JAFIB
Featured Review
Journal of Atrial Fibrillation
WWW. jafib.com

Atrial Fibrillation Complicating Acute Coronary Syndromes

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Abstract

Atrial fibrillation frequently complicates myocardial infarction. Patients with atrial fibrillation complicating acute coronary syndrome have increased morbidity and mortality relative to patients that remain in normal sinus rhythm. No studies have identified a mortality benefit to rhythm control compared with rate control in the setting of acute coronary syndrome. Stroke prevention should be pursued with oral anticoagulation therapy, although the majority of patients with atrial fibrillation associated with acute coronary syndrome receive only antiplatelet therapy. There are several novel oral anticoagulant therapies now available, but these agents have not been well studied in combination with dual antiplatelet therapy. Therefore, warfarin as part of triple therapy is the most conservative approach until additional data becomes available.

Introduction

Scope of the Problem

Atrial fibrillation (AF) is the most common arrhythmia and accounts for one-third of hospitalizations for rhythm disorders.[1] 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.[2] 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.[3-8] 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.[9-11] Strokes secondary to AF have a worse prognosis than in patients without AF.[12,13] 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.[14] 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.[15,16] The incidence of non-STEMI has increased, particularly following the introduction of highly sensitive troponin.[17, 18] Although mortality has decreased over the past two decades, 30-day mortality remains significant at 8%.[7, 19]

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-

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ing to initiation and sustained reentry of AF.[20, 21] Canines with atrial ischemia develop gap junction uncoupling that facilitates AF.[22] Other infarct related causes of AF include pericarditis,[23, 24] hypoxia,[25, 26] sinus node ischemia,[27] ventricular dysfunction ,[28] and increase in atrial pressure.[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.[30]

Incidence of AF after ACS

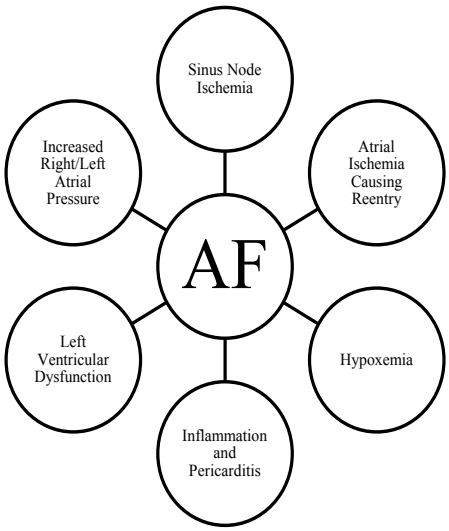
In the pre-thrombolytic era approximately one in ten patients with ACS developed AF.[31-34] As shown in Table 1, the incidence of AF in the post-thrombolytic era has been more varied, ranging between 3-25%,[35-56] as has been described in previous review and systematic review articles.[57, 58] At the 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.[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

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

Author/Study	Publication Date	Treatment of ACS	Patients Included	Incidence of New AF	Incidence of Pre-existing AF
Jabre	2011	100% Throm bolysis/PCI	3,220	24.69%	9%
Lau/ACACIA	2009	100% Throm bolysis/PCI	3,393	4.96%	11%
Berton	2009	40% Throm bolysis	505	9.10%	3.60%
Lopes	2008	N/A	120,566	7.50%	N/A
Siu	2007	47% Throm bolysis/PCI	431	13.70%	N/A
Kober/VALIANT	2006	50% Throm bolysis/PCI	14,703	12.30%	2.30%
Lehto/OPTIMAAL	2005	54% Throm bolysis	5,477	7.20%	12%
Stenestrand/RIKS-HIA	2005	N/A	82,565	7.60%	N/A
Laurent/RICO	2005	N/A	1,701	7.60%	N/A
McMurray/CAPRICORN	2005	46% Throm bolysis/PCI	1,959	2.60%	9%
Kinjo/OACIS	2003	100% PCI	2,475	7.70%	4.30%
Mehta/GRACE	2003	71% Throm bolysis/PCI	21,785	6.20%	7.90%
Goldberg	2002	29% Throm bolysis	2,596	13.20%	N/A
Al-Khatib/PURSUIT	2001	100% Eptifibatide,PCI	9,432	6.40%	N/A
Pizetti/GISSI-III	2001	50% Throm bolysis	17,749	7.80%	1.10%
Rathore/CCP	2000	N/A	106,780	11.30%	10.80%
Wong(17)/GUSTO-III	2000	100% Throm bolysis	13,858	6.50%	N/A
Pedersen(33)/TRACE	1999	41% Throm bolysis	6,676	17.10%	3.90%
Eldar	1998	46% Throm bolysis	2,866	8.90%	N/A
Crenshaw/GUSTO-I	1997	100% Throm bolysis	40,891	8.00%	2.50%
Sakata	1997	13% PCI	1,039	9.60%	N/A
Madias	1996	17% Throm bolysis	517	11.20%	2.70%
		Total	**461,184**		

