Prescribing of two potentially interacting cardiovascular medications in atrial fibrillation patients on direct oral anticoagulants

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ABSTRACT

Background: Amiodarone and diltiazem are commonly recommended cardiovascular medications for use in atrial fibrillation (AF) patients. They are known to have drug-drug interactions (DDIs) with direct oral anticoagulants (DOACs). We aimed to evaluate frequency of use of amiodarone or diltiazem among continuous users of DOACs in AF patients and to determine factors associated with their co-use.
Methods: The study population included all AF patients with continuous DOAC use in Ontario, Canada, ≥66 years, from April 1, 2017 to March 31, 2018. Concurrent use of amiodarone or diltiazem was determined by identifying the presence of an overlapping prescription. Multivariable logistic regression models were used to identify predictors of amiodarone or diltiazem use.
Results: In total, 5,390 AF patients, ≥66 years, with continuous DOAC use were identified. Amiodarone was co-prescribed in 6.4% patients and diltiazem was co-prescribed in 11.2% patients. Prior percutaneous coronary intervention (PCI) and coronary artery bypass surgery (CABG) were associated with significantly increased odds of amiodarone co-use (OR 2.51 [95% CI 1.54, 4.09], p = 0.0002 and OR 5.28 [95% CI 3.52, 7.93], p= <0.001, respectively). Patients with a heart failure (HF) history also had increased co-use of amiodarone (OR 2.05 [95% CI 1.57, 2.67], p < 0.001). The presence of chronic obstructive pulmonary disease (COPD) was associated with significantly increased odds of diltiazem co-use (OR 1.58 [95% CI 1.31, 1.9], p=<0.001).
Conclusions: Among AF patients with continuous DOAC use, amiodarone was co-prescribed in 1 in 16 patients and diltiazem was co-prescribed in 1 in 9 patients. Predictors such as history of HF, PCI, CABG or COPD help identify vulnerable populations at increased risk of DDIs.

1. Introduction

Atrial fibrillation (AF) has emerged as the next epidemic in cardiovascular medicine [1]. In the United States, at least 3 to 6 million people have AF, and the numbers are projected to reach up to 16 million by 2050 [2,3]. In the last few years, use of direct oral anticoagulant (DOAC) prescriptions have increased substantially among patients with nonvalvular AF initiating oral anticoagulation therapy [4]. DOACs were assumed to overcome some of the limitations of Vitamin K antagonists (VKA) due to fewer drug interactions and more predictable pharmacokinetic and pharmacodynamic profiles [5]. However, recent data have highlighted potential drug-drug interactions (DDIs) among DOAC users with potentially increased risk of bleeding [6–12]. This is related to the absorption, metabolism and elimination of DOACs that are dependent on the permeability glycoprotein (P-gp) transporter system and cytochrome P450 3A4 (CYP3A4) enzymes. All

DOACs are substrates of P-gp, and, with the exception of dabigatran, are metabolized to some extent by CYP3A4. Hence inhibition of P-gp or CYP3A4 can increase serum DOAC levels, potentially increasing anticoagulant effects leading to an increased bleeding risk [12,13].

Amiodarone and diltiazem are commonly recommended cardiovascular medications in AF patients. Amiodarone is a moderate P-gp inhibitor and weak CYP3A4 inhibitor, increasing serum levels of DOACs by 40–60%. Diltiazem is a P-gp inhibitor and weak CYP3A4 inhibitor, increasing the serum levels of DOACs by 40% [14]. In a recent retrospective cohort study, the combination of a DOAC with amiodarone or diltiazem was associated with an increased risk of major bleeding [7].

Given the concerns related to DDIs, current consensus guidelines recommend that clinicians should consider alternative combinations to minimize the risk of bleeding [15–17]. While the recent literature highlights the significant risk of bleeding with such combinations [7,14], the knowledge on the current frequency and predictors of use of amiodarone or diltiazem among AF DOACs users is limited. Hence, our study aimed to evaluate frequency of use of amiodarone or diltiazem among continuous users of DOACs in AF patients and assess factors associated with their use.

2. Methods

2.1. Study design and data sources

We conducted a retrospective cohort study using multiple administrative databases in Ontario, Canada. The study population included all AF patients with continuous DOAC use in Ontario, Canada, ≥66 years, from April 1, 2017 to March 31, 2018. We used linked datasets housed at ICES (formerly known as the Institute for Clinical Evaluative Sciences), Ontario. As a prescribed entity under Ontario's privacy legislation, ICES is authorized to collect and use health care data for the purposes of health system analysis, evaluation and decision support. These datasets were linked using unique encoded identifiers and analyzed at ICES.

