

# Risk of Thromboembolism, Recurrent Hemorrhage, and Death After Warfarin Therapy Interruption for Gastrointestinal Tract Bleeding

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**Background:** Patients who not only survive a warfarin-associated gastrointestinal tract bleeding (GIB) event but also have an ongoing risk for thromboembolism present 2 clinical dilemmas: whether and when to resume anticoagulation. The objective of this study was to determine the incidence of thrombosis, recurrent GIB, and death, as well as the time to resumption of anticoagulant therapy, during the 90 days following a GIB event.

**Methods:** In this retrospective, cohort study using administrative and clinical databases, patients experiencing GIB during warfarin therapy were categorized according to whether they resumed warfarin therapy after GIB and followed up for 90 days. Variables describing the management and severity of the index GIB were also collected. Kaplan-Meier curves were constructed to estimate the survival function of thrombosis, recurrent GIB, and death between the “resumed warfarin therapy” and “did not resume warfarin therapy” groups, with Cox proportional hazards modeling to adjust for potentially confounding factors.

**Results:** There were 442 patients with warfarin-associated index GIB included in the analyses. Following the index GIB, 260 patients (58.8%) resumed warfarin therapy. Warfarin therapy resumption after the index GIB was associated with a lower adjusted risk for thrombosis (hazard ratio [HR], 0.05; 95% CI, 0.01-0.58) and death (HR, 0.31; 95% CI, 0.15-0.62), without significantly increasing the risk for recurrent GIB (HR, 1.32; 95% CI, 0.50-3.57).

**Conclusions:** The decision to not resume warfarin therapy in the 90 days following a GIB event is associated with increased risk for thrombosis and death. For many patients who have experienced warfarin-associated GIB, the benefits of resuming anticoagulant therapy will outweigh the risks.

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**G**ASTROINTESTINAL TRACT bleeding (GIB) affects an estimated 4.5% of warfarin-treated patients annually and is associated with a significant risk for death.<sup>1</sup> A history of major bleeding is an important predictor for future serious bleeding, suggesting that patients with GIB might be considered for discontinuation of warfarin therapy.<sup>2,3</sup> However, interruption or permanent discontinuation of warfarin therapy increases the risk of thromboembolic complications.<sup>4</sup> Thus, patients with warfarin-associated GIB present 2 clinical dilemmas: should warfarin therapy be stopped and, if so, when should it be resumed?

Although some have suggested that anticoagulation can be safely restarted relatively soon after a major bleeding event, there is neither high-quality evidence nor consensus about the ideal timing or risk

of reanticoagulation. Indeed, surprisingly little is known about warfarin therapy interruption and resumption following GIB.<sup>2,5</sup> An observational study of patients newly initiated on anticoagulation therapy for venous thrombosis who had

## See Invited Commentary at end of article

major bleeding reported an association between resuming anticoagulation and rebleeding.<sup>6</sup> However, patients whose index bleeding event occurred during long-term anticoagulation therapy were not evaluated. Other studies examining the resumption of anticoagulation therapy following major bleeding have been limited by small numbers of patients, selection bias, or both.<sup>2,5,7,8</sup>

In this study of warfarin-treated patients who experienced GIB, we sought to

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determine the incidence of subsequent thrombosis, recurrent GIB, and death as well as the time to resumption of warfarin therapy during 90 days of follow-up. We evaluated patient characteristics as well as the duration of warfarin therapy interruption to identify factors associated with thromboembolism, recurrent GIB, or death.

## METHODS

### STUDY DESIGN AND OUTCOMES OF INTEREST

We conducted a retrospective, cohort study using administrative and clinical databases from Kaiser Permanente Colorado (KPCO). Anticoagulation services at KPCO are provided by a centralized Clinical Pharmacy Anticoagulation Service (CPAS).<sup>9</sup> We used integrated, electronic medical, pharmacy, and laboratory record systems along with the CPAS database (Dawn-AC; 4S Systems Ltd) to identify patients, treatments, and outcomes for this study. Approval to conduct this study was obtained from the KPCO institutional review board.

We used administrative coding data (see the eAppendix for a complete listing of *International Classification of Diseases, Ninth Revision [ICD-9]* codes; <http://www.archinternmed.com>) to identify adult KPCO members who (1) were hospitalized or had an emergency department (ED) encounter for GIB (index GIB) between January 1, 2005, and December 31, 2008; (2) had an outpatient purchase of warfarin and an international normalized ratio (INR) in the 60 days prior to the index GIB; (3) had continuous KPCO membership in the 180 days prior to and 90 days after the index GIB (patients who died within 90 days after the index GIB were included); and (4) did not have a GIB diagnosis recorded during the 6 months prior to the index GIB.

