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Evolution and Evidence-Practice Gaps of Antithrombotic Management of Atrial Fibrillation Patients After Percutaneous Coronary Intervention

Running Title: Antithrombotic Management of AF Patients After PCI

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Brief Summary

A retrospective cohort of AF patients who underwent percutaneous coronary intervention (PCI) with placement of a coronary stent was created using Quebec provincial administrative databases from 2010-2017and analyzed for the antithrombotic regimen received in the following year. When found that oral anticoagulation (OAC) prescription following PCI increased over time, but, up to 2017, substantial further changes in practice patterns would be required to achieve the recommended rates of OAC.

Abstract

Background: The management of atrial fibrillation and flutter (AF) patients undergoing percutaneous coronary intervention (PCI) has evolved rapidly in the last decade. We determine whether the publication of the 2016 Canadian Cardiovascular Society AF guidelines were associated with a shift in practice patterns.

Methods: Using Quebec provincial administrative databases from 2010-2017, a retrospective cohort of patients with inpatient or outpatient coding for AF who subsequently underwent PCI with placement of a coronary stent was created and analyzed for the antithrombotic regimen received in the following year. Prescribing behavior was compared between three time periods (2010-2011, 2012-2015, 2016-2017) and antithrombotics were compared to guideline-predicted therapy using the Chi-square test. Predictors of oral anticoagulation (OAC) prescription were identified using adjusted logistic regression.

Results: A total of 3,740 AF patients undergoing PCI were included. The proportion of OAC prescription increased over time (2010-2011=51.4%; 2012-2015=54.3%; 2016-2017=56.6%; p=0.13), with a significant increase in direct OAC (DOAC) prescription (p<0.01). A substantial treatment gap in OAC prescription persisted after publication of the 2016 guidelines (56.6% observed vs 89.7% predicted; p<0.01). Previous stroke, $CHADS_2$ score, Charlson Comorbidity Index ≥ 4, prior use of DOAC or warfarin were predictors of being exposed to OAC claims; previous major bleeding, low-dose acetylsalicylic acid or P2Y12 inhibitor use were predictors of not being exposed to OAC.

Conclusion: Expert guidance contributed to an increase in OAC prescription following PCI, but, up to 2017, substantial further changes in practice patterns would be required to achieve the recommended rates of OAC.

Key words: atrial fibrillation, antithrombotic therapy; oral anticoagulation; percutaneous coronary intervention.

Introduction

Contemporary antithrombotic management of patients with either atrial fibrillation/flutter (AF) or coronary artery disease (CAD) is well established in clinical guidelines.[1-4] Up to 30% of patients with AF also have CAD,[5] and the optimal management of AF patients requiring percutaneous coronary intervention (PCI) has, up until recently, been ill defined. While oral anticoagulation (OAC) is preferred for the prevention of stroke and systemic embolism for most AF patients and age 65 years or older or $CHADS_2$ score ≥ 1 (strong recommendation; high quality evidence),[3] dual antiplatelet therapy (DAPT) is the standard of care after PCI in the absence of AF.[6,7] However, combining these two recommendations in patients with AF who require PCI (so-called triple antithrombotic therapy [TATT]) increases the bleeding risk significantly.[8]

Recently, an international multicenter analysis demonstrated that the availability of newer antiplatelet and anticoagulant agents in the absence of guidance was associated with increased practice variability in the antithrombotic management of AF patients post-PCI.[9] However, the Canadian Cardiovascular Society (CCS) and European Society of Cardiology (ESC) published recommendations in 2016 to help clinicians balance bleeding and thrombotic risks in these patients.[1,3] The landmark PIONEER AF-PCI[10] was also published in 2016, followed by REDUAL[11] in 2017, both of which supported the use of dual pathway (OAC + P2Y12-inhibitor) antithrombotic regimens using direct oral anticoagulants (DOAC) to reduce bleeding risk in AF patients who underwent PCI. We therefore sought to determine whether these publications were associated with significant

changes in OAC prescription using province-wide Quebec healthcare claims databases.

Methods

We conducted a retrospective cohort analysis using Quebec healthcare claims databases in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[12] The study protocol was consistent with the ethical guidelines of the 1975 Declaration of Helsinki. Ethics approval of the project was obtained from the University of Montreal Ethics Committee.

Data Sources

Administrative databases (hospital discharges from Med-Echo; medical services; and public drug plan) administered by the *Régie de l'Assurance Maladie du Quebec* (RAMQ) were linked using encrypted health insurance numbers and used to derive the study cohort. [13-16] The RAMQ covers all Quebec residents for the cost of physician visits, hospitalizations and procedures, and 94% of Quebec citizens aged 65 and older for the drug insurance plan.[15]

Population

We identified patients aged 18 years and over with one inpatient or two outpatient diagnostic coding for AF within a 2-year period from January 1, 2010, to December 31, 2017, using International Classification of Diseases (ICD)-9 (427.3, 427.31 or 427.32) or ICD-10 (I48) codes.[17,18] AF patients data from the RAMQ database are available until the 31st of December 2017. The follow-up of the antithrombotic regimen can be followed up to a year after the diagnosis depending on the year of

the cohort entry. The first instance of AF coding was used to determine eligibility. ICD-9 diagnostic codes for AF have a median positive predictive value of 89%.[19] The cohort was then restricted to patients who subsequently underwent coronary stenting before December 31, 2017 using the procedural code 20521 in RAMQ databases.[20] The date of the PCI was defined as the date of cohort entry. Patients who were hospitalized for 14 days or more following the PCI procedure were excluded, as were patients who resided in long-term care facilities that typically provide medications to patients. Patients were required to have been enrolled in the provincial drug insurance plan for a minimum of 12 months prior to cohort entry. We then excluded any patient who underwent PCI for an acute coronary syndrome (ACS) indication and with coding for any non-AF or non-PCI condition or procedure that might have impacted the choice of antithrombotic regimen at discharge (Supplemental Table S1).

