

## NEWSLETTER

Supporting the Derbyshire Health Community

Volume 7: Issue 10

January 2009

*Happy New Year to all our readers*

<b>Further in this issue</b>	<b>Page 2</b>	<b>Beta-blockers for heart failure</b>
	<b>Page 3</b>	<b>What is the drug of choice to manage inadequate lactation?</b>
	<b>Page 4</b>	<b>Prevention of GI adverse events with antiplatelet drugs</b>
	<b>Page 5</b>	<b>Drug safety update</b>
		<b>Statin update</b>
	<b>Page 7</b>	<b>JUPITER study</b>

### JAPC Update

The Joint Area Prescribing Committee (JAPC) is a countywide group covering Derbyshire County PCT and Derby City PCT. It provides recommendations on drugs and medicines management issues.

RED drugs are those where prescribing responsibility lies with a hospital consultant or a specialist. AMBER drugs are those that are initiated within a hospital/specialist setting but are suitable for shared care with a GP under a shared care agreement. GREEN drugs are regarded as suitable for primary care prescribing. BROWN drugs are those that JAPC does not recommend for use, except in exceptional circumstances, due to lack of data on safety, effectiveness, and/or cost-effectiveness.

The most recent updates are in the table below; the full list is available at

<http://www.derbyshirecountypct.nhs.uk/guidelines/default.asp>

The guidelines, formulary chapters, newsletters, etc can now be found via this link.

Drug	Date considered	Decision
Lanthanum	January 2009	AMBER (with Derby hospitals only – remains RED with Sheffield)
Eplerenone	December 2008	GREEN (only if spironolactone not tolerated - correction)
Liothyronine	December 2008	AMBER (for depression)
Alitretinoin	November 2008	RED
Amantadine	November 2008	BROWN
Promixin	November 2008	BROWN
Quetiapine MR	November 2008	GREEN (only on consultant recommendation)
Rivaroxaban	November 2008	RED
Rosiglitazone	November 2008	BROWN
Duloxetine	October 2008	GREEN (third line for diabetic neuropathy) (already approved as third line antidepressant)
Anagrelide	October 2008	RED

### Cancer risk with ezetimibe?

The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study<sup>1</sup> compared simvastatin and ezetimibe with placebo to determine whether intensive lipid-lowering improved clinical outcomes in 1873 patients with mild to moderate asymptomatic aortic stenosis. Patients were followed up for an average of 4.35 years.

Treatment with simvastatin and ezetimibe had no effect on the primary endpoint of major cardiovascular events (hazard ratio [HR] 0.96 [95% CI 0.83 to 1.12]), despite reducing serum LDL-cholesterol levels by approximately 50%. Overall mortality did not differ between the two treatment groups.

An unexpected increase in cancer incidence and mortality was observed in the active treatment arm. Newly incident cancers (of mixed origin) were recorded for 101 (10.7%) patients in the treated group versus 65 (7%) patients in the placebo group (HR 1.55 [1.13 to 2.12], p=0.01). Deaths from cancer were more frequent in the treated group compared with placebo: 39 patients (4.1%) vs 23 patients (2.5%), respectively (HR 1.67 [1.00 to 2.79], p=0.05). However, the SEAS study is limited by its relatively small size and short duration, and it was not powered to detect comparatively infrequent and long-term side-effects.

There is no good evidence that statins increase the risk of cancer,<sup>2</sup> and so the findings of the SEAS study cast suspicion on ezetimibe rather than on simvastatin.

There remains no good evidence that ezetimibe either alone or added to a statin reduces the risk of CV events compared to a statin alone. Although a 55% increased risk of cancer was seen in SEAS, the P value of 0.01 indicates that there was a 1 in 100 possibility that the difference in incidence was a chance finding. The data currently available suggest that such a large increase in the risk of cancer is unlikely. However, further data are required to clarify this important safety issue. As the accompanying editorial<sup>3</sup> says “Physicians and patients are unfortunately left for now with uncertainty about the efficacy and safety of the drug.”

