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A Review of the Relationship of Atrial Fibrillation and Acute Coronary Syndrome

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia encountered by clinicians. Clinical decision-making focuses on reducing ischemic stroke risk in AF patients; however, AF is also associated with an increased risk of acute coronary syndromes (ACS). Patients with ACS and concurrent AF are less likely to receive appropriate therapies and more likely to experience adverse outcomes than ACS patients in sinus rhythm (SR). Clinicians may be able to stratify ACS patients at increased risk of AF development based on clinical characteristics. Evidence supporting specific therapeutic options for prevention of ACS in AF patients or for prevention of AF in ACS patients is limited, however there is some evidence of differing effects among oral anticoagulant regimens in these populations. Investigations of the relationship of AF with the full spectrum of ACS are not well described and should be the focus of future research.

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Keywords

Atrial Fibrillation; Acute Coronary Syndrome; Clinical Decision-Making; Myocardial Infarction; Unstable Angina; Sinus Rhythm

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the world, affecting an estimated 33 million people in 2010 [1]. In the United States, AF affected an estimated 2.6 million Americans in 2010 and is projected to increase by 250% to 15.9 million Americans by 2030 [2]. Symptoms of AF are often subclinical and therefore, its prevalence is likely underestimated. Costs associated with AF are high, with an estimated \$6.65 billion per year spent on hospitalizations, outpatient physician care, and medical treatments [3]. AF has significant morbidity and mortality; up to 25% of strokes in the elderly are attributed to AF, a five-fold increase from the normal population [4]. However, a recent trial examining causes of death in AF patients receiving anticoagulant therapy reported that stroke accounted for approximately 7% of mortality while cardiac causes accounted for 37% [5]. In 2010, there were an estimated 1,141,000 unique hospitalizations for acute coronary syndrome (ACS); 813,000 for myocardial infarction (MI), 322,000 for unstable angina (UA) alone, and 6000 for both [2]. Medical costs for an ACS event ranged from \$34,087 to 86,914 in 2005 [2]. A recent analysis found that direct and indirect costs of ACS increased by 40% in patients with comorbid AF [6].

Although clinicians primarily aim to decrease stroke risk in AF patients through oral anticoagulation therapy, AF and ACS also frequently occur together, and rarely do providers prescribe long-term anticoagulation therapy for ACS patients. Thus, in this literature review we summarize current research findings regarding the bidirectional relationship between atrial fibrillation (AF) and acute coronary syndrome (ACS), including risk factors implicated in one disease progressing to the other, corresponding patient outcomes and implications for providers.

ACS is a provisional description for conditions along a continuum from demand ischemia to myocardial infarction (MI); however, the studies we found focused primarily on MI outcomes including non-ST elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI), with more limited data on unstable angina (UA). A significant number of articles were single site studies, many of which were underpowered or had potential confounders. Because of these issues, we will not directly discuss these articles unless they offer a mechanistic explanation of the relationship between AF and ACS. The remainder of these single site studies are listed in table 2.

Atrial fibrillation as a Risk Factor for Acute Coronary Syndromes

Compared to the evidence establishing AF as a predictor for stroke, the risk of MI predicted by AF and potential underlying mechanisms are less understood and contradictory at times.

While a narrative review by Desai et al in 2012 did not find a consistent association between AF and MI [7], more recent investigations have shown an association between AF and MI. The results of two large retrospective cohort studies are listed in Table 1. A retrospective analysis of the REGARDS cohort (Table 1), which examined regional and racial differences in stroke risk, revealed an increased rate of MI in AF patients compared to those not in AF (12.0%; 95% CI 9.6 – 14.9 vs 6.0%; 95% CI 5.6 – 6.6) [8]. An increased risk of MI remained after adjusting for clinical and socioeconomic factors (HR 1.70; 95% CI 1.26–2.30). Chao et al 2015 also found an association in a study of Taiwanese national health database records [9], where AF patients at low risk for stroke (CHA₂DS₂-VASc score of 0 [if male] or 1 [if female]) were matched to non-AF patients by age, sex, and CHA₂DS₂-VASc score. CHA₂DS₂-VASc is a risk stratification score used by clinicians to predict risk of stroke or thromboembolism in patients, with 0 in males and 1 in females indicating low risk [10] without use of anticoagulants or antiplatelet agents. AF patients had higher rates of MI compared with controls, with an absolute event rate of 1.6% for AF and 0.6% for controls after adjusting for variables more common in the AF group (HR 2.96; 95% CI 2.21–3.87). Potential limitations of this study include lack of a diverse population (only Taiwanese patients), and lack of data on lifestyle choices such as tobacco use.