The total cohort study cohort was subsequently divided into three time periods of interest: (1) Sub-cohort 2010-2011 represents a “historic” period before the commercial availability of DOACs; (2) Sub-cohort 2012-2015 corresponds to a “pre-guidelines” period once DOACs and newer P2Y12 inhibitors were commercially available, but prior to publication of the 2016 CCS AF guidelines; and (3) Sub-cohort 2016-2017 represents a period where guidance from CCS AF guidelines and early landmark studies were emerging.

Patient Demographics and Clinical Characteristics

Demographic data were extracted at cohort entry, whereas comorbidities were determined using inpatients and outpatients ICD-9 and ICD-10 diagnoses

occurring in the 3 years preceding cohort entry.[18,21,22] Using this information, we calculated the $CHADS_2$ score (Supplemental Table S2), modified HAS-BLED score (Supplemental Table S3), and Charlson Comorbidity Index for each patient.[23] Estimated glomerular filtration rate (eGFR) was estimated with an algorithm based on diagnosis code, drug use, and nephrologist visits from administrative databases that shown to be valid when compared with medical chart reviews in older adults.[24] The algorithm used for eGFR definition had a positive predictive value ranging from 94.5% to 97.7%.[24]

Outcomes

The primary outcome of interest was the antithrombotic regimen (antiplatelet and anticoagulant) claimed after the cohort entry, which was assessed at the following four time points: (1) at 1 month; (2) at 3 months; (3) at 6 months; and (4) at 12 months. In Quebec, most medications are dispensed 30 days at the time. Consequently, medication exposure was measured within the 14 days preceding and the 14 days following each time point of follow-up.

Statistical Analysis

Data is presented for the total cohort and the three sub-cohorts. Continuous data are expressed as mean with standard deviation, while categorical data are expressed as count and percentage. Comparisons between the three sub-cohorts were made using the Kruskal-Wallis test for continuous data and the Chi-square test for categorical data.

The primary analysis consisted of an evaluation of the difference in prescription patterns across sub-cohorts using the Chi-square test. Secondarily,

we also used the Chi-square test to perform an evaluation of the differences between antithrombotic prescription patterns in Sub-cohort 2012-2015 and Sub-cohort 2016-2017 and the patterns that would have been expected with perfect adherence to the 2016 CCS AF guidelines. Individual guideline-expected treatment was determined by assessing the indication for anticoagulation according to the $CHADS_2$ score and the patient's age. Patients with age 65 years or older or $CHADS_2$ score ≥ 1 were expected to receive an OAC prescription while patients age less than 65 years and with $CHADS_2$ score < 1 were not expected to receive an OAC prescription 1 month after cohort entry.

To better take into consideration the time necessary for guidelines assimilation into clinical practice, a sub-analysis of the difference in prescription patterns entry was performed as sensitivity analysis using the Chi-square test across the following sub-cohorts: (1) Sub-cohort January 1st, 2010 to December 31st, 2011 represents a "historic" period before the commercial availability of DOACs; (2) Sub-cohort January 1st, 2012 to August 31st, 2017 corresponds to a "pre- and early guidelines" period once DOACs and newer P2Y12 inhibitors were commercially available, but prior to publication of the 2016 CCS AF guidelines; and (3) Sub-cohort September 1st, 2017 to December 31st, 2017 represents a period where guidance from CCS AF guidelines were most likely assimilated into clinical practice. To consider deaths during the follow-up period, incident rates (per 100 persons-year) of antithrombotic therapy (ASA, P2Y12 inhibitor and OAC) during the year following cohort entry were also provided.

Determinants of OAC prescription 1 month following PCI were identified using multivariable logistic regression analysis. Covariates were included if they were judged to be potential confounders, based on a combination of expert opinion and results of univariate analyses ($p<0.05$). The variables included in the final model were: age ≥ 65, female, $CHADS_2$ score ≥ 3, HAS-BLED score ≥ 3, Charlson Comorbidity Index ≥ 4, previous stroke, prior major bleeding, chronic renal failure (eGFR ≤ 30 mL/min), peripheral artery disease, liver disease, DOAC use within the 2 weeks prior to cohort entry as well as warfarin use, low-dose acetylsalicylic acid (ASA) use and P2Y12 inhibitor use within the 2 weeks. Crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) are reported.

All analyses were performed using SAS 9.4 statistical software (SAS Institute, Cary, North Carolina). A two-tailed p-value less than 0.05 was considered statistically significant without correction for multiple analyses.

Results

A total of 3,740 patients with AF undergoing PCI were included in the cohort (Fig. 1). 88% of AF patients were hospitalized during their index PCI. The mean duration of hospitalization was 6.2 ± 5.9 days, where 75.6% of AF patients was hospitalized for less than 4 days. Baseline and demographic characteristics for the entire cohort as well as the three sub-cohorts are detailed in Table 1. Medication received within the two weeks prior to cohort entry are available in Supplemental Table 4.

