SHORT CUTS

ALL YOU NEED TO READ IN THE OTHER GENERAL JOURNALS
Alison Tonks, associate editor, *BMJ* atonks@bmj.com

"In the Hanseatic ports of the Baltic in the 17th century, Protestant, Catholic, and Jewish merchants would trade avidly with each other, and although they would disagree over the Last Supper, they would all agree over lunch"
See Richard Lehman's journal blog on doc2doc.bmj.com

U shaped association between glycaemic control and mortality in type 2 diabetes

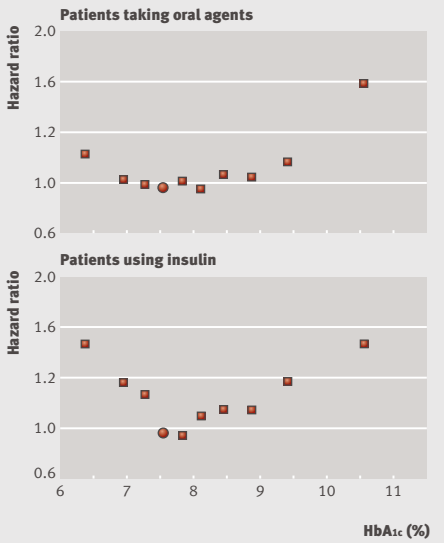
The association between diabetic control and mortality seems to be U shaped in people with type 2 diabetes. In a large observational analysis from the UK, people with mean glycated haemoglobin (HbA_{1c}) concentrations around 7.5% had the lowest mortality. Risk of death rose significantly on both sides of this reference group, reaching a hazard ratio of 1.52 (1.32 to 1.76) for patients in the bottom 10th of HbA_{1c} concentration (median 6.4%), and 1.79 (1.56 to 2.06) for patients in the top 10th (median 10.5%). Researchers analysed data from nearly 48 000 primary care patients who had stepped up their hypoglycaemic treatment. The U shape persisted after multiple adjustments and sensitivity analyses, and it looked most convincing for patients who had switched from oral drugs to regimens that included insulin.

We can't draw firm causal inferences from retrospective observations, however statistically powerful they are, says a linked comment (doi:10.1016/S0140-6736(09)62192-9). It is tempting to speculate that hypoglycaemia might be behind some of the excess deaths in people with the tightest control though, particularly those taking insulin.

These authors also report a U shaped association between glycaemic control and risk of cardiovascular disease, which was harder to explain. Again, an HbA_{1c} of 7.5% was associated with the lowest risk.

Lancet 2010; doi:10.1016/S0140-6736(09)61969-3

ALL CAUSE DEATH



Adapted from *Lancet* 2010; doi:10.1016/S0140-6736(09)61969-3

Uncertainty prevails over glucose control for adults with septic shock

Despite years of research, doctors still have little hard evidence to go on when trying to decide how much insulin, if any, to give critically ill patients with hyperglycaemia. The latest trial—in patients with septic shock treated with hydrocortisone—failed to settle the controversy, and at least one expert says mega trials that recruit many thousands of patients may be the only remaining option (p 365).

The new trial looked at 509 patients given hydrocortisone and one of four treatment options: tight glucose control with insulin, plus or minus fludrocortisone; or conventional glucose control with insulin, plus or minus fludrocortisone. Tight control had no discernible effect on mortality (relative risk 1.07, 95% CI 0.88 to 1.30) and neither did the fludrocortisone (0.94, 0.77 to 1.14). The more intensive insulin regimen was associated with significantly more hypoglycaemia.

After unpicking the numbers, the expert concluded that the trial was underpowered and hard to interpret. An important difference could have been missed, and the authors were probably overoptimistic about the expected benefits of intensive insulin in their sample size calculations. Patients also fell short of their target glucose concentrations, blurring the difference between the two insulin regimens and complicating interpretation still further.