In some patients, AF may be asymptomatic and detected incidentally. In an examination of the Clinical Practice Research Datalink, Martinez et al 2014 identified a cohort of patients who, at the time of AF diagnosis, were asymptomatic and had no history of possible AF symptoms, including palpitations and syncope [11]. Compared with controls matched by age and sex, the AF group had a crude increase of 2.5 MI per 1,000 person-years (9.0 vs 6.5 events per 1,000 person-years). However, this study did not appear to control for treatment type in the AF group. The relationship between AF and ACS has been examined in other populations as well. In a review the FRENA registry, which is a prospective cohort of Spanish patients with peripheral artery disease, the presence of AF was an independent predictor of MI. After multivariate analysis, AF was associated with a three times greater risk of MI (HR 3.11 [95% CI 1.52–6.37]). [12]

Pathophysiology: MI due to embolization in the setting of AF?

Our search returned several case reports of patients with MI due to embolus, citing AF as the likely or possible cause in each case [13–17]. In four of five reports, patients presented with STEMI. In addition to these individual reports, a retrospective review of STEMI patients at a single institution found that those with single vessel disease and AF, often had more filling defects on angiography suggestive of embolus than controls in sinus rhythm [18]. Though this study was limited by small numbers (n = 14 in AF group and n = 30 in controls), its findings suggests that cardioembolic MI may play a role in the pathogenesis of STEMI in patients with AF.

And yet, in Soliman et al's 2015 analysis of patients free from coronary artery disease at baseline in the ARIC cohort (Table 1), AF was associated with increased risk of NSTEMI (HR 1.80; 95% CI 1.39 – 2.31), and no increased risk of STEMI (HR 0.49; 95% CI 0.18 – 1.34), after adjusting for clinical factors including heart rate [19]. The age-adjusted MI event rate was 11.60 (95% CI 10.49 – 12.83) for those in AF vs 3.96 (95% CI 3.71 – 4.22) for

those without AF per 1000 person-years. Their study implies that cardioembolic phenomenon is not the primary pathophysiologic mechanism of MI in patients with AF, as NSTEMI is caused by incomplete occlusion of a coronary artery rather than complete occlusion such as in a STEMI.

While the pathophysiology of STEMI in the setting of AF is unclear, NSTEMI is more likely caused by the reduction in coronary blood flow during AF or due to supply/demand mismatch due to a high ventricular rate in rapid AF leading to a troponin leak. Luo et al 2013 examined coronary blood flow by Thrombolysis in Myocardial Infarction (TIMI) frame count (TFC) in patients with AF and sinus rhythm (SR). They found that AF was independently associated with a higher TFC, indicating poorer blood flow even when controlled for heart rate [20]. Other studies in our search reported a greater proportion of NSTEMI events in patients with AF compared with patients in sinus rhythm [21–25]. In patients with MI, studies that stratified by onset of AF and sinus rhythm, showed that those with a **p**rior history of **AF** (PRAF) generally had higher rates of NSTEMI (41.5% – 63.6%), but those who presented with **n**ew-onset **AF** (NAF) in the setting of an MI had higher rates of STEMI (48.5% – 68.8%) compared to those presenting in sinus rhythm [25–28].

AF as a predictor of ACS: Special Populations

Women—Women with AF are at a high for developing ACS. In the REGARDS cohort, Soliman et al's subgroup analysis by gender revealed that women are at increased risk of MI compared with men (HR 2.16 [95% CI 1.41 – 3.31] vs HR 1.39 [95% CI 0.91–2.10]). [8]. Additionally, in an analysis of the Women's Health Study, the rate of MI was 6.5 events per 1,000 person years for AF patients and 2.5 MI per 1,000 person-years in non-AF patients. After adjustment for clinical characteristics, the risk of MI was only significantly increased the first five-years after AF diagnosis (HR 3.87; 95% CI 1.43 – 10.44); after this time, women were at similar risk as those in normal sinus rhythm [29].

Race—Most of the reviewed studies did not compare the risk of ACS in AF patients based on race, but where examined, blacks with AF had a statistically significant increased risk of MI (HR, 2.53 [95% CI, 1.67–3.86]) [8], but whites did not (HR 1.26 [95% CI, 0.83–1.93]) [8]. O'Neal et al 2014, similarly found a significant interaction where blacks AF patients (HR: 3.1 [95% CI, 1.7–5.6]) had an increased risk of MI compared to whites (HR: 1.6 [95% CI, 1.2–2.1; P interaction =0.03]) [30].

