Original Article

Antithrombotic Therapy After Percutaneous Coronary Intervention in Patients With Atrial Fibrillation: Findings From the CONNECT AF+PCI Study

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ABSTRACT

Background: In patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI), selecting an antithrombotic regimen requires balancing risks of ischemic cardiac events, stroke, and bleeding.
Methods: We studied 467 patients with AF undergoing PCI in the time period from December 2015 to July 2018 identified via a chart audit

RÉSUMÉ

Introduction : Les patients atteints de fibrillation auriculaire (FA) qui subissent une intervention coronarienne percutanée (ICP) et choisissent un schéma posologique antithrombotique ont besoin de peser les risques d'événements cardiaques d'origine ischémique, d'accidents vasculaires cérébraux et d'hémorragies.

Antithrombotic regimen selection after percutaneous coronary intervention (PCI) in patients with atrial fibrillation is a challenge for clinicians. Atrial fibrillation is associated with increased risk of stroke and systemic embolization, and oral anticoagulant mitigates such risk.[1] Dual antiplatelet therapy (DAPT) is the cornerstone for treatment after acute coronary syndrome (ACS) and PCI to reduce the risk of ischemic cardiac events and stent thrombosis.[2] DAPT is inferior to oral anticoagulant to prevent stroke and systemic embolization in

by 47 Canadian cardiologists in the CONNECT AF+PCI (the **Co**ordinated **N**ational **N**etwork to **E**ngage Interventional **C**ardiologists in the Antithrombotic **T**reatment of Patients With **A**trial **F**ibrillation Undergoing **P**ercutaneous **C**oronary **I**ntervention) study, to determine patterns of initial antithrombotic therapy selection.

Results: The median (25th, 75th percentile) CHADS$_2$ score was 2 (1, 3), and PCI was performed in the setting of acute coronary syndrome in 62.1%. Triple antithrombotic therapy (TAT) was the initial treatment in 62.7%, dual-pathway therapy in 25.7%, and dual antiplatelet therapy in 11.6%, with a temporal increase in use of dual-pathway therapy during the course of the study; median intended TAT duration was 1 (1, 3) month. Compared with patients selected for TAT, patients selected for dual-pathway therapy were less likely to have prior myocardial infarction (35.8% vs 25.8%, $P = 0.045$) and prior PCI (33.8% vs 23.3%, $P = 0.03$), and they received shorter total length of stents (38 [23, 56] vs 30 [20, 46] mm, $P = 0.03$). Patients selected for dual-pathway therapy had a higher prevalence of prior stroke/transient ischemic attack (13.0% vs 23.3%, $P = 0.01$). There was no difference in prevalence of anemia (21.5% vs 25.8%, $P = 0.30$). Use of dual-pathway therapy was similar among patients with acute coronary syndrome and those with stable disease (24.1% vs 28.2%, $P = 0.32$).
Conclusions: Approximately one-quarter of AF patients undergoing PCI are treated with dual-pathway therapy in Canadian practice, with its use increasing during the studied period. Patients selected for dual-pathway therapy have less-complex coronary disease history and intervention.

Méthodes : Les 467 patients atteints de FA ayant subi une ICP de décembre 2015 à juillet 2018 qui ont fait l'objet de notre étude ont été trouvés lors de la vérification des dossiers par 47 cardiologues canadiens de l'étude CONNECT AF+PCI (*Coordinated National Network to Engage Interventional Cardiologists in the Antithrombotic Treatment of Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention*) pour déterminer les schémas de sélection du traitement antithrombotique initial.
Résultats : Le score CHADS$_2$ médian (25e, 75e percentile) était de 2 (1, 3), et l'ICP avait été réalisée dans le cadre du syndrome coronarien aigu chez 62,1 % des patients. La trithérapie antithrombotique (TTA) était le traitement initial chez 62,7 % des patients, la bithérapie, chez 25,7 % des patients, et la bithérapie antiplaquettaire, chez 11,6 % des patients, mais il y avait une augmentation temporelle dans l'utilisation de la bithérapie durant l'étude; la durée médiane prévue de la TTA était de 1 (1, 3) mois. Comparativement aux patients sélectionnés pour la TTA, les patients sélectionnés pour la bithérapie étaient moins susceptibles d'avoir eu un infarctus du myocarde précédent (35,8 % vs 25,8 %, $P = 0,045$) et une ICP précédente (33,8 % vs 23,3 %, $P = 0,03$), et recevaient des endoprothèses de longueur totale plus courte (38 [23, 56] vs 30 [20, 46] mm, $P = 0,03$). Les patients sélectionnés pour la bithérapie montraient une prévalence plus élevée d'accidents vasculaires cérébraux/accidents ischémiques transitoires (13,0 % vs 23,3 %, $P = 0,01$). Il n'existait aucune différence dans la prévalence de l'anémie (21,5 % vs 25,8 %, $P = 0,30$). L'utilisation de la bithérapie était similaire chez les patients atteints d'un syndrome coronarien aigu et chez les patients dont la maladie était stable (24,1 % vs 28,2 %, $P = 0,32$).
Conclusions : Dans la pratique canadienne, environ le quart des patients atteints de FA qui subissent une ICP sont traités par bithérapie, mais durant la période étudiée, son utilisation avait augmenté. Les patients sélectionnés pour la bithérapie ont des antécédents et des interventions liées aux maladies coronariennes moins complexes.

