Risk of gastrointestinal bleeding associated with oral anticoagulants: population based retrospective cohort study

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- Analysis: Dabigatran, bleeding, and the regulators (*BMJ* 2014;349:g4517)
- Editorial: The trouble with dabigatran (*BMJ* 2014;349:g4681)
- Research News: Dabigatran "non-inferior" to warfarin, but only just (*BMJ* 2013;346:f1219)

STUDY QUESTION

What is the real world safety of dabigatran or rivaroxaban compared with warfarin in terms of gastrointestinal bleeding?

SUMMARY ANSWER

Although no statistically significant difference was seen in the risk of gastrointestinal bleeding between dabigatran or rivaroxaban and warfarin, a greater than 50% increased risk with dabigatran and twofold increased risk with rivaroxaban relative to warfarin cannot be ruled out.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Most evidence on the increased risk of gastrointestinal bleeding for novel oral anticoagulants compared with warfarin comes from clinical trials providing limited duration of follow-up and selective inclusion criteria.
Although rates of gastrointestinal bleeding seem to be similar in this commercially insured sample of adults in the United States, increased risks associated with dabigatran and rivaroxaban compared with warfarin cannot be ruled out.

Participants and setting

We included commercially insured enrolees with a prescription for warfarin, dabigatran, or rivaroxaban between 1 October 2010 and 31 March 2012 in the United States who were aged 18 years or older, had continuous enrolment and no oral anticoagulant use during the six months before the entry date, had known age and sex, and had no gastrointestinal bleeding for at least six months before the cohort entry date. The final study sample included 4907 users of dabigatran, 1649 users of rivaroxaban, and 39 607 users of warfarin.

Design, size, and duration

This was a cohort study. The cohort entry date was the date of a patient's first prescription for any of the three study drugs. We defined a patient's observation ending date as the earliest of the last date of the same drug exposure, the date of the loss of enrolment, the end date of the study, the date before the first date of non-gastrointestinal bleeding related hospital admission, and the first date of gastrointestinal bleeding. We censored a patient if the observation ending date was not the first bleeding date. To control for possible confounders between groups, we developed two propensity scores: one for dabigatran (comparing warfarin and dabigatran users; n=44 514) and another for rivaroxaban (comparing warfarin and rivaroxaban users; n=41 256), and calculated the average treatment effect of the treated weighting. We used Cox proportional hazard models with propensity score weighting and robust estimates of errors for statistical analyses.

Multivariable association between novel oral anticoagulant use (compared with warfarin) and gastrointestinal bleeding

Analysis	Dabigatran (n=44 514)	Rivaroxaban (n=41 256)
Crude hazard ratio* (95% CI)	1.20 (0.96 to 1.52)	0.95 (0.31 to 2.94)
Adjusted hazard ratio† (95% CI)	1.21 (0.96 to 1.53)	0.98 (0.36 to 2.69)

Source: IMS Health LifeLink® Health Plan Claims Database, 2010-12.
*No control variables.
†Age groups, Clinical Classification Software categories, and non-steroidal anti-inflammatory drug use as stratification factors and others as regression covariates.

Main results and the role of chance

The rate of gastrointestinal bleeding was highest among dabigatran users (dabigatran *v* rivaroxaban *v* warfarin: 9.01 *v* 3.41 *v* 7.02 cases per 100 person years). After adjusting for potentially confounding covariates and applying average treatment effect of the treated weighting, we found no evidence of a statistically significant difference in the risk of gastrointestinal bleeding between dabigatran and warfarin users (adjusted hazard ratio 1.21, 95% confidence interval 0.96 to 1.53) or between rivaroxaban and warfarin users (0.98, 0.36 to 2.69).

Bias, confounding, and other reasons for caution

We assumed that prescription fill data reflected actual usage by patients. We had a low number of events, which might result in inadequate statistical power. The length of observation was different across drug user groups.

Generalisability to other populations

The generalisability to European cohorts and patients taking the lower 110 mg dose of dabigatran is unknown.

Study funding/potential competing interests

GCA is supported by the National Heart, Lung and Blood Institute; is chair of the FDA's Peripheral and Central Nervous System Advisory Committee; serves as a paid consultant to IMS Health; and serves on an IMS Health scientific advisory board.

Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study

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Research: The association between kidney function and major bleeding in older adults with atrial fibrillation starting warfarin treatment (*BMJ* 2015; 350: h246)
Editorial: Refined bleeding estimates in adults starting anticoagulants (*BMJ* 2014;349:g4800)

STUDY QUESTION

What is the real world risk of gastrointestinal bleeding associated with dabigatran and rivaroxaban compared with warfarin, and does the risk change with age?

