

# Research

## Impact of adverse events on prescribing warfarin in patients with atrial fibrillation: matched pair analysis

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### Abstract

**Objectives** To quantify the influence of physicians' experiences of adverse events in patients with atrial fibrillation who were taking warfarin.

**Design** Population based, matched pair before and after analysis.

**Setting** Database study in Ontario, Canada.

**Participants** The physicians of patients with atrial fibrillation admitted to hospital for adverse events (major haemorrhage while taking warfarin and thromboembolic strokes while not taking warfarin). Pairs of other patients with atrial fibrillation treated by the same physicians were selected.

**Main outcome measures** Odds of receiving warfarin by matched pairs of a given physician's patients (one treated after and one treated before the event) were compared, with adjustment for stroke and bleeding risk factors that might also influence warfarin use. The odds of prescriptions for angiotensin converting enzyme (ACE) inhibitor before and after the event was assessed as a neutral control.

**Results** For the 530 physicians who had a patient with an adverse bleeding event (exposure) and who treated other patients with atrial fibrillation during the 90 days before and the 90 days after the exposure, the odds of prescribing warfarin was 21% lower for patients after the exposure (adjusted odds ratio 0.79, 95% confidence interval 0.62 to 1.00). Greater reductions in warfarin prescribing were found in analyses with patients for whom more time had elapsed between the physician's exposure and the patient's treatment. There were no significant changes in warfarin prescribing after a physician had a patient who had a stroke while not on warfarin or in the prescribing of ACE inhibitors by physicians who had patients with either bleeding events or strokes.

**Conclusions** A physician's experience with bleeding events associated with warfarin can influence prescribing warfarin. Adverse events that are possibly associated with underuse of warfarin may not affect subsequent prescribing.

### Introduction

Clinical trials have shown that long term anticoagulation reduces the risk of stroke associated with atrial fibrillation,<sup>1</sup> but warfarin is taken by only 30-60% of appropriate patients.<sup>2-4</sup> Because about 15% of all strokes are attributable to atrial fibrillation,<sup>5</sup> the clinical and economic consequences of underprescription of warfarin are profound.<sup>6</sup>

Physicians' overestimation of the risks of anticoagulation is the most consistently cited explanation for the observed patterns

of warfarin use.<sup>7</sup> These perceptions may be influenced by physicians' experiences with warfarin use in their patients<sup>8,9</sup>; physicians whose patients have had adverse events from anticoagulation may be less likely to prescribe warfarin.<sup>10</sup> Unfortunately, the one study that assessed this association had a small sample size and asked physicians about the quality of their experiences prescribing warfarin to patients with atrial fibrillation without further characterising the adverse events.<sup>10</sup>

Adverse events associated with an action (for instance, a major haemorrhage in a patient with atrial fibrillation who had been prescribed warfarin) may have more influence on a physician's practice than adverse events associated with inaction (for instance, not prescribing warfarin to a patient with atrial fibrillation who subsequently has a thromboembolic stroke).<sup>11,12</sup> Accordingly, we sought to quantify the influence of both types of events on warfarin use for patients with atrial fibrillation.

### Methods

#### Setting and design

We assembled a retrospective cohort of patients aged  $\geq 66$  with non-valvular non-transient atrial fibrillation who were living in the community. We linked large healthcare databases that have been used extensively in other population based studies.<sup>13,14</sup>

We included all patients admitted to hospital from 1 January 1994 to 31 March 2002 with a primary ("most responsible") diagnosis or major comorbid diagnosis of atrial fibrillation (ICD-9 (international classification of diseases, ninth revision) code 427.3) on the basis of Canadian Institutes of Health Information (CIHI) records. We excluded patients for whom atrial fibrillation was a complication after admission, who had valvular heart disease (defined as having inpatient diagnoses of mitral stenosis, prosthetic heart valves, or mitral or aortic valve repair or replacement before their admission with atrial fibrillation), who were likely to have perioperative atrial fibrillation (defined as having coronary artery bypass surgery, pericardial surgery, or structural cardiac repair within 30 days before their atrial fibrillation admission), who had hyperthyroidism or thyrotoxicosis within the past 12 months (based on discharge abstracts and prescriptions for antithyroid medications), who died during admission or within 60 days after discharge, who were residents of chronic care facilities, or who did not have a valid health card number.

