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Combined Aspirin and Anticoagulant Therapy in Patients with Atrial Fibrillation

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Abstract

Background—The combined use of aspirin and oral anticoagulant therapy in patients with atrial fibrillation (AF) and stable coronary artery disease (CAD) has been questioned due to an increased risk of major bleeding with little to no benefit in preventing ischemic events.

Objective—(1) To better understand patterns and indications for combined antiplatelet and anticoagulant therapy and identify patients who might reasonably be treated with oral anticoagulant (OAC) therapy alone. (2) To perform an updated literature review regarding the use of combined antiplatelet and OAC therapy in patients with AF and stable CAD.

Design and Participants—Retrospective review. Patients within the University of Cincinnati Health System with a diagnosis of non-valvular AF, excluding those with acute coronary syndrome or revascularization within the last 12 months.

Main Measures—Numbers and indications for combined antiplatelet and anticoagulant therapy and sequence of events leading to the initiation of each.

Key Results—Of 948 patients receiving OAC, 430 (45%) were receiving concomitant OAC and aspirin. Among patients receiving combined antiplatelet and anticoagulant therapy, 49% and 42% of patients respectively, had CAD or DM. In a more detailed analysis including chart review of 219 patients receiving combined OAC and aspirin, 27% had a diagnosis of CAD and 14% had a diagnosis of DM prior to the development of AF. These patients were initially treated with aspirin. Warfarin was added when they subsequently developed AF but aspirin wasn't discontinued. A surprisingly large proportion of patients (22.8%) had no obvious indication for dual therapy.

Conclusions—Prior myocardial infarction, CAD, vascular disease and DM (among others) increase the likelihood of receiving combined antiplatelet and anticoagulant therapy among

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Conflict of Interest:

Charlotte H. So – has no conflicts of interest.

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patients with AF. A literature review suggests this may lead to increased major bleeding with little benefit in decreasing either AF-related stroke or cardiovascular events.

Keywords

atrial fibrillation; coronary artery disease; anticoagulation; performance improvement; warfarin; aspirin

Introduction

Atrial fibrillation (AF) is the most common significant cardiac rhythm disorder and is also a powerful common risk factor for stroke: about 15% of all strokes in the U.S. are attributable to AF.[1] The use of combined antiplatelet and anticoagulant therapy in patients with AF has recently come under scrutiny. It is common for patients with AF to have co-morbidities that may necessitate the use of antiplatelet therapy. However, multiple studies examining outcomes of combined antiplatelet and anticoagulant therapy in patients with indications for both have demonstrated an increased risk of major hemorrhage compared with either treatment alone; and among patients with stable coronary artery disease (CAD), in particular, combined antiplatelet and anticoagulant therapy has not been shown to reduce either AF-related stroke or cardiovascular events.[2–8] The 2012 AF guidelines from the American College of Chest Physicians (ACCP) recommends against the use of combined antiplatelet and anticoagulant therapy for AF patients with stable CAD, indicating that warfarin alone within a therapeutic INR range of 2–3 is sufficient.[9] As part of a system-wide performance improvement initiative focused on improving antithrombotic therapy decisions for patients with AF in our UC Health Primary Care Network, we discovered a large number of patients who were receiving treatment with both aspirin and oral anticoagulant (OAC) therapy. Our goal was to determine the indications for combined antiplatelet and anticoagulant therapy in these patients and to identify those who might reasonably be treated with OAC therapy alone. Furthermore, we evaluated the time course in which these therapies were initiated to elucidate what led to the use of dual therapy. We hypothesized that the majority of these patients likely had a prior indication for antiplatelet therapy, such as stable CAD or diabetes (DM) with a 10-year predicted risk of cardiovascular disease exceeding 10%[10], subsequently developed AF and had warfarin added to their regimen without discontinuing aspirin.

Methods

The study was approved by the Institutional Review Board of the University of Cincinnati.

Study design and patients

We used our health system's clinical data store to identify 9,270 patients with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), diagnosis of atrial fibrillation (427.31) or atrial flutter (427.32) who did not have diagnoses of mitral valve disease (394.x), aortic valve disease (395.x), heart valve transplant (V42.2) or heart valve replacement (V42.3) in their active problem list. The data pull to form our inception cohort was performed in February of 2014. Since our university hospital is a

tertiary/quaternary care center, many patients who are hospitalized in our health system do not have outpatient care delivered in our system. Thus, only 4,021 of these patients were seen in any of the outpatient practices in our health system. Finally, many patients receiving specialty care in our system do not receive primary care in our system, thus only 1,877 were seen in the Primary Care Network (PCN). We further excluded patients who were receiving triple therapy (i.e., aspirin, clopidogrel, and oral anticoagulant therapy) assuming that these patients had likely experienced acute cardiac syndrome (ACS) or undergone percutaneous cardiac intervention with stent placement within the past 12 months. A total of 948 patients were receiving OAC therapy, with or without concomitant aspirin therapy. This population was then stratified by the use of aspirin – OAC alone versus treatment with OAC and aspirin. Baseline characteristics, comorbidities, stroke and bleeding risk profiles were compared between these groups (Table 1). Risk scores for stroke were calculated using CHA_2DSVAS_2c[11] and risk scores for bleeding were calculated using HAS-BLED.[12] Categorical variables are presented as counts and proportions and differences between groups were assessed with the X^2 test. Continuous variables are presented as means and differences were assessed with the t test. We also calculated the odds ratio for combined treatment versus OAC alone for each of the comorbidities studied.

