Introduction

Scope of the Problem

Atrial fibrillation (AF) is the most common arrhythmia and accounts for one-third of hospitalizations for rhythm disorders. The prevalence of AF in the United States is 0.89% and increases with age, such that approximately 70% of cases of AF are in patients between 65 and 85 years of age. With the aging of the population, the number of patients with AF is expected to increase 150% by 2050, with more than 50% of patients being over the age of 80. The increasing burden of AF is expected to lead to a higher incidence of stroke, as patients with AF have a five to seven fold greater risk than the general population. Strokes secondary to AF have a worse prognosis than in patients without AF. Moreover, AF is an independent risk factor for mortality with an adjusted odds ratio of 1.5 in men and 1.9 in women in the Framingham population.

Each year there are more than one million hospitalizations for Acute Coronary Syndrome (ACS) in the US. Despite a decrease in the proportion of ST-segment elevation myocardial infarctions (STEMI) over the past 10 years, 29% of ACS episodes are STEMI events. The incidence of non-STEMI has increased, particularly following the introduction of highly sensitive troponin. Although mortality has decreased over the past two decades, 30-day mortality remains significant at 8%. AF is a known, common complication of ACS. There are multiple mechanisms for induction of AF during myocardial infarction (see Figure 1). Animal models of atrial ischemia have shown that there is an increase in spontaneous atrial ectopic activity and in slowing of atrial conduction, lead-
ing to initiation and sustained reentry of AF.\textsuperscript{20, 21} 
Canines with atrial ischemia develop gap junction uncoupling that facilitates AF.\textsuperscript{22} Other infarct related causes of AF include pericarditis,\textsuperscript{23, 24} hypoxia,\textsuperscript{25, 26} sinus node ischemia,\textsuperscript{27} ventricular dysfunction,\textsuperscript{28} and increase in atrial pressure.\textsuperscript{29} While myocardial ischemia promotes AF, the ventricular irregularity caused by AF can initiate or exaggerate existing subendocardial ischemia by creating a myocardial oxygen demand mismatch.\textsuperscript{30}

### Incidence of AF after ACS

In the pre-thrombolytic era approximately one in ten patients with ACS developed AF.\textsuperscript{31-34} As shown in Table 1, the incidence of AF in the post-thrombolytic era has been more varied, ranging between 3-25\%,\textsuperscript{35-56} as has been described in previous review and systematic review articles.\textsuperscript{57, 58} At the higher end, a community cohort study of 3220 patients identified an incidence of 25\%, and the majority (54\%) of patients developed AF more than 30-days out from their ACS event.\textsuperscript{35} Overall, in the post-thrombolytic era, the mean incidence of AF complicating ACS, after adjusting for study size, was 8.8\%. One of the limitations of these observational studies is the unknown rate of pre-existing, undiagnosed AF. Estimates of pre-existing AF have ranged from 1.1\% to 11\% with a mean of 3.6\%, after adjusting for study size. Lopes, et al. conducted a pooled analysis of 120,566 patients from ten randomized clinical trials (GUSTO-I, GUSTO-IIb, GUSTO-III, ASSENT-2, ASSENT-3, ASSENT-3 Plus, PURSUIT, PARAGON-A, PARAGON-B, and SYNERGY). In a substudy of 40,000 patients for whom baseline electrocardiograms were available, an incidence of 7.5\% was found with a mean of 3.6\%. Lopes, et al. also conducted a pooled analysis of 40,000 patients for whom baseline electrocardiograms were available, an incidence of 7.5\% was found with a mean of 3.6\%.

