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Original Article

Experiences of Patients With Atrial Fibrillation With Combination Antithrombotic Therapy Post–Percutaneous Coronary Intervention

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ABSTRACT

Background: Up to 30% of patients with atrial fibrillation (AF) have coronary artery disease, and many undergo percutaneous coronary intervention (PCI). In the setting of acute coronary syndrome with PCI, or high-risk elective PCI, Canadian AF guidelines recommend 1-30 days of acetylsalicylic acid, 1-12 months of clopidogrel, and oral anticoagulation (OAC) with doses that may change throughout the 12 months post-PCI. The complexity of these regimens may contribute to unplanned modifications (UPMs), increasing the risk of thrombosis and/or bleeding. We describe what happens

RÉSUMÉ

Contexte : Jusqu'à 30 % des patients atteints de fibrillation auriculaire (FA) ont une coronaropathie, et nombre d'entre eux doivent subir une intervention coronarienne percutanée (ICP). En présence d'un syndrome coronarien aigu nécessitant une ICP ou dans le cas d'une ICP non urgente associée à un risque élevé, on recommande, dans les lignes directrices canadiennes sur la FA, un traitement de 1 à 30 jours par l'acide acétylsalicylique, de 1 à 12 mois par le clopidogrel, et une anticoagulothérapie orale (ACO) à des doses pouvant varier durant les 12 mois suivant l'ICP. La complexité de ces schémas posologiques

Patients with atrial fibrillation (AF) require pharmacologic management with oral anticoagulants (OACs) to prevent the occurrence of stroke or embolism.[1] Up to 30% of these patients also have coronary artery disease (CAD), with many requiring percutaneous coronary intervention (PCI) for revascularization.[2] Patients with CAD or an acute coronary syndrome who are undergoing PCI with stent implantation require dual-antiplatelet therapy with acetylsalicylic acid (ASA) and a P2Y12 inhibitor, such as clopidogrel, prasugrel, or ticagrelor, to prevent stent thrombosis and further coronary events.[3,4]

Based on data from key trials, including PIONEER AF-PCI [**O**pen-label, Randomized, Controlled, Multicenter Study Explor**i**ng Tw**o** Treatmen**t** Strat**e**gi**e**s of **R**ivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With **A**trial **F**ibrillation Who Undergo **P**ercutaneous **C**oronary **I**ntervention], RE-DUAL PCI [**R**andomized **E**valuation of **Dual** Antithrombotic Therapy With Dabigatran versus Triple Therapy With Warfarin in Patients With Nonvalvular AF Undergoing **PCI**], AUGUSTUS [An Open-Label, 2×2 Factorial, Randomized, Controlled Clinical Trial to Evaluate the Safety of Apixaban versus Vitamin K Antagonist and Aspirin versus Aspirin Placebo in Patients With AF and ACS and/or PCI], and ENTRUST-AF PCI [**E**doxaba**n** **Tr**eatment Vers**us** Vitamin K Antagonist in Pa**t**ients With **AF** Undergoing **PCI**],[5-8] the recommendation is that patients with AF who have just undergone PCI receive combination antithrombotic therapy (ATT) consisting of one or more antiplatelet agent(s) plus an OAC.[1] Dual therapy with an OAC and a P2Y12 inhibitor (mainly clopidogrel) is commonly prescribed; however, patients at high risk of thrombotic events may require triple therapy with an OAC, ASA, and a P2Y12 inhibitor.[1] Duration of therapy varies depending on factors such as the thrombosis risk, the bleeding risk, and the type of stent. Dual therapy is recommended to be continued for up to 12 months.[1] ASA in the triple-therapy regimen is currently

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to these patients and their antithrombotic therapy (ATT) after discharge.

Methods: Prospective follow-up was conducted of patients with AF requiring OAC who underwent PCI and were discharged on combination ATT. Patients were contacted at 1, 3, 6, and 12 months post-PCI.

Results: Sixty-five patients were enrolled, with data at any time point available for 61 of them (94%). Of these, 44 (68%) experienced at least one UPM to ATT. In total, 105 UPMs occurred. The most common UPM was an extended duration of P2Y12 inhibitor (23 instances; 22%). The most common UPM with acetylsalicylic acid was extended (11 instances; 11%) or shortened (11 instances; 11%) duration. Thirty-nine UPMs (37%) were related to OACs; 9 (23%) were related to warfarin, and 30 (77%) were related to direct OACs. Of all patients with at least one UPM, 33 (75%) experienced bleeding.

Conclusions: More than 2 in 3 patients with AF undergoing PCI experienced a UPM to their ATT. This study underscores the challenges of combination ATT for patients and clinicians alike, emphasizing the need for patient support after discharge.

peut contribuer à des modifications non planifiées (MNP) du traitement, ce qui accroît le risque de thrombose et/ou de saignement. Nous décrivons ce qui advient de ces patients et de leur traitement antithrombotique (TAT) après le congé de l'hôpital.

Méthodologie : Un suivi prospectif a été réalisé chez des patients atteints de FA nécessitant une ACO, ayant subi une ICP et recevant un TAT lors de leur congé de l'hôpital. Les patients ont été contactés 1, 3, 6 et 12 mois après leur ICP.

Résultats : Parmi les soixante-cinq patients inscrits, des données ont été obtenues pour 61 d'entre eux (94 %) à un moment ou à un autre. Au moins une MNP du TAT a eu lieu chez 44 (68 %) de ces 61 patients, pour un total de 105 MNP. La MNP la plus fréquente était la prolongation de la durée du traitement par un inhibiteur du P2Y12 (23 cas, soit 22 %). La MNP la plus fréquente du traitement par l'acide acétylsalicylique était la prolongation (11 cas, soit 11 %) ou le raccourcissement (11 cas, soit 11 %) de la durée du traitement. Au total, 39 MNP (37 %) étaient liées à des anticoagulants oraux, 9 (23 %) à la warfarine et 30 (77 %) à des anticoagulants oraux directs. Sur l'ensemble des patients ayant fait l'objet d'au moins une MNP, 33 (75 %) ont subi un saignement.

