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Atrial Fibrillation in Acute Coronary Syndrome

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Abstract

Atrial fibrillation (AF) is a common cardiac arrhythmia occurring in an estimated 2.7 to 6.1 million people in the United States. The risk factors for the development of AF are very similar to those for developing coronary artery disease, and AF is often associated with acute coronary syndrome (ACS) and acute myocardial infarction (MI). Overall, AF complicates approximately 10% of acute infarcts and the incidence rate is comparable between the thrombolytic and percutaneous coronary intervention (PCI) eras. Prior to widespread use of thrombolysis, the incidence of AF during acute MI was as high as 18%. Moreover, AF is a marker for increased long term mortality post infarct. Over the past 20 years, the relative mortality risk for patients with AF post MI has remained around 2.5 times that for patients without AF.

The treatment of AF in the setting of MI and ACS is similar to without; however there is often an increased urgency to limiting rapid heart rates which may exacerbate acute ischemia. Cardioversion and IV amiodarone may be utilized more liberally in this setting than otherwise. Anticoagulation is usually required both for the treatment of MI and possible PCI, as well as for cerebral vascular accident prevention from AF-induced thromboembolism. Often patients require triple-therapy for optimal treatment of both conditions, and special considerations for bleeding risk must be analyzed.

Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia occurring in an estimated 2.7 to 6.1 million people in the United States (US). AF prevalence increases with age affecting 6% of the US population ≥ age 65.[1,2] By age 40, the lifetime risk of AF for females and males is 23% and 26% respectively.[3] European statistics are comparable such that an estimated 5.5% of persons above the age 55 have AF with a lifetime risk of 22-24%.[4]

Given the high burden of the arrhythmia, AF accounts for many annual hospitalizations. In fact, the rates of AF admissions increased 34% from 1996 to 2001 in the US.[2] More recently, a study that reviewed all hospital admissions in Australia found that there was a greater than 200% increase in hospitalizations due to AF between 1993 and 2008 representing an annual rise of 8.3%.[5] A review of the data from US healthcare claims from 2004 through 2006 found that the 12 month direct cost for a patient with AF was $20,670 compared to $11,965 for a patient with a similar co-morbidity profile without AF. With an incremental cost of $8705, inpatient services were the most important cause of the cost difference followed by office then emergency department visits.[6]

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Risk Factors

Many risk factors have been associated with AF including heart failure, diabetes, hypertension, valvular pathology, obstructive sleep apnea, age, angina and myocardial infarction (MI).[7] AF is more likely to complicate an MI in older patients such that those ≥ 70 years have a 16.0% risk for developing AF post infarct compared 4.2% for those ≤ 59 years.[8] Additional characteristics that increase the likelihood of AF include hypertension history, prior infarct, hypotension on admission, tachycardia on presentation, a higher Killip class, non ST elevation MIs and inferior infarcts.[9-11] Moreover, patients with new onset AF were more likely to have left main coronary artery disease versus patients with a prior AF history.[12]

Outcomes - Morbidity and Mortality

Overall, AF complicates approximately 10% of acute infarcts and the incidence rate is comparable between the thrombolytic and percutaneous coronary intervention (PCI) eras. However, prior to widespread use of thrombolysis, the incidence of AF during acute MI was as high as 18%.

AF is also a marker for increased long term mortality post infarct. Over the past 20 years, the relative mortality risk for patients with AF post MI has remained around 2.5 times that for patients without AF.[13] AF also increases the likelihood of heart failure, from 62% to 70%, and incidence of ventricular tachyarrhythmias post infarct.[9,11] In fact, one study found that AF was an independent predictor of in-hospital ventricular fibrillation (VF) post infarct with an OR of 2.6. Despite the elevated risk of VF, there was no difference in the in hospital mortality between those who had AF and those who did not though the long term mortality was higher in the AF group, 29% versus 11.8%.[14] Prior history of AF has been shown to predict outcomes. Patients with new onset AF are more likely to develop adverse events acutely while those with a prior history of AF have higher long term event rates.[12]

Medical therapy may differ depending on the existence of and type of AF. The GISSI-3 data showed that patients with AF were less likely to receive beta blockade, 31% vs. 25%, and lytics, 73% vs. 65%, compared to patients without AF. GISSI-3 also showed that patients with AF were more often treated with digoxin, 32.5% vs. 5.7%, and antiarrhythmic drugs, 39.8 vs. 5.6%. (9) Another study showed that new onset AF patients were less apt to receive clopidogrel post infarct than those with a prior AF diagnosis.[12]

