SHORT CUTS

ALL YOU NEED TO READ IN THE OTHER GENERAL JOURNALS

Alison Tonks, associate editor, *BMJ* atonks@bmj.com

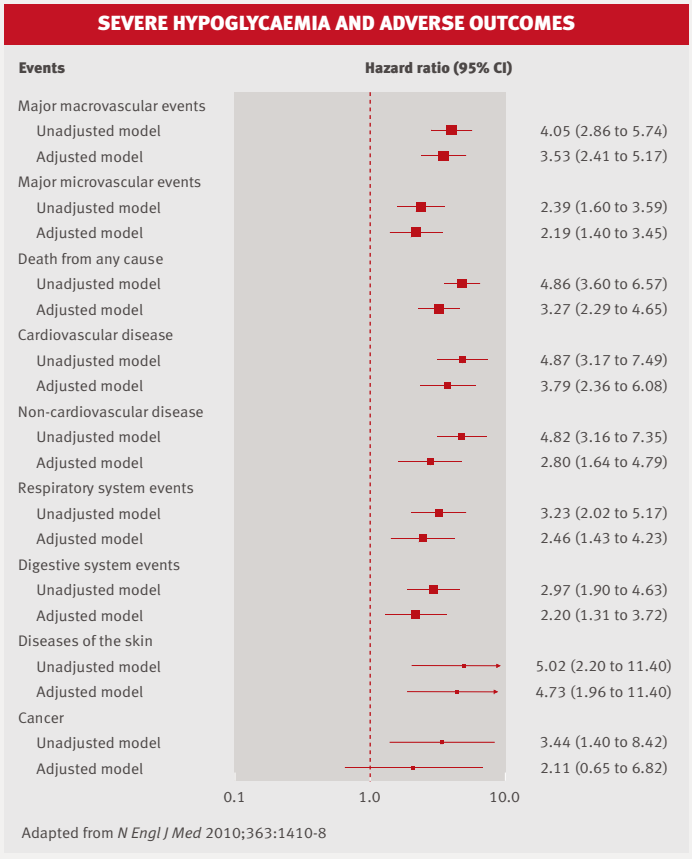
Severe hypoglycaemia is a bad sign for people with type 2 diabetes

Intensive control of type 2 diabetes became controversial when landmark trials failed to show a clear benefit to patients while at the same time reporting an increased risk of hypoglycaemia among those given a glycated haemoglobin target of 6.5% or less. Researchers are now re-examining trial data to explore whether episodes of severe hypoglycaemia were associated with lasting harm, or even death.

One such re-analysis has found a clear link between severe hypoglycaemia during the ADVANCE trial and a whole series of adverse outcomes, including cardiovascular events (hazard ratio 3.45, 95% CI 2.34 to 5.08), microvascular complications (2.07, 1.32 to 3.26), death from cardiovascular causes (3.78, 2.34 to 6.11), and death from all causes (3.30, 2.31 to 4.72) over a follow-up of five years. The associations were independent of treatment received during the trial (intensive or standard) and many other potential confounding factors such as age, sex, smoking, duration of diabetes, vascular history, and baseline glucose control.

Severe hypoglycaemia is a bad sign, say the authors, and it may trigger more sinister events directly. Or it could simply be a signal that someone is clinically vulnerable—more prone to all kinds of health problems including heart attacks and strokes. Either way, extra vigilance might be wise, they write. The 11 140 patients in ADVANCE had longstanding diabetes and a high risk of vascular and microvascular complications. Just over 2% had at least one episode of severe hypoglycaemia during the trial.

N Engl J Med 2010;363:1410-8



Adapted from *N Engl J Med* 2010;363:1410-8

Sleep well while dieting

A restful night's sleep is good for everyone, but it may be particularly important for overweight adults on calorie controlled diets, say researchers. Their experiment in 10 overweight volunteers suggested that sleep deprivation during a diet was associated with fat sparing and loss of fat-free mass instead. The volunteers spent two 14 day periods in the laboratory, eating 10% less than their calorie requirement each day. They were allowed 5.5 hours sleep a night during one period and up to 8.5 hours during the control period.

The volunteers lost the same amount of weight during each fortnight (3 kg), but the proportion lost from fat stores fell by half during sleep deprivation (0.6 *v* 1.4 kg; P=0.043). The volunteers felt hungrier when deprived of sleep and had significantly higher serum concentrations of ghrelin, a hormone released by the stomach to signal a need for food. They also had a significantly lower metabolic rate. Daytime naps were not allowed.