PCI=Percutaneous Coronary Intervention, N/A=Data Not Available

Figure 1: Schematic representation of mechanisms of AF in the setting of ACS



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

were available, pre-existing AF was identified in nearly 1 in 5 patients (18%).[49]

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,[41] which is similar timing as seen in the non-STEMI population.[37] 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.[44] 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.[48] 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.[35] 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.[59] 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.[60]

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.[40] 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.[61] There is no data available regarding the impact of direct current cardioversion on patients with AF in the setting of ACS.

Table 2 30-day and 1-year postoperative morbidity and mortality

Predicators of AF	Frequency in Studies (n=22)	Frequency (%)
Age	21	95%
Killip	15	68%
Prior HTN	10	45%
Female	9	41%
Heart rate	8	36%
Prior DM	5	23%
Lower SBP	4	18%
Prior MI	4	18%
Anterior MI	3	14%
Caucasian	3	14%
Prior CHF	3	14%
Less thrombolytics	3	14%
Creatinine	2	9%
Male	2	9%
Prior angina	2	9%

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

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]).[47] 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

Table 3 Mortality with AF after ACS

Author/Study	Publication Date	In-hopital Mortality	Follow-up	Risk of Death	Follow-up	Risk of Death
Jabre	2011	N/A	6.6 year	HR 3.77(3.37-4.21)	N/A	N/A
Lau/ACACIA	2009	OR 2.2(1.0-4.6)	1 year	HR 1.36(0.84-2.20)	N/A	N/A
Berton	2009	OR 1.9(0.8 to 4.6)	N/A	N/A	7 years	OR 1.6(1.2-2.3)
Lopes	2008	N/A	7 day	NSTEMI HR 2.30(1.83-2.90), STEMI HR 1.65(1.44-	1 year	NSTEMI HR 1.67(1.41-1.99), STEMI HR 2.37(1.79-
Siu	2007	N/A	2 year	Not Significant	N/A	N/A
Kober/VALIANT	2006	N/A	3 year	HR 1.32(1.20-1.45)	N/A	N/A
Lehto/OPTIMAAL	2005	N/A	30 day	HR 3.83(1.97-7.43)	3 years	HR 1.82(1.39-2.39)
Kinjo/OACIS	2003	HR 1.42(0.88-2.31)	1 year	HR 3.04(1.24-7.48)	N/A	N/A
Mehta/GRACE	2003	OR 1.65(1.30-2.09)	N/A	N/A	N/A	N/A
Goldberg	2002	OR 1.38(0.98-1.94)	5 year	HR 1.23(0.99-1.52)	N/A	N/A
Al-Khatib/PURSUIT	2001	N/A	30 day	HR 4.4(3.3-5.8)	6 months	HR 3.0(2.4-3.8)
Pizetti/GISSI-III	2001	RR 1.98(1.67-2.34)	6 months	OR 1.42(0.88-2.31)	4 years	RR 1.78(1.60-1.99)
Rathore/CCP	2000	OR 1.35(1.28-1.42)	30 day	OR 1.31(1.25-1.37)	1 year	OR 1.51(1.44-1.58)
Wong(17)/GUSTO-III	2000	N/A	30 day	OR 1.49(1.17-1.89)	1 year	OR 1.64(1.35-2.01)
Pedersen(33)/TRACE	1999	OR 1.5(1.2-1.9)	5 year	OR 1.3(1.2-1.4)	N/A	N/A
Eldar	1998	N/A	30 day	OR 1.32(0.92-1.87)	1 year	RR 1.33(1.05-1.87)
Crenshaw/GUSTO-I	1997	13.8% AF vs 5.9% no AF	30 day	OR 1.5(1.2-1.9)	N/A	N/A
Sakata	1997	40% AF vs 14% no AF	8 year	OR3.05(1.85-5.00)	N/A	N/A
Madias	1996	Not Significant	N/A	N/A	N/A	N/A

HR=Hazard Ratio, OR=Odds Ratio, RR=Relative Risk, N/A=Data Not Available, NSTEMI=Non ST-Segment Elevation Myocardial Infraction

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.[33] 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.[63] 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.[64] 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-exisiting 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

