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RESEARCH

THIS WEEK'S RESEARCH QUESTIONS

Cardiovascular risk from calcium supplements with or without vitamin D

CRISTINA PEDRAZZINI/SPL

Last year, Mark Bolland and colleagues reported on their meta-analysis of cardiovascular events in randomised controlled trials of calcium supplements (without co-administered vitamin D), which found that the supplements significantly increased the risk of myocardial infarction (*BMJ* 2010;341:c3691). Subsequently, the Women's Health Initiative reported no adverse effect of co-administered calcium and vitamin D supplements on any cardiovascular end point in its large randomised controlled trial. However, those results were complicated by 54% of the participants taking personal (non-protocol) calcium supplements at randomisation and 47% taking personal vitamin D supplements, effectively rendering the trial a comparison of higher dose and lower dose calcium and vitamin D for most of the participants.

Bolland and colleagues have now reanalysed the data from the Women's Health Initiative study, isolating the data from women not using personal calcium supplements, and updated their meta-analysis (p 962). They conclude that calcium supplements, with or without vitamin D, modestly increased the risk of cardiovascular events, especially myocardial infarction, and they suggest that the use of calcium supplements in osteoporosis management in older people should be reassessed.

Oral contraceptives and thrombosis

Two case-control studies in this week's *BMJ* address the risk of non-fatal venous thromboembolism in women taking oral contraceptives that contain drospirenone versus those containing levonorgestrel. In the first, Susan Jick and colleagues looked at data from a US company (p 960) and in the second they used the UK General Practice Research database (p 961). Both analyses found an increased risk associated with drospiredone compared with levonorgestrel—about double in the US study and triple in the UK study. Importantly, though, overall rates of events were still low.

In the online versions of the papers the authors explain how they add methodologically to two previous *BMJ* papers on oral contraceptives and thrombosis, published in 2009—both of which showed a small increase in risk for drospiredone compared with levonorgestrel. But we didn't do a good enough job with one of those papers. In a recent editorial (*BMJ* 2010;341:c4830), Gerd Gigerenzer pointed out that while one made the absolute risks clear in the abstract the other reported that "oral contraceptives increased the risk of venous thrombosis fivefold" without giving the crude numbers.

CRISTINA PEDRAZZINI

Given alone, relative risks such as "fivefold" provide an incomplete and misleading message, because they don't inform about the baseline risk. This point is well illustrated by an older example cited by Gigerenzer: in 1995, the UK Committee on Safety of Medicines issued a warning that third generation oral contraceptive pills increased the risk of thrombosis twofold, provoking great anxiety. Many women stopped taking the pill, leading to unwanted pregnancies and abortions, along with extra costs for the NHS. But the actual increase in risk was small: from one thrombosis per 7000 women taking second generation pills to two per 7000 for third generation pills.

Risk exaggeration can make for a more dramatic story, but journals have a responsibility to provide all the information and promote good risk reporting. Groups like Sense About Science (http://senseaboutscience.org.uk) are also backing a drive for the general public, as well as journalists, to become more stats-savvy. Worth bearing in mind when reading or submitting papers.

CRISTINA PEDRAZZINI

LATEST RESEARCH: For this and other new research articles see www.bmj.com/research

Treating heavy menstrual bleeding The theme of "women's health" continues online this week with a paper from T E Roberts and colleagues. The UK group looked at the cost effectiveness of different treatments for heavy menstrual bleeding; endometrial ablative techniques, hysterectomy, and the levonorgestrel releasing intrauterine system Mirena. Their model took an NHS perspective. Despite expectations that the newer, cheaper, and less invasive techniques might be preferable, hysterectomy turned out to be the most cost effective as a first intervention for heavy menstrual bleeding. The incremental cost effectiveness ratio for hysterectomy compared with Mirena was £1440 (€1633, $2350) per additional QALY, and for hysterectomy compared with second generation ablation £970 per additional QALY—NICE tends to accept new technologies if the incremental cost effectiveness ratio is within £20 000 per additional QALY.

Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data

Susan S Jick, Rohini K Hernandez

EDITORIAL by Dunn
RESEARCH p 961

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Research: The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type (*BMJ* 2009;339:b2921)
Research: Hormonal contraception and risk of venous thromboembolism (*BMJ* 2009;339:b2890)

STUDY QUESTION Is the risk of non-fatal idiopathic venous thromboembolism in women receiving oral contraceptives containing drospirenone greater than that in those receiving oral contraceptives containing levonorgestrel?