The primary outcomes of interest were thrombosis (stroke, systemic embolism, and venous thromboembolism), recurrent GIB, and death from any cause during the 90 days following index GIB. Gastrointestinal tract bleeding (index and recurrent) and thrombotic events were identified first through electronic queries of inpatient and ED claims databases using ICD-9 codes (see eAppendix) and then confirmed via manual medical record review by study investigators (D.M.W. and N.P.C.) using a standardized abstraction form. Validation of study outcomes required objective evidence of either clinically overt gastrointestinal tract hemorrhage (eg, visualization of blood in stool, vomit, or gastric aspirate; positive guaiac test result; evidence from endoscopy or colonoscopy) or thrombosis (eg, positive computed tomographic scan, magnetic resonance image, ventilation-perfusion scan, or ultrasonogram). Date and cause of death were ascertained from death certificates and medical record review. All records were independently reviewed by 2 investigators (D.M.W. and N.P.C.), with disagreements resolved by a third reviewer (E.M.H.).

The following variables describing the management and severity of the index GIB were collected: presentation INR, warfarin therapy interruption, plasma or blood transfusion, phytonadione administration, intensive care unit (ICU) admission, length of ED/inpatient stay, and warfarin therapy resumption. We also recorded age, sex, warfarin indication, INR range, time from warfarin therapy initiation to index GIB, aspirin and nonsteroidal anti-inflammatory drug (NSAID) use before index GIB, low-molecular-weight heparin use after index GIB, and proportion of INR values in range during the 3 months before index GIB. Information about comorbidities was collected using ICD-9 codes. A validated aggregate measure of patient comorbidity, the Chronic Disease Score (CDS), was calculated for each patient using ambulatory prescription medication data re-

corded before the index GIB.<sup>10,11</sup> For patients with atrial fibrillation, the CHADS<sub>2</sub> score, a clinical prediction rule for estimating the risk of stroke, was calculated by assigning 1 point for diagnoses of congestive heart failure, hypertension, age 75 years or older, and diabetes mellitus and 2 points for prior stroke or transient ischemic attack.<sup>12</sup>

### STATISTICAL ANALYSES

All patients were assigned to 1 of 2 groups defined by warfarin therapy resumption after the index GIB (ie, “resumed warfarin therapy” and “did not resume warfarin therapy” groups). When warfarin therapy was not interrupted, patients were included in the resumed warfarin therapy group. Categorical data were reported as percentages, and continuous data were reported as means (standard deviations) and medians (interquartile ranges [IQRs]). Comparisons between groups for categorical data were made with the  $\chi^2$  or Fisher exact tests, whereas continuous data were compared using 2-sample *t* tests or Wilcoxon rank sum tests. Kaplan-Meier curves were constructed to estimate the survival function of thrombosis, recurrent GIB, and death between the resumed warfarin therapy and did not resume warfarin therapy groups. Patients were censored at thrombosis, recurrent GIB, death, or 90 days after index GIB, whichever came first.

A propensity score<sup>13</sup> for resumption of warfarin therapy after the index GIB was estimated for each patient using logistic regression (see the eAppendix for factors included in the propensity score). Cox proportional hazards modeling was used to adjust for potentially confounding factors in the assessment of the association of warfarin resumption with time to thrombosis, recurrent GIB, or death (see the eAppendix for factors included in each model).

To limit the effect of the severity of the index GIB on death, post hoc adjusted hazards modeling on time to death was performed, in which patients who died within 1 week of the index GIB were excluded. In addition, discrete time-varying and categorical variables were constructed based on length of time patients were off warfarin therapy after the index GIB to assess if there was a time-dependent effect of warfarin therapy interruption on the outcomes. Length of warfarin therapy interruption was categorized as 0 days, 1 to 7 days, 8 to 14 days, 15 to 90 days, and warfarin therapy not resumed. Individual post hoc adjusted hazards models for time to recurrent GIB, thrombosis, and death were constructed with the time-varying warfarin exposure variable. Because warfarin therapy was not interrupted in all cases, individual post hoc adjusted hazards models for time to recurrent GIB, thrombosis, and death were constructed with binary and time-varying warfarin exposure variables after removing patients who did not interrupt warfarin therapy and had an index GIB location of rectum-anus (*n* = 24) and then all patients who did not interrupt warfarin therapy (*n* = 41). Post hoc tests of association were performed with the categorical exposure variables and study outcomes. Because adjusted hazard modeling subanalyses using time-varying warfarin exposure and/or removing patient groups who did not have warfarin therapy interruption revealed similar results for the thrombosis, recurrent GIB, and death outcomes, only results of the initial analysis are reported.

Further analyses included comparisons of outcomes and patient characteristics between patients who did and did not experience a recurrent GIB and were and were not dead at the end of follow-up, respectively. Statistical analyses were performed using Intercooled STATA version 9.0 software (Stata-Corp). The  $\alpha$  level was set at .05, and all tests were 2-sided.