Author/ Study	Publication Date	Follow-up	CVA	Length of Hospital Stay	In-Hospital					
					Re-infarction	Major Bleeding	CHF	Cardio-genic Shock	VT	VF
Lau/ACA-CIA	2009	N/A	N/A	9.7 days vs 5.5 days	OR 3.7(2.0-7.0)	OR 5.8(3.1-10.6)	OR 3.1(1.7-5.7)	N/A	N/A	N/A
Lopes	2008	30 days	NSTEMI HR 3.45(2.41-4.95), STEMI HR 1.46(1.17-	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Siu	2007	2 year	HR 5.1(2.4-11.2)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Kober/ VALIANT	2006	3 year	8.1% AF vs 3.7% no AF	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Lehto/OP-TIMAAL	2005	30 day	HR 14.6(5.87-36.3)	14.1 days vs 12.3 days	N/A	N/A	N/A	N/A	N/A	N/A
Kinjo/ OACIS	2003	In-hos-pital	2.3% AF vs 0.6% no AF	N/A	N/A	N/A	34.8% vs 16.6%	15.7% vs 6.1%	27.3% vs 14.7%	
Mehta/ GRACE	2003	In-hos-pital	OR 1.33(0.80-2.20)	12.5 days vs 7.8 days	OR 2.0(1.37-2.93)	OR 1.64(1.25-2.14)	OR 2.83(2.27-3.52)	OR 2.4(1.88-3.06)	OR 1.97(1.56-1.25)	
Goldberg	2002	N/A	N/A	N/A	N/A	N/A	55% vs 27%	12.8% vs 5.9%	N/A	N/A
Al-Khatib/ PURSUIT	2001	6 months	HR 2.9(1.7-4.8)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Pizetti/ GISSI-III	2001	In-hos-pital	Not Signifi-cant	15 days vs 13 days	N/A	N/A	51.5% vs 23.6%	N/A	4.3% vs 1.9%	4.4% vs 2.3%
Rathore/ CCP	2000	In-hos-pital	2.8% AF vs 1.7% no AF	11 days vs 7.6 days	4.4% vs 3.6%	N/A	60.1% vs 42.2%	N/A	N/A	N/A
Wong(17)/ GUSTO-III	2000	30 days	4% AF vs 2% no AF	N/A	9% vs 4%	N/A	44% vs 14%	14% vs 3%	10% vs 3%	10% vs 4%
Ped-ersen(33)/ TRACE	1999	N/A	N/A	N/A	N/A	N/A	48% vs 34%	6% vs 3%	18% vs 11%	11% vs 6%
Eldar	1998	In-hos-pital	OR 4.6(1.9-10.8)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Crenshaw/ GUSTO-I	1997	In-hos-pital	3.1% AF vs 1.3% no AF	14.3 days vs 10 days	8% vs 4%	N/A	39% vs 14%	16% vs 5%	16% vs 5%	15% vs 6%
Sakata	1997	N/A	N/A	N/A	N/A	N/A	63% vs 30%	44% vs 25%	N/A	N/A

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].[40] ACE inhibition has also been shown to decrease arrhythmic death post MI.[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]).[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]).[66, 67]

Rate & Rhythm Control

Randomized clinical trials have failed to identify a superior survival advantage with either a rate versus rhythm control strategy.[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.[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.[1] Vaughan-Williams Class IC medications have a Class III recommendation (evidence of harm) due to increased mortality in the CAST trials.[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.[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.[53] 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.[1] In general, observational data from ACS trials have failed to identify a survival advantage with anti-arrhythmic therapy for the maintenance of sinus rhythm.[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.[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.[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.[75] Despite these recommendations, only a minority (13.5-29%) of patients with AF complicating ACS are being discharged on OAC.[37, 38] In the VALIANT trial only 25% of patients with AF were on OAC at 1-year follow-up after the ACS event.[53] Lopes et al. conducted an analysis with 23,208 patients from three IIb/IIIa 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]).[50, 76]

Jang et al. conducted a study of 362 patients with AF and ACS who were treated with PCI. The average $CHADS_2$ 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).[77] 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]).[78] 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-

fold increase in major bleeding, and the incidence of death and myocardial infarction were statistically similar between the two groups.[79]

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.[80] 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]).[81] A similar trend was seen when ximelgatran was compared with warfarin for the treatment of AF.[82, 83] 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.[84] 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]).[85] Importantly, all three of the novel oral anticoagulants lead to significant reductions in intracranial hemorrhage.[80, 84, 85] 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.[86]

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.[87] 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 .[88] 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.[89, 90] 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).[75] 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.