Elderly—Both ACS and AF independently increase in frequency with age [1], and when O'Neal et al 2014 examined them together using the Cardiovascular Health Study (CHS) cohort, which assesses risk factors for coronary heart disease and stroke in the elderly, they found that AF increased the risk of MI by 70% (HR 1.70; 1.4–2.2). However, this effect was only significant for those younger than 80 years old [30]. For those greater than 67 years old with new onset AF (NAF), ACS outcomes appear to be influenced by comorbidities [31]. In a sample of Medicare beneficiaries with AF, the incidence of subsequent MI was strongly related to hospitalizations just prior to their arrhythmia diagnosis. Those who did not have hospitalizations for any cause three months prior to AF diagnosis had MI rates of 3.9% over five years compared to 12.6% in patients with hospitalizations for MI, gastrointestinal

hemorrhage, stroke, or heart failure within three months of their AF diagnosis over the same time period [31].

Other single site studies investigating the relationship between AF and ACS are included in Table 2.

Risk Stratification in the Emergency Department

When patients present to the emergency department (ED) with AF, they often complain of symptoms of chest pain, dyspnea or palpitations, in the setting of rapid ventricular rate (RVR). These patients may have a detectable troponin without ischemic injury from a supply/demand mismatch. According to the Third Universal Definition of Myocardial Infarction, these supply/demand mismatch conditions should not be considered an MI, and instead should be categorized as myocardial injury [32]. And while an elevated troponin could be considered an NSTEMI, controlling a RVR can reveal the underlying disease and if the patient is on the ACS continuum. Gupta et al investigated the association of minor troponin levels of patients who were admitted from ED with a primary diagnosis of AF and their prognosis [33]. They excluded patients with primary diagnoses of STEMI, NSTEMI (troponin I > 5ng/ml), or patients treated as an NSTEMI, and stratified AF primary diagnoses groups based on troponin tested, troponin negative, and troponin not tested. During the one year of follow-up, the troponin tested group with a mean 0.56 ng/ml (range of 0.05–4.17ng/ml) had higher rates of MI (7%) compared to those who had a negative troponin (1%). In addition to this, two other single site studies found similar results to Gupta et al and are listed in Table 2 [34, 35].

The EKG can also be used to stratify patients presenting with AF for increased risk of MI. In addition to assessing ischemia, they can also detect morphologic changes such as left ventricular hypertrophy (LVH) in patients. In the RE-LY cohort, a non-inferiority trial of two doses of dabigatran versus warfarin for prevention of systemic embolism and stroke in AF patients with at least one additional risk factor for stroke, the presence of left ventricular hypertrophy (LVH) was associated with increased risk of MI in those with CHA2DS2-VASc scores of 3 or more (HR 1.92; 95% CI 1.35–2.73) [36]. The risk of cardiovascular death when adjusted for the same clinical factors also increased in those with CHA2DS2-VASc scores of 3 or more (HR 2.22; 95% CI 1.85 – 2.67) [36].

Thus, in the Emergency Department, patients with atrial fibrillation (without a primary diagnosis of STEMI or NSTEMI), elevated levels of troponin, and/or EKG readings indicating left ventricular hypertrophy (LVH), may indicate an increased risk of ACS, particularly MI, within the next year and should alert the astute physician of this potential prognosis for the need for close follow-up.

AF as a prognostic factor in ACS

Not only did our review show that AF may be associated with increased rate of MI, but we also found that AF in the setting of ACS portends a worse prognosis compared to those in normal sinus rhythm. Four studies examined the prognosis of AF in the setting of MI [23, 37–39]. While all four found a positive correlation with mortality, one was not significant

[39]. Additionally, co-morbidities such as chronic kidney disease (CKD) in the setting of AF after percutaneous intervention (PCI) have an increased mortality rate than MI patients without AF or CKD [40]. When adjusted for clinical variables and treatments post-discharge, the COREA-AMI study, showed that those with AF and CKD still had an elevated risk of major adverse cardiovascular and cerebrovascular events (MACCE: death, recurrent MI, hospitalization for heart failure and stroke) (HR 2.10; 95% CI 1.42 – 3.13) and death (HR 2.54; 95% CI 1.60 – 4.03) than those with neither condition. Heart rate at presentation may also play an important role in the outcomes of ACS patients with AF. Those with heart rates ≥ 95 bpm had increased risk of mortality compared to those at lower heart rates [40]. Though the aforementioned studies looked at AF globally, most of the work in this area has centered on **prior-onset AF (PRAF)** and **new-onset AF (NAF)** prognosis in ACS.

For PRAF, several investigations found a statistically significant increase in mortality for patients suffering an ACS [22, 25–28, 41, 42]. In addition to mortality, PRAF patients were more likely to develop heart failure [22, 27, 28], and ventricular arrhythmia [27, 28, 43, 44]. In two studies, PRAF patients had similar risk of in-hospital stroke compared with those in sinus rhythm [27, 28].