patients with atrial fibrillation,[3] and oral anticoagulant with vitamin-K antagonists is inferior to DAPT to prevent stent thrombosis after PCI.[4] Thus, patients with atrial fibrillation who undergo PCI have traditionally been treated with triple antithrombotic therapy (TAT), a combination of oral anticoagulant for stroke prevention, and DAPT for reduction of ischemic vascular events. TAT, however, is associated with a high risk of bleeding,[5] which is well recognized to be associated with a worse prognosis.[6] Given the lower risk of stent thrombosis associated with current-generation drug-eluting stents,[7] the duration of required DAPT can be shortened,[8] particularly when the risk of bleeding is high, raising interest in whether patients with atrial fibrillation are undergoing PCI can safely be treated with dual-pathway therapy, consisting of oral anticoagulant and a P2Y$_{12}$ receptor inhibitor, with early discontinuation of aspirin.

Over the past half-decade, several randomized trials have demonstrated a favourable safety profile of dual-pathway therapy in comparison with TAT that included a vitamin-K antagonist.[9-13] Use of dual-pathway therapy is associated with a lower risk of bleeding, without an increase in ischemic cardiovascular events, compared with TAT.[11] Whether these data have been incorporated in clinical practice with uptake of dual-pathway therapy for such patients is unknown. Thus, the **Co**ordinated **N**ational **N**etwork to **E**ngage Interventional **C**ardiologists in the Antithrombotic **T**reatment of Patients

With **A**trial **F**ibrillation Undergoing **P**ercutaneous **C**oronary **I**ntervention (CONNECT AF+PCI) study was designed to provide a cross-sectional understanding of the antithrombotic management of patients with atrial fibrillation who underwent PCI in Canada. We specifically determined factors associated with use of dual-pathway therapy vs TAT, duration of TAT, and selection of oral anticoagulation (OAC) and antiplatelets in dual-pathway therapy and TAT.

Methods

Study population

For this observational study, both academic and community-based cardiologists in Canada were invited to participate. These included physicians who have participated in prior ACS or PCI studies; 47 cardiologists from 7 different provinces in Canada participated in this study. Each participating cardiologist performed a chart audit of their own practice and enrolled approximately 10 of their cases. Cardiologists were asked to identify and include if possible consecutive patients who met all the following inclusion criteria: (i) being at least age 18 years; (ii) having persistent, permanent, or paroxysmal atrial fibrillation; and (iii) having undergone PCI with implantation of at least 1 stent within the preceding 12 months. Exclusion criteria were history of

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previous intracranial hemorrhage, severe renal insufficiency (creatinine clearance < 30 mL/min), history of clinically significant gastrointestinal bleeding within the previous 12 months, anemia of unknown source with hemoglobin < 100 g/L, or the presence of any other condition known to increase the risk of bleeding. For every identified patient, anonymous data regarding demographics, stroke and bleeding risk, PCI complexity, and the plan for antiplatelet and antithrombotic regimen initially after PCI were collected. The local research ethics board at each participating centre provided either a waiver or an ethics approval for the study.