Conclusions : Une MNP du TAT a eu lieu chez plus des deux tiers des patients atteints de FA ayant subi une ICP. Cette étude souligne les difficultés que pose un TAT d'association, tant pour les patients que pour les médecins, ce qui met en évidence la nécessité d'accompagner les patients après leur congé de l'hôpital.

recommended to be continued for a period from 1 day to 1 month post-PCI[1]; this recommendation is supported by a post hoc analysis of the AUGUSTUS data that evaluated the risk-vs-benefit tradeoff of combination ATT in the early and late time periods after PCI.[9] Within the first 30 days, an equal tradeoff occurred between increased severe bleeding and reduced severe ischemic events with the use of ASA in addition to a P2Y12 inhibitor and an OAC.[9] Beyond 30 days, ASA was associated with more bleeding without an apparent reduction in ischemic events.[9] The guidelines also advocate the use of a proton pump inhibitor in patients on a combination ATT regimen that includes ASA to reduce the risk of gastrointestinal adverse effects, including gastrointestinal bleeding.[1]

Combining antithrombotic therapies increases the risk of bleeding. Deviations from the prescribed post-PCI ATT regimen may increase both avoidable bleeding events and ischemic events. If a patient is initiated on ASA as part of a triple-therapy regimen and does not discontinue it when recommended, their bleeding risk increases. Further, the use of an OAC dose that is different from that approved for stroke prevention in AF may also impact outcomes. Patients treated with the PIONEER AF-PCI strategy (rivaroxaban 15 mg daily) would require an increase in the dose of the OAC once the antiplatelet(s) is discontinued, to ensure evidence-based optimal stroke prevention.[1] These drug and dose adjustments after discharge introduce a layer of complexity for patients and clinicians alike.

Published real-world data on what happens to patients and their ATT over the subsequent 12 months after leaving the acute care setting are very limited. As any change made to a patient's regimen could increase thrombosis or bleeding risk, identifying the incidence of unplanned therapy modifications may better inform our understanding of how best to optimize patients' ATT regimens to realize the intended reduction of bleeding and thromboembolic events. Our objective was to describe what really happens to patients and their ATT as they progress from discharge to 12 months post-PCI.

Methods

Project design

This observational study with prospective follow-up took place at an urban quaternary academic centre. As the study was deemed to be a quality-improvement initiative, our institution's research ethics board waived formal review. All patients undergoing PCI at our academic centre were consecutively screened over a 19-month period. Patients with a documented history or new onset of AF undergoing PCI were included if they were discharged with a plan for combination ATT that spanned the ensuing 6-12 months. Patients were excluded if they met any of the following criteria: (i) being deemed palliative; (ii) having active cancer or undergoing active cancer treatment; and (iii) being unable to be contacted (ie, could not communicate in English, French, or Cantonese, or did not have a means to follow-up via telephone). Prospective telephone follow-up was used to gather data related to any changes made to the patients' ATT.

Data collection

The planned ATT regimens were identified through review of the discharge summary in the electronic patient record. If this information was not explicitly available, it was obtained from the interventional catheterization procedure note. Patients (or their caregivers) were contacted at approximately 1 month, 3 months, 6 months, and 12 months following their PCI. Phone calls were completed 1-2 weeks after the specified

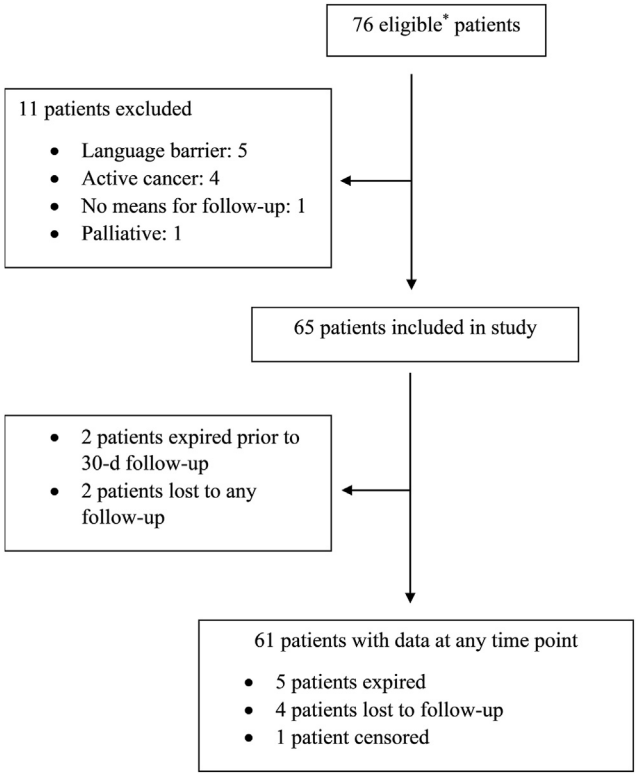

Figure 1. Screening and enrollment. *Patients were eligible if they had a documented history or new onset of atrial fibrillation undergoing percutaneous coronary intervention (PCI), and were discharged with a plan for combination antithrombotic therapy during the 19-month screening period.

time points (ie, for 1-month follow-up, patients were called the week after, but no later than 2 weeks after their 1-month post-PCI date), allowing patients the opportunity to make the instructed changes to their ATT regimens. At each follow-up time point, 3 attempts were made to contact the patient. If all 3 were unsuccessful, no data were obtained for that time point. If no data were obtained for 2 subsequent time points, the patient was considered lost to follow-up. For patients who were readmitted to our centre at the time of planned follow-up, information from the patient record also was used to clarify patient responses. Patients were interviewed using a standardized script. If patients were unsure of their medication regimen, and this uncertainty had an associated risk to their health at the time of any follow-up phone call, consent to contact their community pharmacy and/or physician was obtained, and their last dispensed ATT regimen was confirmed. An unplanned modification (UPM) was defined as any change to the originally planned ATT regimen that occurred after discharge post-PCI. A UPM could include changes to antithrombotic dose or duration, a temporary hold, discontinuation, or initiation of another antithrombotic medication. Reasons for the UPMs were sought during the patient interview.