We used the following databases: (1) Ontario Drug Benefit Program, which records prescription drugs dispensed to all Ontario residents aged 65 years or older; 2) hospitalization records from the Canadian Institute for Health Information Discharge Abstract Database, which contains a detailed record of all hospital admissions, including diagnostic and procedural information; 3) the Ontario Health Insurance Plan, which provides information on physician claims for inpatient and outpatient services; and 4) the Ontario Registered Persons Database, which contains basic demographic information for each Ontario resident [18].

2.2. Study population and individual observation period

Initially, we created a cohort of adults with AF (≥66 years) using a previously validated algorithm, from April 1, 2011 to March 31, 2018 [19]. Then we limited the cohort to AF patients between April 1, 2017 to March 31, 2018 with at least a single DOAC prescription. We limited our cohort to the most recent year to reflect the current practice in light of the recent literature highlighting the potential DDIs with amiodarone or diltiazem.

Finally, we restricted our cohort to continuous DOACs users. We applied a commonly used definition for continuous DOAC use [20]. To define the continuous DOAC use, a maximum gap of 30 days between DOACs prescriptions was allowed, otherwise patients would be considered to have discontinued DOACs and were excluded from the cohort. DOAC fill dates and days supplied per prescription were used to determine treatment duration. A similar method has been used previously to define courses of continuous drug utilization [20–23].

2.3. Outcomes

Our outcomes are the co-use of amiodarone or diltiazem among continuous users of DOACs in AF patients. We captured any amiodarone or diltiazem co-prescription, of any duration, among our AF continuous DOAC user cohort from April 1, 2017 to March 31, 2018.

2.4. Covariates

Several covariates were examined in this study related to patients' demographics, comorbidities and relevant medications. Patient demographic characteristics included age, sex, and geographic factors (rural vs urban). Covariates such as hypertension, diabetes (DM), stroke, heart failure (HF), myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass surgery (CABG), chronic obstructive pulmonary disease (COPD), chronic kidney disease, liver disease, deep vein thrombosis, cognitive Impairment/dementia, peripheral vascular disease, rheumatic disease, any cancer – metastatic, any cancer – primary, and anemia were included. ICD-10 codes used to identify patients with chronic kidney disease This includes patients with chronic kidney disease stage 1 to stage 5. Baseline drugs such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, digoxin, clopidogrel, insulin, oral hypoglycemic agents, lipid lowering agents, nonsteroidal anti-inflammatory drugs and proton pump inhibitors were also assessed. We included the Charlson Comorbidity Index that assesses comorbidity level by taking into account both the number and severity of pre-defined comorbid conditions. It provides a weighted score of a patient's comorbidities which can be used to predict short term and long-term outcomes.

3. Statistical analysis

Two separate analyses were performed to estimate rates and identify predictors of prescribing amiodarone or diltiazem among AF continuous DOACs users. Baseline characteristics were compared between those co-prescribed either amiodarone or diltiazem with those not co-prescribed. The normality of continuous variables was assessed by visually inspecting histograms and quantile–quantile (q-q) plots, and performing the Shapiro-Wilk test of normality. Continuous, normally distributed variables were compared using Student's T-test. For continuous non-normally distributed variables, the Wilcoxon Rank Sum test was used. Associations between categorical variables were assessed with the chi-square test or Fisher's exact test. To identify factors associated with the co-prescription of amiodarone or diltiazem, a multivariable logistic regression was constructed. Patient-related independent variables were selected *a priori* for this model based on clinical judgement. Variables were assessed for collinearity. Selection for exclusion or inclusion of collinear variables was performed on the basis of clinical judgement. A p-value of < 0.05 was considered to be statistically significant.

Model assumptions were verified. Model fit was assessed using the Hosmer-Lemeshow test for fit. Model overspecification was mitigated by limiting the maximum number of independent variables to the clinically important ones for our hypothesis. Potential influential outliers were verified by inspection of several casewise diagnostics plots. We performed a sensitivity analysis capturing the rate and identifying predictors of co-prescribing amiodarone or diltiazem among AF patients with at least a single DOAC prescription. Analyses were conducted at ICES using SAS version 9.4.

The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

4. Results

4.1. AF patients on continuous DOACs

There were 11,204 AF patients, $\geq$66 years, with at least a single DOAC prescription dispensed identified between April 1, 2017 to March 31, 2018. We restricted our cohort to AF patients who are continuous DOAC users, where a maximum gap of 30 days between DOAC prescriptions was allowed, resulting in 5,390 patients Fig. 1.

A total of 5,390 patients AF patients on continuous DOAC use, with median age of 81 years (IQR 75–87), 48.8% were male, 88.8% patients had HTN, 41% patients had DM, 38% patients had HF and 10.8% patients had MI. In the cohort, 4% patients had history of PCI and 3.3% patients had CABG. Amiodarone was used in 6.4% of patients, diltiazem was used in 11.2% of patients, beta blockers were used in 44.8% and lipid lowering agents in 52.3% of patients. Baseline characteristics of the AF patients on continuous DOACs are shown in Table 1.

