Impact of wound edge protection devices on surgical site infection after laparotomy: multicentre randomised controlled trial (ROSSINI Trial)

Thomas D Pinkney,[1 2] Melanie Calvert,[1 3] David C Bartlett,[1] Adrian Gheorghe,[3] Val Redman,[3] George Dowswell,[1 3] William Hawkins,[1] Tony Mak,[1] Haney Youssef,[1] Caroline Richardson,[1] Steven Hornby,[1] Laura Magill,[1 4] Richard Haslop,[3] Sue Wilson,[1 3] Dion Morton,[1 2 4] on behalf of the West Midlands Research Collaborative and the ROSSINI Trial Investigators

[1]West Midlands Research Collaborative, Old Queen Elizabeth Hospital, Edgbaston, Birmingham, UK
[2]Academic Department of Surgery, University of Birmingham, Birmingham, UK
[3]Primary Care Clinical Sciences, University of Birmingham, Birmingham, UK
[4]Birmingham Clinical Trials Unit, University of Birmingham, Birmingham, UK
Correspondence to: TD Pinkney
thomas.pinkney@uhb.nhs.uk

Cite this as: *BMJ* 2013;347:f4305
doi: 10.1136/bmj.f4305

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;347:f4305

Trial registration
Current Controlled Trials ISRCTN 40402832

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STUDY QUESTION

Does the use of a wound edge protection device (WEPD) in adult patients undergoing laparotomy reduce the risk of postoperative surgical site infection?

SUMMARY ANSWER

WEPDs do not reduce the rate of surgical site infection in this population; this lack of benefit was consistent across all subgroups of patients and operations.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Systematic reviews pooling multiple small randomised controlled trials have suggested that WEPDs might reduce surgical site infections after abdominal surgery. This large trial, recruited from 21 centres, had broad inclusion criteria and dealt with many of the methodological limitations of previous studies but failed to show any benefit on the rates of surgical site infection.

Design

Multicentre observer blinded randomised controlled trial stratified by baseline infection risk. Patients were randomised 1:1 to standard care or to standard care plus the use of a wound edge protection device during surgery by using a secure centralised computer generated allocation.

Participants and setting

760 patients undergoing laparotomy for any emergency or elective indication with any major abdominal incision at 21 hospitals in the United Kingdom.

Primary outcome

Occurrence of surgical site infection within 30 days of the operation, according to the Centers for Disease Control (CDC) definition and assessed by blinded clinicians at seven and 30 days and by patients' self report for the intervening period.

Outcomes after laparotomy with and without use of wound edge protection device (WEPD). Figures are numbers (percentage) of patients unless specified otherwise

Outcome	WEPD	Control	Estimate (95% CI)	P value
Primary outcome				
Surgical site infection within 30 days	91/369 (24.7)	93/366 (25.4)	0.97* (0.69 to 1.36)	0.85
Secondary outcomes				
Mean (SD) EQ-5D	0.69 (0.29)†	0.69 (0.30)‡	0.001§ (−0.04 to 0.05)	0.95
Median (IQR) length of hospital stay (days)	9 (6 to 15)	9 (6 to 14)	1.03¶ (0.88 to 1.19)	0.82

IQR=interquartile range, EQ-5D= EuroQol health related quality of life score.
*Odds ratio.
†n=318.
‡n=313.
§Difference in means.
¶Hazard ratio.

Main results and the role of chance

760 patients were enrolled, with 382 patients assigned to the WEPD group and 378 to the control group. Five patients in the control group and six in the WEPD group did not undergo laparotomy, and 14 patients, seven in each group, were lost to follow-up. In total, 184 patients experienced an infection at the site of surgery within 30 days of the operation, 91/369 (24.7%) in the WEPD group and 93/366 (25.4%) in the control group (odds ratio 0.97, 95% confidence interval 0.69 to 1.36; P=0.85). This lack of benefit was consistent across wound assessments performed by clinicians and those reported by patients and across all secondary outcomes (including level of contamination, health related quality of life, and time to hospital discharge). In our secondary analyses we did not identify any subgroup for which use of the device conferred evidence of clinical benefit.

Harms No adverse events were reported.

Bias, confounding, and other reasons for caution

The baseline rate of surgical site infection in this study was high but closely comparable with that reported in other recent studies that used a similarly intensive wound follow-up regimen in equivalent patient cohorts. Patients diagnosed with an infection in our trial experienced longer lengths of stay in hospital, reduced health related quality of life, and additional use of health services, which all confirms diagnostic accuracy. We used only the single ring variant of WEPD. One recent pooled analysis of small single centre studies indicated a difference in outcomes between single ring and two ring WEPDs, but there are currently no head to head data comparing the different designs.