In order to better understand the time course and sequence of events that led to the initiation of each treatment we performed a detailed chart review on a randomly selected convenience sample of 219 patients and categorized each indication(s) for antithrombotic therapy. For example, if a patient was diagnosed with CAD before the development of AF, we labeled them as “CAD before AF”. For the purposes of our study, we defined stable CAD according to the 2012 ACCP guidelines as “presence (or absence) of angina without revascularization procedure (percutaneous coronary intervention or coronary artery bypass graft surgery) or hospitalization for ACS (i.e., unstable angina, non-ST-segment elevation MI, or ST-segment elevation MI) in the past year.”

Evidence Review

Defining the Clinical Question – Population, Intervention, Comparator, and Outcome—First we defined the scope of our clinical question. We wished to review the evidence addressing the question, “does the net clinical benefit of combined antiplatelet and anticoagulant therapy in patients with stable CAD and AF, warrant its use?” We defined the relevant population, alternative management strategies (intervention and comparator), and the outcomes (i.e., population, intervention, comparator, and outcome [PICO] format), as described in the Methodology review for the 9th American College of Physicians Antithrombotic Therapy and Prevention of Thrombosis Guideline.[13] Readers can find the PICO questions at the top of Table 3, which summarizes the results of our literature review. Although we prioritized randomized controlled trials (RCTs) in our search we included observational studies given the paucity of RCT data addressing this question.

To identify the relevant evidence we conducted literature searches of Medline. We supplemented these searches using relevant references from the studies we identified. We searched for both systematic reviews and for original studies encompassing the main populations and interventions of interest.

Results

In our UC Health Primary Care Network cohort of 1,877 AF patients, 948 were receiving OAC with or without concomitant aspirin therapy. Five hundred and eighteen were receiving OAC alone, while 430 were receiving OAC and aspirin (Figure 1). Table 1 details the baseline characteristics of patients overall and in both groups. There are significant differences between the two groups. Patients receiving OAC plus aspirin were significantly more likely to be male, and have hypertension, CAD, DM, congestive heart failure, vascular disease, a history of myocardial infarction, stroke, kidney disease, and liver disease as comorbidities. Patients receiving combined antiplatelet and anticoagulant therapy also had higher CHA_2DSVAS_2c and HAS-BLED scores.

Table 2 describes the odds ratios of receiving combined antiplatelet and anticoagulant therapy for each of the comorbidities studied. Patients with AF and prior myocardial infarction were most likely to receive combined therapy (OR – 3.5, 95% CI, 2.4–5.2). Patients with CAD or vascular disease were also very likely to receive combined therapy (OR – 2.5, 95% CI, 1.9–3.4, and 2.1, 95% CI, 1.6–2.8, respectively).

Detailed Analysis of Patients Receiving Combined antiplatelet and anticoagulant Therapy

Of the 219 patients receiving combined treatment with OAC and aspirin whose charts we reviewed, 97 (44.3%) had DM and 90 (41.1%) had stable CAD as co-morbidities resulting in combined antiplatelet and anticoagulant therapy. For 50 patients (22.8%) we could find no clear reason for combined antiplatelet and anticoagulant therapy; these were classified as “unknown.” 34 patients (15.5%) had diagnoses of both CAD and DM and were counted in both categories.

As detailed in Figure 2, we further classified patients based on the timeline and sequence of events that led to the initiation of dual therapy. 59 patients (27%) initially had a diagnosis of CAD (22 of whom also had DM), during which time they were started on aspirin therapy. They subsequently developed AF and were started on warfarin therapy but aspirin therapy was not discontinued. In comparison, only 7 patients (3.2%) initially had a diagnosis of AF, for which they were started on anticoagulation therapy, followed by the addition of aspirin when they developed CAD (see supplemental Figure 1). In the cases of 10 patients (5%) with CAD and AF we could not determine the time course of events. Including patients with both CAD and DM, 30 patients (14%) had a diagnosis of DM and were receiving aspirin, but treatment with aspirin was not stopped when warfarin was started for a subsequent diagnosis of AF. There were 5 patients with both CAD and DM receiving combined therapy for whom we could not determine the time course of events. Eleven patients (5%) who were initially receiving aspirin for AF, had therapy escalated to warfarin therapy due to a change in their AF-related stroke risk but treatment with aspirin was not stopped.

Evidence Review

Table 3 summarizes the results of our literature review. Most were observational studies with the exception of the WOEST trial.[3] In addition we found 2 meta-analyses that provided information relevant to our research question.[2,4] The Outcomes Registry for Better Informed

Treatment of Atrial Fibrillation (ORBIT-AF) study explored the role of concomitant aspirin therapy in patients with AF who were already receiving OAC therapy.[7] The registry enrolled 10,126 AF patients from 176 US practices between June 2010 and August 2011. Of these, 7,347 were receiving OAC therapy. Two thousand five-hundred and forty three patients were also receiving aspirin, representing 25% of the entire AF registry population and 35% of those receiving OAC therapy. They found that the strongest predictor for combined antiplatelet and anticoagulant therapy were patients with CAD (OR 2.23), which is consistent with our study's findings. However, one of the most striking results was that a large proportion of patients on combined antiplatelet and anticoagulant therapy (39%) had no history of atherosclerotic disease. They followed these patients over a 6-month period looking for episodes of bleeding, hospitalization, ischemic events and mortality. They found that major bleeding (adjusted hazard ratio 1.53, 95% confidence interval, 1.17–1.97) and bleeding hospitalizations (adjusted hazard ratio, 1.52; 95% confidence interval, 1.17–1.97) were significantly higher in the OAC+ASA group compared with those on OAC alone. The rates of ischemic events were found to be low in both groups. The caveat with this study was the short follow up and that patients with ischemic heart disease were only a subcategory. There was not enough power to statistically analyze the risk for recurrent MI or stroke in this particular population.