Disclosures

- Jonathan P. Piccini receives research support from Boston Scientific, Johnson & Johnson, and Bayer Healthcare and serves as a consultant to Forest Laboratories, Johnson & Johnson, Medtronic, and Sanofi-Aventis.
- Kent R. Nillson receives research support from Medtronic and receives honoraria from Jansen Pharmaceuticals.
- The remaining authors have no financial disclosures to report

References

1. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC, Jr., Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL. Acc/aha/esc 2006 guidelines for the management of patients with atrial fibrillation: A report of the american college of cardiology/american heart association task force on practice guidelines and the european society of cardiology committee for practice guidelines (writing committee to revise the 2001 guidelines for the management of patients with atrial fibrillation): Developed in collaboration with the european heart rhythm association and the heart rhythm society. Circulation 2006;114:e257-354.

2. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation: Analysis and implications. Archives of internal medicine 1995;155:469.

3. Novaro GM, Asher CR, Bhatt DL, Moliterno DJ, Harrington RA, Lincoff AM, Newby LK, Tcheng JE, Hsu AP, Pinski SL. Meta-analysis comparing reported frequency of atrial fibrillation after acute coronary syndromes in asians versus whites. The American journal of cardiology 2008;101:506-509.

4. Go AS, Hylek EM, Phillips KA, Chang YC, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults. JAMA: the journal of the American Medical Association 2001;285:2370-2375.

5. Furberg CD, Psaty BM, Manolio TA. Prevalence of atrial fibrillation in elderly subjects (the cardiovascular health study). The American journal of cardiology 1994;74:236-241.

6. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg CD, Rautaharju PM. Incidence of and risk factors for atrial fibrillation in older adults. Circulation 1997;96:2455-2461.

7. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in olmsted county, minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation 2006;114:119-125.

8. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. JAMA: the journal of the American Medical Association 1994;271:840-844.

9. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: A major contributor to stroke in the elderly: The framingham study. Archives of internal medicine 1987;147:1561.

10. Wolf PA, Dawber TR, Thomas Jr HE, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke. Neurology 1978;28:973-973.

11. Flegel K, Shipley M, Rose G. Risk of stroke in non-rheumatic atrial fibrillation. The Lancet 1987;329:526-529.

12. Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, D'Agostino RB. Stroke severity in atrial fibrillation: The framingham study. Stroke 1996;27:1760-1764.

13. Miyasaka Y, Barnes ME, Bailey KR, Cha SS, Gersh BJ, Seward JB, Tsang TS. Mortality trends in patients diagnosed with first atrial fibrillation: A 21-year community-based study. Journal of the American College of Cardiology 2007;49:986-992.

14. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: The framingham heart study. Circulation 1998;98:946-952.

15. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB. Heart disease and stroke statistics--2012 update: A report from the american heart association. Circulation 2012;125:e2-e220.

16. Roe MT, Parsons LS, Pollack Jr CV, Canto JG, Barron HV, Every NR, Rogers WJ, Peterson ED. Quality of care by classification of myocardial infarction: Treatment patterns for st-segment elevation vs non-st-segment elevation myocardial infarction. Archives of internal medicine 2005;165:1630.

17. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. New England Journal of Medicine 2010;362:2155-2165.

18. Roger VL, Weston SA, Gerber Y, Killian JM, Dunlay SM, Jaffe AS, Bell MR, Kors J, Yawn BP, Jacobsen SJ. Trends in incidence, severity, and outcome of hospitalized myocardial infarction. Circulation 2010;121:863-869.