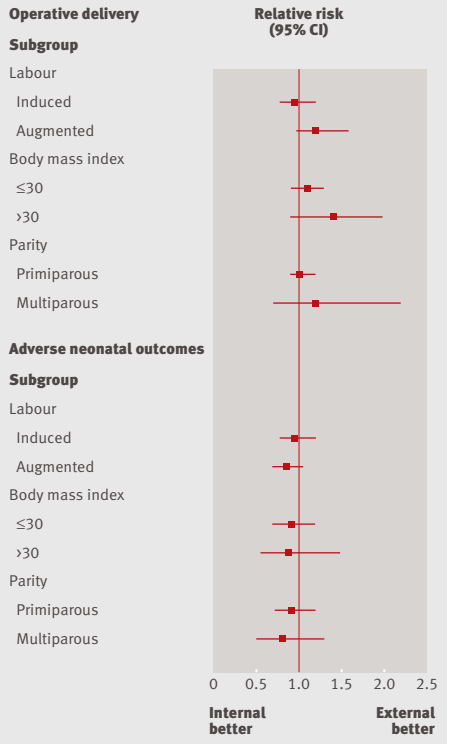
Uncertainty prevails for now but could be overcome by international collaboration between researchers and funding agencies, he writes. Large scale cooperation is already a reality in cardiology and oncology research. Critical care medicine should follow, urgently. It could take at least 70 000 patients to settle this controversy with confidence.

JAMA 2010;303:341-8

Trial challenges guidelines on internal monitoring of uterine contractions

National guidelines from the Netherlands recommend internal monitoring of uterine contractions during induced or augmented labour. A new trial suggests that the recommendations should be reviewed. Intrauterine monitoring didn't reduce operative deliveries or protect neonates compared with traditional external monitoring.

SUBGROUP ANALYSES



Adapted from *N Engl J Med* 2010;362:306-13

The 1456 women delivered in six Dutch hospitals where staff followed labour protocols informed by readings from a sensor tipped intrauterine catheter or an external tocodynamometer. Two thirds of the women were induced (with amniotomy followed by oxytocin if needed) and a third needed augmentation of spontaneous labour (with oxytocin).

Women monitored internally were no less likely to have an operative delivery than were controls (31.3% *v* 29.6%; relative risk with internal monitoring 1.1, 95% CI 0.91 to 1.2). Their babies were no less likely to have a low Apgar score, a low blood pH, or to need admission to a neonatal unit (14.3% *v* 15%; 0.95, 0.74 to 1.2). Subgroup analyses in women being induced or augmented, in women with a body mass index above or below 30, and in primiparous or multiparous women all echoed the main findings. Internal monitoring didn't seem to help mothers or their babies. Internal monitoring caused no serious complications, but the trial was too small to rule out rare events

such as damage to blood vessels, infections, and anaphylaxis, say the authors.
N Engl J Med 2010;362:306-13

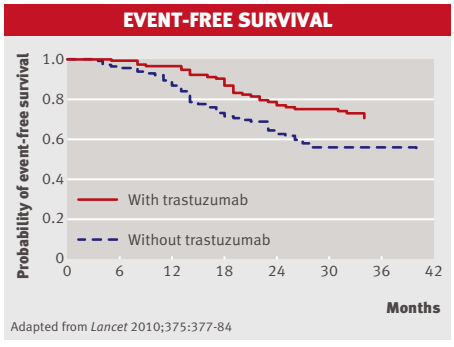
More evidence linking exercise to a healthier old age

It has become clear over the past 20 years or so that keeping active is linked to a better, fitter, and possibly even longer old age. Four new studies support this optimistic view, write two observers (p 124). Two, one from Canada and one from Germany, suggest that physical activity can help protect you from cognitive decline. Another study finds that exercise in middle age is associated with "successful survival" beyond 70 in women, by which the authors mean a life largely free from mental or physical illness. In the last study, older women who exercised for 18 months had a lower risk of falls and a healthier bone mineral density than controls.

The evidence is good, but not yet good enough to inform policies aimed at whole populations of ageing people, the observers write. Studies of exercise and ageing tend to recruit the younger healthier end of the spectrum. And many of them make observations, rather than test interventions. We don't yet know whether large scale exercise programmes are practical, safe, or effective for those older people at greatest risk of decline and disability. And we don't yet know how much they will cost. Large long term randomised trials in representative populations are still the only way to find out, and at least one is recruiting now.
Arch Intern Med 2010;170:170-8, 179-85, 186-93, 194-201

Trastuzumab works for locally advanced or inflammatory breast cancer

The monoclonal antibody trastuzumab is already approved for early and late breast cancers that overexpress human epidermal growth factor receptor 2 (HER2). The latest trial focused on women with locally advanced or inflammatory cancers, and it found that one year of treatment reduced the risk of progression, recurrence, or death (event-free survival at three years 71% *v* 56%; hazard ratio 0.59, 95% CI 0.38 to 0.90).