Post-PCI Antithrombotic Treatment

Antithrombotic therapy during the first year after cohort entry for the total cohort and the sub-cohorts is presented in Table 2. Among patients receiving OAC and antiplatelet therapy at 1 month, the first prescriber was a cardiologist in 44.8% and 25.2% of patients, respectively. Over time, the proportion of patients receiving newer, more potent P2Y12 inhibitors (prasugrel or ticagrelor) increased at the expense of a decrease in clopidogrel prescription in the first month after PCI ($p<0.05$ for all). The proportion of patients receiving ASA during the first year after cohort entry decreased significantly ($p<0.01$ for all). More patients made OAC prescription claims over time ($p<0.01$, except for OAC at 1 month), driven by a significant increase in DOAC prescription ($p<0.01$ for all) and despite a concomitant decrease in warfarin prescription ($p<0.01$ for all). Dual pathway (DOAC + single antiplatelet therapy) increased, while TATT prescription remained stable within 3 months after the index PCI, and then decreased. Accordingly, DAPT decreased significantly during the first year after cohort entry. Results from the sensitivity analysis were similar to the primary analysis (Supplemental Table S5). Incident rates of antithrombotic therapy during the year following cohort entry are available in Supplemental Table S6. The incident OAC rate in the study cohort was 57.6 per 100 persons-year (2012-2011= 47.2; 2012-2015=57.8; 2016-20117=60.9 per 100 person years).

DOAC choice and dosage 1 month after cohort entry are presented in Supplemental Table S7. Prescription of full- and reduced-dose DOAC increased over time for all, except for full-dose dabigatran. Reduced-dose DOACs were more frequently prescribed than full-dose DOACs as part of dual pathway and TATT

regimens, except for full-dose apixaban as part of a dual pathway regimen. Rivaroxaban and apixaban were the most frequently prescribed DOACs in these cohorts.

Guidelines Adherence

Observed and guideline-expected proportions and type of OAC are presented in Table 3. The observed proportion of OAC was significantly below the 2016 CCS guidelines-expected proportion in both the early (54.3% vs 88.4%; p<0.01) and later (56.6% vs 89.7%; p<0.01) periods.

Determinants of Oral Anticoagulant Prescription

Determinants of OAC prescription are presented in Table 4. Significant determinants of OAC prescription 1 month following cohort entry in the adjusted model were $CHADS_2$ score ≥ 3 (OR 1.67; 95% CI 1.33-2.09), Charlson Comorbidity Index ≥ 4 (OR 1.28; 95% CI 1.08-1.52), previous stroke (OR 1.33; 95% CI 1.05-1.68), DOAC use within the 2 weeks prior to cohort entry (OR 7.79; 95% CI 5.94-10.23) as well as warfarin use (OR 6.18; 95% CI 4.52-8.45). Conversely, prior major bleeding (OR 0.81; 95% CI 0.68-0.96), low-dose ASA use (OR 0.49; 95% CI 0.41-0.58), and P2Y12 inhibitor use (OR 0.54; 95 % CI 0.42-0.70) were determinants of being less likely to be exposed to OAC. Again, the determinants of warfarin claims were similar to OAC prescription, with the exception of Charlson Comorbidity Index ≥ 4, previous stroke, previous major bleeding and DOAC use within the 2 weeks prior to cohort entry, the latter being a predictor of being less likely to be exposed to warfarin (OR 0.71; 95% CI 0.59-0.89). The only significant predictor of being exposed to DOAC is a prior use within

the 2 weeks prior to cohort entry (OR 9.04; 95% CI 7.29-11.21). Having a prior exposure to low-dose ASA (OR 0.60; 95% CI 0.48-0.75) and warfarin (OR 0.37; 95% CI 0.24-0.57) within the two weeks prior to cohort entry as well as having chronic renal failure (eGFR ≤ 30 mL/min) (OR 0.51; 95% CI 0.33-0.79) were determinants of being less likely to be exposed to DOACs.

Discussion

This retrospective cohort analysis reveals several findings pertinent to clinical practice, as well as to the design of professional educational initiatives. Significant changes in baseline medication over time were observed. Despite a decline in warfarin prescription, OAC prescription both at cohort entry and within the first year following PCI increased, due to a substantial uptake of DOAC therapy, associated with an increase in both TATT and dual pathway antithrombotic regimens. However, in spite of these significant shifts in clinical practice, the overall proportion of OAC prescription remains below the proportions expected with perfect guidelines adherence up to 2017. Lastly, we identified important clinical determinants of both OAC and DOAC prescription at discharge.

The observed increase in OAC prescription is in line with the 2016 CCS AF guidelines and landmark studies[3,10,11] recommendation of TATT for 3 to 6 months in patients with $CHADS_2$ score ≥ 1 who undergo PCI for an ACS, placing greater weight on reduction of thromboembolic events and comparatively less weight on risk of major bleeding.[3] A course of TATT up to 6 months for patients with a $CHADS_2$ score ≥ 1 in the setting of an ACS or elective PCI with a high thrombotic

risk is suggested in a recent update of the CCS antiplatelet guidelines.[25,26] The emergence of a dual pathway regimen up to 2017 represents an integration of randomized trial data from PIONEER AF-PCI (rivaroxaban) and REDUAL (dabigatran) that showed that such a regimen could reduce bleeding risk without a signal for increase in ischemic events.[10,11] While dual pathway was only recommended in AF patients who undergo an elective PCI in the 2016 CCS AF guidelines,[3] a broader shift to dual pathway antithrombotic management is advocated in the 2018 updates of the CCS antiplatelet and AF guidelines.[25,26] The subsequently published AUGUSTUS (apixaban) and ENTRUST-AF trials reinforced the safety advantage of dual pathway over triple therapy,[27,28] and similar results were found in recent retrospective studies of AF patients undergoing PCI in Asia and Europe.[29,30]