19. Nabel EG, Braunwald E. A tale of coronary artery disease and myocardial infarction. New England Journal of Medicine

2012;366:54-63.
20. Sinno H, Derakhchan K, Libersan D, Merhi Y, Leung TK, Nattel S. Atrial ischemia promotes atrial fibrillation in dogs. Circulation 2003;107:1930-1936.
21. Nishida K, Qi XY, Wakili R, Comtois P, Chartier D, Harada M, Iwasaki YK, Romeo P, Maguy A, Dobrev D, Michael G, Talajic M, Nattel S. Mechanisms of atrial tachyarrhythmias associated with coronary artery occlusion in a chronic canine model. Circulation 2011;123:137-146.
22. Shiroshita-Takeshita A, Sakabe M, Haugan K, Hennan JK, Nattel S. Model-dependent effects of the gap junction conduction-enhancing antiarrhythmic peptide rotigaptide (zp123) on experimental atrial fibrillation in dogs. Circulation 2007;115:310-318.
23. Tofler GH, Muller JE, Stone PH, Willich SN, Davis VG, Poole WK, Robertson T, Braunwald E. Pericarditis in acute myocardial infarction: Characterization and clinical significance. American Heart Journal 1989;117:86-92.
24. Nagahama Y, Sugiura T, Takehana K, Hatada K, Inada M, Iwasaka T. The role of infarction-associated pericarditis on the occurrence of atrial fibrillation. European heart journal 1998;19:287-292.
25. Fearon IM, Palmer AC, Balmforth AJ, Ball SG, Mikala G, Schwartz A, Peers C. Hypoxia inhibits the recombinant alpha 1c subunit of the human cardiac l-type ca2+ channel. The Journal of physiology 1997;500 (Pt 3):551-556.
26. Pichlmaier AM, Lang V, Harringer W, Heublein B, Schaldach M, Haverich A. Prediction of the onset of atrial fibrillation after cardiac surgery using the monophasic action potential. Heart 1998;80:467-472.
27. Kyriakidis M, Barbetseas J, Antonopoulos A, Skouros C, Tentolouris C, Toutouzas P. Early atrial arrhythmias in acute myocardial infarction. Role of the sinus node artery. Chest 1992;101:944-947.
28. Rechavia E, Strasberg B, Mager A, Zafrir N, Kusniec J, Sagie A, Sclarovsky S. The incidence of atrial arrhythmias during inferior wall myocardial infarction with and without right ventricular involvement. American Heart Journal 1992;124:387-391.
29. Sugiura T, Iwasaka T, Takahashi N, Yuasa F, Takeuchi M, Hasegawa T, Matsutani M, Inada M. Factors associated with atrial fibrillation in q wave anterior myocardial infarction. American Heart Journal 1991;121:1409-1412.
30. Kochiadakis G, Skalidis E, Kalebubas M, Igoumenidis N, Chrysostomakis S, Kanoupakis E, Simantirakis E, Vardas P. Effect of acute atrial fibrillation on phasic coronary blood flow pattern and flow reserve in humans. European heart journal 2002;23:734-741.
31. Askey JM, Neurath O. The prognostic significance of auricular fibrillation in association with myocardial infarction. American Heart Journal 1945;29:575-580.
32. DeSanctis RW, Block P, HUTTER JR AM. Tachyarrhythmias in myocardial infarction. Circulation 1972;45:681-702.
33. Cristal N, Szwarcberg J, Gueron M. Supraventricular arrhythmias in acute myocardial infarction. Annals of internal medicine 1975;82:35-39.