In an observational study using a nationwide Danish administrative registry, Lamberts et. al., followed a cohort of 8,700 patients with AF and stable CAD (defined as 12 months from an acute coronary event).[6] Thus, this cohort included patients with a prior history of percutaneous coronary intervention (PCI). They found that relative to vitamin K antagonist (VKA) monotherapy, the risk of myocardial infarction (hazard ratio, 1.12 [95% confidence interval 0.94–1.34]) and thromboembolism was similar in the VKA plus ASA group. However, the risk of bleeding was significantly higher in the VKA+ASA group (hazard ratio, 1.50 [95% confidence interval, 1.23–1.82]). In subgroup analyses focused on patients with previous PCI, the risk of thrombosis and bleeding among patients receiving VKA with or without ASA was comparable to results of the main analysis.

Another observational Danish registry study enrolling 118,606 patients surviving a first hospitalization for AF noted an increased risk of fatal and non-fatal bleeds in patients receiving aspirin plus warfarin compared with OAC alone [HR 1.83; 95% CI, 1.72 – 1.96], without any increased efficacy in reducing the risk of fatal or non-fatal ischemic strokes.[5]

The CORONER study (Suivi d'une cohorte de patients COROnariens stables en region NORd-Pas-de-Calais) also echoed similar results- increased risk of bleeding on combined antiplatelet and anticoagulant therapy with no added benefits in terms of ischemic events.[8] CORONER was a prospective multicenter study that enrolled 4,184 consecutive outpatients with stable CAD (free from any MI or coronary revascularization for >1 year at inclusion). Patients with AF were a small subgroup (7.2%) of the larger cohort with stable CAD. The major goal of the study was to assess bleeding risk in patients receiving combined treatment with a VKA and an antiplatelet agent (ASA or clopidogrel). Slightly more than 11% of the cohort was receiving treatment with both antiplatelet agents and oral anticoagulants (n=342). In age and gender-adjusted analyses, patients receiving VKA and antiplatelet therapy had a 7.3-fold [95% CI, 3.91–13.64] risk of major bleeding compared with patients receiving with

a single antiplatelet agent. The cumulative incidence of cardiovascular death, myocardial infarction, or non-hemorrhagic stroke was similar among patients receiving VKA alone and VKA plus an antiplatelet agent.

The two meta-analyses came to similar conclusions. Dentali et. al. using data from 10 randomized controlled trials found that the incidence of arterial thromboembolism (defined as MI, unstable angina leading to hospitalization, CVA, TIA, or other systemic embolism) was not significantly different among patients with non-valvular AF receiving aspirin plus OAC therapy compared with OAC therapy alone, OR – 0.99 [95% CI 0.47 – 2.07].[2,14] However, the risk of major bleeding was higher in those receiving combined antiplatelet and anticoagulant therapy, OR – 1.43 [95% CI, 1.00 – 2.02]. The meta-analysis by Flaker and colleagues included results from the two ximelegatran trials, SPORTIF III and IV.[4] They concluded that there was no significant difference in MI risk between those receiving warfarin alone vs. warfarin plus aspirin (1.0% vs. 0.6%, p=0.40) or in stroke risk (1.5% vs. 1.7%, p=0.71). However, there was a significant increase in risk of major bleeding in those receiving combined antiplatelet and anticoagulant therapy with warfarin and aspirin, 3.9%, compared to those receiving warfarin alone, 2.3% (p=0.01).

In the higher risk setting of PCI with stenting in patients who have an indication for chronic OAC therapy, such as AF, there is increasing evidence that OAC therapy and clopidogrel may be sufficient. The risk of bleeding with double and triple therapy is increasingly being recognized. The 2014 AHA Guidelines state “in patients with AF undergoing PCI, bare-metal stents may be considered to minimize the required duration of dual antiplatelet therapy. Following coronary revascularization…in patients with AF and CHADSVASC score of 2 or greater, it may be reasonable to use clopidogrel (75 mg once daily) concurrently with oral anticoagulants but without aspirin (Level of Evidence: B).” These recommendations were based on results of a randomized controlled study called the “What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing” (WOEST) trial.[3] This study followed patients who were receiving chronic oral anticoagulation who also had severe CAD and an indication for PCI. Results at 1 year showed a lower incidence of bleeding in the combined treatment group (OAC +clopidogrel) compared to triple therapy group (OAC+clopidogrel+ASA) with an HR 0.36 (95% CI 0.26–0.5). However, the combined secondary endpoint of death, MI, stroke, target vessel revascularization and stent thrombosis was similar between the two groups with a HR 0.56 (0.35–0.91).