**Table 1. Baseline Characteristics According to Warfarin Therapy Status Following GIB<sup>a</sup>**

Characteristic	Overall Cohort (N = 442)	Resumed Warfarin Therapy (n = 260)	Did Not Resume Warfarin Therapy (n = 182)	P Value <sup>b</sup>
Age, mean (SD), y <sup>c</sup>	74.2 (12.1)	71.8 (12.0)	77.7 (11.3)	<.001
Male, No.	222 (50.2)	129 (49.6)	93 (51.1)	.76
INR target <sup>c</sup>				
2.0	17 (3.8)	7 (2.7)	10 (5.5)	.13
2.5	363 (82.4)	203 (78.1)	160 (88.4)	.008
≥3.0	61 (13.8)	50 (19.2)	11 (6.1)	<.001
Chronic Disease Score, mean (SD) <sup>d</sup>	8.4 (3.1)	8.2 (3.0)	8.6 (3.2)	.24
INR at GIB, median (IQR)	3.0 (2.3-4.3)	2.9 (2.3-4.2)	3.2 (2.4-4.5)	.19
Primary indication for anticoagulation therapy <sup>2</sup>				
Atrial fibrillation	223 (50.5)	120 (46.2)	103 (56.6)	.03
Venous thromboembolism <sup>d</sup>	108 (24.4)	67 (25.8)	41 (22.5)	.44
Prosthetic heart valve	42 (9.5)	40 (15.4)	2 (1.1)	<.001
Other	69 (15.6)	33 (12.7)	36 (19.8)	.04
Risk factors <sup>e</sup>				
Alcoholism	4 (0.9)	3 (1.2)	1 (0.6)	.65
Diabetes mellitus	12 (2.7)	6 (2.3)	6 (3.3)	.53
Hypertension	237 (53.6)	128 (49.2)	109 (59.9)	.03
Heart failure	110 (24.9)	63 (24.2)	47 (25.8)	.70
Renal insufficiency	49 (11.1)	26 (10.0)	23 (12.6)	.39
Prior venous thrombosis	70 (15.8)	44 (16.9)	26 (14.3)	.46
Prior arterial thrombosis	1 (0.2)	0	1 (0.6)	.41
Prior ischemic stroke/TIA	39 (8.8)	4 (10.3)	35 (8.6)	.61
Cancer	6 (1.4)	3 (1.2)	3 (1.7)	.69
GIB location				
Large intestine	116 (26.2)	73 (28.1)	43 (23.6)	.26
Mouth-esophagus	30 (6.8)	20 (7.7)	10 (5.5)	.37
Rectum-anus	64 (14.5)	51 (19.6)	13 (7.1)	<.001
Small intestine	14 (3.2)	7 (2.7)	7 (3.9)	.50
Stomach-duodenum	125 (28.3)	65 (25.0)	60 (32.7)	.07
Not identified	93 (21.0)	44 (16.9)	49 (26.9)	.01
Aspirin use, mg				
None	237 (53.6)	145 (55.8)	92 (50.3)	.28
50	2 (0.5)	1 (0.4)	1 (0.6)	.83
81	187 (42.3)	107 (41.2)	80 (44.0)	.56
162	3 (0.7)	1 (0.4)	2 (1.1)	.57
325	13 (2.9)	6 (2.3)	7 (3.9)	.35
Days from warfarin therapy initiation, median (IQR) <sup>c</sup>	891 (167-2477)	1026 (267-2877)	688 (115-2086)	.006
Percentage of INRs in range, mean (SD) <sup>f</sup>	47.7 (27.6)	50.1 (28.4)	44.4 (26.2)	.08
CHADS <sub>2</sub> score, median (IQR) [No. of patients] <sup>g</sup>	2 (1-2) [223]	2 (1-2) [120]	2 (1-2) [103]	.16

Abbreviations: CHADS<sub>2</sub>, congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, and prior stroke or TIA; GIB, gastrointestinal tract bleeding; INR, international normalized ratio; IQR, interquartile range; TIA, transient ischemic attack.

<sup>a</sup>Data are given as number (percentage) of patients unless otherwise specified.

<sup>b</sup>Comparison between "resumed warfarin therapy" and "did not resume warfarin therapy" groups.

<sup>c</sup>As of date of the initial GIB event.

<sup>d</sup>Deep vein thrombosis of the upper or lower extremity and pulmonary embolism.

<sup>e</sup>During the 180 days prior to the initial GIB event.

<sup>f</sup>During the 90 days prior to the initial GIB event.

<sup>g</sup>Among patients with atrial fibrillation only.