Patients who developed NAF after MI also had increased adverse outcomes. Mortality was also increased in this group compared with those who stayed in sinus rhythm [27, 28, 41, 45]. The largest of these studies was done by Bang et al, who examined the health records of 89,703 Danish patients who suffered an MI. After controlling for clinical variables, including year of treatment, NAF was associated with an increased risk of all-cause mortality (HR 1.89 [95% CI 1.84–1.95]) and fatal re-infarction (HR 1.67 [95% CI 1.55–1.80]). When compared with PRAF, Almendro-Delia et al found that NAF nearly doubled the risk of death (HR 1.70 [95% CI 1.12–3.40]) [28]. The risk of death may also be time dependent, and there are some differing results in the reviewed literature. McManus et al found that NAF was associated with increased risk of in-hospital death (OR 2.0 [95% CI 1.8–2.3]), but not 30-day post-discharge death. However, Jabre et al also found statistically significant increases in mortality in NAF patients within 30 days, he also found increased risk of death after 30 days in his three NAF subgroups (onset with 2 days, 2–30 days, or >30days of MI). [41]. A potential explanation for this increased risk is that NAF may increase the risk of ventricular arrhythmias. In a review of the CARISMA trial, a cohort of post-MI patients with LVEF $\geq 40\%$ who had implantable cardiac monitors placed, Ruwald et al found that AF was associated with increased risk of sustained ventricular tachycardia (HR 6.71 [95% CI 1.83–24.62]). This implies that AF is a marker for worse ischemia compared to those without AF, despite adjusting for variables such as CHF[44]. Recently, two meta-analyses have examined the evidence of the effect of AF in ACS [42, 46]. Both investigations examined the literature prior to 2010. Even though both studies had slightly different inclusion criteria, they both found an increased risk of death in all patients with AF. Jabre et al examined 43 studies and found an OR of 1.36 [95% CI 1.35 – 1.58]. Angeli et al examined 27 papers using fixed and random effect models, showing an OR of 2.00 [95% CI 1.93 – 2.08] and 2.40 [95% CI 2.05 – 2.80], respectively. In an analysis of those with pre-existing versus new onset AF and mortality, both groups had increased risk of mortality. In

particular, Angeli et al found an 87% increased risk of death in those with NAF vs permanent AF (OR 1.87 [95% CI 1.16 – 3.04])[46].

To summarize, adverse outcomes are greater in both those of who develop NAF after MI as well as those with PRAF with subsequent ACS, compared to those who maintain sinus rhythm.

Predicting those with ACS who will develop AF

The incidence of AF after MI varies by population and occurs in 5 – 23% of patients [25]. One review used pooled data to calculate that ACS increases risk of AF by 77% (HR 1.77–95% CI 1.44–2.19) [47], while another study that aimed to develop a risk model for predicting AF found MI increased the risk of AF by about 60% (HR 1.60; 95% CI 1.34 – 1.91) [48]. Even in subclinical MIs detected solely by the presence of pathologic Q waves, the risk of AF doubled, and was equivalent to a 10% absolute risk increase in men [49]. As AF, and NAF in particular, seems to be associated with increased risk of mortality it would be beneficial to identify those at high risk for NAF in the setting of ACS. Unfortunately, many of the papers that investigate this subtopic are single site studies. We will not discuss these in detail here, and but have listed relevant results from these studies in Table 2.

Baseline characteristics related to New-onset AF

Characteristics that were repeatedly more common in those who developed NAF included female gender [27, 41, 45, 50, 51]), higher Killip Class [27, 52–54], lower LVEF [27, 50–54], diabetes mellitus [27, 50, 55], hypertension, [56, 57], and lower renal function [50, 52, 54–57]. Parashar et al found that diabetes was less common in those who developed NAF [57]. A surprising finding was that smoking was less common in those who developed AF [27, 50, 56, 57]. Age was frequently cited as a risk for NAF, which is expected. One study of MI patients showed increased incidence of NAF based on age groups in the Worcester, MA area. Those younger than age 65 had NAF rates of 7.5%, while those older than 75 had rates of 23.8% [58].

Labs upon presentation

An analysis of BNP levels, troponin, and high-sensitivity C-reactive Protein (hsCRP) in the TRIUMPH cohort, a multicenter prospective cohort of MI patients, showed a relationship between BNP, hsCRP, and NAF [57]. They found the risk of NAF correlated with BNP and hsCRP levels, but there was no relation with troponin. Though interesting, the clinical utility of this association is uncertain as the authors separated the values into deciles, but did not provide the actual values for these deciles. Two single site studies listed in Table 2 also found a correlation between NAF and higher levels of BNP [59, 60], however, this could be confounded by the fact that AF tends to occur in sicker patients rather than AF leading directly to worse outcomes.