Data analysis

Baseline characteristics of the enrolled patients were analyzed via Excel (Microsoft, Redmond, WA) using descriptive statistics. Patients with UPMs to their ATT regimen were identified. UPMs were described using information such as who initiated the modification, the reason for the modification (if available), and events leading to or resulting from the modification, if any.

Results

A total of 65 patients (86%) were enrolled (Fig. 1). The mean age of enrolled patients was 74 years; 20 (31%) were female; and 28 (43%) experienced an acute coronary syndrome (unstable angina, non−ST-elevation myocardial infarction, or ST-elevation myocardial infarction) during the index admission. The median baseline creatinine clearance was 55.8 mL/min, and 7 patients (11%) had a creatine clearance of less than 30 mL/min. The median CHA_2DS_2-VASc [**C**ongestive Heart Failure, **H**ypertension, **A**ge ($\geq$ 75 Years) (doubled), **D**iabetes Mellitus, **S**troke (doubled), **V**ascular Disease, **A**ge (65-74 Years), **S**ex **C**ategory (Female)] and HAS-BLED [**H**ypertension, **A**bnormal Renal/Liver Function, **S**troke, **B**leeding History or Predisposition, **L**abile INR, **E**lderly ($>$65 Years), **D**rugs/Alcohol Concomitantly] scores were 5 and 3, respectively. Prior to PCI, 43 patients (66%) were taking a direct OAC (DOAC) (51% of these were apixaban), 13 (20%) were taking warfarin, and 9 (14%) were not on any anticoagulation. At discharge, 11 patients (17%) had a plan for dual-pathway therapy, and 54 (83%) had a plan for triple therapy. Fifty-two patients (80%) were discharged on a DOAC (66% of these were apixaban), and 41 (67%) were discharged on a proton pump inhibitor. Forty-nine (75%) were discharged on the same OAC they were on prior to PCI. The majority of patients were discharged home (57 of 65; 88%). One patient's discharge destination was unknown (Table 1).

Follow-up was complete for at least one time point in 61 patients (94%) and for all 4 time points in 32 patients (49%). A total of 201 patient−time point follow-ups were available for analysis (Table 2). Two patients died prior to the 1-month time point, and 2 patients were lost to any follow-up. Seven patients (11%) died during the 12 months after enrollment. At the 1-month time point, 38 of 58 patients with 1-month data (66%) recalled receiving any discharge medication counselling, either in the hospital prior to discharge or from their community pharmacist.

A total of 105 UPMs from the original post-PCI plan occurred (Table 3). These included modifications related to prescribing errors, modifications made in response to planned procedures or acute illness (including bleeding), modifications resulting from not stopping therapy at the planned time, patient self-management, and prescription extensions for delayed follow-up. There were 44 patients (68%) with at least 1 UPM. Of those, 30 (68%) experienced more than 1 UPM. UPMs occurred more frequently in patients discharged on triple therapy (38 of 54) than in those on dual-pathway therapy (6 of 11). Twenty-seven patients (61%) with at least 1 UPM recalled receiving any discharge medication counselling.

A breakdown of all UPMs based on antithrombotic class can be found in Table 4. The most common UPM with ASA was an extended (11 UPMs; 11%) or shortened duration (11 UPMs; 11%), and this occurred most commonly at the

Table 1. Baseline characteristics

Characteristic (n = 65)	Value	
Age, y, mean (range)	74.4 (53–93)	
Female	20 (30.8)	
ACS during admission	28 (43.1)	
CrCl, mL/min, mean (SD)	56.7 (21.7)	
CrCl ≥ 60 mL/min	26 (40)	
Discharge disposition*		
Home	57 (87.7)	
Rehab	3 (4.6)	
Long-term care	2 (3.1)	
Other acute care institution	2 (3.1)	
PPI prescribed at discharge	41 (63.1)	
Oral anticoagulant	Admission	Discharge
Warfarin	13 (20)	13 (20)
Dabigatran	3 (4.6)	2 (3.1)
Rivaroxaban	6 (9.2)	5 (7.7)
Apixaban	33 (50.8)	43 (66.2)
Edoxaban	1 (1.5)	2 (3.1)
None	9 (13.8)	0 (0)
ATT regimen		
Dual therapy (1 antiplatelet + OAC)	11 (16.9)	
Triple therapy (2 Antiplatelets + OAC)	54 (83.1)	

Values are n (%), unless otherwise indicated.

ACS, acute coronary syndrome; ATT, antithrombotic therapy; CrCl, creatinine clearance; OAC, oral anticoagulant; PPI, proton pump inhibitor; SD, standard deviation.

*One patient's discharge disposition was not indicated in the patient record.

