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Management of Major Bleeding Events in Patients Treated With Dabigatran for Nonvalvular Atrial Fibrillation: A Retrospective, Multicenter Review

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Abstract

Study objective—There are limited data on the clinical presentations and management of dabigatran-associated major bleeding outside the clinical trial setting. The aim of this study is to describe clinical characteristics, interventions, and outcomes in patients with dabigatran-associated major bleeding who present to the emergency department (ED).

Methods—We performed a retrospective observational chart review study of dabigatran-treated patients with nonvalvular atrial fibrillation who presented with acute major bleeding to the ED. We searched electronic medical record databases cross-referencing medication lists and hemorrhage *International Classification of Diseases*, *Ninth Revision* (*ICD-9*) and *ICD-10* codes. We studied the resulting charts to yield confirmed nonvalvular atrial fibrillation in patients with an index event of major bleeding and at least 1 dose of dabigatran in the 5 preceding days.

Results—The electronic search yielded 284 cases, and we assessed 93 as ineligible, leaving 191 in the final cohort. Of these, 118 patients (62%) had gastrointestinal hemorrhage; 36 (19%) had intracranial hemorrhage, 8 (4%) of which were nontraumatic cases and 28 (15%) traumatic. Thirty-six (19%) of the index events were in "other" locations and 1 (0.5%) "unknown." There were 12 deaths (6%): 8 from patients presenting with gastrointestinal bleeding events, 2 from

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Author contributions: TJM had full access to all the data and takes responsibility for the integrity and accuracy of the data analysis. TJM participated in study design and concept, collected data, analyzed results, wrote the manuscript, and edited all subsequent drafts. CF, MG, DJP, and AJS collected data and edited manuscript drafts. JC provided statistical advice, analyzed results, and edited manuscript drafts. All authors contributed substantially to manuscript revision and approved it for submission. TJM takes responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Trial registration number: NCT02149303

intracranial hemorrhage (both nontraumatic), and 2 from other. Although RBC and plasma transfusions were common, only 11 patients (6%) received purified coagulation factors.

Conclusion—Despite rare use of reversal strategies, mortality was low and outcomes were favorable, similar to reported outcomes from clinical trials, in this sample of patients with major bleeding while receiving dabigatran.

INTRODUCTION

Background

The first decades of the 21st century have seen a significant change in the options for oral anticoagulation, with the advent of non–vitamin K oral anticoagulant agents for stroke prevention in nonvalvular atrial fibrillation, and prevention and treatment of venous thromboembolism. The non–vitamin K oral anticoagulant agents are rapidly replacing warfarin, the mainstay of oral anticoagulation for the past 50 years, prescribed 22 million times annually in the United States.[1] Warfarin has long been a leading cause of drug-related adverse bleeding events. Multiple clinical trials have established that the non–vitamin K oral anticoagulant agents are at least as efficacious as warfarin for the prevention of stroke and systemic emboli in patients with nonvalvular atrial fibrillation and for the management of venous thromboembolism.[2–4] Furthermore, the non–vitamin K oral anticoagulants have been associated with fewer major bleeding events than warfarin and tend to lead to less intracranial hemorrhage but more gastrointestinal bleeding.[4]

Warfarin-related hemorrhages historically have been managed with vitamin K and fresh frozen plasma and more recently with prothrombin complex concentrates.[5,6] Until recently, no specific reversal agents for the non–vitamin K oral anticoagulant agents have been available outside clinical trials. The first non–vitamin K oral anticoagulant agent approved for clinical use was dabigatran, a direct thrombin inhibitor. Dabigatran is most commonly prescribed for the risk reduction of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. As a consequence of their age and comorbidities, these patients are also the most likely to experience bleeding complications.[7] For this reason, we focused on the population of nonvalvular atrial fibrillation patients who were receiving dabigatran to characterize a sample of anticoagulated major bleeding episodes.

Importance

The non–vitamin K oral anticoagulant agents, including dabigatran, were associated with fewer major bleeding events than warfarin in phase 3 clinical trials,[2,4] and early reports after Food and Drug Administration approval suggested that dabigatran-induced bleeding had a more benign clinical course compared with that of warfarin.[8] We sought to describe the characteristics, treatment, and outcomes of patients with major bleeding while receiving dabigatran in routine clinical practice.