The NPC<sup>4</sup> offers the following advice:

“It would seem sensible to use ezetimibe ▼ only with caution as there is no published evidence of its benefit on clinically important outcomes such as cardiovascular events and its long-term safety is unknown. Prescribers should continue to use statins first-line in most patients who require a lipid-lowering agent. As ezetimibe ▼ is a black triangle drug, all suspected adverse drug reactions should be reported to the MHRA.”

1. N.Engl J Med 2008; 359:1343-56
2. Lancet 2005; 366:1267-78
3. N.Engl J Med 2008; 359:1398-99
4. [www.npci.org.uk/blog/?p=199](http://www.npci.org.uk/blog/?p=199)

### **Beta-blockers for heart failure**

Beta-blockers are accepted therapy in chronic heart failure (CHF), however only a few (bisoprolol, carvedilol, metoprolol succinate mlr and nebivolol) of the many available have actually been studied in controlled trials in patients with CHF. Two epidemiological studies have been conducted to determine whether, in routine practice, patients with CHF treated with the beta-blockers studied in controlled trials (‘evidence-based’) did better than patients treated with other beta-blockers.

The first study<sup>1</sup> used data from pharmacy databases to identify all oral beta-blocker therapy taken by 11,326 patients a year before, and a year after, hospitalisation with HF. Patients were followed-up for a year after discharge, and the study outcome was death during follow-up.

7,976 patients received beta-blockers at discharge or follow-up. Their mean age was 73.9 years and they had a high prevalence of pre-existing cardiovascular disease. Atenolol and metoprolol (as tartrate) were the beta-blockers most frequently received and there were few baseline differences between the patients who received them. Compared with these patients, those who received carvedilol were younger, with less co-morbidity, and were more likely to be receiving other medications for HF.

Crude mortality rate was lowest with carvedilol, followed by atenolol, other beta-blockers, and metoprolol tartrate (17.7 vs. 20.1, 21.9 and 22.8 per 100 patient-years, respectively). The rate was highest for periods of non-use (37.0 per 100 patient-years), and the differences for risk of death compared to atenolol were only significant for metoprolol (p=0.04) and non-use (p<0.001). After adjustment for confounding factors, the increased risk for metoprolol compared with atenolol was just significant (hazard ratio 1.16; [95% CI 1.01 to 1.34]) and for non-use was statistically significant (1.63; [1.44 to 1.84]). The difference between atenolol and carvedilol was not statistically significant (1.16; [0.92 to 1.44]).

The authors conclude that in patients with CHF, carvedilol was not associated with a significantly different risk of death compared to atenolol. Metoprolol tartrate (short-acting) was associated with a slightly higher risk. However, they comment that the results should be interpreted with caution due to the potential for unmeasured confounding factors.

In the second study<sup>2</sup> data from two healthcare databases were used to identify 11,959 patients aged over 65 years (79% female, 26% aged over 85 years) with at least one hospitalisation for HF and at least six months' claims data prior to hospitalisation. Patients were divided into three groups by beta-blocker dispensed in the 30 days after hospital discharge: evidence-based, other, or no beta-blocker. The primary outcome was survival between 30 days and one year from discharge; secondary outcomes included hospitalisation for HF.

More than half of the patients (59%) received no beta-blocker; 23% received an evidence-based beta-blocker and the remaining 18% another beta-blocker. Baseline characteristics of the three groups differed significantly, however adjustment by propensity score reduced the differences. Mortality was highest in the no beta-blocker group, both before and after adjustment (adjusted rate 28.3% at one year). Rates (adjusted) for those on beta-blockers were lower for both the non-evidence-based (22.8%) and evidence-based (24.2%). There was no statistically significant difference in death rate between the two groups (difference -1.4; [-4.8 to 2.0]; p=0.43). Patients in the non-evidence-based group had a lower rate of hospitalisation that was statistically significant.

The authors conclude that in this diverse elderly population of patients with CHF, survival rates were similar with evidence-based and non-evidence-based beta-blockers. Survival in those not taking beta-blockers was significantly poorer. Patients prescribed evidence-based beta-blockers had slightly more hospitalisations, however they caution that this may be due to unmeasured confounding factors and suggest several possible explanations.