1-month time point. The most common UPM with P2Y12 inhibitors was an extended duration, which was also the most common UPM overall (23 UPMs; 22%). With regard to anticoagulation, the most common UPM involving warfarin was a switch to another OAC (3 of 9 UPMs; 33%), and the most common UPM involving DOACs was a temporary interruption in therapy mostly related to bleeding (6 of 30 UPMs; 20%) or in preparation for procedures (4 of 30 UPMs; 13%). One temporary interruption of DOAC use was due to the new palliative status of a patient (1 of 30 UPMs; 3%). A total of 5 of 6 UPMs (83%) that involved temporary interruption of DOAC due to bleeding involved patients who were discharged on triple therapy. Overall, 20 UPMs (19%) involved temporary interruption in any ATT. Nine UPMs (45%) were associated with bleeding, 8 UPMs (40%) were associated with a procedure, and 3 UPMs (15%) were due to other factors, including new palliative status, being directed to hold the antithrombotic by a prescriber, or the patient not refilling their prescription.

During follow-up, 44 patients (68%) reported any bleeding, and 23 patients (35%) experienced bleeding requiring them to seek medical advice. Within the first month, 30 patients reported any bleeding, 27 (90%) of whom had been discharged on triple therapy, and 3 (10%) who were on dual-pathway therapy. Nine patients sought medical advice for bleeding within the first month after discharge; 7 (78%) were discharged on triple therapy. In total, 33 patients (75%) with a UPM to their ATT experienced bleeding. In 13 patients (39%), 21 UPMs were made in direct response to bleeding. Fourty-one UPMs (39%) were reported to be in response to unexpected clinical events such as procedures and acute illnesses (including bleeding, stroke, and allergic reactions).

Table 2. Follow-up data summary

Planned time point, mo	Patients with data, n (%)
1	58 (95.1)
3	52 (85.2)
6	50 (82)
12	41 (67.2)

Discussion

To the best of our knowledge, this is the first publication describing what happens with the combination ATT of AF patients post-PCI using individual patient and caregiver feedback. More than half of all patients experienced a UPM to the original ATT prescription over the 12 months post-PCI. Further, more than 50% of those patients had more than one UPM, highlighting the complexity of ATT management in post-PCI patients with AF.

Several randomized trials, the most recent comparing DOACs to warfarin, and triple therapy to dual therapy, provide evidence of how best to strike the "optimal" balance between antiplatelet therapy for prevention of stent thrombosis post-PCI and the anticoagulation recommended for stroke prevention in AF, while minimizing bleeding.[5-8] Evidence of an increase in major bleeding without a significant reduction in ischemic events beyond 30 days with ASA in combination with dual-pathway therapy has also been demonstrated.[9] These trials have facilitated clear guidelines on the post-PCI ATT "plan" out to 12 months. However, modifications to this plan may upset the balance between stroke and ischemic event prevention and bleeding.

UPMs, by definition, are unanticipated. In our cohort, 2 in every 3 patients experienced a UPM. The nature of these modifications ranged from prescription errors to modifications following acute health events to temporary suspension of therapy for an invasive procedure. Perhaps not surprisingly, these occurred more frequently in patients receiving triple therapy than in those receiving dual-pathway therapy. More UPMs were reported with antiplatelet therapy than with anticoagulants. Most commonly, these UPMs involved use for a longer duration than originally intended. ASA, when used for longer than the intended duration, particularly beyond 30 days post-PCI, has been associated with an increased risk of major bleeding. In our cohort, the most common reason for extended ASA use was ongoing administration by the patient, despite the discharge summary indicating a specific timeframe for taking it, most often 30 days post-PCI. Six UPMs (6%) involving extended duration of ASA due to some form of miscommunication or unawareness of the ATT regimen duration were associated with bleeding.

Extended duration of P2Y12 inhibitor, mainly clopidogrel, was even more frequent, and most of these UPMs occurred at the 12-month follow-up time point. One third of the patients had their clopidogrel treatment duration extended by their primary care provider or cardiologist. Although the prescriptions were written clearly as being for 12 months, most patients either forgot this, assumed the prescription should continue, or were reluctant to stop their medication without seeing their specialist first.

Among anticoagulants, the most common UPM was temporary or permanent suspension of therapy. With

Table 3. Summary of antithrombotic therapy (ATT) modifications

ID	Age, y + Sex	Original ATT regimen post-PCI	1 mo	3 mo	6 mo	12 mo
1	74F	- ASA* x 3 mo - Clopidogrel† x 12 mo - Warfarin	- ASA stopped by cardiologist **(1)** - Warfarin dose reduced by patient **(2)** *Some blood when coughing when readmitted to hospital for influenza*	- Warfarin stopped by prescriber (temporarily) **(3)** - Admitted for lacunar stroke a wk later	NM *Reports minor small bruises with no identifiable cause*	- Clopidogrel continued by patient in blister pack (original stop date at 12 mo). Was unaware of when it was meant to be discontinued **(4)** *Notes occasional small bruising on stomach & upper arm that are not persistent*
2	85M	- Clopidogrel x 12 mo - Warfarin	NM	NM	- Warfarin stopped by prescriber **(1)** - ASA initiated after new stent **(2)**	NM *Bruising at site of dialysis access*
3	85F	- ASA x 1 mo - Clopidogrel x 12 mo - Apixaban 2.5 mg BID	- Patient had stroke on day of PCI then, - ASA stopped by cardiologist **(1)** - Apixaban dose increased by prescriber **(2)**	NM *Has had a few nosebleeds lasting about 5 min*	- Clopidogrel stopped by cardiologist **(3)**	NM
4	84M	- ASA x 1 mo - Clopidogrel x 12 mo - Apixaban 5 mg BID	- Apixaban held for about 5 d while admitted to hospital *due to hematuria* **(1)** *Experienced hematuria*	- Apixaban dose decreased from 5 mg BID to 2.5 mg BID **(2)**	NM	PE
5	63F	- ASA x 1 mo - Clopidogrel x 12 mo - Apixaban 5 mg BID	- ASA continued by patient as it was still in their blister pack from pharmacy **(1)** *Patient has history of nosebleeds and had recent nosebleed lasting < 1 min*	NM *Always bruises easily but nothing the patient would consider severe*	NM *Some bad bruising on right side of body after a fall 3 wk prior*	NM *Gets nosebleeds when nose is very dry*
6	72M	- ASA x 1 mo - Clopidogrel x 12 mo - Rivaroxaban 15 mg daily	- ASA continued by nurse in retirement home since original prescription written for 12 mo instead of 1 mo **(1)**	- ASA continued by prescriber **(2)** *Patient had frequent nosebleeds lasting 4 −5 h*	No modifications (for comment: ASA stopped at incorrect time point; internist discontinued ASA *due to bleeding hemorrhoids*) *Experienced bleeding from hemorrhoids*	- Patient still taking clopidogrel daily as per nurse. Confirmed prescription was extended by a mo by local internist **(3)** *Bruises easily*
8	73M	- ASA x 1 mo - Clopidogrel x 12 mo - Apixaban 5 mg BID	NM *Has hemorrhoids that bleed (chronic issue prior to blood thinners)*	NM *Has hemorrhoids that bleed (chronic issue)*	NM *Has hemorrhoids that bleed (chronic issue)*	- Clopidogrel continued by patient in blister pack (original stop date at 12 mo). Was unaware of when it was meant to be discontinued **(1)** *Patient noted that cuts take longer to stop bleeding (ie, when cuts self while shaving)*