Generalisability to other populations

This pragmatic trial included all laparotomy operations in various surgical disciplines to maximise the generalisability of the results. Secondary analyses including level of contamination during the operation found no beneficial effect in any category.

Study funding/potential competing interests

This study was funded by NIHR; Research for Patient Benefit programme (PB-PG-1208-18234). Wound edge protection devices were provided free of charge by 3M (Bracknell, UK), who also hosted the online e-learning module and quiz. ROSSINI is the first trial from the West Midlands Research Collaborative (WMRC), a trainee-led surgical research group who designed, disseminated, and managed the trial in conjunction with the Primary Care Clinical Research and Trials Unit and the Birmingham Clinical Trials Unit at the University of Birmingham.

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Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis

Atsushi Goto,[1 2] Onyebuchi A Arah,[3 4] Maki Goto,[1 2] Yasuo Terauchi,[2] Mitsuhiko Noda[1]

[1]Department of Diabetes Research, Diabetes Research Center, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan
[2]Department of Endocrinology and Metabolism, Yokohama City University Graduate School of Medicine, Yokohama, Japan
[3]Department of Epidemiology, UCLA Fielding School of Public Health, Los Angeles, CA, USA
[4]Department of Public Health, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands
Correspondence to: M Noda
mnoda@hosp.ncgm.go.jp

Cite this as: *BMJ* 2013;347:f4533
doi: 10.1136/bmj.f4533

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;347:f4533

STUDY QUESTION

Is severe hypoglycaemia associated with risk of cardiovascular disease in people with type 2 diabetes?

SUMMARY ANSWER

This meta-analysis suggests that severe hypoglycaemia is associated with approximately twice the risk of cardiovascular disease in people with type 2 diabetes. A bias analysis indicates that the observed association between severe hypoglycaemia and cardiovascular disease may not be entirely due to confounding by comorbid severe illness.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The association between severe hypoglycaemia and risk of cardiovascular disease is controversial and some researchers have proposed that severe hypoglycaemia is merely a marker of comorbid severe illness. Our meta-analysis with a bias analysis indicates that comorbid severe illness alone may not entirely explain the positive association between severe hypoglycaemia and risk of cardiovascular disease.

Selection criteria for studies

We searched Medline, Embase, the Cochrane Library, and Web of Science databases to February 2013, without any language restrictions. We selected cohort studies that evaluated the association of severe hypoglycaemia with cardiovascular events in people with type 2 diabetes. Studies defined severe hypoglycaemia as at least one episode that impaired level of consciousness or required medical intervention, or was coded as 251.0, 251.1, 251.2, and 250.8 (international classification of diseases, ninth revision, clinical modification) or E16.0, E16.1 and E16.2 (international classification of diseases, 10th revision). We excluded studies from acute hospital settings.

Primary outcomes

Cardiovascular events.

Main results and role of chance

Six studies with 903 510 participants were included. In the conventional random effects meta-analysis, severe hypoglycaemia was strongly associated with a higher risk of cardiovascular disease (relative risk 2.05, 95% confidence interval 1.74 to 2.42; P<0.001). The excess fraction of cardiovascular disease incidence attributable to severe hypoglycaemia (the population attributable fraction) was 1.56% (95% confidence interval 1.32% to 1.81%; P<0.001).We further examined the sensitivity of the association to possible uncontrolled confounding by unmeasured comorbid severe illness using a bias analysis. The bias analysis indicated that comorbid severe illness alone may not explain the association between hypoglycaemia and cardiovascular disease. To explain this association, comorbid severe illness would have had to be extremely strongly associated with both severe hypoglycaemia and cardiovascular disease.

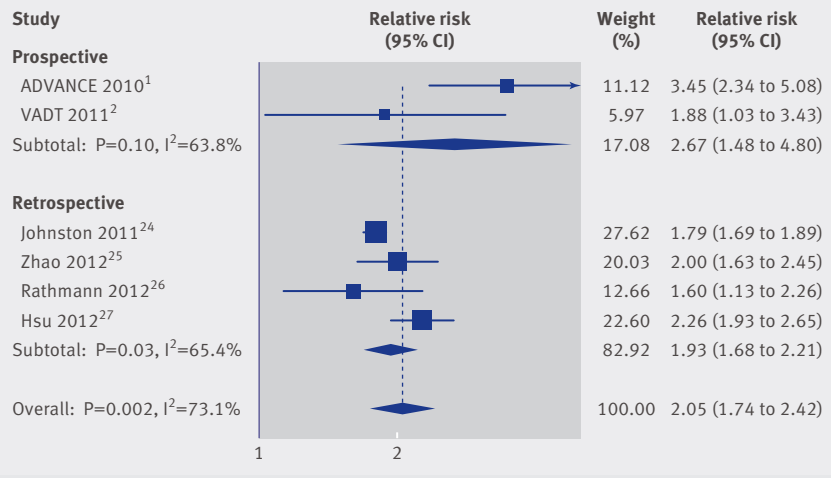
Bias, confounding, and other reasons for caution