4.2. Rates and predictors of co-use amiodarone

Among the AF continuous DOAC user cohort, amiodarone was co-used in 343 (6.4%) patients. Patients with co-use of amiodarone were younger (median 78 years (IQR 71–85) vs. 81 years (IQR 75–87), $p < 0.001$), had lower rates of prior stroke (5.5% vs. 11.3%, $p < 0.001$) but more HF (50.4% vs. 37.1%, $p < 0.001$), MI (17.7% vs. 10.2%, $p < 0.001$), PCI (9.6% vs. 3.6%, $p < 0.001$) and CABG (14.5% vs. 2.5%, $p < 0.001$) in comparison to patients with no amiodarone co-use. The remaining variables are highlighted in Table 1S.

In the multivariable logistic regression model, a history of PCI or CABG was associated with significantly increased odds of co-use of amiodarone among AF DOAC patients (OR 2.51 [95% CI 1.54, 4.09], $p = 0.0002$ and OR 5.28 [95% CI 3.52, 7.93], p= <0.001, respectively). Patients with a HF history also had increased co-use of amiodarone (OR 2.05 [95% CI 1.57, 2.67], $p < 0.001$). There were no other variables associated with increased co-use of amiodarone as shown in Table 2. History of stroke and digoxin use were associated with decreased co-use of amiodarone (OR 0.53 [95% CI 0.32, 0.89], $p = 0.0165$ and OR 0.37 [95% CI 0.17, 0.82], $p = 0.0149$) (Table 2).

4.3. Rates and predictors of co-use diltiazem

Among the AF continuous DOACs users, diltiazem was co-used in 604 (11.2%) patients. Patients with co-use of diltiazem were younger (median 80 years (IQR 74–86) vs. 81 years (IQR 75–87) $p = 0.011$), less male (37.0% vs 50.2%, $p < 0.001$), less likely to have had a stroke history (7.4% vs. 11.4%, $p = 0.003$), HF (33.1% vs. 38.6%, $p = 0.009$), MI (4.8% vs. 11.5%, $p < 0.001$), PCI (1.8% vs. 4.3% $p = 0.003$) and CABG (1.1% vs. 3.5%, $p = 0.002$), but more often had COPD (19.2% vs. 11.2%, $p < 0.001$). The remaining clinical variables are highlighted in Table 2S,

The presence of COPD was associated with significantly increased diltiazem co-use among AF DOAC patients (OR 1.58 [95% CI 1.31, 1.9], p=<0.001), among other factors shown in Table 3. Patients with history of MI or stroke were less likely to have diltiazem co-use (OR 0.48 [95% CI 0.31, 0.75], $p = 0.0014$ and OR 0.63 [95% CI 0.45, 0.9], $p = 0.0127$, respectively) when adjusted for important patient-level factors. Other factors associated with lower odds of co-use are shown in Table 3.
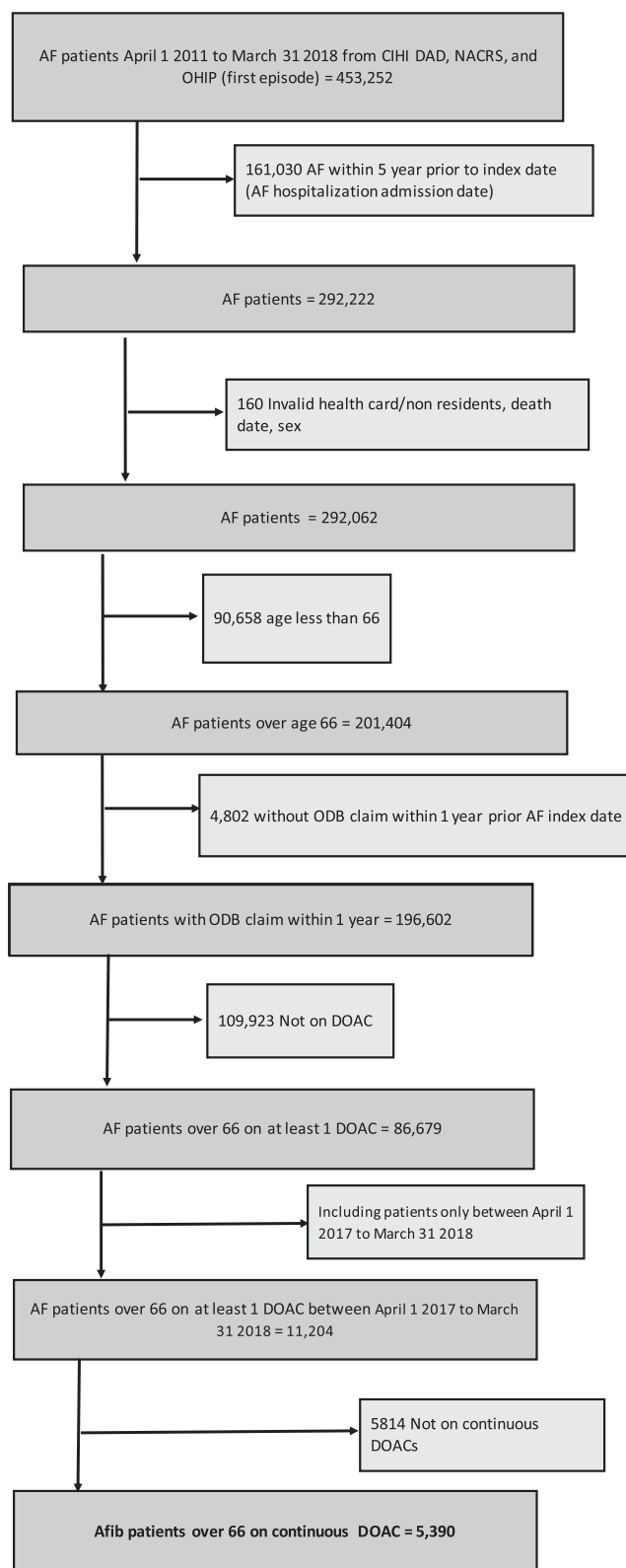

