

THIS WEEK'S RESEARCH QUESTIONS

- 1134** Can clinical officers in the developing world carry out caesarean sections as effectively and safely as doctors?
- 1135** Is concomitant treatment with aspirin and proton pump inhibitors associated with an increased risk of cardiovascular events?
- 1136** Did a UK recommendation to stop antibiotic prophylaxis for all patients at risk of infective endocarditis affect prescribing of antibiotic prophylaxis and incidence of infective endocarditis?
- 1137** To what extent do published cluster randomised trials adhere to the two basic requirements of reporting research ethics review and informed consent?



Clinical officers and caesarean section

“Clinical officers”—non-medics who are trained to do tasks usually done by doctors—are an important part of healthcare in many countries, especially in those with lower resources and a shortage of medically trained doctors. Obstetric care is one setting that makes great use of clinical officers, but uncertainty remains about their ability to perform emergency operations, and their scope to do so varies between countries.

To address the safety concerns, Amie Wilson and colleagues did a systematic review and meta-analysis of studies looking at the effectiveness of clinical officers in caesarean section (p 1134). Data came from Zaire, Mozambique, Malawi, Burkina Faso, and Tanzania. They found no significant differences between clinical officers and medical doctors for maternal or perinatal death, although a higher rate of wound infection and dehiscence for clinical officers might indicate a particular training need.

There is some uncertainty about the results, because no randomised trials were available for assessment. The authors also found statistical heterogeneity in the results, possibly because of the diversity of the studies' settings. For example, in the full paper online the authors discuss how the way clinical officers are used can vary and introduce bias. In one study, clinical officers were only asked to do the procedure in emergencies, and as emergency caesarean section is associated with worse outcomes than elective ones, the results could have been biased in the favour of doctors. In another setting, though, the perceived severity of an emergency caesarean could result in doctors rather than clinical officers carrying out the operation, leading to bias in favour of clinical officers.

Despite this uncertainty, it's important to assess the available evidence. Since caesarean section is the most common major surgical procedure in sub-Saharan Africa and can be lifesaving if delivered quickly, clinical officers could potentially play an important part in increasing accessibility and availability of emergency obstetric care—and, in turn, in meeting Millennium Development Goals 4 (reducing child mortality) and 5 (improving maternal health). Staffan Bergström discusses this further in an Editorial (p 1094).

Reporting of ethics review and consent in cluster randomised trials

It's a prerequisite of any randomised controlled trial that participants give informed consent, isn't it? Well, not always: in cluster randomised controlled trials the consent may be given by a proxy on behalf of a large group of people, something that surely ought to be fully described in any paper reporting such a trial. Yet Monica Taljaard and colleagues' review of a random sample of 300 cluster randomised trials published between 2000 and 2008 found that

the ethics aspects, including the details of ethics approval, were unreported in 77 of the papers and inadequately reported in many others (p 1137). In the full version of their paper they illustrate why cluster randomised trials pose ethical challenges that need particularly clear reporting, and cite a paper where “responsible authorities at each hospital, as well as birth attendants, provided written consent to participate in the trial; no consent was sought from patients, as outcomes were part of routine data collected at each hospital with no personal identifying information transmitted” (*N Engl J Med* 2008;358:1929-40).



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Dietary calcium intake and risk of fracture and osteoporosis In a prospective longitudinal study of data from the Swedish Mammography Cohort, Eva Warensjö and colleagues found that the lowest levels of dietary calcium intakes (below about 700 mg per day) were associated with increased risk of hip fracture, any fracture, and osteoporosis in women. Above this level, they saw only minor differences in risk as dietary calcium increased, and the rate of hip fracture was even increased in women with the highest dietary calcium intakes (doi:10.1136/bmj.d1473).

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A comparison of clinical officers with medical doctors on outcomes of caesarean section in the developing world: meta-analysis of controlled studies

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EDITORIAL by Bergström

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STUDY QUESTION

Can clinical officers in the developing world carry out caesarean sections effectively and safely compared with doctors?

SUMMARY ANSWER

Clinical officers and doctors did not differ significantly for maternal or perinatal death after caesarean section, although wound infection and dehiscence were increased with clinical officers.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Clinical officers are the backbone of obstetric care in many developing countries, carrying out as many as four fifths of caesarean sections in some countries. The effectiveness and safety of clinical officers in this role is uncertain. Our meta-analysis of six controlled studies found no differences between clinical officers and doctors for maternal or perinatal death, although wound infection and dehiscence were increased with clinical officers.