For patients with more than one eligible admission, we included data only from the first.

### Identification of adverse events

To identify patients who experienced severe bleeding events associated with warfarin we searched for patients in our cohort who were readmitted with an upper gastrointestinal bleed (ICD-9 codes 531, 532, 534, 578.0, 578.1, 578.9)<sup>15</sup> or intracerebral haemorrhage (ICD-9 code 431)<sup>16</sup> after their initial admission and who had received a prescription for warfarin during the 120 days before the admission for bleeding. If a patient had more than one bleeding event, we included data only from the first.

To identify patients with atrial fibrillation who had a thromboembolic stroke while not on warfarin, we searched for patients who were readmitted with ischaemic stroke (ICD-9 code 434 or 436) and who had not received a prescription for warfarin in the 120 days before this admission. If a patient had more than one stroke, we included data only from the first.

### Identification of physicians and creation of cohorts

Using billing claims from the Ontario Health Insurance Plan database, we identified the physicians responsible for the care of patients who experienced adverse events. The “principal provider” was defined as the physician who submitted the greatest number of outpatient service claims for care related to cardiac diagnoses (that is, hypertension, ischaemic heart disease, pulmonary embolism, conduction defects and arrhythmias, congestive heart failure, valvular heart disease, arteriosclerosis and aneurysms, and other diseases of the heart and circulatory system) in the six months after a patient experienced an adverse event. The date of hospital discharge for this patient was considered as the physician’s “exposure date.” If a physician had more than one exposure to a bleeding or stroke event, we considered only the first of each type. If a physician had exposure to both a bleeding and a stroke event, we considered each separately.

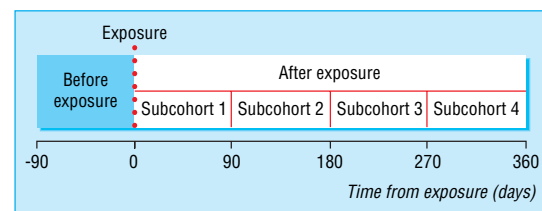
Using these definitions of exposure, we created two main cohorts. Our first cohort consisted of all patients with atrial fibrillation cared for by the principal providers of patients with bleeding events associated with warfarin. We excluded the actual patients who had experienced the bleeding events (that is, the index cases) and classified all other patients as having an admission before or after their physician’s exposure date. Our second cohort was created by repeating this procedure for all patients cared for by the principal providers of atrial fibrillation patients who had had a stroke while not on warfarin.

### Patients’ comorbidity

We identified comorbidities in patients by searching hospital discharge abstracts and physicians’ claims data for the presence of relevant diagnostic codes for the five years up to and including their index admission date as well as drug claims for the year before this date. Age > 75, previous ischaemic stroke, congestive heart failure, hypertension, diabetes, and coronary artery disease were identified as risk factors for stroke. We also identified previous upper gastrointestinal bleeding, lower gastrointestinal bleeding, intracerebral haemorrhage, renal disease, liver disease, dementia or cognitive impairment, and use of antiplatelet agents and non-steroidal anti-inflammatory agents as risk factors for bleeding. We determined whether a cardiologist was involved in their care by assessing whether a cardiologist had submitted a claim for that patient in the six months after the hospital discharge date.

### Statistical analyses

We used a matched pair before and after design to evaluate the impact of adverse events associated with warfarin on a physician’s subsequent prescribing of warfarin. We selected pairs of patients treated by each exposed physician, one patient before



Strategy for analysis

and one patient after exposure, and compared their odds of warfarin receipt. Separate analyses were conducted for physicians who were exposed to bleeding and stroke events.

Our primary analysis compared warfarin use by the most recently admitted patient of a physician during the 90 days immediately before exposure with his or her first newly discharged patient during the 90 days after exposure. In subsequent analyses, we evaluated physicians who treated patients newly discharged in the same 90 days before exposure and the first newly discharged patient with atrial fibrillation in three other periods after exposure (91–180 days, 181–270 days, and 271–360 days), thus creating four subcohorts (figure).

By using this method, physicians served as their own controls, thereby reducing confounding due to fixed characteristics such as specialty training and practice style (for example, preferences for warfarin prescribing and tolerance of risk). We chose a 90 day exposure window to allow sufficient time for filling of prescriptions as patients covered by the Ontario Drug Benefit Program are dispensed a maximum of three months of medication.