Fig. 1. Cohort Creation.

4.4. Sensitivity analysis

Among 11,204 AF patients with at least a single DOAC prescription, amiodarone was co-used in 7.7% patients and diltiazem was co-used in 12.5% patients.

Table 1
Characteristics and comorbidities at baseline among atrial fibrillation patients on DOACs with amiodarone or diltiazem co-prescription.

Predictor	AF patients on DOACs	AF on DOACs with Amiodarone	AF on DOACs with Diltiazem
	(N = 5,390)	(N = 343)	(N = 604)
Age (median, IQR), y	81 (75–87)	78 (71–85)	80 (74–86)
Sex (# of male, (n, %))	2631 (48.8%)	185 (53.9%)	224 (37.0%)
Rural (n, %)	697 (13%)	43 (12.5%)	102 (16.8%)
Charlson grp (0) (n, %)	1894 (35.1%)	112 (32.6%)	242 (40.0%)
Charlson grp (1) (n, %)	1129 (21%)	74 (21.5%)	120 (19.8%)
Charlson grp (2) (n, %)	832 (15.3%)	52 (15.1%)	111 (18.3%)
Charlson grp (3 +) (n, %)	1544 (28.9%)	105 (30.6%)	131 (21.6%)
Hypertension (n, %)	4787 (88.8%)	308 (89.8%)	535 (88.5%)
Diabetes (n, %)	2207 (41%)	147 (42.8%)	233 (38.5%)
Stroke (n, %)	593 (11.0%)	19 (5.5%)	45 (7.4%)
Congestive Heart failure (n, %)	2048 (38.0%)	173 (50.4%)	200 (33.1%)
Myocardial Infarction (n, %)	580 (10.8%)	61 (17.7%)	29 (4.8%)
Percutaneous Coronary Intervention (n, %)	218 (4.0%)	33 (9.6%)	11 (1.8%)
Coronary Artery Bypass Surgery (n, %)	179 (3.3%)	50 (14.5%)	7 (1.1%)
Chronic obstructive pulmonary disease (n, %)	1837 (34.1%)	118 (34.4%)	116 (19.2%)
Chronic kidney disease (n, %)	256 (4.8%)	19 (5.5%)	15 (2.4%)
Deep vein thrombosis (n, %)	260 (4.8%)	16 (4.6%)	20 (3.3%)
Cognitive Impairment/ Dementia (n, %)	962 (17.9%)	35 (10.2%)	105 (17.3%)
Peripheral vascular disease (n, %)	1008 (18.7%)	85 (24.7%)	80 (13.2%)
Any Cancer - primary (n, %)	495 (9.2%)	32 (9.3%)	49 (8.1%)
Anemia (n, %)	677 (12.6%)	54 (15.7%)	65 (10.7%)
Number of all cause ED visits in previous year (Median (IQR))	1 (1–3)	1 (1–2)	1 (1–2)
Number of All cause hospitalization in previous year (Median (IQR))	1 (1–1)	1 (1–2)	1 (0–1)
Medication use in preceding 90 days, (n, %)			
Angiotensin-converting enzyme inhibitors	1679 (31.2%)	118 (34.4%)	181 (29.9%)
Angiotensin II receptor blockers	1091 (20.2%)	63 (18.3%)	121 (20.0%)
Beta-blockers	2417 (44.8%)	173 (50.4%)	168 (27.8%)
Digoxin	217 (4.0%)	7 (2.0%)	24 (3.9%)
Clopidogrel	485 (9%)	38 (11.0%)	41 (6.7%)
Insulin	334 (6.2%)	19 (5.5%)	30 (4.9%)
Oral hypoglycemic agents	1099 (20.4%)	67 (19.5%)	118 (19.5%)
Lipid lowering agents	2821 (52.3%)	193 (56.2%)	290 (48.0%)
Nonsteroidal anti-inflammatory drugs	389 (7.2%)	31 (9.0%)	45 (7.4%)
Proton pump inhibitors	1979 (36.7%)	137 (39.9%)	223 (36.9%)

Table 2
Association between prescribing Amiodarone and clinical predictors among atrial fibrillation patients on DOACs.

