

THIS WEEK'S RESEARCH QUESTIONS

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Long term statins and atrial fibrillation

Atrial fibrillation is a common problem, and likely to become more so as the life expectancies of populations increase. Some have looked to statins as a potential solution, attractive by virtue of their falling costs and good safety profiles as well as their effectiveness against a wide range of cardiovascular conditions. And indeed, the findings of some studies suggest that the drugs do have a protective effect against atrial fibrillation.

Kazem Rahimi and colleagues reviewed the evidence in search of a conclusive answer (p 693). They found that while shorter term studies supported the use of statins to prevent atrial fibrillation, longer term and larger trials showed no protective effect. The meta-analysis, say the authors, does not completely exclude a real reduction in risk, but "casts doubt over the existence of any sustained and clinically relevant beneficial effect."



Supplementing parenteral nutrition with glutamine or selenium

Many critically ill patients have gastrointestinal dysfunction and so require parenteral nutrition. However, standard parenteral nutrition formulations are lacking in glutamine and selenium, both necessary for optimal immune function and recovery from disease. Several small trials have suggested that supplementing parenteral nutrition with glutamine or selenium can reduce mortality and new infections, but the results are not conclusive.

The SIGNET Trials Group has conducted a large randomised controlled trial (reported by Peter Andrews and colleagues, p 695) to test whether the inclusion of glutamine, selenium, or both



in a standard preparation of parenteral nutrition influenced the rate of new infections and mortality in 502 critically ill patients. The primary (intention

to treat) analysis found no difference in either outcome with the trial interventions, but a preplanned subgroup analysis of those patients who received at least five days of parenteral nutrition found a significant reduction in new infections with selenium supplementation.

Parenteral nutrition is also discussed in this week's clinical review by Geert Wanten and colleagues (p 696); in this case its use at home for patients with long term intestinal failure. The main problems stem from complications related to venous access and from liver dysfunction and altered bone mineralisation.

Comparative cardiovascular effects of thiazolidinediones

Last October rosiglitazone was withdrawn from the European market in response to mounting concerns about its cardiovascular safety, regulatory failures (see the *BMJ*'s investigation, *BMJ* 2010;341:c4848), and a belated recommendation from the European Medicines Agency (*BMJ* 2010;341:c727). Yet the drug is still on the market in the US, albeit with prescribing restrictions.

What about pioglitazone? There have been no long term trials directly comparing the cardiovascular harms of the two thiazolidinediones. But observational studies, including two in the *BMJ* (*BMJ* 2009;339:b2942, *BMJ* 2009;339:b4731) have suggested that pioglitazone is safer than rosiglitazone. And now Yoon Kong Loke and colleagues' meta-analysis of 16 observational studies with 810 000 mostly older patients adds much weight to this message (p 692). Numbers needed to treat to harm, depending on the population at risk, suggest 170 excess myocardial infarctions, 649 excess cases of heart failure, and 431 excess deaths for every 100 000 patients who receive rosiglitazone rather than pioglitazone.

Reviewing the rosiglitazone saga, editorialists Victor Montori and Nilay Shah from the Mayo Clinic in the United States ask, "Has the corruption of healthcare advanced so far that it is unreasonable, even naive, to expect responsible drug companies, enlightened regulators, and thoughtful prescribers?" (p 666). And they warn that inadequate regulation of the newest diabetes agents, dipeptidyl peptidase 4 inhibitors and glucagon-like peptide 1 agonists, could lead to a similar mess.



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EDITORIAL by Montori and Shah

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Review: Keeping big pharma in check (*BMJ* 2011;342:d1103)

Comparative cardiovascular effects of thiazolidinediones: systematic review and meta-analysis of observational studies

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STUDY QUESTION

What is the evidence on the comparative cardiovascular effects of rosiglitazone and pioglitazone in patients with type 2 diabetes in real world settings?

SUMMARY ANSWER

Compared with pioglitazone, use of rosiglitazone is associated with a small but statistically significant increase in the odds of myocardial infarction (about 16%), congestive heart failure (about 22%), and death (about 14%).

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Both thiazolidinediones (rosiglitazone and pioglitazone) have been found to increase the risk of heart failure, and rosiglitazone is also thought to increase the risk of myocardial infarction. This meta-analysis of 16 observational studies shows that rosiglitazone is associated with a significant increase in the odds of myocardial infarction, congestive heart failure, and death compared with pioglitazone; numbers needed to treat to harm, depending on the population at risk, suggest 170 excess myocardial infarctions, 649 excess cases of heart failure, and 431 excess deaths for every 100 000 patients who receive rosiglitazone rather than pioglitazone.