Discussion

Many patients with AF have co-morbidities that necessitate the use of aspirin and are subsequently prescribed anticoagulant therapy. In our study of AF patients in a primary care cohort of an academic medical center, 23% of patients were receiving treatment with both aspirin and an oral anticoagulant. This is similar to findings in the ORBIT registry in which 25% of the entire AF cohort was receiving combined antiplatelet and anticoagulant therapy.[7] Of interest, an even larger proportion of patients were receiving concomitant low dose (< 165 mg) aspirin in several of the large, multicenter clinical trials investigating the direct oral anticoagulants, roughly 30% of patients in both the apixaban and warfarin arms of

ARISTOTLE, and approximately 40% of patients in the dabigatran and warfarin arms of RE-LY.[15,16] While the majority of patients in our primary care cohort receiving combined antiplatelet and anticoagulant therapy had a diagnosis of CAD or DM, 21% had no obvious indication for the addition of aspirin. This is lower than findings in other studies such as the ORBIT registry, where nearly 40% of patients receiving combined antiplatelet and anticoagulant therapy had no clear indication for the addition of aspirin.[7] Among patients with CAD or DM, a significant proportion had aspirin initiated prior to the diagnosis of AF but aspirin was not discontinued when warfarin was started (27.9%). In contrast, there were fewer patients on combined antiplatelet and anticoagulant therapy who had a diagnosis of AF prior to the development of stable CAD (3.2%). One could speculate that clinicians simply forgot to stop aspirin when OAC therapy was started. Alternatively, clinicians may view aspirin as a benign medication, not appreciating the significant bleeding risk associated with aspirin monotherapy and even greater bleeding risk associated with the addition of aspirin to OAC therapy.

In our larger primary care cohort of AF patients, we also found that patients receiving OAC plus aspirin compared with OAC alone were significantly more likely to male, and have hypertension, CAD, DM, congestive heart failure, vascular disease, a history of myocardial infarction, stroke, kidney disease, and liver disease as comorbidities. Patients receiving combined antiplatelet and anticoagulant therapy also had higher CHA_2DSVAS_2c and HAS-BLED scores. Even if one corrected the HAS-BLED score to adjust for bleeding risk absent the use of antiplatelet therapy, patients receiving combined antiplatelet and anticoagulant therapy were not at lower risk for bleeding.

In our study, the largest group of patients receiving combined antiplatelet and anticoagulant therapy had stable CAD as an indication for aspirin. While aspirin is commonly used for both primary [17] and secondary prevention in patients with known CAD [18,19] the optimal anticoagulation regimen for patients with both AF and ischemic heart disease remains a subject of debate. The 2012 American College of Chest Physicians (ACCP) for Antithrombotic Therapy Guidelines for AF indicate that there is insufficient evidence to warrant combined antiplatelet and anticoagulant therapy in AF patients with stable CAD.[9] The 2012 focused update for the European Society of Cardiology Guidelines specifically states that “patients with AF and stable vascular disease…can be managed with OAC alone… In such stable patients, there is no need for concomitant aspirin, which could increase the risk of serious hemorrhage, including intracranial hemorrhage.”[20]

Summarizing our own study, we found that patients with multiple comorbidities are more likely to receive combined therapy with aspirin and OAC. For many of these patients aspirin had been started for a diagnosis of CAD or DM but not discontinued when OAC was started due to a new diagnosis of AF. It would seem counterintuitive that patients at higher risk of bleeding complications, as noted by their higher HASBLED scores, were more likely to be receiving combined therapy. What could possibly explain this finding? A vexing challenge in decision-making for thromboprophylaxis in patients with AF is that many of the same comorbidities that increase the risk of AF-related stroke are also risk factors for major bleeding. The high correlation between CHA_2DSVAS_2c and HASBLED scores is well documented.[21] As we found in our study, patients receiving combined therapy had both

higher CHA_2DSVAS_2c and HASBLED scores, highlighting this challenge. Finally, a large proportion of patients don't have any obvious explanation for receiving combined therapy.

What can we conclude from evidence in the peer-reviewed medical literature? First, it is clear that among AF patients receiving OAC therapy, who have no primary indication for antiplatelet therapy that the addition of aspirin results in increased bleeding risk and no benefit with regards to decreased risk of AF-related stroke. Aspirin should be stopped in these patients. Second, although oral anticoagulation therapy is not generally used for primary prevention of cardiovascular events due to the higher risk of bleeding compared with aspirin, older studies have demonstrated comparable effectiveness even with low intensity warfarin (international normalized ratio [INR], 1.5).[22] Therefore, there is no need to continue aspirin in AF patients who were receiving aspirin for primary prevention of CAD. With regards to secondary prevention, the Warfarin-Aspirin Reinfarction (WARIS) II study found that warfarin alone or with aspirin was superior to aspirin alone for the combined endpoint - prevention of death, nonfatal reinfarction, and stroke.[23] Furthermore, when comparing warfarin alone vs. warfarin plus aspirin, there was no difference in the combined end point. Finally, although much of the data is observational, there is good evidence that among patients with stable CAD who have not required revascularization with stent placement, the addition of antiplatelet agents to OAC therapy leads to increased risk of major bleeding without benefit in terms of decreased risk of either AF-related stroke or cardiovascular events.