This meta-analysis has several limitations. Firstly, the analysis was confined to published studies, and individual patient data were not available. Secondly, selection bias and information bias are likely to exist. Thirdly, there may be other confounders in addition to comorbid severe illness. Fourthly, the outcomes included heterogeneous manifestations of cardiovascular disease. Fifthly, all of the included studies examined the association between hypoglycaemia and cardiovascular disease in secondary analyses. Finally, our study was restricted to people with type 2 diabetes, which may limit generalisability to type 1 diabetes.

Study funding/potential competing interests

This work was funded by health sciences research grants (H22-019 and H25-016) from the Ministry of Health, Labour and Welfare of Japan. OAA has been supported by Veni career grant No 916.96.059 awarded by the Netherlands Organization for Scientific Research.

Conventional random effects meta-analysis of severe hypoglycaemia and risk of cardiovascular disease according to study design



Association of visit-to-visit variability in blood pressure with cognitive function in old age: prospective cohort study

Behnam Sabayan,[1 2] Liselotte W Wijsman,[1 3] Jessica C Foster-Dingley,[4] David J Stott,[5] Ian Ford,[6] Brendan M Buckley,[7] Naveed Sattar,[8] J Wouter Jukema,[9] Matthias J P van Osch,[2] Jeroen van der Grond,[2] Mark A van Buchem,[2] Rudi G J Westendorp,[1 3] Anton J M de Craen,[1 3] Simon P Mooijaart[1 3 10]

[1]Department of Gerontology and Geriatrics, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, Netherlands
[2]Department of Radiology, Leiden University Medical Center, Netherlands
[3]Netherlands Consortium for Healthy Ageing, Leiden, Netherlands
[4]Department of Psychiatry, Leiden University Medical Center, Netherlands
[5]Academic Section of Geriatrics, Faculty of Medicine, University of Glasgow, UK
[6]Robertson Center for Biostatistics, University of Glasgow, UK
[7]Department of Pharmacology and Therapeutics, University College Cork, Ireland
[8]British Heart Foundation, Glasgow Cardiovascular Research Centre, University of Glasgow, UK
[9]Department of Cardiology, Leiden University Medical Center, Leiden, Netherlands
[10]Institute for Evidence-Based Medicine in Old age, Leiden, the Netherlands
Correspondence to: S P Mooijaart
s.p.mooijaart@lumc.nl

Cite this as: *BMJ* 2013;347:f4600
doi: 10.1136/bmj.f4600

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;347:f4600

STUDY QUESTION

Are older people (>70 years) with higher visit-to-visit variability in blood pressure at higher risk of cognitive impairment compared with older people with a lower visit-to-visit variability in blood pressure?

SUMMARY ANSWER

Higher visit-to-visit variability in blood pressure, independent of average blood pressure, was associated with impaired cognitive function in old age.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Current evidence indicates that people with higher visit-to-visit variability in blood pressure are at risk of developing silent and clinically evident cerebrovascular damage. We found a similar association with impaired cognitive function in old age.

Participants and setting

5461 people at risk of cardiovascular disease with a mean age of 75.3 years.

Design, size, and duration

Blood pressure was measured during an average study period of 3.2 years with an automatic electronic sphygmomanometer (Omron M4, Kyoto, Japan) at baseline and every three months with participants in the sitting position at the same clinical setting. Blood pressure variability, the standard deviation of visit-to-visit blood pressure measurements during the study period, was correlated with performance in four domains of cognitive function at the end of the study period: selective attention, processing speed, and immediate and delayed memory. In a magnetic resonance imaging substudy of 553 participants, structural brain volumes, cerebral microbleeds, infarcts, and white matter hyperintensities were also correlated with blood pressure variability.