Predictor	Multivariable Analysis	
	OR (95% CI)	p-value
Age	0.96 (0.94, 0.97)	**<0.001**
Sex M vs F	0.93 (0.74, 1.19)	0.6004
Rural	0.89 (0.63, 1.26)	0.5264
Charlson grp 1 vs 0	1.04 (0.73, 1.47)	0.8111
Charlson grp 2 vs 0	0.76 (0.49, 1.16)	0.2072
Charlson grp 3 + vs 0	0.62 (0.36, 1.07)	0.0914
Hypertension	1.11 (0.75, 1.65)	0.5751
Diabetes	1.09 (0.8, 1.5)	0.5619
Stroke	0.53 (0.32, 0.89)	**0.0165**
Congestive Heart failure	2.05 (1.57, 2.67)	**<0.001**
Myocardial Infarction	1.01 (0.68, 1.49)	0.9597
Percutaneous Coronary Intervention	2.51 (1.54, 4.09)	**0.0002**
Coronary Artery Bypass Surgery	5.28 (3.52, 7.93)	**<0.001**
COPD	0.91 (0.71, 1.17)	0.4957
Chronic kidney disease	1.27 (0.72, 2.22)	0.3967
Liver disease	1.2 (0.46, 3.13)	0.6957
Deep vein thrombosis	0.84 (0.48, 1.45)	0.5349
Cognitive Impairment/Dementia	0.69 (0.47, 1.01)	0.0598
Peripheral vascular disease	1.49 (0.98, 2.27)	0.0598
Rheumatic disease	0.75 (0.26, 2.15)	0.5953
Any Cancer - metastatic	0.64 (0.23, 1.75)	0.3929
Any Cancer - primary	1.38 (0.86, 2.2)	0.1748
Anemia	1.22 (0.87, 1.71)	0.2378
Number of all cause ED visits in previous year	0.95 (0.88, 1.02)	0.1936
Number of All cause hospitalization in previous year	1.07 (0.92, 1.24)	0.3688
Medication use in preceding 90 days		
Angiotensin-converting enzyme inhibitors	0.97 (0.74, 1.28)	0.867
Angiotensin II receptor blockers	0.84 (0.61, 1.15)	0.2899
Beta-blockers	1.02 (0.8, 1.3)	0.8495
Digoxin	0.37 (0.17, 0.82)	**0.0149**
Clopidogrel	1.01 (0.68, 1.5)	0.943
Insulin	0.67 (0.39, 1.13)	0.1386
Oral hypoglycemic agents	0.74 (0.51, 1.08)	0.1294
Lipid lowering agents	0.97 (0.75, 1.25)	0.8275
Nonsteroidal anti-inflammatory drugs	1.26 (0.84, 1.88)	0.2587
Proton pump inhibitors	1.08 (0.84, 1.37)	0.5346

When adjusted for important patient-level factors, among the cohort of AF patients with at least a single DOAC prescription, the presence of PCI or CABG significantly increased the odds of co-use amiodarone among AF DOAC patients (OR 1.58 [95% CI 1.27, 2.23], p = 0.0082 and OR 5.79 [95% CI 4.49, 7.48], p= <0.001, respectively). Patients with a HF history also had increased co-use of amiodarone (OR 1.726 [95% CI 1.452, 2.053], p < 0.001).

Table 3
Association between prescribing Diltiazem and clinical predictors among atrial fibrillation patients on DOACs.

