Comparison of Bleeding Events, Strokes, and Myocardial Infarctions on Warfarin or Dabigatran for Treatment of Atrial Fibrillation: Results of a Real-World Data Analysis

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BACKGROUND

Atrial fibrillation (AF) causes substantial morbidity and is associated with a 1.5- to 1.9-fold mortality risk in both genders across a wide range of ages (1). Therapy of choice for AF is anticoagulation with the objective to reduce the risk of [embolic] stroke without causing major bleedings. For a long time, Warfarin had been the only drug approved for the prevention of stroke in patients with AF.

Dabigatran is one of three new oral anticoagulants and has been associated with lower rates of stroke than Warfarin in trials of AF (2). However, large-scale evaluations in clinical practice were limited. Just recently a retrospective cohort study on claims data was published (3) and provided first insights in usual care settings (See figure 1).


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Outcomes of Dabigatran and Warfarin for Atrial Fibrillation in Contemporary Practice
A Retrospective Cohort Study

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Background: Dabigatran (150 mg twice daily) has been associated with lower rates of stroke than warfarin in trials of atrial fibrillation, but large-scale evaluations in clinical practice are limited.

Objective: To compare incidence of stroke, bleeding, and myocardial infarction in patients receiving dabigatran versus warfarin in practice.

Design: Retrospective cohort.

Setting: National U.S. Food and Drug Administration Sentinel network.

Patients: Adults with atrial fibrillation initiating dabigatran or warfarin therapy between November 2010 and May 2014.

Measurements: Ischemic stroke, intracranial hemorrhage, extracranial bleeding, and myocardial infarction identified from hospital claims among propensity score-matched patients starting treatment with dabigatran or warfarin.

Results: Among 25 289 patients starting dabigatran therapy and 25 289 propensity score-matched patients starting warfarin therapy, those receiving dabigatran did not have significantly different rates of ischemic stroke (0.80 vs. 0.94 events per 100 person-years; hazard ratio [HR], 0.92 [95% CI, 0.65 to 1.28]) or extracranial hemorrhage (2.12 vs. 2.63 events per 100 person-years; HR, 0.89 [CI, 0.72 to 1.09]) but were less likely to have intracranial bleeding (0.39 vs. 0.77 events per 100 person-years; HR, 0.51 [CI, 0.33 to 0.79]) and more likely to have myocardial infarction (0.77 vs. 0.43 events per 100 person-years; HR, 1.88 [CI, 1.22 to 2.90]). However, the strength and significance of the association between dabigatran use and myocardial infarction varied in sensitivity analyses and by exposure definition (HR range, 1.13 [CI, 0.78 to 1.64] to 1.43 [CI, 0.99 to 2.08]). Older patients and those with kidney disease had higher gastrointestinal bleeding rates with dabigatran.

Limitation: Inability to examine outcomes by dabigatran dose (unacceptable covariate balance between matched patients) or quality of warfarin anticoagulation (few patients receiving warfarin had available international normalized ratio values).

Conclusion: In matched adults with atrial fibrillation treated in practice, the incidences of stroke and bleeding with dabigatran versus warfarin were consistent with those seen in trials. The possible relationship between dabigatran and myocardial infarction warrants further investigation.

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Figure 1: *Recently published FDA-Sentinel study.*
Source: Literature (3)

OBJECTIVES

Our study intended to replicate findings of a recently published retrospective cohort study on data identified from hospital claims (FDA Sentinel program) to answer the following questions:

- Can the results of the FDA-Sentinel study comparing Warfarin and Dabigatran be replicated with electronic medical records (EMR)?
- Are there any flavors which the use of EMR can add as compared to a mainly claims-based real-world study?