Main results and the role of chance

The average systolic and diastolic blood pressures were 153.1 mm Hg and 82.5 mm Hg. The average visit-to-visit variability in systolic and diastolic blood pressures was 14.8 mm Hg and 7.1 mm Hg. Participants with higher visit-to-visit variability in systolic blood pressure had worse performance on all cognitive tests: attention (mean difference high versus low thirds) 3.08 seconds (95% confidence interval 0.85 to 5.31), processing speed −1.16 digits coded (95% confidence interval −1.69 to −0.63), immediate memory −0.27 pictures remembered (95% confidence interval −0.41 to −0.13), and delayed memory −0.30 pictures remembered (95% confidence interval −0.49 to −0.11). Similarly, participants with higher visit-to-visit variability in diastolic systolic blood pressure had lower performance in all the tested cognitive domains. In the magnetic resonance imaging substudy, higher variability in diastolic blood pressure was associated with lower hippocampal volume (P=0.01), cerebral microbleeds (P=0.01), and cortical infarcts (P=0.02). Likewise, higher variability systolic blood pressure was associated with lower hippocampal volume (P=0.01) and higher risk of cortical infarcts (P=0.02). All these associations were independent of average blood pressure and cardiovascular risk factors.

Bias, confounding, and other reasons for caution

All analyses were adjusted for potential confounders, and sensitivity analyses were performed by separately excluding participants with a history of cardiovascular diseases and risk factors. In all analyses the observed associations did not essentially change. Nevertheless, we cannot exclude the possibility of residual confounding from unmeasured cardiovascular risk factors.

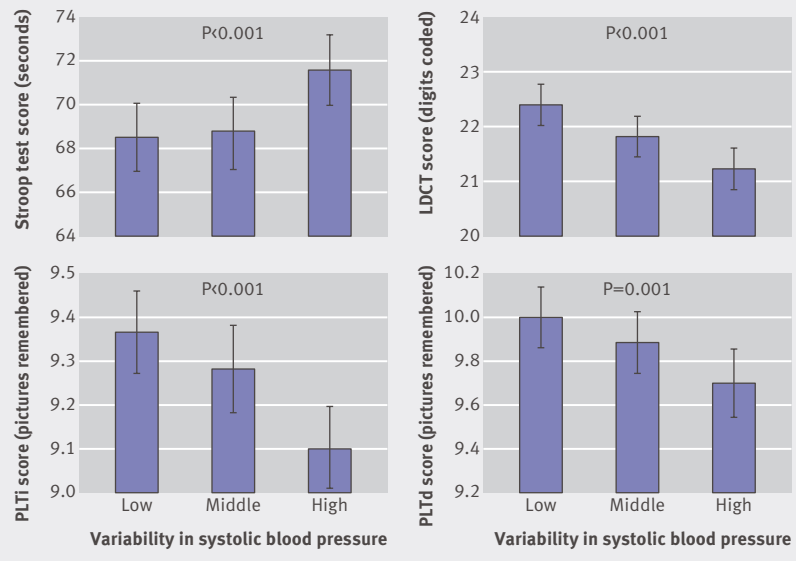
Generalisability to other populations

We included older participants at risk of cardiovascular diseases with relatively good cognitive function, which might limit the extrapolation of our findings to a general population of older people.

Study funding/potential competing interests:

The authors are independent of the funder. We have no competing interests.

Stroop test, letter-digit coding test (LDCT), and picture- word learning test (i=immediate, d=delayed) scores in thirds of visit-to-visit variability in systolic blood pressure



Bars represent mean (95% confidence interval)
Analyses adjusted for sociodemographic and cardiovascular factors

Association of plasma uric acid with ischaemic heart disease and blood pressure: mendelian randomisation analysis of two large cohorts

Tom M Palmer,[1] Børge G Nordestgaard,[3 4 5] Marianne Benn,[3 4] Anne Tybjærg-Hansen,[3 4 5 6] George Davey Smith,[2] Debbie A Lawlor,[2] Nicholas J Timpson[2]

[1]Division of Health Sciences, Warwick Medical School, University of Warwick, Warwick, UK
[2]Medical Research Council Integrative Epidemiology Unit at the University of Bristol, Bristol BS8 2BN, UK
[3]Department of Clinical Biochemistry and The Copenhagen General Population Study, Herlev Hospital, Copenhagen University Hospital, Copenhagen, Denmark
[4]Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[5]The Copenhagen City Heart Study, Frederiksberg Hospital, Copenhagen University Hospital, Denmark
[6]Department of Clinical Biochemistry, Rigshospitalet, Copenhagen University Hospital, Denmark
Correspondence to: N J Timpson
n.j.timpson@bristol.ac.uk

Cite this as: *BMJ* 2013;347:f4262
doi: 10.1136/bmj.f4262

This is a summary of a paper that was published on bmj.com as *BMJ* 2013;347:f4262

STUDY QUESTION

What is the causal relation between uric acid and hyperuricaemia with ischaemic heart disease and blood pressure?