In patients with stable CAD who have undergone revascularization with stent placement or bypass surgery the optimal antithrombotic regimen is less clear, as data in patients with stable CAD and modern management (i.e., wide use of coronary revascularization, including drug-eluting stent implantation) is limited. Recent health technology assessments and systematic reviews of combined anticoagulation and antiplatelet therapy for high risk patients with AF have called for a definitive prospective randomized controlled trial in a population of AF patients at high risk of atherosclerotic coronary artery and other vascular events to finally answer the question of optimal AF thromboprophylaxis in the common setting of comorbid CAD.[24,25]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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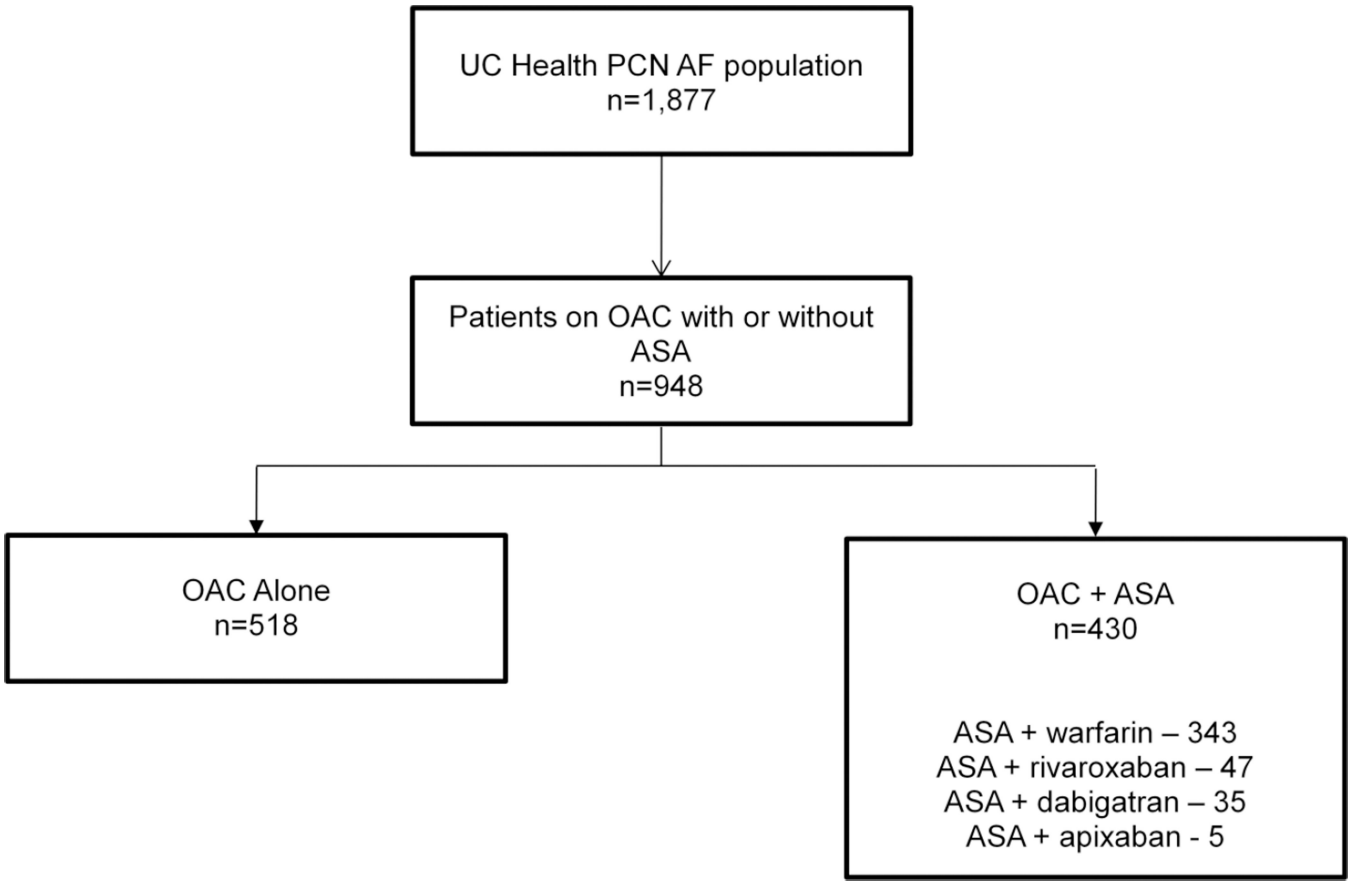

Figure 1. Flow diagram of AF patients in our UC Health Primary Care Network study population

PCN indicates primary care network; AF, atrial fibrillation; OAC, oral anticoagulant therapy; and ASA, aspirin.

