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Short communication

Long-term stroke and bleeding risk in patients with atrial fibrillation treated with oral anticoagulants in contemporary practice: Providing evidence for shared decision-making

Peter A. Noseworthy [a,b,c,*], Xiaoxi Yao [b,d,e], Bernard J. Gersh [c], Ian Hargraves [a], Nilay D. Shah [a,b,d,e], Victor M. Montori [b,d]

[a] Knowledge and Evaluation Research Unit, Mayo Clinic, Rochester, MN, United States
[b] Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, Rochester, MN, United States
[c] Heart Rhythm Section, Cardiovascular Diseases, Mayo Clinic, Rochester, MN, United States
[d] Division of Health Care Policy and Research, Department of Health Sciences Research, Rochester, MN, United States
[e] Optum Labs, Cambridge, MA, United States

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ABSTRACT

Background: Oral anticoagulation is recommended as a lifelong therapy for most patients with atrial fibrillation (AF). However, data on long-term outcomes in clinical practice on these drugs are scarce, particularly for the recently approved agents. We aimed to describe differences in characteristics between patients in everyday practice and those enrolled in the pivotal trials, and to report long-term outcomes on oral anticoagulation in practice.
Methods: We performed a retrospective cohort analysis using a large U.S. administrative database to identify patients with AF initiating oral anticoagulation and examine incident stroke (effectiveness endpoint, including ischemic stroke and systemic embolism) and major bleeding (safety endpoint).
Results: We identified 107,373 patients with AF initiating anticoagulants 7/1/2006-6/30/2016. These patients were more likely to be elderly, female, or to have advanced kidney disease in comparison to those enrolled in the trials. The event rates for major bleeding (3.1%, 2.8%, 4.0% and 4.9%/year for in apixaban-, dabigatran-, rivaroxaban- and warfarin-treated patients, respectively) were higher than those observed in trials. The event rates for stroke 0.9%, 1.0%, 0.9% and 1.4%/year the four drug cohorts), were similar to the trials. The three-year risk of stroke was 2.3%, 2.1%, 2.3% and 3.5%, and the three year risk of major bleeding was 5.4%, 7.0%, 8.2%, and 11.7% in the four drug cohorts.
Conclusions: Clinical trials represent a narrow spectrum of the general AF population. The trials may underestimate the bleeding risk observed in practice. This study provides important data to help clinicians communicate expected outcomes to patient during shared decision-making.

1. Introduction

Oral anticoagulation, with either warfarin or a non-vitamin K antagonist oral anticoagulant (NOAC), is recommended for stroke prevention for most patients with atrial fibrillation (AF). When making anticoagulation decisions, the most recent U.S. guidelines made a new class I recommend that "antithrombotic therapy should be individualized based on shared decision-making" after discussing the risks and patient's preferences [1]. However, it is often challenging for clinicians to communicate expected outcomes to patients due to lack of data, particularly for the recently approved NOACs. For instance, the Phase III NOAC clinical trials provided long-term risk up to 2-3.5 years of follow up [2–5]. The time frame of in observational studies was even shorter, approximately 1-2.5 years [6–8]. Extrapolation of absolute risks from the idealized trial setting to practice is also difficult because the patient characteristics and realized outcomes may differ from the trials. Furthermore, the trials and most observational studies report risks as event rates per 100 person-years [2–5]. Because oral anticoagulation is generally recommended as a lifelong therapy, a patient's concept of risk should be framed over a longer time horizon.

As such, we aimed to describe differences in patient characteristics in pivotal NOAC trials and everyday practice, and to report long-term outcomes on oral anticoagulation.

* Corresponding author at: Division of Cardiovascular Diseases, Mayo Clinic College of Medicine, Rochester, MN 55902, United States.
E-mail address: noseworthy.peter@mayo.edu (P.A. Noseworthy).