Statistical analysis

The primary criterion for evaluation was the proportion of patients treated initially with DAPT, dual-pathway therapy, or TAT. Dual-pathway therapy was defined as a combination of oral anticoagulant and a $P2Y_{12}$ receptor inhibitor, whereas TAT was defined as a combination of oral anticoagulant a $P2Y_{12}$ receptor inhibitor, and aspirin. Oral anticoagulant includes both vitamin-K antagonists and direct oral anticoagulants, in both full and reduced doses. Descriptive statistics were summarized as medians with 25th and 75th percentiles for continuous variables, and as percentages for categorical variables. Differences between groups were compared using the Kruskal—Wallis test for continuous variables, and Pearson's χ^2 test for categorical variables. Using multivariate logistic regression modelling, among patients treated with an OAC, in a post hoc analysis, we determined factors associated with use of dual-pathway therapy vs TAT; among patients treated with TAT, we determined factors associated with intended TAT duration of ≤ 1 or > 1 month. Variables included in the multivariate models included variables with a P value < 0.2 in univariate analyses. For factors associated with use of dual-pathway therapy vs TAT, variables included prior myocardial infarction (MI), prior PCI, hypertension, smoking, prior transient ischemic attack (TIA)/stroke, and number of stents used. For factors associated with intended TAT duration of ≤ 1 or > 1 month, variables included age, prior MI, prior PCI, diabetes, smoking, atrial fibrillation, number of stents, multivessel stenting, and renal function (as assessed by estimated glomerular filtration rate). Results are presented as odds ratio with 95% confidence interval. A value of $P < 0.05$ was considered statistically significant for all tests. All statistical analyses were performed in SAS software version 9.4 (SAS Institute, Cary, NC).

Results

Study population

From December 2015 to July 2018, a total of 467 subjects were enrolled. The median (25th, 75th percentile) patient age was 75 (68, 82) years; 86.9% were aged ≥ 65 years; 68.5% were male; 15.6% had prior stroke/TIA; and 23.6% had anemia. The median time between atrial fibrillation diagnosis and PCI was 3 years. The median (25th, 75th percentile) $CHADS_2$ (Congestive Heart Failure, Hypertension, Age ≥ 75, Diabetes, and Prior Stroke/Transient Ischemic Attack [doubled]) and CHA_2DS_2-VASc (Congestive Heart Failure, Hypertension, Age ≥ 75 Years, Diabetes Mellitus, Stroke,

Vascular Disease, Age 65 to 74 Years, Sex Category) scores were 2 (1, 3) and 4 (3, 5), respectively. PCI was performed in the setting of ACS in 62.1% of patients. The median (25th, 75th percentile) number of stents used was 2 (1, 2), and total stent length was 33 (22, 52) mm. Multivessel stenting was performed in 24.6% of patients, 2-stent bifurcation stenting in 6.4%, and left main or proximal left anterior descending artery stenting in 21.8%. The initial antithrombotic regimen consisted of DAPT in 54 patients (11.6%), dual-pathway therapy in 120 (25.7%), and TAT in 293 (62.7%) patients. Among the 120 patients treated with dual-pathway therapy, 114 (95.0%) received oral anticoagulant and a $P2Y_{12}$ receptor inhibitor, and 6 (5.0%) received oral anticoagulant and aspirin.

Selection of DAPT as initial antithrombotic strategy

Among 453 patients age ≥ 65 years or with a $CHADS_2$ score ≥ 1, a total of 41 (9.1%) were treated with DAPT, 119 (26.3%) with dual-pathway therapy, and 293 (64.7%) with TAT. Among 14 patients age < 65 years or with a $CHADS_2$ score = 0, a total of 13 (92.9%) were treated with DAPT, and 1 (7.1%) received dual-pathway therapy. Compared with patients receiving dual-pathway therapy or TAT, patients receiving DAPT were younger and more likely to have paroxysmal atrial fibrillation and a $CHADS_2$ score of 0 or 1 (Table 1), and to receive PCI in the setting of ACS (Table 2). Among patients treated with DAPT, 66.7% were treated with clopidogrel, 29.6% with ticagrelor, and 3.7% with prasugrel.

Selection of OAC for atrial fibrillation

Among 413 patients treated with an OAC in either dual-pathway therapy or TAT, 84 (20.3%) received warfarin, 193 (46.7%) received rivaroxaban, 98 (23.7%) received apixaban, 38 (9.2%) received dabigatran, and 0 (0%) received edoxaban (Table 3). Reduced dosing was used in 82.9% receiving rivaroxaban, 54.1% receiving apixaban, and 71.1% receiving dabigatran. Only 30.2% of the patients receiving a reduced 2.5-mg twice daily dose of apixaban met the dose-reduction criteria (≥ 2 of the following 3: (i) serum creatinine level ≥ 133 μmol/L; (ii) age ≥ 80 years; (iii) body weight ≤ 60 kg). A total of 19.9% of patients receiving rivaroxaban in a 15-mg dose had creatinine clearance of ≤ 50 mL/min, and 33.3% of patients receiving rivaroxaban in a 10-mg dose had creatinine clearance of > 50 mL/min.