34. Behar S, Zahavi Z, Goldbourt U, Reicher-Reiss H. Long-term prognosis of patients with paroxysmal atrial fibrillation complicating acute myocardial infarction. European heart journal 1992;13:45.
35. Jabre P, Jouven X, Adnet F, Thabut G, Bielinski SJ, Weston SA, Roger VL. Atrial fibrillation and death after myocardial infarction: A community study. Circulation 2011;123:2094-2100.
36. Lau DH, Huynh LT, Chew DP, Astley CM, Soman A, Sanders P. Prognostic impact of types of atrial fibrillation in acute coronary syndromes. The American journal of cardiology 2009;104:1317-1323.
37. Al-Khatib SM, Pieper KS, Lee KL, Mahaffey KW, Hochman JS, Pepine CJ, Kopecky SL, Akkerhuis M, Stepinska J, Simoons ML. Atrial fibrillation and mortality among patients with acute coronary syndromes without st-segment elevation: Results from the pursuit trial. American Journal of Cardiology 2001;88:76-79.
38. Berton G, Cordiano R, Cucchini F, Cavuto F, Pellegrinet M, Palatini P. Atrial fibrillation during acute myocardial infarction: Association with all-cause mortality and sudden death after 7-year of follow-up. International journal of clinical practice 2009;63:712-721.
39. Rathore SS, Berger AK, Weinfurt KP, Schulman KA, Oetgen WJ, Gersh BJ, Solomon AJ. Acute myocardial infarction complicated by atrial fibrillation in the elderly: Prevalence and outcomes. Circulation 2000;101:969-974.
40. Pizzetti F, Turazza F, Franzosi M, Barlera S, Ledda A, Maggioni A, Santoro L, Tognoni G. Incidence and prognostic significance of atrial fibrillation in acute myocardial infarction: The gissi-3 data. Heart 2001;86:527-532.
41. Wong C. New atrial fibrillation after acute myocardial infarction independently predicts death: The gusto-iii experience. American Heart Journal 2000;140:878-885.
42. Crenshaw M, Brian S, Ward M, Samuel R, Granger M, Christopher B, Stebbins M, Amanda L, Topol M, Eric J. Atrial fibrillation in the setting of acute myocardial infarction: The gusto-i experience. Journal of the American College of Cardiology 1997;30:406-413.
43. Pedersen O, Bagger H, Køber L, Torp-Pedersen C. The occurrence and prognostic significance of atrial fibrillation/-flutter following acute myocardial infarction. European heart journal 1999;20:748-754.
44. Madias JE, Patel DC, Singh D. Atrial fibrillation in acute myocardial infarction: A prospective study based on data from a consecutive series of patients admitted to the coronary care unit. Clinical cardiology 1996;19:180-186.
45. Eldar M, Canetti M, Rotstein Z, Boyko V, Gottlieb S, Kaplinsky E, Behar S. Significance of paroxysmal atrial fibrillation complicating acute myocardial infarction in the thrombolytic era. Circulation 1998;97:965-970.
46. Goldberg RJ, Yarzebski J, Lessard D, Wu J, Gore JM. Recent trends in the incidence rates of and death rates from atrial fibrillation complicating initial acute myocardial infarction: A community-wide perspective. American Heart Journal 2002;143:519-527.
47. Kinjo K, Sato H, Sato H, Ohnishi Y, Hishida E, Nakatani D, Mizuno H, Fukunami M, Koretsune Y, Takeda H. Prognostic significance of atrial fibrillation/atrial flutter in patients with acute myocardial infarction treated with percutaneous coronary inter-

