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Oral Anticoagulant Prescription Trends, Profile Use and Determinants of Adherence in Patients with Atrial Fibrillation

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Disclosure statement

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There are no conflicts of interest to declare:

- Drs Perreault, White-Guay, Schnitzer and Mr. Dorais report no disclosures.

Disclosure:

- Dr Côté (Honoraria for lectures, Sanofi, Bayer in past 2 years);
- Dr de Denus has received grants from Pfizer, AstraZeneca, Roche Molecular Science, DalCor and Novartis (in the last 3 years).
- Dr Dubé (A patent pertaining to pharmacogenomics-guided CETP inhibition was granted and J.-C.Tardif and M.-P. Dubé.
- Dr Dubé has received honoraria from Dalcor and research support (access to samples and data) from AstraZeneca, Pfizer, Servier, Sanofi and GlaxoSmithKline).
- Dr. Tardif reports grants from Amarin, AstraZeneca, DalCor, Esperion, Ionis, Sanofi and Servier; honoraria from Amarin, DalCor, Sanofi and Servier; minor equity interest in DalCor; and is an author of a patent on pharmacogenomics-guided CETP inhibition

Introduction

- Atrial fibrillation (AF) is a condition involving an irregular heart rhythm.
- AF is the most common cardiac arrhythmia **affecting 1-2%** of the general population and its prevalence can increase up to **15% in people older than 80 years of age**.
- AF increases **mortality by 2-fold and the risk of stroke by 5-fold** with associated increased hospital admissions, reduced quality of life, impaired exercise capacity, tachycardia-induced cardiomyopathy, and heart failure.
- People with AF are at high risk of blood clots that can lead to stroke. To prevent clots, doctors usually prescribe **oral anticoagulants (OAC).**
- Warfarin has been the mainstay oral anticoagulant medication in AF patients. It confers up to **60% relative risk reduction in stroke** and **thromboembolic events** compared to placebo.

Introduction

- Direct oral anticoagulants (**DOACs**) have been approved by Health Canada from 2011 by dabigatran (RE-LY) followed by rivaroxaban (ROCKET-AF) and apixaban (ARISTOTLE) and edoxaban (ENGAGE).
- DOACs are associated with **rapid onset of action**, which implies that the efficacy of in clinical practice is likely to be closely dependent on strict adherence. However, adherence remains a challenge in real life context.
- The **complexities** in DOAC dosing regimens, renal function and drug interactions can contribute to suboptimal use of DOAC.
- Again, patient-related factors such as advanced age, associated CVD and adherence level could play an integral role in risk stratification to identify patients who are at risk of **suboptimal use**.
- Thus having real-life evidence regarding **OAC adherence** and ultimately, patient outcomes, is critical.
- The **study aims** to report on trends in claim utilization, persistence rate, adherence level and the predictors.

Objectives

- To describe the trends of OAC use from 2011-2017
- To assess the persistence rate in a cohort study of new OAC users from 2011 to 2017.
- To assess the adherence level adherence level in a cohort study of new OAC users from 2011 to 2017.
- To assess the predictors of adherence level.

Methods

Data sources

- Databases of the *Régie de l'assurance maladie du Québec* (RAMQ)
  - 3 types of files :
    - The **demographic information**
    - The **medical services** file comprises claims for all inpatient or ambulatory medical services and includes data associated with the procedure and the diagnostic code ;
    - The **pharmaceutical file** : all prescriptions for covered drugs prescribed to patients living in the community whose medications are insured by the RAMQ.
- Databases of MedEcho
  - Data on acute care hospitalizations

Methods – Cohort Study

Inclusion Criteria

- **Cohort study** using administrative claims data from **Quebec RAMQ and Med-Echo databases.** We identified adults aged ≥ 18 years from January 1, 2011 to December 31, 2017
- Patients with a primary or secondary diagnosis of **AF using inpatient** coding ICD-9 (427.3, 427.31 or 427.32) or ICD-10 codes (I48), who were discharged alive in community.
- The patients need to have a completed **coverage by RAMQ drug** plan for the year preceding the hospitalization.
- Thereafter, we identified patients **who filled a claim of DOACs or warfarin** within the year after hospital discharge.
- **New user** will be defined as having no claim of oral anticoagulant in the year prior the index date.