The authors of two accompanying editorials<sup>3,4</sup> comment that any differences between beta-blockers in the studies should be interpreted with caution, and that ideally large controlled trials are needed to clarify whether any significant differences exist. Both also note that such trials are unlikely. In conclusion, one suggests that the differences between the drugs may be significant and that for patients with left-ventricular dysfunction, only the evidence-based drugs should be used; the other author considers that clinicians can be comfortable with using non-evidence based beta-blockers in CHF, but that in the absence of randomised trial data it would be understandable if others felt differently. Both agree that mortality was substantially lower in those taking beta-blockers than in those not taking beta-blockers.

The advice from CKS<sup>5</sup> (Prodigy) is "if the person is already taking a beta-blocker, either continue with the beta-blocker that the person is already taking or switch to carvedilol, bisoprolol, or nebivolol. Switching may be the better option, as there is increasing evidence that the beneficial effects of beta-blockers in heart failure are not a class effect". Bisoprolol and carvedilol are the formulary choices in Derbyshire.

1. Arch Intern Med 2008; 168: 2415-2421
2. Arch Intern med 2008; 168: 2422-2428
3. Arch Intern Med 2008; 168: 2428-2431
4. Arch Intern Med 2008; 168: 2431-2432
5. [http://cks.library.nhs.uk/heart\\_failure/management/](http://cks.library.nhs.uk/heart_failure/management/)

### **What is the drug of choice to manage inadequate lactation?**

Having been asked if it is appropriate to prescribe domperidone to increase breast milk supply, I obtained the following advice from the UK Medicines Information Service (Q&A 73.2).

#### **Use of drugs to initiate or augment milk supply**

Galactagogues (drugs for faltering milk supply) should only be used after thorough evaluation for treatable causes such as poor attachment and when increased frequency of breastfeeding, pumping or hand expression of milk has not been successful.

Indications for the use of galactagogues are:

- Increase of a faltering milk supply due to maternal or infant illness and prematurity.
- Separation of mother and infant.
- After a period of milk expression by hand or with a pump when a decline in milk production may occur after several weeks.
- Adoptive nursing.
- Relactation (re-establishing milk supply after weaning).

There are no products in the UK that are licensed for use as galactagogues. Such use is “off-label”.

## Summary

- A health professional should always be involved in the decision to use a galactagogue.
- Drugs to manage inadequate lactation should only be used where there is objective evidence to support diagnosis and where non-drug methods have failed.
- There are no drugs licensed in the UK to improve lactation.
- Domperidone is considered to be the agent of choice for inadequate lactation because of its superior side effect profile, efficacy, and minimal passage into breast milk.
- The most commonly used regimen for domperidone is 10-20mg, orally, three to four times daily.
- Further studies are needed to determine the optimum regimen and duration of treatment.
- There are insufficient data to support the use of herbal remedies.

## Limitations

Published reports of drug use in lactation are generally limited to small numbers of subjects or to single case reports. Quantitative reports are often limited to single time point estimations. Many of the studies were performed before the introduction of modern lactation management. Few studies have provided encouragement and instruction to mothers. There are often inconsistencies in inclusion criteria that could minimise possible differences between drug and placebo groups.

## Guidelines on prevention of GI adverse events with antiplatelet drugs

The American College of Cardiology, American Heart Association, and American College of Gastroenterology have published a joint consensus statement on reducing the gastrointestinal risks of antiplatelet drugs and NSAID<sup>1</sup>.

The authors note that there is limited data of clinical trial quality in this area, therefore this statement has been produced based on the evidence that is available plus clinical expertise from cardiology and gastroenterology specialists. Antiplatelet therapy is widely used, and increasingly is used for prolonged periods: the authors therefore consider that it is essential that clinicians are aware of the risks associated with these drugs, especially in combination with NSAID, and how to manage them.