Selection criteria for studies

We searched, without language restriction, Medline, Embase, the Cochrane Central Register of Controlled Trials, CINAHL, BioMed Central, the Reproductive Health Library, and the Science Citation Index (inception-2010). For the systematic review we selected controlled studies that compared clinical officers with medically trained doctors for caesarean section in the developing world setting and that reported on any clinically relevant maternal or perinatal outcomes. To identify relevant studies we used the search terms clinical

officer, medical officer, assistant medical officer, medex, and non physician clinicians.

Primary outcomes

Maternal and perinatal death.

Main results and role of chance

We included six non-randomised controlled studies (16 018 women) comparing the performance of clinical officers with doctors for caesarean section in the developing world. The two groups did not differ significantly for maternal death or perinatal death. Clinical officers were associated with a higher incidence of wound infection (1.58, 1.01 to 2.47; $P=0.05$) and wound dehiscence (1.89, 1.21 to 2.95; $P=0.005$) compared with doctors. Two studies adjusted for confounding factors.

Bias, confounding, and other reasons for caution

Caution is needed when interpreting the findings of this meta-analysis owing to the non-randomised nature of the included studies and the potential for bias. Maternal and perinatal outcomes were statistically significantly heterogeneous, which may reflect the diversity of the setting, the population, indications for surgery, surgical approach, training, and the role of the clinical officers in these studies. When adjustments were made for confounding factors, however, the observed heterogeneity decreased.

Study funding/potential competing interests

This study was funded by the registered charity Ammalife (www.ammalife.org) and Birmingham Women's NHS foundation Trust R&D department.

CLINICAL OFFICERS COMPARED WITH DOCTORS ON OUTCOMES OF CAESAREAN SECTION

Outcome	No of studies	Summary odds ratio (95% CI)	Effect size	Heterogeneity, I ² (%)
Maternal mortality	6	1.46 (0.78 to 2.75)	$P=0.24$	60
Perinatal mortality	5	1.31 (0.87 to 1.95)	$P=0.19$	88

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Proton pump inhibitor use and risk of adverse cardiovascular events in aspirin treated patients with first time myocardial infarction: nationwide propensity score matched study

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STUDY QUESTION

Is concomitant treatment with aspirin and proton pump inhibitors associated with an increased risk of cardiovascular events?

SUMMARY ANSWER

Concomitant treatment with aspirin and proton pump inhibitors in patients with first time myocardial infarction was associated with an increased risk of adverse cardiovascular events.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The possible interaction between clopidogrel and proton pump inhibitors is widely debated, but recent evidence from ex vivo studies suggests that proton pump inhibitors may reduce the platelet inhibitory effect of aspirin in patients with cardiovascular disease. In aspirin treated patients with first time myocardial infarction, treatment with proton pump inhibitors was associated with an increased risk of adverse cardiovascular events.

Participants and setting

Participants comprised all adults in Denmark aged 30 or more admitted to hospital with a first myocardial infarction from 1997 to 2006. We only included patients that filled a prescription for aspirin within 30 days after discharge and survived 30 days after discharge. Patients treated with clopidogrel were excluded.

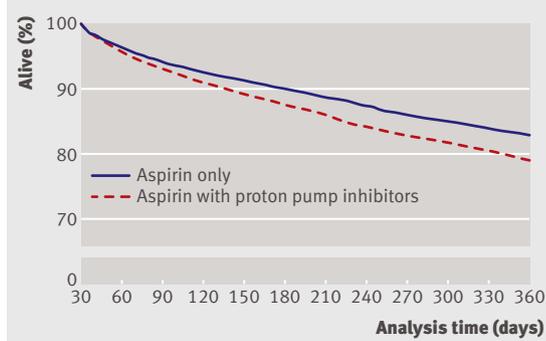
Design, size, and duration

This was a nationwide retrospective cohort study based on data from several Danish registries linked at the individual level. A total of 19 925 aspirin treated patients were included. We analysed the cardiovascular risk related to use of proton pump inhibitors during one year's follow-up. Overall, 4306 patients were treated with proton pump inhibitors during the study period; 4159 of these were matched with an equal number of patients not treated with proton pump inhibitors in a propensity score matched model.