Methods – Cohort Study

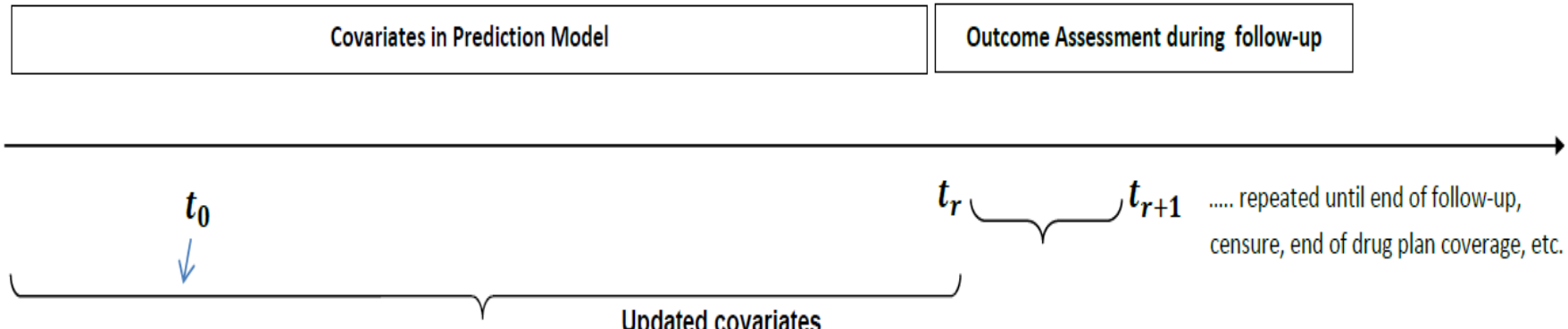
Exclusion Criteria

- Patients with ESRD, kidney transplant, or dialysis within 3-year period.
- Patients with coagulation deficiency in the 3-year period.
- Patients who underwent hip or knee replacement surgery within 6 weeks prior to the index date.
- Patients who had a diagnosis of deep vein thrombosis or pulmonary embolism during hospitalization.
- Patients with recent procedures in last 3 months: cardiac catherization, stent, CABG, carotid endartectomy.
- No valve replacement/procedures within 3 months prior to the index date.

Methods – Cohort Study

- ***Follow-up***
  - Followed until outcomes, death or the end of the study period (December 31th, 2018).
  - And, individuals who lost coverage under the RAMQ drug insurance, being institutionalized, being hospitalized for more than 15 days or who died during follow-up were censored.

Subjects will be included after hospital discharge with a primary or secondary diagnosis of AF between 2011 to 2017. Follow-up begins at first treatment initiation (index date t_0).



Sociodemographics: age, sex, type of health plan, site of residency at the index date, urban, rural, Pampalon deprivation index for health and welfare

Associated comorbidity from hospital chart, and RAMQ medical files: CHA_2DS_2-VASc score, modified HASBLED score, congestive heart failure, myocardial infarction, coronary artery disease, valvular heart disease, prior stroke/TIA, peripheral artery disease, hypertension, dyslipidemia, diabetes, chronic obstructive pulmonary disease, chronic renal disease, prior bleeding, liver disease, depression.

(1 year preceding **time point t_r**)

Health care use: Number of hospitalizations, length of hospital stay, number of outpatient visits, inpatient or emergency department use, number of physicians.

Outcomes assessed during follow-up between t_r and t_{r+1}

1. Persistence rate of non-exclusive use
2. Adherence level: warfarin or a DOAC (categorical) ≥ 80% PDC
3. Predictors of adherence level at baseline

Outcomes

1) Persistence rate:

- Incident OAC users were defined as ‘persistent’ as long as they refilled their OAC prescription.
- A permissible gap between refills was allowed, which was 2.0 times the duration of the previous prescription.
- Patients who switched from one OAC agent to another, within the permissible gap, were considered as ‘persistent’ for non-exclusive use.

2) **Adherence level:**

- OACs adherence level was assessed using the PDC, which is the total number of days of medication supply divided by 365 days, expressed as percentage.
- When the dispensing overlapped, the full length of each filled claim was accounted for and the start date of the second claim was forwarded at the end of the previous claim.
- PDC was defined as being ≥ 80%

Covariables

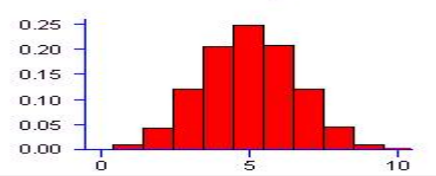
- **Demographic variables:** Defined at the cohort entry: Age, gender and social assistance status
- The **cardiovascular comorbidities and risk of stroke** at baseline were evaluated with the CHA_2DS_2-VASc score, and we determined bleeding risk with a modified **HAS-BLED score** not INR lability
- **Associated morbidities:** Defined by the presence of ICD-9 or ICD-10 codes or medical procedures were ascertained by including hospitalization dates up to **3 years prior to** cohort entry.
- **Other concomitant medications** were defined as filled prescriptions up to 3 months before the cohort entry.
- We assessed comorbidities using the **Charlson** comorbidity index up to **3 years prior to** cohort entry.