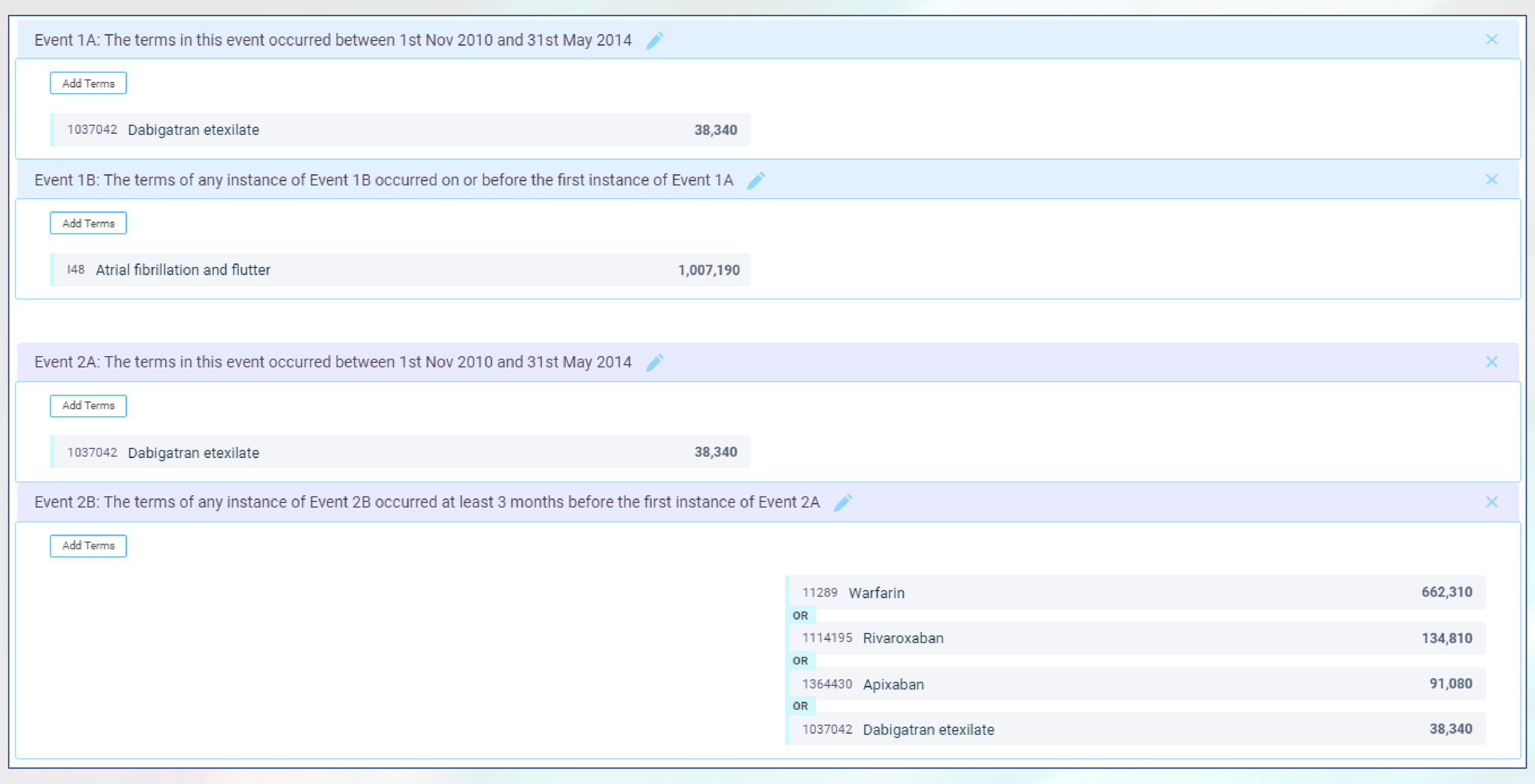
METHODS

Data Source: We used TriNetX, a global health research network with the ability to perform real-time analyses on EMRs of >43 million patients, predominantly in the US (numbers as of January 2018). The network contained 1,007,140 patients with AF (ICD10 code I48), of which 88,000 started on Warfarin or Dabigatran between Nov. 2010 and May 2014 (the time frame of the Sentinel study (3)).

Patient Cohorts and Definition: Non-rheumatic cardiac valve diseases, kidney transplant status, and end stage renal disease were excluded, which left a total of 49,610 patients (Warfarin: 42,130; Dabigatran: 7480).