Etiology of AF in ACS

Initiation of AF is typically due to focal automaticity within the pulmonary vein musculature.[15] Triggers include ganglionic plexi that reside near the antral portion of the pulmonary vein-left atrial junction. Islands of fibrosis and scar within the left atrium then provide a substrate for rotors and wavelets of re-entry that, combined with a shorter atrial effective refractory period, provide the substrate allowing for arrhythmia persistence.[16] In fact, a recent study that examined left atrial tissue autopsy specimens found that the presence of fibrosis, lymphomononuclear and fatty infiltration was associated with a prior history of AF. Additionally, the degree of fibrosis directly correlated with the duration of AF such that those specimens with a prior history of longstanding persistent AF had a greater amount of fibrosis than those with paroxysmal AF. Conversely, there were insignificant amounts of fibrosis in patients without AF despite histories of congestive heart failure, coronary artery disease and hypertension. Interestingly, and in contrast to prior studies, age was not found to be a factor that correlated with the level of fibrosis.[17]

The high incidence of AF post MI may be secondary to neurohormonal factors that accompany acute infarcts and/or changes in the atrial substrate due to atrial ischemia.[18] A recent single institution study found among 149 patients presenting with acute coronary syndrome, 4.9% developed AF within the first week of presentation. While there was a similar comorbidity profile

Table 1 | CHADS Score(35)

Risk Factor	Score
Congestive Heart Failure	1
Hypertension	1
Age 75 years	1
Diabetes Mellitus	1
Stroke or TIA history	2

between the groups, patients with AF were more likely to have atrial branch disease.[10,19] In fact, an animal model study showed that acute cessation of atrial blood flow correlated with prolonged atrial conduction, increased conduction heterogeneity and increased likelihood of AF induction and persistence compared to left anterior descending infarcts and controls. These results suggest that the atrial ischemia rather than the neurohormonal changes associated with infarct may be the etiology of AF given that LAD infarcts should result in similar neurohormonal activation.[20]

Table 2 | $CHADS_2$ Score and Stroke Risk(35)

$CHADS_2$ Score	National Registry of AF Adjusted Stroke Rate per 100 patient-years (95% CI) Score
0	1.9
1	2.8
2	4.0
3	5.9
4	8.5
5	12.5
6	18.2

Screening for CAD w/ AF

While AF commonly complicates acute infarct, ischemia is rarely the cause of AF in those patients without typical CAD features.[21] One study that prospectively followed 255 patients presenting to the emergency room with a primary AF diagnosis found that 43% of the patients were admitted for purposes of ruling out an acute infarct. However, only 5.5% of those patients were found to have an acute infarct. Diagnostic tools that were predictive of infarction included ST segment elevation and ST depression greater than 2mm. Meanwhile, chest pain and mild ST segment depression was common among these patients and not specific enough to predict ACS.[22] Another study evaluated patients in AF with ST depressions as defined by exercise stress guidelines. They found that the presence of ST depression did not necessarily predict coexisting coronary artery disease. Of the 83 patients completing the testing, 27 patients (32.5%) had angiographic evidence of obstructive disease (≥70% luminal narrowing) with 19 of the patients having only single vessel disease.[23]

Moreover, when patients with AF but without symptoms for CAD underwent myocardial perfusion imaging the mean summed stress scores were similar when compared to age and gender matched asymptomatic patients without AF. Both groups had similar incidences of high risk studies, 14.4% in each group. However, despite the similarities in stress test results, the AF group had higher 5 and 10 year mortality rates, 27% vs. 18% and 47% vs. 40% respectively.[24] When stress testing was performed in conjunction with multi slice computed tomography (MSCT) coronary angiography, patients with AF were more likely to have obstructive CAD per MSCT, 40% vs. 25%, compared to patients without AF though both groups had a similar prevalence of abnormal stress tests.[25]

EKG Diagnosis of Ischemia during atrial fibrillation

Consistent with the above data, the typical interpretation of ST-segment shift, either depression or elevation, may be less accurate in the setting of AF, especially with RVR. ST segment depression can often occur during rapid rates, even without CAD, and is not specific for ischemia particularly if the depression is <2mm.[26,27] The converse is also true, where rapid rates may mask ST segment shift, making the 12-lead EKG less sensitive for the detection of acute MI in the setting of AF with rapid ventricular rates. Often, cardiac enzymes are required for diagnosis when ST-elevation is not evident due to rapid AF.[21]

Management of Atrial Fibrillation During Acute Coronary Syndrome

The primary algorithm for the treatment of atrial fibrillation is similar in the setting of ACS as compared to without, but may have a special urgency in these settings. First, it must be determined if the atrial fibrillation is causing hemodynamic instability or other end-organ damage. In the setting of ACS, it may be difficult to determine if rapidly conducted heart rates are worsening cardiac ischemia by increasing cardiac oxygen demand, or if the ischemia is unrelated to the atrial fibrillation. A lower threshold therefore is needed as to the acceptable maximum conducted heart rates. If heart rates cannot be controlled acutely, often with IV β-blockers (BBs), then ur-

