資料　９

11 月 18 日の会議は欠席させていただきますので、これまでの議論をもとに意見をまとめさせていただきました。

１．救済制度設計上の問題

（１）　抗がん剤の性質

抗がん剤は、がん細胞と正常細胞の性質の差を利用して、がん細胞を殺すために開発されたものであるので、最近開発された一部のがん分子標的治療薬を除き、多くの場合、正常細胞にも影響をきたし、それが副作用という形で出現する。進行がん患者に抗がん剤を投与する場合、全身状態が悪いために抗がん剤の副作用が出現しやすいだけでなく、原疾患の悪化によるものと区別が難しいこともあり、薬剤と有害事象との因果関係を判別することが困難である場合が多いと考えられる。

（２）　病期による区別と公平性

抗がん剤が術前療法や術後再発予防として利用される場合には、進行がんに比して、因果関係の判定は比較的容易であるが、同じ治療法による副作用が病期によって区別されることが公平性の観点から妥当かどうかの議論が必要である。

（３）　他の治療法との比較

放射線療法による副作用も対象として議論しないと不公平感は否めない。

２．適正使用と委縮医療の問題

標準療法後や標準療法が確立されていない場合に、保険収載されていないような抗がん剤を利用した場合、適正かどうかをどのような基準で誰が判定するのかが大きな課題である。また、適正でないとされた場合、それ自体が賠償請求や訴訟につながるリスクとなるため、現場の医療に大きな混乱と萎縮を引き起こす可能性がある。心房細動などに対する抗凝固治療薬ワルファリンに関して、副作用として出血を経験した医師にはワルファリンの投与を手控える傾向が認められたが、ワルファリンの治療効果が不十分で心原性脳梗塞を起こした場合には医師は自分の責任ではなく、原病の悪化ととらえて投与には影響を与えなかったとの報告がある。同列ではないものの、医師が治療行為の結果として副作用を起こすリスクを回避するために、治療を手控えるといった医療行動をとる可能性が考えられる。

さらに、救済制度が適応される場合に、その手続きなどが煩雑であれば、医療現場の負担が増すことが確実であり、制度設計にはこれらの点に関する配慮が求められる。

上記のような課題を検討する必要はあると思いますが、個人的には医療現場での負荷、医療経済学的な観点を考慮すると、まず、限定的な形でも救済制度を運用していく方向で進めるべきではないかと考えます。抗がん剤すべてに関して、また、がんの病期を考慮せずに救済制度を運用することは現実的には無理があると思います。限定的な運用を実施する

場合には、公平性を損なうことは明白です。私は法律家ではありませんので、法の下の平等という観点では不適切であるとの指摘を受けるかもしれませんが、がん医療を質の高いものにしていくためには、一歩ずつより良いものにしていく努力が必要ではないかと考えます。たとえ限定的であるにせよ、一部の患者さんの救済につながりますし、制度の運用に関する課題を浮かび上がらせることにもなれば、拡大していく場合の医療現場での負担軽減策につながるのではないでしょうか。そして、最も重要なのは、萎縮医療による患者さんへの不利益の回避になることです。これが議論の参考になればと思い書面をしたためました。

また、副作用の軽減・回避を図るための研究の推進とその成果の実用化は、本委員会の趣旨からは的外れですが、患者さんにとっては副作用が起こって救済されるよりは、副作用を回避する方がよりベネフィットが大きいことは明らかですので、国としての取り組みをお考えいただければと願っております。

がんの治療薬は日進月歩であり、これまでの毒性の強い化学療法剤から、より選択的な分子標的薬、抗体医薬、そしてがんワクチン療法と作用する仕組みが異なるものが開発されてきています。抗がん剤とひとくくりで議論するのは無理があると思われますので、結論を急ぐことなく、患者さんにとって、どのような方策が最大限の利益につながるのかを継続的に検討していくべきではないかと思います。

中村祐輔

ワーファリン使用時の出血が臨床に及ぼす影響

心房細動患者におけるwarfarin関連有害事象が処方に及ぼす影響：マッチドペア解析

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

■目的　心房細動患者に起きたワルファリン(商品名:ワーファリン)関連の有害事象が担当医師に及ぼす影響を定量的に評価する。

■研究デザイン　有害事象経験の前後で比較する一般集団対象のマッチドペア解析。

■設定　カナダ・オンタリオ地域のデータベース(Ontario Health Insurance Planへの医療費請求)を用いた研究。

■参加者　有害事象(ワルファリン服用中の大量出血、ワルファリン非服用中の血栓塞栓性脳卒中)のために入院した心房細動患者の担当医師。同じ担当医師から治療を受けた、他の心房細動患者のペア。

■主要評価項目　任意の医師のマッチドペアによるワルファリン処方の頻度について、ワルファリン使用に影響しうる脳卒中と出血の危険因子で補正したうえで、有害事象の経験前後で比較した。中立的な対照として、有害事象の前後におけるアンジオテンシン変換酵素(ACE)阻害薬の処方率についても評価した。