Baseline medications

Hormone replacement therapy, a commonly prescribed group of medications for postmenopausal women, has been studied for its effect on NAF in the setting of MI. A

retrospective registry of 32,925 Danish women over age 40yo showed a decreased rate of NAF women taking HRT over 80yo on any kind of HRT (HR 0.63 [95% CI 0.42 – 0.94]) and specifically, vaginal estrogen when stratified by HRT type (HR 0.58 [95% CI 0.34 – 0.99]) [61]. Vaginal estrogen in other age groups was associated with lower risk of AF, however no other groups reached statistical significance.

Angiotensin converting enzyme inhibitor (ACEI) and angiotensin receptor blockers (ARB) are believed to reduce remodeling of the myocardium in heart failure, and therefore, a theoretic benefit exists for reducing the risk of NAF in ACS patients. However, in a study of 28,620 Medicare beneficiaries hospitalized for acute MI or revascularization, investigators found that renin-angiotensin system modulators in a univariate analysis actually increased the risk of NAF by 16% after a mean follow up of 3.8 years. After adjusting for clinical factors, however, this association was no longer significant [55]. Again, this may be due to AF occurring in sicker patients than AF worsening patient outcomes.

Preventive therapy

Preventing New Onset AF in ACS

Overall, studies examining medical therapy that decreased the rate of NAF in ACS are scarce. Given that elevated levels of hsCRP may be associated with increased AF, and prior statin therapy may also be associated with decreased incidence of NAF in low CHADS₂ patients, early statin therapy might theoretically lead to improved outcomes in those presenting in ACS. An analysis by Bang et al of ACS patients showed that the absolute risk reduction of NAF in patients with ACS receiving statin therapy was 5% (10% vs 15%), with a calculated relative risk reduction (RRR) of 33%. However, those who did not receive statin therapy had more comorbidities [62]. When adjusted for clinical factors, the relative risk reduction was 17%, thus the number needed to treat (NNT) is unclear for statins. A meta-analysis of statin therapy for prevention of NAF pooled data from six trials of over 160,000 patients. ACS patients who were taking a statin at baseline had a 35% reduction in NAF (RR 0.65 [95% CI 0.55 – 0.77]); however, the analysis was weighted predominantly by the Bang study (31.39%) and calculated an unadjusted RRR of 32% to support their finding [63]. However, all the other studies had significantly reduced rates of NAF (RR range 0.36 – 0.84) as well.

Ranolazine is the only other medication examined within the last five years for prevention of NAF. In a retrospective analysis of the MERLIN-TIMI36 trial, those assigned to ranolazine had a lower incidence of NAF after one year. The ARR was 1.2%, with NNT of 83 [64]. While both therapies reduce the risk NAF after ACS, there is more evidence supporting statins than ranolazine.

Preventing ACS in AF patients

As noted previously, the focus of AF therapy revolves around the prevention of ischemic stroke. However, there have been some investigations into pharmacotherapies and their effect on ACS risk reduction.

Oral Anticoagulants

Extensive evaluations of oral anticoagulants as a therapy for atrial fibrillation are found elsewhere and are not the primary focus of this review. We briefly describe them here, and refer the interested reader to these more in-depth articles for further information [65–73].

Warfarin has been a mainstay in AF treatment for stroke prophylaxis, but it is not traditionally associated with risk reduction of ACS. In the SWEDEHEART cohort, which includes all patients from Swedish hospitals requiring care for ACS, those with AF prescribed warfarin had reduced rates of adverse events, including reinfarction [74]. The patients were stratified according to renal function, and the effect was modest in those with normal renal function (ARR 2.5%, NNT 40). Warfarin did not significantly reduce risk in patients with a GFR 15 – 60ml/min/1.73m², but was most effective in those with a GFR <15, reducing the risk of MI by 46% (ARR 11%, NNT 9). However, this was an unadjusted analysis and the results may not reflect actual effects [74]. For patients already on warfarin, maintenance of a therapeutic international normalized ratio (INR), can minimize ACS risk. In a large prospective study of patients with nonvalvular AF newly initiated on warfarin, subtherapeutic INR led to increased incidence of ACS compared with those with therapeutic INR (13.7 vs 1.6 per 100-person-years)[75].