To assess the specificity of our findings, we repeated our analyses using prescriptions for angiotensin converting enzyme (ACE) inhibitors in the same patients. If our results were attributable to adverse events associated with warfarin and not differences in patients’ characteristics or changes in physicians’ general tendencies to prescribe medications, the odds of ACE inhibitor prescribing should be the same for patients treated before and after exposure.

We compared the baseline characteristics of patients before and after exposure with paired *t* tests and McNemar’s tests. Odds ratios for the association between exposure to an adverse event and the likelihood of prescribing warfarin were estimated with univariate and multivariable conditional logistic regression. An odds ratio < 1 indicates a reduced likelihood of prescribing warfarin after exposure. All analyses were performed with SAS version 8.2 (SAS Institute, Cary, NC).

## Results

Of the 116 200 patients with non-valvular non-transient atrial fibrillation identified during the study period, 3921 (3.4%) were readmitted to hospital with an upper gastrointestinal (n = 3478) or intracranial haemorrhage (n = 443) while on anticoagulation. We identified the physician responsible for the care of 3120 (79.6%) of these patients. Of these physicians, 530 treated other patients with atrial fibrillation in the 90 days before and the 90 days after the exposure. Table 1 shows the baseline characteristics from these 1060 patients. According to the guidelines of the American College of Chest Physicians (ACCP),<sup>17</sup> 91.5% of the patients before exposure and 92.1% of the patients after exposure group were at high risk of stroke associated with atrial fibrillation.

Patients treated in the 90 days after a physician’s exposure to an adverse bleeding event were significantly less likely to receive

**Table 1** Patients' characteristics by time period according to whether their physician had had a patient who had an adverse event related to warfarin use. Figures are numbers (percentages) of patients

Characteristic	Bleeding analysis*			Stroke analysis*		
	Before exposure (n=530)	After exposure (n=530)	P value†	Before exposure (n=704)	After exposure (n=704)	P value
Women	262 (49.4)	245 (46.2)	0.29	344 (48.9)	334 (47.4)	0.58
Coronary artery disease	219 (41.3)	223 (42.1)	0.80	320 (45.5)	283 (40.2)	0.04
Cardiology involvement	185 (34.9)	176 (33.2)	0.43	202 (28.7)	203 (28.8)	0.94
<b>Risk factors for stroke</b>						
Age >75	315 (59.4)	317 (59.8)	0.90	414 (59.8)	425 (60.4)	0.55
Previous stroke	32 (6.0)	29 (5.5)	0.70	54 (7.7)	60 (8.5)	0.57
Congestive heart failure	211 (39.8)	183 (34.5)	0.07	245 (34.8)	247 (35.1)	0.91
Hypertension	397 (74.9)	401 (75.7)	0.77	501 (71.2)	523 (74.3)	0.18
Diabetes	134 (25.3)	124 (23.4)	0.47	161 (22.9)	144 (20.5)	0.26
<b>Risk factors for bleeding</b>						
Previous upper GI bleed	35 (6.6)	42 (7.9)	0.42	45 (6.4)	36 (5.1)	0.30
Previous lower GI bleed	50 (9.4)	46 (8.7)	0.67	57 (8.1)	60 (8.5)	0.77
Previous intracerebral haemorrhage	3 (0.6)	3 (0.6)	1.00	1 (0.1)	0 (0.0)	0.68
Liver disease	4 (0.8)	3 (0.6)	0.71	7 (1.0)	0 (0.0)	0.02
Renal disease	60 (11.3)	76 (14.3)	0.15	78 (11.1)	95 (13.5)	0.17
Dementia	11 (2.1)	6 (1.1)	0.23	12 (1.7)	9 (1.3)	0.49
NSAID use	160 (30.2)	133 (25.1)	0.07	191 (27.1)	189 (26.9)	0.90
Anti-platelet use	206 (38.9)	219 (41.3)	0.41	318 (45.2)	321 (45.6)	0.87
Warfarin use	257 (48.5)	222 (41.9)	0.03	260 (36.9)	253 (35.9)	0.70
ACE inhibitor use	276 (52.1)	281 (53.0)	0.76	353 (50.1)	335 (47.6)	0.33

GI=gastrointestinal; NSAID=non-steroidal anti-inflammatory drug; ACE=angiotensin converting enzyme.