Goals of This Investigation

Our goal was to assemble a multicenter cohort of nonvalvular atrial fibrillation patients with major bleeding while receiving dabigatran and characterize clinical presentations, treatment, and outcomes.

MATERIALS AND METHODS

Study Design and Setting

We performed a study of nonvalvular atrial fibrillation patients who were receiving dabigatran, had an acute major bleeding event (index event), and presented to an emergency department (ED) at 5 sites in the United States. We identified subjects by electronic medical record searches cross-referencing medication lists and *International Classification of Diseases*, *Ninth Revision* (*ICD-9*) and *ICD-10* codes for hemorrhage. We then manually reviewed the charts for patients meeting the major bleeding criteria of the International Society for Thrombosis and Haemostasis. The 5 sites obtained individual institutional review board or independent ethics committee approval from their local institutional review board to conduct the study.

The period under review was from October 19, 2010 (when dabigatran was approved for the US market), to the date of institutional review board approval and subsequent electronic medical record query, which varied by site.

Because this study abstracted anonymous data devoid of patient identifiers, all institutional review boards granted patient written informed consent waivers. One or more experienced research assistants or coordinators at each site collected the data. They were aware of the general purpose of the study but not the details. Cases were reviewed by investigators at each site and entered into an electronic case report form and finally into a central database managed by an independent contract research organization. We did not formally assess interrater reliability by reabstracting a subset of the charts. The contract research organization's medical monitor did query database entries for accuracy.

Selection of Participants

Patients were eligible for inclusion if they were aged 18 years or older, had a documented diagnosis of nonvalvular atrial fibrillation, had received a dose of dabigatran within 5 days of the index event, and presented to the hospital with a major bleeding episode (see Figure 1 for a complete list of inclusion and exclusion criteria). The International Society for Thrombosis and Haemostasis criteria defined major bleeding and included one of the following: fatal bleeding, bleeding into a major organ or critical area (eg, intracranial, retroperitoneal, pericardial, intraspinal, intra-articular, intraocular), a decrease in hemoglobin level of 20 g/L, or transfusion of at least 2 units of blood.[9] Patients receiving additional oral or parenteral anticoagulants or thrombolytics were excluded.

Data Collection and Processing

We used a standardized electronic case report form to abstract information from the medical records. We collected specific details in regard to the timing and dosing of dabigatran, as well as the estimated time since nonvalvular atrial fibrillation diagnosis. We also noted the presence of renal failure, comorbidities, and concomitant medications, and the characteristics of the index bleeding event (type and location of bleeding).

Outcome Measures

The primary outcomes were the number of patients with an index event (ongoing, resolved, or deceased) at hospital discharge or release, the proportion of patients receiving different types of interventions to manage the index event (including intravenous fluids, blood and blood products, factor concentrates, and hemodialysis), frequencies of bleeding types, and anatomic locations of the index events at ED presentation. The status “ongoing” was not clinically defined and was left to the investigators’ discretion according to their review of the medical records. We also calculated total length of stay in the hospital and ICU.

Primary Data Analysis

We used descriptive statistics to summarize the study outcomes. We present binary data as the number and proportion of occurrence and continuous data as means and SDs or medians and interquartile ranges (IQR), as appropriate. We stratified outcomes according to baseline characteristics such as age and type of bleeding. We used SAS (version 9.2; SAS Institute, Inc, Cary, NC) to perform all statistical analyses.

RESULTS

Characteristics of Study Subjects

Of 284 patient charts we identified at the initial screening, 93 did not to meet the International Society for Thrombosis and Haemostasis major bleeding criteria, and we excluded them from the study, leaving 191 eligible charts. See Table 1 for enrollment by site.

Main Results

Figure 2 is a Strengthening the Reporting of Observational Studies in Epidemiology flow diagram.[10] Table 2 details participant characteristics. The cohort was composed of mostly elderly non-Hispanic whites with public insurance. Of the 179 subjects (93.7%) who were alive at discharge, 165 (86.4%) cases were resolved and 14 (7.3%) ongoing; a majority, 103 (58%), were discharged to their homes, whereas 34 (19%) were discharged to a rehabilitation center and 14 (8%) to long-term care. Twelve subjects (6%) died before discharge. Two of 36 patients (6%) with intracranial hemorrhage died, and 8 of 118 (7%) with gastrointestinal bleeding died. See Figures 3 and 4 for intracranial hemorrhage and gastrointestinal bleeding outcomes. Three deaths (2%) were deemed directly related to the index event.