Direct oral anticoagulants (DOACs) were introduced to market in 2010 and now include factor IIa inhibitor dabigatran etexilate and factor Xa inhibitors rivaroxaban, apixaban, and edoxaban. While NOACs have similar benefits such as eliminating the need for repeated INR checks in patients, research suggests that the two types of DOACs might have different effects on ACS outcomes in the setting of AF. An analysis of the ROCKET-AF trial, which compared rivaroxaban with warfarin for prevention of stroke and systemic embolism in AF patients, found that the risk of MI was similar between the two groups, with a trend towards decreased MI in rivaroxaban treated patients [76]. A meta-analysis by Loffredo et al investigated the effect on risk of MI in AF patients treated with DOACs compared with warfarin [68]. They investigated factor II and factor Xa inhibitors separately, but only four trials met their inclusion criteria (RELY [68], ARISTOTLE [77], ENGAGE [78], ROCKET-AF [76]). The RE-LY trial was the only analysis of a factor IIa inhibitor, dabigatran. Dabigatran was associated with increased risk of MI compared with warfarin (RR: 1.38; 95% CI, 1.1–1.7; p = 0.005). The absolute risk increase was 0.41%, with a calculated number needed to harm (NNH) of 243. The authors found no difference in risk between factor Xa inhibitors and warfarin [68]. This particular analysis is interesting, but limited as it only draws from four studies, and only one for the dabigatran analysis. Studies comparing all NOACs and warfarin head-to-head, especially in the high-risk ACS-AF population, are lacking. The optimal antithrombotic regimen, including anticoagulants and antiplatelet therapies, is especially important as the highest risk patients can experience cardiovascular event rates that approach 30–40% after four years [79].

Antiarrhythmic Agents

Dofetilide is an antiarrhythmic agent developed to treat AF and atrial flutter. Schmiegelow et al performed a retrospective analysis of the DIAMOND-MI cohort, which was a Danish

RCT examining those with LV dysfunction and recent MI on dofetilide or placebo, and found that those with recent MI had an incidence of NAF of 2.9% after 42-months of follow-up. Treatment with dofetilide was not associated with a significant reduction in the risk of NAF [80].

Dronedarone is an antiarrhythmic agent also approved in recent years. The ATHENA trial was a randomized controlled trial of dronedarone in AF patients and was found to increase the time to first hospitalization. In a post-hoc analysis of this trial, the rate of hospitalizations for ACS had a significant decrease in the dronedarone group. However, calculating absolute risk reduction (ARR) showed a modest 1.8% decrease in hospitalizations, with NNT of 56 [81]. Though this trial did not measure mortality, a subsequent retrospective analysis of the ATHENA trial did. Investigators stratified the patients based on their history of coronary heart disease (CHD). AF patients free of CHD at baseline treated with dronedarone did not have a statistically significant decrease in ACS occurrence or cardiovascular death. However, in those with CHD at baseline, they found a significant absolute reduction in ACS of 2.8%, NNT of 36 [82]. The reduction in cardiovascular death was also significant, with ARR of 2.43%, NNT of 41.

Antihypertensive Drugs

Irbesartan is a newer angiotensin receptor blocker whose effect on cardiovascular events in AF patients was evaluated in the ACTIVE I trial. The patient pool included those from two parallel trials: ACTIVE A and ACTIVE W. Irbesartan appeared to have limited benefit in the outcomes assessed by the Active I investigators; there was no change in risk of MI [83].

Conclusions

AF appears to be an independent risk factor for development of ACS, specifically MI. Except for cases of cardioembolic MI, AF as a causative factor of ACS has not yet been established, and could simply be a surrogate marker for risk factors common to both conditions. Ideal study design to definitely prove causation is difficult to realize given the confounding associated with AF occurring with sicker patients. Because AF has been noted as a sequela of MI, our review supports a bidirectional relationship between AF and ACS. Additionally, in those who suffer an ACS, AF portends a worse prognosis; however, physicians may be able to identify those who are at higher risk of developing AF based on patients' baseline characteristics (female gender, higher Killip class, renal function), labs (BNP, hsCRP), EKG, or echocardiogram. Initiation and maintenance of the optimal antithrombotic regimen in high-risk AF-ACS patients is crucial but not widespread. Further options for interrupting the bidirectional relationship between AF and ACS are limited as all recent studies have only involved retrospective reviews or cohort studies and no RCTs have been performed for evaluating interventions on this relationship. Future research may need to focus on the area of prevention of AF in ACS or vice-versa, and subsequent effects on mortality.