Table 3. Continued.

ID	Age, y + Sex	Original ATT regimen post-PCI	1 mo	3 mo	6 mo	12 mo
9	86M	- ASA - Clopidogrel - Apixaban 2.5 mg BID (durations unknown)	- ASA taken every second d **(1)** *Has had nosebleeds for a few years. Most recent was a couple days prior to call*	NM	- ASA switched back to daily by prescriber after another PCI (POBA) in June prior to the 6-mo call **(2)** *Had a nosebleed a couple nights prior to call that went away after a couple min*	- Previous 6-mo call reported patient was taking ASA daily post-PCI; however, when speaking to patient at 1-y time point, both patient and caregiver confirmed they have been taking ASA every other d, as ordered by prescriber **(3)** - Apixaban put on hold for 2 d by prescriber for *nosebleed* **(4)** *Experienced a nosebleed*
12	75M	- ASA x 1 mo - Clopidogrel x 12 mo - Apixaban 5 mg BID	NM	NM	NM	- Held clopidogrel and apixaban for 3−4 d during acute care admission for *GI bleed*, requiring transfusion **(1)(2)** - Held clopidogrel and apixaban for 4−5 d (as per patient) for a percutaneous stone removal (gallstones) **(3)(4)** - Still taking clopidogrel (original plan 12 mo) **(5)** *Experienced a GI bleed*
13	55M	- ASA x 1 mo - Clopidogrel x 12 mo - Apixaban 5 mg BID	NM	NM	NM *Reported a couple of mild nosebleeds*	- Patient is still taking clopidogrel beyond the 1-y duration **(1)** *Patient reported some bruising on belly*
14	76M	- ASA x 12 mo - Clopidogrel x 1 mo - Warfarin	NM	NM *Bad nosebleed about 1 mo prior to call. Required follow-up with ear, nose and throat specialist.*	- ASA discontinued at 3 mo by prescriber due to *prolonged and extensive nosebleeds requiring hospitalizations* **(1)** *Prolonged and extensive nosebleeds*	NM *Still gets nosebleeds; however, severity and frequency have decreased significantly since stopping ASA*

Continued

Table 3. Continued.

ID	Age, y + Sex	Original ATT regimen post-PCI	1 mo	3 mo	6 mo	12 mo
15	89M	- Clopidogrel x 12 mo - Apixaban 5 mg BID	NM	- Apixaban dose decreased to 2.5 BID by prescriber due to *easy bleeding and bruising of skin including face and arms from scratching* **(1)**	URP	- Clopidogrel continued beyond 1-y duration **(2)**
			Reports easy bleeding and bruising of his skin from scratching	*Easy bleeding and bruising of skin*		*Continues to endorse easy bleeding with scratching as well as a history of nosebleeds (although cannot recall when last one was)*
16	78M	- ASA x 3 mo - Clopidogrel x 12 mo - Apixaban 5 mg BID	- ASA stopped by prescriber due to side effects **(1)** - Apixaban held for 2 d and dose decreased by cardiologist **(2)** related *to nosebleeds* - *Experienced nosebleeds* - *Has some bruising on arms and has had some nosebleeds lasting a few seconds*	- Apixaban stopped temporarily by patient because patient has been *having a few nosebleeds lasting for a few seconds* **(3)** *Experienced nosebleeds*	NM *Reported a nosebleed "a while ago"*	- Continues to take clopidogrel beyond 1-y plan in blister pack **(4)** *Had a nosebleed wk prior to call*
17	79F	- ASA x 3 mo - Clopidogrel x 12 mo - Apixaban 2.5 mg BID then 5 mg BID when ASA stopped	- ASA duration changed from 3 mo to 1 mo by cardiologist in external acute care hospital **(1)**	- Apixaban dose was not increased after ASA stopped **(2)**	NM *Small amounts of bruising on legs that go away quickly*	- Patient continuing to take clopidogrel beyond 1-y plan **(3)**
20	71M	- ASA x 1 mo - Clopidogrel x 6 mo - Rivaroxaban 20 mg daily	NM *Some easy bruising if bumps into things. Patient reports some bleeding on feet as per diabetic foot specialist*	NM: (Described that clopidogrel would be stopped 1 mo later than original plan [not stopped yet]) *Some hematuria during self-catheterization and some bruising on arms*	- Clopidogrel still continued beyond 6 mo; cardiologist increased duration by 1 mo **(1)** - Rivaroxaban dose decreased from 20 mg to 15 mg daily **(2)** *Gets nosebleeds and has some small bruising on arms*	- Rivaroxaban increased back to 20 mg by prescriber **(3)** *Occasional nosebleeds requiring cauterization 1 mo prior to phone call*

Table 3. Continued.