Main results and the role of chance

In total, 3366 of the 19 925 (16.9%) included patients experienced recurrent myocardial infarction, stroke, or cardiovascular death during follow up. The hazard ratio for the combined end point in patients receiving proton pump inhibitors based on the time dependent Cox proportional hazard model was 1.46 (1.33 to

PROPSENSITY SCORE MATCHED KAPLAN-MEIER ANALYSIS OF RISK FOR CARDIOVASCULAR DEATH, MYOCARDIAL INFARCTION, OR STROKE IN RELATION TO TREATMENT WITH PROTON PUMP INHIBITORS



1.61; $P < 0.001$) and for the propensity score matched model based on 8318 patients it was 1.61 (1.45 to 1.79; $P < 0.001$). A sensitivity analysis showed no increase in risk related to use of H_2 receptor blockers (1.04, 0.79 to 1.38; $P = 0.78$).

Bias, confounding, and other reasons for caution

In observational studies unmeasured confounders may influence the results. However, our calculations showed that if an unmeasured confounder or a combination of confounders was present in 20% of the cohort treated with proton pump inhibitors, the confounder would have to increase the risk fourfold to explain the increased risk observed in our study. Existence of such a confounder or combination of confounders is unlikely but not impossible as we had no information on other important risk factors such as lipid levels, body mass index, or smoking.

Generalisability to other populations

The study included all hospital admissions in Denmark and was therefore not affected by selection bias from, for example, selective inclusion of specific hospitals, health insurance systems, or age groups. The studied cohort was thus representative of patients in a clinical setting. Importantly, the Danish population is largely white and generalisation of these data to other racial and ethnic groups should be made with caution.

Study funding/potential competing interests

All researchers are independent of the study funder, the Danish Heart Foundation.

Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: before and after study

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STUDY QUESTION

Did the recommendation by the National Institute for Health and Clinical Excellence (NICE) to cease antibiotic prophylaxis in the United Kingdom for all patients thought to be at risk of infective endocarditis result in a decrease in prescribing of antibiotic prophylaxis and an increase in the incidence of infective endocarditis?

SUMMARY ANSWER

The NICE recommendation resulted in a 78.6% reduction in prescribing of antibiotic prophylaxis for dental procedures but no significant change in the long term upward trend in cases of infective endocarditis. Statistically we could exclude the possibility of a 9.3% or more increase in cases of infective endocarditis.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The provision of antibiotic prophylaxis to patients at risk of infective endocarditis undergoing invasive dental and other procedures has been universal practice despite no data from randomised clinical trials to support its efficacy. This study lends weight to the argument that antibiotic prophylaxis is not required for patients thought to be at risk of infective endocarditis.

Participants and setting

In March 2008, NICE produced guidance recommending the complete cessation of antibiotic prophylaxis for all patients at risk of infective endocarditis undergoing dental and other invasive procedures. This was in contrast with American and European guidelines. We obtained monthly prescribing data for England from the Prescription Pricing

Division of the NHS Business Services Authority for single oral doses of amoxicillin 3 g or clindamycin 600 mg between January 2004 and April 2010. We used Dr Foster Intelligence to access hospital activity data for inpatients in England between January 2000 and April 2010. All patients with a primary or secondary discharge diagnosis of “acute or subacute infectious endocarditis” were identified.

Design

Retrospective observational study.

Primary outcome

Monthly prescribing of antibiotic prophylaxis and monthly incidence of infective endocarditis before and after the introduction of the NICE guideline.

Main results and the role of chance

After the introduction of the guideline, prescribing of antibiotic prophylaxis declined rapidly. Comparing the 12 month period before the introduction of the guideline with the 12 month period 14 to 25 months after, a mean 78.6% reduction in prescribing of antibiotic prophylaxis occurred, from a mean 10 727 (SD 1068) prescriptions per month to 2292 (SD 176). Evidence was lacking that the long term upward trend in cases changed after introduction of the guideline ($P=0.61$ comparing the trend before and after the guideline change), and statistically we were able to exclude the possibility of a 9.3% or more change in cases of infective endocarditis above baseline.