METHOD

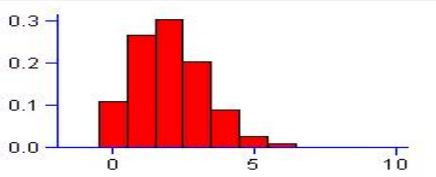
Statistical Analyses

Descriptive data

Continuous Variables



Mean, (SD)



Median, (IQ)

Categorical Variables

- Test exact de Fisher
- Test du chi-carré (χ^2)

Proportions (%)

Persistence rate, adherence level and predictors

- Trends of use overtime of claims
- Kaplan Meier of Persistence Rate
- Mean Proportions of Days Covered, PDC
- Cox Regression Model: Crude and adjusted Hazard ratio (HRs) of probability of being non persistent
- Predictors of nonadherence (PDC <80%) and baseline characteristics using multivariate logistic regression models for each OAC.

95% Confidence Interval

SAS

RESULTS

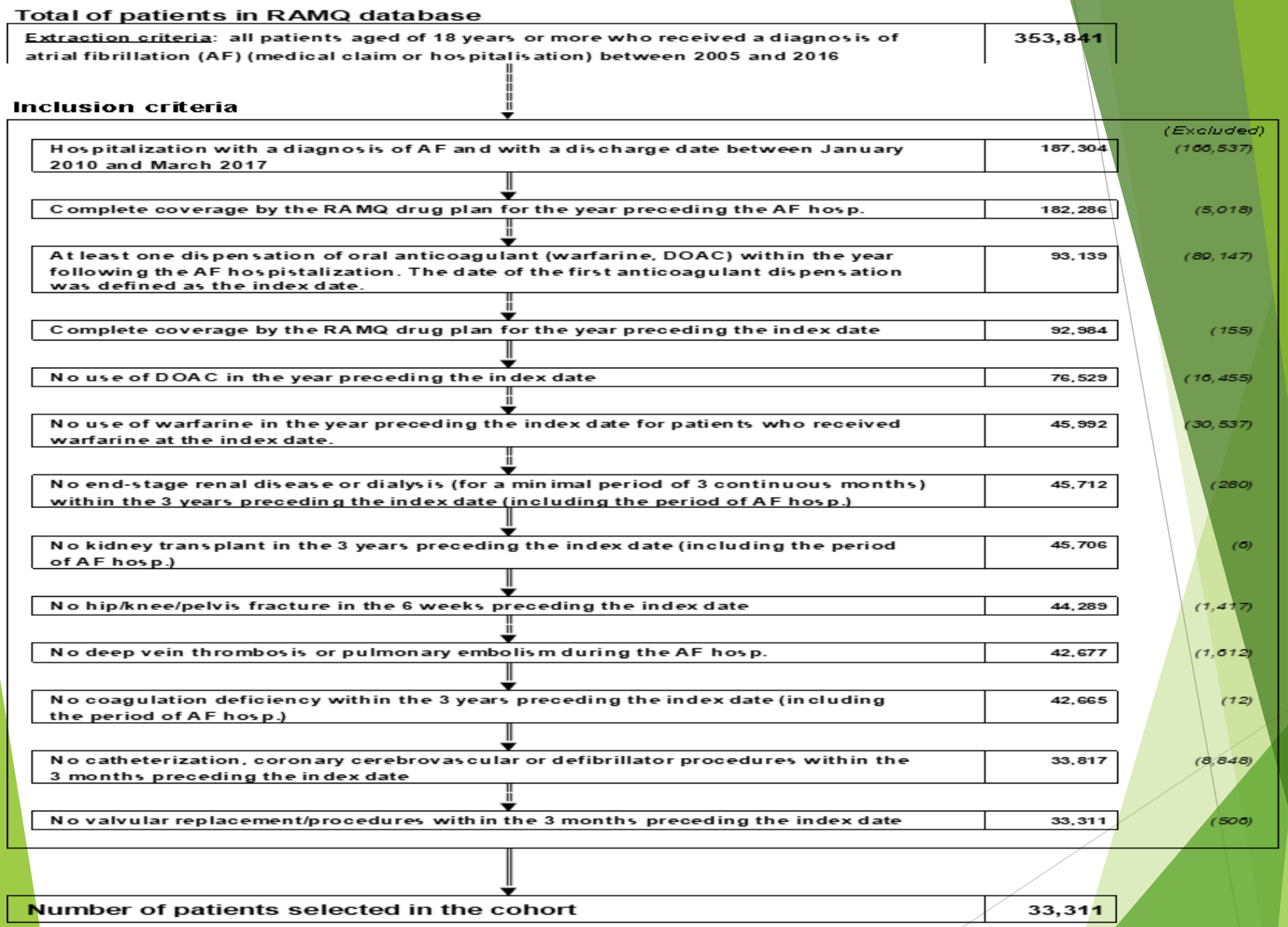


Figure 1. Flow chart of the study (AF: atrial fibrillation; OAC: oral anticoagulants).

