Underuse of Full Dose Factor Xa Inhibition in Atrial Fibrillation: Insights the Stroke Prevention and Rhythm Interventions in Atrial Fibrillation (SPRINT-AF) Registry

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BACKGROUND

- Stroke prevention with oral anticoagulation (OAC) is an important treatment goal for patients with atrial fibrillation (AF), particularly those at elevated risk.
- Recent clinical trials with the factor Xa inhibitors rivaroxaban (ROCKET-AF) and apixaban (ARISTOTLE, AVERROES) have demonstrated comparable or superior efficacy compared to warfarin (or aspirin) for stroke prevention.
- In these trials, reduced doses of factor Xa inhibitors were used in patients with moderate renal dysfunction or in those considered to be at high risk for bleeding. Between 5 and 10% of the study populations met criteria for reduced dosing.
- It is unknown whether or not reduced dose factor Xa inhibition is used appropriately in clinical practice.
- To answer this question, we used data from the **S**troke **P**revention and **R**hythm **Int**erventions in **A**trial **F**ibrillation (SPRINT-AF) registry.

SPRINT-AF (PHASE 1): STUDY OBJECTIVES

PRIMARY

- To determine how Canadian physicians assess stroke risk in adults with atrial fibrillation and make therapeutic decisions around oral anticoagulation.

SUB-ANALYSIS

- To estimate the proportion of AF patients eligible for reduced-dose factor Xa inhibition, and to determine if this is congruent with clinical trial populations.

INCLUSION CRITERIA

- Documentation of AF (based on a 12-lead electrocardiogram (ECG), rhythm strip, or from device interrogation) within the past 36 months.
- The patient must have been assessed by the participating physician within 12 months from the date of enrollment.
- Age ≥ 18 years.

EXCLUSION CRITERIA

- Presence of prosthetic heart valve or significant valvular heart disease (defined as: mitral stenosis, moderate or severe aortic stenosis, or severe mitral regurgitation).
- Active malignancy.
- Life expectancy < 12 months.
- An existing clinical indication for OAC treatment other than AF (e.g. venous thromboembolism, hypercoagulable disorders)
- Prior participation in an OAC randomized trial.

METHODS

STUDY DESIGN

- Phase 1 of SPRINT-AF was a multicenter, cross-sectional, retrospective study involving 936 patients from 109 practices in 10 Canadian provinces.
- Subjects were recruited from December 1, 2012 to July 31, 2013.
- During the study period, dabigatran and rivaroxaban were included in provincial formulary coverage plans in all Canadian provinces. There was limited provincial formulary coverage for apixaban during the study period.
- Eligibility criteria to qualify for formulary coverage of NOAC agents varied amongst provinces.

METHODS

- We applied the reduced dosing criteria in ROCKET-AF and ARISTOTLE/AVERROES to the SPRINT-AF patient population to determine what proportion of SPRINT-AF patients would be eligible for reduced dose factor Xa inhibitor therapy.
- We compared these findings to Canadian IMS sales data for the same period of time for rivaroxaban and apixaban, when prescribed for stroke prevention in atrial fibrillation.
- SPRINT-AF patients with a $CHADS_2$ score of zero were excluded from the analysis.

RESULTS

Table 1. Baseline demographics of patients with $CHADS_2$ ≥1 (n = 846/936) in the SPRINT-AF cohort

Clinical variable (n (%), median (IQR))	SPRINT-AF Cohort $CHADS_2$ ≥1 (n=846/936)
Male	517 (61.1%)
Caucasian	733 (87%)
Age	77.1 (69.5, 83.1)
Age ≥ 75	491 (58%)
Hypertension	689 (81.4%)
Dyslipidemia	542 (64.1%)
Diabetes	277 (32.7%)
History of smoking	386 (45.6%)
History of CAD	223 (26.4%)
Stroke or TIA	140 (16.5%)
PAD	50 (5.9%)
Congestive heart failure	176 (20.8%)
New AF diagnosis	27 (3.2%)
Non-paroxysmal AF	575 (71.6%)
$CHADS_2$ ≥2	603 (71.3%)
CHA_2DS_2 –VASC ≥2	793 (93.7%)
HAS-BLED	
0	58 (6.9%)
1 or 2	667 (79.5%)
≥3	114 (13.6%)

CAD, coronary artery disease; IQR, interquartile range; PAD, peripheral arterial disease; TIA, transient ischemic attack.