SUMMARY ANSWER

Patients under 65 years had fewer bleeds when treated with dabigatran or rivaroxaban than with warfarin; however, risk increased after age 65 and exceeded the risk with warfarin in patients over 75.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Meta-analyses of randomised trials examining gastrointestinal bleeding rates for dabigatran and rivaroxaban, compared with warfarin, have identified higher rates of bleeds for the novel oral anticoagulants.
The risk of dabigatran or rivaroxaban related gastrointestinal bleeding is similar to that for warfarin in patients under 65 years, but caution should be used when prescribing these agents to older people.

Participants and setting

We included 92 816 new users of dabigatran, rivaroxaban, and warfarin from 1 November 2010 to 30 September 2013 identified from Optum Labs Data Warehouse, a large US claims database.

Design, size, and duration

We estimated incidence rates of gastrointestinal bleeding for dabigatran and rivaroxaban, compared with warfarin, in patients with and without atrial fibrillation and used propensity score matched Cox proportional hazards models to calculate adjusted risk. We used a marginal effects model to examine heterogeneity of treatment effect related to age.

Main results and the role of chance

Unadjusted gastrointestinal bleeding rates were similar between patients treated with dabigatran or rivaroxaban and warfarin. In propensity score matched models, the risk was similar to warfarin in patients with atrial fibrillation (hazard ratios: dabigatran *v* warfarin 0.79, 95% confidence interval 0.61 to 1.03; rivaroxaban *v* warfarin 0.93, 0.69 to 1.25) and in non-atrial fibrillation patients (1.14, 0.54 to 2.39; 0.89, 0.60 to 1.32). The risk increased after age 65; by age 76, the risk of bleeding exceeded that with warfarin in atrial fibrillation patients taking dabigatran (hazard ratio 2.49, 1.61 to 3.83) and in patients with and without atrial fibrillation taking rivaroxaban (2.91, 1.65 to 4.81, and 4.58, 2.40 to 8.72).

Bias, confounding, and other reasons for caution

We could not assess apixaban related gastrointestinal bleeding owing to the limited number of patients prescribed this drug. We accounted for selection bias related to treatment choice by using propensity score matching, but the possibility of unobserved confounding still exists. The inability to capture over the counter aspirin limits examination of its effect on overall bleeding rates, but we suspect no differential misclassification among patients prescribed new anticoagulants versus warfarin. Finally, we created an incident cohort of users, and the risk among a prevalent cohort or patients switched from warfarin to a new agent might be different.

Generalisability to other populations

Our diverse, real world population and assessment of the gastrointestinal bleeding profile of dabigatran and rivaroxaban by age permitted discovery of important safety concerns among older adults. However, we were unable to assess rates of gastrointestinal bleeding associated with 110 mg twice daily dabigatran, as this dose is not approved in the United States.

Study funding/potential competing interests

This study was funded by the Mayo Clinic Robert D and Patricia E Kern Center for the Science of Health Care Delivery. GCA serves as a paid consultant to IMS Health, and serves on an IMS Health scientific advisory board.

Events and adjusted hazards of gastrointestinal bleeding

	Events per 100 patient years (95% CI)		Hazard ratio* (95% CI) for bleeding: dabigatran *v* warfarin	Events per 100 patient years (95% CI)		Hazard ratio* (95% CI) for bleeding: rivaroxaban *v* warfarin
	Dabigatran	Warfarin		Rivaroxaban	Warfarin	
Atrial fibrillation						
Total bleeding events	2.29 (1.88 to 2.79)	2.87 (2.41 to 3.41)	0.79 (0.61 to1.03)	2.84 (2.30 to 3.52)	3.06 (2.49 to 3.77)	0.93 (0.69 to 1.25)
Upper GI bleeding events	1.42 (1.11 to 1.83)	1.81 (1.45 to 2.25)	0.78 (0.56 to 1.09)	1.83 (1.40 to 2.39)	1.74 (1.32 to 2.28)	1.05 (0.72 to 1.54)
Lower GI bleeding events	0.86 (0.63 to 1.19)	1.06 (0.80 to 1.41)	0.81 (0.53 to 1.24)	1.02 (0.97 to1.82)	1.33 (0.97 to 1.82)	0.77 (0.48, 1.24)
Non-atrial fibrillation						
Total bleeding events	4.10 (2.47 to 6.80)	3.71 (2.16 to 6.40)	1.14 (0.54 to 2.39)	1.66 (1.23 to 2.24)	1.57 (1.25 to 1.99)	0.89 (0.60 to 1.32)
Upper GI bleeding events	2.73 (1.47 to 5.08)	2.57 (1.34 to 4.94)	1.09 (0.44 to 2.69)	1.03 (0.70 to 1.51)	0.99 (0.74 to 1.33)	0.87 (0.53 to 1.44)
Lower GI bleeding events	1.37 (0.57 to 3.28)	1.14 (0.43 to 3.04)	1.23 (0.33 to 4.59)	0.63 (0.39 to 1.03)	0.58 (0.40 to 0.86)	0.91 (0.48 to 1.73)

GI=gastrointestinal.