## RESULTS

Of 502 patients identified as having GIB using administrative data, the index GIB was not confirmed during medical record review in 57 patients, and 3 patients were not receiving warfarin. Therefore, 442 patients with warfarin-associated index GIB were included in the analyses (**Table 1**). The mean age was 74.2 years, 50.2% were male, and 46.4% used aspirin at some point during the 90 days prior to the index GIB. Indications for warfarin therapy included the following: prevention of atrial fibrillation-related stroke or systemic embolization (50.5%); treatment or secondary prevention of venous thrombo-

sis (24.4%); and prevention of prosthetic heart valve thromboembolic complications (9.5%). The median (IQR) INR on presentation was 3.0 (2.3-4.3). Approximately one-third of patients (30.5%) were initially treated in the ICU; 24.2% were evaluated and discharged directly from the ED (**Table 2**). Following the index GIB, 260 patients (58.8%) resumed warfarin therapy, including 41 patients whose warfarin therapy was never stopped. Median (IQR) time to resumption of warfarin was 4 days (2-9 days). Prosthetic heart valve indication for warfarin therapy (15.4% vs 1.1%;  $P < .001$ ) and GIB localized to the rectum-anus (representing predominately hemorrhoidal bleeds) (19.6% vs 7.1%;  $P < .001$ ) were more

**Table 2. Overall Outcomes Among Warfarin-Treated Patients With GIB<sup>a</sup>**

Outcome	Overall Cohort (n = 442)	Resumed Warfarin Therapy (n = 260)	Did Not Resume Warfarin Therapy (n = 182)	P Value <sup>b</sup>
Index GIB management				
Warfarin therapy stopped	400 (90.7)	219 (84.2)	182 (100)	<.001
Phytonadione administered	282 (63.8)	157 (60.4)	125 (68.7)	.07
Fresh-frozen plasma provided	211 (47.7)	106 (40.8)	105 (57.7)	<.001
Blood transfusion	252 (57.0)	119 (45.8)	133 (73.1)	<.001
Treated in ED only	107 (24.2)	83 (31.9)	24 (13.2)	<.001
Treated in ICU	135 (30.5)	55 (21.2)	80 (44.0)	<.001
Length of stay, median (IQR), d	3 (1-4)	2 (1-4)	3 (2-5)	<.001
Days to warfarin therapy resumption, median (IQR) <sup>c,d</sup>	4 (2-9)	4 (2-9)	NA	NA
Low-molecular-weight heparin use	44 (10.0)	39 (15.0)	5 (2.8)	<.001
Primary outcomes <sup>e</sup>				
Thrombosis	11 (2.5)	1 (0.4)	10 (5.5)	<.001
Recurrent GIB	36 (8.4)	26 (10.0)	10 (5.5)	.09
Deceased	52 (11.8)	15 (5.8)	37 (20.3)	<.001

Abbreviations: ED, emergency department; GIB, gastrointestinal tract bleeding; ICU, intensive care unit; INR, international normalized ratio; IQR, interquartile range; NA, not applicable.

<sup>a</sup>Data are given as number (percentage) of patients unless otherwise specified.

<sup>b</sup>Comparison between “resumed warfarin therapy” and “did not resume warfarin therapy” groups.

<sup>c</sup>In the 90 days following the initial GIB event but before recurrent GIB, where applicable.

<sup>d</sup>Including only patients who restarted warfarin therapy.

<sup>e</sup>In the 90 days following the initial GIB event.

**Table 3. Description of Thrombotic Events**

Patient No./ Sex/Age, y	Indication	Resumed Warfarin Therapy	Days From the Index GIB to Thrombosis	Thrombosis Type	Fatal
1/M/74	Deep vein thrombosis	No	90	Pulmonary embolism	No
2/F/85	Atrial fibrillation	No	8	Systemic embolism	No
3/M/75	Deep vein thrombosis	Yes	74	Deep vein thrombosis	No
4/M/85	Atrial fibrillation	No	27	Stroke	No
5/F/84	Atrial fibrillation	No	8	Stroke	Yes
6/M/76	Atrial fibrillation	No	23	Stroke	Yes
7/M/65	Pulmonary embolism	No	39	Pulmonary embolism and deep vein thrombosis	No
8/M/71	Stroke	No	8	Stroke	No
9/F/91	Atrial fibrillation	No	73	Stroke	Yes
10/M/62	Pulmonary embolism	No	13	Pulmonary embolism	No
11/F/95	Pulmonary embolism	No	17	Deep vein thrombosis	No

common among the 260 patients who resumed warfarin therapy compared with those who did not, respectively. In contrast, compared with those resuming warfarin therapy, older patients (mean age, 71.8 years [resumed warfarin therapy] vs 77.7 years [did not resume warfarin therapy];  $P < .001$ ) and patients for whom the GIB source was not identified (16.9% [resumed warfarin therapy] vs 26.9% [did not resume warfarin therapy];  $P = .01$ ) were less likely to resume warfarin therapy (Table 1).