RESULTS

- The SPRINT-AF patient population was comparable to the patient populations in ROCKET-AF, ARISTOTLE and AVERROES (Table 2).

Table 2. Comparison of the SPRINT-AF cohort (n=936) to major OAC RCT's

Clinical factor (% or mean (IQR))	SPRINT–AF	ROCKET-AF	ARISTOTLE	AVERROES
Male	62.1%	60.3%	64.7%	58.5%
Age	75.7 (67.5, 83)	73 (65, 78)	70 (63, 76)	70 ± 9.5
Hypertension	73.6%	90.5%	87.4%	86.5%
Diabetes	29.7%	39.9%	24.9%	19.5%
Stroke or TIA	15%	54.8%	19.4%	13.5%
HF	18.8%	62.5%	35.5%	39%
Previous MI	16.2%	17.3%	14.2%	–
Persistent/Permanent AF	70.3%	82.1%	84.7%	73%
$CHADS_2$ ≥2	64.5%	100%	66.0%	63.5%
GFR (mL/min²)	64 (56, 80)	67 (52, 86)	16.5% had a CrCl ≤50 ml/min	30.3% had a CrCl <60 ml/min
AP use	27%	36.5%	32.8%	-

MI indicates myocardial infarction; AP, antiplatelet; GFR, glomerular filtration rate; HF, heart failure.

- In ROCKET-AF, reduced-dose rivaroxaban (15 mg od vs. 20 mg od) was used for patients with an estimated creatinine clearance of 30-49 mL/min, representing 10.3% of the ROCKET-AF population.
- In ARISTOTLE and AVERROES, reduced-dose apixaban (2.5 mg bid vs. 5 mg bid) was used for patients with any 2 of the following criteria: an age ≥80 yr, a body wt. ≤60 kg, or serum creatinine ≥1.5mg/dL.
- 4.6% of ARISTOTLE participants and 6.5% of AVERROES participants met these criteria.
- When we applied the reduced-dose criteria from ROCKET-AF to the SPRINT-AF population, we found that 11.8% of SPRINT-AF participants would be eligible for reduced-dose rivaroxaban.
- When we applied the reduced-dose criteria from ARISTOTLE and AVERROES to the SPRINT-AF population, we found that 8.7% of SPRINT-AF participants would be eligible for reduced-dose apixaban.

- Canadian sales data for factor Xa inhibitors during this time period revealed that approximately one third of prescriptions were for reduced doses (Table 3).
- Assuming that SPRINT-AF is representative of the general AF population in Canada, it is likely that a substantial number of patients are inappropriately receiving reduced dose factor Xa inhibition for stroke prevention.

Table 3. Canadian IMS sales data showing distribution by dose for rivaroxaban and apixaban during the same study period as phase 1 of SPRINT –AF (Dec 2012 to July 2013)

Factor Xa inhibitor	Reduced Dose	Full Dose
Apixaban	34%	66%
Rivaroxaban	29%	71%

RESULTS

- Script data presented are not specific to only the atrial fibrillation indication, as these anticoagulants are also approved/used for other conditions.
- Based on the prevalence of AF, as compared to other conditions, it is assumed that the script data provided by IMS Brogan Canadian Compuscript and IMS Brogan Compuscript Market Dynamics are predominantly for atrial fibrillation patients, and the scripts for other indications are negligible.

CONCLUSIONS

- In large randomized trials of factor Xa inhibitors for AF stroke prevention, roughly 5-11% of patients qualified for reduced doses, based upon presence of renal disease or increased bleeding risk.
- In SPRINT-AF, a contemporary Canadian AF population, 9-12% of patients would qualify for reduced-dose factor Xa inhibition.
- Canadian sales data for factor Xa inhibitors for stroke prevention reveal a substantially higher use of reduced-dose prescriptions, in the range of 29-34%.
- It is likely therefore that a substantial number of AF patients in Canada are receiving inappropriately low doses of factor Xa inhibitors, potentially placing them at higher risk for stroke.
- If these findings are confirmed in prospective evaluations of real-world practice, it will be imperative to disseminate appropriate prescribing instructions for reduced dose factor Xa inhibition for stroke prevention.

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