# SHORT CUTS

**ALL YOU NEED TO READ IN THE OTHER GENERAL JOURNALS**

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## Biased reporting of trials continues despite compulsory registration

The registration of clinical trials has increased dramatically in recent years but the quality of registered trials remains poor, according to a study of trials published in 2008 by major journals. More than half of the 323 included trials were not properly registered (176/323 (54.5%)): nearly 14% (45/323) were registered retrospectively after the trial had finished and one in eight (39/323) had a register entry without an adequate description of the primary outcome. More than one quarter of trials weren't registered at all (89/323).

Among the 147 trials that were properly registered, 46 (31.3%) had different primary outcomes in the register entry from the matched published report. Suspecting biased reporting, the authors looked for changes in the published paper that would favour a statistically significant result. In the 23 evaluable pairs of papers and register entries, 19 had been changed to favour significant results. In some, a new and significant primary outcome had been introduced for publication. In others, a non-significant primary outcome had been left out or redefined for publication.

Tweaking trial outcomes to make the results look better or more publishable is misleading and unacceptable, say the authors. Earlier, more detailed, and more comprehensive registration would help. Editors and peer reviewers should also do a better job of checking that a submitted manuscript is consistent with its register entry.

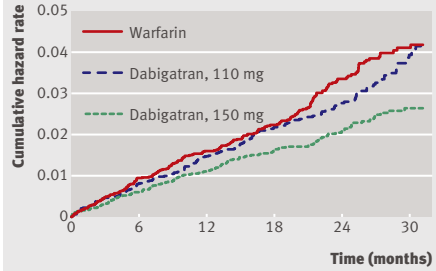
***JAMA*** 2009;302:977-84

## New anticoagulant works well for people with atrial fibrillation

Dabigatran is an oral thrombin inhibitor and a potential alternative to warfarin for people with atrial fibrillation. The new drug has several theoretical advantages over warfarin: it is less susceptible to drug interactions, and people taking dabigatran do not need monitoring or dose adjustments.

Dabigatran also helps prevent ischaemic strokes and systemic emboli, and compared well against warfarin in a recent large trial. The lower dose investigated (110 mg twice daily) worked as well as warfarin over 2 years

**CUMULATIVE HAZARD RATES FOR STROKE OR SYSTEMIC EMBOLISM**




Adapted from *N Engl J Med* 2009;doi:10.1056/NEJMoa0905561

(1.53% *v* 1.69% experienced stroke or systemic embolism, relative risk 0.91, 95% confidence interval 0.74 to 1.11), but the higher dose (150 mg twice daily) worked better (1.11% *v* 1.69%, 0.66; 95% CI 0.53 to 0.82). People given either dose of dabigatran had significantly fewer haemorrhagic strokes than controls given warfarin (0.38% per year *v* 0.12% per year (110 mg dabigatran) and 0.1% per year (150 mg dabigatran); P<0.001 for both comparisons).

An accompanying editorial says this industry sponsored trial is reliable and suggests that some patients with atrial fibrillation could benefit from switching to dabigatran (doi:10.1056/NEJMe0906886). The lower dose seemed safer overall, but the higher dose looked more effective. Problems associated with this new drug include an unexplained increase in heart attacks. Patients taking the higher dose also had significantly more gastrointestinal bleeds than controls taking warfarin, possibly because dabigatran capsules contain tartaric acid to lower stomach pH and aid absorption.

***N Engl J Med*** 2009;doi:10.1056/NEJMoa0905561

## Collagenase injections improve Dupuytren's contracture

Auxilium Pharmaceuticals is currently testing a new non-invasive treatment for Dupuytren's contracture—an injectable enzyme that lyses the pathological collagen responsible for disabling joint contractures. In their placebo controlled trial, up to three injections of collagenase *Clostridium histolyticum* reduced nearly two thirds of contractures (130/203 (64.0%)) to less than 5 degrees of full extension. Only 6.8% (7/103) of contractures treated with placebo injections improved to the same extent.

At the start of the trial, all participants had contractures of at least 20 degrees in one or more metacarpophalangeal or proximal interphalangeal joints. The injections, which were placed directly into cords of collagen, were followed by standardised manipulation, and patients were given a splint to wear at night for four months. Joints treated with collagenase *C histolyticum* improved significantly more than control joints on all clinical measures including range of motion.