Selection of dual-pathway therapy vs TAT

Compared with patients treated with TAT, patients treated with dual-pathway therapy had a lower likelihood of prior MI and prior PCI (Table 1) and received a shorter total length of stents (Table 2). Patients treated with dual-pathway therapy also had numerically fewer multivessel stenting, left main or left anterior descending artery stenting, and chronic total occlusion stenting. Among 290 ACS patients who underwent PCI, 60.7% were treated with TAT, and 24.1% were treated with dual-pathway therapy. Among 177 patients undergoing elective PCI, 66.1% were treated with TAT, and 28.2% were treated with dual-pathway therapy. There was no difference in history of prior bleeding or anemia. Prior history of stroke/ TIA was more prevalent in patients treated with dual-pathway

Table 1. Patient characteristics stratified by initial antithrombotic therapy

Characteristic	TAT (n = 293)	Dual-pathway therapy (n = 120)	DAPT (n = 54)	P
Age, y	75 (69, 82)	77 (69, 83)	73 (64, 80)	0.08
Age ≥ 65 y	260 (88.7)	109 (90.8)	37 (68.5)	0.0001
Male sex	199 (67.9)	84 (70.0)	37 (68.5)	0.92
Weight, kg	82 (70, 98)	81 (70, 90)	81 (70, 95)	0.50
Prior stroke/TIA	38 (13.0)	28 (23.3)	7 (13.0)	0.03
Prior MI	105 (35.8)	31 (25.8)	15 (27.8)	0.11
Prior PCI	99 (33.8)	28 (23.3)	13 (24.1)	0.07
Anemia	63 (21.5)	31 (25.8)	16 (29.6)	0.34
LVEF ≤ 40%	73 (24.9)	31 (25.8)	10 (18.5)	0.55
Heart failure	70 (23.9)	34 (28.3)	7 (13.0)	0.09
Hypertension	222 (75.8)	82 (68.3)	29 (53.7)	0.003
Diabetes mellitus	124 (42.3)	48 (40.0)	19 (35.2)	0.60
Peripheral artery disease	40 (13.7)	13 (10.8)	7 (13.0)	0.74
Smoking history				0.11
Current	32/256 (12.5)	10//99 (10.1)	9/46 (19.6)	
Former	121/256 (47.3)	37/99 (37.4)	22/46 (47.8)	
Glomerular filtration rate, mL/min	64 (51, 79)	61 (51, 80)	60 (42, 81)	0.42
Mechanical heart valve	4 (1.4)	2 (1.7)	0 (0)	0.65
Duration of atrial fibrillation, y	3 (1, 8)	3 (1, 6)	2 (1, 8)	0.43
Atrial fibrillation type				0.01
Paroxysmal	139 (47.9)	63 (52.9)	39 (72.2)	
Persistent	52 (17.9)	25 (21.0)	5 (9.3)	
Permanen	99 (34.1)	31 (26.1)	10 (18.5)	
CHADS$_2$ score	2 (1, 3)	2 (1, 3)	2 (0, 3)	0.02
CHA$_2$DS$_2$-VASc score	4 (3, 5)	4 (3, 5)	4 (1, 5)	0.05

Values are n (%) or median (25th, 75th) percentiles, unless otherwise specified.

CHADS2, **C**ongestive Heart Failure, **H**ypertension, **A**ge ≥ 75, **D**iabetes, and Prior **S**troke/Transient Ischemic Attack (doubled); CHA$_2$DS$_2$-VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge ≥ 75 Years, **D**iabetes Mellitus, **S**troke, **V**ascular Disease, **A**ge 65 to 74 Years, **S**ex **C**ategory; DAPT, dual antiplatelet therapy; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; TAT, triple antithrombotic therapy; TIA, transient ischemic attack.

therapy. Proton pump inhibitor use was 63.5% in patients treated with TAT, compared with 53.3% in patients treated with dual-pathway therapy. After multivariable adjustment, prior TIA/stroke was associated with greater use of dual-pathway therapy, and history of smoking and a greater number of stents was associated with lower use of dual-pathway therapy, compared with use of TAT (Supplemental Table S1). Use of dual-pathway therapy increased, whereas use of TAT decreased during the course of the study (Fig. 1).