\*Cohort before exposure consists of the last patients of exposed physicians during the 90 days immediately before exposure and the after exposure cohort consists of the first patients of exposed physicians during the 90 days after exposure.

†Based on paired *t* tests and McNemar's tests.

a prescription for warfarin (odds ratio 0.77, 95% confidence interval 0.61 to 0.98) than patients before the exposure. The results were unchanged after we adjusted for patients' covariates and involvement of a cardiologist in the care (0.79, 0.62 to 1.00) (table 2). Analyses based on other lengths of time after exposure yielded greater reductions in the odds of warfarin use (table 2). We found no significant association between exposure to bleeding events associated with warfarin and prescriptions for ACE inhibitors (table 2).

The cohort for our stroke analysis consisted of 8720 patients who had ischaemic strokes while not on warfarin. We were able to identify physicians for 6218 (71.3%) of these patients, and 704 physicians treated patients in both the 90 days before and the 90 days after the exposure. Compared with patients treated before the exposure, patients treated after the exposure were less likely to have coronary artery disease ( $P=0.04$ ) or liver disease ( $P=0.02$ ) (table 1). According to criteria from the American College of Chest Physicians, 92.2% of the patients before exposure

and 92.5% of the patients after exposure were at high risk of stroke associated with atrial fibrillation. All the patients (both from before and after exposure) had a similar likelihood of receiving warfarin (odds ratio 0.96, 0.77 to 1.19). Multivariable adjustment did not change the results nor did the use of different comparison periods (table 2). There was no association between exposure to ischaemic stroke in a patient with atrial fibrillation not on warfarin and use of ACE inhibitors (table 2).

## Discussion

We studied the impact of adverse events associated with warfarin on prescribing in a population based cohort of patients with atrial fibrillation. Physicians were less likely to prescribe warfarin after one of their other patients had experienced a major adverse bleeding event associated with warfarin. Patients treated by physicians in the 90 days after the adverse event had a 21% reduced odds of receiving warfarin compared with patients treated by these same physicians before exposure. More strikingly, patients treated in the period 91-180 days after the adverse event had a 40% reduction in the odds of receiving warfarin compared with patients treated before the adverse event. This odds reduction, based on a baseline (before exposure) prescribing rate of 48%, is equivalent to a 12% absolute and 26% relative decrease in the likelihood that a patient will receive warfarin. In contrast, a thromboembolic stroke in a patient with atrial fibrillation not on anticoagulation did not influence the odds that a physician will use warfarin in subsequent patients. As expected, the odds of ACE inhibitor prescribing were not influenced by a physician's exposure to either a bleeding or stroke event.

### Theoretical basis for the results

These results provide empirical evidence for the existence of two frequently cited cognitive biases that affect clinical decisions. Firstly, Tversky and Kahneman's "availability heuristic" suggests that assessments of the probability of an event are influenced by the ease with which instances of the event can be recalled.<sup>18</sup>

**Table 2** Association between adverse events associated with warfarin and prescriptions for warfarin and ACE inhibitors in different comparison periods

Comparison period (days after exposure)	No of physicians evaluated	Odds ratio (95% CI)	
		Warfarin use*	ACE inhibitor use*
<b>Bleeding analysis</b>			
0-90	530	0.79 (0.62 to 1.00)	1.13 (0.87 to 1.47)
91-180	521	0.60 (0.46 to 0.79)	1.16 (0.90 to 1.51)
181-270	488	0.61 (0.46 to 0.81)	1.11 (0.84 to 1.46)
271-360	469	0.72 (0.54 to 0.97)	1.06 (0.79 to 1.41)
<b>Stroke analysis</b>			
0-90	704	0.95 (0.75 to 1.19)	0.88 (0.70 to 1.11)
91-180	664	1.05 (0.82 to 1.34)	0.99 (0.78 to 1.26)
181-270	656	1.22 (0.96 to 1.55)	1.17 (0.92 to 1.50)
271-360	621	1.23 (0.96 to 1.58)	1.08 (0.84 to 1.40)

\*Analyses adjusted for risk factors for stroke and bleeding as well as cardiology involvement in patient's care.