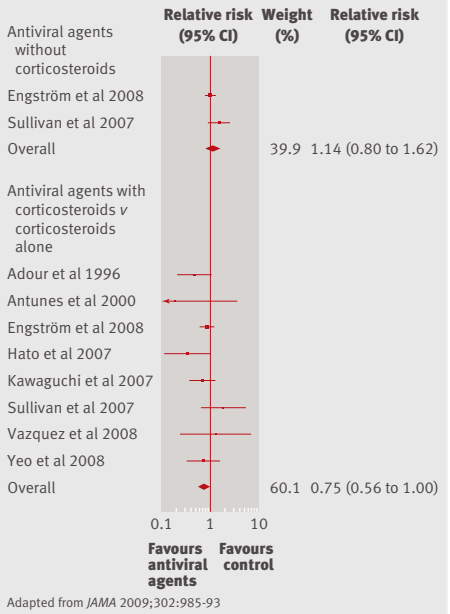
The active injections commonly caused pain, swelling, and bruising. More serious side effects included two patients with ruptured tendons and one case of a complex regional pain syndrome. The trial was too brief to assess the long term risk of recurrence, which is high following conventional surgery.

***N Engl J Med*** 2009;361:968-79

## Uncertainty continues over antiviral agents for Bell's palsy

A meta-analysis of randomised trials has confirmed that corticosteroids are an effective treatment for Bell's palsy (relative risk of unsatisfactory recovery 0.69, 95% CI 0.55 to 0.87). The analysis also confirms that antiviral agents are not effective when used alone (1.14, 0.80 to 1.62). Uncertainty remains over the efficacy of using both treatments together. The authors

**FACIAL RECOVERY AFTER ANTIVIRALS**




Adapted from *JAMA* 2009;302:985-93

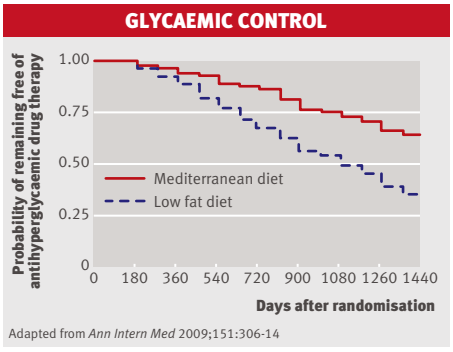
find a suggestion that adding antiviral agents to corticosteroids could reduce the likelihood of unsatisfactory facial recovery by 25% compared with corticosteroids alone. But the result wasn't statistically conclusive (relative risk *v* corticosteroids alone 0.75, 95% CI 0.56 to 1.00; P=0.05).

The 18 trials analysed included a total of 2786 patients followed up for a median of 6 months. More trials should be done though, says an editorial (p 1003-4). Generic antiviral agents such as aciclovir are widely available and relatively cheap. We'd all like to know for certain if they can make a difference to this potentially disfiguring disease. Although most patients with Bell's palsy recover, one in seven is left with persistent facial weakness, contracture, or involuntary movements known as synkinesis.

In the absence of definitive evidence, patients and their doctors must decide between them whether or not to use antiviral drugs, taking into account likely benefits, likely adverse effects, costs, and personal preferences, says the editorial.

***JAMA*** 2009;302:985-93

## Mediterranean diet is best for people with type 2 diabetes




Adapted from *Ann Intern Med* 2009;151:306-14

A Mediterranean style diet worked better than a low fat diet for 215 overweight Italian adults with newly diagnosed type 2 diabetes in a randomised trial. The two diets had similar calorie content and both groups lost weight over four years. But those who ate the Mediterranean diet were significantly less likely to need drug treatment for their diabetes (44% *v* 70%, hazard ratio 0.63, 95% CI 0.51 to 0.86). They had better glycaemic control for four years and better cardiovascular risk profiles for at least the first year.

The Mediterranean diet included plenty of fruit, vegetables, fish, and chicken. The carbohydrate content was equivalent to less than 50% of the total calories and the main source of fat was olive oil. The principal goal of the low fat diet was to keep fat intake to below 30% of the total calories with a diet rich in whole grains.