Selection of OAC and antiplatelets in patients treated with dual-pathway therapy and TAT

Among patients who received TAT, warfarin was used in 23.2%, with a direct OAC (DOAC) used in 76.8% (rivaroxaban 37.5%, apixaban 28.3%, dabigatran 10.9%; Table 3). Among patients that received dual-pathway therapy, warfarin

was used in 13.3%, with a DOAC used in 86.7% (rivaroxaban 69.2%, apixaban 12.5%, dabigatran 5.0%). Reduced dosing of rivaroxaban, but not apixaban or dabigatran, was more frequent in patients treated with dual-pathway therapy, compared with those receiving TAT. Clopidogrel was the most common P2Y$_{12}$ receptor inhibitor used in both dual-pathway therapy and TAT (85.0% and 95.2%, respectively), with ticagrelor use being greater in dual-pathway therapy compared with TAT (11.7% vs 4.4%).

Intended duration of TAT

Among the 293 patients for whom TAT was the initial selected antithrombotic regimen, the median (25th, 75th percentile) planned duration of TAT was 1 (1, 3) month, with the intended duration of TAT ≤ 3 months in 86.4%, and ≥ 6 months in 12.8% of patients. Compared

Table 2. PCI characteristics stratified by initial antithrombotic therapy

Characteristic	TAT (n = 293)	Dual-pathway therapy (n = 120)	DAPT (n = 54)	P
PCI setting				0.007
Elective	117 (39.9)	50 (41.7)	10 (18.5)	
Acute coronary syndrome	176 (60.1)	70 (58.3)	44 (81.5)	
Number of stents implanted	2 (1, 2)	1 (1, 2)	1 (1, 2)	0.15
Total stent length, mm	38 (23, 56)	30 (20, 46)	33 (19, 46)	0.03
Drug-eluting stents use	279 (95.2)	116 (98.3)	51 (98.1)	0.25
Multivessel stenting	79 (27.0)	27 (22.5)	9 (16.7)	0.22
Left main/left anterior descending artery stenting	66 (22.5)	24 (20.0)	12 (22.2)	0.85
Two-stent bifurcation PCI	20 (6.8)	6 (5.0)	4 (7.4)	0.75
Chronic total occlusion PCI	16 (5.5)	3 (2.5)	0 (0)	0.11

Values are n (%) or median (25th, 75th) percentiles, unless otherwise specified.

DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; TAT, triple antithrombotic therapy.

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Table 3. Oral anticoagulation selection and dose in patients treated with TAT or dual-pathway therapy

Treatment	Total (n = 413)	TAT (n = 293)	Dual-pathway therapy (n = 120)
Rivaroxaban, mg, daily	193 (46.7)	110 (37.5)	83 (69.2)
20	33 (17.1)	23 (20.9)	10 (12.0)
15	151 (78.2)	80 (72.7)	71 (85.5)
10	9 (4.7)	7 (6.4)	2 (2.4)
Apixaban, mg, twice daily	98 (23.7)	83 (28.3)	15 (12.5)
5	45 (45.9)	38 (45.8)	7 (46.7)
2.5	53 (54.1)	45 (54.2)	8 (53.3)
Dabigatran, mg, twice daily	38 (9.2)	32 (10.9)	6 (5.0)
150	11 (28.9)	9 (28.1)	2 (33.3)
110	27 (71.1)	23 (71.9)	4 (66.7)
Warfarin	84 (20.3)	68 (23.2)	16 (13.3)

Values are n (%).
TAT, triple antithrombotic therapy.

with patients selected for TAT duration of $\leq$ 1 month, patients selected for TAT duration of > 1 month had a higher prevalence of diabetes, prior MI, and prior PCI (Table 4). Use of drug-eluting stents and multivessel stenting was also greater among patients treated with TAT for > 1 month (Table 5). There was no difference in prevalence of anemia or clinical presentation between the 2 groups. After multivariable adjustment, compared with TAT duration $\leq$ 1 month, worse renal function was associated with TAT duration > 1 month; point estimates favoured TAT duration > 1 month but did not reach statistical significance in patients with history of smoking and use of drug-eluting stents (Supplemental Table S2). At cessation of triple therapy, the combination of oral anticoagulant with single-antiplatelet therapy was the planned antithrombotic regimen in 93.2%, with $P2Y_{12}$ receptor inhibitor being the selected antiplatelet agent in 81.0%, and aspirin in 19.0%.