An international multicenter analysis, including AF patients undergoing PCI from 2010 to 2015 showed that the availability of newer antiplatelet and anticoagulant agents increased practice variability in the antithrombotic management of AF patients post-PCI. Similarly to the present analysis using administrative data, it also revealed that a major change in clinical practice would be necessary to achieve a high degree of agreement with AF guidelines.[9] A recent analysis of an Alberta administrative database showed that, after the publication of the 2016 CCS AF guidelines and landmark PIONEER-AF-PCI and REDUAL trials, more patients were anticoagulated and choice of agent favoured DOAC over warfarin.[31] However, almost half of the post-guidelines cohort did not receive an OAC prescription.[31] This treatment gap has also been reported in large observational

studies of AF patients without PCI. Introductions of DOACs combined with professional guidance and early landmark trials reduced, but did not eliminate OAC underuse.[31-33] While clinically appropriate reasons for this discrepancy may not have been captured in observational studies, clinicians might still place a greater weight on reduction of stent thrombosis/restenosis and comparatively lesser weight on the risk of stroke early after the index PCI. Nevertheless, the short period of observation after publication of landmarks trials is not sufficient to explain this treatment gap, given that our sensitivity analysis examining the antithrombotic regimen received after PCI longer after the publication of the 2016 AF CCS Guidelines led to similar results. Similarly to our analysis, female sex and concomitant use of ASA and other antiplatelets have repeatedly been identified as determinants of OAC non-prescription, while high $CHADS_2$ or CHA_2DS_2-Vasc scores have been identified as determinants of OAC prescription in the AF population.[32-34] As for agent choice, an eGFR ≥ 30mL/min has also been identified as a predictor of being prescribed DOAC instead of warfarin among AF patients.[34] Certain limitations of the present analysis must be acknowledged. First, this retrospective observational analysis relied on administrative data that depend on complete and accurate recording of diagnoses, as well as procedure and drug codes. Reassuringly, however, diagnostic, procedural and drug codes have been well validated in this dataset,[13-16,19] but there is still a risk of ascertainment bias. Second, the use of over-the-counter medications (e.g. ASA) may lead to inadequate assessment of the antithrombotic regimen therapy received within the first year after PCI. However, the probability of inadequate assessment is very low,

since that more than 95% older patients are using the ASA claims instead of over-the-counter use. Third, clinically appropriate reasons for the discrepancy between the overall proportion of OAC prescription and the expected proportion under perfect guidelines adherence might have not been captured in our analysis (ex: short duration, transient AF). Forth, the antithrombotic regimen therapy received within the first 14 days after PCI was not assessed as it may be imprecise (ex: some patients who were prescribed P2Y12 inhibitors prior to their PCI might have been able to wait before filling their new prescription. Fifth, we did not have the exact eGFR values. However, the algorithm used to estimate eGFR has been validated by chart review.[24] Sixth, the transferability is limited to AF patients who were hospitalized for more than 14 days and patients with an ACS since they were excluded from the analysis. Lastly, AF patients data from the RAMQ database were available until the 31st of December 2017; therefore, we were unable to assess antithrombotic regimen prescription patterns in the AF population undergoing PCI after this date.

Conclusion

The overall OAC proportion remained significantly lower than expected according to current guidelines at the time. Understanding impediments to OAC prescription in this patient population is critical to the planning of educational initiatives. Prior major bleeding and the use of antiplatelet therapy at cohort entry were determinants of non-OAC prescription 1 month after PCI in this cohort.

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References

1. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur J Cardiothorac Surg 2016;50:e1-e88.
2. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34:2949-3003.
3. Macle L, Cairns J, Leblanc K, et al. 2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. Can J Cardiol 2016;32:1170-1185.
4. Mancini GBJ, Gosselin G, Chow B, et al. Canadian Cardiovascular Society Guidelines for the Diagnosis and Management of Stable Ischemic Heart Disease. Can J Cardiol 2014;30:837-849.
5. Budhraja V. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. Ann Intern Med 2010;152:265-265.
6. Bell AD, Roussin A, Cartier R, et al. The Use of Antiplatelet Therapy in the Outpatient Setting: Canadian Cardiovascular Society Guidelines. Can J Cardiol 2011;27:S1-S59.
7. Tanguay J-F, Bell AD, Ackman ML, et al. Focused 2012 Update of the Canadian Cardiovascular Society Guidelines for the Use of Antiplatelet Therapy. Can J Cardiol 2013;29:1334-1345.
8. Lamberts M, Olesen JB, Ruwald MH, et al. Bleeding After Initiation of Multiple Antithrombotic Drugs, Including Triple Therapy, in Atrial Fibrillation Patients Following Myocardial Infarction and Coronary Intervention. Circulation 2012;126:1185.
9. Potter BJ, Andò G, Cimmino G, et al. Time trends in antithrombotic management of patients with atrial fibrillation treated with coronary stents: Results from TALENT-AF (The internAtionaL stENT – Atrial Fibrillation study) multicenter registry. Clin Cardiol 2018;41:470-475.
10. Gibson CM, Mehran R, Bode C, et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. N Engl J Med 2016;375:2423-2434.
11. Cannon CP, Bhatt DL, Oldgren J, et al. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. N Engl J Med 2017;377:1513-1524.
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for reporting observational studies. Int J Surg 2014;12:1495-1499.
13. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. J Clin Epidemiol 1995;48:999-1009.
14. Eguale T, Winslade N, Hanley JA, Buckeridge DL, Tamblyn R. Enhancing pharmacosurveillance with systematic collection of treatment indication in electronic prescribing: a validation study in Canada. Drug Saf 2010;33:559-567.