### Table 1: Incidence of AF after ACS in Post-thrombolytic Era

<table>
<thead>
<tr>
<th>Author/Study</th>
<th>Publication Date</th>
<th>Treatment of ACS</th>
<th>Patients Included</th>
<th>Incidence of New AF</th>
<th>Incidence of Pre-existing AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jabre</td>
<td>2011</td>
<td>100% Thrombolysis/PCI</td>
<td>3,220</td>
<td>24.69%</td>
<td>9%</td>
</tr>
<tr>
<td>Lau/ACACIA</td>
<td>2009</td>
<td>100% Thrombolysis/PCI</td>
<td>3,393</td>
<td>4.96%</td>
<td>11%</td>
</tr>
<tr>
<td>Berton</td>
<td>2009</td>
<td>40% Thrombolysis</td>
<td>505</td>
<td>9.10%</td>
<td>3.60%</td>
</tr>
<tr>
<td>Lopes</td>
<td>2008</td>
<td>N/A</td>
<td>120,566</td>
<td>7.50%</td>
<td>N/A</td>
</tr>
<tr>
<td>Siu</td>
<td>2007</td>
<td>47% Thrombolysis/PCI</td>
<td>431</td>
<td>13.70%</td>
<td>N/A</td>
</tr>
<tr>
<td>Kober/VALIANT</td>
<td>2006</td>
<td>50% Thrombolysis/PCI</td>
<td>14,703</td>
<td>12.30%</td>
<td>2.30%</td>
</tr>
<tr>
<td>Lehto/OPTIMAAL</td>
<td>2005</td>
<td>54% Thrombolysis</td>
<td>5,477</td>
<td>7.20%</td>
<td>12%</td>
</tr>
<tr>
<td>Stenestrand/RIKS-HIA</td>
<td>2005</td>
<td>N/A</td>
<td>82,565</td>
<td>7.60%</td>
<td>N/A</td>
</tr>
<tr>
<td>Laurent/RICO</td>
<td>2005</td>
<td>N/A</td>
<td>1,701</td>
<td>7.60%</td>
<td>N/A</td>
</tr>
<tr>
<td>McMurray/CAPRICORN</td>
<td>2005</td>
<td>46% Thrombolysis/PCI</td>
<td>1,959</td>
<td>2.60%</td>
<td>9%</td>
</tr>
<tr>
<td>Kinjo/OACIS</td>
<td>2003</td>
<td>100% PCI</td>
<td>2,475</td>
<td>7.70%</td>
<td>4.30%</td>
</tr>
<tr>
<td>Mehta/GRACE</td>
<td>2003</td>
<td>71% Thrombolysis/PCI</td>
<td>21,785</td>
<td>6.20%</td>
<td>7.90%</td>
</tr>
<tr>
<td>Goldberg</td>
<td>2002</td>
<td>29% Thrombolysis</td>
<td>2,596</td>
<td>13.20%</td>
<td>N/A</td>
</tr>
<tr>
<td>Al-Khatib/PURSUIT</td>
<td>2001</td>
<td>100% Eptifibatide,PCI</td>
<td>9,432</td>
<td>6.40%</td>
<td>N/A</td>
</tr>
<tr>
<td>Pizetti/GISSI-III</td>
<td>2001</td>
<td>50% Thrombolysis</td>
<td>17,749</td>
<td>7.80%</td>
<td>1.10%</td>
</tr>
<tr>
<td>Rathore/CCP</td>
<td>2000</td>
<td>N/A</td>
<td>106,780</td>
<td>11.30%</td>
<td>10.80%</td>
</tr>
<tr>
<td>Wong(17)/GUSTO-III</td>
<td>2000</td>
<td>100% Thrombolysis</td>
<td>13,858</td>
<td>6.50%</td>
<td>N/A</td>
</tr>
<tr>
<td>Pedersen(33)/TRACE</td>
<td>1999</td>
<td>41% Thrombolysis</td>
<td>6,676</td>
<td>17.10%</td>
<td>3.90%</td>
</tr>
<tr>
<td>Eldar</td>
<td>1998</td>
<td>46% Thrombolysis</td>
<td>2,866</td>
<td>8.90%</td>
<td>N/A</td>
</tr>
<tr>
<td>Crenshaw/GUSTO-I</td>
<td>1997</td>
<td>100% Thrombolysis</td>
<td>40,891</td>
<td>8.00%</td>
<td>2.50%</td>
</tr>
<tr>
<td>Sakata</td>
<td>1997</td>
<td>13% PCI</td>
<td>1,039</td>
<td>9.60%</td>
<td>N/A</td>
</tr>
<tr>
<td>Madias</td>
<td>1996</td>
<td>17% Thrombolysis</td>
<td>517</td>
<td>11.20%</td>
<td>2.70%</td>
</tr>
</tbody>
</table>

**Total 461,184**

PCI=Percutaneous Coronary Intervention, N/A=Data Not Available
were available, pre-existing AF was identified in nearly 1 in 5 patients (18%).