Discussion

Selecting the optimal antithrombotic regimen for an AF patient treated with PCI requires balancing the risks of ischemic coronary events, stroke or systemic embolization, and bleeding. When the risk of stroke is very low (age < 65 years and the $CHADS_2$ score = 0), DAPT is usually sufficient. However, in patients age $\geq$ 65 years or with a $CHADS_2$ score of $\geq$ 1, oral anticoagulant is recommended for reduction of stroke risk. DOACs are preferred to vitamin-K antagonists due to a lower associated risk of bleeding. Comparisons of efficacy and safety of TAT compared with dual-pathway therapy have been conducted in several randomized controlled trials[9-13] and in pooled analyses of these trials.[11,14] When appraised individually, each trial showed evidence of lower bleeding risk in the dual-pathway therapy group, without apparent major tradeoffs for ischemic events, as compared with the risk with TAT. Ischemic events, however, are significantly less prevalent compared with the bleeding events captured as the primary endpoint of these studies. As a result, each of these individual studies was largely underpowered to detect a potentially clinically meaningful difference in ischemic events between treatment strategies. In a meta-analysis of 4 trials encompassing 10,234 patients, comparing dual-pathway therapy with TAT in atrial fibrillation patients undergoing PCI, dual-pathway therapy was associated with a reduction in bleeding, including major and intracranial hemorrhage, but this benefit was counterbalanced by a higher risk of cardiac, mainly stent-related, but not cerebrovascular ischemic events.[14] This finding carries relevant and pathophysiological implications and reinforces the notion that the upfront selection of TAT vs dual-pathway therapy and/or the optimal timing for aspirin discontinuation after invention or ACS should be individualized. Such individualized selection of TAT vs dual-pathway therapy is endorsed by the 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Guidelines for the Use of Antiplatelet Therapy.[2]
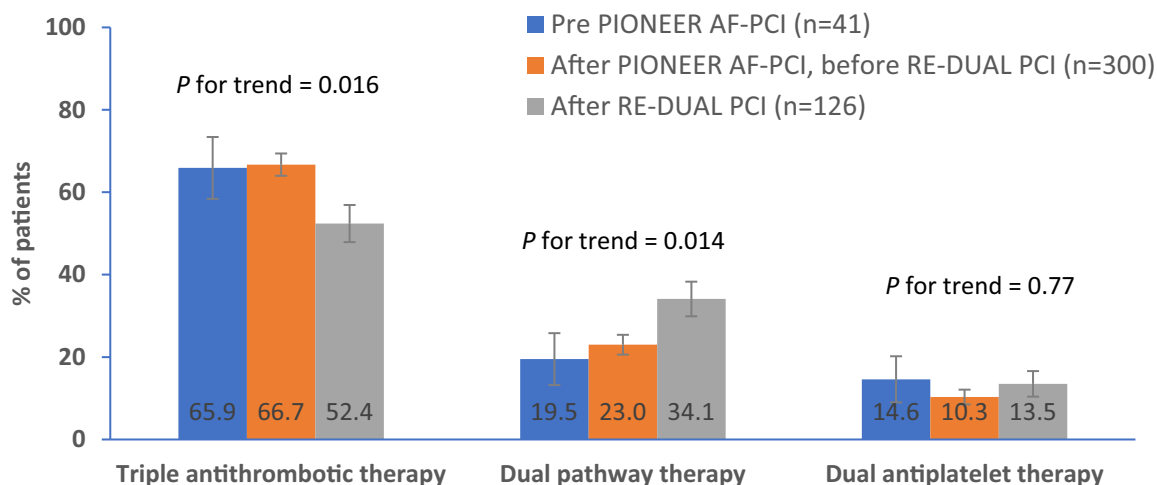

Figure 1. Temporal trends in initial antithrombotic therapy. PIONEER AF-PCI, Open-label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RE-DUAL PCI, Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran vs Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention.

Table 4. Patient characteristics stratified by triple antithrombotic therapy duration