Selection criteria for studies

We identified controlled observational studies in Medline and Embase (up to September 2010) among patients with type 2 diabetes, which compared rosiglitazone with pioglitazone and reported on cardiovascular outcomes.

Primary outcome(s)

We did random effects meta-analysis on patient oriented outcomes of myocardial infarction, congestive heart failure, and mortality.

Main results and role of chance

We included 16 observational studies involving 810 000 thiazolidinedione users with type 2 diabetes. Geographical locations of the studies included the United States, Canada, United Kingdom, and Taiwan. On average, the study participants were above the age of 60 years. Compared with pioglitazone, use of rosiglitazone was associated with a small but statistically significant increase in the odds of myocardial infarction (odds ratio 1.16, 95% confidence interval 1.07 to 1.24; $P < 0.001$), congestive heart failure (1.22, 1.14 to 1.31; $P < 0.001$), and death (1.14, 1.09 to 1.20; $P < 0.001$). We did not find evidence of substantial heterogeneity, and the pooled estimates were robust to different sensitivity analyses.

Bias, confounding, and other reasons for caution

The studies included in our analysis are observational, with inherent methodological limitations such as selection bias leading to differential cardiovascular risk between patients on rosiglitazone and pioglitazone, as well as residual confounding. As the studies relied mainly on electronic medical and prescription databases, misclassification of drug use and outcomes could have occurred.

Study funding/potential competing interests

This study received no external funding. SS is supported by the NCCRRa component of the National Institutes of Health and NIH Roadmap for Medical Research.

EFFECT SIZES AND NUMBERS NEEDED TO TREAT TO HARM FOR USE OF ROSIGLITAZONE COMPARED WITH PIOGLITAZONE IN OBSERVATIONAL STUDIES OF PATIENTS WITH TYPE 2 DIABETES

Outcome	Odds ratio (95% CI)	Annualised number needed to treat to harm (95% CI)
Myocardial infarction (n=15 studies)	1.16 (1.07 to 1.24)	587 (392 to 1339)
Congestive heart failure (n=8 studies)	1.22 (1.14 to 1.31)	154 (110 to 214)
Overall mortality (n=8 studies)	1.14 (1.09 to 1.20)	232 (163 to 360)

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CME

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Effect of statins on atrial fibrillation: collaborative meta-analysis of published and unpublished evidence from randomised controlled trials

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STUDY QUESTION Does longer term treatment with statins (in trials with at least six months' treatment and at least 100 participants) reduce the risk of atrial fibrillation?

SUMMARY ANSWER A comprehensive review of published and unpublished evidence from larger scale statin trials showed no beneficial effect of statins on atrial fibrillation.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Some research in patients undergoing cardiac surgery or cardioversion suggests that statins could reduce the risk of atrial fibrillation by more than a third. In a comprehensive assessment of published and unpublished results from larger scale statin trials, many of which included people at risk of atrial fibrillation, there was no evidence for a protective effect of longer term statin treatment on atrial fibrillation.

Selection criteria for studies

We searched Embase, Medline, and the Cochrane's CENTRAL up to October 2010 for randomised trials comparing statin with no statin or comparing high dose versus standard dose statin. Trials had to have at least 100 participants and at least six months' follow-up. Unpublished data from longer term trials were obtained through contact with investigators.

Primary outcome

Our primary outcome was occurrence of first diagnosed or recurrent atrial fibrillation.

Main results and role of chance:

In published data from 13 short term trials (4414 randomised patients, 659 events), treatment with statins seemed to reduce the odds of an episode of atrial fibrillation by 39% (odds ratio 0.61, 95% confidence interval 0.51 to 0.74; $P<0.001$), but there was significant heterogeneity ($P<0.001$) between the trials. In contrast, among 22 longer term and mostly larger trials of statin versus control (105 791 randomised patients and 2535 events), treatment with statins was not associated with a significant reduction in atrial fibrillation (0.95, 0.88 to 1.03; $P=0.24$; $P<0.001$ for difference between the two sets of trials). There was also no evidence in seven longer term trials of more intensive versus standard statin regimens (28 964 randomised patients and 1419 events) of a reduction in the risk of atrial fibrillation (1.00, 0.90 to 1.12; $P=0.99$).