Outcomes:

- **Cardiovascular Event**: Myocardial Infarction (ICD10 code I21) or Stroke (ICD10 code I63).
- **Major Bleeding**: Any of a series of 23 different ICD10 codes representing intracranial, pericardial, esophageal, gastrointestinal, oropharyngeal-nasal, or respiratory bleeding or internal hemorrhage.


Event 1A: The terms in this event occurred between 1st Nov 2010 and 31st May 2014
Add Terms
1037042 Dabigatran etexilate 38,340
Event 1B: The terms of any instance of Event 1B occurred on or before the first instance of Event 1A
Add Terms
I48 Atrial fibrillation and flutter 1,007,190
Event 2A: The terms in this event occurred between 1st Nov 2010 and 31st May 2014
Add Terms
1037042 Dabigatran etexilate 38,340
Event 2B: The terms of any instance of Event 2B occurred at least 3 months before the first instance of Event 2A
Add Terms
11289 Warfarin 662,310
OR
1114195 Rivaroxaban 134,810
OR
1364430 Apixaban 91,080
OR
1037042 Dabigatran etexilate 38,340


CANNOT Have
Search Term...
I34 Nonrheumatic mitral valve disorders 647,770
OR
I35 Nonrheumatic aortic valve disorders 438,020
OR
02RF Aortic valve 38,290
OR
02RG Mitral valve 9,780
OR
Z94.0 Kidney transplant status 87,340
OR
N18.6 End stage renal disease 214,950

Figure 2: *Cohort definitions (example for Dabigatran), first anticoagulation therapy between Nov. 2010 and May 2014 due to AF (ICD10 code I45), no valvular heart disease.*

RESULTS

- Mean age in the Dabigatran group was 72 years with 34% female patients versus 76 years and 41% in the Warfarin group, respectively, which does not represent a clinically relevant difference in this context.
- Mean INR in the Dabigatran group was 1.37 units, compared to 1.85 units in the Warfarin group, which supports the appropriate selection and reasonable compliance within the cohorts, especially quality of Warfarin anticoagulation (See figure 3).
- 170 (2.27%) patients experienced a major bleeding event under Dabigatran, compared to 5,250 (12.46%) with Warfarin.
- 910 (12.2%) patients experienced a cardiovascular event under Dabigatran, compared to 6,705 (15.9%) with Warfarin.
- For myocardial infarction as component of the CV event, the respective numbers were 320 (4.3%) and 2,620 (6.2%), respectively.

