New intravenous antiplatelet agent disappoints in early trials

The first antiplatelet agent that is potent, fast acting, reversible, and readily controlled by intravenous infusion (cangrelor) has been tested in patients having a percutaneous coronary intervention (PCI). Results from twin trials were disappointing. Compared with clopidogrel, the new drug did not reduce the risk of death, heart attack, or revascularisation in the two days after PCI. The combined primary end point occurred in 7.8% of patients. Cangrelor was associated with a significantly higher risk of minor bleeding in both trials and a higher risk of major bleeding, which approached statistical significance in one trial (odds ratio 1.26, 95% CI 0.99 to 1.60).

Together, the trials included more than 14 000 patients scheduled for PCI, mostly for acute coronary syndrome. Cangrelor was started after angiography but before PCI in both trials and given for the duration of the procedure. Controls had clopidogrel alone, which was started before PCI in one trial and after in the other. Both trials ended early, when data monitoring committees decided that further recruitment wouldn’t alter the primary results. An editorial (doi:10.1056/NEJMoa0910677) argues that this decision seriously undermined secondary results, some of which favoured cangrelor.

Further trials are still justified, it says. These trials were brief and complicated by treatment strategies that don’t match current guidelines, a confusion of different primary analyses, and at least three different definitions of bleeding complications. N Engl J Med 2009; doi:10.1056/NEJMoa0908629 N Engl J Med 2009; doi:10.1056/NEJMoa0908628

“innocuous” ECG abnormality linked to cardiac deaths

The J point joins the QRS complex to the beginning of the ST segment on a 12 lead electrocardiogram (ECG). A raised or spiked J point was thought to be an innocuous sign of early repolarisation, but a cohort study from Finland recently found that middle aged adults with this abnormality had an increased risk of death from heart disease.

The link was strongest for men and women with a raised J point in the inferior ECG leads, who were 28% more likely to die of cardiac causes (adjusted relative risk 1.28, 95% CI 1.04 to 1.59) and 43% more likely to die of an arrhythmia (1.43, 1.06 to 1.94) than those with a normal J point.

The 10 864 participants were recruited at a mean age of 44 and followed up for 30 years. Overall, 630 had an abnormal J point somewhere (5.8%), and 384 had abnormalities in the inferior leads (3.5%). Bigger abnormalities in the inferior leads were associated with bigger risks (2.98, 1.85 to 4.92 for cardiac causes and 2.92, 1.45 to 5.89 for arrhythmias). The main analyses were adjusted for other risk factors for a death from cardiac causes, including evidence of heart disease on ECG.

A raised J point was an enduring feature, being present in four of five serial ECGs done five years apart in this study. The authors think it may signal heterogeneous or patchy repolarisation of the ventricular wall and an increased vulnerability to ventricular arrhythmias. N Engl J Med 2009; doi:10.1056/NEJMoa0907589

High dose folic acid associated with excess cancer risk

Between 1998 and 2005, Norwegian researchers conducted two large placebo controlled trials to test whether folic acid and B vitamins could help prevent further cardiovascular events in people with ischaemic heart disease by lowering concentrations of homocysteine. After 39 months the trials drew a blank, but the researchers noticed a slight and suspicious increase in cancers in participants who took both folic acid and vitamin B12. So they continued to track all participants in national registers of cancers and deaths for a further three years. They found a significant excess of cancer diagnoses (hazard ratio 1.21, 95% CI 1.03 to 1.41) and cancer deaths (1.38, 1.07 to 1.79) in adults who had taken supplements containing folic acid and vitamin B12 during the trials. These people also had significantly higher mortality from all causes than controls who had taken placebo or vitamin B6 supplements (1.18, 1.04 to 1.33).

The authors think that the effects of folic acid on cell growth could be to blame. Folic acid may speed up cell division in preclinical cancers or premalignant lesions. Both trials used high doses of folic acid (800 μg/day) that exceed recommended daily allowances for adults. Even in countries that fortify grains and cereals, such as the US, average daily intake is thought to be well below 400 μg/day. These preliminary observations deserve further scrutiny, says an editorial (p 2152), but they should not threaten national public health policies aimed at preventing neural tube defects in newborns. JAMA 2009;302:2119-26
Researchers engineer human epidermis from embryonic stem cells

A French team has bioengineered human epidermis from embryonic stem cells and successfully grafted it on to immunodeficient mice. The grafts lasted for at least 12 weeks, with no sign of rejection or tumours, paving the way for a bioengineered skin product to treat patients with burns.