Major points made include:

- All NSAIDs, including selective COX-2 inhibitors, raise the risk of GI ulcers and bleeding when combined with aspirin taken chronically for cardioprotection.
- Even on its own, chronic aspirin for cardioprotection increases the risk of upper-GI events and should generally be limited to low doses.
- Patients at increased GI bleeding risk should go on a proton-pump inhibitor (PPI); those with a history of ulcers should be evaluated and, as appropriate, treated for *Helicobacter pylori* infection before starting antiplatelet therapy.
- Substituting clopidogrel for aspirin does not cut the risk of GI bleeding and is not as effective as the combination of aspirin and a PPI.
- PPIs are preferred over misoprostol, sucralfate, or histamine 2 (H2)-receptor antagonists for both the prevention and treatment of gastro-duodenal lesions associated with aspirin and other NSAIDs.
- Communication between cardiologists, gastroenterologists, and primary-care physicians is critical to weigh the ischaemic and bleeding risks in an individual patient who needs antiplatelet therapy but who is at risk for or develops significant GI bleeding.

The authors conclude that while appropriate use of antiplatelet drugs decreases the risk of ischaemic events, it increases the risk of bleeding complications. This risk increases further if NSAID therapy is added. Prophylaxis with a PPI is gastro-protective, but in high-risk patients communication between cardiologist, gastroenterologist, and primary care physician is essential to weigh the relative risks of bleeding and ischaemic events.

The formulary choice of PPI is omeprazole 20mg.

1. Circulation 2008; 118:1894-1909

## **Drug safety update**

This can be found at [www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/index.htm](http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/index.htm)

Here are some key points from the December issue.

### **Rituximab and efalizumab: *progressive multifocal leukoencephalopathy***

Progressive multifocal leukoencephalopathy (PML) has been reported in association with the use of some monoclonal antibodies. Patients should be monitored regularly for neurological symptoms or signs that might suggest PML. If PML is suspected, treatment must be suspended until PML has been excluded.

#### *Advice for healthcare professionals:*

- Patients on rituximab or efalizumab should be monitored clinically at regular intervals for neurological symptoms or signs that might suggest PML.
- If PML is suspected, treatment must be suspended until PML has been excluded.
- If doubt exists, further evaluation including MRI, testing of cerebrospinal fluid for JC viral DNA, and repeat neurological assessment should be considered.

### **Norfloxacin: *restricted use in urinary infections***

The European Medicines Agency has concluded that the oral fluoroquinolone norfloxacin (Utinor) should not be used to treat acute or chronic complicated pyelonephritis. The Agency's Committee for Medicinal Products for Human Use concluded that this indication should be withdrawn because efficacy has not been adequately shown for this type of infection, and because the benefits of norfloxacin do not outweigh the potential risks in this indication.

#### *Advice for healthcare professionals:*

- Oral norfloxacin should no longer be prescribed for newly diagnosed complicated pyelonephritis.
- Prescribers should review any patient taking oral norfloxacin for complicated pyelonephritis at their next scheduled visit, and should consider the need for alternative treatment if signs or symptoms of infection are persisting.

### **Hedrin: *keep treated hair away from sources of fire***

Hedrin contains dimeticone and is used in the treatment of headlice. In 2007, a patient who was using the product set fire to his hair. Although the product itself is not flammable, the labelling was updated to include the following statement:

"Warning: Hair should be kept away from naked flames, cigarettes and other sources of ignition while treatment with Hedrin is underway. Hedrin is not water based and will not prevent hair from burning"

Some older stock that does not include this warning in the product labelling may still be circulating in the supply chain. Pharmacists are asked to remind parents and patients who purchase Hedrin to ensure that while treatment is under way hair should be kept away from sources of fire.

## **Statin update**

### ***Statins in chronic kidney disease***

Patients with CKD are at increased risk of cardiovascular disease, but the role of statins in CKD is controversial. A meta-analysis analysed the benefits and harms of statins in patients with CKD<sup>1</sup>.