15. Wilchesky M, Tamblyn RM, Huang A. Validation of diagnostic codes within medical services claims. J Clin Epidemiol 2004;57:131-141.
16. Tamblyn R, Reid T, Mayo N, McLeod P, Churchill-Smith M. Using medical services claims to assess injuries in the elderly: sensitivity of diagnostic and procedure codes for injury ascertainment. J Clin Epidemiol 2000;53:183-194.
17. Humphries KH, Jackevicius C, Gong Y, et al. Population rates of hospitalization for atrial fibrillation/flutter in Canada. Can J Cardiol 2004;20:869-876.
18. Perreault S, Shahabi P, Cote R, et al. Rationale, design, and preliminary results of the Quebec Warfarin Cohort Study. Clin Cardiol 2018;
19. Jensen PN, Johnson K, Floyd J, Heckbert SR, Carnahan R, Dublin S. A systematic review of validated methods for identifying atrial fibrillation using administrative data. Pharmacoepidemiol Drug Saf 2012;21 Suppl 1:141-147.
20. Manuel des médecins spécialistes: rénumération à l'acte. https://www.ramq.gouv.qc.ca/fr/professionnels/medecins-specialistes/manuels/Pages/remuneration-acte.aspx. Accessed November 28th 2021, 2021.
21. Blais C LL, Hamel D, Brown K, Rinfret S, Cartier R, Giguère M, Carroll C, Beauchamp C, Bogaty P. Évaluation des soins et surveillance des maladies cardiovasculaires de santé publique du Québec et de L'institut national d'excellence en santé et services sociaux. Gouvernement du Québec, Institut national de santé publique , Institut national d'excellence en santé et des services sociaux 2012;1-9.
22. Roy L, Zappitelli M, White-Guay B, Lafrance JP, Dorais M, Perreault S. Agreement Between Administrative Database and Medical Chart Review for the Prediction of Chronic Kidney Disease G category. Can J Kidney Health Dis 2020;7:2054358120959908.
23. D'Hoore W, Bouckaert A, Tilquin C. Practical considerations on the use of the Charlson comorbidity index with administrative data bases. J Clin Epidemiol 1996;49:1429-1433.
24. Roy L, Zappitelli M, White-Guay B, Lafrance J-P, Dorais M, Perreault S. Agreement Between Administrative Database and Medical Chart Review for the Prediction of Chronic Kidney Disease G category. Can J Kidney Health Dis 2020;7:2054358120959908-2054358120959908.
25. Andrade JG, Verma A, Mitchell LB, et al. 2018 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation. Can J Cardiol 2018;34:1371-1392.
26. Mehta SR, Bainey KR, Cantor WJ, et al. 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Focused Update of the Guidelines for the Use of Antiplatelet Therapy. Can J Cardiol 2018;34:214-233.
27. Lopes RD, Heizer G, Aronson R, et al. Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. N Engl J Med 2019;380:1509-1524.
28. Vranckx P, Valgimigli M, Eckardt L, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. Lancet 2019;394:1335-1343.

29. Lane DA, Dagres N, Dan GA, et al. Antithrombotic treatment in patients with atrial fibrillation and acute coronary syndromes: results of the European Heart Rhythm Association survey. Europace 2019;21:1116-1125.
30. Park J, Choi EK, Han KD, et al. Temporal trends in prevalence and antithrombotic treatment among Asians with atrial fibrillation undergoing percutaneous coronary intervention: A nationwide Korean population-based study. PLoS One 2019;14:e0209593.
31. Eberhardt TE, Bungard TJ, Graham MM, Picard M, Wang GT, Ackman ML. Effect of New Evidence on Antithrombotic Therapies in Atrial Fibrillation Patients Who Undergo Percutaneous Coronary Intervention in Alberta, Canada. CJC Open 2021;4:378-382.
32. Lubitz SA, Khurshid S, Weng L-C, et al. Predictors of oral anticoagulant non-prescription in patients with atrial fibrillation and elevated stroke risk. Am Heart J 2018;200:24-31.
33. Marzec LN, Wang J, Shah ND, et al. Influence of Direct Oral Anticoagulants on Rates of Oral Anticoagulation for Atrial Fibrillation. J Am Coll Cardiol 2017;69:2475-2484.
34. Brais C, Larochelle J, Turgeon MH, et al. Predictors of Direct Oral Anticoagulants Utilization for Thromboembolism Prevention in Atrial Fibrillation. J Pharm Pharm Sci 2017;20:8-14.

Table 1. Baseline and demographic characteristics at cohort entry.

