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Warfarin use and the risk of motor vehicle crash in older drivers

J. A. 'Chris' Delaney, Lucie Opatrny & Samy Suissa

Division of Clinical Epidemiology, Royal Victoria Hospital, McGill University Health Center, and the Department of Epidemiology and Biostatistics, McGill University, Montreal, Canada

Correspondence
Samy Suissa, Division of Clinical Epidemiology, Royal Victoria Hospital, 687 Pine Avenue West, Ross 4.29, Montreal, Quebec, Canada, H3A 1A1.
Tel: + 1 514 843 1564
Fax: + 1 514 843 1493
E-mail: samy.suissa@clinepi.mcgill.ca

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Aim
On the basis of a recent report, we assessed whether the use of warfarin by elderly drivers results in an increased risk of motor vehicle crash.

Methods
We used computerized records of Quebec insurance programmes, covering a population of 7 million people, to conduct a case–control study based on 5579 cases and 12 911 controls.

Results
The rate of injurious motor vehicle crash associated with the use of warfarin in the past year was not elevated (rate ratio 0.74; 95% confidence interval 0.55, 1.05).

Conclusions
Warfarin therapy does not appear to increase the risk of motor vehicle accidents in elderly drivers.

Introduction

Motor vehicle crashes associated with prescription drug use are an important public health issue for older adults, who are the fastest growing sector of the driving population [1]. Older adults use many prescription drugs [2], with possible interactions, and so the risk of motor vehicle crashes is especially important in this population. Identifying drug classes that pose a higher risk of injurious motor vehicle crashes may help clinicians give appropriate advice when prescribing different medications to their patients.

Warfarin is used in the prevention and treatment of venous and arterial thrombotic events [3]. A previous study in active elderly drivers showed some evidence that anticoagulants might increase the risk of motor vehicle crashes [4]. Current clinical practice does not include the recommendation to stop driving [5]. Therefore, in our study we examined the effect of warfarin exposure in a cohort of older Canadian drivers to see if further evidence can be found either for or against this adverse effect.

Methods

The database used in this study was previously used to report on benzodiazepine use in elderly drivers where

the methods are described in much more detail [6]. To summarize briefly the methods used to construct the database, we formed a cohort of all eligible drivers between 1 June 1990 and 31 May 1993 in the province of Quebec, Canada. We identified these drivers from the Quebec automobile insurance agency (SAAQ) driver's licence file. Eligible subjects were 67–84 years old. Sixty-seven was chosen as entry age to allow a complete 2-year history of drug exposure. In Quebec, the universal drug programme covered only residents who were 65 or older during the time period of the study. An upper age of 84 was chosen because it was rare that subjects had a licence beyond this age and we were concerned with selection bias beyond this point. Other inclusion criteria included: possession of a valid driver's licence and residence in Quebec for at least the 2 years prior to the entry date of the cohort. The subject exited the study upon on 31 May 1993 unless they reached age 85 or emigrated before that point. If they passed our cut-off age or emigrated they were censored. We also selected a random 6.2% subsample of the database of eligible drivers to create our controls.

The study outcome, identified from the SAAQ accident report file, was defined as involvement of a cohort member as the driver in a motor vehicle crash. At least one victim, not necessarily the driver, needed to have sustained bodily injury. Crashes with property damage alone were not included due to concerns of underreporting [7]. In the event of multiple crashes, only the first crash was used. The index date for subjects involved in motor vehicle crashes was defined as the date of the first injurious motor vehicle crash in the time period of our study.

Prescription drug use and other covariate information were identified from files for the RAMQ (Quebec health insurance agency), the agency responsible for administering universally insured healthcare services for the province. RAMQ has been previously shown to be a valid database for drug research [8].

Our study was designed as an unmatched case–control design because of the size of the cohort and the time-varying exposure of warfarin. Cases were elderly drivers who had an injurious motor vehicle crash in the study period. Controls were a subsample of elderly drivers who did not have an injurious motor vehicle crash in the study period. The controls were each assigned a random day during the study period to represent background drug exposure in the population. This random day was taken as the index date for the controls.

The following exclusion criteria were applied to all subjects in the study: residence in a long-term care setting during the study period (defined as at least one physician visit in a long-term healthcare setting) and previous hospitalization (defined as a hospitalization of any length in the 60 days before the index date or being admitted to hospital in the year before the index date for a duration of 30 days or more).

Anticoagulant exposure

Exposure to warfarin was defined as any use (one or more prescriptions) of warfarin in the 30 days before the index date. We also considered exposures of any use in 1 year as well as frequent use (five or more prescriptions filled in a 1-year period).

Previous cardiovascular disease and stroke

This study defined stroke as any admission to hospital for stroke or other severe neurological disorder in the year prior to the index date (ICD-9 codes: 431, 432, 433, 434 and 436). This study defined cardiovascular events as any hospitalization for either myocardial infarction or congestive heart failure in the 1 prior to the index date (ICD-9 codes: 402, 410, 412 and 432).

