Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis

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STUDY QUESTION

What is the risk of venous thrombosis in 10 frequently prescribed combined oral contraceptives?

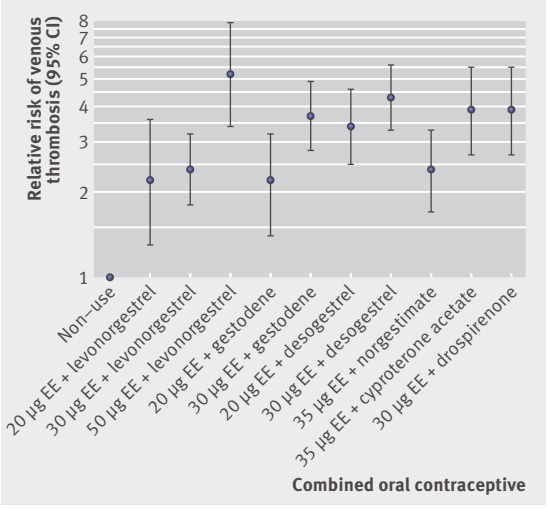
SUMMARY ANSWER

All combined oral contraceptives investigated in this analysis increased the risk of venous thrombosis twofold or more, with the highest risk observed for 50 µg ethinylestradiol (EE) with levonorgestrel; the lowest risk was observed for 20 µg or 30 µg EE with levonorgestrel and for 20 µg EE with gestodene.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Many women use combined oral contraceptives, despite such use being associated with an increased risk of venous thrombosis. Because thrombosis risk is related to EE dose, the oral contraceptive combining the lowest possible amount of EE with good effectiveness should be prescribed—that is, 30 µg EE with levonorgestrel.

Risk of venous thrombosis per combined oral contraceptive versus non-use



Selection criteria for studies

PubMed, Embase, Web of Science, Cochrane, Cumulative Index to Nursing and Allied Health Literature, Academic Search Premier, and ScienceDirect were searched up to 22 April 2013 for cohort or (nested) case-control studies that included healthy women using combined oral contraceptives. Primary outcome of interest was a first event of venous thrombosis. We performed a network meta-analysis that incorporated direct as well as indirect comparisons.

Primary outcome(s)

Non-fatal or fatal first event of venous thrombosis, with the main focus on deep vein thrombosis of the leg and pulmonary embolism.

Main results and role of chance

Of 3110 publications retrieved from the search, 26 studies were included in the network meta-analysis. Incidence of venous thrombosis in non-users from two included cohorts was 1.9 and 3.7 per 10 000 woman years, in line with previously reported incidences of 1-6 per 10 000 woman years. Based on studies providing comparisons with non-users, use of combined oral contraceptives was associated with an increased risk of venous thrombosis (relative risk 3.5, 95% confidence interval 2.9 to 4.3). The highest risk of venous thrombosis was observed in users of 50 µg EE with levonorgestrel (5.2, 3.4 to 7.9). Three contraceptives were found to have the lowest risk of venous thrombosis (20 µg EE with levonorgestrel (2.2, 1.3 to 3.6), 30 µg EE with levonorgestrel (2.4, 1.8 to 3.2), and 20 µg EE with gestodene (2.2, 1.4 to 3.2)). Compared with 30 µg EE with desogestrel, combined contraceptives 35 µg EE with cyproterone acetate and 30 µg EE with drospirenone had a similar risk of venous thrombosis (0.9, 0.6 to 1.3 and 0.9, 0.7 to 1.3, respectively).

Bias, confounding, and other reasons for caution

Because crude numbers are needed for calculations in a network meta-analysis, confounding might have been present. However, variables that are commonly adjusted for (such as body mass index) are only weakly associated with contraceptive use, or were dealt with by design (matching). Furthermore, only a minority of included studies objectively confirmed venous thrombosis in all patients. However, because the diagnostic procedure used was independent from the type of oral contraceptive, presented results could have underestimated the true association, which was confirmed by our sensitivity analysis.

Study funding/potential competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; BHS was supported by the Netherlands Organization for Scientific Research; MdB was supported by a grant from Capes-Nuffic, Brazil; no other relationships or activities that could appear to have influenced the submitted work. Funding agencies had no role in study design, implementation, or preparation of results.