■結果　担当していた心房細動患者に出血イベント(曝露)が発生した経験をもち、曝露の前後それぞれ90日間に他の心房細動患者を治療した医師530人について調べた結果、曝露後のワルファリン処方率(オッズ)は21%低下した(補正オッズ比, 0.79; 95%信頼区間[CI], 0.62～1.00)。曝露時点から患者治療までの時間経過が長いほど、ワルファリン処方の減少がより大きくなる傾向が認められた。ワルファリン非服用中の受け持ち患者が脳卒中を発症した場合のワルファリン処方ならびに患者に出血イベントあるいは脳卒中が起きた医師のACE阻害薬処方に関しては、有意な変化がみられなかった。

■結論　ワルファリンに関連した出血イベントの経験は、医師のワルファリン処方に影響を及ぼしうる。ワルファリン過少使用との関連が示唆される有害事象は、その後の処方には影響しないようである。

表　ワルファリン関連有害事象とワルファリンおよびACE阻害薬の処方の関連

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*
Bleeding analysis			
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)
Stroke analysis			
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.

補足:comparison period (days after exposure):ワルファリンに関連した有害事象(出血、脳卒中イベント)を起こした患者の診察(曝露)後の期間

解説 患者を目の前にした医師はハムレット

三田村 秀雄
東京都済生会中央病院副院長

心房細動患者を目の前にするたびに医師はハムレットの心境になる。「ワルファリンを投与すべきか、すべきでないか、それが問題だ」

なぜ問題かと言われると、それはヒポクラテスの教えが邪魔をするからである。「First, do no harm」。たとえ善意とはいえ、ワルファリンを投与した結果、脳出血を引き起こしでもすれば、この教えに反することになる。しかし何もしないで脳梗塞が起これば、まともな医師ならやはり良心の呵責を感じるはずである。

本研究は、出血か脳梗塞の有害事象を合併した66歳以上の非弁膜症性心房細動例を管理していた医師のワルファリン処方動向を調査したものである。有害事象の発生にともない、医師は“acts of commission”による罪の意識と、“acts of omission”による罪の意識のどちらをより重く感じるかを明らかにした。

まずワルファリンを投与中に出血事故に遭遇した530人の医師は、ほかの患者へのワルファリン投与率がその前後で48.5%から41.9%に低下した($P = 0.03$)。一方、ワルファリンを投与していない時に脳梗塞を起こした患者に遭遇した704人の医師では、ほかの患者へのワルファリン投与率が事故の前後で36.9%から35.9%へとほとんど増減しなかった。出血にはビビったが、脳梗塞にはビビらなかった、という解釈である。「ヒポクラテスの誓い」に従う医師が多かった、ということなのか。

この論文は後向き調査に基づいており、そもそも出血に遭遇した医師のほうが、脳梗塞に遭遇した医師よりも高頻度にワルファリンを投与していた。患者の特徴が同じであれば、そこは医師の流儀が違うため、ということになる。実際、出血群に循環器医の関与が34.9%と脳梗塞群における28.7%よりも多かったことから、循環器医は日ごろからワルファリン投与をより重視しているが出血事故には慎重になりやすいのに対し、非循環器医はワルファリン投与を軽視しているうえ、脳梗塞を経験しても“及び腰”にならない、という傾向を反映しているのかもしれない。確かに出血はドラマチックではあるが、9割は上部消化管出血であり、脳出血は1割に過ぎない。長期予後への影響はワルファリン非投与による脳梗塞のほうがはるかに大きいはずである。

本調査の対象群には高齢に加え、高血圧症、心不全、糖尿病など、塞栓症の危険因子を有する症例が多く含まれていたのに、ワルファリンの使用は最初から半数以下であった。出血という有害事象を経験していなくても、ワルファリン投与に最初から躊躇している、あるいは軽視している医師がいかに多いかを示している。

この研究は単に同一患者における同一医師によるワルファリン投与の有無を追跡したものであるが、実際には医師はワルファリンの投与を継続したまま目標INRを微調節することも決して少なくない。その辺のことも知りたいところである。

Cite this article as: BMJ, doi:10.1136/bmj.38698.709572.55 (published 10 January 2006)

Research

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 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,[1] but warfarin is taken by only 30-60% of appropriate patients.[2–4] Because about 15% of all strokes are attributable to atrial fibrillation,[5] the clinical and economic consequences of underprescription of warfarin are profound.[6]

Physicians' overestimation of the risks of anticoagulation is the most consistently cited explanation for the observed patterns of warfarin use.[7] These perceptions may be influenced by physicians' experiences with warfarin use in their patients[8 9]; physicians whose patients have had adverse events from anticoagulation may be less likely to prescribe warfarin.[10] 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.[10]

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).[11 12] 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 ≥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.[13 14]

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)[15] or intracerebral haemorrhage (ICD-9 code 431)[16] 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.