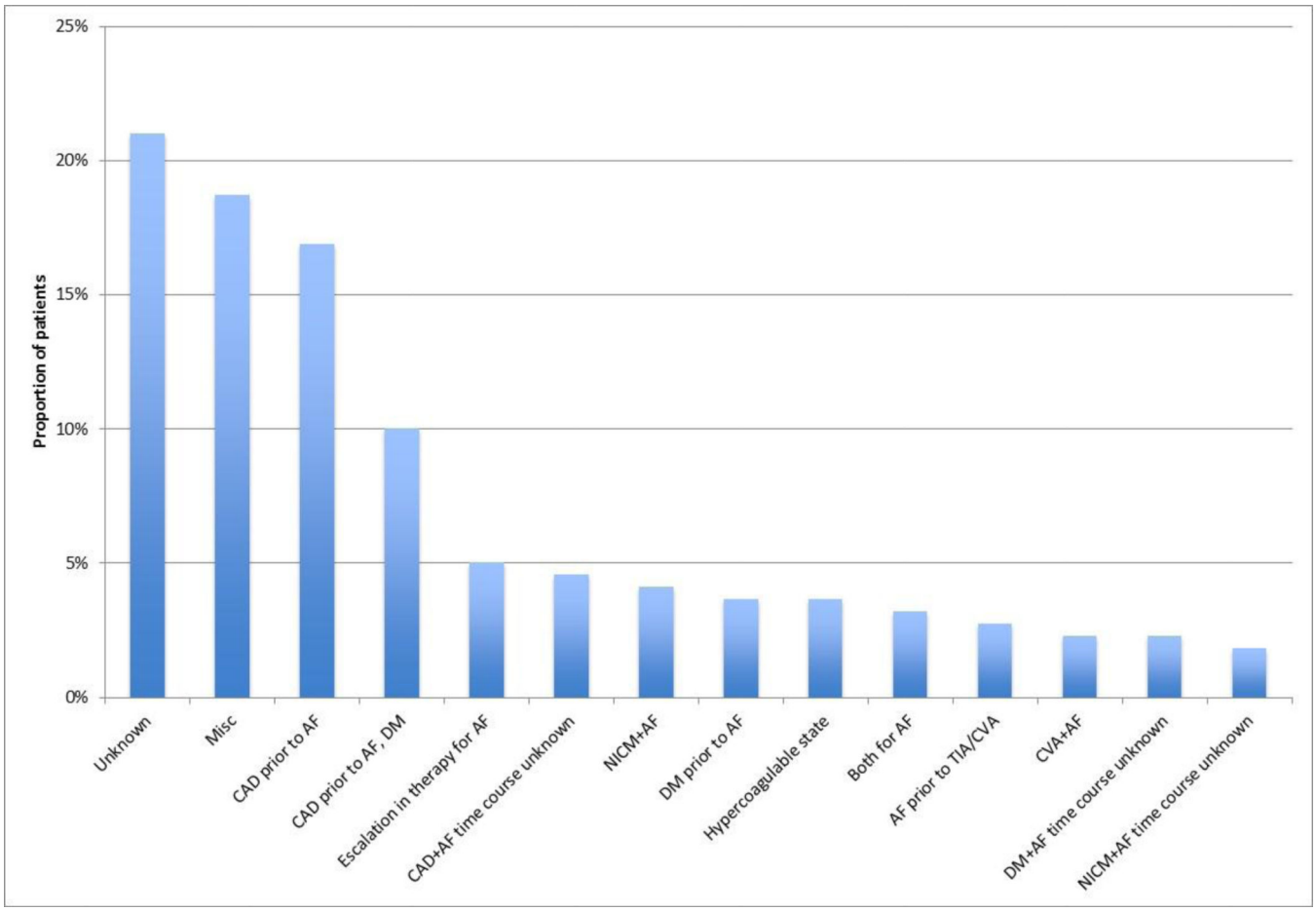

Figure 2. Indications for combined antiplatelet and anticoagulant therapy and their time course

The primary indications for combined antiplatelet and anticoagulant therapy and the sequence of events that led to its initiation, shown as proportions. Unknown are those who have no obvious indication for dual therapy; Miscellaneous includes categories with smaller numbers of patients (see supplemental figure 1); CAD prior to AF indicates those who were first diagnosed with CAD (with the initiation of aspirin) and then developed AF (with the addition of warfarin); CAD prior to AF, DM indicates the same as "CAD prior to AF" but also with the additional risk factor of having DM; Escalation in therapy for AF indicates those who were initially receiving aspirin for AF, which was then escalated to warfarin therapy due to a change in their AF-related stroke risk without discontinuing the aspirin; CAD+AF time course unknown indicates patients where it is unclear which diagnosis came first; NICM+AF indicates those who were diagnosed with NICM and AF at the same time; DM prior to AF indicates those who had an initial diagnosis of DM (with the initiation of aspirin) and then developed AF (with the addition of warfarin); Both for AF indicates patients who were started on aspirin and warfarin at the same time for AF; AF prior to TIA/CVA indicates those who had a diagnosis of AF (initiated on warfarin) and then developed a TIA/CVA (with the addition of aspirin); CVA+AF indicates those who were diagnosed with a CVA and AF at the same time; DM+AF time course unknown and NICM

+AF time course unknown indicates patients where the specific sequence of events were not able to be determined.

	All Patients	OAC Alone	OAC + ASA	*p*-value †
	948	518	430	
Age, y (mean, SD)	71.5 (12.1)	72.8 (12.2)	70.1 (12.0)	0.0003
Female (%, n)	46 (435)	51 (265)	40 (170)	0.0004
Comorbidities (%,n)				
Hypertension	82 (780)	80 (412)	86 (368)	0.015
Coronary Artery Disease	33 (311)	19 (100)	49 (211)	< 0.0001
Diabetes Mellitus	33 (310)	25 (128)	42 (181)	< 0.0001
Congestive Heart Failure	35 (335)	28 (145)	44 (190)	< 0.0001
Vascular Disease	46 (432)	30 (156)	64 (276)	< 0.0001
Prior Myocardial Infarction	14 (132)	7 (34)	23 (98)	< 0.0001
Prior Stroke	27 (255)	23 (120)	31 (135)	0.004
Kidney Disease	26 (244)	20 (106)	32 (137)	< 0.0001
Liver Disease	5 (49)	4 (19)	7 (30)	0.02
Prior Bleeding	29 (279)	29 (149)	30 (130)	0.62
Prior Intracranial Hemorrhage	2 (23)	2 (11)	3 (12)	0.51
Stroke Risk (%,n)				
CHADSVASc 0	1 (12)	1 (6)	2 (8)	0.26
CHADSVASc 1	6 (54)	8 (41)	3 (12)	0.0008
CHADSVASc ≥ 2	93 (886)	91 (475)	96 (411)	0.006
CHADSVASc (mean, SD)	3.94 (1.89)	3.71 (1.66)	4.22 (1.74)	< 0.0001
Bleeding Risk				
HASBLED (mean, SD)	2.37 (1.26)	1.9 (1.14)	2.94 (1.21)	< 0.0001

† Statistical comparison is between OAC alone and OAC +ASA.