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Provision of rapid HIV tests within a health service and frequency of HIV testing among men who have sex with men: randomised controlled trial

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Research News: ART sooner rather than later for adults with HIV (*BMJ* 2013;346:f377)
Practice: Maximising opportunities for increased antiretroviral treatment in children in an existing HIV programme in rural South Africa (*BMJ* 2013;346:f550)
Feature: Mass economic migration: the greatest threat to HIV control in India (*BMJ* 2013;346:f550)

STUDY QUESTION

Does offering men who have sex with men point of care (rapid) testing for HIV in a clinical setting increase their rate of HIV testing?

SUMMARY ANSWER

Men who have sex with men and have access to rapid HIV testing did not have HIV tests at a significantly higher rate than men with access to conventional HIV testing over an 18 month period.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Increased HIV testing in at risk populations is required to help stem further HIV transmission. We now have robust evidence from a randomised controlled trial to show that while offering rapid HIV testing initially increased the frequency of testing, this was not sustained over time.

Design

Randomised controlled trial with block randomisation with two computer generated random sequences per block. Allocation was concealed up to the point of randomisation. MSM were randomised 1:1 to either ongoing access to rapid HIV testing obtained by finger prick (Determine HIV-1/2 Antigen/Antibody Combo) or to conventional HIV serology obtained through venepuncture over 18 months. Men in both groups were sent regular text reminders to have HIV tests.

Participants and setting

Men were eligible if they reported having a male sexual partner within the previous year and an HIV test within the previous two years. Of 400 men entered in the study, 370 (92.5%) completed it. Rapid testing was available only after a clinical consultation at the Melbourne Sexual Health Centre.

Primary outcome

All HIV tests at any clinic were ascertained, and the incidence rate of HIV testing was compared in the two study arms.

Main results and the role of chance

Of 200 men randomised to the rapid testing arm, 196 were followed for 288 person years. Of 200 men randomised to the conventional testing arm, 194 were followed for 278 person years. The median time since the last HIV test was six months for both arms. Men in the rapid test arm had 469 tests (mean 1.63 tests a year) and men in the conventional test arm had 396 tests (mean 1.42 tests a year); incidence rate ratio 1.15, 95% confidence interval 0.96 to 1.38; P=0.12. In a post hoc analysis, rates of initial HIV testing during follow-up (excluding all subsequent tests) were 1.32 and 1.01 tests a year, respectively (incidence rate ratio 1.32, 95% confidence interval 1.05 to 1.65; P=0.02). HIV was diagnosed in five men at baseline and in five during follow-up; half in each study arm.

Harms

Unconfirmed reactive tests, representing false positive results, were more common with HIV rapid tests than with conventional serology (9/596 (1.5%, 95% confidence interval 0.6% to 2.8%) *v* 1/534 (0.2%, 0% to 1.0%); P=0.02).

Bias, confounding, and other reasons for caution

Both groups had similar numbers of recent sexual partners and similar times since their last HIV test (median six months).

Generalisability to other populations

Application of these findings to other populations should take into account that our study population comprised men who have sex with men who had been tested for HIV relatively recently; access to rapid testing required a clinical consultation; and men in the control arm were required to return to the centre for their results.

Study funding/potential competing interests

The study was funded in part by a National Health and Medical Research Council of Australia program grant No 568971. Rapid HIV tests were provided by the manufacturer, Alere.

Trial registration number ACTR12610000430033.

Incidence rate of HIV testing over time among men who have sex with men according to allocation to rapid HIV test or conventional HIV test in public health service in Australia

	Rapid HIV test			Conventional HIV test				
Outcome	No of tests	Person years	Tests/year (95% CI)	No of tests	Person years	Tests/year (95% CI)	Incidence rate ratio (95% CI)	P value
HIV tests over 18 months	469	288	1.63 (1.49 to 1.79)	396	278	1.42 (1.29 to1.57)	1.15 (0.96 to 1.38)	0.12
First HIV test after enrolment test	161	122	1.32 (1.13 to 1.54)	141	140	1.01 (0.86 to 1.19)	1.32 (1.05 to 1.65)	0.02
Subsequent HIV tests (excluding first tests)	308	166	1.86 (1.66 to 2.07)	255	139	1.83 (1.62 to 2.07)	1.01 (0.86 to 1.20)	0.90