SUMMARY ANSWER The risk of non-fatal idiopathic venous thromboembolism in users of oral contraceptives containing drospirenone seems to be around twice that of users of those containing levonorgestrel, although the overall risk is still low.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
Previous studies that evaluated the risk of venous thromboembolism in users of drospirenone oral contraceptives have found inconsistent results; some showed no increased risk compared with other oral contraceptives, and others showed small increased risks. Users of oral contraceptives containing drospirenone have around a twofold increased risk of idiopathic venous thromboembolism compared with users of those containing levonorgestrel, which remained when prescribing bias and confounding were taken into account.

Participants and setting

The study was based on information from PharMetrics, a United States based company that collects information on claims paid by managed care plans. The study encompassed all women aged 15 to 44 who received an oral contraceptive containing either drospirenone or levonorgestrel after 1 January 2002. Cases were women with current use of a study oral contraceptive and a diagnosis of venous thromboembolism in the absence of identifiable clinical risk factors. Up to four controls were matched to each case by age and calendar time.

ODDS RATIOS FOR VENOUS THROMBOEMBOLISM IN USERS OF ORAL CONTRACEPTIVES CONTAINING DROSPIRENONE COMPARED WITH THOSE CONTAINING LEVONORGESTREL

Exposure	No (%) cases	No (%) controls	Crude* odds ratio (95% CI)	Adjusted† odds ratio (95% CI)
Overall				
Levonorgestrel	65 (15)	368 (85)	1.0	1.0
Drospirenone	121 (28)	313 (72)	2.3 (1.6 to 3.2)	2.4 (1.7 to 3.4)
New episodes of use only				
Levonorgestrel	42 (14)	253 (86)	1.0	1.0
Drospirenone	102 (28)	264 (72)	2.5 (1.7 to 3.8)	2.7 (1.7 to 4.1)

*For overall analysis, crude odds ratio is a conditional odds ratio; for stratified analyses, crude odds ratios are adjusted for age and index year.
†Also adjusted for duration.

Design, size, and duration

This was a nested case-control study with an additional cohort analysis. We identified 186 newly diagnosed, idiopathic cases of venous thromboembolism in the study population and 681 matched controls during the study period (January 2002 to September 2009).

Primary outcome, risks, exposure

The primary outcome was a first time idiopathic venous thromboembolism, and the exposure was current use of an oral contraceptive containing either drospirenone or levonorgestrel.

Main results and the role of chance

In the case-control analysis, the conditional odds ratio for venous thromboembolism comparing use of oral contraceptives containing drospirenone versus levonorgestrel was 2.3 (95% confidence interval 1.6 to 3.2). The incidence rates for venous thromboembolism in the study population were 30.8 (95% confidence interval 25.6 to 36.8) per 100 000 woman years among users of oral contraceptives containing drospirenone and 12.5 (9.61 to 15.9) per 100 000 woman years among users of those containing levonorgestrel. The age adjusted incidence rate ratio for venous thromboembolism for current use of drospirenone compared with levonorgestrel contraceptives was 2.9 (2.1 to 3.9). Chance is an unlikely explanation for these findings.

Bias, confounding, and other reasons for caution

We adjusted for many potential confounders and biases through restriction, matching, stratification, and modelling. Although obesity and history of menstrual disorders were independently associated with venous thromboembolism, these factors did not confound the main effect. When we restricted the analysis to women with no previous use of oral contraceptives, the results did not materially change. We were not able to adjust for family history of venous thromboembolism, but this is unlikely to be a strong confounder.

Generalisability to other populations

Our data covered women in the United States, most of whom were insured, which could somewhat limit the generalisability of the study. However, the finding that drospirenone pills carry a higher risk of venous thromboembolism relative to levonorgestrel pills should be generalisable to oral contraceptive users elsewhere.

Study funding/potential competing interests

This study was unfunded.

Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database

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EDITORIAL by Dunn
RESEARCH p 960

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STUDY QUESTION Do women using a combined oral contraceptive containing drospirenone have a higher risk of non-fatal idiopathic venous thromboembolism than women taking oral contraceptives containing levonorgestrel?