	Odds Ratio	95% CI
Comorbidities		
Prior Myocardial Infarction	3.5	(2.4–5.2)
Coronary Artery Disease	2.5	(1.9–3.4)
Vascular Disease	2.1	(1.6–2.8)
Liver Disease	1.9	(1.1–3.4)
Diabetes Mellitus	1.7	(1.3–2.2)
Congestive Heart Failure	1.6	(1.2–2.1)
Kidney Disease	1.6	(1.2–2.1)
Prior Stroke	1.4	(1.0–1.8)
Prior Intracranial Hemorrhage	1.3	(0.6–3.0)
Hypertension	1.1	(0.8–1.5)
Prior Bleeding	1.1	(0.8–1.4)

First author/Study name/Year	Study design	Primary patient population	Comparison Groups	Mean Follow Up	Combined antiplatelet and anticoagulant therapy impact on MI	Combined antiplatelet and anticoagulant therapy impact on ischemic CVA	Combined antiplatelet and anticoagulant therapy impact on bleeding
ORBIT-AF 2013 [7]	Observational. Multicenter registry. Enrolled 7,347 pts	All pts with AF receiving OAC	OAC alone vs. ASA+OAC	6 months	Cumulative probability of events in 6 months low in both groups (MI–OAC alone 0.38%; ASA+OAC 0.48%)	Cumulative probability of events in 6 months low in both groups (stroke–OAC alone 0.42%; ASA+OAC 0.65%)	Major bleeding more likely in pts receiving ASA+OAC compared to OAC alone (HR 1.53; 95% CI 1.2–1.96)
Lamberts 2014 [6]	Observational. Nationwide Danish registry. Enrolled 8,700 pts	AF with stable CAD (including pts with h/o PCI)	APT alone (either ASA or clopidogrel), VKA alone, dual APT therapy, VKA+APT, and VKA+dual APT	3.3 years	No significant difference in incidence of MI in VKA+ASA compared to VKA alone (HR 1.12; 95% CI 0.94–1.34)	No significant difference in incidence of thrombo-embolism in VKA+ASA compared to VKA alone (HR 0.86; 95% CI 0.67–1.09)	Major bleeding more likely in pts receiving VKA+ASA compared to VKA alone (HR 1.5; 95% CI 1.23–1.82)
Hansen 2010 [5]	Observational. Nationwide Danish registry. Enrolled 118,606 pts	AF pts surviving first time hospitalization for AF as primary or secondary diagnoses	Various combinations of ASA, warfarin, and clopidogrel	3.3 years	N/A	Increased risk of fatal/non-fatal ischemic stroke in pts receiving ASA plus warfarin compared to warfarin alone (HR 1.27; CI 1.14–1.40)	Increased risk of combined fatal/non-fatal bleeding in pts receiving ASA plus warfarin compared to warfarin alone (HR 1.83; 95% CI 1.72–1.96)
CORONER Study 2014 [8]	Observational prospective. Multicenter study. Enrolled 4,184 pts	Stable CAD	Single antiplatelet agent, dual antiplatelet therapy, VKA alone, VKA plus antiplatelet agent.	2 years	No difference in risk of CV death, MI, or non-hemorrhagic stroke in pts on combined antiplatelet and anticoagulant therapy vs. VKA alone (HR 1.15; 95% CI 0.58–2.27)	No difference in risk of CV death, MI, or non-hemorrhagic stroke in pts on combined antiplatelet and anticoagulant therapy vs. VKA alone (HR 1.15; 95% CI 0.58–2.27)	No significant difference in bleeding risk in VKA alone compared to APT alone (HR 1.69; CI 0.39-7.3). Significantly increased bleeding risk in pts on VKA+APT compared to APT alone (HR

First author/Study name/Year	Study design	Primary patient population	Comparison Groups	Mean Follow Up	Combined antiplatelet and anticoagulant therapy impact on MI	Combined antiplatelet and anticoagulant therapy impact on ischemic CVA	Combined antiplatelet and anticoagulant therapy impact on bleeding
							7.3; CI 3.91-13.64).
Dentali 2007 [2,14]	Meta-analysis using 10 RCTs selected from MEDLINE, EMBASE, and CCRCT, total of 4,180 patients.	Pts taking ASA+OAC or OAC only w/ MHVs (5), AF (2), CAD (2) or CAD RF (1).			see comments	see comments	Major bleeding much more likely in pts taking OAC+ASA versus OAC only (OR 1.43, 95%CI 1.00-2.02, absolute risk increase 1.0%, number needed to harm - 100. However, no sig diff in ICH (OR 1.36, 95%CI 0.55-3.32) or fatal bleeding (OR 1.20, 95%CI 0.42–3.46
Flaker 2006 [4]	Meta-analysis for SPORTIF III and IV studies. Enrolled 7,304 pts.	Pts w/ AF on warfarin +/− ASA or ximelagaran +/−ASA	Ximelagatran, ximelegatran +ASA, warfarin, warfarin+ASA	16.5 months	No significant difference in rate of MI for pts receiving warfarin alone versus warfarin+ASA (1.0% vs 0.6%/pt years, p=0.40) or ximelagatran versus ximelagatran+ ASA (1.0% vs 1.4%/pt years, p=0.23).	No significant difference in stroke rate for pts receiving warfarin alone vs warfain+ASA (1.5% vs 1.7%/pt years, p=0.71) or ximelagatran vs ximelagatran+ ASA (1.2% vs 1.6%/pt years, p=0.43)	Increased major bleeding (3.9% versus 2.3%, p=0.01) and major/minor bleeding (62.8% versus 36.8%, p<0.01) when combined with warfarin. No significant increase in major bleeding was observed (2.0 % vs 1.9%, p=0.83) when added to ximelagatran but major/minor bleeding was