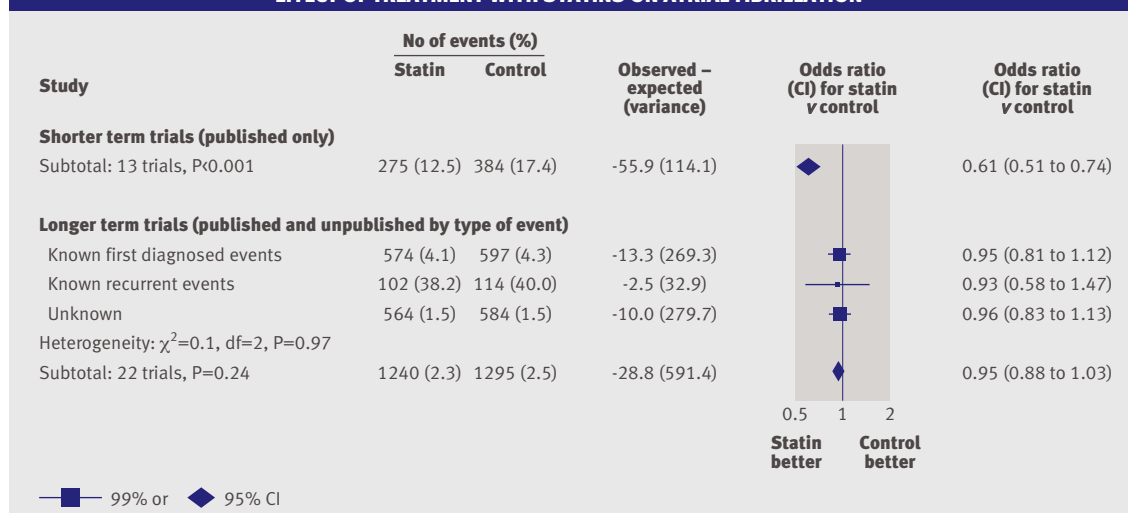
Bias, confounding, and other reasons for caution

Our study does not exclude a real reduction in risk of about 10%, and we cannot entirely rule out statins preventing the atrial population in certain types of patients because the underlying causes of the significant difference between shorter term and longer terms studies remain uncertain.

Study funding/potential competing interests

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

EFFECT OF TREATMENT WITH STATINS ON ATRIAL FIBRILLATION



Prevention of pain on injection of propofol: systematic review and meta-analysis

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STUDY QUESTION

What are the best current interventions for preventing pain from propofol injection?

SUMMARY ANSWER

The two most efficacious interventions are using the antecubital vein as the injection site, and, when using a hand vein, using a tourniquet for venous occlusion before pretreatment with lidocaine (lignocaine).

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

While a tourniquet for venous occlusion before pretreatment with lidocaine has been known to be very effective, other, less effective techniques, such as pretreatment with lidocaine without a tourniquet and lidocaine propofol admixture, are more commonly practised. Interestingly, the best approach appears to be using the antecubital vein instead of a hand vein, although this approach is not statistically superior to venous occlusion with lidocaine pretreatment. However, we now know that these two interventions are significantly more efficacious than all other interventions, including lidocaine propofol admixture and lidocaine pretreatment alone.

Selection criteria for studies

We searched PubMed, Embase, the Cochrane Library, www.clinicaltrials.gov, and references of identified studies for randomised controlled trials comparing drug and placebo or other intervention to alleviate pain on injection of propofol in adults.

Primary outcome(s)

Incidence of pain on injection of propofol.

Main results and role of chance

About 60% of patients experience pain on injection of propofol alone. Selecting an antecubital vein instead of the hand vein was numerically the most efficacious intervention to prevent such pain, followed by venous occlusion with a tourniquet and pretreatment with lidocaine. In addition, we identified six other commonly used efficacious interventions—namely, lidocaine propofol admixture; pretreatment with lidocaine alone, opioids, non-steroidal anti-inflammatory drugs, or ketamine; and propofol emulsions containing medium and long chain triglycerides. Furthermore, indirect comparisons across meta-analyses showed that choosing the antecubital vein and venous occlusion with lidocaine pretreatment were equally efficacious, but clearly superior to the other more commonly used interventions.

Bias, confounding, and other reasons for caution

A sensitivity analysis was carried out to assess the potential effect of four criteria for the risk of bias assessment. When the point estimates or confidence intervals of individual risk of bias domains were compared with the overall point estimates, there was no appreciable difference that would change the interpretation of results.

Study funding/potential competing interests

This study was funded by CCA's Perioperative Clinical Research Core, Department of Anesthesia and Perioperative Care, University of California, San Francisco, CA. LJ, VK, EG, YYS, OR, and CCA have no financial or non-financial competing interests. NLP is an unpaid statistical editor for the Cochrane Collaborative Review Group.