	Total Cohort (n=3,740)	Sub-cohort 2010-2011 (n=474)	Sub-cohort 2012-2015 (n=1,914)	Sub-cohort 2016-2017 (n=1,352)	p-value[a]
Age, mean ± SD median ± IQR	75.3 ±8.8 75.8 (69.7-81.9)	74.0 ± 9.7 75.0 (67.8-81.2)	75.1 ± 8.7 75.5 (69.5-81.5)	76.1 ± 8.7 76.4 (70.5-82.8)	<0.01
Male, n (%)	2,458 (65.7)	307 (64.8)	1,264 (66.0)	887 (65.6)	0.87
$CHADS_2$ score, mean ± SD median ± IQR	3.7 ± 1.5 4.0 (3.0-5.0)	3.6 ± 1.5 4.0 (3.0-5.0)	3.8 ± 1.5 4.0 (3.0-5.0)	3.8 ± 1.5 4.0 (3.0-5.0)	0.03
$CHADS_2$ score categories, n (%)					
Score 0-1	229 (6.1)	41 (8.7)	115 (6.0)	73 (5.4)	0.10
Score 2-3	1,410 (37.7)	187 (39.4)	704 (36.8)	519 (38.4)	
Score 4	991 (26.5)	125 (26.4)	517 (27.0)	349 (25.8)	
Score ≥ 5	1,110 (29.7)	121 (25.5)	578 (30.2)	411 (30.4)	
HAS-BLED score, mean ± SD median ± IQR	3.0 ± 1.3 3.0 (2.0-4.0)	2.8 ± 1.2 3.0 (2.0-3.0)	3.0 ± 1.3 3.0 (2.0-4.0)	3.0 ± 1.3 3.0 (2.0-4.0)	<0.01
HAS-BLED score ≥ 3, n (%)	2,427 (64.9)	276 (58.2)	1,283 (67.0)	868 (64.2)	<0.01
Charlson Comorbidity Index, mean ± SD median ± IQR	5.2 ± 3.5 5.0 (3.0-7.0)	4.6 ± 3.2 4.0 (2.0-6.0)	5.3 ± 3.4 5.0 (3.0-7.0)	5.3 ± 3.6 5.0 (3.0-7.0)	<0.01
Comorbidities within the 3 years prior to cohort entry, n (%)					
Hypertension	3,237 (86.6)	396 (83.5)	1,673 (87.4)	1,168 (86.4)	0.09
Coronary artery disease	3,697 (98.9)	471 (99.4)	1,900 (99.3)	1,326 (98.1)	<0.01
Acute myocardial infarction	2,300 (61.5)	285 (60.1)	1,233 (64.4)	782 (57.8)	<0.01
Chronic heart failure	1,795 (48.0)	205 (43.3)	943 (49.3)	647 (47.9)	0.06
Valvular heart disease	916 (24.5)	106 (22.4)	477 (24.9)	333 (24.6)	0.50
Stroke	449 (12.3)	53 (11.2)	234 (12.2)	172 (12.7)	0.68
Cardiomyopathy	397 (10.6)	49 (10.3)	201 (10.5)	147 (10.9)	0.92
Other cardiac dysrhythmias	995 (26.6)	107 (22.6)	541 (28.3)	347 (25.7)	0.03
Peripheral arterial disease	1,173 (31.4)	141 (29.8)	610 (31.9)	422 (31.2)	0.66
Dyslipidemia	2,829 (75.6)	342 (72.2)	1,451 (75.8)	1,036 (76.6)	0.14
Diabetes	1,686 (45.1)	201 (42.4)	882 (46.1)	603 (44.6)	0.32
Major bleeding	1,265 (33.8)	129 (27.2)	660 (34.5)	476 (35.2)	<0.01
Chronic renal failure (eGFR ≤ 30 mL/min)	239 (6.4)	29 (6.1)	125 (6.5)	85 (6.3)	0.93
Acute renal failure	921 (24.6)	73 (15.4)	495 (25.9)	353 (26.1)	<0.01
Liver disease	100 (2.7)	9 (1.9)	55 (2.9)	36 (2.7)	0.50
Chronic obstructive pulmonary disease	1,394 (37.3)	155 (32.7)	715 (37.4)	524 (38.8)	0.06
Systemic embolism	95 (2.5)	7 (1.5)	47 (2.5)	41 (3.0)	0.17
Helicobacter Pylori infection	30 (0.8)	5 (1.1)	15 (0.8)	10 (0.7)	0.80
Depression	331 (8.9)	37 (7.8)	180 (9.4)	114 (8.4)	0.44
Hypothyroidism	761 (20.4)	84 (17.7)	389 (20.3)	288 (21.3)	0.25
Neurological disorder	785 (21.0)	78 (16.5)	417 (21.8)	290 (21.5)	0.03
Malign cancer	895 (23.9)	88 (18.6)	451 (23.6)	356 (26.3)	<0.01
Medical procedures within the 3 years prior to cohort entry, n (%)					
Coronary artery bypass grafting	176 (4.7)	18 (3.8)	92 (4.8)	66 (4.9)	0.60
Implantable cardiac devices	18 (0.5)	8 (1.7)	8 (0.4)	2 (0.2)	<0.01
Medical services within the year prior to cohort entry, mean ± SD					
Number of specialty visits	4.2 ± 6.1	3.8 ± 5.4	4.3 ± 6.5	4.3 ± 5.7	0.18
Number of family physician visits	3.2 ± 7.9	4.4 ± 7.7	3.3 ± 9.0	2.7 ± 6.1	<0.01
Hospital services within the year prior to cohort entry, mean ± SD					
Number of emergency visits	6.0 ± 6.0	4.9 ± 4.7	6.2 ± 6.0	6.2 ± 6.4	<0.01
Number of all-cause hospital admissions	3.1 ± 2.2	3.0 ± 2.0	3.2 ± 2.3	3.1 ± 2.3	<0.01

ASA, acetylsalicylic acid; eGFR, estimated glomerular filtration rate; IQR, interquartile range.

[a] Significance applies to the difference between the three sub-cohorts.

473 **Table 2.** Medication and antithrombotic therapy during the year following cohort entry.