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2. Methods and results

Using a large U.S. administrative claims database, OptumLabs Data Warehouse, which contains privately insured and Medicare Advantage enrollees of all ages and races from all 50 states, we identified adult patients (≥18 years) with AF who were new users of oral anticoagulants between July 1st, 2006 and June 30th, 2016, including warfarin, apixaban, dabigatran, or rivaroxaban. Because edoxaban was approved in 2015, we did not assess edoxaban in this study. We used the fill dates and days supplied per prescription to determine patients' treatment episodes. Patients were considered as continuing on treatment as long as they had another fill of the same medication within 90 days of the end of the last treatment episode. We required patients to have at least 12 months of continuous enrollment in health insurance, defined as the baseline, used to capture baseline characteristics. Patients were censored at the end of study period (i.e., 6/30/2016), discontinuation of the medication, switch to another oral anticoagulant, or the end of enrollment in health insurance, whichever occurred first.

The outcomes were inpatient admission for either stroke (effectiveness endpoint, including ischemic stroke and systemic embolism) or major bleeding (safety endpoint). We also used Kaplan-Meier survival analysis to calculate the cumulative incidence of each outcome. Because the first NOAC was approved in 2010, we calculated 3-year cumulative risk for each drug, but 5-year risk for warfarin-treated patients only. In this analysis, we stratified patients by CHA_2DS_2-VASc (the risk score endorsed by contemporary guidelines) for stroke risk and by HAS-BLED for bleeding risk, as these risk scores are more commonly used in contemporary guidelines and practice. We also plotted Kaplan-Meier curves for major bleeding, and overlaid the curves reported in the trials. When comparing outcomes to trials, we calculated the event rates per 100 years and stratified patients based on the $CHADS_2$ score (a stroke risk score used in the trials). All the analyses were based on the time to the first event, an approach used in the trials. The study was exempt by the Mayo Clinic Institutional Review Board for approval as we used only pre-existing, de-identified data.

We identified 107,373 patients with AF treated with warfarin, apixaban, dabigatran, or rivaroxaban. The Table 1 provides the patient characteristics the long-term (3-year) risk of stroke and bleeding (overall and stratified by CHA_2DS_2-VASc and HAS-BLED scores). In addition, the five-year cumulative risk of ischemic stroke or systemic embolism was 5.5% (5.0%, 6.0%) overall, and 3.1% (2.5%, 3.9%), 4.8% (3.9%, 5.8%), and 8.5% (7.5%, 9.6%) stratified by CHA_2DS_2-VASc of ≤3, 4, and ≥5, respectively. The five-year cumulative risk of bleeding was 16.6% (15.8%, 17.4%) overall, and 8.3% (7.0%, 9.9%), 15.0% (13.8%, 16.3%), 19.9% (18.4%, 21.6%), and 24.4% (22.2%, 26.8%) stratified by HAS-BLED scores of 0 or 1, 2, 3, and ≥4, respectively. The Fig. 1 demonstrates the cumulative incidence of major bleeding occurring on each of the anticoagulants in our cohort and the trials. The major bleeding risk in our cohort was particularly high in warfarin-treated patients, even when compared to that seen in ROCKET AF and ENGAGE AF-TIMI 48 which primarily enrolled high-risk patients. A linked "data-in-brief" publication [9], demonstrates that, in comparison to the trials overall, the event rates per 100 person years for stroke were largely similar, whereas the bleeding risk was higher in practice, particularly in high-risk patients with $CHADS_2$ ≥ 3. In addition to the differences in age, gender and baseline risk of stroke relative to the clinical trials, our cohort included 10.4% of patients with stage 4-5 chronic kidney disease (12.5%, 6.3%, 7.9% and 11.2% in apixaban-, dabigatran, rivaroxaban- and warfarin-treated patients, respectively). Overall 17.4% of NOAC-treated patients received a reduced dose NOAC (19.5% of apixaban-treated patients, 9.3% of dabigatran-treated patients and 20.5% of rivaroxaban-treated patients). Among 7873 warfarin-treated patients with linked laboratory data (in whom the time in therapeutic rage [TTR] can be calculated), the median TTR was 45% (IQR 20%-67%).