vention. The American journal of cardiology 2003;92:1150-1154.
48. Lehto M, Snapinn S, Dickstein K, Swedberg K, Nieminen MS. Prognostic risk of atrial fibrillation in acute myocardial infarction complicated by left ventricular dysfunction: The optimaal experience. European heart journal 2005;26:350-356.
49. Lopes RD, Pieper KS, Horton JR, Al-Khatib SM, Newby LK, Mehta RH, Van de Werf F, Armstrong PW, Mahaffey KW, Harrington RA, Ohman EM, White HD, Wallentin L, Granger CB. Short- and long-term outcomes following atrial fibrillation in patients with acute coronary syndromes with or without st-segment elevation. Heart 2008;94:867-873.
50. Stenestrand U, Lindback J, Wallentin L. Anticoagulation therapy in atrial fibrillation in combination with acute myocardial infarction influences long-term outcome: A prospective cohort study from the register of information and knowledge about swedish heart intensive care admissions (riks-hia). Circulation 2005;112:3225-3231.
51. Laurent G, Dentan G, Moreau D, Zeller M, Laurent Y, Vincent-Martin M, Lhuillier I, Makki H, Wolf J, Cottin Y. Atrial fibrillation during myocardial infarction with and without st segment elevation]. Archives des maladies du coeur et des vaisseaux 2005;98:608.
52. McMurray J, Kober L, Robertson M, Dargie H, Colucci W, Lopez-Sendon J, Remme W, Sharpe DN, Ford I. Antiarrhythmic effect of carvedilol after acute myocardial infarction: Results of the carvedilol post-infarct survival control in left ventricular dysfunction (capricorn) trial. Journal of the American College of Cardiology 2005;45:525-530.
53. Kober L, Swedberg K, McMurray JJ, Pfeffer MA, Velazquez EJ, Diaz R, Maggioni AP, Mareev V, Opolski G, Van de Werf F, Zannad F, Ertl G, Solomon SD, Zelenkofske S, Rouleau JL, Leimberger JD, Califf RM. Previously known and newly diagnosed atrial fibrillation: A major risk indicator after a myocardial infarction complicated by heart failure or left ventricular dysfunction. European journal of heart failure 2006;8:591-598.
54. Siu CW, Jim MH, Ho HH, Miu R, Lee SW, Lau CP, Tse HF. Transient atrial fibrillation complicating acute inferior myocardial infarction: Implications for future risk of ischemic stroke. Chest 2007;132:44-49.
55. Sakata MD K, Kurihara MD H, Iwamori MD K, Maki MD A, Yoshino MD H, Yanagisawa MD A, Ishikawa MD K. Clinical and prognostic significance of atrial fibrillation in acute myocardial infarction. The American journal of cardiology 1997;80:1522-1527.
56. Mehta RH, Dabbous OH, Granger CB, Kuznetsova P, Kline-Rogers EM, Anderson FA, Fox KAA, Gore JM, Goldberg RJ, Eagle KA. Comparison of outcomes of patients with acute coronary syndromes with and without atrial fibrillation. The American journal of cardiology 2003;92:1031-1036.
57. Schmitt J, Duray G, Gersh BJ, Hohnloser SH. Atrial fibrillation in acute myocardial infarction: A systematic review of the incidence, clinical features and prognostic implications. European heart journal 2009;30:1038-1045.
58. Bhatia GS, Lip GYH. Atrial fibrillation post-myocardial infarction: Frequency, consequences, and management. Current heart failure reports 2004;1:149-155.
59. Jons C, Jacobsen UG, Joergensen RM, Olsen NT, Dixen U, Johannessen A, Huikuri H, Messier M, McNitt S, Thomsen PE. The incidence and prognostic significance of new-onset atrial fibrillation in patients with acute myocardial infarction and left ventricular systolic dysfunction: A carisma substudy. Heart rhythm : the official journal of the Heart Rhythm Society 2011;8:342-348.
60. Nilsson KR, Jr., Al-Khatib SM, Zhou Y, Pieper K, White HD, Maggioni AP, Kober L, Granger CB, Lewis EF, McMurray JJ, Califf RM, Velazquez EJ. Atrial fibrillation management strategies and early mortality after myocardial infarction: Results from the valsartan in acute myocardial infarction (valiant) trial. Heart 2010;96:838-842.
61. Asanin M, Perunicic J, Mrdovic I, Matic M, Vujisic-Tesic B, Arandjelovic A, Vojvodic A, Marinkovic J, Ostojic M, Vasiljevic Z. Significance of recurrences of new atrial fibrillation in acute myocardial infarction. International journal of cardiology 2006;109:235-240.
62. Piccini JP, Hammill BG, Sinner MF, Jensen PN, Hernandez AF, Heckbert SR, Benjamin EJ, Curtis LH. Incidence and prevalence of atrial fibrillation and associated mortality among medicare beneficiaries, 1993-2007. Circulation Cardiovascular quality and outcomes 2012;5:85-93.
63. Pedersen OD, Bagger H, Kober L, Torp-Pedersen C. Impact of congestive heart failure and left ventricular systolic function on the prognostic significance of atrial fibrillation and atrial flutter following acute myocardial infarction. International journal of cardiology 2005;100:65-71.
64. Pedersen OD, Abildstrom SZ, Ottesen MM, Rask-Madsen C, Bagger H, Kober L, Torp-Pedersen C. Increased risk of sudden and non-sudden cardiovascular death in patients with atrial fibrillation/flutter following acute myocardial infarction. European heart journal 2006;27:290-295.
65. Yusuf S. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.
66. Ozaydin M, Turker Y, Erdogan D, Karabacak M, Dogan A, Varol E, Gonul E, Altinbas A. The association between previous statin use and development of atrial fibrillation in patients presenting with acute coronary syndrome. International journal of cardiology 2010;141:147-150.
67. Ramani G, Zahid M, Good CB, Macioce A, Sonel AF. Comparison of frequency of new-onset atrial fibrillation or flutter in patients on statins versus not on statins presenting with suspected acute coronary syndrome. The American journal of cardiology 2007;100:404-405.
68. Wyse D, Waldo A, DiMarco J, Domanski M, Rosenberg Y, Schron E, Kellen J, Greene H, Mickel M, Dalquist J. A comparison of rate control and rhythm control in patients with atrial fibrillation. The New England journal of medicine 2002;347:1825.
69. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJM, Tijssen JGP. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. New England Journal of Medicine 2002;347:1834-1840.
70. Hohnloser SH, Kuck K-H, Lilienthal J. Rhythm or rate control in atrial fibrillation—pharmacological intervention in atrial fibrillation (piaf): A randomised trial. The Lancet 2000;356:1789-1794.