SUMMARY ANSWER Women who were current users of the drospirenone oral contraceptive were about three times as likely to develop non-fatal idiopathic venous thromboembolism as were current users of pills containing levonorgestrel, although the overall risk is still low.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Two population based studies have found a small increase in the risk of venous thromboembolism in users of the drospirenone oral contraceptive compared with users of levonorgestrel pills; two other studies have found no excess risk, although concerns exist about the methods used. This paper adds to emerging evidence that the drospirenone oral contraceptive carries a higher risk of venous thromboembolism than do preparations containing levonorgestrel.

Participants and setting

We used data from the UK General Practice Research Database for this study. The study population comprised women aged 15-44 years without major risk factors for venous thromboembolism who started a new episode of use of an oral contraceptive containing drospirenone or levonorgestrel after the drospirenone pill was introduced on to the market. Cases were women with a first diagnosis of non-fatal idiopathic venous thromboembolism. We randomly selected up to four controls, matched by age, duration of recorded information, and general practice, for each case.

Design, size, and duration

This was a nested case-control study based on a cohort of 318 825 women. We identified 61 cases and 215 matched controls during the study period, which was May 2002 to September 2009.

Primary outcome(s), risks, exposures

The primary outcome was a first diagnosis of non-fatal idiopathic venous thromboembolism. The exposures were current use of an oral contraceptive containing 30 µg oestrogen in combination with either drospirenone or levonorgestrel.

Main results and the role of chance

In the case-control analysis, current use of the drospirenone contraceptive was associated with a threefold higher risk of non-fatal idiopathic venous thromboembolism, compared with levonorgestrel use; the odds ratio adjusted for body mass index was 3.3 (95% confidence interval 1.4 to 7.6). The crude incidence rates were 23.0 (95% confidence interval 13.4 to 36.9) per 100 000 woman years in current users of drospirenone oral contraceptives and 9.1 (6.6 to 12.2) per 100 000 woman years in current users of levonorgestrel oral contraceptives. The age adjusted incidence rate ratio was 2.7 (1.5 to 4.7). Chance is an unlikely explanation for these findings.

Bias, confounding, and other reasons for caution

Subanalyses suggested that referral, diagnostic, first-time user, duration of use, and switching biases were unlikely explanations for the key results. Confounding by age, body mass index, smoking, concomitant drug use, or underlying medical conditions is also unlikely: we excluded cases and controls with major risk factors for venous thromboembolism, controls were matched to cases by age, and we explored potential confounding in the analysis. We did not have information about family history of venous thromboembolism, although any confounding by this risk factor would seem unlikely to be of sufficient magnitude to explain a threefold elevated risk.

Generalisability to other populations

The magnitude of the absolute risks in users of drospirenone and levonorgestrel oral contraceptives may not be generalisable to other populations with differing background rates of venous thromboembolism. However, the finding that drospirenone pills carry a higher risk of venous thromboembolism than do levonorgestrel pills should be generalisable to oral contraceptive users elsewhere.

Study funding/potential competing interests

This study was not funded.

CURRENT USE OF ORAL CONTRACEPTIVES AND VENOUS THROMBOEMBOLISM

Progestogen in oral contraceptive	Cases (n=61)	Controls (n=215)	Unadjusted matched odds ratio (95% CI)	Adjusted matched odds ratio (95% CI)*
Levonorgestrel	44	189	1.0	1.0
Drospirenone	17	26	3.2 (1.5 to 7.0)	3.3 (1.4 to 7.6)

*Adjusted for body mass index as continuous variable.

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- Research: The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type (*BMJ* 2009;339:b2921)
- Research: Hormonal contraception and risk of venous thromboembolism (*BMJ* 2009;339:b2890)

Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis

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STUDY QUESTION Do calcium supplements, with or without vitamin D, affect cardiovascular events?

SUMMARY ANSWER Yes, calcium supplements increased the risk of myocardial infarction by about 25% and the risk of myocardial infarction or stroke by about 15% in meta-analyses of placebo controlled trials with 29 000 participants.