Gastrointestinal bleeding was the most common type of index event, occurring in 118 subjects (62%); lower gastrointestinal tract bleeding (n=65; 34%) was more frequent than upper gastrointestinal tract bleeding (n=43; 23%). Intracranial bleeding was the next most common type of bleeding, occurring in 36 subjects (19%), with traumatic cases (n=28; 15%) being more common than nontraumatic ones (n=8; 4%); of the 28 traumatic intracranial bleeding cases, 27 (14%) were associated with falls and 1 (0.5%) was related to a motor vehicle crash. The index event type was “other” (eg, epistaxis, hemoptysis, urogenital, intraspinal, intra-articular) in 36 subjects (19%); the incidence of each of these “other” bleeding events was less than 1.7%. One subject (0.5%) had an “unknown” bleeding type

that was found to meet the International Society for Thrombosis and Haemostasis criteria for major bleeding. See Table 3 for a summary of index events by anatomic location and type.

Intracranial bleeding accounted for a higher proportion of all bleeding events in older patients: 21% of subjects (n=26) older than 75 years, 18% (n=8) of those aged 65 years to younger than 75 years, and 9.5% (n=2) of those younger than 65 years.

Treating physicians used intravenous fluid most commonly to manage the index event in the cohort, administered in 139 subjects (73%), with a mean 1,219 mL (SD 2,070 mL). Blood transfusion was the second most commonly used intervention. Clinicians used transfusion of packed RBCs to manage the index event in 99 subjects (52%) (with a mean of 1,073 mL administered [SD 661 mL]) while using whole RBC transfusion in 10 subjects (5%).

Clinicians used fresh frozen plasma in 47 subjects (25%), with a mean 1,297 mL (SD 952 mL) administered. They less commonly used plasma cryoprecipitate and platelets, in only 3 (2%) and 11 (6%) subjects, respectively. Coagulation factor concentrates were given rarely (to only 11 subjects [6%]); 5 subjects (3%) received recombinant factor VIIa, 6 (3%) were given 3-factor prothrombin complex concentrate, and 1 (0.5%) was given 4-factor prothrombin complex concentrate (1 subject received 2 factor concentrates, which is the reason the total number of subjects receiving factor concentrates is 11 and not 12). None of the patients receiving factor products died, and length of stay was short (2 to 3 days), but the small numbers do not allow statistical comparisons.

Seven patients received vitamin K (4%). Only 1 patient (0.5%) underwent hemodialysis. See Table 4 for summary data.

At presentation, 138 subjects (72%) were receiving dabigatran 150 mg twice daily and 41 (22%) subjects were receiving dabigatran 75 mg twice daily; the dabigatran dosage was unknown in 12 subjects (6%). The mean duration of dabigatran exposure at presentation (in the 113 patients for whom it was available) was 233 days (SD 243 days).

Overall, a higher proportion of subjects receiving dabigatran 150 mg twice daily (high dose) received blood transfusions, as well as a higher volume of blood transfusions, compared with the subjects receiving 75 mg twice daily (low dose). A similar pattern was observed for other transfusions, although a notable divergence was observed with fresh frozen plasma and fluids; a greater percentage of the high-dose group received these transfusions but a greater volume of these was used in the low-dose patients. Table 5 provides a summary of the use of transfusions and infusions.

The mean hospital length of stay was 7 days (SD 6 days; n=190), median was 5 days (IQR 3 to 8 days). In 145 (76%) of the subjects, the length of hospital stay was less than or equal to 10 days, whereas it was 11 to 20 days and 21 to 30 days for 21 (11%) and 6 (3%) subjects, respectively. The length of stay was reported as greater than 100 days for 1 subject (0.5%). Mean ICU length of stay was 5 days (SD 7 days; n=77); median was 3 days (IQR 1 to 5 days).

Approximately 17% of the subjects (n=32) had had a previous bleeding event at presentation. The most common types of previous bleeding events were gastrointestinal (n=16; 8.4%), urogenital (n=4; 2.1%), and intracranial (n=3; 1.6%).

