Abstracts

High-potency statins and the risk of acute renal failure

We know that there is a relationship between the use of statins and adverse renal effects. The JUPITER trial, which compared high-dose rosuvastatin with placebo in 18 000 patients, found an albeit non-significant rise of 19% in acute renal failure risk, which rose to 35% when the endpoint included doubling of serum creatinine. In another study of over 2 million patients, statin used was found to be associated with a more than 50% increase in the risk of acute renal failure, with evidence of raised risk within the first year of statin use and a dose-reponse effect.

In this study published recently in the *British Medical Journal* researchers sought to quantify an association between acute kidney injury and use of high-potency statins versus low-potency statins. They used a retrospective observational analysis of administrative databases, using nine population-based cohort studies and meta-analysis.

The setting was seven Canadian provinces and two databases in the UK and the USA.

A total of 2 067 639 patients aged 40 years or older and newly treated with statins between 1 January 1997 and 30 April 2008 participated. Each person hospitalised for acute kidney injury was matched with 10 controls.

A dispensing event was new if no cholesterol-lowering drug or niacin prescription was dispensed in the previous year. High-potency statin treatment was defined as ≥10 mg rosuvastatin, ≥20 mg atorvastatin, and ≥40 mg simvastatin; all other statin treatments were defined as low potency. Statin potency groups were further divided into cohorts with or without chronic kidney disease.

The main outcome measure was relative hospitalisation rates for acute kidney injury.

Within 120 days of current treatment, there were 4 691 hospitalisations for acute kidney injury in patients with non-chronic kidney injury, and 1 896 hospitalisations in those with chronic kidney injury. In patients with non-chronic kidney disease, current users of high-potency statins were 34% more likely to be hospitalised with acute kidney injury within 120 days after starting treatment. Users of high-potency statins with chronic kidney disease did not have as large an increase in admission rate.

Use of high-potency statins is associated with an increased rate of diagnosis for acute kidney injury in hospital admissions compared with low-potency statins. The effect seems to be strongest in the first 120 days after initiation of statin treatment.

Dormuth CR, et al. BMJ 2013;346:f880. [http://dx.doi.org/10.1136/bmj.f880]

Cardiovascular risks of radiotherapy for breast cancer

Radiotherapy is a risk factor for heart disease in women with breast cancer, according to a case-control study from Scandinavia. Risk of myocardial infarction, revascularisation, or death from heart disease rose by 7.4% (95% CI 2.9 - 14.5%) for every 1 Gy increase in radiation dose delivered to the heart during treatment.

The linear association between radiation dose and risk of heart disease emerged within 5 years of treatment and seemed to persist for at least 20 years. Higher doses looked more damaging in absolute terms for women with a history of ischaemic heart disease or other risk factors.

The authors studied a cohort of women with a record of radiotherapy for breast cancer in registries in Denmark and Stockholm, Sweden. They compared estimated dose to the heart in 963 cases with a new coronary event and 1 205 matched controls without a new event. Doses ranged from 0.03 to 27.7 Gy, but were generally higher for women with left-sided cancers.

Radiotherapy has also been linked to pericardial disease, valve dysfunction, cdiomyopathy as well as arrhythmias. Also, radiotherapy is not the only cancer treatment that has an adverse effect on the heart. The authors point out that oncologists and cardiologists need to collaborate more closely to manage all cardiovascular risks in women with breast cancer.

Darby SC, et al. N Engl J Med 2013;368:987. [http://dx.doi.org/10.1056/NEJMoa1209825]

Atherosclerosis is an ancient disease

We are all repeatedly led to believe that atherosclerosis is a modern disease, associated with modern lifestyles. However, this study published recently in the *Lancet* suggests otherwise.

Randall Thompson and colleagues obtained whole body CT scans of 137 mummies from four different geographical regions or populations spanning more than 4 000 years. Individuals from ancient Egypt, ancient

Peru, the Ancestral Puebloans of southwest America, and the Unangan of the Aleutian Islands were imaged. Atherosclerosis was regarded as definite if a calcified plaque was seen in the wall of an artery and probable if calcifications were seen along the expected course of an artery.