All 235 women had standard preoperative chemotherapy then postoperative radiotherapy. Half (117) also had trastuzumab for one year, starting alongside their preoperative chemotherapy and continuing after surgery. The authors enrolled a parallel group of women with similar cancers who tested negative for HER2. Their event-free survival was not significantly different from that of the control group (no trastuzumab). All treatments were open label. The trial was paid for by Hoffmann-La Roche.

Cardiotoxicity is a serious concern for women given trastuzumab alongside preoperative chemotherapy that includes anthracyclines, such as doxorubicin, says a linked comment (p 349), so all participants had regular electrocardiography and cardiac imaging. Cardiac side effects were surprisingly rare. Only two women given trastuzumab developed symptomatic heart failure, and another two had a potentially important but asymptomatic drop in left ventricular ejection fraction. The combination may be safer than we thought, says the comment, and could be made safer still with careful dose adjustments, patient selection, and monitoring.
Lancet 2010;375:377-84

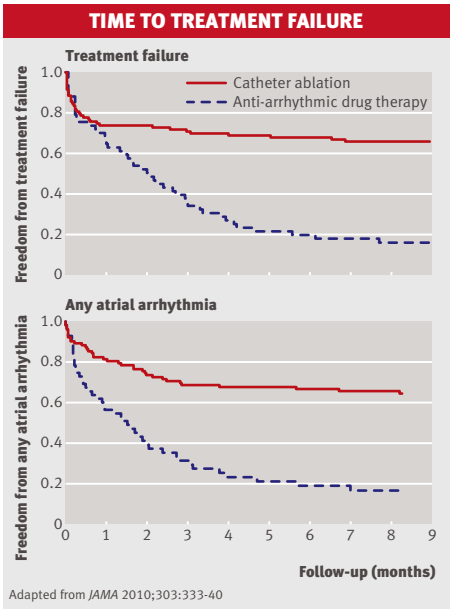
Ventilated patients don't always need sedation

Can critically ill people be ventilated without sedation? One intensive care unit in Denmark has been doing it since 1999 and recently reported a randomised trial testing their unusual strategy against more conventional sedation with propofol then midazolam. Patients treated without sedation had four fewer days on a ventilator during the 28 day trial (mean difference 4.2, 95% CI 0.3 to 8.1) than controls. They also left the intensive care unit and the hospital sooner. They were no more likely to extubate themselves or develop pneumonia than sedated controls, but they had a higher incidence of agitated delirium (11 patients (20%) *v* 4 patients (7%); P=0.0400).

This was a preliminary trial in 140 adults, most of whom had respiratory diseases or sepsis. Those treated without sedation were given boluses of morphine for pain relief and boluses of haloperidol for delirium. Controls were woken each day during a break in sedation, and both groups were mobilised daily to a chair.

The results look promising, says a linked comment (doi:10.1016/S0140-6736(10)60103-1), although long term psychological complications are a potential concern. In this trial, 11 of the unsedated patients and three controls needed an extra person for comfort and reassurance (P=0.0247).
Lancet 2010;375:475-80

Radiofrequency ablation looks better for refractory paroxysmal atrial fibrillation



Radiofrequency catheter ablation is a good second line option for adults with paroxysmal atrial fibrillation who have failed to respond to at least one anti-arrhythmic drug, according to a head to head trial. Participants who had catheter ablation had significantly fewer treatment failures over nine months than controls who tried a new drug instead, usually flecainide or propafenone (hazard ratio 0.30, 95% CI 0.19 to 0.47). The authors' definition of treatment failure included further paroxysmal atrial fibrillation, a repeat ablation, or the termination of a drug treatment because of intolerable side effects. Radiofrequency ablation was also better at preventing both symptomatic and asymptomatic atrial arrhythmias, and was associated with greater improvements in quality of life during the first three months.

Recruitment stopped early when an interim analysis showed an emphatic result in favour of radiofrequency ablation. The final analyses looked at 106 adults treated with ablation and 61 who continued with drugs. Five patients in each group had a serious adverse event related to treatment but none died. Bigger trials are already under way to find out if radiofrequency ablation can help prevent strokes, heart failure, or progression from paroxysmal to more permanent forms of atrial fibrillation.

The patients in this trial had had paroxysmal atrial fibrillation for a mean of six years. They were younger and fitter than unselected patients seen in practice, say the authors.
JAMA 2010;303:333-40

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