| Characteristic | Triple antithrombotic therapy | | |
	≤ 1 mo (n = 154)	> 1 mo (n = 134)	P
Age, y	76 (71−82)	74 (68−82)	0.13
Age ≥ 65 y	140 (90.9)	116 (86.6)	0.24
Male sex	104 (67.5)	91 (67.9)	0.95
Weight, kg	82 (70−99)	83 (70−96)	0.91
Prior stroke/TIA	23 (14.9)	15 (11.2)	0.35
Prior MI	45 (29.2)	57 (42.5)	0.02
Prior PCI	45 (29.2)	54 (40.3)	0.048
Anemia	33 (21.4)	29 (21.6)	0.97
LVEF ≤ 40%	40 (26.0)	31 (23.1)	0.58
Heart failure	37 (24.0)	30 (22.4)	0.74
Hypertension	115 (74.7)	104 (77.6)	0.56
Diabetes mellitus	56 (36.4)	67 (50.0)	0.02
Peripheral artery disease	19 (12.3)	20 (14.9)	0.52
Smoking history			0.009
Current	16/138 (11.6)	16/115 (13.9)	
Former	54/138 (39.1)	64/115 (55.7)	
Glomerular filtration rate, mL/min	66 (54−79)	61 (49−77)	0.11
Mechanical heart valve	1 (0.6)	3 (2.2)	0.34
Duration of atrial fibrillation, y	3 (1-7)	4 (1-8)	0.21
Atrial fibrillation type			0.18
Paroxysmal	78 (51.3)	58 (43.6)	
Persistent	22 (14.5)	30 (22.6)	
Permanent	52 (34.2)	45 (33.8)	
CHADS$_2$ score	2 (2, 3)	2 (1, 3)	0.69
CHA$_2$DS$_2$-VASc score	4 (3, 5)	4 (3, 5)	0.85

Values are n (%), median (25th, 75th) percentiles, unless otherwise specified.

CHADS2, **C**ongestive Heart Failure, **H**ypertension, **A**ge ≥ 75, **D**iabetes, and Prior **S**troke/Transient Ischemic Attack (doubled); CHA$_2$DS$_2$-VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge ≥ 75 Years, **D**iabetes Mellitus, **S**troke, **V**ascular Disease, **A**ge 65 to 74 Years, **S**ex **C**ategory; DAPT, dual antiplatelet therapy; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

In the present multicentre observational study of atrial fibrillation patients treated with PCI in Canada, TAT was the most frequent initial antithrombotic regimen, with use of dual-pathway therapy increasing over the course of the study after publication of randomized trials supporting its use. We found that patients selected for treatment with dual-pathway therapy had less-complex coronary disease, including a lower prevalence of prior MI and prior PCI, with lower level of complexity of coronary intervention, including shorter length of stents, as well as multivessel, left main/left anterior descending artery, and chronic total occlusion stenting. Interestingly, we found prevalence of anemia to be similar in patients receiving dual-pathway therapy vs TAT, but patients with history of clinically important bleeding, including intracranial hemorrhage or recent major bleeding, were excluded from the study. We also did not find use of TAT (vs dual-pathway therapy) to be greater in patients with ACS vs those who underwent elective PCI, as endorsed by the Canadian Guidelines for the Use of Antiplatelet Therapy,[2] suggesting that physicians may not place as much value on clinical presentation or anemia as on the complexity of the coronary anatomy for selecting the initial antithrombotic regimen.

Table 5. Percutaneous coronary intervention (PCI) characteristics stratified by triple antithrombotic therapy duration

| Characteristic | Triple antithrombotic therapy | | |
	≤ 1 mo (n = 154)	> 1 mo (n = 134)	P
PCI setting			0.62
Elective	63 (40.9)	51 (38.1)	
Acute coronary syndrome	91 (59.1)	83 (61.9)	
Number of stents implanted	1 (1, 2)	2 (1, 3)	0.08
Total stent length, mm	33 (20, 53)	38 (23, 60)	0.20
Drug-eluting stent use	142 (92.2)	132 (98.5)	0.01
Multivessel stenting	35 (22.7)	44 (32.8)	0.06
Left main/left anterior descending artery stenting	34 (22.1)	32 (23.9)	0.72
Two-stent bifurcation PCI	10 (6.5)	10 (7.5)	0.75
Chronic total occlusion PCI	6 (3.9)	8 (6.0)	0.41

Values are n (%) or median (25th, 75th) percentiles, unless otherwise specified.