Probable or definite atherosclerosis was noted in 47 (34%) of 137 mummies and in all four geographical populations: 29 (38%) of 76 ancient Egyptians, 13 (25%) of 51 ancient Peruvians, 2 (40%) of 5 Ancestral Puebloans, and 3 (60%) of 5 Unangan hunter-gatherers (p=NS). Atherosclerosis was present in the aorta in 28 (20%) mummies, iliac or femoral arteries in 25 (18%), popliteal or tibial arteries in 25 (18%), carotid arteries in 17 (12%), and coronary arteries in 6 (4%). Of the 5 vascular beds examined, atherosclerosis was present in 1 - 2 beds in 34 (25%) mummies, in 3 - 4 beds in 11 (8%), and in all 5 vascular beds in 2 (1%). Age at time of death was positively correlated with atherosclerosis (mean age at death was 43 years for mummies with atherosclerosis v. 32 years for those without; p<0.0001) and with the number of arterial beds involved (mean age was 32 years for mummies with no atherosclerosis, 42 years for those with atherosclerosis in 1 or 2 beds, and 44 years for those with atherosclerosis in 3 - 5 beds; p<0.0001).

Atherosclerosis was common in four pre-industrial populations including pre-agricultural hunter-gatherers. Although commonly assumed to be a modern disease, the presence of atherosclerosis in premodern human beings raises the possibility of a more basic predisposition to the disease.

Thompson RC, et al. Lancet. [http://dx.doi.org/10.1016/S0140-6736(13)60598-X]

Still no malaria vaccine in sight

A candidate malaria vaccine RTS, S/AS01E has entered phase 3 trials, but data on long-term outcomes are limited. Ally Olotu and colleagues followed up children who had been randomly assigned at 5 - 17 months of age to receive 3 doses of RTS, S/AS01E vaccine (223 children) or rabies vaccine (224 controls) for 4 years. The end-point was clinical malaria and each child's exposure to malaria was estimated.

Over the 4 years of the study, 118 of 223 children who had received the malaria vaccine and 138 of the children who had received the rabies vaccine had at least 1 episode of clinical malaria. For every 100 vaccinated children, 65 cases of clinical malaria were averted. However, the efficacy of the vaccine declined over time and with increasing exposure to malaria. Vaccine efficacy was 43.6% in the first year, but declined to -0.4% in the fourth year. In children with an average or lower exposure to malaria, vaccine efficacy was 45%, but in those with a higher than average exposure to malaria efficacy dropped to 15.9%.

Results are equivocal – some benefit in the short term and for children with relatively low exposure to malaria.

Olotu A, et al. N Engl J Med 2013;368:1111-1120. [http://dx.doi.org/10.1056/NEJMoa1207564]

Single suture

New malaria drug packs a triple punch

'There's nowhere to hide.' Michael Riscoe of the Oregon Health and Science University in Portland is talking about *Plasmodium falciparum* – a species of parasite that causes the most dangerous kind of malaria. His team's new drug hits the parasites at three vital stages in their life cycle, in blood, in the liver and in mosquitoes too. Most existing drugs only kill the parasite in blood.

The drug, called ELQ-300, wrecks the parasites' ability to reproduce by disabling their mitochondria, the factories that produce two of the building blocks they need to make DNA. The drug does not harm human mitochondria, which produce energy rather than DNA.

ELQ-300 rapidly cured infected mice and killed parasites in mosquitoes that were allowed to feed on the mice shortly after infection, blocking further transmission to new victims.

Riscoe says that if ELQ-300 passes the obligatory safety tests, trials could begin in humans within two years.

'This is an excellent evaluation of an exciting new series of antimalarial drugs,' says Nick White of the Mahidol University in Bangkok, Thailand, a country where resistance is developing fast to artemisinins, the most potent class of antimalarial drugs now in use. 'Let's hope they make it through to the clinic,' he says.

Journal reference: Science Translational Medicine [http://dx.doi.org/kwk]

New Scientist, 25 March 2013 (online)