71. Preliminary report: Effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. The cardiac arrhythmia suppression trial (cast) investigators. N Engl J Med 1989;321:406-412.
72. Effect of the antiarrhythmic agent moricizine on survival after myocardial infarction. The cardiac arrhythmia suppression trial ii investigators. N Engl J Med 1992;327:227-233.
73. Wong C, White H, Wilcox R, Criger D, Califf R, Topol E, Ohman E. Management and outcome of patients with atrial fibrillation during acute myocardial infarction: The gusto-iii experience. Heart 2002;88:357-362.
74. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC, Jr., Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK. Acc/aha guidelines for the management of patients with st-elevation myocardial infarction--executive summary: A report of the american college of cardiology/american heart association task force on practice guidelines (writing committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). Circulation 2004;110:588-636.
75. Lip GY, Huber K, Andreotti F, Arnesen H, Airaksinen JK, Cuisset T, Kirchhof P, Marin F. Antithrombotic management of atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing coronary stenting: Executive summary--a consensus document of the european society of cardiology working group on thrombosis, endorsed by the european heart rhythm association (ehra) and the european association of percutaneous cardiovascular interventions (eapci). European heart journal 2010;31:1311-1318.
76. Lopes RD, Starr A, Pieper CF, Al-Khatib SM, Newby LK, Mehta RH, Van de Werf F, Mahaffey KW, Armstrong PW, Harrington RA, White HD, Wallentin L, Granger CB. Warfarin use and outcomes in patients with atrial fibrillation complicating acute coronary syndromes. The American journal of medicine 2010;123:134-140.
77. Jang SW, Rho TH, Kim DB, Cho EJ, Kwon BJ, Park HJ, Shin WS, Kim JH, Lee JM, Moon KW, Oh YS, Yoo KD, Youn HJ, Lee MY, Chung WS, Seung KB, Kim JH. Optimal antithrombotic strategy in patients with atrial fibrillation after coronary stent implantation. Korean circulation journal 2011;41:578-582.
78. Zhao HJ, Zheng ZT, Wang ZH, Li SH, Zhang Y, Zhong M, Zhang W. "Triple therapy" rather than "triple threat": A meta-analysis of the two antithrombotic regimens after stent implantation in patients receiving long-term oral anticoagulant treatment. Chest 2011;139:260-270.
79. Gao F, Zhou YJ, Wang ZJ, Yang SW, Nie B, Liu XL, Jia de A, Yan ZX. Meta-analysis of the combination of warfarin and dual antiplatelet therapy after coronary stenting in patients with indications for chronic oral anticoagulation. International journal of cardiology 2011;148:96-101.
80. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J. Dabigatran versus warfarin in patients with atrial fibrillation. New England Journal of Medicine 2009;361:1139-1151.
81. Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: Meta-analysis of noninferiority randomized controlled trials. Arch Intern Med 2012;172:397-402.
82. Olsson SB. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (sportif iii): Randomised controlled trial. Lancet 2003;362:1691-1698.
83. Flaker GC, Gruber M, Connolly SJ, Goldman S, Chaparro S, Vahanian A, Halinen MO, Horrow J, Halperin JL. Risks and benefits of combining aspirin with anticoagulant therapy in patients with atrial fibrillation: An exploratory analysis of stroke prevention using an oral thrombin inhibitor in atrial fibrillation (sportif) trials. Am Heart J 2006;152:967-973.
84. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. New England Journal of Medicine 2011.
85. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A. Apixaban versus warfarin in patients with atrial fibrillation. New England Journal of Medicine 2011;365:981-992.
86. Ruff CT, Giugliano RP, Antman EM, Crugnale SE, Bocanegra T, Mercuri M, Hanyok J, Patel I, Shi M, Salazar D, McCabe CH, Braunwald E. Evaluation of the novel factor xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: Design and rationale for the effective anticoagulation with factor xa next generation in atrial fibrillation-thrombolysis in myocardial infarction study 48 (engage af-timi 48). Am Heart J 2010;160:635-641.
87. Alexander JH, Lopes RD, James S, Kilaru R, He Y, Mohan P, Bhatt DL, Goodman S, Verheugt FW, Flather M. Apixaban with antiplatelet therapy after acute coronary syndrome. New England Journal of Medicine 2011.
88. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KAA. Rivaroxaban in patients with a recent acute coronary syndrome. New England Journal of Medicine 2012;366:9-19.
89. Wann LS, Curtis AB, January CT, Ellenbogen KA, Lowe JE, Estes NA, 3rd, Page RL, Ezekowitz MD, Slotwiner DJ, Jackman WM, Stevenson WG, Tracy CM, Fuster V, Ryden LE, Cannom DS, Le Heuzey JY, Crijns HJ, Lowe JE, Curtis AB, Olsson SB, Ellenbogen KA, Prystowsky EN, Halperin JL, Tamargo JL, Kay GN, Wann LS, Jacobs AK, Anderson JL, Albert N, Hochman JS, Buller CE, Kushner FG, Creager MA, Ohman EM, Ettinger SM, Stevenson WG, Guyton RA, Tarkington LG, Halperin JL, Yancy CW. 2011 accf/aha/hrs focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): A report of the american college of cardiology foundation/american heart association task force on practice guidelines. Circulation 2011;123:104-123.
90. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, Baigent C, Huber K, Jespersen J, Kristensen SD, Lip GY, Morais J, Rasmussen LH, Siegbahn A, Verheugt FW, Weitz JI. New oral anticoagulants in atrial fibrillation and acute coronary syndromes: Esc working group on thrombosis-task force on anticoagulants in heart disease position paper. Journal of the American College of Cardiology 2012;59:1413-1425.