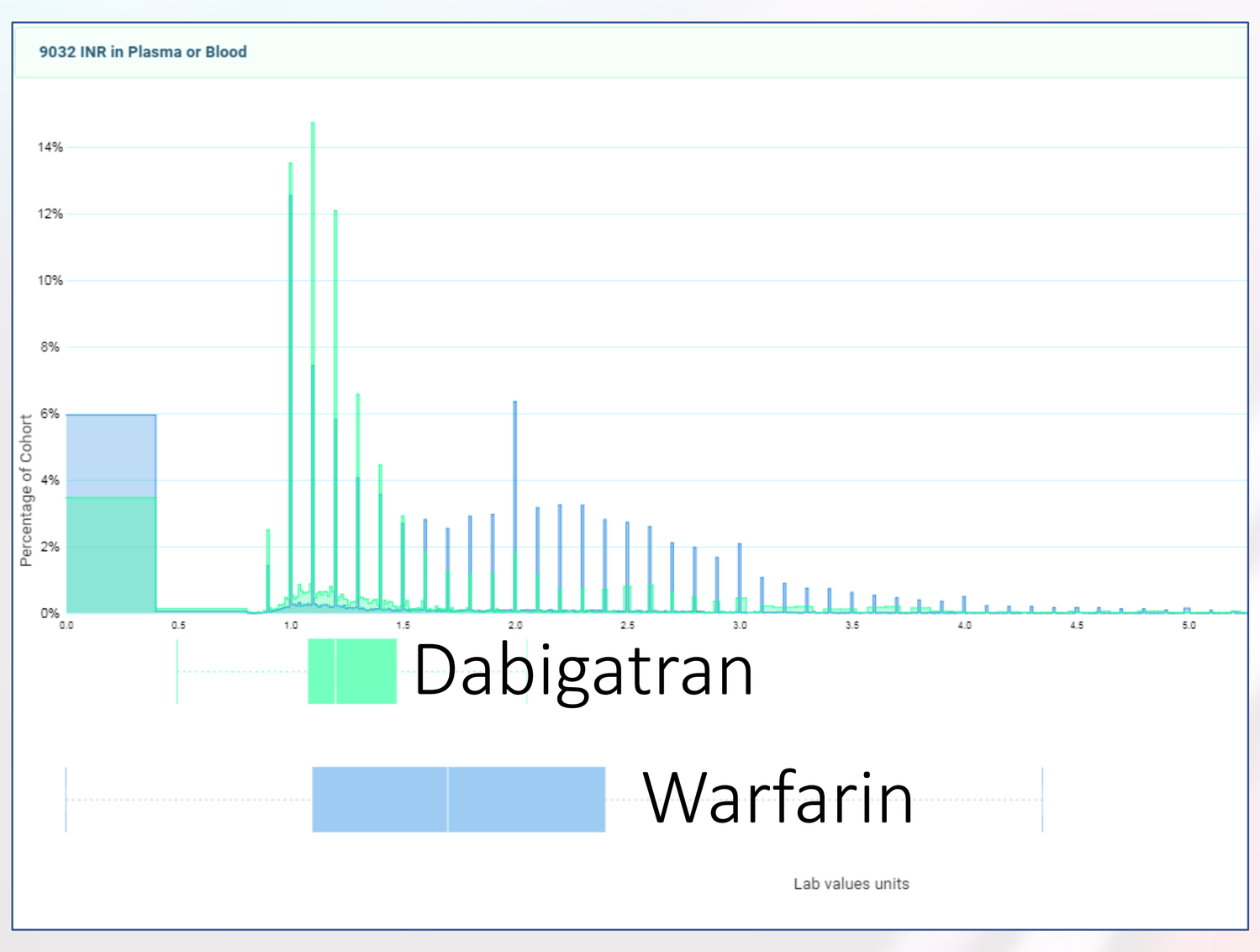
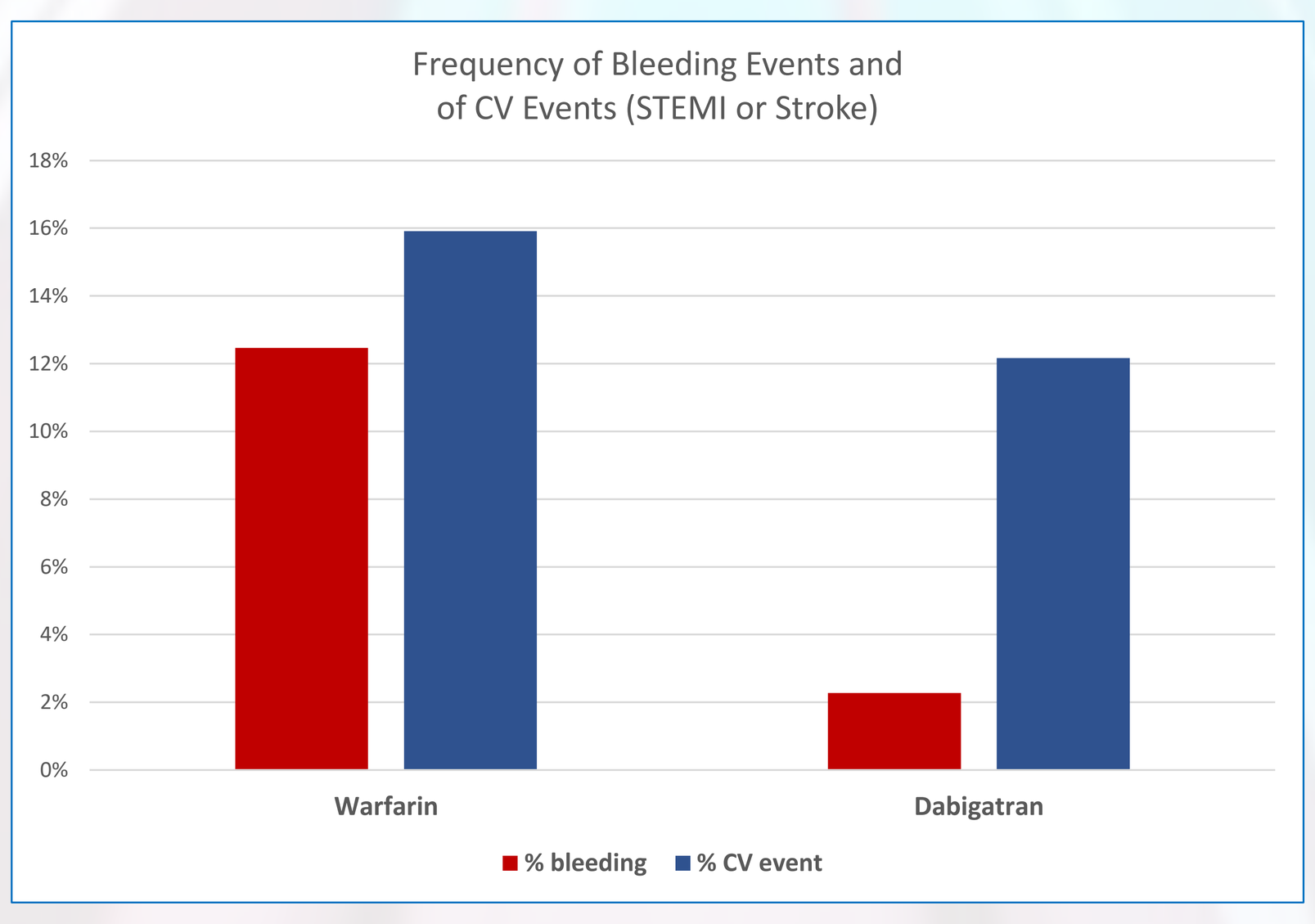