Planned duration of TAT was < 3 months in the majority of the patients, with only 12% treated with TAT beyond 6 months. Treatment with TAT for > 1 month was associated with more-complex coronary history and use of drug-eluting stents as well as with multivessel PCI. Given the low risk of stent thrombosis with the current generation of drug-eluting stents, with the risk of stent thrombosis being higher up front early after PCI,[15] very few if any patients require prolonged TAT of > 1 month. Very early discontinuation of aspirin within the first week after PCI, however, may have adverse effects in some patients with complex coronary disease and/or coronary intervention. The mechanisms through which early aspirin discontinuation may expose patients to higher ischemic risks are likely multifactorial and include the importance of cyclooxygenase-1 (COX-1) inhibition in the prevention of cardiovascular ischemic events, as well as exposure of clopidogrel nonresponders or hypo-responders to insufficient P2Y$_{12}$ receptor inhibition early after PCI or ACS. Whether the use of ticagrelor or prasugrel in the context of dual-pathway therapy minimizes the ischemic risks while preserving the bleeding benefit, as compared with TAT, remains to be studied. The use of higher potency P2Y$_{12}$ receptor inhibitor in dual-pathway therapy in our study population was 15%, higher than the 5%-7% use in dual-pathway therapy in the randomized trials.[9-13] Upon cessation of triple therapy, P2Y$_{12}$ receptor inhibitor was continued considerably more frequently than aspirin as part of dual-pathway therapy. This approach is in accordance with North American[16] and European[17] guidelines, which recommend that P2Y$_{12}$ receptor inhibitors be continued, as opposed to aspirin, when transitioning from TAT to dual-pathway therapy. This recommendation is based on demonstration of superiority of clopidogrel compared with aspirin in reducing ischemic events, as well as a more favourable safety profile (ie, less hospitalization for gastrointestinal bleeding).[18,19]

With the exception of the Apixaban Versus Warfarin in Patients with AF and ACS or PCI (AUGUSTUS) trial,[13] all other studies examined the TAT regimen with only vitamin-K antagonist. In the real world, we note the widespread use of DOACs in TAT with use of both reduced and full-dose regimens not evaluated in randomized trials. Although it is reasonable to substitute warfarin for direct oral anticoagulant

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in TAT, the optimal DOAC dose in TAT is unknown. For the most part, it might be reasonable to extrapolate the DOAC dose used in the dual-pathway therapy regimen arms for use in TAT, with the exception of dabigatran, of which110 mg twice daily may be the preferred dose in TAT, but a 150-mg twice daily dose maybe preferred in dual-pathway therapy, due to the high thrombotic risk with the lower dose. We noted heterogeneity in DOAC dosing with use of unstudied full 20-mg dose rivaroxaban and inappropriate dose reduction for apixaban and rivaroxaban in patients who do not meet dose-reduction criteria. These dose alterations may expose patients to adverse events that cannot be detected in the present study. After discontinuation of antiplatelets, oral anticoagulant is recommended at full stroke-prevention dose, a practice not evaluated in this study.

Limitations

Several limitations should be considered. Physician participation in this study was voluntary, and treatment patterns therefore may not be generalizable to all Canadian physicians involved in the antithrombotic therapy decision-making for atrial fibrillation patients undergoing PCI. In addition, patient enrollment was not necessarily consecutive, possibly creating a bias toward enrolling patients more likely to be treated with dual-pathway therapy. The study was initiated prior to and was ongoing during publication of the Open-label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention (PIONEER AF-PCI)[10] and Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran vs Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (RE-DUAL PCI)[12] trials, and was completed prior to publication of the AUGUSTUS[13] and Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (ENTRUST-AF PCI)[11] trials. We observed an increase in the utilization of dual-pathway therapy during the course of the study, and suspect that utilization of dual-pathway therapy may be even greater, and/or the duration of TAT shorter, now after publication of the AUGUSTUS[12] and ENTRUST AF-PCI[10] studies. Although we did shed some light on reasons for selection of dual-pathway therapy vs TAT, there may be factors beyond those captured on the data-collection form that are unmeasured confounders that contributed to selection of therapies. These may include drug availability, cost considerations, allergies or intolerances, and patient or physician preferences. The small study sample size also limits the ability to determine factors independently associated with selection of dual-pathway therapy vs TAT. In this study, we did not evaluate the more novel treatment strategy of DAPT in combination with left atrial appendage occlusion, instead of oral anticoagulant, which has the potential upside of providing stroke prevention without exposure to additional bleeding risk. The efficacy and safety of such a strategy require further evaluation. Finally, clinical outcomes according to antithrombotic regimens and/or dosing were not ascertained in this study.

Conclusions

Approximately one-quarter of AF patients undergoing PCI are treated with dual-pathway therapy in Canadian practice, with evidence of a temporal increase in dual-pathway therapy use after publication of randomized trial data supporting its use. TAT remained the most frequent initial antithrombotic strategy, albeit with a short median 1-month duration. Patients selected for treatment with dual-pathway therapy have less-complex coronary disease, but its use was not associated with ACS vs elective presentation in our study sample. Opportunities remain for further study of optimization of antithrombotic regimen selection, duration of TAT, selection and dosing of DOACs, as well as P2Y$_{12}$ receptor inhibitor selection in dual-pathway therapy.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2021.07.003.

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