**Timing of AF**

The timing of new-onset AF varies following ACS. Among 13,858 STEMI patients treated with thrombolytic therapy in the GUSTO III clinical trial, the median onset of AF was 2 days after ACS, which is similar timing as seen in the non-STEMI population. Madias et al. conducted a single center study of 517 patients and found that AF developed in 43%, 24%, 14%, and 19% of patients at post-ACS days 1, 2, 3, and > 3, respectively. Other studies have suggested a more protracted evolution of new-onset AF. For example, in the OPTIMAAL trial, only 28% of those who developed AF in long-term follow-up (3 years) had AF at 3 months post-ACS. Similarly, the distribution of onset of AF after ACS in Jabre et al. was 30% within 2 days, 16% between 3 and 30 days, and 54% greater than 30 days. A subgroup of the CARISMA trial followed post-MI patients with left ventricular ejection fraction ≤ 40% and an implantable cardiac monitor for 2 years. Of the 101 patients, 39% had an episode of AF: 16% at 2 months, 32% at 12 months, and 29% at 24 months after ACS. These disparate data likely reflect two periods of risk: an acute phase, similar to the risk observed after cardiothoracic surgery, and a longer, chronic risk of AF that is related to progressive risk factors, including left atrial hypertension and heart failure. In support of there being multiple phases to post-ACS AF, a substudy analysis of 1131 patients included in the VALIANT study found a differential response to treatment strategies for AF based upon time from myocardial infarction.

Few data are available regarding the type of AF and subsequent treatment of AF complicating ACS. Larger studies, such as GISSI-III have shown that fewer than 25% of patients with AF complicating ACS return to sinus rhythm prior to hospital discharge. Long-term follow-up suggests that the risk of recurrent AF after ACS is substantial. Asanin et al. followed 320 patients with AF after ACS for a mean of 7 years (5.5 to 8.5 years) to monitor for frequency of recurrence of AF. All patients were in sinus rhythm at discharge of their ACS hospitalization, and 22.5% developed recurrences of AF. Of note in this study, amiodarone was the only antiarrhythmic used, and 10% of patients (more in the recurrence group), received amiodarone. There is no data available regarding the impact of direct current cardioversion on patients with AF in the setting of ACS.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>30-day and 1-year postoperative morbidity and mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictors of AF</td>
<td>Frequency in Studies (n=22)</td>
</tr>
<tr>
<td>Age</td>
<td>21</td>
</tr>
<tr>
<td>Killip</td>
<td>15</td>
</tr>
<tr>
<td>Prior HTN</td>
<td>10</td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
</tr>
<tr>
<td>Heart rate</td>
<td>8</td>
</tr>
<tr>
<td>Prior DM</td>
<td>5</td>
</tr>
<tr>
<td>Lower SBP</td>
<td>4</td>
</tr>
<tr>
<td>Prior MI</td>
<td>4</td>
</tr>
<tr>
<td>Anterior MI</td>
<td>3</td>
</tr>
<tr>
<td>Caucasian</td>
<td>3</td>
</tr>
<tr>
<td>Prior CHF</td>
<td>3</td>
</tr>
<tr>
<td>Less thrombolitics</td>
<td>3</td>
</tr>
<tr>
<td>Creatinine</td>
<td>2</td>
</tr>
<tr>
<td>Male</td>
<td>2</td>
</tr>
<tr>
<td>Prior angina</td>
<td>2</td>
</tr>
</tbody>
</table>

Higher body mass index, cardiac arrest, creatine kinase level, prior chronic obstructive pulmonary disease, height, history of hyperlipidemia, left main disease, lower ejection fraction, left ventricular hypertrophy, non-smoker, North American, and STEMI were all listed in 1 study with a frequency of 5%.

Abbreviations: RA, right atrium; LA, left atrium; TV, Tricuspid valve; MV, mitral valve; PV, pulmonary vein; SVC, superior vena cava; IVC inferior vena cava; LAA, left atrial appendage.
Predictors of AF