3. Comment

Patients treated in routine clinical practice differ in many respects from those studied in the pivotal clinical trials. In particular, elderly patients and women were under-represented in the trials. For example, nearly half of the patients in our study were 75 years or older, a proportion larger than that in any pivotal NOAC trials. There are also important differences in baseline risk profile. One in ten of our patients had stage 4-5 chronic kidney disease, a group who were largely excluded from the trials and have a particularly high risk of both stroke and bleeding. Two of the trials, ROCKET AF and ENGAGE AF-TIMI 48, excluded patients with low-to-moderate risk of stroke, i.e., those with $CHADS_2$ 0-1. The ARISTOTLE and RE-LY trials also had very few of these patients. However, in practice, about 7.4% and 22.1% of patients have $CHADS_2$ of 0 and 1, respectively, and many of these patients may be candidates for oral anticoagulation based on current guidelines which employ the CHA_2DS_2-VASc score.

Our findings also highlight a potentially important difference in bleeding risk observed in practice compared to the trials. Although the risks of stroke were largely similar, the risks of bleeding were higher in practice, particularly in those with high baseline risks. This finding

Table 1
Baseline characteristics and long-term outcomes among anticoagulated patients in OLDW.

	Warfarin	Apixaban	Dabigatran	Rivaroxaban
	(*N* = 68,804)	(*N* = 12,949)	(N-9412)	(*N* = 16,208)
Baseline characteristics				
Age, median	73 (64-80)	74 (67, 81)	69 (61-77)	71 (63-78)
Age ≥ 75 yr (%)	45.2%	47.5%	31.9%	37.4%
Female (%)	42.7%	48.0%	38.7%	41.2%
HTN	85.7%	87.2%	83.5%	83.9%
DM	36.9%	34.8%	32.4%	32.6%
CHF	37.9%	31.4%	25.0%	26.5%
Prior TE	16.7%	15.2%	12.6%	12.0%
Prior Bleeding	9.8%	8.3%	7.3%	7.2%
Anemia	33.1%	28.1%	22.0%	23.6%
CHA_2DS_2-VACs				
≤3	41.4%	42.0%	56.4%	52.4%
4	21.1%	22.0%	19.6%	20.6%
≥5	37.4%	35.9%	23.9%	27.0%
HAS-BLED				
0,1	21.5%	19.5%	31.6%	26.8%
2	34.2%	36.3%	36.3%	37.1%
3	27.3%	27.3%	21.9%	24.5%
≥4	17.1%	16.8%	10.2%	11.6%
	3-Year Cumulative Risk			
Long-term outcomes				
Ischemic stroke or SE				
Overall	3.5% (3.2%, 3.7%)	2.3% (1.2%, 4.5%)	2.1% (1.5%, 2.8%)	2.3% (1.6%, 3.1%)
CHA_2DS_2-VACs				
≥3	1.8% (1.5%, 2.1%)	1.3% (0.4%, 4.5%)	1.8% (1.1%, 2.9%)	1.0% (0.4%, 2.4%)
4	3.1% (2.6%, 3.7%)	1.9% (0.7%, 5.1%)	1.1% (0.6%, 2.3%)	2.6% (1.4%, 4.6%)
≥5	5.5% (5.0%, 6.1%)	4.1% (1.4%, 12.0%)	3.4% (2.3%, 5.1%)	4.4% (3.0%, 6.5%)
Major bleeding				
Overall HAS-BLED	11.7% (11.2%, 12.1%)	5.4% (4.4%, 6.7%)	7.0% (5.9%, 8.2%)	8.2% (7.1%, 9.4%)
0,1	5.3% (4.6%, 6.0%)	1.2% (0.5%, 2.8%)	3.0% (1.7%, 5.3%)	4.5% (2.9%, 7.1%)
2	9.7% (9.1%, 10.4%)	3.8% (2.6%, 5.6%)	7.2% (5.5%, 9.3%)	7.4% (5.9%, 9.3%)
3	14.3% (13.3%, 15.2%)	8.5% (5.7%, 12.5%)	7.9% (5.8%, 10.7%)	10.3% (8.1%, 13.0%)
≥4	19.6% (18.2%, 21.1%)	9.1% (7.0%, 11.8%)	13.2% (9.4%, 18.5%)	13.3% (10.0%, 17.5%)

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