These experimental findings add to other evidence of a link between poor sleep, metabolism, and diet that tends to work against the efforts of adults trying to lose weight, says an editorial (p 475). Metabolism isn't the only problem. People who sleep less have more time for snacking and may be too tired to exercise.

Ann Intern Med 2010;153:435-41

Cardiovascular interaction between omeprazole and clopidogrel looks unlikely

A new trial of antiplatelet treatment for vascular disease gives some reassurance to practitioners and patients worried about combining clopidogrel with omeprazole. The authors found no evidence of any clinically meaningful interaction between the two. Adults given the combination had no more cardiovascular events than adults given clopidogrel with a placebo (4.9% (55/1876) *v* 5.7% (54/1885); hazard ratio 0.99, 95% CI 0.68 to 1.44), but they did have significantly fewer gastrointestinal side effects including bleeds (1.1% (13/1876) *v* 2.9% (38/1885); 0.34, 0.18 to 0.63). All the participants took aspirin.

The trial was designed and paid for by Cogentus Pharmaceuticals to explore the safety and efficacy of a pill that combined fixed doses of clopidogrel (75 mg) and omeprazole (20 mg). The authors were mainly interested in whether the combination helped prevent gastrointestinal side effects, and they recruited enough patients for a conclusive positive result. Omeprazole clearly worked better than placebo.

The more pressing question about cardiovascular safety is harder to answer with confidence. The possibility that omeprazole might blunt the antiplatelet activity of clopidogrel and increase cardiovascular risk first emerged (inconsistently) from observational studies. A clinically important problem now looks less likely, say the authors, but it can't be ruled out completely. The trial was smaller and weaker than planned because the sponsors went bust and funding vanished before the authors reached their targets.

N Engl J Med 2010; doi:10.1056/NEJMoa1007964

"On some yet undiscovered Sumerian clay tablet or Egyptian papyrus there must be a reference to honey as a pacifying agent for babies in pain, and I will send a piece of honeycomb to any reader who can find a suitably ancient reference to what is undoubtedly a very ancient practice"
Richard Lehman's journal blog at www.bmj.com/blogs

Mobile van detects tuberculosis better than house calls in Zimbabwe

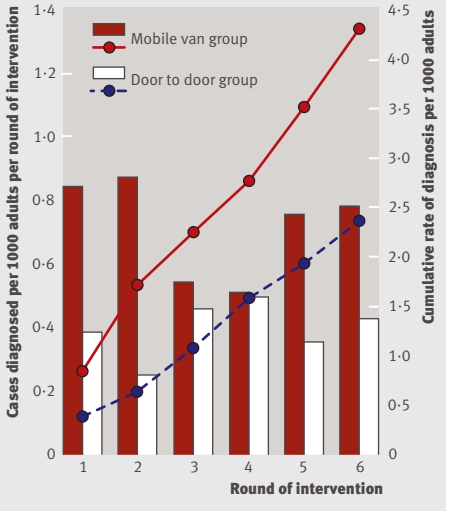
Researchers comparing two strategies to identify undiagnosed tuberculosis in poor suburbs of Harare were surprised to find that a mobile van and a loudspeaker worked significantly better than knocking on doors. In a cluster randomised trial, the mobile unit diagnosed almost 50% more smear positive tuberculosis than a team making house calls (adjusted risk ratio 1.48, 95% CI 1.11 to 1.96). Both strategies targeted people reporting chronic cough, who then provided two sputum samples for smear testing. The study lasted three years and covered 46 suburbs. Prevalence of culture positive tuberculosis fell significantly from 6.5 per 1000 adults to 3.7 per 1000 adults (adjusted risk ratio 0.59, 0.4 to 0.89) across all suburbs combined.

Most adults diagnosed by both strategies had never sought medical care despite their suspicious symptoms, and despite living within walking distance of a health clinic. These infectious adults will stay infectious unless we find and treat them, say the authors. People with tuberculosis were offered HIV testing, and around 70% of those who agreed tested positive. The background prevalence of HIV in these suburbs was 21% (1916/9060)

This study should encourage policy makers to scale up their outreach efforts, says a linked comment (doi:10.1016/S0140-6736(10)61503-6). It should also encourage researchers to look harder for a quick, easy, and reliable test for tuberculosis. Having to rely on sputum smears (too inaccurate) and cultures (too slow) is a serious barrier to progress.