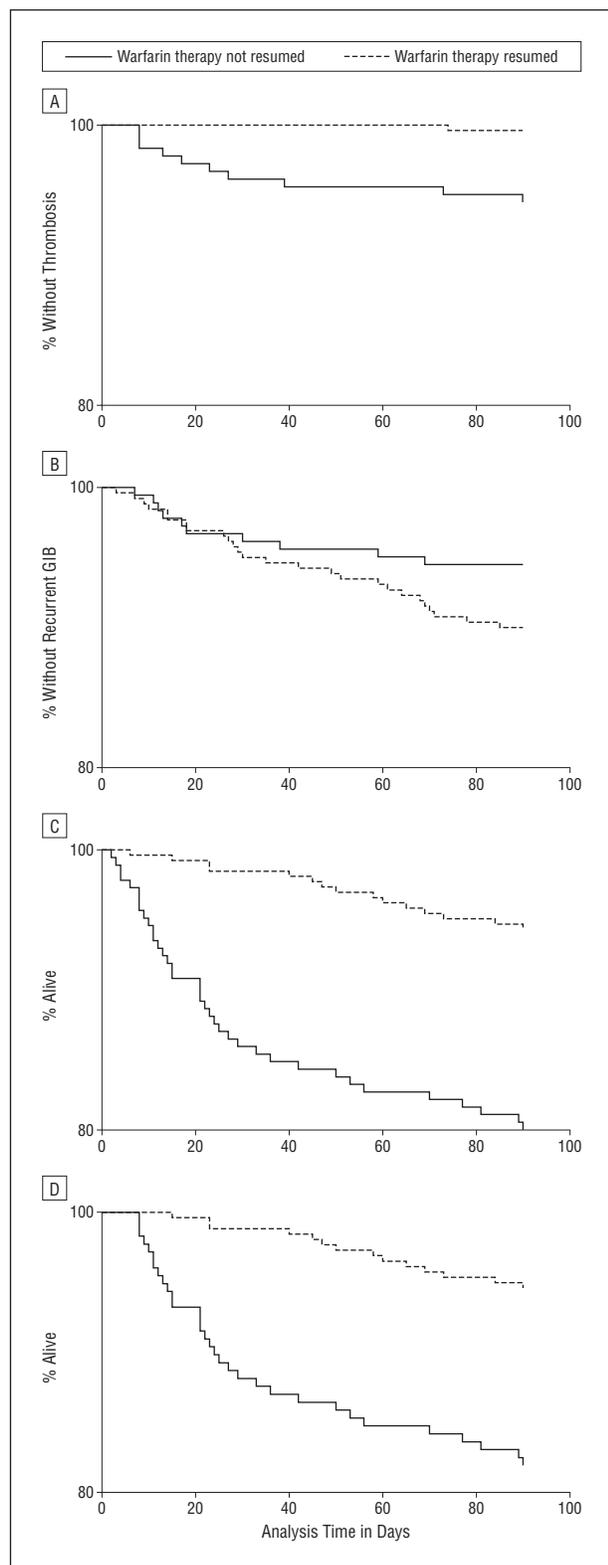
#### 90-DAY OUTCOMES: THROMBOSIS

During the 90-day follow-up period, 11 patients (2.5%) experienced a thrombotic event (6 arterial [5 strokes and 1 systemic embolus] and 5 venous [3 pulmonary emboli and 2 deep vein thromboses]), and 3 of the strokes were fatal (Table 3). Of the 260 patients who resumed warfarin therapy following the index GIB, 1 (0.4%) had

a thrombotic event (deep vein thrombosis) compared with 10 of 182 patients (5.5%) who did not resume warfarin therapy ( $P < .001$ ). Warfarin therapy resumption after the index GIB was associated with a lower risk for thrombosis (hazard ratio [HR], 0.05; 95% CI, 0.01-0.58) in a multivariable analysis that controlled for the propensity score, CDS, age, and sex (Figure, A). For patients resuming warfarin therapy, thrombosis rates were similar regardless of the duration of warfarin therapy interruption. Patients who either never interrupted warfarin therapy or resumed therapy within 14 days of the index GIB experienced no thromboses.