Many studies have investigated the risk factors associated with the development of AF after ACS (Table 2). Age is the most frequently identified predictive factor, consistent with the prominent age-related incidence of AF in the overall population. \(^{62}\) Killip classification at presentation is a significant, independent predictor for the development of AF in several cohorts, with odds ratios between 1.58 and 5.55. \(^{39, 47, 48, 61}\) As expected, the presence of cardiogenic shock (Killip Class IV) carries the greatest risk. Hypertension, female sex, and heart rate are also frequently associated with AF after ACS. \(^{34-51, 53-56}\) A heart rate > 100 beats per minute was associated with a 3-fold increased risk of AF in the OACIS cohort (OR 3.0 [1.94-4.64]). \(^{57}\) Finally, among STEMI patients, delayed revascularization (> 4 hours from symptom onset) had a higher incidence of AF. \(^{49}\) Delayed treatment > 12 hours accentuates risk further (OR 2.19 [1.00-4.79]). \(^{61}\)

A single-center study of 1039 patients admitted with ACS found that patients who developed AF within 24 hours of ACS had a higher frequency of proximal RCA lesions (67%) when compared to...
those with sinus rhythm. Patients with AF at < 24 hours had the most significant elevation in right atrial pressure; right ventricular dilation; and incidence of cardiogenic shock, right ventricular acute myocardial infarction, and high grade atrioventricular block. Patients with onset of AF > 24 hours more frequently had proximal occlusion of the left anterior descending artery, increased wedge pressure, and decreased left ventricular ejection fraction.55

**AF & Mortality following ACS**

AF is associated with higher mortality following ACS (Table 3).35-49, 53-56 The increased risk of death is observed in-hospital but persists in long-term follow-up. In general, the risk of death at one year is 1.5 to 1.75 times greater when compared to patients without AF.

Decreased survival in patients with AF after ACS was first identified in the 1940s, when mortality at 30 days was 89%.31 By 1975, mortality with AF after ACS had improved to 49%, as compared to 16% in patients without AF.35 Data from the SPRINT trial in the pre-thrombolytic era showed a higher long-term (mean 5.5 years) mortality in patients developing AF after ACS with hazard ratio of 1.28 (1.12-1.46).34 Eldar et al. completed a prospective study of 25 Coronary Care Units in Israel (2866 patients) in the thrombolytic era. When compared to the historical data from SPRINT, AF patients in the thrombolytic era had improved mortality with a 30 day OR of 0.64 (0.44-0.94) and a 1 year OR of 0.69 (0.54-0.88).45

More recently, the TRACE study randomized patients with ACS to ACE-inhibition with trandolapril or placebo. Within TRACE, patients with both AF and depressed left ventricular ejection fraction (< 35%) had a two-fold increase of in-hospital mortality.43 Patients with AF had a higher mortality at 2 years with adjusted relative risk of 1.33 (1.19-1.49). When examining the relation between AF and cause-specific death, the relative risk of sudden cardiac death and death from other causes were not statistically different at 1.31 (1.07-1.60) and 1.43 (1.21-1.70), respectively.44 The increase in both cardiac and non-cardiac mortality implies that the impact of AF on mortality is multifactorial.

As might be expected, patients with recurrence of AF have worse prognoses. Patients with recurrent paroxysmal AF after discharge have increased long-term mortality (mean 7-year follow-up) when compared to patients without recurrences (OR of 3.08 [1.45-6.53] and relative risk of 1.52 [1.0-2.31], respectively).61 Furthermore, persistent AF at discharge is associated with a higher adjusted relative risk of death than paroxysmal AF.43

Similar to findings with ventricular arrhythmias after myocardial infarction, mortality is also affected by the timing of AF onset post-ACS. New-onset AF more than 24 hours after ACS is associated with increased mortality at 8-year follow-up compared to AF within 24 hours of ACS (OR 3.7 [1.84-7.52] vs. OR 2.5 [1.23-5.00]).55 There are conflicting data regarding the relative risks of pre-existing versus new-onset AF.36, 39, 48, 55

**Complications and Length of Stay in Patients with AF**

AF complicating ACS is associated with a host of adverse cardiovascular outcomes, including an increased risk of in-hospital stroke, major bleeding, re-infarction, heart failure, and ventricular arrhythmias (Table 4). Multiple studies have documented increased in-hospital stroke among patients with AF after ACS. For example, GUSTO-I demonstrated a statistically significant increase of in-hospital stroke of 3.1% with AF compared to 1.3% without AF, and this was driven mainly by ischemic strokes (1.8% with AF, 0.5% without AF).42 AF has also been associated with an increased risk of acute renal failure after ACS (OR 2.7 [1.2-6.1]).36 As shown in Table 4, AF consistently is associated with increased length of stay (range 1.8-4.7 days).