ID	Age, y + Sex	Original ATT regimen post-PCI	1 mo	3 mo	6 mo	12 mo
22	78M	- Ticagrelor‡ x 12 mo - Apixaban 5 mg BID	NM *Gets blistering and bleeding of skin*	NM	NM *Gets itchy skin that can blister and bleed*	- Ticagrelor continued beyond 12 mo by patient **(1)** - *Patient had a tooth extraction and continued bleeding* so cardiologist said to stop apixaban for 3 d. It was restarted after 3 d **(2)** - *Persistent bleeding after tooth extraction* - *Bleeding easily after scratching that can last a wk or so with bandages required*
23	88M	- ASA x 1 mo - Clopidogrel x 12 mo - Apixaban 2.5 mg BID	NM *Noticed small amount of blood in urine*	NM *Some bruising (if provoked by hitting something)*	NM - *Blood in urine 2–3 wk prior to follow-up* - *2 episodes of blood in stool during bowel movement*	- *Patient was experiencing many nosebleeds leading to* doctor stopping apixaban and started ASA therapy around the 8-mo mark **(1)(2)** *Experienced nosebleeds*
24	81M	- ASA - Clopidogrel - Dabigatran 150 mg BID (durations unknown)	- Dabigatran dose decreased by prescriber post-TAVI procedure to 110 mg BID **(1)** *Patient went to ED for leg pain and was found to have "bleeding in the muscles." This was a few days after the dose decrease*	NM *Some anal bleeding due to radiation proctitis*	- Held clopidogrel for 5 d and dabigatran for 2 d for a polypectomy **(2)** **(3)** - Held clopidogrel for 5 d and dabigatran for 2 d for a removal of a noncancerous lesion on the face **(4)** **(5)**	URP
25	68M	- ASA x 3 mo - Clopidogrel x 12 mo - Apixaban 5 mg BID	NM	NM	NM *1 episode of blood in urine 2 mo prior to call*	- Clopidogrel continued beyond 12 mo; family doctor sent new prescription to pharmacy **(1)**
27	80M	- ASA x 3 mo - Clopidogrel x 12 mo - Apixaban 5 mg BID	- Apixaban dose decreased by prescriber **(1)** *Bruising on back of hand and forearm, jaw from biting himself while eating*	NM *Profuse bleeding after tooth extraction which lasted about 4 d*	NM	URP

Continued

Table 3. Continued.

ID	Age, y + Sex	Original ATT regimen post-PCI	1 mo	3 mo	6 mo	12 mo
29	67F	- ASA x 3 mo - Clopidogrel x 12 mo - Apixaban 2.5 mg BID	NM *Lots of bruising after shunt placement*	- ASA discontinued 4−5 wk earlier by prescriber due to *spontaneous bleeding and leg hematoma resulting in hospital visit* **(1)** *Spontaneous bleeding and leg hematoma*	NM	NM *Easily bruises on legs and arms*
30	75M	- ASA x 1 mo - Clopidogrel x 6 mo - Warfarin	- ASA continued by patient as it was still in the blister pack **(1)**	- ASA continued to be taken daily in blister pack **(2)** *Bruising at site where blood is drawn*	NM. (warfarin dose increased to 4 mg daily by nurse at time of call due to fluctuating INR. INR fluctuating since acute care admission *for potential GI bleed*) ASA stopped early by prescribers in acute care. *Experienced a GI bleed*	PE
32	80M	- ASA x 3 mo - Clopidogrel x 12 mo - Warfarin	NM *Experienced hematuria which resolved on its own*	- ASA continued by patient **(1)** - Warfarin dose reduced for a few d by patient as a result **(2)** - *Bleeding with shaving* - *Some hematuria*	- Patient held warfarin for a couple of d*secondary to hematuria*, NOT on prescriber advice **(3)** *Experienced hematuria*	- Patient's clopidogrel duration is extended beyond 1 y, based on cardiologist choice **(4)** *Some bruising if bumps into things around the house*
33	82M	- ASA x 12 mo - Clopidogrel x 12 mo - Apixaban 2.5 mg BID	NM *Some bruising (if provoked by bumping into something)*	NM *Some bruising (if provoked by bumping into something)*	URP	- Clopidogrel is extended by cardiologist so patient still taking past 12 mo **(1)**
34	76M	- ASA x 6 mo - Clopidogrel x 12 mo - Warfarin	NM *One short nosebleed a couple weeks prior to follow-up*	NM *Nosebleeds that usually last 30−45 min*	URP	- Clopidogrel continued beyond 12 mo by patient **(1)**
35	82F	- ASA x 1 mo - Clopidogrel x 12 mo - Dabigatran 110 mg BID	- Dabigatran dose decreased to 110 mg once daily by cardiologist due to low patient weight **(1)** *Easy bruising (provoked)*	NM *Easy bruising from bumping into things*	NM *Easy bruising from bumping into things*	NM *Easy bruising from bumping into things and when getting blood work done*
36	74M	- ASA x 1 mo - Clopidogrel x 12 mo - Warfarin	- ASA not taken after PCI; unclear if patient-led or if occurred when patient sent back to an external hospital **(1)**	PE	PE	PE

Table 3. Continued.