The analysis concluded that statins significantly reduce lipid concentrations and CV endpoints in patients with CKD, irrespective of stage of disease, but no benefit on all cause mortality or the role of statins in primary prevention has been established. Reno-protective effects of statins are uncertain because of relatively sparse data and possible outcomes reporting bias. The accompanying editorial suggests that criteria for treatment with statins for people with CKD should be the same as for people with normal kidney function<sup>2</sup>. Low glomerular filtration rate or dialysis alone should not be considered indications for treatment with statins.

### ***Statins and prostate tests***

A case series study<sup>3</sup> of the records of 1,214 men who were prescribed a statin between 1990 and 2006 at the Durham Veterans Affairs Medical Centre attracted some attention in the national press, with the *Daily Mail* suggesting that statins could dampen a key indicator of prostate cancer. These men were selected from the

original 23,428 who started taking statins at this medical centre in this time period. The average age was 60 years and the majority were either overweight or obese (85%). The median change in PSA levels after starting statins was a decline of 4.1%. For half the participants, this ranged from -22.1% to +12.5% (i.e. an increase in PSA levels).

The NHS Knowledge Service has reviewed this study<sup>4</sup>. They note important points to bear in mind when interpreting the results of this study:

- Firstly, the news report does not mention the alternative explanation of these results, that statins protect against prostate cancer (hence the decline in PSA levels). This is a theory that the researchers discuss at length, and which has also been suggested by other studies. If this were the case, then it would be an additional benefit of statins, rather than the other interpretation that potential cases of prostate cancer are being missed. Only further study in prospective cohort studies that have a proper control group will clarify this issue.
- The point about a 'control group' is important. In this study, the researchers used medical records to assess changes in PSA levels from before and after statin treatment. There was no parallel group of similar men not taking statins with whom fluctuating PSA could be compared. PSA levels decline with age and can change for other reasons, therefore in such studies it is important that a similar group of men are assessed to see whether statins really are responsible. The researchers attempted a control, using men from the larger cohort who had two PSA tests before statin treatment. They compared the difference between these with the difference between the pre- and post-statin levels. This is not an ideal control because the qualities that make these men candidates for statin treatment means they have different characteristics from men who are not prescribed these drugs.
- The participants in the analysis do not represent all the men who took statins through this medical centre. This raises issues of selection bias – i.e. that this group may be systematically different from the larger cohort.
- The results of this study are important mainly because they bring attention to an area for further research. Men who currently take statins should not be alarmed by these findings. The study does not prove that PSA tests are made less accurate by statins.

### ***Cheaper generic statins achieve QoF targets***

A study has shown that PCTs that had a high proportion of simvastatin and pravastatin use were just as successful achieving QoF cholesterol targets for patients with CHD, diabetes and stroke as those that used more atorvastatin and rosuvastatin<sup>5</sup>. The authors conclude that this supports the policy to use the less expensive generic statins. The NPC blog<sup>6</sup> concludes that this study provides reassurance that prescribers can continue to prescribe cheaper, generic statins, with simvastatin 40mg usually being first-choice. They point out that it is important to note that the NICE guidance on lipid modification sets no lipid targets which patients are expected to achieve.

### ***Statins in familial hypercholesterolaemia***

There are no RCTs with patient-orientated outcomes investigating statin use in people with FH. A long-term cohort study<sup>7</sup>, designed to mimic a controlled primary prevention trial, suggests that simvastatin (mean dose of 33mg daily) is very effective at reducing the risk of CHD in people with FH. The risk was reduced by 80% and the risk of MI in treated patients was not significantly greater than that in an age-matched sample from the general population.

### ***Statin induced myopathy***

A comprehensive review has recently been published<sup>8</sup>. The mechanism of statin induced myopathy is unknown. Myopathy correlates most closely with dose of statins and is independent of reductions in LDL-cholesterol. The usefulness of coenzyme Q10 in statin induced myopathy is unclear.