Table 3 | CHA_2DS_2-VASc Score (37)

Risk Factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age 75 years	2
Diabetes mellitus	1
Stroke/TIA/Thromboembolism	2
Vascular disease (prior MI, peripheral artery disease, aortic plaque)	1
Age 65-74 years	1
Sex category (female gender)	1

gent direct-current cardioversion (DCCV) should be considered.[28,29] Ideally conversion to sinus should only be undertaken if the duration of AF can be assured to be less than 48 hours, or after a negative transesophageal echocardiogram (TEE) or the patient has been on therapeutic anticoagulation for 3-4 weeks. However, if the AF appears to be life-threatening, the risks of stroke during cardioversion must be weighed against the risks of allowing rapid ventricular rates to perhaps exacerbate cardiac ischemia. Current AHA guidelines list DCCV as a Class I recommendation in the setting of acute MI, if there is severe hemodynamic compromise, intractable ischemia, or when adequate rate control cannot be obtained.[30] negative inotropic effects of non-dihydropyridine CCBs, their use should be limited during ACS particularly if there are any signs of CHF. Digoxin is a class IIa recommendation, and can be added for synergistic effects with BBs, if additional rate control is needed despite maximum BB doses, or if doses are limited by hypotension.[28,29] It should also be noted that utilizing ace-inhibitors and/or carvedilol in the early post-MI setting have been shown to reduce the rate of AF recurrence.[31,32]

Medical rate control agents used will be similar to non-ACS AF management. However, special preference should be given for beta blockers, which are also part of the acute MI treatment algorithm, unless the patient is in active CHF or significantly bradycardic. Intravenous (IV) beta blockers and non-dihydropyridine calcium channel blockers are class I AHA recommendations for slowing rapid ventricular response to AF.[30] However, due the negative inotropic effects of non-dihydropyridine CCBs, their use should be limited during ACS particularly if there are any signs of CHF. Digoxin is a class IIa recommendation, and can be added for synergistic effects with BBs, if additional rate control is needed despite maximum BB doses, or if doses are limited by hypotension.[28,29] It should also be noted that utilizing ace-inhibitors and/or carvediolol in the early post-MI setting have been shown to reduce the rate of AF recurrence.[31,32]

If rhythm control is the optimal treatment strategy for AF in ACS, an anti-arrhythmic medication (AAD) may be added especially if AF recurs after cardioversion. Like DCCV, AADs should ideally only be started when the patient is in NSR, or after negative TEE or 3-4 weeks of therapeutic anticoagulation. All AAD have some risk of causing a medical cardioversion, and therefore carry a risk of CVA. The choice of antiarrhythmic medication is based on the patients other comordities. A flowsheet of the decision making process for AAD drug selection has been previous published.[30] Current guidelines recommend only dofetilide, sotalol, and amiodarone be considered in the setting of coronary artery disease.[30] IV amiodarone can be considered for control of rapidly conducting AF, a class I AHA recommendation; it should be noted that amiodarone can sometimes acutely convert AF and so all precautions related to AF duration and stroke prevention should be considered. It is important to emphasize that some AAD have been linked to an increased risk of ventricular arrhythmia in the setting of acute ischemia, and would be contraindicated during ACS. Moricizine, encainide and flecainide have all demonstrated to increase mortality over placebo when used in a post-MI setting.[33,34]

Table 4 | CHA_2DS_2-VASc Score and Stroke Risk(37)

CHA2DS2-VASc Score	TE Rate 1 Year	TE Rate 1 Year (Adjusted for ASA)
0	0%	0%
1	0.6%	0.7%
2	1.6%	1.9%
3	3.9%	4.7%
4	1.9%	2.3%
5	3.2%	3.9%
6	3.6%	4.5%
7	8.0%	10.1%
8	11.1%	14.2%
9	100%	100%

Table 5 HAS-BLED Score (38)

Risk Factor	Points
Hypertension	1
Abnormal renal and liver function (1 each)	1 or 2
Stroke	1
Bleeding (history or predisposition)	1
Labile INRs	1
Elderly (>65 years)	1
Drugs or alcohol (1 each)	1 or 2