The researchers grew keratinocytes from established human stem cell lines on a matrix of fibroblasts in a specially adapted culture. It took 40 days to develop a multi-layered structure with genetic and protein markers consistent with human epidermis, then another 12 weeks to mature after grafting.

Eventually, it may be possible to use bioengineered epidermis to cover large area burns while patients wait the three weeks it takes to grow enough autologous keratinocytes for grafting, says a linked comment (p 1725). Using it for more permanent grafts would be difficult, however, without a fully functioning dermis containing associated structures such as sweat glands and hair follicles.

The keratinocytes in this epidermis expressed few or no HLA antigens, reducing but not abolishing the risk of rejection, says the comment. The other challenge, shared by all embryonic stem cell treatments, is how to scale up small experiments into industrial operations while maintaining the quality, safety, consistency, and stability of the product. Lancet 2009;374:1745-53

Computerised decision aid streamlines complex diagnostic work-up

Patients with suspected pulmonary embolism need a potentially complex diagnostic work-up, which lends itself to a computerised decision support system (CDSS). One such system, loaded on to hand held devices, worked better than paper guidelines for doctors in emergency departments in France. The CDSS encouraged doctors in 10 departments to enter a clinical probability of pulmonary embolus based on the revised Geneva score. It then prompted them to work through a recommended series of tests until they had ruled out (post-test probability less than 5%) or ruled in (post-test probability of more than 85%) a pulmonary embolus. Paper based guidelines distributed on posters and pocket cards in 10 control departments did the same.

Doctors in both clusters got better at completing the appropriate work-up. In departments randomised to use the CDSS, the proportion of patients correctly investigated rose from 23.5% to 54.5%. In control departments the same proportion increased from 20.5% to 25.8%. The adjusted absolute difference was a significant 19.3% (95% CI 2.9% to 35.6%). The CDSS was most effective at helping doctors rule out pulmonary embolus (adjusted absolute difference between groups 26.4%, 10.1% to 42.7%), and it was much better than posters and cards at making doctors estimate the clinical probability of disease before ordering the first test, usually a D-dimer blood test. Ann Intern Med 2009;151:677-86

Correcting iron deficiency improves the lives of people with heart failure

Iron deficiency is common in people with heart failure, whether or not they also have anaemia. Intravenous iron is one way to replace depleted iron stores, and treatment seemed to improve patients’ quality of life and functional status in a large multinational trial.

Adults with heart failure and iron deficiency were treated with weekly, then monthly, intravenous injections of ferric carboxymaltose, guided by laboratory measures of iron metabolism, or a saline placebo. After 24 weeks, people given iron were significantly more likely than controls to move up one New York Heart Association (NYHA) functional class (odds ratio 2.40, 95% CI 1.55 to 3.71) and to report being much improved or moderately improved (50% v 28%; odds ratio for improvement 2.51, 95% CI 1.75 to 3.61). They had a better quality of life than controls and could also walk further on a six minute walk test.

The iron seemed to work equally well for patients with and without anaemia, which an editorial (doi:10.1056/nejme0910313) describes as puzzling. It is not yet clear how intravenous iron helps people with heart failure feel better, or whether oral iron might do the same. The patients in this trial had a mean ejection fraction of 32%, and most had New York Heart Association class III symptoms at baseline. Half were anaemic. N Engl J Med 2009; doi:10.1056/NEJMoa0908355

Misguided regulation cripples European research

European regulations governing clinical trials are threatening non-commercial research across the continent, and by extension threatening public health. A team of experts from the UK writes that a directive introduced in 2004 to harmonise the conduct of trials has increased bureaucracy and costs to such an extent that research activity in some clinical areas has crashed. One cancer research network reports an 85% increase in trial costs, a five month delay working through the directive’s requirements, and a fall in the number of new trials from 38 in 2001 to just seven in 2005. Emergency medicine has been badly affected by unresolved problems about consent. Paediatric trials in general and paediatric oncology trials in particular are struggling to recruit, they write. Cancer patients enrolled in trials often do better than those treated outside of trials, so this is a direct assault on children’s health.

There is no evidence that onerous new standards of data management and documentation, developed originally for the drug industry, have improved the care of patients in essential non-commercial trials. Researchers across Europe should challenge those elements of the new regulations that are not already legally binding. Other parts of the world will be watching and learning from Europe’s mistakes. PLoS Med 2009; doi:10.1371/journal.pmed.1000131

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