Participants on the Mediterranean diet lost more weight in the first year than those on the low fat diet, although the difference attenuated after that. Results adjusted for weight loss still favoured the Mediterranean diet (0.70, 0.59 to 0.90). This suggests there is more to the diet of fish, fruit, vegetables, and olive oil than simple weight loss, say the researchers. The monounsaturated fat in olive oil may also improve insulin sensitivity, which would help delay the need for hypoglycaemic drugs.

***Ann Intern Med*** 2009;151:306-14

## Proton pump inhibitors affect platelets not patients

US and European regulatory authorities have already warned doctors of a likely drug interaction between proton pump inhibitors and clopidogrel, a widely used antiplatelet agent. Reassuring evidence of the safety of these two agents combined has emerged from a careful analysis of two randomised trials in patients having a planned percutaneous coronary intervention.

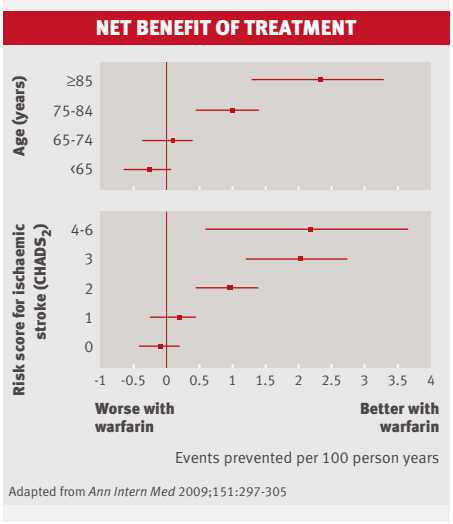
In the first trial, proton pump inhibitors reduced the platelet inhibiting effect of both clopidogrel and prasugrel, as measured in the laboratory, although the effect was modest.

In the second trial, however, the drug interaction made no difference to clinical outcomes including heart attack, stroke, stent thrombosis, or death in over 13 000 adults. Participants took either clopidogrel or prasugrel after a percutaneous coronary intervention for acute coronary syndrome. Proton pump inhibitors were given at their doctors' discretion. Clinical outcomes were similar for patients who did and did not receive a proton pump inhibitor (adjusted hazard ratio 0.94, 95% CI 0.80 to 1.11 for clopidogrel; 1.00, 0.84 to1.20 for prasugrel). The results remained unchanged through comprehensive adjustments for the many clinical and demographic factors that can influence a doctor's decision to prescribe proton pump inhibitors.

The interaction between proton pump inhibitors and thienopyridine platelet inhibitors is real in the laboratory but probably too weak to affect the relatively young fit patients in this trial, says an editorial (doi:10.1016/S0140-6736(09)61562-2). It remains unclear what might happen to people with a higher risk of ischaemic events.

***Lancet*** 2009;doi:10.1016/S0140-6736(09)61525-7

## People with a high risk of stroke gain most from warfarin therapy for atrial fibrillation




Adapted from *Ann Intern Med* 2009;151:297-305

In general, the benefits of warfarin for atrial fibrillation (fewer strokes) outweigh the harms (more bleeding). The balance, however, depends critically on each patient's overall risk of ischaemic stroke, say researchers. In their cohort study, the balance was most favourable for people with a history of ischaemic stroke and those over 84 years of age. It was least favourable and close to zero for the 50% of the cohort with low risk of stroke, including all patients under 65.

The balance of benefits and harms seems to have shifted since the original trials of warfarin were published two decades ago, says an editorial (p 355-6). People with atrial fibrillation are less likely to have an ischaemic stroke these days, possibly because they get better treatment for hypertension. In this study, the risk of ischaemic stroke among untreated patients with atrial fibrillation and one other risk factor was just 1.2% per year—the lowest on record.

The cohort included 13 559 American adults who were followed up for a median of six years. Just over half received warfarin. After adjustments, warfarin treatment was associated with an absolute decrease of 1.04% a year in ischaemic strokes and systemic emboli (from 2.29% per year to 1.25% per year), compared with a 0.24% increase in intracranial haemorrhages (from 0.33% per year to 0.57% per year). The authors were unable to factor in harm from other serious bleeds.

***Ann Intern Med*** 2009;151:297-305

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