Lancet 2010; doi:10.1016/S0140-6736(10)61425-0)

DETECTION OF SMEAR POSITIVE TUBERCULOSIS



Adapted from *Lancet* 2010; doi:10.1016/S0140-6736(10)61425-0

Implants for opiate addiction are effective in preliminary trials

Buprenorphine implants are an effective maintenance treatment for people dependent on opioids, according to a placebo controlled trial. Addicted young adults given the new formulation delivered more "clean" urine samples (40.4% of 48 samples *v* 28.3%) and were less troubled by withdrawal symptoms or cravings than controls given placebo implants. They also took fewer rescue drugs, in the form of sublingual buprenorphine with naloxone. The implants lasted for six months, and researchers analysed the primary outcomes after four.

An editorial (p 1612) gave the new formulation of buprenorphine a cautious welcome. Not because it works better than a placebo—we already know that buprenorphine is a good maintenance drug—but because implants, unlike tablets, cannot be sold on. Diversion is one of the biggest challenges for doctors treating adults addicted to opioids. Adherence is another. It is clearly harder to abandon a treatment placed under the skin. Adherence to active treatment was generally good in this trial. Two thirds (65.7%; 71/108) of those given active implants made it to the end.

The sponsor, Titan Pharmaceuticals, had to include a placebo group for regulatory purposes. Now we need to know how buprenorphine compares with more traditional maintenance treatments, including sublingual formulations of buprenorphine, says the editorial. There is still plenty of room for improvement. During the full six months of the trial, two thirds of the urine samples from actively treated adults tested positive for illegal opioids.

JAMA 2010;304:1576-83

Hypertonic solutions fail to protect adults with a traumatic brain injury

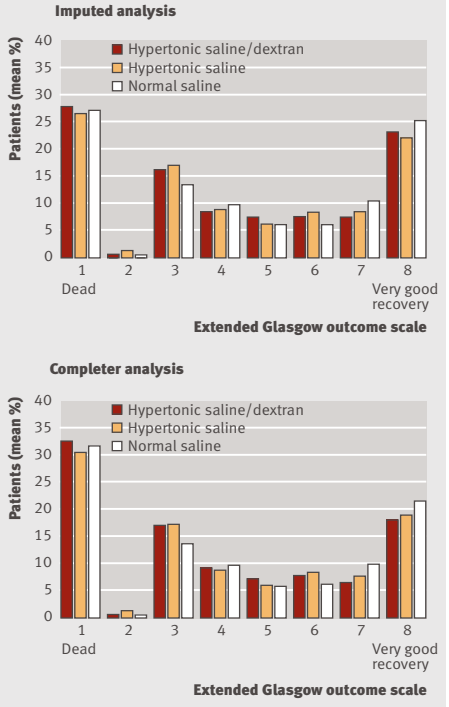
There are good biological reasons why osmotically active solutions such as mannitol and hypertonic saline should help control the brain swelling and neurological damage that swiftly follow a severe head injury. But trials have been disappointing, including the most recent, which tested a single bolus of hypertonic saline (7.5%) or saline plus dextran 70 (7.5%/6%), given early during resuscitation outside hospital. Neither solution improved neurological outcomes compared with 0.9% saline. Just over half the 1331 participants scored four or less on the extended Glasgow outcome scale six months after injury, indicating severe neurological impairment or death (53.7% for hypertonic saline plus dextran, 54.3% for hypertonic saline, and 51.5% for 0.9% saline). Three quarters of each group survived for at least 28 days (74.3%, 75.7%, 75.1%). Authors report no significant differences between the groups.

Emergency personnel gave the 250 ml bolus as soon as they established venous access. Further treatment was guided by local protocols, and a quarter of the participants received mannitol in hospital. All participants had traumatic brain injury after blunt trauma. Those with hypovolaemic shock were excluded.

These two hypertonic solutions didn't work in the out of hospital setting, and the trial ended early when a data monitoring committee decided further recruitment was futile.

JAMA 2010;304:1455-64

NEUROLOGICAL OUTCOME AT SIX MONTHS



Adapted from *JAMA* 2010;304:1455-64

Cite this as: *BMJ* 2010;341:c5612