MOST EFFECTIVE INTERVENTIONS FOR REDUCING THE RISK OF PAIN FROM PROPOFOL INJECTION

No of patients (No of studies)	Interventions	Control	Relative risk (95% CI)
411 (6)	Antecubital vein	Hand vein	0.14 (0.07 to 0.30)
1072 (14)	Lidocaine pretreatment and venous occlusion	No venous occlusion	0.29 (0.22 to 0.38)
3210 (25)	Lidocaine-propofol admixture	No pretreatment	0.40 (0.33 to 0.48)
2053 (24)	Lidocaine pretreatment	No pretreatment	0.47 (0.40 to 0.56)
1522 (17)	Opioid pretreatment	No pretreatment	0.49 (0.41 to 0.59)
910 (7)	Ketamine pretreatment	No pretreatment	0.52 (0.46 to 0.57)
628 (7)	Non-steroidal anti-inflammatory drugs pretreatment	No pretreatment	0.67 (0.49 to 0.91)
2344 (24)	Propofol emulsion with medium and long chain triglycerides	Propofol emulsion with long chain triglycerides	0.75 (0.67 to 0.84)

Randomised trial of glutamine, selenium, or both, to supplement parenteral nutrition for critically ill patients

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STUDY QUESTION

Does the inclusion of glutamine, additional selenium, or both, in a standard preparation of parenteral nutrition improve the outcome for critically ill patients requiring parenteral nutrition?

SUMMARY ANSWER

The primary intention to treat analysis showed no difference with trial interventions, but a preplanned subgroup analysis found a significant reduction in new infections among those who received ≥ 5 days of parenteral nutrition supplemented with selenium.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

In critically ill patients mortality is high and gastrointestinal failure is common. Glutamine administered as part of parenteral nutrition did not decrease new infections or reduce mortality, but parenteral nutrition supplemented with selenium 500 μ g daily for at least 5 days may reduce new infections.

Design

Randomised, double blinded, factorial, controlled trial of parenteral glutamine (20.2 g/day) or selenium (500 μ g/day), or both, for up to seven days.

Participants and setting

Adults in level 2 and 3 (or combined) critical care units in the National Health Service in Scotland for ≥ 48 hours, with gastrointestinal failure and requiring parenteral nutrition.

Primary outcome(s)

Primary outcomes were participants with new infection(s) in the first 14 days after randomisation and mortality.

Main results and the role of chance

A total of 502 patients were recruited to this trial. Sele-

nium supplementation did not significantly affect participants developing a new infection (odds ratio 0.81 (95% CI 0.57 to 1.15)), except for those who had received at least five days of supplementation (odds ratio 0.53 (0.30 to 0.93)). There was no effect of glutamine on new infections (odds ratio 1.07 (0.75 to 1.53)), even in participants who received at least five days of trial nutrition (odds ratio 0.99 (0.56 to 1.75)). Six month mortality was not significantly different for selenium (odds ratio 0.89 (0.62 to 1.29)) or glutamine (odds ratio 1.18 (0.82 to 1.70)).

Harms

None demonstrated.

Bias, confounding, and other reasons for caution

The analysis of those who received at least five days of trial intervention, while prespecified, included only a subset of the randomised participants. This finding requires confirmation.

Generalisability to other populations

These data are generalisable to all critically ill patients requiring parenteral nutrition.

Study funding/potential competing interests

A pilot trial was funded by the Chief Scientist Office of the Scottish Government Health Directorates, followed by funding from the UK Medical Research Council. Fresenius-Kabi and Oxford Nutrition gave unrestricted grants for the trial nutrition components. JC holds a MRC fellowship. AA received a career scientist award of the Chief Scientist Office of the Scottish Government Health Directorates.

Trial registration number

ISRCTN87144826

EFFECTS OF TRIAL OF PARENTERAL NUTRITION FORMULATIONS ON CRITICALLY ILL PATIENTS

Outcome	Glutamine supplemented formulations*		Selenium supplemented formulations†	
	Yes	No	Yes	No
All patients randomised	n=250	n=252	n=251	n=251
All new infections within 14 days:	134 (54%)	131 (52%)	126 (50%)	139 (55%)
Odds ratio (95% CI)	1.07 (0.75 to 1.53)		0.81 (0.57 to 1.15)	
Mortality within 6 months:	115 (46%)	106 (42%)	107 (43%)	114 (45%)
Odds ratio (95% CI)	1.18 (0.82 to 1.70)		0.89 (0.62 to 1.29)	
Received ≥ 5 days of trial formulation	n=124	n=106	n=111	n=119
All new infections within 14 days:	80 (65%)	71 (67%)	65 (59%)	86 (72%)
Odds ratio (95% CI)	0.99 (0.56 to 1.75)		0.53 (0.30 to 0.93)	
Mortality within 6 months:	55 (44%)	42 (40%)	45 (41%)	52 (44%)
Odds ratio (95% CI)	1.17 (0.68 to 2.02)		0.88 (0.51 to 1.52)	

*With or without selenium supplementation.

†With or without glutamine supplementation.