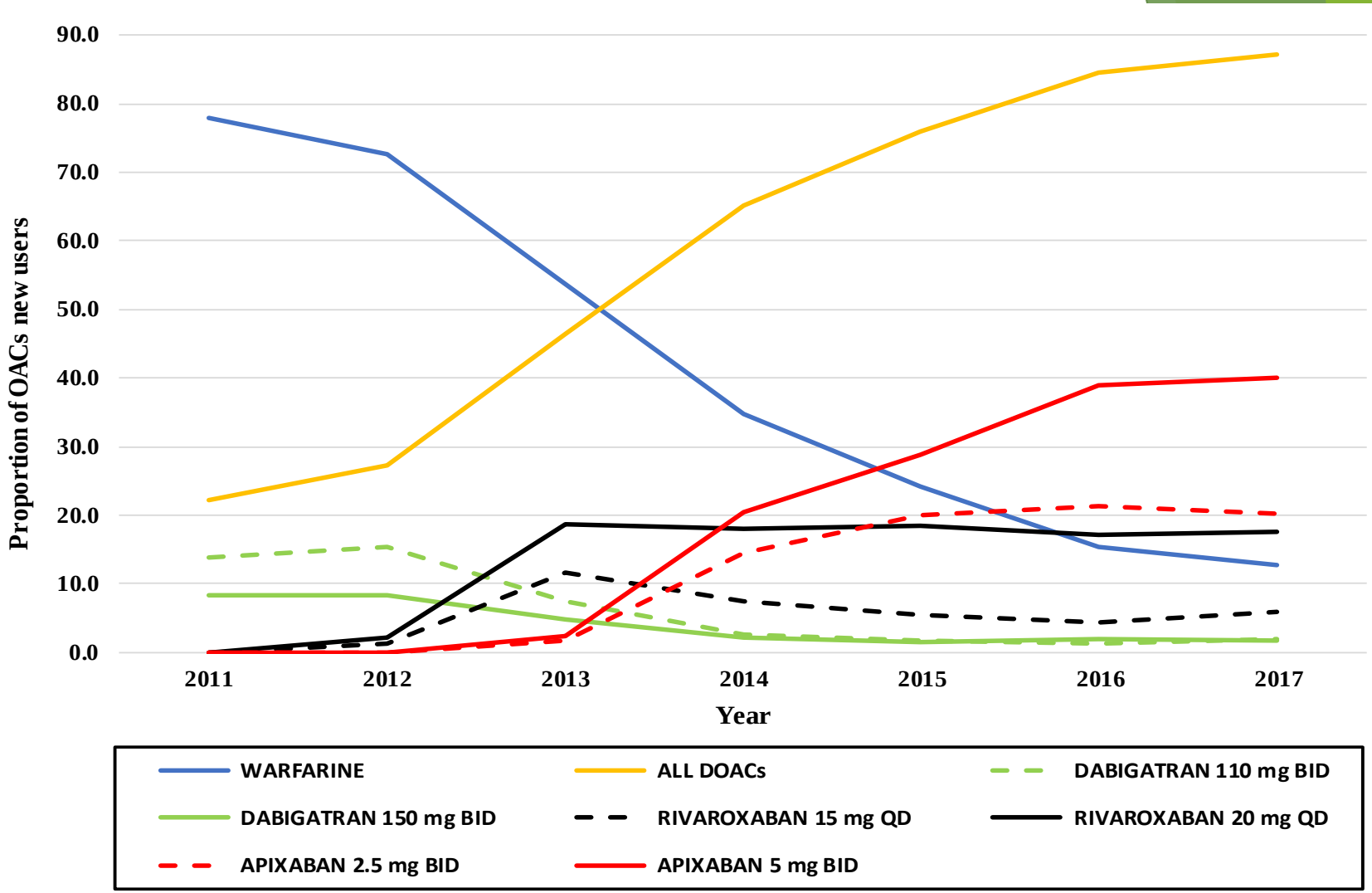
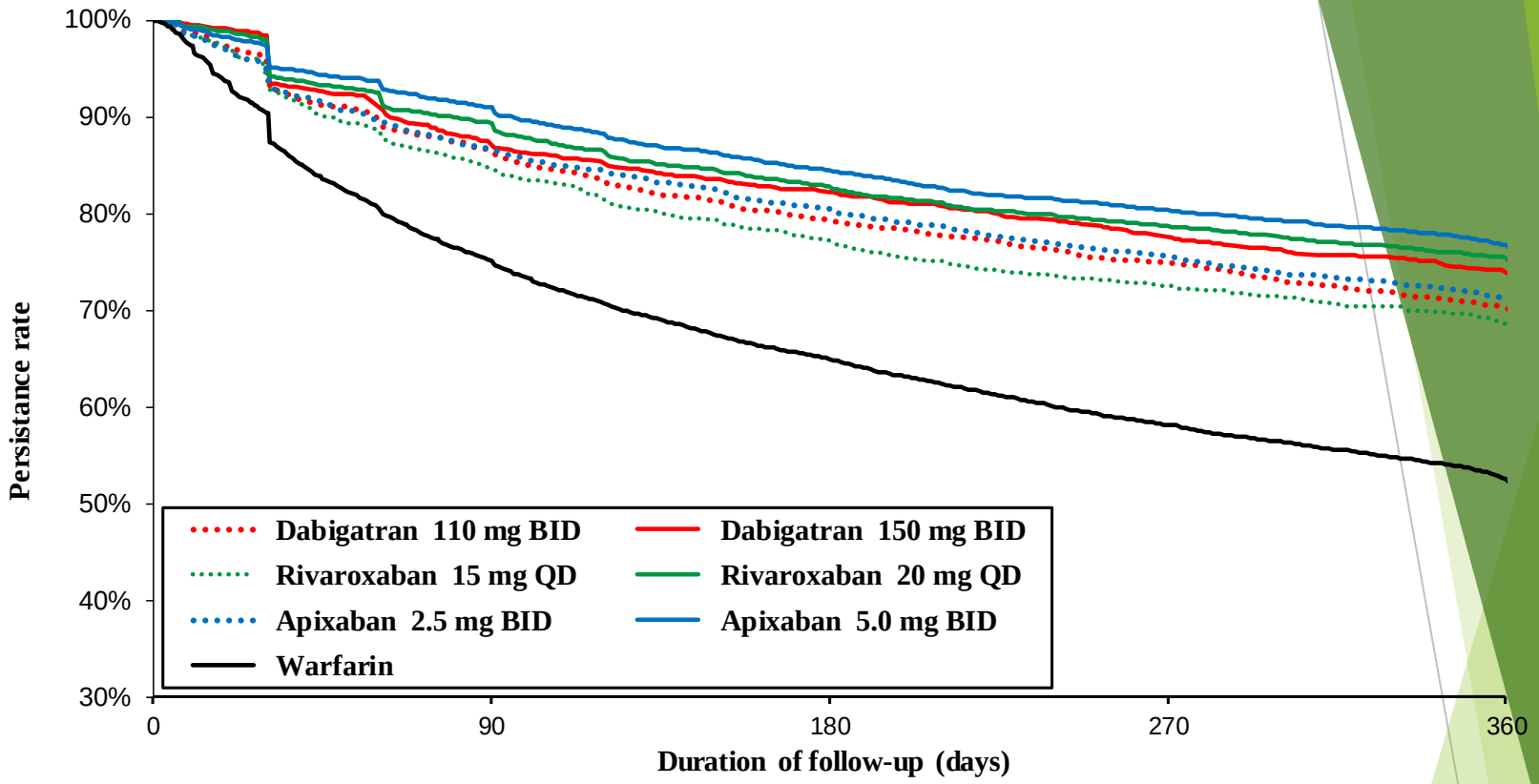


Figure 2. Trends of new users of oral anticoagulants (OAC) from 2011-2017

Table 1. Demographic and clinical characteristics of new user of OACs from 2011 to 2017.