### ***Factors that may increase the risk of statin induced myopathy***

Advanced age (>80 years old)      Female sex      Low body mass index  
Multisystem diseases (for example, diabetes mellitus)  
Diseases affecting kidney or liver function      Hypothyroidism (untreated)  
Vigorous exercise      Excess alcohol      Intercurrent infections  
Major surgery or trauma      Diet (excessive grapefruit or cranberry juice)

Genetic factors (for example, polymorphisms of the cytochrome P450 isoenzymes or drug transporters, inherited defects of muscle metabolism, traits that affect oxidative metabolism of fatty acids)  
Drug interactions, especially with drugs that are inhibitors or substrates of the cytochrome P450 pathway (e.g. fibrates, nicotinic acid, calcium channel blockers, ciclosporin, amiodarone, glitazones, macrolide antibiotics, azole antifungals, protease inhibitors, warfarin)

#### *Tips for non-specialists*

- Slightly increased creatine kinase is common in the general population.
- Myopathy that develops after a patient has been taking statins for several years is unlikely to have been caused by these drugs.
- Thyroid stimulating hormone should be checked in patients on statins who develop a myopathy because hypothyroidism is a common cause of hypercholesterolaemia and raised creatine kinase.
- If muscle-related symptoms or raised creatine kinase concentrations persist after statin therapy is stopped, consider further investigations such as electromyography and muscle biopsy, in conjunction with a specialist.

#### *Summary points*

- Four types of muscle disorders are associated with statins: myalgias, myositis, rhabdomyolysis, and asymptotically increased creatine kinase
- Although the rate of statin induced myopathy among statin users is low, the high volume of statin prescriptions means that the condition is commonly encountered in clinical practice.
- Statin induced myopathy correlates most closely with the dose of statins, but any factor that increases the serum concentration of a statin potentially increases the risk of myopathy.
- If a patient presents with features suggesting statin induced myopathy, first line management is to stop statin therapy and observe any effect on symptoms and concentration of creatine kinase.

The recommended statins in the Derbyshire Statin Policy are simvastatin 40mg, simvastatin 20mg, and pravastatin 40mg, in that order.

1. BMJ 2008; 336: 645-51
2. BMJ 2008; 336: 624-5
3. Journal of the National Cancer Institute 2008; advance access published online October 28
4. [www.nhs.uk/news/2008/10October/Pages/Statinsandprostatetests.aspx](http://www.nhs.uk/news/2008/10October/Pages/Statinsandprostatetests.aspx)
5. J Health Serv Res Policy 2008; 13: 99-102
6. [www.npci.org.uk/blog/?p=234](http://www.npci.org.uk/blog/?p=234)
7. BMJ 2008; 337: a2423
8. BMJ 2008; 337: 1159-62

#### **JUPITER study (N Engl J Med 2008; 359: 2195-207)**

Rosuvastatin has been trialled against placebo in two previous studies. CORONA<sup>1</sup> involved people with chronic heart failure of ischaemic cause and in GISSI-HF<sup>2</sup> they had chronic heart failure of any cause. In both studies rosuvastatin 10mg daily had no significant effect on patient-orientated outcomes. For JUPITER, the investigators hypothesised that people with elevated high-sensitivity C-reactive protein levels but without hyperlipidaemia might benefit from statin treatment. The results received a lot of media attention. Was it justified?

#### **Method**

- JUPITER was a randomised, double-blind, placebo-controlled trial. Men aged 50+ and women aged 60+ were eligible if they did not have a history of CV disease and if, at the initial screening visit, they had an LDL-cholesterol level of less than 3.4 mmol/L, a high sensitivity C-reactive protein level of 2.0mg/L or more, and a triglyceride level of less than 5.6mmol/L.
- All potentially eligible patients underwent a 4-week run-in phase, during which they received placebo, to identify a group of willing and eligible participants who demonstrated good compliance. Only subjects who successfully completed the run-in phase were enrolled. Eligible subjects were randomly assigned in a 1:1 ratio to receive either rosuvastatin 20mg daily or matching placebo.
- The primary outcome was the occurrence of a first major cardiovascular event, defined as nonfatal myocardial infarction, nonfatal stroke, hospitalisation for unstable angina, an arterial revascularisation procedure, or confirmed death from cardiovascular causes. Secondary end points included the components of the primary end point considered individually – arterial revascularisation or hospitalisation for unstable angina, myocardial infarction, stroke, or death from cardiovascular causes – and death from any cause.

