have failed to improve over the past few decades, despite steadily declining morbidity and mortality from cardiovascular disease in general. It is such an important public health problem that the American Heart Association says it should be a reportable disease. Every community should get to "know its numbers," identify local problems in the chain of survival, and take steps to remedy them, says an editorial (p 1462). Previous studies from Arizona, Seattle, and Wisconsin show that improvements are possible.

JAMA 2008;300:1423-31

New antidiabetic agent given a cautious welcome

Incretin mimetics are a relatively new class of antidiabetic drug. They act by boosting insulin secretion in response to food. Exenetide is already licensed for people with type 2 diabetes, and drug manufacturers Novo Nordisk are currently testing their drug liraglutide. The results of a large phase III trial look promising. In patients with early disease, a once daily injection of liraglutide reduced glycated haemoglobin values significantly more than oral glimepiride over 52 weeks (effect differences –0.62% for liraglutide 1.8 mg, 95% CI –0.83% to –0.42%; –0.33% for liraglutide 1.2 mg, –0.53% to –0.13%) and decreased both fasting and postprandial glucose concentrations. Patients given liraglutide lost

EFFICACY OF GLYCAEMIC CONTROL



Adapted from *Lancet* 2008 doi:10.1016/S0140-6736(08)61246-5

2-2.5 kg in weight, compared with a small weight gain in controls. They also had lower systolic blood pressures than controls at the end of the trial. The most common side effects were nausea (27-29%), vomiting (9-12%), and diarrhoea (16-19%). Liraglutide was associated with fewer episodes of hypoglycaemia than glimepiride.

An editorial (doi:10.1016/S0140-6736(08)61247-7) gives the new drug a cautious welcome but says it is not yet clear where incretin mimetics fit in the overall therapeutic picture. Long term safety is unknown and pancreatitis is a particular worry with these agents. Two patients in this trial developed pancreatitis after treatment with liraglutide.

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Many key drug trials supporting FDA approval remain unpublished

The US Food and Drug Administration approved 90 new drugs between 1998 and 2000. More than half (515/909, 57%) of the 909 drug trials supporting these approvals were still unpublished five years later, according to researchers who looked for them in all the standard databases. A quarter of even the most important trials had not been published by 2006.

The researchers found powerful evidence of publication bias. Trials with statistically significant results were three times more likely to be published than the rest (odds ratio 3.03, 95% CI 1.78 to 5.17). So were those with larger sample sizes (1.33 per twofold increase in sample size, 1.17 to 1.52). The findings were similar for pivotal trials—those important enough for a mention on the drug label.

Publication bias tends to distort the evidence in favour of new drugs, say the researchers. So last year the Food and Drug Administration ruled that the basic results from all drug trials must be made publicly available within one year of trial completion or of the drug's approval. Hopefully, the new amendment will reduce the considerable bias currently operating in the evidence base for new drugs, they write.

PLoS Med 2008 5:e191; doi:10.1371/journal.pmed.0050191

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