	Warfarin (n=14,592)	Dabigatran 110 mg BID (n=2,202)	Dabigatran 150 mg BID (n=1,414)	Rivaroxaban 15 mg QD (n=1,695)	Rivaroxaban 20 mg QD (n=4,300)	Apixaban 2.5 mg BID (n=3,485)	Apixaban 5 mg BID (n=5,623)
Sociodemographics							
Age – mean ± SD	80.9 ± 913	81.2 ± 7.1	69.9 ± 8.0	82.9 ± 7.1	73.1 ± 9.1	86.2 ± 6.1	76.2 ± 8.5
Male (n,%)	45.0 %	42.3 %	58.4 %	39.0 %	55.5 %	32.4 %	52.0 %
Comorbidities (%)							
Hypertension	84.8 %	82.6 %	75.4 %	83.5 %	74.7 %	84.1 %	79.4 %
Coronary artery disease	60.5 %	53.1 %	47.7 %	54.3 %	42.9 %	54.5 %	47.0 %
Acute MI	15.4 %	9.2 %	7.4 %	13.6 %	8.4 %	15.8 %	11.1 %
Chronic heart failure	44.2 %	36.5 %	26.9 %	39.4 %	26.1 %	42.6 %	32.4 %
Valvular heart disease	23.4 %	16.6 %	11.0 %	19.8 %	13.0 %	22.1 %	15.8 %
Stroke/TIA	21.1 %	22.5 %	17.0 %	18.0 %	14.4 %	19.7 %	18.9 %
PAD	25.2 %	18.9 %	13.4 %	22.1 %	16.0 %	21.6 %	18.6 %
Dyslipidemia	53.9 %	50.7 %	49.1 %	49.8 %	48.8 %	49.8 %	54.7 %
Diabetes	39.0 %	30.7 %	33.4 %	30.4 %	31.1 %	29.1 %	35.9 %
Major bleeding	11.4 %	12.8 %	8.4 %	10.9 %	9.3 %	14.0 %	12.0 %
Chronic renal failure <30 mL/min	8.0 %	1.6 %	1.2 %	3.1 %	0.9 %	3.6 %	2.2 %
CHA2DS2-VASc Score	4.0 ± 1.4	3.8 ± 1.3	2.7 ± 1.4	4.0 ± 1.3	3.0 ± 1.4	4.3 ± 1.2	3.4 ± 1.4
HAS-BLED score	3.3 ± 1.3	3.0 ± 1.2	2.5 ± 1.2	3.1 ± 1.3	2.6 ± 1.3	3.3 ± 1.3	2.9 ± 1.3
Charlson score	5.0 ± 3.4	4.2 ± 3.3	3.4 ± 3.2	4.6 ± 3.4	3.6 ± 3.2	4.7 ± 3.3	4.4 ± 3.4



No. at risk

Warfarin	14,592	9,982	8,226	7,090	6,153
Dabi 110	2,202	1,766	1,560	1,418	1,295
Dabi 150	1,414	1,188	1,100	1,026	959
Riva 15	1,695	1,326	1,142	1,029	932
Riva 20	4,300	3,645	3,283	3,054	2,855
Apix 2.5	3,485	2,756	2,422	2,159	1,931
Apix 5	5,623	4,843	4,358	4,035	3,740

Figure 3. Kaplan Meier estimator of persistance rate of oral anticoagulant

Table 2. Adjusted hazard ratios (HRs) of non-persistence to OAC non-exclusive use (95% confidence interval (CI)) after 1-year of follow-up.

	Warfarin	Dabigatran 110 mg BID	Dabigatran 150 mg BID	Rivaroxaban 15 mg QD	Rivaroxaban 20 mg QD	Apixaban 2.5 mg BID	Apixaban 5.0 mg BID
Grace period of 2 times time duration§							
Adjusted HRs							
Warfarin	reference	0.79; 0.75-0.83	0.74; 0.70-0.79	0.80; 0.75-0.84	0.72; 0.69-0.76	0.76; 0.73-0.80	0.70; 0.67-0.73
Apixaban 5.0 mg BID	1.43; 1.37-1.49	1.13; 1.06-1.21	1.06; 1.00-1.13	1.14; 1.06-1.22	1.03; 0.99-1.08	1.09; 1.02-1.16	reference
Sensitivity Analyses*							
Grace period of 1.5 times duration§¶							
Adjusted HRs							
Warfarin	reference	0.74; 0.70-0.77	0.68; 0.64-0.73	0.72; 0.68-0.76	0.65; 0.62-0.68	0.70; 0.67-0.73	0.64; 0.61-0.67
Apixaban 5.0 mg BID	1.57; 1.50-1.64	1.15; 1.08-1.23	1.07; 1.00-1.13	1.13; 1.05-1.21	1.01; 0.97-1.06	1.10; 1.03-1.16	reference
Grace period of 3 times duration§¶							
Adjusted HRs							
Warfarin	reference	0.86; 0.82-0.91	0.82; 0.77-0.87	0.87; 0.82-0.92	0.81; 0.77-0.85	0.83; 0.80-0.87	0.77; 0.74-0.81
Apixaban 5.0 mg BID	1.30; 1.24-1.35	1.12; 1.04-1.19	1.06; 0.99-1.13	1.12; 1.05-1.21	1.05; 1.00-1.09	1.08; 1.01-1.15	reference
Grace period of 4 times duration§¶							
Adjusted HRs							
Warfarin	reference	0.89; 0.85-0.94	0.85; 0.80-0.91	0.90; 0.85-0.95	0.85; 0.81-0.89	0.86; 0.82-0.90	0.81; 0.77-0.84
Apixaban 5.0 mg BID	1.24; 1.19-1.29	1.10; 1.03-1.18	1.06; 0.99-1.13	1.11; 1.03-1.19	1.05; 1.00-1.09	1.06; 1.00-1.13	reference

