RESEARCH

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WHAT OUR READERS ARE SAYING

Neglected tropical diseases

According to this network meta-analysis published on 22 October [http://www.bmj.com/content/345/bmj.e6512], considerable variation exists in the amount of evidence from randomized controlled trials for each of the 16 major neglected tropical diseases. Even in diseases with substantial evidence some recommended treatments have limited supporting data and lack head to head comparisons, say the authors.

RAJESH KUMAR SINGH/AP/PA

2 year old Indian boy with Japanese encephalitis

Here's what rapid respondent Neeru Gupta said:

"The authors…made no mention of Japanese encephalitis, which is a major public health problem in Asia including India. According to a review published in 2009, despite the catastrophes it causes, Japanese encephalitis has remained a tropical disease uncommon in the West. With rapid globalisation and climatic shift, the virus has started to emerge in areas where the threat was previously unknown (for example, Australia and Pakistan). Scientific evidence predicts that Japanese encephalitis virus will soon become a global pathogen and cause of worldwide pandemics. Although some research documents pathogenesis and drug discovery, worldwide awareness of the need for extensive research to deal with Japanese encephalitis is still lacking."

RESEARCH ONLINE

See www.bmj.com/research

Use of Mendelian randomisation to assess potential benefit of clinical intervention

Mendelian randomisation is a useful tool for exploring causal relations between modifiable risk factors and outcomes of interest. It is one of the few epidemiological methods that can help in the selection of targets for therapeutic intervention. However, it is important to be aware of the limitations of Mendelian randomisation estimates when using this technique in target based drug development, say the authors.

Impact of smoking on mortality and life expectancy in Japanese smokers: a prospective cohort study

R Sakata,[1] P McGale,[2] E J Grant,[1] K Ozasa,[1] R Peto,[2] S C Darby[2]

EDITORIAL by Daube and Chapman

[1]Department of Epidemiology, Radiation Effects Research Foundation, Hiroshima, Japan
[2]Clinical Trial Service Unit, University of Oxford, Oxford OX3 7LF, UK
Correspondence to: S C Darby
sarah.darby@ctsu.ox.ac.uk

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bmj.com/podcasts
Coauthor Sarah Darby talks about the findings of this paper

STUDY QUESTION

What are the lifelong hazards of smoking and the benefits of stopping in Japanese people?

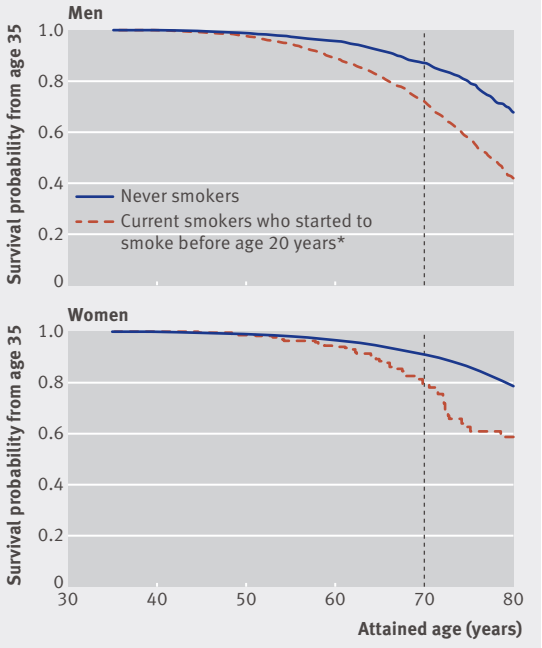
SUMMARY ANSWER

In Japan as elsewhere, men or women who smoke throughout adult life lose about a decade of life expectancy, but most of the risk can be avoided by stopping smoking before age 35—and preferably well before age 35.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Previous studies in Japan had suggested that smoking reduced life expectancy by only a few years (as compared with about a decade of life lost in Britain and the US), but those studies were mainly of people born before 1920, when most Japanese smokers did not start until well into adult life and smoked only a few cigarettes a day. We now find that if Japanese people start smoking before age 20 then they too lose about a decade of life expectancy, and both the hazards of smoking and the benefits of stopping are as great as elsewhere.

Survival of Japanese men and women born between 1920 and 1945 who never smoked or who have smoked since before age 20



*Mean smoking intensity 23 cigarettes/day for men, 17 cigarettes/day for women

Design, size, participants, setting, and duration

Prospective cohort study of 27 311 men and 40 662 women born in or before 1945 who were living in Hiroshima or Nagasaki in 1950 and who provided their smoking status in surveys carried out during 1963-92. Sixty per cent of men and 11% of women were current smokers, while 26% of men and 6% of women were former smokers. Participants were followed up for an average of 23 years.