Predictor	Multivariable Analysis	
	OR (95% CI)	p-value
Age	0.97 (0.96, 0.98)	**0.0002**
Sex M vs F	0.54 (0.45, 0.65)	**<0.001**
Rural	1.41 (1.11, 1.79)	**0.0048**
Charlson grp 1 vs 0	1.05 (0.8, 1.37)	0.7055
Charlson grp 2 vs 0	1.61 (1.18, 2.21)	**0.0027**
Charlson grp 3 + vs 0	1.29 (0.85, 1.96)	0.222
Hypertension	1.23 (0.92, 1.65)	0.1508
Diabetes	0.96 (0.75, 1.22)	0.7424
Stroke	0.63 (0.45, 0.9)	**0.0127**
Congestive Heart failure	0.91 (0.74, 1.13)	0.4308
Myocardial Infarction	0.48 (0.31, 0.75)	**0.0014**
Percutaneous Coronary Intervention	0.76 (0.38, 1.49)	0.4297
Coronary Artery Bypass Surgery	0.49 (0.22, 1.09)	0.0816
COPD	1.58 (1.31, 1.9)	**<0.001**
Chronic kidney disease	0.56 (0.31, 1.0)	0.0525
Liver disease	0.66 (0.25, 1.72)	0.4002
Deep vein thrombosis	0.65 (0.40, 1.06)	0.0855
Cognitive Impairment/Dementia	1.01 (0.79, 1.29)	0.9225
Peripheral vascular disease	0.76 (0.54, 1.08)	0.1348
Rheumatic disease	1.18 (0.58, 2.39)	0.6425
Any Cancer - metastatic	1.17 (0.59, 2.33)	0.646
Any Cancer - primary	0.74 (0.5, 1.1)	0.1395
Anemia	0.95 (0.71, 1.28)	0.7679
Number of all cause ED visits in previous year	0.99 (0.94, 1.05)	0.966
Number of All cause hospitalization in previous year	0.86 (0.76, 0.98)	**0.0259**
Medication use in preceding 90 days		
Angiotensin-converting enzyme inhibitors	1.11 (0.9, 1.37)	0.3236
Angiotensin II receptor blockers	0.98 (0.77, 1.25)	0.8817
Beta-blockers	0.44 (0.36, 0.53)	**<0.001**
Digoxin	1.24 (0.79, 1.95)	0.3414
Clopidogrel	0.99 (0.69, 1.41)	0.9809
Insulin	0.86 (0.56, 1.31)	0.4873
Oral hypoglycemic agents	1.14 (0.85, 1.54)	0.3696
Lipid lowering agents	1.0 (0.82, 1.21)	0.9936
Nonsteroidal anti-inflammatory drugs	0.86 (0.61, 1.2)	0.3825
Proton pump inhibitors	1.1 (0.91, 1.34)	0.286

The presence of COPD was associated with significantly increased diltiazem co-use among AF DOAC patients (OR 1.49 [95% CI 1.32, 1.69], p=<0.001) when adjusted for important patient-level factors. Patients with history of MI or stroke were less likely to have a diltiazem co-use (OR 0.544 [95% CI 0.398, 0.743], p = 0.001 and 0.515 [95% CI 0.388, 0.684], p < 0.001, respectively). Clinical variables and factors associated with co-use of amiodarone or diltiazem are shown in Supplementary Appendix.

5. Discussion

In this population-based study of unselected AF patients with continuous DOAC use, we found the following: 1) amiodarone was co-prescribed in 6.4% and diltiazem was co-prescribed in 11.2% patients, 2) the presence of HF, PCI or CABG significantly increased the odds of co-use of amiodarone, and 3) the presence of COPD was associated with significantly increased diltiazem co-use.

A recent retrospective cohort study using data from the Taiwan National Health Insurance database; including 91 330 patients with nonvalvular atrial fibrillation who received at least 1 DOAC prescription, amiodarone was co-prescribed in 21.1%, and diltiazem in 22.7% of the patients. This is somewhat higher than what is reported in our cohort and in the original DOAC trials, such as, the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) and the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trials, which reported that approximately 10% of DOAC users were prescribed amiodarone [24–26]. There is no specific data on diltiazem frequency among AF patients on continuous DOACs, but the ARISTOTLE trial reported that 30% of the patients on DOACs were also on calcium channel blockers [25]. The current literature on the rates of use amiodarone or diltiazem among AF DOAC patients is limited. Our cohort is likely to represent the actual frequency of use of amiodarone or diltiazem in current clinical practice. This is related to the fact that our cohort was limited to continuous DOAC users; applying a rigorous definition for continuous use while capturing any prescription of amiodarone or diltiazem. Also, when performing a sensitivity analysis among AF with at least single DOAC prescription, we found a similar frequency of use of amiodarone or diltiazem.

Similar to our results, in a subgroup analysis of the ARISTOTLE trial, AF patients on DOACs who received amiodarone were younger, more likely to have heart failure and less likely to have had a previous stroke [24]. Nevertheless, the current literature is very limited on identifying predictors of use of amiodarone or diltiazem among AF patients on DOACs. To the best of our knowledge, our study provides the first comprehensive data on the predictors of the use of amiodarone or diltiazem in such patient populations.

Recent studies have highlighted the risk of bleeding related to the concurrent use of DOACs and some medications that share the same metabolic pathway with subsequent DDIs [7,27]. Amiodarone and diltiazem are known to have DDIs with DOACs with potentially increasing risk of bleeding [7,14]. Amiodarone is considered a moderate P-gp competitor and weak CYP3A4 inhibitor increasing serum levels of DOACs by 40–60%. Diltiazem is a P-gp competitor and weak CYP3A4 inhibitor increasing the serum levels of DOACs by 40%. There is limited data on the risk of bleeding with the use of amiodarone or diltiazem in AF patients on DOACs and future studies should focus on the risk of bleeding with the use of cardiovascular medications among DOAC users as the current literature has been so far focusing mostly on DDIs related to non-cardiac medications [8,11,27].