Renal function testing was performed for 181 of the patients (94.8%) at presentation, and their mean creatinine clearance was 58.9 mL/minute (SD 29.95 mL/minute) (Cockroft-Gault method).

Seventy-five of the subjects (39%) were receiving concomitant antiplatelet medications. Of these subjects, data were not reported for 7. Overall, 68 subjects who were receiving concomitant antiplatelet therapy had a median length of stay of 5.5 days (IQR 4 to 8 days); the mean length of stay was 7.2 days (SD 5.52 days). Of the 68 subjects in the hospital, 32 were in ICU for a median of 3.5 days (IQR 2 to 6 days); the mean was 5 days (SD 5 days). Six subjects (9%) died. Outcomes were similar whether patients were receiving aspirin or clopidogrel (data not shown).

LIMITATIONS

Because this was a study based on chart review, the quality and extent of the data obtained were dependent on the quality and accuracy of routine documentation. A lack of documented medical intervention or procedure does not necessarily mean it did not occur, and any incomplete information in the records could also be because of the possibility that part of the usual care was provided at a different medical center before transfer to the participating center, and we might not have captured this in all cases. There were undoubtedly bleeding cases in the communities that were not treated in participating EDs or were treated in other settings, and some patients may have died before reaching the hospital.

The data abstractors were trained research assistants and coordinators at the sites, accessing an electronic medical record and completing electronic case report forms, and no attempts were made to assess interrater reliability. The data coordinating center's medical monitor queried inconsistent or unusual findings.

The algorithmic approach using *ICD-9* or *ICD-10* codes suffers from the well-described limitations of using an administrative database for clinical research.[11] Furthermore, the assessment of the effect of interventions was subject to confounding by indication; that is, the most intensive treatments were likely given to patients with the most severe disease. There is also the possibility that certain information was selectively reported in the medical charts. Generalizability is limited because only 5 study sites were included.

The small sample size renders additional analyses by bleeding location or type unfeasible. We did not collect data on a control group, such as nonanticoagulated bleeding patients or patients bleeding while receiving other anticoagulants. We decided to focus our resources on collecting as much data on dabigatran-related bleeding scenarios as possible because less is known about these outside of clinical trials.

The inclusion criterion was at least 1 dose of dabigatran in the 5 days preceding the bleeding presentation, so some patients might not have received anticoagulation. However, if

clinicians documented dabigatran in the setting of hemorrhage, it is likely they believed it had some role in the clinical setting.

DISCUSSION

Patients in this cohort appeared to have relatively good clinical outcomes despite limited interventions. These results are in agreement with those of previously published studies.[2–4]

Investigators have described the characteristics, treatment, and outcomes of patients with major hemorrhage while receiving dabigatran and of controls in clinical trials (5 randomized trials in atrial fibrillation and venous thromboembolism).[2–4] A major finding in the combined analysis of the 5 trials, which was conducted by Majeed et al,[4] was that dabigatran patients required more RBC transfusions and warfarin patients received more plasma. Patients receiving dabigatran also had a shorter stay in the ICU and a trend toward lower mortality. A somewhat surprising finding in study by Majeed et al[4] was how little appeared to have been done to reverse the effects of either drug, despite guidelines at the time recommending vitamin K, plasma, and various coagulation factor products for warfarin reversal in major hemorrhage[12] and RE-LY trial steering committee guidance for similar approaches to bleeding dabigatran patients not responding to supportive care.[4]

Some postmarketing work has been published on bleeding complications of dabigatran versus warfarin. For example, Berger et al[8] found that dabigatran-induced hemorrhages had a more benign course and resulted in a shorter hospital length of stay than similar warfarin-induced bleeding episodes. Mortality of dabigatran-associated hemorrhage was similar in our data set, 6% versus 9% (compared with 13% for warfarin) in the pooled clinical trial data,[4] although lower than observed in the data set of Berger et al,[8] which found 12% mortality (compared with 13% for warfarin).[8]