Main results and the role of chance

Smokers born in later decades (1920-45) tended to smoke more cigarettes per day than those born earlier (before 1920) and to have started smoking at a younger age. Among those born during 1920-45 (median 1933) who started smoking before age 20 years, men smoked on average 23 cigarettes/day, while women smoked 17 cigarettes/day, and, for those who continued smoking, overall mortality was more than doubled in both sexes (rate ratios versus never smokers: men 2.21 (95% CI 1.97 to 2.48), women 2.61 (1.98 to 3.44)) while life expectancy was reduced by almost a decade (8 years for men, 10 years for women) (see figure). Those who stopped smoking before age 35 avoided almost all the excess risk experienced by continuing smokers, while those who stopped smoking before age 45 avoided most of it.

Bias, confounding, and other reasons for caution

The most recent survey information available for study participants dates from 1992. Any individuals who gave up smoking after then remained classified as current smokers until the end of the study. As a result, the true risks of continuing to smoke are probably underestimated even in this study. The study participants form part of a cohort set up to investigate the effects of radiation from the atomic bombs, but about half of them had little or no radiation exposure, and our estimates of smoking related risk scarcely changed after adjusting for radiation exposure.

Generalisability to other populations

This paper has worldwide relevance, as there are many countries where the epidemic of smoking related diseases is not yet sufficiently mature—especially among women—for the full risks of smoking yet to be apparent.

Study funding/potential competing interests

The study was funded by the Japanese Ministry of Health, Labour, and Welfare; US Department of Energy; Cancer Research UK; British Heart Foundation; and Medical Research Council. The authors declare no competing interests.

bmj.com Cardiovascular updates from BMJ Group http://www.bmj.com/specialties/cardiovascular-medicine

Use of varenicline for smoking cessation and risk of serious cardiovascular events: nationwide cohort study

Henrik Svanström, Björn Pasternak, Anders Hviid

EDITORIAL by Harrison-Woolrych

Department of Epidemiology Research, Statens Serum Institute, 2300 Copenhagen, Denmark
Correspondence to: H Svanström
htr@ssi.dk

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STUDY QUESTION

Are people who take varenicline to help them to stop using tobacco at an increased risk of serious cardiovascular events compared with those taking bupropion?

SUMMARY ANSWER

This large nationwide cohort study found no significantly increased risk of any major cardiovascular events, including acute coronary syndrome, ischaemic stroke, and cardiovascular death associated with use of varenicline compared with bupropion.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Recent studies have shown that that use of varenicline, a drug used to help with smoking cessation, can increase the risk of cardiovascular events. Our study investigated the risk of cardiovascular events in a population based cohort of real world users of varenicline and showed no associated increased risk of serious cardiovascular events.

Participants and setting

New users of varenicline and bupropion in Denmark.

Design, size, and duration

Nationwide historical cohort study, 2007-10. Individual level data on dispensed drug prescriptions, cardiovascular events, and potential confounders were linked between registries. Cox regression was used to estimate hazard ratios of cardiovascular events, comparing 17 926 new users of varenicline and 17 926 new users of bupropion in analyses matched for propensity score. Bupropion was chosen as comparator because it has the same treatment indication as varenicline (in Denmark bupropion is not used to treat depression) and has no known cardiovascular risk. Propensity scores included a range of potential confounders, including demographic variables, comorbidities, concomitant drugs used, and variables indicating use of healthcare. The primary outcomes at six months after the start of treatment were acute coronary syndrome, ischaemic stroke, and cardiovascular death analysed individually and as a composite of any major event. The secondary outcomes were other serious cardiovascular events, the individual end points being ischaemic heart disease (including angina pectoris, ischaemic heart disease, and coronary revascularisation), heart failure, peripheral arterial disease, transient ischaemic attack, and cardiac arrhythmia.

We also carried out subgroup analyses by duration of use and in participants with and without pre-existing cardiovascular disease.