	Total Cohort (n=3,740)	Sub-cohort 2010-2011 (n=474)	Sub-cohort 2012-2015 (n=1,914)	Sub-cohort 2016-2017 (n=1,352)	p-value[a]
Antithrombotic therapy at 1 month following the cohort entry ‡, n (%)	*(n=3,552)*	*(n=451)*	*(n=1,812)*	*(n=1,289)*	
Low dose ASA (%)	3,141 (88.4)	414 (91.8)	1,613 (89.0)	1,114 (86.4)	<0.01
P2Y12 inhibitor					
Ticagrelor	332 (9.4)	1 (0.2)	171 (9.4)	160 (12.4)	<0.01
Clopidogrel	3,040 (85.6)	426 (94.5)	1,540 (85.0)	1,074 (83.3)	<0.01
Prasugrel	52 (1.5)	5 (1.1)	37 (2.0)	10 (0.8)	0.01
Oral anticoagulant					
Warfarin	1,118 (31.5)	223 (49.5)	676 (37.3)	219 (17.0)	<0.01
DOAC	865 (24.4)	12 (2.7)	327 (18.1)	526 (40.8)	<0.01
Warfarin and/or DOAC	1,945 (54.8)	232 (51.4)	983 (54.3)	730 (56.6)	0.13
Combination therapy					
DAPT	1,407 (39.6)	193 (42.8)	725 (40.0)	489 (37.9)	0.02[d]
Dual pathway[b]	232 (6.5)	15 (3.3)	111 (6.1)	106 (8.2)	
TATT[c]	1,652 (46.5)	209 (46.3)	843 (46.5)	600 (46.7)	
Antithrombotic therapy at 3 months following the cohort entry ‡, n (%)	*(n=3,477)*	*(n=442)*	*(n=1,770)*	*(n=1,265)*	
Low dose ASA (%)	2,753 (79,2)	394 (89.1)	1,465 (82.8)	894 (70.7)	<0.01
P2Y12 inhibitor					
Ticagrelor	269 (7.7)	1 (0.2)	143 (8.1)	125 (9.9)	<0.01
Clopidogrel	2,478 (71.3)	314 (71.0)	1,170 (66.1)	994 (78.6)	<0.01
Prasugrel	47 (1.4)	6 (1.4)	32 (1.8)	9 (0.7)	0.04
Oral anticoagulant					
Warfarin	1,037 (29.8)	206 (46.6)	624 (35.3)	207 (16.4)	<0.01
DOACDOAC	934 (26.9)	16 (3.6)	371 (21.0)	547 (43.2)	<0.01
Warfarin and/or DOAC	1,935 (55.7)	222 (50.2)	973 (55.0)	740 (58.5)	<0.01
Combination therapy					
DAPT	1,284 (36.9)	186 (42.1)	657 (37.1)	441 (34.9)	<0.01[d]
Dual pathway[b]	478 (13.8)	17 (3.9)	173 (9.8)	288 (22.8)	
TATT[c]	929 (26.7)	109 (24.7)	458 (25.9)	362 (28.6)	
Antithrombotic therapy at 6 months following the cohort entry ‡, n (%)	*(n=3,373)*	*(n=431)*	*(n=1,710)*	*(n=1,232)*	
Low dose ASA (%)	2,422 (71.8)	375 (87.0)	1,340 (78.4)	707 (57.4)	<0.01
P2Y12 inhibitor					
Ticagrelor	225 (6.7)	0 (0.0)	116 (6.8)	109 (8.9)	<0.01
Clopidogrel	2,119 (62.8)	284 (65.9)	982 (57.4)	853 (69.2)	<0.01
Prasugrel	42 (1.3)	4 (0.9)	29 (1.7)	9 (0.7)	0.06
Oral anticoagulant					
Warfarin	917 (27.2)	194 (45.0)	549 (32.1)	174 (14.1)	<0.01
DOAC	971 (28.8)	20 (4.6)	396 (23.2)	555 (45.1)	<0.01
Warfarin and/or DOAC	1,868 (55.4)	214 (49.7)	931 (54.4)	723 (58.7)	<0.01
Combination therapy					
DAPT	1,178 (34.9)	180 (41.8)	605 (35.4)	393 (31.9)	<0.01[d]
Dual pathway[b]	631 (18.7)	19 (4.4)	198 (11.6)	414 (33.6)	
TATT[c]	462 (13.7)	79 (18.3)	260 (15.2)	123 (10.0)	
Antithrombotic therapy at 12 months following the cohort entry ‡, n (%)	*(n=3,219)*	*(n=411)*	*(n=1,639)*	*(n=1,169)*	
Low dose ASA (%)	2,178 (67.7)	340 (82.7)	1,213 (74.0)	625 (53.5)	<0.01
P2Y12 inhibitor					
Ticagrelor	180 (5.6)	0 (0.0)	87 (5.3)	93 (8.0)	<0.01
Clopidogrel	1,668 (51.8)	248 (60.3)	742 (45.3)	678 (58.0)	<0.01
Prasugrel	35 (1.1)	3 (0.7)	24 (1.5)	8 (0.7)	0.13
Oral anticoagulant					
Warfarin	766 (23.8)	158 (38.4)	484 (29.5)	124 (10.6)	<0.01
DOAC	1,036 (32.2)	33 (8.0)	441 (26.9)	562 (48.1)	<0.01
Warfarin and/or DOAC	1,787 (55.5)	188 (45.7)	914 (55.8)	685 (58.6)	<0.01

Combination therapy					
DAPT	982 (30.5)	164 (39.9)	488 (29.8)	330 (28.2)	<0.01[d]
Dual pathway[b]	536 (16.7)	18 (4.4)	173 (10.6)	345 (29.5)	
TATT[c]	251 (7.8)	53 (12.9)	137 (8.4)	61 (5.2)	

ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; TATT, triple antithrombotic therapy.

[†] Medication at cohort entry was evaluated within the first 30 days following the discharge of the percutaneous coronary intervention (PCI) hospitalization, or within the first 30 days following the PCI diagnosis for patients not hospitalized for PCI.

[‡] Medication exposure was measured within the 14 days preceding and the 14 days following the time of follow-up (1 month, 6 months, 12 months).