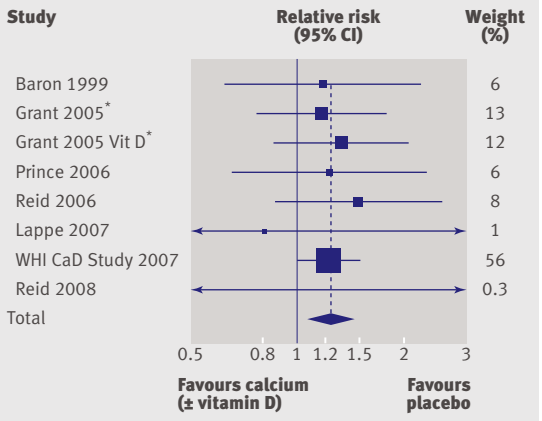
WHAT IS KNOWN AND WHAT THIS PAPER ADDS Calcium supplements without vitamin D increased the risk of myocardial infarction in a recent meta-analysis. In a re-analysis of the Women's Health Initiative dataset, women not taking personal calcium supplements were at increased risk of cardiovascular events if randomised to receive calcium and vitamin D supplements. In meta-analyses of trials, calcium supplements used with or without vitamin D modestly increased cardiovascular risk, suggesting their use in osteoporosis should be reassessed.

Selection criteria for studies

The Women's Health Initiative Calcium/Vitamin D Supplementation (WHI CaD) Study was a seven year, randomised, placebo controlled trial of calcium and vitamin D (1 g calcium, 400 IU vitamin D daily) in 36 282 community dwelling, postmenopausal women. Unusually, many of the participants were also taking personal (non-protocol) calcium supplements at randomisation.

For the meta-analysis, we included studies from our previous meta-analysis of calcium supplementation, together with women not using personal calcium supplements in the WHI CaD Study and one new study of co-administered calcium and vitamin D.

EFFECT OF CALCIUM SUPPLEMENTS WITH OR WITHOUT VITAMIN D ON RISK OF MYOCARDIAL INFARCTION



*"Grant 2005" shows calcium *v* placebo arms, "Grant 2005 Vit D" shows calcium + vitamin D *v* placebo + vitamin D arms

Primary outcome(s)

Primary end points for the re-analysis of the WHI CaD Study were the incidence of cardiovascular events. For the meta-analysis, the primary end points were myocardial infarction, stroke, and the composite of myocardial infarction or stroke.

Main results and the role of chance

In the WHI CaD Study there was an interaction between personal calcium supplement use and allocation to calcium and vitamin D for cardiovascular events. In 16 718 women (46% of cohort) not taking personal calcium supplements at randomisation, the hazard ratios for cardiovascular events with calcium and vitamin D ranged from 1.13 to 1.22 (P=0.05 for clinical myocardial infarction or stroke, P=0.04 for clinical myocardial infarction or revascularisation), whereas in women taking personal calcium supplements, allocation to calcium and vitamin D did not alter cardiovascular risk.

In the meta-analyses of three placebo controlled trials involving 20 090 participants calcium and vitamin D increased the risk of myocardial infarction (relative risk 1.21 (95% CI 1.01 to 1.44), P=0.04), stroke (1.20 (1.00 to 1.43), P=0.05), and the composite of myocardial infarction or stroke (1.16 (1.02 to 1.32), P=0.02). In meta-analyses of eight placebo controlled trials of calcium or calcium and vitamin D, with complete trial-level data available for 28 072 participants, calcium or calcium and vitamin D increased the risk of myocardial infarction (relative risk 1.24 (1.07 to 1.45), P=0.004) (see figure) and the composite of myocardial infarction or stroke (1.15 (1.03 to 1.27), P=0.009).

Bias, confounding, and other reasons for caution

Subgroup analysis of the WHI data carries a risk of false positive results and over-interpretation of findings. We minimised these risks by pre-specifying the variable of interest (personal calcium supplement use), assessed its effect using interaction tests, and followed recommended approaches for analysis and interpretation. Confounding is a possible explanation of our findings, as subgroup analysis may interfere with the balancing effects of randomisation on potential confounders, though personal calcium use was defined at the time of randomisation. However, within each subgroup, the baseline characteristics of the participants allocated to calcium and vitamin D were well matched to those allocated to placebo.

Study funding/potential competing interests

Funded by the Health Research Council of New Zealand, and the University of Auckland School of Medicine Foundation. IRR has received research support from and acted as a consultant for Fonterra, and IRR and AA have received study medications for trials of calcium and vitamin D supplementation from Mission Pharmacal, Shire Pharmaceuticals, and Nycomed.

Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study

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STUDY QUESTION What is the incidence of adverse events after medical abortion in adolescents compared with adults?