Minimally invasive decompression versus open laminectomy for central stenosis of the lumbar spine: pragmatic comparative effectiveness study

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STUDY QUESTION

Is microdecompression equivalent to laminectomy in the surgical treatment of central stenosis of the lumbar spine?

SUMMARY ANSWER

This study suggests that the effectiveness of microdecompression is equivalent to laminectomy in the surgical treatment of central stenosis of the lumbar spine. Favourable outcomes were observed at one year in both treatment groups.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Laminectomy has traditionally been the standard surgical treatment for central stenosis of the lumbar spine, but in recent years less invasive procedures such as microdecompression have emerged. This paper suggests that the effectiveness of microdecompression is equivalent to that of laminectomy.

Design

We carried out a multicentre observational study using prospective data from the Norwegian Registry for Spine Surgery. A blinded biostatistician performed predefined statistical analyses in unmatched and propensity matched cohorts.

Participants and setting

885 patients with central stenosis of the lumbar spine underwent surgery at one or two lumbar levels with either laminectomy or microdecompression in 34 Norwegian orthopaedic or neurosurgical departments.

Primary outcome

The primary outcome was change in Oswestry disability index score for low back pain at one year. The study was powered to detect a difference of eight points between the groups.

Main results and the role of chance

721 patients (81%) completed the one year follow-up. Equivalence between microdecompression and laminectomy was shown for Oswestry disability index score (difference 1.3 points, 95% confidence interval −1.36 to 3.92, P<0.001 for equivalence). Equivalence was confirmed in the propensity matched cohort and full information regression analyses. The groups did not differ for health related quality of life (EuroQol-5D) one year after surgery. Patients in the microdecompression group had shorter hospital stays, for both single level (difference 1.5 days, 95% confidence interval 1.7 to 2.6, P<0.001) and two level decompression (0.8 days, 1.0 to 2.2, P=0.003).

Harms

12.2% of patients had one or more complications within three months of surgery, with no differences between treatment groups after propensity score matching.

Bias, confounding, and other reasons for caution

The main limitation of this study is the lack of randomised treatment allocation. Although propensity score matching adjusts for known interactions, residual or introduction of confounding cannot be ruled out (even if unlikely).

Generalisability to other populations

This study has high external validity for patients with central stenosis of the lumbar spine undergoing surgery.

Study funding/potential competing interests

This study received a grant from the Norwegian Medical Association. We have no competing interests.

Trial registration number ClinicalTrials.gov NCT02006901.

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Complete case analysis and mixed linear model analysis for outcomes at one year in patients with central stenosis of the lumbar spine

	Complete case analysis								Mixed linear model analysis							
	Laminectomy			Microdecompression			Difference in mean change between groups (95% CI)	P for equivalence	Laminectomy			Microdecompression			Difference in mean change between groups (95% CI)	P for equivalence
Outcomes	Baseline	One year	Mean change	Baseline	One year	Mean change			Baseline	One year	Mean change	Baseline	One year	Mean change		
Aggregate cohort:																
ODI	42.1	25.0	−17.1	38.0	19.6	−18.4	1.28 (−1.36 to 3.92)	<0.001	42.5	25.3	−17.2	38.6	20.0	−18.6	1.40 (−0.93 to 3.76)	<0.001
EQ-5D	0.34	0.65	0.31	0.41	0.69	0.28	0.03 (−0.03 to 0.08)	—	0.33	0.64	0.31	0.38	0.68	0.30	0.01 (−0.06 to 0.04)	—
Matched cohort:																
ODI	40.3	23.3	−17.0	38.0	19.5	−18.5	1.50 (−2.41 to 5.49)	0.001	40.2	24.2	−16.0	40.2	21.2	−19.0	2.99 (0.41 to 5.58)	<0.001
EQ-5D	0.36	0.68	0.32	0.40	0.66	0.26	0.06 (−0.04 to 0.16)	—	0.35	0.66	0.31	0.35	0.67	0.32	−0.01 (−0.07 to 0.04)	—

ODI=Oswestry disability index.