There are several clinical implications of our findings. First, our study highlights despite potential adverse effects of co-use of amiodarone or diltiazem with DOACs, they were still relatively frequently used. More efforts should focus in minimizing this care

gap by consideration of alternative drugs combinations with less potential DDIs; and close monitoring if such combinations are being used. Second, our study identifies specific vulnerable patient populations, such as those with HF, PCI, CABG, or COPD, that are at risk for possible DDIs with potential increased bleeding risk. More attention should be given while co-prescribing drugs with possible DDIs in those patients. Future efforts should examine the risk of bleeding on such vulnerable patient populations. Also, we identified patients that are less likely to have DDIs, such as patients with MI who were less likely to have diltiazem co-use (OR 0.48 [95% CI 0.31, 0.75], p = 0.0014). We believe that this is related to the fact that the majority of AF patients with MI are likely to be started on other medications (such as B-blockers). Also, many of the patients with MI suffer from LV dysfunction that preclude the use of diltiazem. Finally, awareness of existing DDIs with amiodarone or diltiazem is critical while managing AF patients on DOACs to reduce the risk of major bleeding in such patients with multiple comorbidities.

5.1. Limitations

The retrospective nature of this study is a limitation despite careful adjustment for important clinical factors. To define continuous DOAC use, a maximum gap of 30 days between DOAC prescriptions was allowed. This method was used previously to define courses of continuous drug utilization but has some limitations [20]. For example, patients who had gaps of more than 30 days might have continued to take DOACs and had co-use in-between the gaps, yet were still excluded from our continuous use cohort. Also, we were not able to verify whether patients took the medications and could not identify short interruptions or actual discontinuation of medications. The co-prescribing rates may have even been higher, but pharmacists may have intervened to recommend to avoid such combinations if possible. The lack of the incidence of bleeding is a limitation of this study. Finally, the data reflects the practice on a specific population in Canada and therefore cannot be extrapolated to other regions.

Efforts have been made to overcome some of the limitations of our study. The use of multiple data sources, along with the application of well validated algorithms would minimize misclassification. Also, including inpatient and outpatient AF will ensure external generalizability of our results.

6. Conclusions

Among AF patients with continuous DOAC use, amiodarone was co-prescribed in 6.4% patients and diltiazem was co-prescribed in 11.2% patients. The presence of HF, PCI or CABG was associated with increased amiodarone co-prescription. The odds of co-use of amiodarone were five times higher in patients who had CABG. The presence of COPD was associated with increased diltiazem co-prescription. Future efforts should focus on examining the risk of bleeding in these vulnerable populations exposed to major DOAC DDIs.

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Declaration of Competing Interest

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2021.100788.

References

[1] G.Y. Lip, P. Kakar, T. Watson, Atrial fibrillation–the growing epidemic, Heart 93 (2007) 542–543.

[2] B.A. Williams, A.M. Honushefsky, P.B. Berger, Temporal Trends in the Incidence, Prevalence, and Survival of Patients With Atrial Fibrillation From 2004 to 2016, Am. J. Cardiol. 120 (2017) 1961–1965.

[3] J. Kornej, C.S. Borschel, E.J. Benjamin, R.B. Schnabel, Epidemiology of Atrial Fibrillation in the 21st Century: Novel Methods and New Insights, Circ. Res. 127 (2020) 4–20.

[4] J. Zhu, G.C. Alexander, S. Nazarian, J.B. Segal, A.W. Wu, Trends and Variation in Oral Anticoagulant Choice in Patients with Atrial Fibrillation, 2010–2017, Pharmacotherapy 38 (2018) 907–920.

[5] A. Di Minno, B. Frigerio, G. Spadarella, A. Ravani, D. Sansaro, M. Amato, J.P. Kitzmiller, M. Pepi, E. Tremoli, D. Baldassarre, Old and new oral anticoagulants: Food, herbal medicines and drug interactions, Blood Rev. 31 (2017) 193–203.

[6] I. Celikyurt, C.R. Meier, M. Kuhne, B. Schaer, Safety and Interactions of Direct Oral Anticoagulants with Antiarrhythmic Drugs, Drug Saf. 40 (2017) 1091–1098.

[7] S.H. Chang, I.J. Chou, Y.H. Yeh, M.J. Chiou, M.S. Wen, C.T. Kuo, L.C. See, C.F. Kuo, Association Between Use of Non-Vitamin K Oral Anticoagulants With and Without Concurrent Medications and Risk of Major Bleeding in Nonvalvular Atrial Fibrillation, JAMA 318 (2017) 1250–1259.

[8] M. Fralick, D.N. Juurlink, T. Marras, Bleeding associated with coadministration of rivaroxaban and clarithromycin, CMAJ 188 (2016) 669–672.