Also similar between our study and that by Majeed et al[4] was the relative rarity of factor product (activated prothrombin complex concentrate, 3- and 4-factor nonactivated prothrombin complex concentrate, and recombinant factor VIIa) administration for anticoagulant reversal, at 6% compared with 2% for dabigatran and 3% for warfarin in clinical trials. The evidence for factor product use in non–vitamin K oral anticoagulant reversal is sparse (although not for warfarin reversal when the evidence is compelling[5,6]) and largely based on 2 randomized trials in nonbleeding healthy normal volunteers (a total of 22 subjects) with somewhat conflicting results.[13,14] A specific, rapid, and effective reversal agent for dabigatran, the monoclonal antibody antigen-binding fragment idarucizumab, was Food and Drug Administration approved for use in the United States on October 16, 2015, for emergency surgery or urgent procedures or in life-threatening or uncontrolled bleeding.[15]

Pollack et al[15] recently reported data for the first 90 patients in the RE-VERSE AD study, which includes life-threatening bleeding or need for emergency surgical intervention as 2 separate groups. The interim report concluded that idarucizumab completely reversed the anticoagulant effect of dabigatran in 88% to 98% of the patients at the conclusion of intravenous administration. There were 18 deaths overall, with 9 in each group, although underlying severity of medical condition was not an exclusion criterion in the trial. The

major hemorrhage cohort of RE-VERSE AD reported 9 deaths out of 51 patients, for a mortality rate of 18%. In this study, the mortality rate was 6%. RE-VERSE AD had 35% intracranial hemorrhages compared with 19% in this study. The mortality rates may not be directly comparable because of the differences in the study design, patient population, and type of major bleeding events between these 2 studies.

Hemodialysis, a reversal method for dabigatran with pharmacokinetic and pharmacodynamic mechanistic and clinical evidence,[16] was performed for only 1 patient in our data set (and 1 in the analysis by Majeed[4]). This may respect the difficulty of arranging and managing dialysis in these life-threatening presentations.

In regard to other interventions in our cohort, treating physicians used fluid administration most frequently to manage the index event (n=139; 73%). Fluid use was not reported on clinical trial patients. Clinicians gave blood transfusion (whole blood or packed RBCs) second most commonly (n=109; 57%), using plasma in 47 subjects (25%) and platelet transfusions to 11 (6%). In the clinical trial data, 59% of dabigatran patients received RBCs, 20% received plasma, and 4% received platelets.[4] It is difficult to determine from the data of Majeed et al[4] or ours whether plasma was being used as a volume expander or a “reversal” agent for dabigatran, the former of which might be clinically reasonable but the latter of questionable utility. Plasma would not be expected to contain factor IIa levels sufficient to have an effect on dabigatran-mediated anticoagulation.[17] Similarly the 7 patients (4%) in our study (and 10% in the analysis by Majeed et al[4]) who received vitamin K either represent clinician confusion with warfarin because it would be unlikely to affect dabigatran, which directly binds thrombin (factor IIa) and does not affect vitamin K, or attempted reversal of a concomitant coagulopathy such as from nutritional deficiency. Cryoprecipitate (n=3; 2%) and plasma expanders (n=2; 1%) also were rarely used in our cohort, as they were in that of Majeed et al.[4] Our cohort highlights the various approaches to management and attempted reversal of dabigatran-induced bleeding that may be standardized and simplified now that idarucizumab is approved.

The median length of stay in the hospital was 5 days compared with 8 days in study by Majeed et al.[4] For 76% of our subjects, the hospital length of stay was less than or equal to 10 days, whereas it was 11 to 20 days and 21 to 30 days for 21 (11%) and 6 (3%) subjects, respectively. Median ICU length of stay was 3 days in our data. ICU length of stay in the study by Majeed et al[4] was reported as 1.6 days for dabigatran. Our data offer an actual comparison to the combined clinical trial data in the study by Majeed et al.[4] There were 32 subjects (17%) in our sample who had previous bleeding events and who thus had an increased risk of a recurrence. Furthermore, 75 subjects (39%) were receiving concomitant medications, such as clopidogrel and aspirin, that are known to increase bleeding risk of patients receiving dabigatran.[18]

We enrolled approximately 44% of eligible patients at an 11-hospital network in central Texas (Seton Dell Medical School). The remaining 56% were from 4 Northeast US hospitals (Long Island, Brooklyn, and Boston [2 hospitals]). This allows some geographic diversity in the sample, and the number of sites increases external validity.

Overall, for patients with major bleeding events, outcomes in this study were consistent with those observed in clinical trials and subsequent combined analyses. A majority of the index events in this study cohort were treated successfully with conventional strategies.

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Editor's Capsule Summary

What is already known on this topic

Dabigatran-associated bleeding is poorly described.