[a] Significance applies to the difference between the three sub-cohorts.

[b] Dual pathway: P2Y12 inhibitor + oral anticoagulant.

[c] TATT: DAPT + oral anticoagulant.

[d] P-value for the association between the three categories of combination therapy (mutually exclusive) and the three categories of sub-cohort.

Table 3. Observed at 1 month following cohort entry versus guideline-expected proportions of oral anticoagulation.

	Pre-guidelines period (2012-2015) (n=1,812)†		
	Observed	**Expected dispensation according to 2016 CCS AF guidelines**	**p-value**
Anticoagulation, n (%)	983 (54.3)	1,601 (88.4)	<0.01
	Post-guidelines period (2016-2017) (n=1,289)‡		
	Observed	**Expected dispensation according to 2016 CCS AF guidelines**	**p-value**
Anticoagulation, n (%)	730 (56.6)	1,186 (89.7)	<0.01

AF, Atrial fibrillation; CCS, Canadian Cardiovascular Society.

† Among the 1,914 patients present in the sub-cohort 2012-2015, 1,812 had available data concerning the medication exposure at 1 month following the cohort entry.

‡ Among the 1,352 patients present in the sub-cohort 2016-2017, 1,289 had available data concerning the medication exposure at 1 month following the cohort entry.

493 **Table 4**. Determinants of oral anticoagulation prescribed within the month following
494 cohort entry.

Determinants	OAC Odds ratio (95% CI)		Warfarin Odds ratio (95% CI)		DOACs Odds ratio (95% CI)	
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
Age ≥ 65 vs < 65	1.72 (1.40-2.12)	1.29 (0.99-1.67)	1.59 (1.25-2.01)	1.18 (0.88-1.57)	1.27 (0.99-1.62)	1.18 (0.87-1.62)
Female vs male	1.08 (0.94-1.25)	0.91 (0.78-1.08)	1.11 (0.95-1.29)	0.98 (0.83-1.16)	0.98 (0.83-1.15)	0.88 (0.73-1.07)
$CHADS_2$ score ≥ 3 vs < 3	1.74 (1.48-2.04)	1.67 (1.33-2.09)	1.84 (1.52-2.22)	1.60 (1.25-2.05)	1.07 (0.89-1.29)	1.12 (0.86-1.46)
HAS-BLED score ≥ 3 vs < 3	0.91 (0.79-1.05)	0.85 (0.70-1.03)	1.15 (0.99-1.34)	1.00 (0.82-1.23)	0.75 (0.64-0.87)	0.84 (0.67-1.04)
Charlson Comorbidity Index ≥ 4 vs <4	1.33 (1.16-1.53)	1.28 (1.08-1.52)	1.40 (1.20-1.62)	1.18 (0.99-1.41)	1.02 (0.87-1.20)	1.17 (0.96-1.43)
Previous stroke (yes vs no)	1.43 (1.16-1.75)	1.33 (1.05-1.68)	1.39 (1.12-1.71)	1.32 (1.05-1.66)	1.09 (0.87-1.38)	1.04 (0.80-1.37)
Prior major bleeding (yes vs no)	0.87 (0.76-0.99)	0.81 (0.68-0.96)	1.03 (0.89-1.20)	0.88 (0.74-1.06)	0.80 (0.68-0.95)	0.87 (0.71-1.07)
Chronic renal failure (eGFR ≤ 30 mL/min) vs ≥ 30?	0.93 (0.71-1.23)	0.96 (0.71-1.29)	1.53 (1.16-2.02)	1.35 (0.99-1.84)	0.43 (0.29-0.64)	0.51 (0.33-0.79)
Peripheral artery disease (yes vs no)	1.03 (0.89-1.18)	0.90 (0.76-1.06)	1.11 (0.95-1.29)	0.99 (0.84-1.18)	0.90 (0.76-1.06)	0.84 (0.69-1.03)
Liver disease (yes vs no)	0.63 (0.41-0.95)	0.65 (0.41-1.03)	0.68 (0.42-1.10)	0.66 (0.39-1.09)	0.80 (0.48-1.34)	0.94 (0.54-1.63)
Medication use within the two weeks prior to cohort entry						
DOAC	6.27 (4.82-8.15)	7.79 (5.94-10.23)	0.60 (0.48-0.75)	0.71 (0.56-0.89)	9.22 (7.50-11.35)	9.04 (7.29-11.21)
Warfarin	4.42 (3.27-5.97)	6.18 (4.52-8.45)	8.19 (6.26-10.71)	8.14 (6.17-10.75)	0.24 (0.16-0.36)	0.37 (0.24-0.57)
Baseline ASA use at cohort entry (excluding antiplatelet)	0.54 (0.46-0.62)	0.49 (0.41-0.58)	0.68 (0.58-0.80)	0.61 (0.51-0.74)	0.61 (0.51-0.74)	0.60 (0.48-0.75)
Baseline P2Y12 inhibitor use	0.44 (0.35-0.55)	0.54 (0.42-0.70)	0.56 (0.43-0.73)	0.62 (0.46-0.83)	0.58 (0.43-0.77)	0.72 (0.52-1.00)

495 ASA, acetylsalicylic acid; CI, confidence interval; DOAC, direct oral anticoagulant; OAC, oral anticoagulation.

Figure 1. Flow chart of study design and patients of the study cohort. AF, Atrial fibrillation; CABG, Coronary artery bypass graft surgery; ICD (9-10), International Classification of Diseases; PCI, Percutaneous coronary intervention; RAMQ, *Régie de l'assurance maladie du Québec*.