Impact of 2008 global economic crisis on suicide: time trend study in 54 countries

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EDITORIAL by Hawton and Haw

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- Lithium in the prevention of suicide in mood disorders (*BMJ* 2013;346:f3646)
- Research: Method of attempted suicide as predictor of subsequent successful suicide (*BMJ* 2010;341:c3222)
- Research: Effect of a barrier at Bloor Street Viaduct on suicide rates in Toronto (*BMJ* 2010;341:c2884)
- Effect of assertive outreach after suicide attempt in the AID (assertive intervention for deliberate self harm) trial (*BMJ* 2012;345:e4972)

STUDY QUESTION

Was there an association between the 2008 global economic crisis and time trends in suicide rates around the world?

SUMMARY ANSWER

Suicide rates increased significantly in the 27 European and 18 American countries studied, particularly among men and in countries with higher levels of job loss.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Suicide rates in several European countries increased after the 2008 global financial crisis. The latest study shows that similar increases were seen in other European and American countries, specifically among men (with those aged 15-24 worst affected in Europe) and in countries experiencing greater increases in unemployment.

Population and setting

People aged 15 and over in 54 countries in Europe, Asia, and North, Central, and South America.

Design

Time trend analysis comparing the observed numbers of suicides in 2009 with expected numbers based on trends before the crisis (2000-07) ("excess suicides"). Suicide data for 53 countries were collected from the World Health Organization mortality database (version released on 11 November 2012); for the US data were obtained from the CDC online database.

Primary outcome

Suicide rates and numbers of excess suicides.

Excess suicides in 2009 relative to expected based on trend 2000-07 in 54 countries*

	Excess suicide (95% CI)	P value
All study countries (n=54)		
Men	5124 (4219 to 6029)	<0.001
Women	−240 (−607 to 126)	0.20
European countries (n=27)		
Men	2937 (2400 to 3475)	<0.001
Women	49 (−87 to 186)	0.48
American countries (n=18)		
Men	3175 (2692 to 3658)	<0.001
Women	305 (144 to 466)	<0.001
Non-European and non-American countries (n=9)		
Men	−989 (−1533 to −444)	<0.001
Women	−595 (−895 to −295)	<0.001

*27 European countries (Austria, Bulgaria, Croatia, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Republic of Moldova, Romania, Russian Federation, Serbia, Slovenia, Spain, Sweden, UK); 18 American countries (Argentina, Aruba, Belize, Brazil, Canada, Chile, Colombia, Costa Rica, Cuba, Ecuador, El Salvador, Guatemala, Mexico, Nicaragua, Panama, Paraguay, Suriname, US); 8 Asian countries (Hong Kong SAR, Israel, Japan, Kuwait, Republic of Korea, Singapore, Kazakhstan, Kyrgyzstan); and 1 African country (Mauritius).

Main results and the role of chance

In 2009, there were an estimated 4884 (95% confidence interval 3907 to 5860) excess suicides across the 54 study countries. Increases in suicide were concentrated in men in the 27 European and 18 American countries studied: rates were respectively 4.2% (95% confidence interval 3.4 to 5.1%) and 6.4% (5.4 to 7.5%) over and above rates that would have been expected if past trends had continued. Rates in women in the Americas rose, but to a lesser extent than the rates in men; rates in European women did not change. Men aged 15-24 experienced the largest rise in Europe (11.7%); in American countries men aged 45-64 showed the largest increase (5.2%). Compared with the 4.2% rise in suicide in men in the 27 European countries in 2009, an even larger rise (10.8%, 10.1% to 11.6%) was seen in the 20 European countries with available data for 2010. Rises in national suicide rates in men were significantly associated with the magnitude of increases in unemployment, particularly in countries with low unemployment levels before the crisis (Spearman's r_s=0.48, P=0.016).

Bias, confounding, and other reasons for caution

This study is an observational analysis based on aggregate data. Events other than the economic crisis could have influenced suicide trends in individual countries, but it is unlikely that all study countries were affected at the same time as the crisis by different specific events. Variations in level of misclassification of suicide could lead to potential bias in comparisons between countries. However, as this study focused on variations within a country over time, such misclassifications will not affect our results, unless levels of misclassification changed at the same time. Furthermore, the sensitivity analysis based on combined data for certified suicides and possible suicides, coded as undetermined deaths, showed similar findings.