**Management Dilemmas in Patients with AF**

**Prevention of AF after ACS**

Many of the risk factors associated with AF after ACS are modifiable. Optimal management of ACS, including prompt revascularization, beta-blockade, optimal afterload reduction, and aggressive treatment of heart failure are core components of quality ACS care. These same interventions should also help minimize the risk of
### Table 4

**Complications Associated with AF after ACS**

<table>
<thead>
<tr>
<th>Author/Study</th>
<th>Publication Date</th>
<th>Follow-up</th>
<th>CVA</th>
<th>Length of Hospital Stay</th>
<th>In-Hospital Reinfarction</th>
<th>Major Bleeding</th>
<th>CHF</th>
<th>Cardiogenic Shock</th>
<th>VT</th>
<th>VF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lau/ACA-CIA</td>
<td>2009</td>
<td>N/A</td>
<td>N/A</td>
<td>9.7 days vs 5.5 days</td>
<td>OR 3.7 [2.0-7.0]</td>
<td>OR 5.8 [3.1-10.6]</td>
<td>OR 3 [1.7-5.7]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Lopes</td>
<td>2008</td>
<td>30 days</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Siu</td>
<td>2007</td>
<td>2 year</td>
<td></td>
<td>9.7 days</td>
<td>OR 3.7 [2.0-7.0]</td>
<td>OR 5.8 [3.1-10.6]</td>
<td>OR 3 [1.7-5.7]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Kober/VALIANT</td>
<td>2006</td>
<td>3 year</td>
<td></td>
<td>8.1% AF vs 3.7% no AF</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Lehto/OP-TIMAAL</td>
<td>2005</td>
<td>30 day</td>
<td></td>
<td>HR 1.46 [1.17-1.81]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Kinjo/OACIS</td>
<td>2003</td>
<td>In-hospital</td>
<td></td>
<td>2.3% AF vs 0.6% no AF</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Mehta/GRACE</td>
<td>2003</td>
<td>In-hospital</td>
<td></td>
<td>OR 1.33 [0.80-2.20]</td>
<td>OR 2.0 [1.37-2.93]</td>
<td>OR 1.64 [1.25-2.14]</td>
<td>OR 2.83 [2.27-3.52]</td>
<td>OR 2.4 [1.88-3.06]</td>
<td>OR 1.97 [1.56-1.25]</td>
<td>N/A</td>
</tr>
<tr>
<td>Goldberg</td>
<td>2002</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Al-Khattib/PURSUIT</td>
<td>2001</td>
<td>6 months</td>
<td></td>
<td>HR 2.9 [1.7-4.8]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Pizetti/GISSI-III</td>
<td>2001</td>
<td>In-hospital</td>
<td></td>
<td>Not Significant</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>4.3%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Rathore/CCP</td>
<td>2000</td>
<td>In-hospital</td>
<td></td>
<td>2.8% AF vs 1.7% no AF</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Wong(17)/GUSTO-III</td>
<td>2000</td>
<td>30 days</td>
<td></td>
<td>4% AF vs 2% no AF</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Pedersen(33)/TRACE</td>
<td>1999</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>18%</td>
<td>11%</td>
</tr>
<tr>
<td>Eldar</td>
<td>1998</td>
<td>In-hospital</td>
<td></td>
<td>OR 4.6 [1.9-10.8]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Crenshaw/GUSTO-I</td>
<td>1997</td>
<td>In-hospital</td>
<td></td>
<td>3.1% AF vs 1.3% no AF</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Sakata</td>
<td>1997</td>
<td>N/A</td>
<td>N/A</td>
<td>63% vs 30%</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

HR=Hazard Ratio, OR=Odds Ratio, N/A=Data Not Available, CVA=Cerebrovascular Accident, CHF=Congestive Heart Failure, VT=Ventricular Tachycardia, VF=Ventricular Fibrillation.

new-onset AF in both the acute and long-term setting.