Bleeding events related to anticoagulation, especially those that result in admission to hospital, are dramatic and easily remembered and, as we observed, seem to actually reduce warfarin prescribing. A similar logic has been proposed for patterns of use of other treatments including thrombolysis,<sup>19</sup> antibiotics,<sup>20</sup> and blood transfusions.<sup>21</sup>

Secondly, Feinstein's "chagrin factor" postulates that when choosing between alternatives, physicians avoid those actions that cause them the most regret.<sup>11</sup> In the case of anticoagulation, physicians may have more chagrin associated with acts of commission (that is, adverse events associated with the administration of anticoagulation) than acts of omission (that is, adverse events associated with withholding anticoagulation),<sup>10</sup> perhaps in keeping with the principle of non-maleficence or "do no harm."

#### Limitations of the study

There are several limitations to our study. Firstly, making causal inferences with administrative data is challenging. Our findings may have resulted from some other coincident event experienced by this group of physicians or differences between patients before and after exposure with respect to important but unmeasured factors. It is reassuring that our results were unchanged when we adjusted for well accepted clinical variables. Moreover, differences in cardiac risk profiles of patients before and after exposure would probably have been reflected in changes in ACE inhibitor prescribing, but this was not observed.

Secondly, our results may not be generalisable to all physicians who treat patients with atrial fibrillation. We included physicians in our analysis if they had had a patient who had experienced a bleeding event associated with warfarin, and these physicians at baseline are most likely to prescribe warfarin. The difference in the rates of warfarin prescribing before exposure in our two sets of analyses (48.5% in the bleeding analyses and 36.9% in the stroke analyses) supports this assertion. Moreover, compared with physicians who were not included in our analysis, physicians in our bleeding cohort were significantly more likely to be cardiologists and to treat more patients with atrial fibrillation—both would be expected to be associated with higher rates of warfarin use.<sup>22</sup>

Thirdly, the relationship between physicians and patients is not directly identifiable within our data and we assigned physicians to patients based on service claims for cardiac related diagnoses. These physicians may not have been aware of the bleeding event and stroke events, especially when they were making prescribing decisions for other patients they treated shortly thereafter. However, this would reduce the likelihood of finding a reduction in warfarin prescribing after an adverse bleeding event; our results may therefore underestimate the true effect of adverse experiences on warfarin prescribing.

Finally, our analysis of the impact of ischaemic stroke on warfarin prescribing may have been underpowered to detect small effects. With our sample of 1408 patients (704 matched pairs), we had 80% power to detect a 30% increase in the odds of warfarin prescribing. A much larger study would have been required to detect a smaller effect (for example, 5000 patients for a 15% increased odds) should such an effect really exist.

#### Implications and conclusions

To our knowledge, this is the first study to use a population based dataset to assess the impact of specific dramatic adverse clinical events on subsequent patterns of care. Given the inherent limitations of prospective assessment methods, including the biases induced by directly questioning physicians,<sup>23</sup> this is a potentially powerful tool for understanding clinical behaviour.

#### What is already known on this topic

Warfarin is underprescribed to patients with atrial fibrillation

Physicians' overestimation of the risks of anticoagulation is a commonly cited explanation for the observed patterns of warfarin use

These perceptions may be influenced by physicians' experiences with warfarin use in their patients

#### What this study adds

Physicians are less likely to prescribe warfarin after one of their patients has a major adverse bleeding event associated with warfarin

A thromboembolic stroke in a patient with atrial fibrillation not on anticoagulation does not influence the odds that a physician will use warfarin in subsequent patients.

Our findings provide further insight about reasons for underuse of warfarin in the treatment of atrial fibrillation and, more generally, about patterns of care for other similar conditions. As the prevalence of atrial fibrillation is increasing<sup>24</sup> and ischaemic strokes related to atrial fibrillation are a burden for patients and the healthcare system, efforts to address specific barriers to appropriate atrial fibrillation care are essential. Based on our results, these interventions should also address physicians' perceptions of risk associated with warfarin use.

**Contributors:** All authors were responsible for concept and design and critical revision of the manuscript. NKC acquired, analysed, and interpreted data, drafted the manuscript, provided statistical expertise, and is guarantor. GMA was responsible for administrative, technical, or material support and supervised the study. AL was responsible for administrative, technical, or material support. DR-D and SBS supervised the study. S-LTN provided statistical expertise and supervised the study.

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**Competing interests:** None declared.

**Ethical approval:** The ethics review board of Sunnybrook and Women's College Health Sciences Centre, Toronto, approved this study.

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