#### 90-DAY OUTCOMES: RECURRENT GIB

Of the 442 patients, 36 (8.4%) had recurrent GIB (Table 2). Compared with those who did not resume warfarin therapy, a numerically higher proportion of patients resuming warfarin therapy had recurrent GIB, but



**Figure.** Time-to-outcome analysis according to resuming warfarin therapy status. A, Thrombosis ( $P = .002$ , log-rank test); B, recurrent gastrointestinal tract bleeding (GIB) ( $P = .10$ , log-rank test); C, death ( $P < .001$ , log-rank test); and D, death including only patients who died at least 7 days after the index GIB ( $P < .001$ , log-rank test).

this difference was not statistically significant (10.0% [resumed warfarin therapy] vs 5.5% [did not resume warfarin therapy];  $P = .09$ ). Multivariable analysis that con-

trolled for the propensity score, CDS, age, sex, indication for warfarin use, prior heart failure diagnosis, location of GIB, pre-GIB target INR, pre-GIB percentage of INRs in range, reception of low-molecular-weight heparin, length of ED/inpatient stay, and acute GIB treatment (blood transfusion) also revealed that the risk for recurrent GIB associated with warfarin therapy resumption was not increased significantly (HR, 1.32; 95% CI, 0.50-3.57) (Figure, B). Compared with all other patients, the rate of recurrent GIB was significantly increased when warfarin therapy was resumed between 1 and 7 days after the index GIB (6.23% vs 12.4%, respectively;  $P = .03$ ). Although 5 of the index GIB events were eventually fatal, no recurrent GIB resulted in death. The median (IQR) time from warfarin therapy resumption to recurrent GIB was 27 days (11-58 days). There was no association between more aggressive management of the index GIB (eg, ICU admission, use of blood products) and recurrent GIB (all  $P > .05$ ) (Table 4).

#### 90-DAY OUTCOMES: DEATH

During the 90-day follow-up period, 52 patients (11.8%) died (Table 5). The most common causes of death were related to malignancy (28.8%), infection (19.2%), and cardiac disease (17.3%). No deaths were attributed to recurrent GIB. Compared with survivors, patients who died were older ( $P = .03$ ) and had higher CDS ( $P = .004$ ). Patients with an index GIB localized to the mouth-esophagus died less frequently, and those with an index GIB with an unidentified bleeding source died more frequently. Warfarin therapy resumption after the index GIB was associated with a lower risk for death (HR, 0.31; 95% CI, 0.15-0.62) in multivariable analysis that controlled for the propensity score, CDS, age, sex, location of GIB, ICU admission, hypertension, prior stroke diagnosis, pre-GIB percent of INRs in range, reception of low-molecular-weight heparin, length of ED/inpatient stay, and acute GIB treatment (blood transfusion) (Figure, C). This strong association persisted in a post hoc analysis excluding all patients who died within 1 week of the index GIB (Figure, D). The death rate during follow-up was lowest when warfarin therapy was resumed between 15 and 90 days after the index GIB (2.3%,  $P = .04$  compared with all other patients).

#### COMMENT

Gastrointestinal tract bleeding is a common complication of warfarin therapy. This retrospective cohort study evaluated 90-day outcomes among warfarin-treated patients with GIB. The results highlight the clinical dilemma of managing warfarin therapy following a hospitalization or ED visit for GIB. Although we observed a numerical increase in recurrent GIB associated with not interrupting or resuming warfarin therapy in the 90 days after the index GIB, this increase was not statistically significant. However, a decision not to resume warfarin therapy was associated with a significantly increased risk for both thrombosis and death from any cause. Furthermore, while no GIB recurrences were fatal, 3 patients with atrial fibrillation had fatal strokes during warfarin therapy

**Table 4. Outcomes According to Recurrent GIB Status<sup>a</sup>**

Outcome	Overall Cohort (N = 442)	Recurrent GIB (n = 36)	No Recurrent GIB (n = 406)	P Value <sup>b</sup>
Index GIB management				
Warfarin therapy stopped <sup>c</sup>	400 (90.7)	33 (91.7)	367 (90.4)	.79
Phytonadione administered <sup>c</sup>	282 (63.8)	26 (72.2)	256 (63.1)	.27
Fresh-frozen plasma provided <sup>c</sup>	211 (47.7)	19 (52.8)	192 (47.3)	.53
Blood transfusion <sup>c</sup>	252 (57.0)	25 (69.4)	227 (55.9)	.12
Treated in ED <sup>c</sup>	107 (24.2)	10 (27.8)	97 (23.9)	.60
Treated in ICU <sup>c</sup>	135 (30.5)	14 (38.9)	121 (29.8)	.26
Warfarin therapy resumed <sup>d</sup>	260 (58.8)	26 (72.2)	234 (57.6)	.09
Length of stay, median (IQR), d	3 (1-4)	3 (2-4)	2 (1-4)	.45
Days to warfarin therapy resumption, median (IQR) <sup>d,e</sup>	4 (2-9)	3 (1-6)	4 (2-9)	.41
Low-molecular-weight heparin use <sup>f</sup>	44 (10.0)	6 (16.7)	38 (9.4)	.16
Primary outcomes				
Thrombosis <sup>f</sup>	11 (2.5)	0	11 (2.7)	.39
Deceased <sup>f</sup>	52 (11.8)	2 (5.6)	50 (12.3)	.23

Abbreviations: ED, emergency department; GIB, gastrointestinal tract bleeding; ICU, intensive care unit; INR, international normalized ratio; IQR, interquartile range.