SUMMARY ANSWER Medical abortion seems to be as safe for medical adverse events among adolescents as it is among adults in short term follow-up.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Although medical abortion is increasingly used, its safety in adolescents has not been properly assessed. We found that medical abortion seems to be at least as safe in adolescents as it is in adults.

Participants and setting

Data on all women undergoing medical abortion in Finland from the Finnish abortion register were linked with three national registries: the hospital register, national register of infectious diseases, and cause of death register.

Design, size, and duration

Population based retrospective cohort study of 3024 adolescents (<18 years) and 24 006 adults (≥18 years) who underwent medical abortion in 2000-06. To assess the potential learning curve in the introduction of medical abortion, we analysed the results in part separately for the first years (2000-03) of its use compared with established use (2004-06).

Main results and the role of chance

Serious adverse events (thromboembolic disease, surgical interventions, death) were rare in both cohorts. Incidence of adverse events among adolescents was similar or lower than among adults. Adolescents had a lower risk of haemorrhage (adjusted odds ratio 0.87, 95% confidence interval 0.77 to 0.99), incomplete abortion (0.69, 0.59 to 0.82), and surgical evacuation (0.78, 0.67 to 0.90). Risk of infection did not differ between the cohorts. In subgroup analysis of primigravid women, the risks of incomplete abortion (0.68, 0.56 to 0.81) and surgical evacuation (0.75, 0.64 to 0.88) were lower in the adolescents. In logistic regression, duration of gestation was the most important risk factor for infection, incomplete abortion, and surgical evacuation. A positive test result for *Chlamydia trachomatis* at the time of abortion was not associated with an increased risk of infections after abortion. The cohorts differed significantly in many aspects, such as number of previous pregnancies and duration of gestation, but these were adjusted for in the calculation of incidences.

Bias, confounding, and other reasons for caution

The registry based data lack detailed information as diagnoses were made on clinical grounds, and the severity of adverse events may vary substantially. As follow-up was only for 42 days no conclusions can be made on the consequences of abortion beyond that time. Psychological sequelae, pain, and satisfaction could not be studied using register data. Risk of surgical evacuation of retained products decreased during 2004–06 compared with 2000–03, whereas the number of incomplete abortions remained the same. These findings probably reflect a learning curve in providing medical abortion and were taken into account by adjusting odds ratios of adverse events by study period.

Generalisability to other populations

The data were derived from one country with a homogeneous population, but can be generalised to populations with high quality healthcare and easy access to specialist treatment.

INCIDENCE OF ADVERSE EVENTS IN STUDY COHORTS FOR ALL WOMEN AND PRIMIGRAVID WOMEN

Adverse events	Adolescent cohort (<18 years)	% (95% CI)	Adult cohort (≥18 years)	% (95% CI)	P value	Adjusted odds ratio (95%CI)*
All women:	n=3024		n=24 006			
Haemorrhage	386	12.8 (11.6 to 14.0)	3690	15.4 (15.0 to 16.0)	<0.001†	0.87 (0.77 to 0.99)†
Infection	60	2.0 (1.5 to 2.6)	489	2.0 (1.9 to 2.2)	0.742	0.97 (0.73 to 1.30)
Incomplete abortion	212	7.0 (6.1 to 8.0)	2450	10.2 (9.8 to 10.6)	<0.001†	0.69 (0.59 to 0.82)†
Surgical evacuation	333	11.0 (9.9 to 12.1)	3121	13.0 (12.6 to 13.4)	0.002†	0.78 (0.67 to 0.90)†
Primigravid women:	n=2913		n=10 474			
Haemorrhage	374	12.8 (11.6 to 14.1)	1505	14.4 (13.7 to 15.0)	0.035†	0.88 (0.78 to 1.00)
Infection	57	2.0 (1.5 to 2.5)	227	2.2 (1.9 to 2.5)	0.486	1.01 (0.75 to 1.37)
Incomplete abortion	201	6.9 (6.0 to 7.9)	887	8.5 (7.9 to 9.0)	0.006†	0.68 (0.56 to 0.81)†
Surgical evacuation	311	10.7 (9.6 to 11.8)	1136	10.8 (10.3 to 11.4)	0.794	0.75 (0.64 to 0.88)†

*Adult cohort as reference for all women adjusted for parity, previous abortions, marital status, type of residence, duration of gestation, and year of abortion; adult cohort as reference for primigravid women adjusted for marital status, type of residence, duration of gestation, and year of abortion.
†Statistically significant.