## Results

- A total of 89,890 people were screened for enrolment and 17,802 were randomly assigned to a study group. 38.2% of the participants were women and 25.2% were black or Hispanic. The mean age was 66 years and 41.4% had the metabolic syndrome.
- At baseline in both groups, the median LDL-C level was 2.8mmol/L, the HDL-C level was 1.3mmol/L, and the triglyceride level was 1.3mmol/L. The C-reactive protein level was 4.2 and 4.3 mg/L in the rosuvastatin and placebo groups respectively.
- The independent data and safety monitoring board voted to recommend early termination of the trial after a median follow-up of 1.9 years.
- At the 12-month visit, the rosuvastatin group, as compared with the placebo group, had a 50% lower median LDL-C level, a 37% lower median high-sensitivity C-reactive protein level, and a 17% lower median triglyceride level ( $p < 0.001$  for all 3 comparisons). These effects persisted throughout the study period.
- Outcomes:

	Rosuvastatin	Placebo	Hazard ratio (95% CI)	P-value	NNT
<b>Primary endpoint</b>	1.60%	2.82%	0.56 (0.46 to 0.69)	< 0.00001	82
<b>Any MI</b>	0.35%	0.76%	0.46 (0.30 to 0.70)	0.0002	244
<b>Any stroke</b>	0.37%	0.72%	0.52 (0.34 to 0.79)	0.002	286
<b>Arterial revascularisation</b>	0.80%	1.47%	0.54 (0.41 to 0.72)	<0.0001	149
<b>Any death</b>	2.22%	2.77%	0.80 (0.67 to 0.97)	0.02	182

- Total number of reported serious adverse events were similar in both groups ( $p=0.60$ ). However, physician-reported diabetes was more frequent in the rosuvastatin group ( $p=0.01$ ) with an NNH of 167.

## Discussion/Implications

- The trial was stopped early with only 1.9 of its proposed 4 years of follow-up concluded. JUPITER was designed to continue until 520 confirmed primary endpoints had been documented, whereas only 393 events had occurred. As 520 had been used in the power calculation, this will have resulted in under powering. As the accompanying editorial<sup>3</sup> states, the early termination probably exaggerated the results to some degree. The results will also be exaggerated by the run-in phase. As only compliant patients were randomised, the NNTs will be higher in the real world.
- The absolute benefit of rosuvastatin was small. For every 1000 people who took rosuvastatin 20mg daily for 2 years, 8 people avoided having an MI or a stroke or dying from CV causes, but 6 people developed diabetes who would not have done so otherwise<sup>4</sup>. Cost per event prevented calculates as £77,000.
- The increased risk of diabetes was perhaps unexpected. The authors state “physicians’ reports of diabetes were not adjudicated by the end-point committee, and careful evaluation of participants’ records will be needed to better understand this possible effect”.
- The endpoint of death from any cause only just reached statistical significance and given the small numbers and premature termination it must be queried how robust this result is.
- An important question is what is the long term safety of lowering LDL-C to very low levels in otherwise healthy people?
- The dose used in JUPITER was 20mg/day. The MHRA have advised caution in initiating this dose: patients should start on 10mg (5mg for Asian patients and those with pre-disposing factors for myopathy), including patients switched from other statins, and the dose should be titrated up after a four week trial.
- The population studied in JUPITER is one that would not qualify for statin therapy under national guidance. Should they be targeted? A BMJ editorial<sup>6</sup> comments “no change in strategy is needed despite the hype surrounding the recent JUPITER study.” JAPC have discussed JUPITER and concluded that no change in current practice is required.

1. N Engl. J Med 2007; 357: 2248-61

2. Lancet 2008; 372: 1231-9

3. N Engl J Med 2008; 359: 2280-2

4. [www.npci.org.uk/?p=236](http://www.npci.org.uk/?p=236)

5. [www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance](http://www.mhra.gov.uk/Publications/Safetyguidance/CurrentProblemsinPharmacovigilance)

6. BMJ 2008; 337: 1182-3