Main results and the role of chance

There were 57 major cardiovascular events among varenicline users and 60 among bupropion users; the hazard ratio for any major event was 0.96 (95% confidence interval 0.67 to 1.39), indicating no increase in risk. Similarly, there was no increased risk of acute coronary syndrome, ischaemic stroke, and cardiovascular death. Furthermore, there was no significantly increased risk of other serious cardiovascular events evaluated as secondary outcomes: ischaemic heart disease (0.89, 0.66 to 1.20), heart failure (0.82, 0.39 to 1.70), peripheral arterial disease (1.11, 0.81 to 1.54), transient ischaemic attack (1.60, 0.62 to 4.13), and cardiac arrhythmia (0.64, 0.36 to 1.11).

In subgroup analyses, the risk of any major cardiovascular event was not significantly different between patients with and without a history of cardiovascular disease (1.24 (0.72 to 2.12) and 0.83 (0.51 to 1.36), respectively; P=0.29), or among those with 0 to 28 days and those with >28 days of use (0.96 (0.64 to 1.45) and 0.97, (0.57 to 1.63), respectively; P=0.29).

Risk of major cardiovascular events* at six months' follow-up in people using varenicline and bupropion to help with smoking cessation in nationwide registry based cohort study in Denmark, with follow-up from January 2007 to December 2010

Outcome event	Rate per 1000 person years	Hazard ratio (95% CI)
Any major cardiovascular event†		
Varenicline	6.9	0.96 (0.67 to 1.39)
Bupropion	7.1	1 (ref)
Acute coronary syndrome		
Varenicline	4.7	1.20 (0.75 to 1.91)
Bupropion	3.9	1 (ref)
Ischaemic stroke		
Varenicline	1.9	0.77 (0.40 to 1.48)
Bupropion	2.5	1 (ref)
Cardiovascular death‡		
Varenicline	0.4	0.51 (0.13 to 2.02)
Bupropion	0.7	1 (ref)

*Study cohort included 35 858 patients, with new users of varenicline and bupropion matched 1:1 on propensity score and followed up to six months after start of treatment. Outcomes reported here were defined as primary outcomes.
†Any of acute coronary syndrome, ischaemic stroke, or cardiovascular death.
‡Includes cardiac death and death from ischaemic stroke.

Bias, confounding, and other reasons for caution

Despite propensity score matching on a wide range of covariates, we cannot rule out residual confounding because of unmeasured differences in health between the groups at baseline. We also had no data on the level of smoking exposure or smoking cessation rates.

Generalisability to other populations

Results from this population based nationwide study in Denmark are applicable to similar populations.

Study funding/potential competing interests

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

bmj.com
- Research: Risk of cardiovascular serious adverse events associated with varenicline use for tobacco cessation: systematic review and meta-analysis (*BMJ* 2012;344:e2856)
- Research: Varenicline and suicidal behaviour: a cohort study based on data from the General Practice Research Database (*BMJ* 2009;339:b3805)
- Research: Stopping smokeless tobacco with varenicline: randomised double blind placebo controlled trial (*BMJ* 2010;341:c6549)
- Letter: Risk of psychiatric side effects with varenicline (*BMJ* 2009;339:b4964)

Risks of adverse pregnancy and birth outcomes in women treated or not treated with mood stabilisers for bipolar disorder: population based cohort study

Robert Bodén,[1 2] Maria Lundgren,[3] Lena Brandt,[2] Johan Reutfors,[2] Morten Andersen,[2] Helle Kieler[2]

EDITORIAL by Gentile

[1]Department of Neuroscience, Psychiatry, Uppsala University, Ing 15 3tr, SE-751 85 Uppsala, Sweden
[2]Centre for Pharmacoepidemiology, Department of Medicine Solna, Karolinska Institutet, Sweden
[3]Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden
Correspondence to: R Bodén
robert.boden@neuro.uu.se

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Head to head: Is underdiagnosis the main pitfall when diagnosing bipolar disorder? Yes (*BMJ* 2010;340:c854)
Head to head: Is underdiagnosis the main pitfall in diagnosing bipolar disorder? No (*BMJ* 2010;340:c855)
Editorial: Hospital admission for schizophrenia and bipolar disorder (*BMJ* 2011;343:d5652)

STUDY QUESTION

What are the risks of adverse pregnancy and birth outcomes in women treated and not treated for bipolar disorder?

SUMMARY ANSWER

Women with bipolar disorder were at an increased risk of several adverse birth outcomes irrespective of treatment using mood stabilisers. Untreated bipolar disorder was associated with outcomes indicating fetal growth restriction, such as microcephaly and hypoglycaemia.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Mood stabilisers have been associated with adverse pregnancy and birth outcomes, but the risks associated with untreated bipolar disorder are largely unknown. We found that untreated bipolar disorder was also associated with adverse birth outcomes.