Data analysis

We estimated the rate ratio (RR) from the odds ratio for injurious motor vehicle crash using logistic regression [9] in SAS version 8.12 (SAS Institute, Cary, NC, USA). The RRs were adjusted for sex, age, residence in an urban region, previous injurious crash and a chronic disease score [10] that accounts for a wide range of medical conditions. We also adjusted the RRs for subjects taking any or all of the following drug classes in the 60 days preceding the accident, given possible confounding [6, 11, 12]: antidepressants, antiepileptics, benzodiazepines, antipsychotics, antimigraine medication, narcotic analgesics and muscle relaxants. In addition, we adjusted for cardiovascular events and strokes in the previous year. We also considered nonsteroidal anti-inflammatory agents and paracetamol, but neither of these covariates entered the final model as they had no effect on the estimate of warfarin in these patients.

Results

We used a total of 5579 cases and 12 911 controls to do a standard case–control analysis. Cases were similar to controls in age, gender, chronic disease score and residence (urban *vs.* rural) but were more likely to have had a previous injurious crash (Table 1).

We saw no evidence of any increased risk for injurious motor vehicle crash among users of warfarin in the 30 days prior to the index date [RR 0.58, 95% confidence interval (CI) 0.36, 0.93]. We also note that risk quickly returns to baseline in subjects who are not cur-

rently exposed to the drug but have been exposed in the recent past (Table 2).

We considered people who had been exposed at any point in the year prior to index date. Over this time span, subjects on warfarin had no increased risk of an injurious motor vehicle crash (RR 0.74, 95% CI 0.55, 1.05) (Table 3). We examined frequent use by looking at those people who filled five or more prescriptions for warfarin in the year prior to the index date. This population showed the lowest degree of risk (RR 0.54, 95% CI 0.33, 0.88). Frequent users averaged 7.7 prescriptions in the cases and 9.0 prescriptions in the controls.

Table 1
Baseline characteristics of cases of injurious motor vehicle crash and controls

Characteristics	Cases	Controls
Number	5579	12911
Age at index date	73.9	73.8
Male (%)	80	73
Rural residence (%)	48.2	45.5
Previous injurious MVC (%)	3.4	1.8
Chronic disease score (SD)	2.8 (2.8)	2.5 (2.7)
Stroke in previous year (%)	0.2	0.4
Cardiac disease (MI or CHF) in previous year (%)	0.5	1.2
Use of sedating agents* (%)	78	76

**This included the use of antidepressants, antiepileptics, benzodiazepines, antipsychotics, antimigraine medication, muscle relaxants and narcotic analgesics in the previous year. MVC, Motor vehicle crash; MI, myocardial infarction; CHF, chronic heart failure.*

Discussion

In this study, we found no evidence that warfarin causes increased risk of an injurious motor vehicle crash in elderly drivers.

We have done our best to ensure that the population on warfarin was comparable to the population not on warfarin in terms of underlying disease risk factors using statistical adjustment. Because of the database, we were not able to determine the exact indication for which warfarin was prescribed to these subjects. The protective effect was strong enough that it is unlikely that residual confounding due to underlying disease processes could disguise an adverse effect of the drug. We could not adjust for the distance (number of kilometers) that each subject drives in a given year and it is possible, if unlikely, that exposed subjects drove less then unexposed subjects.

The observed pattern of protection for warfarin users

Table 2
Rate ratio of injurious motor vehicle crash associated with exposure to warfarin (any use) in the month before the index date

Drug (time period examined)	Cases (*N* = 5579)	Controls (*N* = 12 911)	Crude rate ratio	Adjusted rate ratio	95% CI
Unexposed	5556	12775	Reference	Reference	Reference
Warfarin (30 days)	23	82	0.65	0.58	0.36, 0.93
Warfarin (1 year, not last 30 days)	26	56	1.03	0.98	0.60, 1.59

Table 3
Rate ratio of injurious motor vehicle crash associated with exposure to warfarin in the year before the index date

Drug (time period examined)	Cases (*N* = 5579)	Controls (*N* = 12 911)	Crude rate ratio	Adjusted rate ratio	95% CI
Unexposed	5532	12775	Reference	Reference	Reference
Warfarin (1 year)	47	136	0.80	0.74	0.55, 1.05
1–4 prescriptions	26	55	1.09	1.07	0.67, 1.72
5+ prescriptions	21	81	0.60	0.54	0.33, 0.88

is consistent with evidence for warfarin possibly being protective of cognitive function [13–20]. The protective effect of warfarin on cognition could lend biological plausibly to a lowered risk of motor vehicle crashes attributable to cognitive decline in elderly drivers.

Our study design differed from those of McGwin *et al.* principally in the sample size. McGwin *et al.* had approximately nine cases (at-fault drivers) who were anticoagulant users and nine controls (not at fault drivers and drivers not involved in crashes) [4]. The authors obtained their drug history by interview whereas we assessed our patient's drug history based on database linkage [4]. As a result, the harmful effect of warfarin found in the study by McGwin *et al.* may have been due to recall bias, with cases having stronger recall of using a drug, in this case warfarin, if they had a car crash. Finally, McGwin *et al.* focused on at-fault drivers whereas we looked at injurious crashes. It would be surprising if the difference between our results could be explained based on this difference of definition. Moreover, the study population in McGwin *et al.* had similar exclusion criteria to our study and should have been reasonably representative of older adults who are still driving.

Based on these results, we can find no reason to conclude that anticoagulation by warfarin leads to an increased risk of a motor vehicle crash in elderly drivers. Because of the side-effects of warfarin, notably bleeding, this drug needs to be used with caution [21]. However, based on the results of this study, there is no reason to include excess risk of a motor vehicle crash as a serious adverse effect of taking coumadin.

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