<sup>a</sup>Data are given as number (percentage) of patients unless otherwise specified.

<sup>b</sup>Comparison between "recurrent GIB" and "no recurrent GIB" groups.

<sup>c</sup>At time of the initial GIB event.

<sup>d</sup>In the 90 days following the initial GIB event but before recurrent GIB, where applicable.

<sup>e</sup>Including only patients who restarted warfarin therapy.

<sup>f</sup>In the 90 days following the initial GIB event.

discontinuation following a GIB event. While the increased risk of thrombosis and death associated with any warfarin therapy interruption has been reported previously in a Danish registry of patients with atrial fibrillation,<sup>14</sup> to our knowledge, ours is the first study to report this observation in a cohort of patients receiving warfarin for diverse indications specifically in the context of recent GIB. In our study, the exact date and duration of warfarin therapy interruption and adverse events were verified through medical record review, whereas in the Danish study,<sup>14</sup> the date of warfarin therapy interruption was estimated from warfarin prescription claims data, the reasons why patients interrupted therapy were unknown, and adverse events were not confirmed by medical record review.

The theoretical concern that abrupt warfarin therapy discontinuation following GIB causes a temporary hypercoagulable state may be relevant to the observed increase in thrombosis in patients who did not resume warfarin therapy,<sup>15</sup> although no thrombotic events occurred within 7 days of warfarin therapy interruption. It is difficult, if not impossible, to determine the time course between thrombus formation and subsequent clinical manifestations. However, the laboratory evidence supporting the actual existence of "rebound hypercoagulability" is inconsistent, and clinical trials have failed to demonstrate increased thromboembolic risk associated with abrupt anticoagulant withdrawal.<sup>15</sup>

Our observation that a decision not to resume warfarin therapy is associated with higher overall mortality was unexpected and not readily explained, given that only 3 of the 37 deaths in the group not resuming warfarin therapy were attributed to thrombosis. We attempted to control for possible confounding of the warfarin therapy resumption indicator by including pertinent factors in multivariable analysis and by performing propensity score

analysis; however, the association persisted. It is possible that patients with a more serious index GIB (who would presumably be more likely to die) were also less likely to resume anticoagulation. However, the association between resuming warfarin therapy and lower mortality persisted with modeling that adjusted for ICU admission as well as blood transfusions—interventions that would be expected to be markers of a more serious initial GIB. To further explore explanations for the association between a decision not to resume warfarin therapy and death, we reanalyzed the data after excluding patients who died during the first week after the index GIB because these patients would have had less opportunity to resume warfarin therapy. Despite this, we found that the association remained significant. We acknowledge that residual confounding was likely present despite rigorous efforts at mitigation through various analytical approaches. Therefore, the apparent increase in nonthrombotic deaths when warfarin therapy was not resumed may suggest that the treating physicians were reluctant to resume warfarin therapy in sicker patients with a higher risk of death in general.

Our results provide some guidance regarding the optimal timing of warfarin therapy resumption following GIB, but clinical judgment remains a critical factor in this difficult decision. Resumption of warfarin therapy between days 1 and 7 following a GIB event was associated with a higher risk of recurrent GIB but lower risk of thrombosis. A better understanding of the propensity for recurrent hemorrhage and its severity across the spectrum of anatomic lesions would help to inform the decision of optimal timing of anticoagulation resumption, an issue of major importance for individuals at highest risk of thromboembolism.

Our study is limited in that we used data from administrative databases, and thus not all factors that affect clinical