Participants and setting

The study sample comprised 332 137 Swedish women with a last menstrual period anytime after 1 July 2005 and giving birth anytime before the end of 31 December 2009. We identified women with a record of at least two bipolar diagnoses and grouped them as treated (n=320) or untreated (n=554).

Design, size, and duration

This population based cohort study used data from national health registers. We defined treated women as those who had filled a prescription with mood stabilisers (lithium, antipsychotics, or anticonvulsants) during pregnancy. Both treated and untreated women were compared with all other women giving birth (n=331 263). In addition, we assessed the variation in outcome between the three groups.

Main results and the role of chance

Untreated, as well as treated, women with bipolar disorder had increased risks of non-spontaneous delivery and preterm birth. Infants of untreated women with bipolar disorder had increased risks of microcephaly and neonatal hypoglycaemia.

Bias, confounding, and other reasons for caution

The analyses of variation in outcomes did not support any significant differences between treated and untreated women. We defined drug use as dispensed drugs, which does not necessarily imply usage.

Generalisability to other populations

Because this was a population based study the findings are highly generalisable to the clinical setting.

Study funding/potential competing interests

This study was funded by unrestricted grants from Lennanders Foundation, Gillbergska Foundation, Uppsala County Council (ALF grants) and by the authors' affiliations. We have no competing interests.

Pregnancy and birth outcomes by maternal bipolar disorder and treatment with mood stabilisers during pregnancy

		Untreated bipolar disorder		Treated bipolar disorder	
Birth outcomes	No (%) with no bipolar disorder*	No (%)	Odds ratio (95% CI)†	No (%)	Odds ratio (95% CI)†
Non-spontaneous delivery	68 533 (20.7)	171 (30.9)	1.57 (1.30 to 1.90)	120 (37.5)	2.12 (1.68 to 2.67)
Preterm birth	15 785 (4.8)	42 (7.6)	1.48 (1.08 to 2.03)	26 (8.1)	1.50 (1.01 to 2.24)
Microcephalic infant	7471 (2.3)	21 (3.9)	1.68 (1.07 to 2.62)	10 (3.3)	1.26 (0.67 to 2.37)
Neonatal hypoglycaemia	8302 (2.5)	24 (4.3)	1.51 (1.04 to 2.43)	11 (3.4)	1.18 (0.64 to 2.16)

*Reference group.
†Adjusted for birth order and for maternal age, cohabitation, smoking, height, and diagnosis of alcohol or substance misuse disorder.

Primary and secondary prevention with new oral anticoagulant drugs for stroke prevention in atrial fibrillation: indirect comparison analysis

Lars Hvilsted Rasmussen,[1 2] Torben Bjerregaard Larsen,[1 2] Tina Graungaard,[1 2] Flemming Skjøth,[1 2] Gregory Y H Lip[1 3]

[1]Thrombosis Research Unit, Aalborg University, Aalborg, Denmark
[2]Department of Cardiology, Aalborg AF Study Group, Cardiovascular Research Centre, Aalborg Hospital, Aalborg
[3]University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK
Correspondence to: G Y H Lip
g.y.h.lip@bham.ac.uk

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bmj.com
- Research: Risk of atrial fibrillation and stroke in rheumatoid arthritis: Danish nationwide cohort study (*BMJ* 2012;344:e1257)
- Clinical review: Management of atrial fibrillation (*BMJ* 2009;339:b5216)

STUDY QUESTION

In an indirect comparison analysis, what is the relative efficacy and safety of apixaban, dabigatran etexilate, and rivaroxaban for the secondary prevention of stroke in atrial fibrillation?

SUMMARY ANSWER

For secondary prevention, apixaban, rivaroxaban, and dabigatran have broadly similar efficacy for the main endpoints, although haemorrhagic stroke, vascular death, major bleeding, and intracranial bleeding were less common with dabigatran 110 mg than with rivaroxaban.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Three novel oral anticoagulants (dabigatran, rivaroxaban, apixaban) have completed large phase III clinical trials for stroke prevention in atrial fibrillation with warfarin as the comparator, and data from the secondary prevention subgroups (that is, patients with previous stroke) have recently been published. In the absence of head to head trials, this indirect comparison analysis minimised inter-trial population heterogeneity by particular focus on the secondary prevention cohort.