ID	Age, y + Sex	Original ATT regimen post-PCI	1 mo	3 mo	6 mo	12 mo
37	77M	- ASA x 1 mo - Clopidogrel x 12 mo - Apixaban 2.5 mg BID then 5 mg BID when ASA stopped	- Patient returned to hospital on same day of discharge due to full body allergic reaction/rash; clopidogrel was then switched to ticagrelor **(1)**	NM	NM	- Patient is still taking ticagrelor beyond the 12-mo stop date. Aware of 12-mo duration but wanted to speak to cardiologist before stopping it **(2)**
40	53F	- ASA x 1 mo - Clopidogrel x 12 mo - Warfarin	- ASA was not stopped. We only learned about this at the 3-mo follow-up **(1)**	- Warfarin discontinued and apixaban initiated by prescriber during same admission. Reasons why are unclear **(2)**	URP	- Clopidogrel continued beyond 12-mo duration due to family doctor sending in a new script for 1 mo **(3)**
42	76F	- ASA - Apixaban 5 mg BID (duration unknown)	NM	- Apixaban temporarily stopped by prescriber due to Mitraclip procedure **(1)**	NM	URP
43	64M	- ASA indefinitely - Clopidogrel (unknown duration) - Apixaban 5 mg BID	NM	NM	- Apixaban was switched to dabigatran by a prescriber during a hospital visit for urgent aortocoronary bypass grafting **(1)** - Clopidogrel also stopped at this time **(2)**	- Dabigatran stopped for *lower GI bleed* **(3)** *Experienced a lower GI bleed*
44	90F	- Clopidogrel - Apixaban 5 mg BID (durations unknown)	- Apixaban put on hold by prescriber during admission **(1)** Patient deemed palliative	URP	URP	URP
46	85M	- ASA x 1 mo - Clopidogrel x 12 mo - Apixaban 2.5 mg BID	- ASA discontinued 1 wk early by cardiologist **(1)**	NM	NM	- Clopidogrel continued beyond 1-y duration by patient **(2)**
48	84M	- ASA x 12 mo - Clopidogrel x 6 mo - Apixaban 5 mg BID	- ASA discontinued early by prescriber **(1)**	NM *Ongoing nosebleeds lasting > 10 min*	- Still taking clopidogrel beyond 6 mo **(2)**	URP
49	73M	- ASA x 1 mo - Clopidogrel x 12 mo - Apixaban 5 mg BID	- Patient still taking ASA. Discharge plan was for 1 mo but prescription given for 2 mo **(1)** *Infrequent nosebleeds and large bruise on arm from tripping*	NM *Some bruising if bumps into something*	NM *Some bruising if bumps into something*	- Patient continuing to take clopidogrel **(2)** - Apixaban has been discontinued by the physician & ASA has been restarted by the prescriber **(3)** **(4)** *Occasional bruising on arms (provoked)*

Continued

Table 3. Continued.

ID	Age, y + Sex	Original ATT regimen post-PCI	1 mo	3 mo	6 mo	12 mo
50	86M	- ASA x 1 mo - Clopidogrel x 12 mo - Rivaroxaban 15 mg daily	- Rivaroxaban switched to apixaban by prescriber due to *query GI bleed* in acute care, post-PCI admission **(1)** *Experienced a GI bleed*	- Apixaban discontinued due to *hemoglobin decline with melena stools* **(2)** *Experienced melena and hemoglobin decline*	NM *One episode of bright red blood in stool*	PE
52	65M	- ASA x 1 mo - Clopidogrel x 12 mo - Apixaban 5 mg BID	NM	NM	- Apixaban dose reduced to 2.5 mg BID by prescriber **(1)**	PE
53	78F	- ASA x 1 mo - Clopidogrel x 12 mo - Apixaban 5 mg BID	- Patient still taking ASA (patient-led) **(1)** *Patient experienced unprovoked bruises on legs*	URP	- Clopidogrel not filled (patient had not filled at pharmacy in mo so likely stopped around the 3-mo mark) **(2)** *Bruising on arms (unprovoked)*	- Patient continuing to take clopidogrel beyond 1 y. Was not aware they needed to stop **(3)** *Bruising on hands (unprovoked)*
54	77F	- ASA x 1 mo - Clopidogrel x 12 mo - Rivaroxaban 15 mg daily then 20 mg daily once ASA stopped	- Continues to take ASA despite only 1-mo duration (done by patient/caregiver) **(1)**	URP	NM	- Patient continuing to take clopidogrel beyond 1 y. Was not aware they needed to stop **(2)**
56	66M	- Clopidogrel x 12 mo (duration not specified but given 12-mo prescription) - Warfarin	NM	URP	NM	- Warfarin discontinued by prescriber **(1)** - Continued clopidogrel beyond 12 mo by cardiologist due to warfarin being stopped **(2)**
58	73F	- ASA x 1 mo - Clopidogrel x 12 mo - Apixaban 5 mg BID	- Held all antithrombotics (ASA, clopidogrel, apixaban) for 2 wk on direction of an online physician as a result of *a large bruise down thigh and buttocks from a fall incident.* **(1)(2)(3)** 2 weeks later, contacted family doctor who directed to restart clopidogrel and apixaban only. *Fall resulting in a large bruise down thigh and buttocks*	NM *Some nosebleeds a couple times per wk*	NM *Bruises easily and gets nosebleeds*	- Clopidogrel stopped 2 mo early **(4)** *Patient had hospital visit where they discovered low hemoglobin that required 2 blood transfusions*

Table 3. Continued.