What question this study addressed

What were the major bleeding events, treatments, and outcomes in patients receiving dabigatran for nonvalvular atrial fibrillation before the era of specific antidotal therapy?

What this study adds to our knowledge

Of 191 eligible patients identified retrospectively from 5 emergency departments, 62% had gastrointestinal, 19% had intracranial, and 15% had trauma-related bleeding. The most common interventions were RBC and plasma transfusions, and 6% died (75% of those deaths from gastrointestinal bleeding).

How this is relevant to clinical practice

This knowledge will be useful in guiding development of protocols for the treatment of this condition.

Inclusion Criteria

Patient >18 y

Confirmed diagnosis of NVAF (diagnosis of AF was considered confirmed it there was medical chart documentation that the patient had AF or "AF," or the *ICD-9* code for AF was documented)

- NVAF defined as follows: AF in the absence of rheumatic mitral stenosis or a prosthetic heart valve

Documentation that the patient presented to an ED or was hospitalized primarily for management of a major bleeding event (index event)

- Major bleeding was defined by the ISTH as (Schulman):
  - Fatal bleeding; or
  - Symptomatic bleeding in a critical area/organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; or
  - Bleeding causing a decrease in hemoglobin of 20 g/L or more, or leading to a transfusion of 2 or more units of whole blood or RBCs

Documentation that the index event occurred in a patient who reported having received at least 1 dose of dabigatran within 5 days before the index event

Exclusion Criteria

Confirmed diagnosis of valvular AF (diagnosis of valvular AF was considered confirmed if there was medical chart documentation that the patient had valvular AF or VAF. In the absence of documentation to indicate whether the patient had nonvalvular or valvular AF, nonvalvular AF was assumed)

Documentation that the patient was receiving dabigatran with a concomitant anticoagulant (contemporaneous parenteral anticoagulant or another oral anticoagulant) within 72 h of the index event

- The concomitant administration of antiplatelet medications before the onset of the index event was not exclusionary

Documentation of the patient receiving thrombolytic therapy within 48 h of the onset of the index event

Documentation that the patient was enrolled in an interventional investigational or other Boehringer Ingelheim observational clinical trial at the index event onset

Medical record was not retrievable, or was missing or empty

NVAF, Nonvalvular atrial fibrillation; *AF*, atrial fibrillation; *VAF*, valvular atrial fibrillation; *ISTH*, International Society for Thrombosis and Haemostasis.

Figure 1.
Inclusion and exclusion criteria.

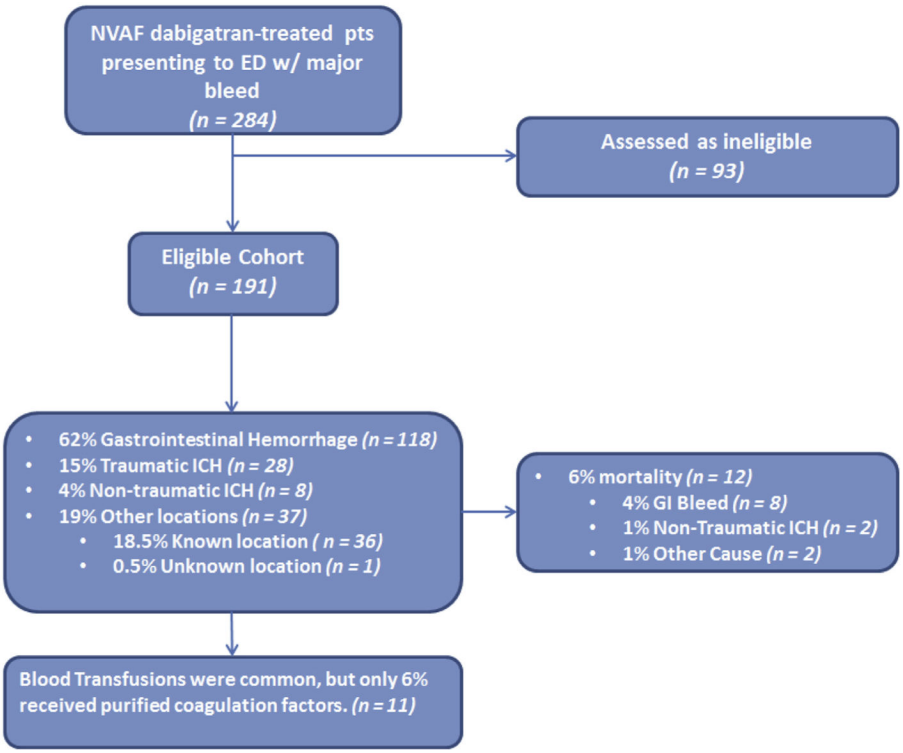

Figure 2.