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Table 1

Major Studies Published from 2011–2015 regarding the ACS-AF relationship

Authors, Year	Study Name/Study Design	Years Studied/ Follow Up (Yrs)	Study Population	Major Findings
Predicting Occurrence of ACS in AF				
Chao et al., 2015 [9]	N/A Registry	2000–2011 5.7±3.6	12 114 AF pts with CHA ₂ DS ₂ -VASC scores of 0 (men) or 1 (women)	AF predicted MI compared to matched controls (HR 2.93 [95% CI 2.21–3.87]). MI risk was higher in men (HR 2.24 [95% CI 1.61–3.11]) after adjustment.
Soliman et al., 2015 [19]	ARIC Prospective	1987–2010 Median 21.6	14 462 participants free of CHD at baseline	AF predicted MI compared to non-AF (HR, 1.63; 95% CI, 1.32–2.02), NSTEMI (HR, 1.80; 95% CI 1.39–2.31) but not STEMI (HR 0.49; 95% CI 0.18–1.34). The association was stronger in women.
Soliman et al., 2014 [8]	REGARDS Prospective	2003–2009 Median 4.5	23 928 participants free of CHD at baseline	MI rates in AF patients were higher than non-AF patients (adjusted HR 1.70 [95% CI, 1.26–2.3]). Women and blacks were at greater risk. Older age did not increase risk.
O'Neal, et al., 2014 [30]	CHS Prospective	1989–2008 Median 12	4608 pts with no evidence of CHD	Presence of AF increased risk of MI (adj. HR: 1.7, 95% CI: 1.4–2.2). Blacks had increased risk compared with whites.
Predicting Occurrence of AF in ACS				
Bretler, et al., 2012[61]		1997–2009	32 925 women discharged after MI with no known AF	HRT use decreased risk of new-onset AF in women with prior MI (HR 0.82, [95% CI 0.68–1.00]). Greatest decrease in women 80 y.o.
Carrero, et al, 2014[74]	SWEDE HEART	2003 – 2010	24 317 MI pts with AF	Warfarin treatment decreased the risk of re-infarction in those with eGFR > 60 and 15.
Prognostic Effect of AF in ACS				
Rene et al., 2014[51]	HORIZON-AMI RCT	2007–2013	3 281 pts with sinus rhythm undergoing PCI	New-onset AF after PCI was an independent predictor of adverse clinical events (HR 1.74, 95% CI 1.30 to 2.34) and major adverse cardiac events (HR 1.73, 95% CI 1.27 to 2.36) at 3 years.
Verdecchia et al., 2014[36]	RE-LY RCT	2005–2009 Median 2.0	10,372 anti-coagulated elderly AF pts	LVH presence increased CV death (HR 2.56, 95% CI 2.14 to 3.06) and MI in elderly AF patients (HR 2.07, 95% CI 1.47 to 2.92).
McManus et al., 2012 [27]	GRACE	2000–2007	59,032 pts hospitalized with an ACS	Patients with AF were less likely than patients without AF to receive evidence-based therapies. Hospital death rates in patients with new-onset and pre-existing AF were 14.5% and 8.9%, compared to 1.2% in those without AF
Almedro-Delia, et al. 2014 [28]	ARIAM Registry	2001–2011	39 237 consecutive pts with ACS	New-onset AF is an independent predictor for in-hospital mortality (HR 1.62, 95% CI 1.09–2.89).
Jabre 2011 [42]	Meta-Analysis	1970–2009	43 studies involving 278,854 subjects	AF increases mortality in pts with acute MI, regardless of its onset being prior to MI (OR 1.28 [95%CI 1.26–1.49]) or after MI (OR 1.46 [95% CI 1.35–1.58])

Authors, Year	Study Name/Study Design	Years Studied/ Follow Up (Yrs)	Study Population	Major Findings
Angeli et al, 2012 [46]	Meta-Analysis	1967–2010	24 studies involving 235,511 subjects	Mortality was higher in pts with AF (OR 2.00, 95 % CI: 1.93–2.08; P<0.0001). In NAF (OR 3.38 [95% CI 2.98–3.83] and permanent AF (OR 2.01 [95% CI 1.70–2.38]).
Ruff et al., 2014 [84]	REACH Registry Prospective	2003–2009 4	44,518 of 68,236 enrolled in REACH	The prevalence of AF at baseline = 10.3% (n = 4582). Pts with AF had a 2-fold increase in the composite of CV death, MI, or stroke compared with patients without AF after adjustment (18.9% vs. 9.4%, p < 0.0001). Only 52% of patients with a history of AF at baseline were receiving anticoagulation at 4 years.

AF atrial fibrillation, ACS Acute Coronary Syndrome, NAF new onset AF, Pts patients, MI myocardial infarction, HR hazard ratio, CI confidence interval CHD coronary heart disease, CV cerebrovascular, SR sinus rhythm, STEMI ST segment elevation MI, NSTEMI non-ST segment elevation MI, PCI percutaneous coronary intervention, HRT hormone replacement therapy, eGFR estimated glomerular filtration rate