Bias, confounding, and other reasons for caution

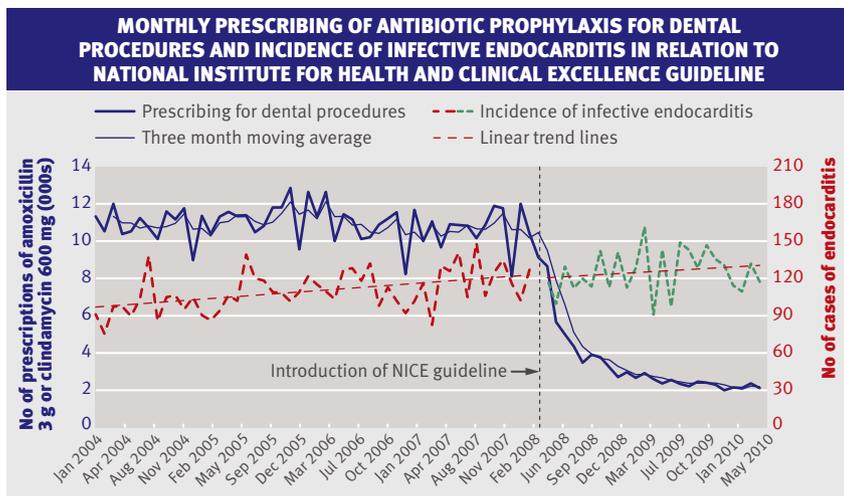
The study is retrospective and relies on hospital coding data, which have inherent inaccuracies. We can exclude a 9.3% increase in the number of cases above baseline, although a smaller increase may have occurred. There is persistent residual prescribing of antibiotic prophylaxis, and it is possible this is being targeted at patients deemed at highest risk from infective endocarditis. To determine if subsets of these patients would still benefit from antibiotic prophylaxis would require a prospective randomised controlled trial.

Generalisability to other populations

The results of this study are generalisable to Western populations where the prescribing of antibiotic prophylaxis to patients at risk of infective endocarditis is still normal practice.

Study funding/potential competing interests

The study was funded in part by the Somerset Heart Research Fund. We have no competing interests.



Inadequate reporting of research ethics review and informed consent in cluster randomised trials: review of random sample of published trials

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STUDY QUESTION

To what extent do published cluster randomised trials adhere to the two basic requirements of reporting research ethics review and informed consent?

SUMMARY ANSWER

Reporting of research ethics review and informed consent in cluster randomised trials is inadequate but has improved over time.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

No comprehensive guidelines exist for the ethical conduct and reporting of cluster randomised trials, which may have multiple kinds of participants who receive different interventions in the same study.

A large proportion of cluster randomised trials are published without disclosure of research ethics approval or informed consent from study participants; failure to disclose ethical protections is associated with characteristics of cluster randomised trials, as well as quality of methods and reporting.

Participants and setting

We included a random sample of 300 cluster randomised trials in health research published in 150 English language journals between 2000 and 2008.

Design

We reviewed a random sample of published cluster randomised trials from an electronic search strategy implemented in Medline.

Primary outcome(s)

The primary outcome was the proportion of cluster randomised trials that reported research ethics review and informed consent.

Main results and the role of chance

Of the 300 included trials, 77 (26%, 95% confidence interval 21% to 31%) failed to report ethics review. The proportion reporting ethics review increased significantly over time ($P<0.001$). Trials with data collection interventions at the individual level were more likely to report ethics review than were trials that used routine data sources only (79% ($n=151$) v 55% (23); $P=0.008$). Trials that accounted for clustering in the design and analysis were more likely to report ethics review. The median impact factor of the journal of publication was higher for trials that reported ethics review (3.4 v 2.3; $P<0.001$). Ninety-three (31%, 26% to 36%) trials failed to report consent. Reporting of consent increased significantly over time ($P<0.001$). Trials with interventions targeting participants at the individual level were more likely to report consent than were trials with interventions targeting the cluster level (87% (90) v 48% (41); $P<0.001$). Trials with data collection interventions at the individual level were more likely to report consent than were those that used routine data sources only (78% (146) v 29% (11); $P<0.001$).

Bias, confounding, and other reasons for caution

The electronic search strategy had a sensitivity of 90%, so 10% of published cluster randomised trials in Medline would not have been identified by our search strategy. Moreover, as identification of trials as “cluster randomised” in titles and abstracts of reports was poor, some trials may have been missed during the screening process. If these trials were also less likely to report on ethical issues, our results may have overestimated the proportions of trials reporting ethical matters.

Study funding/potential competing interests

This study has been funded by operating grants from the Canadian Institutes of Health Research.

Recommendations for reporting of ethical matters in cluster randomised trials

At a minimum, we recommend that authors should report:

1. Whether research ethics approval was obtained; if ethics review was not required, a reason should be given in the report
2. Whether informed consent was sought; if a waiver of consent was obtained, this should be stated, together with a reason for the waiver
3. From whom consent was sought and what consent was for—for example, randomisation, intervention, or data collection