Figure 3: *INR lab test as internal validation of cohort selection.*



	Warfarin	Dabigatran	RR	p
n	42130	7480		
mean age	76	72		
% female	41%	34%		
n bleeding	5250	170		0.0001
% bleeding	12.46%	2.27%	0.18	
n CV event	6705	910		0.0001
% CV event	15.9%	12.2%	0.76	
n STEMI only	2620	320		
% STEMI only	6.2%	4.3%	0.69	

Figure 4 & Table 1: *Results, bleeding and cardiovascular events, after starting Dabigatran or Warfarin for AF.*

DISCUSSION

- INR levels in the Warfarin group showed an overall satisfactory anticoagulation in the Warfarin group.
- Dabigatran patients had significantly fewer bleeding events and significantly fewer cardiovascular events than patients with Warfarin.
- A previously reported signal of potentially higher rates of myocardial infarctions under Dabigatran (3) could not be verified in this data set.

LIMITATIONS

- We did not calculate exposure by person-years. Continuous exposure to the respective anticoagulants was assumed.
- The Dabigatran cohort was slightly younger and had slightly less cardiovascular pre-existing conditions. Ideally, this would have been addressed by censoring or by matching (e.g., propensity score). However, as a real-world study, this shows the current actual use of the two products which includes not only the mechanism of action of the molecule in isolation, but also the prescribing behavior, the medication compliance, the patient population and their concomitant risk factors.

CONCLUSIONS

- The frequency of bleeding events and of CV events (STEMI or stroke) was lower in the Dabigatran group than in the Warfarin group.
- This real-world study conducted on EMRs of large unmatched populations in real practice could confirm the results of randomized clinical trials and of an FDA sponsored, mainly claims-based national surveillance system.
- The access to laboratory values, by using EMR rather than claims data, added value for internal validation, i.e., coagulation parameters.

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