Selection criteria for studies

We included randomised controlled trials of rivaroxaban, dabigatran, or apixaban compared with warfarin for prevention of stroke in atrial fibrillation.

Primary outcome

We estimated hazard ratios of efficacy and safety endpoints by indirect comparison analyses of trial subgroups with and without previous stroke.

Main results and role of chance

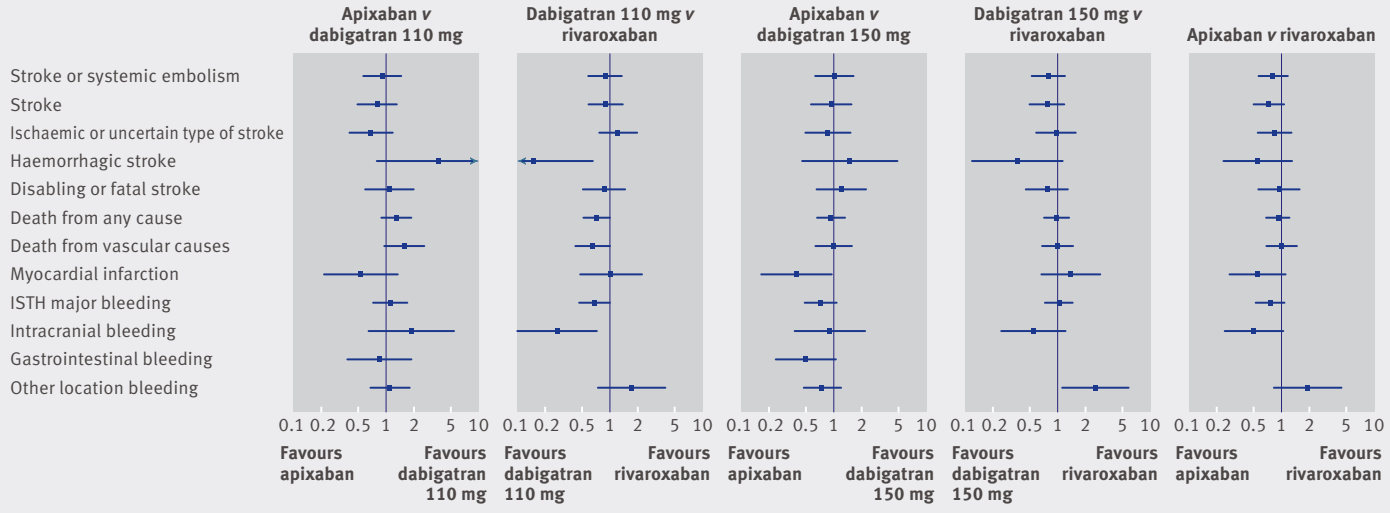
In the secondary prevention (previous stroke) subgroup, when we compared apixaban with dabigatran (110 mg and 150 mg twice daily) for efficacy and safety endpoints, the only significant difference was less myocardial infarction (hazard ratio 0.39, 95% confidence interval 0.16 to 0.95) with apixaban. We found no significant differences in efficacy and most safety endpoints between apixaban or dabigatran 150 mg and rivaroxaban. Less haemorrhagic stroke (hazard ratio 0.15, 0.03 to 0.66), vascular death (0.64, 0.42 to 0.99), major bleeding (0.68, 0.47 to 0.99), and intracranial bleeding (0.27, 0.10 to 0.73) occurred with dabigatran 110 mg twice daily than with rivaroxaban. In the primary prevention (no previous stroke) subgroup, the three drugs showed some differences in relation to efficacy and bleeding.

Bias, confounding, and other reasons for caution

Our data came from published trial populations, and we compared them indirectly. A formal head to head trial could potentially give different results. Indirect comparison analyses have inherent limitations and can be considered to be only hypothesis generating and the basis for a head to head trial. Although the phase III clinical trials used warfarin as the comparator, warfarin is no longer used (or even marketed) in many countries in Europe. Phenprocoumon is more commonly used in these countries, and the efficacy of these new drugs compared with phenprocoumon has not yet been established, which may be a question for future research.

Study funding/potential competing interests: GYHL has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, and Boehringer Ingelheim and has been on the speaker bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi. TBL and LHR have served as speakers for BMS/Pfizer and Boehringer Ingelheim.

Hazard ratios (95% CI) for indirect comparisons between apixaban, dabigatran, and rivaroxaban for secondary prevention of stroke



ISTH = International Society on Thrombosis and Haemostasis