

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

Niteesh K Choudhry, Geoffrey M Anderson, Andreas Laupacis, Dennis Ross-Degnan, Sharon-Lise T Normand, Stephen B Soumerai

### 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.

**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

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> Physicians'

overestimation of the risks of anticoagulation is the most consistently cited explanation for the observed patterns of warfarin use.<sup>5</sup> Physicians whose patients have had adverse events from anticoagulation may be less likely to prescribe warfarin.<sup>6</sup>

### 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 (see [bmj.com](http://bmj.com) for details).

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 on the basis of Canadian Institutes of Health Information (CIHI) records. See [bmj.com](http://bmj.com) for exclusion criteria.

#### Identification of adverse events

We identified patients who experienced severe bleeding events associated with warfarin (that is, those who were readmitted with an upper gastrointestinal bleed<sup>7</sup> or intracerebral haemorrhage<sup>8</sup>) and who had received a prescription for warfarin during the 120 days before the admission for bleeding. 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 and who had not received a prescription for warfarin in the 120 days before this admission. In all cases, if a patient had more than one event, 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 in the six months after a patient experienced an adverse event (see [bmj.com](http://bmj.com)). If a physician had

Harvard Medical School and Brigham and Women's Hospital, Boston, USA 02120  
Niteesh K Choudhry  
*instructor in medicine*

Department of Health Policy, Management and Evaluation, Faculty of Medicine, University of Toronto, Toronto, Canada

Geoffrey M Anderson  
*chair in health management strategies*

Institute of Clinical Evaluative Sciences, Toronto, Canada  
Andreas Laupacis  
*chief executive officer*

Department of Ambulatory Care and Prevention, Harvard Medical School and Harvard Pilgrim Health Care, Boston, USA

Dennis Ross-Degnan  
*associate professor*  
Stephen B Soumerai  
*professor*

Department of Health Care Policy, Harvard Medical School, Boston, USA

Sharon-Lise T Normand  
*professor of biostatistics*

Correspondence to: N K Choudhry  
[nchoudhry@partners.org](mailto:nchoudhry@partners.org)

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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.

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. Our second cohort was created by repeating this procedure for all patients cared for by the principal providers of patients with atrial fibrillation who had had a stroke while not on warfarin.

We identified relevant comorbidities in patients for the five years up to and including their index admission date as well as drug claims for the year before this date (see [bmj.com](http://bmj.com)).

### 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 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). Physicians served as their own controls, thereby reducing confounding due to fixed characteristics such as specialty training and practice style.

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.

## 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. See [bmj.com](http://bmj.com) for baseline characteristics of these 1060 patients.

Patients treated in the 90 days after a physician's exposure to an adverse bleeding event were significantly less likely to receive a prescription for warfarin (odds ratio 0.77, 95% confidence interval 0.61 to 0.98) than patients before the exposure (table). Analyses based on other lengths of time after exposure yielded greater reductions in the odds of warfarin use (table).

The cohort for our stroke analysis consisted of 8720 patients who had ischaemic strokes while not on warfarin. We could 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. All the patients (both from before and after exposure) had a similar likelihood of receiving warfarin (0.96, 0.77 to 1.19).

The odds of ACE inhibitor prescribing were not influenced by a physician's exposure to either a bleeding or stroke event.

## Discussion

Patients treated by physicians in the 90 days after the physician was exposed to an adverse bleeding 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.

### Limitations of the study

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. Secondly, our results may not be generalisable to all physicians who treat patients with atrial fibrillation. 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>9</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.

### Implications and conclusions

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>10</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.

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- Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;131:492-501.

### 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.

- Fang MC, Stafford RS, Ruskin JN, Singer DE. National trends in antiarrhythmic and antithrombotic medication use in atrial fibrillation. *Arch Intern Med* 2004;164:55-60.
- Cohen N, Almozino-Sarafian D, Alon I, Gorelik O, Koopfer M, Chachashvily S, et al. Warfarin for stroke prevention still underused in atrial fibrillation: patterns of omission. *Stroke* 2000;31:1217-22.
- Majeed A, Moser K, Carroll K. Trends in the prevalence and management of atrial fibrillation in general practice in England and Wales, 1994-1998: analysis of data from the general practice research database. *Heart* 2001;86:284-8.
- Bungard TJ, Ghali WA, Teo KK, McAlister FA, Tsuyuki RT. Why do patients with atrial fibrillation not receive warfarin? *Arch Intern Med* 2000;160:41-6.
- Beyth RJ, Antani MR, Covinsky KE, Miller DG, Chren MM, Quinn LM, et al. Why isn't warfarin prescribed to patients with nonrheumatic atrial fibrillation? *J Gen Intern Med* 1996;11:721-8.
- Raiford DS, Perez Gutthann S, Garcia Rodriguez LA. Positive predictive value of ICD-9 codes in the identification of cases of complicated peptic ulcer disease in the Saskatchewan hospital automated database. *Epidemiology* 1996;7:101-4.
- Tirschwell DL, Longstreth WT Jr. Validating administrative data in stroke research. *Stroke* 2002;33:2465-70.
- Kellen JC, Russell ML. Physician specialty is associated with differences in warfarin use for atrial fibrillation. *Can J Cardiol* 1998;14:365-8.
- Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *JAMA* 2001;285:2370-5.

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## How to put NICE guidelines into practice

Producing guidelines can be a laborious job. They have to be evidence based, up to date, and reliable. To produce good ones you have to do a thorough literature search and get input from a range of interested parties, from patients to professors. And you have to do all this on the hoof—the public want guidelines on new drugs as soon as possible rather than in a year's time. It's a proud moment when you publish them, but that is when the real work begins—clinicians putting them into practice. Without this final step, the guidelines will gather dust and nothing will change.

So how best to put them into practice? One route is to provide education for those clinicians who have to implement them. In November 2005 NICE commissioned BMJ Learning to produce a series of learning modules based on its guidance. In this pilot project the modules cover NICE guidelines on how best to refer patients with suspected cancer of the lung, lower gastrointestinal tract, or breast.<sup>1</sup> These modules are a series of interactive case histories. They enable you to assess your baseline knowledge of when and how urgently to refer patients with suspected cancer. You can then learn via case histories about best practice in this area. When you get to the end of the modules you should have

thoroughly trained and tested your knowledge and skills. By learning actively rather than by just reading text, you should remember what you have learnt for much longer.<sup>2,3</sup>

However, you still have to put what you have learnt into practice, and to help you do this we have added an audit tool to BMJ Learning. Using this tool, you can assess how you cared for patients before doing the module and how you cared for them afterwards, and the main changes that completing the module has made to your practice. The modules are available on [www.bmjlearning.com](http://www.bmjlearning.com).

Kieran Walsh *clinical editor, BMJ Learning*  
([bmjlearning@bmjgroup.com](mailto:bmjlearning@bmjgroup.com))

- National Institute for Health and Clinical Excellence. *Referral for suspected cancer*. [www.nice.org.uk/page.aspx?o=261649](http://www.nice.org.uk/page.aspx?o=261649) (accessed 12 Dec 2005).
- Tobun A, Stanley C. *Cognitive psychology on memory*. [www.scism.sbu.ac.uk/inmandw/tutorials/memory/g3.htm](http://www.scism.sbu.ac.uk/inmandw/tutorials/memory/g3.htm) (last updated 21 Jan 1998, accessed 12 Dec 2005).
- Suresh K. *Tips on: effective reading*. *BMJ* 2002;324(suppl):7. (Career Focus <http://careerfocus.bmjournals.com/cgi/content/full/324/7328/S7a>)