[9] J. Perram, J. Joseph, C. Holloway, Novel oral anticoagulants and HIV: dabigatran use with antiretrovirals, BMJ Case Rep. 2015 (2015).

[10] C. Stollberger, Drug interactions with new oral anticoagulants in elderly patients, Expert Rev. Clin. Pharmacol. 10 (2017) 1191–1202.

[11] C. Stollberger, J. Finsterer, Interactions between non-vitamin K oral anticoagulants and antiepileptic drugs, Epilepsy Res. 126 (2016) 98–101.

[12] C. Voukalis, G.Y. Lip, E. Shantsila, Drug-drug interactions of non-vitamin K oral anticoagulants, Expert Opin. Drug Metab. Toxicol. 12 (2016) 1445–1461.

[13] T. Hellwig, M. Gulseth, Pharmacokinetic and pharmacodynamic drug interactions with new oral anticoagulants: what do they mean for patients with atrial fibrillation?, Ann. Pharmacother. 47 (2013) 1478–1487.

[14] Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Collins R, Camm AJ, Heidbuchel H and Group ESCSD. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018;39:1330-1393.

[15] Thrombosis Canada. Clinical guides. http://thrombosiscanada.ca/clinicalguides/#.

[16] Chen A, Stecker E and B AW. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges. J Am Heart Assoc. 2020;9:e017559.

[17] Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Collins R, Camm AJ and Heidbuchel H. [The 2018 European Heart Rhythm Association

Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary]. Kardiol Pol. 2018;76:1283-1298.

[18] D.T. Ko, N.D. Dattani, P.C. Austin, M.J. Schull, J.S. Ross, H.C. Wijeysundera, J.V. Tu, M. Eberg, M. Koh, H.M. Krumholz, Emergency Department Volume and Outcomes for Patients After Chest Pain Assessment, Circ. Cardiovasc Qual. Outcomes. 11 (2018) e004683.

[19] K. Tu, R. Nieuwlaat, S.Y. Cheng, L. Wing, N. Ivers, C.L. Atzema, J.S. Healey, P. Dorian, Identifying Patients With Atrial Fibrillation in Administrative Data, Can. J. Cardiol. 32 (2016) 1561–1565.

[20] P.A. Noseworthy, X. Yao, N.S. Abraham, L.R. Sangaralingham, R.D. McBane, N.D. Shah, Direct Comparison of Dabigatran, Rivaroxaban, and Apixaban for Effectiveness and Safety in Nonvalvular Atrial Fibrillation, Chest 150 (2016) 1302–1312.

[21] D.N. Juurlink, T. Gomes, D.T. Ko, P.E. Szmitko, P.C. Austin, J.V. Tu, D.A. Henry, A. Kopp, M.M. Mamdani, A population-based study of the drug interaction between proton pump inhibitors and clopidogrel, CMAJ 180 (2009) 713–718.

[22] D.N. Juurlink, M. Mamdani, A. Kopp, A. Laupacis, D.A. Redelmeier, Drug-drug interactions among elderly patients hospitalized for drug toxicity, JAMA 289 (2003) 1652–1658.

[23] M.M. Mamdani, K. Tu, C. van Walraven, P.C. Austin, C.D. Naylor, Postmenopausal estrogen replacement therapy and increased rates of cholecystectomy and appendectomy, CMAJ 162 (2000) 1421–1424.

[24] Flaker G, Lopes RD, Hylek E, Wojdyla DM, Thomas L, Al-Khatib SM, Sullivan RM, Hohnloser SH, Garcia D, Hanna M, Amerena J, Harjola VP, Dorian P, Avezum A, Keltai M, Wallentin L, Granger CB, Committees A and Investigators. Amiodarone, anticoagulation, and clinical events in patients with atrial fibrillation: insights from the ARISTOTLE trial. J Am Coll Cardiol. 2014;64:1541-50

[25] Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L, Committees A and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981-92.

[26] S.J. Connolly, M.D. Ezekowitz, S. Yusuf, J. Eikelboom, J. Oldgren, A. Parekh, J. Pogue, P.A. Reilly, E. Themeles, J. Varrone, S. Wang, M. Alings, D. Xavier, J. Zhu, R. Diaz, B.S. Lewis, H. Darius, H.C. Diener, C.D. Joyner, L. Wallentin, Committee R-LS and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation, N. Engl. J. Med. 361 (2009) 1139–1151.

[27] K. Hill, E. Sucha, E. Rhodes, M. Carrier, A.X. Garg, Z. Harel, G.L. Hundemer, E.G. Clark, G. Knoll, E. McArthur, M.M. Sood, Risk of Hospitalization With Hemorrhage Among Older Adults Taking Clarithromycin vs Azithromycin and Direct Oral Anticoagulants. *JAMA*, Intern. Med. (2020).