Generalisability to other populations

Data for some large economies severely affected by the economic crisis—such as Italy and Australia—were not available at the time we carried out this study. Other countries with a large population—such as China and India—were not included because data were not available, but their economies were less affected by the economic crisis. The Asian countries and one African country (Mauritius) included in the study are not representative of all Asian and African countries; in contrast, most European and American populations (78% and 88% respectively) were included.

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The effects of excluding treatments from network meta-analyses: survey

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STUDY QUESTION

Can excluding specific treatments from a network meta-analysis importantly change the results?

SUMMARY ANSWER

Excluding well connected treatments (those for which there are many trials against other treatments) from a network meta-analysis can importantly change point estimates and treatment rankings.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Examples have started to accumulate where network analyses on the same topic have reached different conclusions based on the exclusion of treatment nodes. We now know that excluding well connected treatments from a network meta-analysis can change effect estimates and consequently alter decision making.

Rationale, design, data collection method

Network meta-analysis is an increasingly popular method that allows the evaluation of the comparative effectiveness of multiple treatments. Networks may or may not consider all the available treatment comparators. We assessed whether this would affect study results by rerunning a sample of network meta-analyses.

Participants and setting

Networks that had five or more treatments, contained at least two closed loops, had at least twice as many studies as treatments, and had trial level data available.

Recruitment/sampling strategy

We searched PubMed for network meta-analyses and contacted study authors for access to individual trial data. Investigators abstracted information about study design, participants, outcomes, network geometry, and the exclusion of eligible treatments.

Data analysis method

Using the individual trial data, we reconducted the network meta-analysis for each condition by excluding one treatment at a time. We examined the effect this had on treatment effect estimates and probability rankings of being the best treatment.

Main findings

Among 18 eligible networks involving 757 randomised controlled trials with 750 possible treatment comparisons, 11 had upfront decided not to consider all treatment comparators and only 10 included placebo/no treatment nodes. In 7/18 networks, there was at least one node whose removal caused a more than 1.10-fold average relative change in the estimated treatments effects, and switches in the top three treatments were observed in 9/18 networks. Removal of placebo/no treatment caused large relative changes of the treatment effects (average change 1.16-3.10-fold) for four of the 10 networks that had originally included placebo/no treatment nodes. Exclusion of current uncommonly used drugs resulted in substantial changes of the treatment effects (average 1.21-fold) in one of three networks on systemic treatments for advanced malignancies.

Implications

Excluding treatments in network meta-analyses sometimes can have important effects on their results and can diminish the usefulness of the research to clinicians if important comparisons are missing. Well connected treatments that are unlikely to be the best treatment are the most likely to be influential.

Bias, limitations, generalisability

Our study assumed that the complete networks provided the most likely answer.

Study funding/potential competing interests

Canadian Institutes of Health Research.

Example of fold change calculation and change in rank probabilities when treatment for atrial fibrillation is removed from network

Treatment	Full model		Reduced model		Fold change*
	Relative rate *v* placebo (95% CI)	Probability (%)	Relative rate *v* placebo (95% CI)	Probability (%)	
Warfarin:					
Adjusted standard dose	0.37 (0.26 to 0.53)	3	0.41 (0.27 to 0.7)	2	1.11
Adjusted low dose	0.34 (0.19 to 0.58)	13	0.34 (0.19 to 0.60)	41	1.00
Fixed low dose	0.76 (0.3 to 1.76)	1	0.93 (0.36 to 2.66)	1	1.22
Aspirin	0.62 (0.43 to 0.86)	0	0.66 (0.47 to 1.01)	0	1.06
Fixed low dose warfarin+aspirin	0.98 (0.6 to 1.67)	0	Removed	Removed	NA
Ximelagatran	0.34 (0.18 to 0.62)	14	0.37 (0.21 to 0.83)	13	1.09
Alternate day aspirin	0.17 (0.01 to 1.15)	66	0.45 (0.03 to 18.48)	38	2.65
Indobufen	0.46 (0.19 to 1.14)	5	0.54 (0.23 to 1.57)	6	1.17

NA=not applicable.