Comparing the Real-World and Clinical Trial Bleeding Rates Associated with Anticoagulation Treatment for Atrial Fibrillation

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INTRODUCTION

- Atrial fibrillation (AF) is the most common cardiac arrhythmia, increasing risk of stroke five-fold.[1] Over 95% of the cases in the United States are non-valvular atrial fibrillation (NVAF).[2]
- Stroke prevention with warfarin, an oral anticoagulant, has been the standard therapy for patients with AF. Recently, direct oral anticoagulants (DOACs) were included in the treatment of NVAF.[3]
- Clinical trials (CT) are considered the "gold standard" for generating clinical evidence; however, due to their strict inclusion and exclusion criteria, CT results may not be generalizable to real-world clinical practice.
- There is increasing interest in the use of real-world data (RWD) for decision-making, especially from regulators, as real-world studies can provide insights into the effectiveness and safety of drugs in clinical practice and inform the design of prospective trials.[4]

OBJECTIVE

- To bridge the gap between CT data and real-world clinical practice by examining population characteristics and assessing bleeding outcomes in both settings.

METHODS

Data Source

- The CT data cohort was derived from a pooled dataset of five open-label Phase 3 and 4 studies from the Medidata Enterprise Data Store (MEDS)[5] completed between 2014 and 2019.
  - Patients with AF or NVAF treated with DOACs with an available medical history were included in this study.
  - Data was standardized to the Clinical Data Interchange Standards Consortium Study Data Tabulation Model (CDISC SDTM) for pooling.
  - Study-specific exclusions ranged from patients with active, high-risk, or history of bleeding; transient or reversible AF; thrombosis; stroke and/or recent myocardial infarction.
- The RWD cohort was identified from HealthVerity Private Source 20, a closed administrative medical and pharmacy claims database that includes commercially insured patients, and those with Medicare Advantage.
  - Adult patients (≥18 years) were required to have ≥1 claim(s) with diagnosis of AF and ≥2 prescriptions (on different days) for DOAC (dabigatran, rivaroxaban, apixaban, and edoxaban) between January 01, 2015 and September 30, 2019.
  - Patients were required to have ≥12 months continuous medical enrollment prior to first DOAC prescription (index date). No minimum follow-up was required.

Study Measures

Outcomes of interest

- The presence of major bleed in the respective populations, including time to first major bleed during the 12 months post-DOAC treatment initiation, and the rate of bleeding events per 100 patient-years (PY) were assessed.
- Subgroup analysis was performed with stratification by gender, age, and reported or estimated HAS-BLED score.

METHODS

Bleeding definitions[6-9] and scoring systems[10]

Major Bleed	Gastrointestinal bleed, intracranial hemorrhage, and other major hemorrhage
Minor Bleed	Bleeds classified as non-major
Any Bleed	Any major or minor bleed
HAS-BLED	A scoring system that calculates the risk of major bleeding in patients with AF[9]
CHA_2DS_2-VASc	A validated tool to predict the risk of stroke and systemic emboli in patients with AF[10]

Statistical Analysis

- Kaplan-Meier curves were used to estimate time to first major bleed during the 12 months post-DOAC treatment initiation overall for both cohorts and by subgroup.
- Stratified by the subgroups with log rank tests for intragroup stratifications (not comparing CT and RWD directly — see limitations).
- Baseline characteristics were compared across cohorts using the chi-squared, and student's t test for independent groups, and Mann-Whitney U test as appropriate. A p-value <0.05 was considered statistically significant.
- All statistical analyses were performed using R version 4.0.2.

RESULTS

Study Cohort (Table 1)

- The CT cohort comprised 3,207 AF patients treated with DOACs. A subset of this cohort (n=2,217, 69% of full cohort) had HAS-BLED and CHA2SD2-VASc scores available.
- The RWD cohort included 61,214 eligible patients diagnosed with AF and treated with DOACs.

Table 1. Baseline characteristics

	CT cohort	RWD cohort	p-value
Total, N	3,207	61,214	
Age, mean years (SD)	65.3 (10.7)	72.2 (11.9)	<0.001
Male, %	71	53	<0.001
HAS-BLED scores[a], mean (SD)	1.1 (0.9)	2.1 (1.0)	<0.001
CHA_2DS_2-VASc score[a], mean (SD)	2.9 (1.7)	4.0 (1.9)	<0.001
SSE, n (%)	152 (4.7)	4,188 (6.8)	0.012
Congestive heart failure, n (%)	1,063 (33.1)	21,620 (35.3)	<0.001
Renal disease, n (%)	161 (5.0)	18,551 (30.3)	<0.001
Coronary artery disease, n (%)	578 (18.0)	26,973 (44.0)	<0.001
Hypertension, n (%)	2,429 (75.7)	52,990 (86.6)	<0.001
Diabetes mellitus, n (%)	728 (22.7)	22,472 (36.7)	<0.001
Peripheral arterial disease, n (%)	107 (3.3)	9,005 (14.7)	<0.001

SSE, stroke/systemic embolism
[a] n=2,217 patients in CT cohort.

RESULTS

Patient Characteristics (Table 1)

- Compared to patients in the CT cohort:
  - Patients in the RWD cohort were significantly older.
  - Patients in the RWD cohort had significantly higher HAS-BLED scores and a significantly higher proportion had a history of stroke/systemic embolism (SSE).
  - A significantly higher proportion of patients in the RWD cohort had comorbidities.