The GISSI-III trial randomized patients to lisinopril and nitrates versus placebo, and there was a 24% reduction in AF seen in the treatment arm.
(OR 0.76 [0.65-0.89]).\textsuperscript{40} ACE inhibition has also been shown to decrease arrhythmic death post MI.\textsuperscript{38, 65} Randomized data have also shown that beta-blockade with carvedilol decreased the frequency of AF post-MI (HR 0.41 [0.25-0.68]), including new-onset AF (HR 0.51 [0.28-0.93]).\textsuperscript{52} While disappointing in primary prevention of AF outside of ACS, statin therapy has been associated with lower odds of AF after ACS, including data from the Veterans Administration (adjusted OR of 0.57 [0.39-0.83]).\textsuperscript{66, 67}

**Rate & Rhythm Control**

Randomized clinical trials have failed to identify a superior survival advantage with either a rate versus rhythm control strategy.\textsuperscript{68, 69} The PIAF trial compared rate control with diltiazem and rhythm control with amiodarone in 252 patients to detect changes in symptoms related to AF. While there was no symptomatic benefit with rhythm control in the PIAF trial, there was better exercise tolerance, as measured by 6 minute walk test.\textsuperscript{70} The ACC/AHA guidelines for the management of AF discuss class I indications in the setting of an acute myocardial infarction: direct-current cardioversion in the setting of hemodynamic instability or ongoing ischemia, intravenous amiodarone for treatment of rapid ventricular response with depressed ejection fraction, and intravenous beta blockers or calcium channel blockers for treatment of rapid ventricular response with preserved ejection fraction.\textsuperscript{1} Vaughan-Williams Class IC medications have a Class III recommendation (evidence of harm) due to increased mortality in the CAST trials.\textsuperscript{71, 72}

The preferred antiarrhythmics for AF post-myocardial infarction are amiodarone and sotalol (in the absence of congestive heart failure given its beta blocking properties). In a subgroup analysis of VALIANT, patients treated with anti-arrhythmic drugs in the immediate peri-infarct period had a higher risk of death than patients treated with a “rate” control strategy. These findings did not extend past 45 days.\textsuperscript{60} The DIAMOND-MI trial determined that there was no mortality benefit to treating patients with dofetilide after myocardial infarction in the presence of impaired left ventricular function.\textsuperscript{73} AF was successfully treated with dofetilide in this patient population; therefore, it is a reasonable second line agent. While rarely used, Vaughan-Williams class IA agents are recommended as third line therapy in ACS patients.\textsuperscript{1} In general, observational data from ACS trials have failed to identify a survival advantage with antiarrhythmic therapy for the maintenance of sinus rhythm.\textsuperscript{73}

**Stroke Prevention**

Even transient AF, has been associated with a significantly increased risk of ischemic stroke (10.2\% vs 1.8\%) at 1-year.\textsuperscript{54} The ACC/AHA guidelines for the management of STEMI give a class I recommendation to use of oral anticoagulation (OAC) in patients with persistent or paroxysmal AF.\textsuperscript{74} A consensus document by the European Society of Cardiology Working Group on Thrombosis gave a class IIa recommendation to OAC in combination with aspirin and clopidogrel for AF patients with NSTEMI.\textsuperscript{75} Despite these recommendations, only a minority (13.5-29\%) of patients with AF complicating ACS are being discharged on OAC.\textsuperscript{37, 38} In the VALIANT trial only 25\% of patients with AF were on OAC at 1-year follow-up after the ACS event.\textsuperscript{53} Lopes et al. conducted an analysis with 23,208 patients from three IIb/IIla trials. Only 13.5\% of patients with AF complicating ACS were discharged on warfarin, and consistent with other observational studies, warfarin was independently associated with a lower risk of death or myocardial infarction (HR 0.29 [0.15-0.98]).\textsuperscript{50, 76} Jang et al. conducted a study of 362 patients with AF and ACS who were treated with PCI. The average CHADS, score was 1.6 ± 1.2. Warfarin was prescribed to 23\% of patients, including warfarin, aspirin, and clopidogrel (so called “triple therapy” in 22\%) and warfarin and clopidogrel (1%). While hampered by a small sample size and low statistical power, there was no statistically significant difference between the OAC and no OAC groups in death, stroke, or major adverse cardiac events, but there was a 5-fold increase in major bleeding (10.7\% in OAC group and 2.2\% in non-OAC group, p = 0.002). A meta-analysis of nine clinical trials, including 1996 patients on chronic OAC showed that major adverse cardiovascular events were significantly reduced in patients taking aspirin, clopidogrel, and OAC (triple therapy: OR 0.60 [0.42-0.86]). Patients on triple therapy did have more frequent major bleeding at 6-months (OR 2.12 [1.05-4.29]). A second meta-analysis found that triple therapy was associated with a significantly lower incidence of ischemic stroke (OR 0.29 [0.15-0.58]). The triple therapy patients had a two-
Several novel oral anticoagulants have emerged as alternatives to warfarin. Dabigatran 150 mg twice daily was found to have superior efficacy for the prevention of stroke and systemic embolism with similar risks of major bleeding when compared to dose-adjusted warfarin in an open-label trial. Importantly, when considering its use in patients with AF after ACS, dabigatran may be associated with a small increased risk of MI compared with warfarin. A meta-analysis of 7 trials including 30,514 patients found an increased risk of MI in those treated with dabigatran (1.2 vs. 0.8%; OR 1.33 [1.03-1.71]). A similar trend was seen when ximelagatran was compared with warfarin for the treatment of AF.