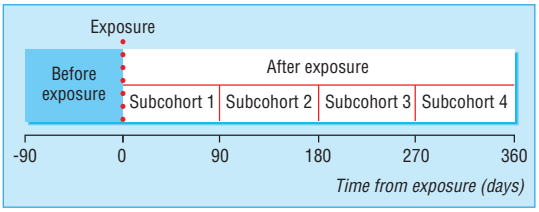
Using these definitions of exposure, we created two main cohorts. Our first cohort consisted of all patients with atrial fibrillation cared for by the principal providers of patients with bleeding events associated with warfarin. We excluded the actual patients who had experienced the bleeding events (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 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.



Strategy for analysis

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),[17] 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
Risk factors for stroke						
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
Risk factors for bleeding						
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).

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*
Bleeding analysis			
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)
Stroke analysis			
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.

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.[18]

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,[19] antibiotics,[20] and blood transfusions.[21]

Secondly, Feinstein's "chagrin factor" postulates that when choosing between alternatives, physicians avoid those actions that cause them the most regret.[11] 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),[10] 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.[22]

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,[23] 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[24] 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.

Funding: Harvard Pilgrim Health Care Foundation and a Canadian Institute for Health Research Chronic Disease New Emerging Theme (NET) programme grant (NET 54010). NKC was also supported by the Harvard Medical School fellowship in pharmaceutical policy research, a Frank Knox scholarship from Harvard University, and a Canadian Institutes of Health Research postdoctoral fellowship. SBS and DR-D are investigators in the HMO Research Network Center for Education and Research in Therapeutics, funded by the US Agency for Healthcare Research and Quality, and were also supported by grant No R01 AG022362-01 from the National Institute on Aging. AL is a senior scientist of the Canadian Institutes of Health Research.

Competing interests: None declared.

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

1 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.
2 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.
3 Cohen N, Almoznino-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.
4 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.
5 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham study. *Arch Intern Med* 1987;147:1561-4.
6 Stewart S, Murphy N, Walker A, McGuire A, McMurray JJV. Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. *Heart* 2004;90:286-92.
7 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.
8 Freeman AC, Sweeney K. Why general practitioners do not implement evidence: qualitative study. *BMJ* 2001;323:1100-2.

9 Gross CP, Vogel EW, Dhond AJ, Marple CB, Edwards RA, Hauch O, et al. Factors influencing physicians' reported use of anticoagulation therapy in nonvalvular atrial fibrillation: a cross-sectional survey. *Clin Ther* 2003;25:1750-64.
10 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.
11 Feinstein AR. The "chagrin factor" and qualitative decision analysis. *Arch Intern Med* 1985;145:1257-9.
12 Monette J, Gurwitz JH, Rochon PA, Avorn J. Physician attitudes concerning warfarin for stroke prevention in atrial fibrillation: results of a survey of long-term care practitioners. *J Am Geriatr Soc* 1997;45:1060-5.
13 Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. *JAMA* 2003;289:1652-8.
14 Bell CM, Redelmeier DA. Mortality among patients admitted to hospitals on weekends as compared with weekdays. *N Engl J Med* 2001;345:663-8.
15 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.
16 Tirschwell DL, Longstreth WT Jr. Validating administrative data in stroke research. *Stroke* 2002;33:2465-70.
17 Singer DE, Albers GW, Dalen JE, Go AS, Halperin JL, Manning WJ. Antithrombotic therapy in atrial fibrillation: the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* 2004;126:429-56S.
18 Tversky A, Kahneman D. Judgement under uncertainty: heuristics and biases. *Science* 1974;185:1124-31.
19 Soumerai SB, McLaughlin TJ, Gurwitz JH, Guadagnoli E, Hauptman PJ, Borbas C, et al. Effect of local medical opinion leaders on quality of care for acute myocardial infarction: a randomized controlled trial. *JAMA* 1998;279:1358-63.
20 Damoiseaux RA, de Melker RA, Ausems MJ, van Balen FA. Reasons for non-guideline-based antibiotic prescriptions for acute otitis media in the Netherlands. *Fam Pract* 1999;16:50-3.
21 Salem-Schatz SR, Avorn J, Soumerai SB. Influence of clinical knowledge, organizational context, and practice style on transfusion decision making. Implications for practice change strategies. *JAMA* 1990;264:476-83.
22 Kellen JC, Russell ML. Physician specialty is associated with differences in warfarin use for atrial fibrillation. *Can J Cardiol* 1998;14:365-8.
23 Adams AS, Soumerai SB, Lomas J, Ross-Degnan D. Evidence of self-report bias in assessing adherence to guidelines. *Int J Qual Health Care* 1999;11:187-92.
24 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.

(Accepted 8 November 2005)

doi 10.1136/bmj.38698.709572.55

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