Table 3. Mean adherence level according to OAC and dose used of non-exclusive use (95% CI).

	Total PDC[¶£] (n=33,311)	PDC < 90% (n=11,329)	PDC ≥ 90% (n=21,982)	PDC < 80% (n=8,298)	PDC ≥ 80% (n=25,013)
Warfarin					
Mean	80.5; 80.0-80.9	59.9; 59.3-60.5	98.0; 97.9-98.0	50.4; 49.8-51.1	95.6; 95.5-95.7
Dabigatran 110 mg BID					
Mean	86.2; 85.2-87.2	55.2; 53.1-57.3	98.7; 98.6-98.9	45.6; 43.5-47.8	97.6; 97.3-97.8
Dabigatran 150 mg BID					
Mean	87.8; 86.5-89.0	53.3; 50.3-56.2	99.0; 98.8-99.1	43.1; 40.1-46.1	97.9; 97.6-98.2
Rivaroxaban 15 mg QD					
Mean	85.9; 84.8-87.1	54.0; 51.6-56.4	98.7; 98.6-98.9	43.9; 41.5-46.3	97.5; 97.3-97.7
Rivaroxaban 20 mg QD					
Mean	88.0; 87.3-88.7	52.5; 50.9-54.2	99.0; 98.9-99.1	43.1; 41.4-44.8	98.1; 97.9-98.2
Apixaban 2.5 mg BID					
Mean	88.6; 87.9-89.3	61.0; 59.4-62.5	98.8; 98.7-98.9	50.7; 49.0-52.4	97.5; 97.3-97.7
Apixaban 5 mg BID					
Mean	90.4; 89.9-91.0	58.9; 57.5-60.4	98.9; 98.8-99.0	48.5; 47.0-50.1	97.9; 97.8-98.0