First author/Study name/Year	Study design	Primary patient population	Comparison Groups	Mean Follow Up	Combined antiplatelet and anticoagulant therapy impact on MI	Combined antiplatelet and anticoagulant therapy impact on ischemic CVA	Combined antiplatelet and anticoagulant therapy impact on bleeding
							increased (39.4%, 31.45%, p<0.01).
WOEST trial [3]	Open label randomized controlled trial, multicenter; 573 pts enrolled	Pts on long term anticoagulation and severe CAD with indication for PCI	Double therapy (OAC+clopidogrel), triple therapy (OAC+clopidogrel+ASA)	12 months	Combined secondary endpoint of death, MI, stroke, target vessel revascularization, and stent thrombosis was reported in 31 (11.1%) of pts in double therapy group and in 50 (17.6%) in the triple therapy group. Once baseline characteristics were accounted for, the HR was similar between the two groups (HR 0.56, 95% CI 0.35–0.91)	see to the left	At 1 year f/u, any bleeding occurred in 54 (19.4%) of pts in double therapy group [OAC + clopidogrel] vs. 126 (44.4%) in triple therapy group [OAC + clopidogrel + asa] with a HR of 0.36 (95% CI 0.26–0.5].

First author/Study name/Year	Methodological concerns	Other findings
ORBIT-AF 2013 [7]	(1) Could not statistically compare events (revascularization, MI, new onset HF, stroke, TIA, major bleeding or death) in the subgroups of pts with h/o previous MI and previous stroke/TIA because of lack of power (2) Short f/u	35% of all pts were receiving ASA+OAC. 39% pts receiving ASA+OAC did not have h/o atherosclerotic disease. Pts were more likely to receive combined antiplatelet and anticoagulant therapy if they had h/o CAD (adjusted OR 2.23; 95% CI 1.82–2.73), previous maze procedure (adjusted OR 1.56; 95% CI, 1.05–2.32), previous DES (adjusted OR 1.53; 95% CI 1.18–2.01) or previous stroke/TIA (adjusted OR 1.45; 95% CI 1.25–1.67).
Lamberts 2014 [6]	(1) Non randomized (2) No report on time in therapeutic INR range for those receiving	The hazard ratio for recurrent MI in the dual antiplatelet group (ASA+clopidogrel) was

First author/Study name/Year	Methodological concerns	Other findings
	VKA.	significantly higher than the VKA monotherapy group. Their possible explanation for this is the increased thrombotic state in AF as evidenced by the data from ACTIVE W trial, which showed more MI events in the ASA+clopidogrel group than VKA.
Hansen 2010 [5]	(1) Non randomized (2) Included patients who were hospitalized with primary/secondary dx of AF, which could represent a sicker population (3) Pts with CAD were only a subset; no subgroup analyses performed	Increased risk of bleeding with combination therapy - warfarin+clopidogrel and warfarin+clopidogrel+ASA being the highest. But no benefit in terms of stroke prevention in these two groups.
CORONER Study 2014 [8]	(1) AF was only a subset of pt population (about 7.2%, p<<0.0001) (2) Study grouped ASA and clopidogrel under the same category "APT" and did not differentiate the two -- this becomes an issue because in other studies (e.g., Hansen 2010) that did differentiate the two, they found that there was a higher bleeding risk in the combination of warfarin+clopidogrel (HR 3.08; CI 2.32–3.91) than warfarin+ASA (HR 1.83; CI 1.72–1.96) when compared to warfarin alone	
Dentali 2007 [2,14]	Different ASA strengths, different goal INRs. Did not differentiate MI versus CVA when defining thromboembolic events.	Arterial thromboembolism defined as MI, unstable angina leading to hospitalization, CVA, TIA, systemic embolism. MI not separated from CVA. No significant difference in risk of arterial thromboembolism in patients with non-valvular AF [OR 0.99, 95% CI 0.47–2.07]. No significant difference for all-cause mortality (OR 0.98, 95%CI 0.76–0.53). However, risk for arterial thromboembolism lower for combined antiplatelet and anticoagulant therapy in patients with MHV (OR 0.27, 95%CI 0.15–0.49).
Flaker 2006 [4]	Addition of ASA in SPORTIF trials was not randomized. Ximelagatran later discontinued due to hepatotoxicity.	No difference in rate of death among groups studied
WOEST trial [3]	(1) Not enough power to detect the differences in occurrence of thrombotic events (such as stent thrombosis) when aspirin was excluded (2) No report on how well anticoagulation was maintained in therapeutic range	