Incidence of First Bleed

- Overall, patients in the RWD cohort had a higher incidence of bleeding events during the 12-month post-DOAC treatment, including major bleed events (CT: 10.69 vs. RWD: 18.97 per 100 PY) and minor bleed events (CT: 30.58 vs. RWD: 51.55 100 PY), compared to patients in the CT cohort **(Table 2).**

Table 2. Overall analysis: Bleeding events during the 12 months post-DOAC treatment

	CT cohort	RWD cohort
Any, event per 100 PY	40.3	59.3
Minor[a], event per 100 PY	30.6	51.6
Major, event per 100 PY	10.7	19.0
Gastrointestinal bleed	3.8 (35.5)	7.6 (40.1)
Intracranial bleed[b]	0.8 (7.2)	0.8 (4.1)
Other major bleed[c]	6.1 (57.4)	10.5 (55.8)

[a] Same-day multiple bleeds were categorized in the following priority: 1. intracranial bleed; 2. GI bleed; 3. other major bleed.
[b] In the RWD cohort, intracranial bleed was defined as intracranial bleed with (0.4 [2.0]) or without (0.4 [2.1]) codes for hemorrhagic stroke.
[c] Includes RWD hemorrhagic stroke. If RWD hemorrhagic stroke was included in intracranial bleed, bleeding event rates for intracranial bleed and other major bleed would be 1.7 (9.2) and 9.6 (50.8), respectively.

Table 3. Subgroup analysis: Major bleed rates during the 12-months post-DOAC treatment

	CT cohort	RWD cohort
Female, event per 100 PY (%)	10.8 (29.4)	22.3 (47.0)
Male, event per 100 PY (%)	10.6 (70.5)	16.1 (53.0)
Age, event per 100 PY (%)		
18-64	7.8 (48.7)	13.0 (30.6)
65-74	11.6 (34.2)	18.6 (28.6)
75-78	15.7 (9.3)	22.8 (11.9)
79+	14.6 (7.8)	24.7 (28.7)
HAS-BLED scores, event per 100 PY (%)		
0	9.1 (71.9)	10.1 (25.2)
1	11.3 (21.2)	17.9 (40.4)
2	17.9 (5.4)	25.5 (25.9)
3+	6.5 (1.2)	35.6 (8.3)

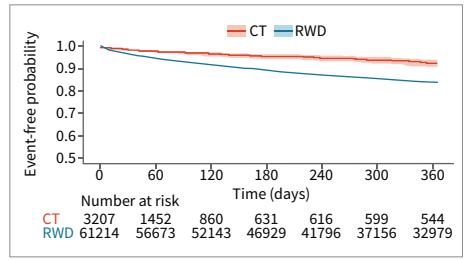
Note: Percentages refer to the proportion of patients in each subgroup.

- In most subgroups, patients in the RWD cohort had a higher incidence of bleeding events during the 12 months post-DOAC treatment compared to patients in the CT cohort (**Table 3**).

Assessing Major Bleeding Risk in CT and Real-world Settings

- Survival analysis showed that patients in the RWD cohort had a higher risk of major bleeding during the 12 months post-DOAC treatment compared to the CT cohort (**Figure 1**).
- Differences in the bleeding rate varied by HAS-BLED scores in the RWD cohort and CT cohort (**Figure 2**).

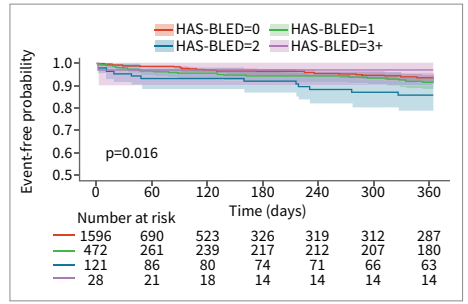
Figure 1. Major bleed risk 12 months after DOAC treatment



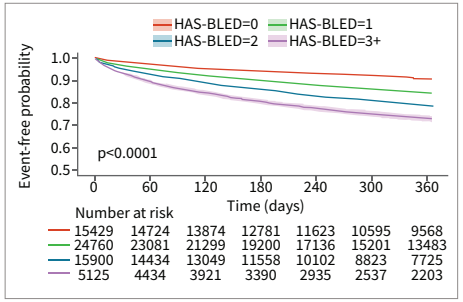
Note: Survival probability scale (vertical axis) shown from 0.5 to 1.

Figure 2. Major bleed risk stratified by HAS-BLED scores

A. CT cohort



B. RWD cohort



Note: Survival probability scale (vertical axis) shown from 0.5 to 1.

LIMITATIONS

- P-values were included in Table 1 to compare baseline characteristics across CT and RWD populations. The large sample size differences between CT and RWD populations should be considered when interpreting these values.
- Patients in the RWD cohort may have had bleeding events prior to the baseline period, which may result in higher HAS-BLED scores than those estimated compared to patients in the CT cohort.
- Additional differences may exist due to differing data sources and methods of calculation.

CONCLUSIONS

- Patients with AF receiving DOACs in the real world were older, had higher HAS-BLED and CHA2DS2-VASc scores, and had more comorbidities than patients enrolled in CTs.
- Patients in the RWD cohort had a numerically higher incidence of bleeding events and increased risk of major bleeds during the 12 months post-DOAC treatment compared to the CT cohort.
- Higher risk of bleeding, assessed by HAS-BLED scores, was associated with significantly increased risk of major bleed in both cohorts.
- These results suggest that CT data underestimate the burden of bleeding in real-world clinical practice and indicate that elderly patients and high-risk populations are under-represented in CTs compared to real-world studies.
- The evaluation of CT data and RWD provides an opportunity to improve future CT design and better align with real-world practice by identifying populations with less representation and subgroups that may influence outcomes.

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