Anticoagulation

Regardless of if a rate or rhythm-control strategy is selected, each patient should have their anticoagulation needs assessed for long-term stroke prevention. Patients should have their stroke risk categorized by one of the common clinical risk calculators, including the $CHADS_2$ or $CHA2DS_2$-VASc scores (see Tables 1-4).[35-37] These risk calculators will help determine if no anticoagulation is needed, aspirin 325mg daily, or full anticoagulation should be recommended.[29] Also, the use of score systems to evaluate bleeding risk must also be considered, in particular, the HAS-BLED score (see Tables 5 and 6).[38] Weighing the risks and benefits of oral anticoagulation is similar to any non-ACS situation where AF is recognized. There are two additional considerations in the setting of ACS. Firstly, are any procedures planned where anticoagulation should be limited or given in a quickly reversible form (like fractionated or unfractionated heparin), such as complex PCI? Secondly, will additional long-term anticoagulation or anti-platelet therapy be required due to PCI?

Patients in AF at moderate to high risk of stroke will likely require long-term oral anticoagulation. Even without PCI, patients who are post-MI will likely require long term aspirin use. However, warfarin has been demonstrated to be superior to aspirin alone in stroke prevention in AF. Low-dose warfarin (INR <1.6) in combination with aspirin is not as effective as the typical goal INR range 2.0-3.0.[39] High-level anticoagulation (INR 3-4) may reduce MI rate compared to aspirin alone, but has a significantly higher bleeding rate.[40] Aspirin and moderate range anticoagulation (INR 2-3) appear to have the best ratio of bleeding risk to ACS prevention.

Management of anticoagulation in the setting of coronary stent placement can be even more difficult. The rate of in-stent thrombosis in both bare metal as well as drug-eluding stents can be high; dual therapy with aspirin and clopidogrel has been demonstrated to be the most effective preventive therapy, and superior to aspirin plus warfarin.[41] However, aspirin plus clopidogrel has been shown to be inferior to warfarin for AF stroke prevention.[42] Because of this, the European Heart Rhythm Association guidelines recommend that triple therapy (oral anticoagulation, aspirin and clopidogrel) be utilized if possible, with a goal INR of 2.0-2.5.[43] For patients at higher bleeding risk, consideration of bare metal stents may allow shortening of the duration of clopidogrel. Triple therapy was associated with increase bleeding risk during PCI especially in patients with left main or three-vessel disease, age > 75, female gender, smoking, kidney disease, or INR > 2.6.[43]

Table 6 HAS-BLED Score and 1 year risk of major bleeding(38)

HAS-BLED Score	Bleeds (Per 100 patient-years)
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5	12.5
8	No data
9	No data

For patients on warfarin prior to presenting with ACS, the question of how to best manage their anticoagulation in the setting of urgent catheterization is often a clinical dilemma. Any delay in catherization is undesirable; however, reversal of OAC (oral anticoagulation) may lead to transient prothrombotic states either during bridging or warfarin re-initiation. It may be desirable to perform the catherization/PCI with therapeutic INRs, utilizing approaches to minimize bleeding complications, such as radial access.[44] If a femoral approach is used in patients at high risk for bleeding complications, the use of a femoral vascular closure device may decrease the risk of post-intervention bleeding. Additionally, the addition of a glycoprotein IIb/IIIa inhibitors in patients with elevated INRs is

associated with as much as a 3-fold increased risk of bleeding[44] and should be used with caution. In patients at high risk of bleeding, or undergoing complex interventions, often warfarin will need to be reversed with oral vitamin K (or fresh frozen plasma in urgent cases). Patients who are at moderate-to-high risk of stroke should be considered for bridging therapy with low molecular weight heparin or unfractionated heparin, but this strategy may be associated with additional bleeding risks.[43] The management of patients on one of the newer oral anticoagulants, like dabigatran or apixaban, which do not have readily available reversal agents, is not yet clear.

Conclusions

Atrial fibrillation is one of the most common heart rhythm disorders, with a prevalence that is only increasing. Risk factors for the development of AF are very similar to those for developing coronary artery disease, so it is no surprise that AF is often associated with acute coronary syndrome and acute MI. It is rare for AF to be the only symptoms of otherwise unrecognized CAD, and routine coronary screening is often unnecessary. However, it is common for AF to be triggered by MI, and the immediate and chronic prognosis in the post-MI setting is worse in patients with AF.

The treatment of AF in the setting of MI and ACS is similar to without; however there is often an increased urgency to limiting rapid heart rates which may exacerbate acute ischemia. Often DCCV and IV amiodarone are used more liberally in this setting than otherwise. Anticoagulation is often required both for the treatment of MI and possible PCI, as well as for CVA prevention from AF-induced thromboembolism. Often patient require triple-therapy for optimal treatment of both conditions, and special considerations for bleeding risk must be analyzed.

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