Strengthening the Reporting of Observational Studies in Epidemiology diagram. *ICH*, Intracranial hemorrhage; *GI*, gastrointestinal.

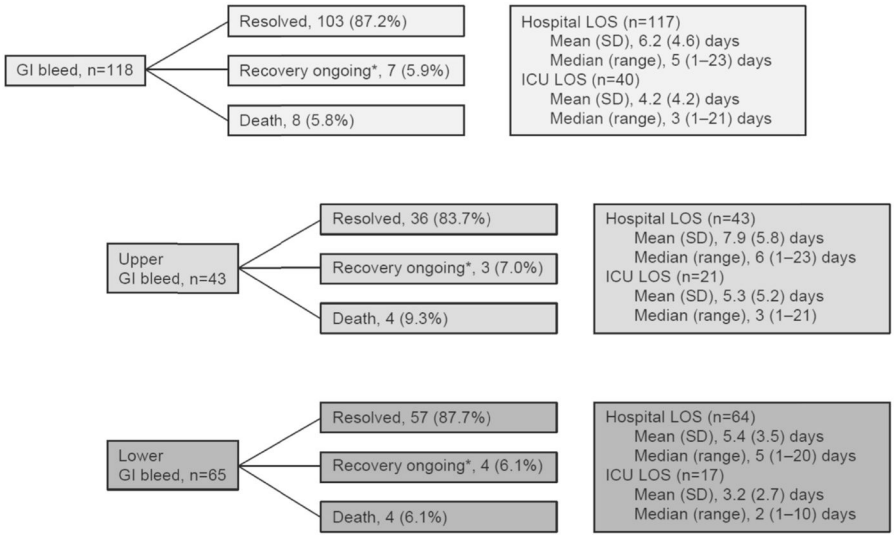

Figure 3.
Outcomes after gastrointestinal bleeding events. *LOS*, Length of stay.

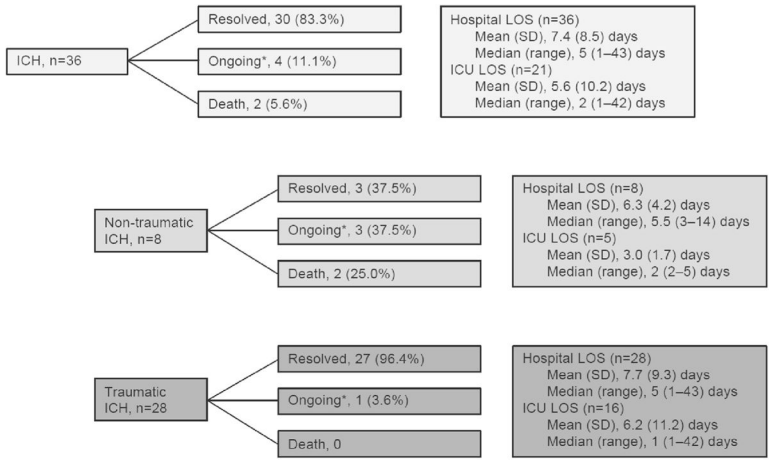

Figure 4.
Outcomes after intracranial hemorrhages.

Table 1

Study enrollment by site.

Site*	Investigator	Screened	Ineligible	Included (%)
Maimonides Medical Center	Christian Fromm, MD	26	5	21 (81)
Beth Israel Deaconess Medical Center	Michael Ganetsky, MD	67	31	36 (54)
Seton Dell Medical School	Truman J. Milling, MD	106	22	84 (79)
Stony Brook University Hospital	Adam Singer, MD	61	28	33 (54)
Brigham and Women's Hospital	Daniel J. Pallin, MD, MPH	24	7	17 (71)
Totals		284	93	191 (67)

* Maimonides Medical Center is an urban, community, tertiary care, teaching hospital in Brooklyn, NY, and a Level I adult and Level II pediatric trauma center. Beth Israel Deaconess Medical Center is a major teaching hospital of Harvard Medical School, a tertiary care center and Level I trauma center. Seton Dell Medical School Stroke Institute serves an 11-hospital (Seton Family of Hospitals) network in central Texas, including a Level I trauma center and pediatric trauma center. Stony Brook University Hospital is a suburban, tertiary care, Level I trauma center. Brigham and Women's Hospital is a 793-bed teaching affiliate of Harvard Medical School, a tertiary referral center and a Level I trauma center.