SUMMARY ANSWER

Our mendelian randomisation results suggest that uric acid is of limited clinical interest in ischaemic heart disease or blood pressure, although there is strong evidence for a causal effect of body mass index (BMI) on uric acid levels.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Previous observational evidence concerning the role of uric acid levels and vascular health is inconsistent in the absence of formal testing. Genetic variation showed little causal association between uric acid, ischaemic heart disease, and blood pressure; however, BMI could be an important confounder in association analyses.

Participants and setting

The analysis included 58 072 Danish participants from the Copenhagen General Population Study (CGPS) and 10 602 from the Copenhagen City Heart Study (CCHS), which comprised 4890 and 2282 patients with ischaemic heart disease, respectively.

Design

Mendelian randomisation analysis investigated causality within observational associations between uric acid levels, blood pressure, risk of ischaemic heart disease, and—as a potential confounder—BMI. Analysis involved genetic variation at *SLC2A9* (rs7442295) as an instrument for uric acid; and *FTO* (rs9939609), *MC4R* (rs17782313), and *TMEM18* (rs6548238) for BMI. Observational adjusted estimates were adjusted for age, sex, smoking, education, and income.

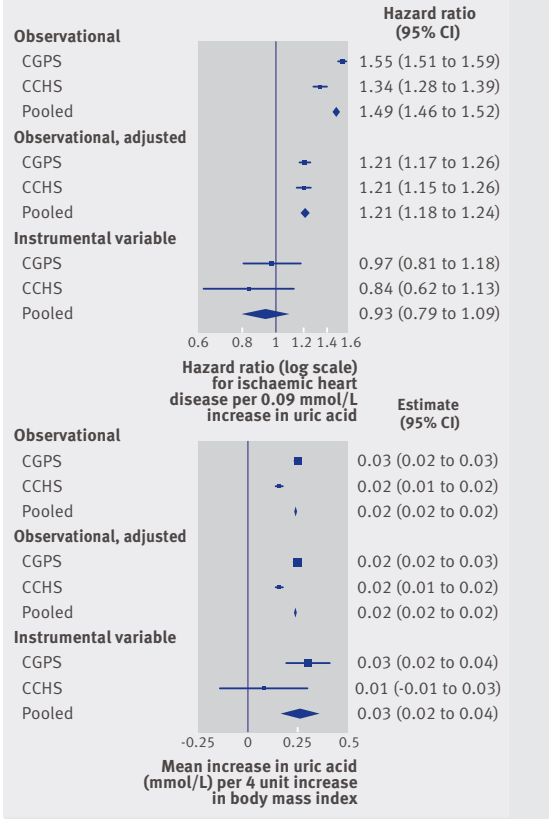
Primary outcomes

Blood pressure and prospectively assessed ischaemic heart disease.

Main results and the role of chance

Estimates confirmed known observational associations between plasma uric acid and hyperuricaemia with risk of ischaemic heart disease and blood pressure. However, analysis of genotypic instruments for uric acid showed no evidence that uric acid and hyperuricaemia status were causally associated with the primary outcomes (fig). Analysis of the genetic instruments for BMI showed evidence of a causal effect of BMI on uric acid and hyperuricaemia (fig; increase of 0.03 mmol/L (95% confidence interval 0.02 to 0.04) in uric acid and increase of 7.5% (3.9% to 11.1%) in risk of hyperuricaemia per 4 unit increase in BMI).

Uric acid as a causal risk factor for ischaemic heart disease and BMI as a causal confounder of uric acid



Bias, confounding, and other reasons for caution

Within recognised limitations, mendelian randomisation can account for unmeasured confounding, bias, and reverse causation by using genotypes robustly associated with the risk factor of interest as instrumental variables to test and estimate the causal effect between a risk factor and an outcome. The causal variants of the *SLC2A9* gene associated with uric acid levels have yet to be fully established. We also did not have data available to identify a small fraction of participants receiving uric acid lowering drugs at measurement, which could have led to underestimates of the findings.

Generalisability to other populations

Analyses were undertaken within large, ethnically homogeneous, clinically assessed case series with access to control sets of comparable quality. The nature and size of the existing sample place it particularly well for the undertaking of mendelian randomisation experiments, but also go some way to ensure the likely generalisability of the results found (bar unlikely population specific differences in the properties of genetic instruments for uric acid levels and BMI).

Study funding/potential competing interests See bmj.com.