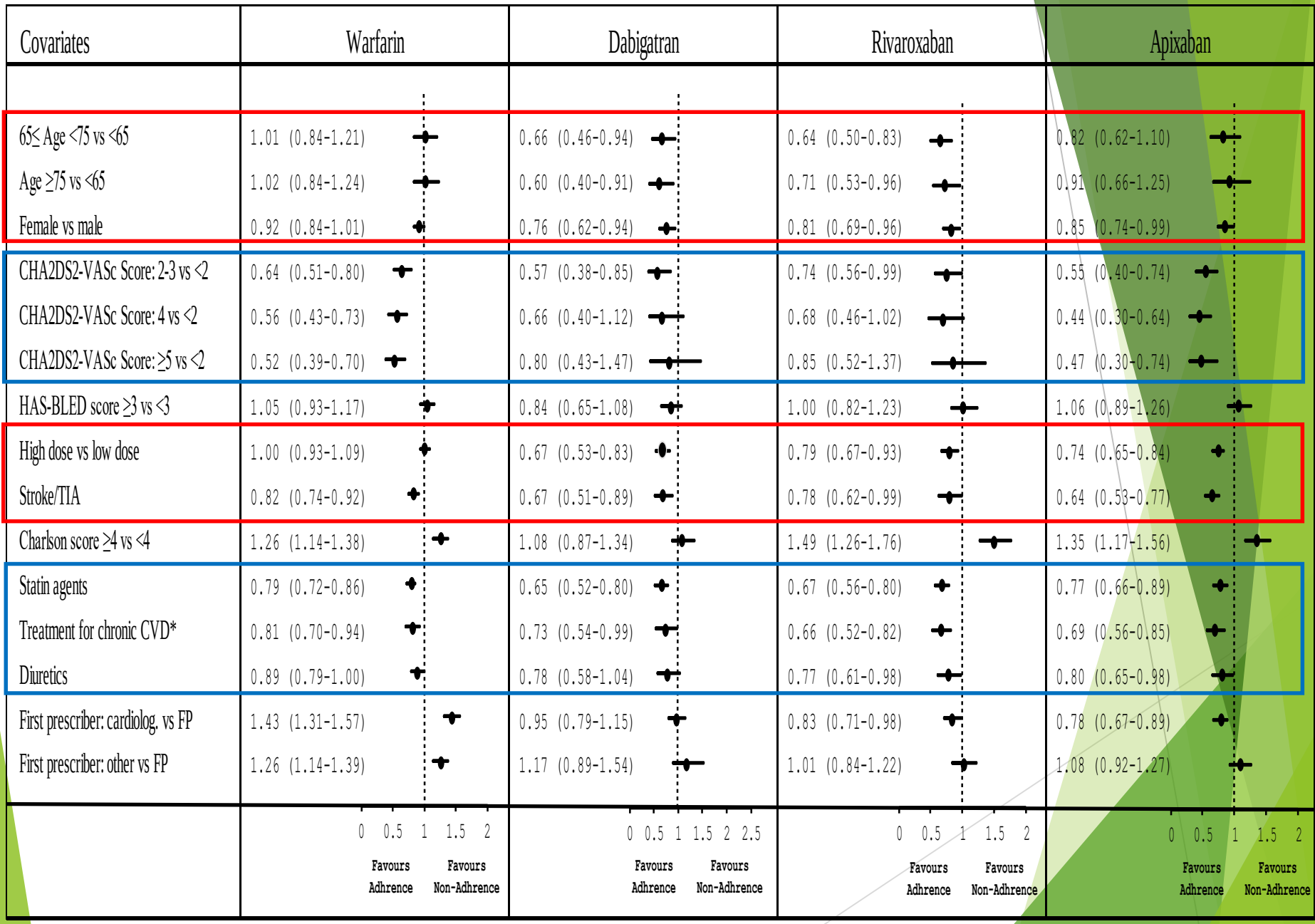


Figure 4. Adjusted predictors of non-adherence (PDC < 80%) of OACs.

Discussion

- Warfarin claims decreased from 77.9% to 12.7% of the total OAC claims, with DOACs accounting for about 87.2% of the claims. Apixaban and rivaroxaban accounted for 60.1% and 23.4%, respectively, of OAC.
- The highest rate of persistence after 1-year of follow-up was with apixaban 5 mg (77%) compared to warfarin, the lowest rate of persistence (53%).
- About 75% of incident OAC users were 'adherent' (PDC ≥ 80; where mean PDC 95.6% to 98.1%) compared to those 'non adherent'; where mean PDC 43.1% to 50.7%.
- Adherence to OACs remains a significant challenge in patients with AF.
- Predictors of non-adherence are being younger, male, lower CHA_2DS_2-VASc score, low doses of OACs, no history of stroke or no treatment for chronic cardiovascular disease may be more likely to benefit from counseling regarding the importance of drug adherence.

LIMITS

- We could not control for all characteristics that may have influenced physicians' choice of medication, including unmeasured comorbidities.
- We could not neither adjust directly for INR, blood glucose, cholesterol levels, blood pressure, etc.
- Some individuals with a history of CVD may not have been identified because of errors in diagnostic coding.
- We utilized prescription refill patterns to assess exposure and therefore we cannot ascertain whether the dispensed medication was actually taken by the patient.
- We may have also residual confounders

Conclusion

- Warfarin use decreased from 77.9% in 2011 to 12.7% of total claims, with DOACs accounting for 86% of claims, of which apixaban and rivaroxaban accounted for 60.1% and 23.4%, respectively.
- Persistence rate with apixaban 5 mg (77%) compared to warfarin (53%).
- Adherence to OAC therapy is good, but in this real-life study, 25% of new OAC users presented a low adherence level.
- Adherence to OACs remains a significant challenge in patients with AF. OAC type and dose, comorbidities and co-medications may help to identify those who are more likely to benefit from counseling.
- Nevertheless, data on the rate of DOAC adoption, pattern of use according to type of DOAC and dosing are still limited.
- Having actual real-life evidence regarding OAC adherence and ultimately, patient outcomes, is critical.

Thanks!

QUESTIONS

- Multidisciplinary conference covering drug R&D from target to market
- 2,000 participants (Americas, Europe, Asia)
  - 60% academia
  - 25% industry
  - 7% clinicians
  - 7% regulatory agencies
- Call for abstracts: Oct. 15 to Dec. 15, 2019
- Registration: early bird until Feb. 20, 2020

https://pswc2020.congress.pharmacy

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