Table 2

Demographics and characteristics of the study population (N=191).

Characteristic	Categories	Values, No. (%)
Age, y	<65	21 (11)
	65–<75	45 (24)
	≥75	125 (65)
Sex	Men	98 (51)
	Women	93 (49)
Race	White	172 (90)
	Black	9 (4.7)
	Other	10 (5.2)
Ethnicity	Not Hispanic	169 (89)
	Hispanic	9 (4.7)
	Unknown	13 (6.8)
Insurance type	Public	147 (77)
	Private	25 (13)
	Uninsured	0
	Unknown	19 (9.9)
Any previous bleeding events	No	159 (83)
	Yes	32 (17)
Duration of treatment with DE, days	Mean (SD)	232.9 (243)
	Median (IQR)	152 (57–335)
Creatinine clearance, mL/min	>50	102 (56)
	30–50	52 (29)
	15–<30	25 (19)
	<15	2 (1.1)

DE, Dabigatran etexilate.

Table 3

Anatomic locations of major bleeding events (N=191).

Anatomic location	Total Patients, No. (%)
Gastrointestinal	
Total	118 (61.8)
Upper GI	43 (22.5)
Lower GI	65 (34.0)
Unknown GI location	10 (5.2)
Brain/intracranial	
Total	36 (18.8)
Nontrauma	8 (4.2)
Trauma	28 (14.7)
MVC	1 (0.5)
Fall	27 (14.1)
Unknown location*	1 (0.5)
Other†	36 (18.8)

MVC, motor vehicle crash.

*Unknown location of bleeding met the major bleeding criteria as defined by ISTH as fatal bleeding or symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, or bleeding causing a decrease in hemoglobin level of 20 g/L or more, or leading to transfusion of 2 or more units of whole blood or RBCs.

†Combined category of all other locations of bleeding; individual incidences of these events are all less than 1.7%.

Table 4

Therapeutic measures undertaken (“reversal” of anticoagulation) (N=191).

Measure	Total Patients, No. (%)
Hemodialysis	1 (0.5)
Fresh frozen plasma	47 (24.6)
Mean volume, mL (SD) *	1,297 (952)
Median volume, mL (IQR) *	1,237 (556–1,840)
Plasma cryoprecipitate	3 (1.6)
Mean volume, mL (SD) *	238 (18)
Median volume, mL (IQR) *	238 (225–250)
Blood coagulation factors	11 (5.8)
Recombinant factor VIIa	5 (2.6)
3FPCC	6 (3.1)
4FPCC (Kcentra) †	1 (0.5)
Vitamin K	2 (1.0)

3FPCC, 3-Factor prothrombin concentrate complex; *4FPCC*, 4-factor prothrombin concentrate complex.

* Some electronic medical records did not include volume.

† Kcentra was not available throughout the entire observation period and may not have been available at all centers.

Table 5

Measures undertaken to support volume of circulation (resuscitation) (N=191).

Measure	Total Patients, No. (%)
Fluids	139 (72.8)
Mean volume, mL (SD) *	1,219 (2,070)
Median volume, mL (IQR) *	215 (75–1,200)
Packed RBCs	99 (51.8)
Mean volume, mL (SD) *	1,073 (661)
Median volume, mL (IQR) *	975 (588–1,400)
RBCs (whole blood)	10 (5.2)
Plasma expanders: normal human serum albumin	2 (1.0)
Mean volume, mL (SD) *	500 (–)
Median volume, mL (IQR) *	500 (500–500)
Other treatment †	52 (27.2)

* Some electronic medical records did not include volume.

† Includes imaging, surgery, and medical procedures. Platelets were given as additional therapy to 11 patients (5.5%) with major bleeding events (mean volume 823 mL [SD 849]).