Rivaroxaban once daily was non-inferior to warfarin for the prevention of stroke and systemic embolization and the composite of major and non-major clinically relevant bleeding in the ROCKET AF trial. Finally, apixaban was studied in the ARISTOTLE trial, which showed superiority to warfarin with respect to stroke or systemic embolism, along with decreased major bleeding (HR 0.69 [0.60-0.80]). Importantly, all three of the novel oral anticoagulants lead to significant reductions in intracranial hemorrhage.

Data on a fourth novel oral agent, edoxaban, will be forthcoming from the ENGAGE AF-TIMI 48 trial, however, these data are not yet available.

Several studies have investigated the use of novel oral anticoagulants in the treatment of patients with ACS (regardless of AF status). Using the same dose of apixaban as the ARISTOTLE trial, APPRAISE-2 evaluated the use of apixaban on top of antiplatelet therapy: aspirin (16% of patients) or aspirin and clopidogrel (81% of patients) for the prevention of recurrent ischemic events. In APPRAISE-2 apixaban increased major bleeding (HR 2.59 [1.50-4.46]), including more frequent fatal and intracranial bleeding events. ATLAS ACS 2-TIMI 51 evaluated the use of rivaroxaban with antiplatelet therapy (99% on aspirin and 93% on clopidogrel). Notably, the doses of rivaroxaban used in ATLAS were much smaller than those used in ROCKET-AF (2.5 and 5 mg twice daily versus 20 mg daily). Those randomized to low-dose rivaroxaban had a 16% reduction in the composite efficacy endpoint (cardiovascular death/myocardial infarction/stroke). While patients treated with rivaroxaban experienced increased major and intracranial bleeding, there was no excess fatal bleeding. Neither of these ACS trials were designed to investigate the impact of triple therapy on stroke or survival for AF patients after ACS and/or PCI.

At present the 2011 ACC/AHA guideline update and a position paper by European Society of Cardiology cite the lack of data and uncertainty regarding combination therapy in patients with AF who undergo PCI. Randomized trials evaluating combination oral anticoagulation and antiplatelet therapy after PCI and ACS are needed; however, the design and execution of these trials will be challenging. Given the increased risk of intracranial hemorrhage in APPRAISE-2 and the differences in dosing and patient populations (AF versus ACS) across these trials, the devil we know (warfarin) may be better than the devil we do not (novel OACs) when prescribing triple therapy. Until more data are available, the most conservative approach will be to restrict triple therapy to the use of warfarin. It is also important to limit the duration of triple therapy by using bare metal stents unless there is a significant benefit to drug eluting stents (class IIa recommendation). Finally, as new antiplatelet agents and new oral anticoagulants become engrained in clinical use, best practice patterns for their dosing and associated methods of percutaneous coronary access (femoral vs radial) will require further investigation.

Conclusions

AF is a common complication of ACS, and it is an independent predictor of mortality and in-hospital complications. Despite guideline recommendations and known mortality benefits, oral anticoagulation remains suboptimal in patients with AF complicating ACS. While we have a wealth of data regarding the epidemiology and outcomes associated with AF after ACS, we have little to no contemporary clinical trial data to guide therapeutic decisions in patients with AF complicating ACS. While preventing stroke, controlling heart rate, and improving quality of life remain inviolable goals in the treatment of AF, we lack clinical
trials that address the most common therapeutic choices in each of these treatment strategies after ACS. Despite the obvious challenges to their design, funding, and completion, randomized trials dedicated to the management of AF after ACS are clearly needed.

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