**Table 5. Patient Characteristics by Death Status at End of Follow-up<sup>a</sup>**

Characteristic	Overall Cohort (n = 442)	Died (n = 52)	Alive (n = 390)	P Value <sup>b</sup>
Age, mean (SD), y <sup>c</sup>	74.2 (12.1)	77.6 (11.0)	73.8 (12.2)	.03
Male	222 (50.2)	29 (55.7)	193 (49.5)	.40
INR target <sup>c</sup>				
2.0	17 (3.8)	2 (3.9)	15 (3.8)	.61
2.5	363 (82.4)	42 (80.8)	321 (82.5)	.79
≥3.0	61 (13.8)	8 (15.3)	53 (13.7)	.73
Chronic Disease Score, mean (SD) <sup>d</sup>	8.4 (3.1)	9.5 (3.3)	8.3 (3.0)	.004
INR at GIB, median (IQR)	3.0 (2.3-4.3)	3.3 (2.1-5.7)	3.0 (2.3-4.2)	.42
Primary indication for anticoagulation therapy <sup>2</sup>				
Atrial fibrillation	223 (50.5)	27 (51.9)	196 (50.3)	.82
Venous thromboembolism	108 (24.4)	10 (25.7)	98 (25.1)	.35
Prosthetic heart valve	42 (9.5)	4 (7.7)	38 (9.7)	.64
Other	69 (15.6)	11 (21.2)	58 (14.9)	.24
Risk factors <sup>d</sup>				
Alcoholism	4 (0.9)	0	4 (1.0)	.61
Diabetes mellitus	12 (2.7)	2 (3.9)	10 (2.6)	.59
Hypertension	237 (53.6)	33 (63.5)	204 (52.3)	.13
Heart failure	110 (24.9)	11 (21.2)	99 (25.4)	.51
Renal insufficiency	49 (11.1)	4 (7.7)	45 (11.5)	.49
Prior venous thrombosis	70 (15.8)	8 (15.4)	62 (15.9)	.92
Prior arterial thrombosis	1 (0.2)	1 (1.9)	0	.12
Prior ischemic stroke/TIA	39 (8.8)	9 (17.3)	30 (7.7)	.02
Cancer	6 (1.4)	1 (1.9)	5 (1.3)	.53
GIB location				
Large intestine	116 (26.2)	18 (34.6)	98 (25.1)	.14
Mouth-esophagus	30 (6.8)	0	30 (7.7)	.04
Rectum-anus	64 (14.5)	5 (9.6)	59 (15.1)	.29
Small intestine	14 (3.2)	1 (1.9)	13 (3.3)	.83
Stomach-duodenum	125 (28.3)	10 (19.2)	115 (29.5)	.12
Not identified	93 (21.0)	18 (34.6)	75 (19.2)	.01
Aspirin dose, mg <sup>e</sup>				
None	237 (53.6)	26 (50.0)	211 (54.1)	.58
50	2 (0.5)	0	2 (0.5)	.78
81	187 (42.3)	22 (42.3)	165 (42.3)	>.99
162	3 (0.7)	2 (3.9)	1 (0.3)	.04
325	13 (2.9)	2 (3.4)	11 (2.8)	.66
Days from warfarin therapy initiation, median (IQR) <sup>c</sup>	891 (167-2477)	988 (162-2450)	886 (167-2477)	.72
CHADS <sub>2</sub> score, median (IQR) [No. of patients] <sup>f</sup>	2 (1-2) [223]	2 (1-2) [27]	2 (1-2) [197]	.21

Abbreviations: CHADS<sub>2</sub>, congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, and prior stroke or TIA; GIB, gastrointestinal tract bleeding; INR, international normalized ratio; IQR, interquartile range; TIA, transient ischemic attack.

<sup>a</sup>Data are given as number (percentage) of patients unless otherwise specified.

<sup>b</sup>Comparison between "dead" and "alive" groups.

<sup>c</sup>As of the date of the initial GIB event.

<sup>d</sup>During the 180 days prior to the initial GIB event.

<sup>e</sup>During the 90 days prior to the initial GIB event.

<sup>f</sup>Among patients with atrial fibrillation only.

cal decision making could be collected. However, the confirmation of thrombosis, recurrent GIB, and death outcomes via medical chart and death certificate review strengthens the validity of our results. The observed results are biologically plausible because the thrombotic events correlated with the indication for warfarin therapy—patients with atrial fibrillation experienced strokes or systemic embolus, while patients with venous thromboembolism had recurrent venous thromboembolism (Table 2). Despite potential confounding, our study likely underestimates the strength of the association between thrombosis and not resuming warfarin therapy because patients at the highest risk of thrombosis (eg, presence of mechanical heart valve, high CHADS<sub>2</sub> score) were probably less likely to remain off warfarin therapy following GIB. Similarly, the strength of asso-

ciation between recurrent GIB and resuming warfarin therapy may be underestimated because patients perceived at high risk for further GIB probably were less likely to resume warfarin therapy. Accurate recording of baseline aspirin use status was facilitated by the records maintained by CPAS. However, aspirin use status was not routinely documented in index GIB discharge summaries, and a sizeable proportion of patients did not resume warfarin therapy and were thus not followed by CPAS after the index GIB. Therefore, we were not able to accurately record aspirin use following the index GIB and acknowledge that lack of information on post-GIB aspirin use and its potential influence on the risk of recurrent GIB, thrombosis, and death is a limitation.

Our study shows that the decision to not resume warfarin therapy in the 90 days following GIB is associated

with increased risk for thrombosis and death. Our analysis suggests that, for many patients who have experienced GIB, the benefits of resuming warfarin therapy will outweigh the risks. Further research will be needed to identify the optimal duration of warfarin interruption after a GIB event and the patients for whom a more prolonged interruption can be justified.

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