Table 2

Hypothesis generating or confirmatory single site studies

Author	N	Population	Findings
Predicting ACS in AF patients			
Potpara et al, 2011 [85]	1,056	Nonvalvular AF pts	No difference in risk of MI in those with mitral annular calcification
Qayyum et al, 2012 [86]	258	In- and outpatients with AF	No association with vitamin D and type of AF, nor IHD, MI, or CVA in AF pts.
van den Bos et al. 2011[34]	407	Consecutive pts admitted with AF	Minor troponin elevation had increased risk of MI and higher adjusted risk of death
Krishnamoorthy, 2013[87]	423	Consecutive pts admitted with AF	Compared with controls, pts who developed MI had a higher median vWF value and sE-sel value
Predicting new-onset AF in ACS patients			
Nunez-Gil, 2013 [88]	237	Consecutive pts admitted with first NSTEMI-ACS	AF was more common in MR group. A higher proportion of pts developed AF at higher MR degrees.
Raposeiras, 2015[89]	1,520	Consecutive pts with ACS who underwent coronary angiography	CIN increased risk of NAF after adjustment for clinical factors; development of CIN is an independent predictor of new-onset AF in the context of acute coronary syndromes.
Athar, 2011 [90]	166	Consecutive pts admitted to CCU with MI receiving PRBC transfusion	7 of 148 transfusion pts and 18 of 1348 non-transfused developed AF
Huang, 2013 [53]	724	Consecutive MI pts admitted to CCU (582 men)	Statin use was associated with reduction in NAF incidence
Dorje, 2013 [59]	268	Consecutive MI pts with BNP measured within 24 hrs of admission	Median BNP levels were 2166 in NAF pts vs 707pg/mL in no AF group. All AF pts had BNP 796pg/mL
Guenancia, 2014 [56]	1,123	Consecutive CCU pts with MI	Obesity increased risk of NAF in men (OR 2.51 [95% CI 1.26–4.99])
Aronson, 2011[52]	1,169	Pts admitted to CCU with MI	Restrictive filling pattern on echo had increased risk of NAF after 6mos (adjusted HR 2.17 [95% CI 1.42–3.32]).
Hwang, 2011 [91]	401	Pts with MI	LAVI 32mL/m ² was associated with increased NAF development (HR 2.47 [95% CI 1.08–5.65])
Alasady, 2011[21]	2,460	Consecutive pts with MI at CCU and documented AF within 7 days of MI	Right coronary atrial branch and left circumflex atrial branch were independent predictors of NAF (P = 0.02)
Asanin, 2012 [60]	180	Consecutive pts with STEMI treated by PCI <12hrs after onset of chest pain	BNP 720pg/mL was predictive of NAF (OR 3.70 [95% CI 1.40–9.77]).
Distelmaier, 2014 [92]	66	Consecutive pts admitted with MI	Those who developed AF had higher median levels of Hgb (14.2 vs 12.9mg/dL), Hct (41.7 vs 38.7%), and erythrocyte count (4.6 vs 4.2)
Yoshizaki, 2012 [93]	176	Consecutive pts admitted with MI	AF pts had higher mean WBC on days 2–4 (12.0 vs 10.6*10 ³ /μL) and 5–7 (9.3 vs 7.5*10 ³ /μL), and had higher CRP on days 2–4 (12.6 vs 4.7mg/dL), 5–7 (12.3 vs 5.2mg/dL) and 8–14 (8.5 vs 2.7mg/dL).
AF as a prognostic factor in ACS			
Author	N	Patients	Findings
Podolecki, 2012 [50]	2,980	Consecutive admitted MI pts	Pre-existing paroxysmal AF had similar rates of death as SR. Those with permanent AF had highest risk of death after 1-yr (45.7% vs 9.4% no AF).
Viliani 2012 [43]	913	Consecutive MI pts treated with primary PCI	AF pts had higher risk of death than those in sinus rhythm (17 vs 5%, p <0.001)
Poci, 2012 [25]	2,335	Consecutive ACS pts	Across all CHADS ₂ scores, AF pts had higher mortality rates. AF almost doubled long-term mortality.

Author	N	Population	Findings
Maagh, 2011[26]	375	Consecutive MI pts	Cardiovascular death in 9 of 22 chronic AF (40.9%) pts, 2 of 16 (12.5%) pts with NAF, and 41 of 337 (12.2%) of those without AF
Lin, 2011[94]	783	Consecutive STEMI pts undergoing primary PCI	No increased risk of death in those that developed AF compared with SR.
Stamboul, 2015 [95]	736	Consecutive MI pts admitted to CCU	After 1 yr, CV death was elevated in those with silent AF (5.7%) and symptomatic AF (18.8%) compared to no AF (2.0%)

AF atrial fibrillation, *NAF* new onset AF, *ACS* Acute Coronary Syndrome, *Pts* patients, *MI* myocardial infarction, *IHD* ischemic heart disease, *CVA* cerebrovascular accident, *vWF* Von Willebrand factor, *sE-sel* soluble E-selectin, *NSTE-ACS* non-ST segment elevation ACS, *MR* mitral regurgitation, *CIN* contrast-induced nephropathy, *CCU* critical care unit, *PRBC* packed red blood cells, *hrs* hours, *LAVI* Left Atrial Volume Index, *BNP* B-type natriuretic peptide, *SR* sinus rhythm, *STEMI* ST segment elevation MI, *Hgb* hemoglobin, *Hct* hematocrit, WBC white blood cell count, CRP C-reactive protein, *PCI* percutaneous coronary intervention