ID	Age, y + Sex	Original ATT regimen post-PCI	1 mo	3 mo	6 mo	12 mo
59	59F	- ASA x 1 mo - Clopidogrel x 12 mo - Apixaban 2.5 mg BID	- Patient still taking ASA **(1)**	- Clopidogrel stopped by prescriber **(2)** - Apixaban put on hold for procedure (x 3 mo) and given warfarin during that time instead (switch) **(3)**	URP	- Warfarin switched back to apixaban by prescriber **(4)**
60	62M	- ASA x 1 mo - Clopidogrel x 12 mo - Apixaban 5 mg BID	- Prescriber stopped apixaban to switch patient to warfarin **(1)** *Experienced nosebleed after switch to warfarin*	- Transplant team stopped clopidogrel and restarted ASA **(2)** **(3)**	- Warfarin stopped for transplant, patient was started on enoxaparin 80 mg BID, and now switched to enoxaparin 120 mg once daily **(4)** - ASA temporarily stopped for 1 wk for lung biopsy **(5)**	NM
65	78M	- ASA x 3 mo - Clopidogrel x 12 mo - Apixaban 5 mg BID	- Clopidogrel stopped, ticagrelor started, due to delayed allergic rash and hives development **(1)**	- Prescriber stopped ASA 1 mo early **(2)**	NM	- Patient continuing ticagrelor beyond 12 mo. Prescriber sent more refills to the pharmacy as per patient **(3)**

Italics indicate a bleeding event.

The numbers in parenthetical indicate a UPM.

ASA, acetylsalicylic acid; BID, twice daily; ED, emergency department; F, female; GI, gastrointestinal; ID, identification; INR, international normalized ratio; M, male; NM, no modifications; PCI, percutaneous coronary intervention; PE, patient expired; POBA, plain old balloon angioplasty; TAVI, transcatheter aortic valve implantation; URP, unable to reach patient.

* Dose for ASA: 81 mg once daily

† Dose for clopidogrel: 75 mg once daily.

‡ Dose for ticagrelor: 90 mg twice daily.

warfarin, permanent discontinuations were the most common, with switching to a DOAC being the most frequent reason. With DOACs, temporary suspension was most common, with the most frequent reason being a response to bleeding events. Most UPMs involving temporary suspension of a DOAC were in patients discharged on triple therapy.

The International Society on Thrombosis and Hemostasis major or clinically relevant nonmajor bleeding rates[10,11] with combination ATT ranged from 15% to 35% annually in the randomized trials.[5-8] In our cohort, 44 patients (68%) reported any bleeding during follow-up, and 23 patients (35%) reported bleeding that required them to seek medical advice. In addition, in 13 patients (39%), a UPM was made in direct response to bleeding. These findings align with the results of the clinical trials; in 12 patients (36%), 17 UPMs were initiated by a healthcare provider in response to a bleeding event, which can be considered clinically relevant nonmajor bleeding, per the International Society on Thrombosis and Hemostasis definition.[11]

Table 4. Proportion of unplanned modifications based on drug class

Unplanned modifications (N = 105)	
Antiplatelets (n = 66)	
Aspirin	30 (45)
P2Y12 inhibitors	36 (55)
Oral anticoagulants (n = 39)	
Warfarin	9 (23)
DOACs	30 (77)

Values are n (%).

DOAC, direct oral anticoagulant.

Patients with AF undergoing PCI for CAD require complex antithrombotic regimens. An anticipated finding is that a number of UPMs would be related to patients' management of their medications, and this indeed was observed. However, the degree to which other influences affected the occurrence of UPMs was unexpected. Throughout the 12-month post-PCI timeframe, patients in our cohort experienced bleeding, the need for unrelated procedures, influences from the healthcare system—including community pharmacies—and other unanticipated influences that all impacted their ability to follow the original ATT plan set out at the time of the PCI. A total of 28 UPMs (27%) were identified as being related to patient nonadherence or unawareness of the planned ATT regimen. These UPMs may be preventable; providing patients

with a follow-up phone call at key time points post-PCI, with the goal of ensuring that planned changes to their ATT regimen are made, may avoid these types of UPMs.

Although we are confident that our findings represent the typical AF patient's post-PCI journey with combination ATT, the study has several limitations. Our data are heavily reliant on patient and caregiver recall. We followed up with patients' pharmacies or long-term care staff to verify the medications when patients or caregivers were unable to reliably provide the information. However, the majority of the data come directly from patients or their caregivers most responsible for medication management. Patient recall not only heavily influenced the reported ATT regimen (and thus, UPMs) at each follow-up, but also at times prevented gaining an understanding of the reasons for UPMs. Additionally, we were unable to capture all follow-up points for all patients. Only 49% of patients have data available from all 4 follow-up time points, which may have altered our data regarding the most common UPMs and their relative frequency. Finally, we were unable to capture the frequency of post-PCI follow-up with a healthcare provider outside of patient recall.

Conclusion

Our data highlight the complexity of managing combination ATT in the AF patient post-PCI and may provide insight into strategies to better support patients and clinicians in mitigating undesirable outcomes during the 12 months post-PCI. Awareness of the frequency of UPMs itself may increase the vigilance of the healthcare team. Medication reconciliation for this patient population, including alignment of the planned regimen with the prescription provided to the patients, can help to ensure that the plan is clear for the combination ATT regimen. Empowering community pharmacists by providing complete details of the combination ATT plan, including specified durations for each medication, may increase their ability to support patients in making the prescribed adjustments at key time points. Further, scheduling a check-in with patients regarding the ATT regimen plan at 30 days post-PCI, at the very least, has the potential to prevent UPMs, especially those involving extended duration of ASA, which clearly increases the risk of bleeding in these patients. Finally, providing the patient with a scheduled follow-up in advance, particularly for the 12-month follow-up appointment, may ensure that combination ATT does not get extended longer than necessary.

A future study looking at implementation of these initiatives along the 12-month time period may facilitate our understanding of how best to optimize stroke and stent thrombosis prevention among these patients, while balancing their risk of bleeding.

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Ethics Statement

As the study was deemed to be a quality-improvement initiative, our institution's research ethics board waived formal review.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a quality-review initiative using de-identified data; therefore, the IRB did not require consent from the patient.

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