ORIGINAL RESEARCH

Atrial Fibrillation and Myocardial Infarction: A Systematic Review and Appraisal of Pathophysiologic Mechanisms

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Background—A growing body of evidence suggests that atrial fibrillation (AF) is associated with myocardial infarction (MI). However, incidence and management of MI in AF is still undefined.

Methods and Results—We searched MEDLINE via PubMed and Cochrane database between 1965 and 2015. All observational clinical studies and interventional trials reporting 1-year incidence of MI in AF were included. We also discussed pathophysiological mechanisms, predictors, and therapeutic approaches to reduce the risk of MI in AF. Twenty-one observational studies and 10 clinical trials were included. The annual rate of MI in observational studies including AF patients ranged from 0.4% to 2.5%. Higher rates of MI were reported in AF patients with stable coronary artery disease (11.5%/year), vascular disease (4.47%/year), heart failure (2.9%/year), and in those undergoing coronary artery interventions (6.3%/year). However, lower annual rates have been described in AF patients from Eastern countries (0.2–0.3%/year), and in those enrolled in clinical trials (from 0.4 to 1.3%/year).

Conclusions—AF patients had a significant residual risk of MI despite anticoagulant treatment. Coexistence of atherosclerotic risk factors and platelet activation account for the increased risk of MI in AF. Identification of high-risk AF patients is a needed first step to develop cost-effective approaches for prevention. A new score, the 2MACE score, has been recently developed to stratify MI risk in AF, and may help not only in allocating resources to high-risk groups, but also in design of studies examining novel therapies for prevention of MI in AF. **(*J Am Heart Assoc*. 2016;5:e003347 doi: 10.1161/JAHA.116.003347)**

Key Words: atherosclerosis • atrial fibrillation • myocardial infarction

Atrial fibrillation (AF) is the most frequent sustained cardiac arrhythmia encountered in Western countries, with millions of individuals expected to suffer from it in the next decades. Progressive increase in the life expectancy is the major drive for the high prevalence of AF in Western countries.[1] Aging has a negative impact not only for the occurrence of AF but also for ischemic stroke, which sharply increases in the elderly population as well.[1] Consequently, the clinical history of most AF patients is often complicated by thromboembolic events; for this reason AF patients are treated with oral anticoagulants such as vitamin K antagonists (VKAs) to prevent the risk of ischemic stroke.[2] In the last decade a new anticoagulant category, non–vitamin K oral anticoagulants (NOACs), has been introduced in the market. This includes a direct thrombin inhibitor such as dabigatran, and factor Xa inhibitors, namely, rivaroxaban, apixaban, and edoxaban. Warfarin and NOACs are equivalent in terms of cerebrovascular events reduction, but NOACs have been associated with less risk of bleeding.[3]

In addition to thromboembolism, AF is characterized by a constellation of atherosclerotic risk factors including hypertension, diabetes, metabolic syndrome, and dyslipidemia and by systemic signs of atherosclerosis such as aortic plaque or peripheral artery disease, which can increase the risk of stroke. It is for this reason that vascular disease has been included in the new score for stroke risk stratification, ie, the CHA_2DS_2-VASc score.

The association between systemic atherosclerosis and AF can explain, at least partially, the complex clinical picture complicating the disease course in AF patients. Thus, atherosclerosis of coronary arteries with ensuing development of acute coronary syndromes, such as myocardial

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infarction (MI), is another typical feature of AF clinical history. Epidemiologic studies on the occurrence of MI provided divergent results[4–24]; also unclear are the clinical and laboratory predictors, which may help to identify AF patients at high risk of MI. The occurrence of MI in AF patients yields serious problems of management. For example, the coexistence of major adverse cardiovascular events (MACE) and thromboembolism could require a more complex antithrombotic treatment.

This systematic review will focus on incidence of MI in clinical trials and in observational studies, mechanisms of disease, predictors of MI, and potential therapeutic approaches to reduce the risk MI in AF.

Methods

Eligibility Criteria

We included all original clinical research articles in English language with full text available. In particular, observational clinical studies and interventional trials that reported data on the incidence of MI in nonvalvular AF patients, with at least 1 year of follow-up and with no limitations regarding the type of antithrombotic treatment, were selected. We did not include the following: (1) case reports, editorials/comments, letters; (2) subgroup analysis from the same clinical trial; (3) studies reporting only cerebrovascular events as primary outcome, and/or combined end point of ischemic events, or other cardiovascular outcomes than MI (ie, mortality or incident heart failure); and (4) studies investigating postacute MI/cardiac revascularization AF.

Information Sources and Search Strategy

We performed a systematic review of the literature searching MEDLINE via PubMed and Cochrane database for a combination of the following keywords: "atrial fibrillation," "myocardial infarction," and "cardiovascular events." The research strategy included only journal articles in English language between 1965 and 2015, and was performed according to PRISMA guidelines.[25]

Study Selection

The study selection was performed in multiple phases. In the first phase, potentially relevant studies were obtained by combined searches of electronic databases using the selected above-mentioned keywords. Then, studies not in English language, with no abstract/full text available or not involving humans, were excluded. In the second phase, studies were reviewed and excluded by study typology; thus, letters, editorials, case reports, and comments were excluded. The third phase consisted of a detailed analysis of full-text articles to assess whether they addressed the specific study question (Figure 1).

Data Collection Process and Data Items

Two physicians (D.P., P.P.) independently screened the titles and abstracts of manuscripts identified through the database searches to identify studies potentially eligible for further assessment. Controversies were resolved by a third investigator (F.V.).

For each study we collected the following information: authors, year of publication, study typology, antithrombotic treatment, number of participants included, percentage of women, age, $CHADS_2$/CHA_2DS_2-VASc scores, follow-up (year), number (n/%), and rate of MI (%/year).

Ethical Review

Given the study type (review article), an ethical approval was not necessary.

Results

Study Selection

Our systematic review of literature yielded 3903 results (Figure 1). Two-thousand ninety-one records were excluded as 642 were not in English language, 842 had no abstract/full text available, 356 were not involving humans, and 251 because they did not report keywords either in the title or the abstract. Moreover, 40 were excluded by study typology (letters/editorials/comments/case reports). Of the 1772 remaining full-text articles, 1175 did not include patients with AF, and 508 included AF patients but did not address the specific study question. Thus, 89 were eligible studies; of these, we excluded 25 subgroup analysis of randomized clinical trials, 25 studies reporting only composite end point/other outcomes than MI, and 8 with a follow-up <1 year. Thirty-one studies were included in the systematic review: 21 observational studies and 10 clinical trials.

Study Characteristics and Results of Individual Studies

Observational studies reported divergent data on the incidence of MI in the AF population[4–24] (Table 1). The first consolidated evidence suggesting that AF per se is an independent predictor of MI has been provided by Soliman et al,[9] who analyzed the incidence of MI in a population-based cohort study that included 1631 participants with and 22 297 without AF from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. The study

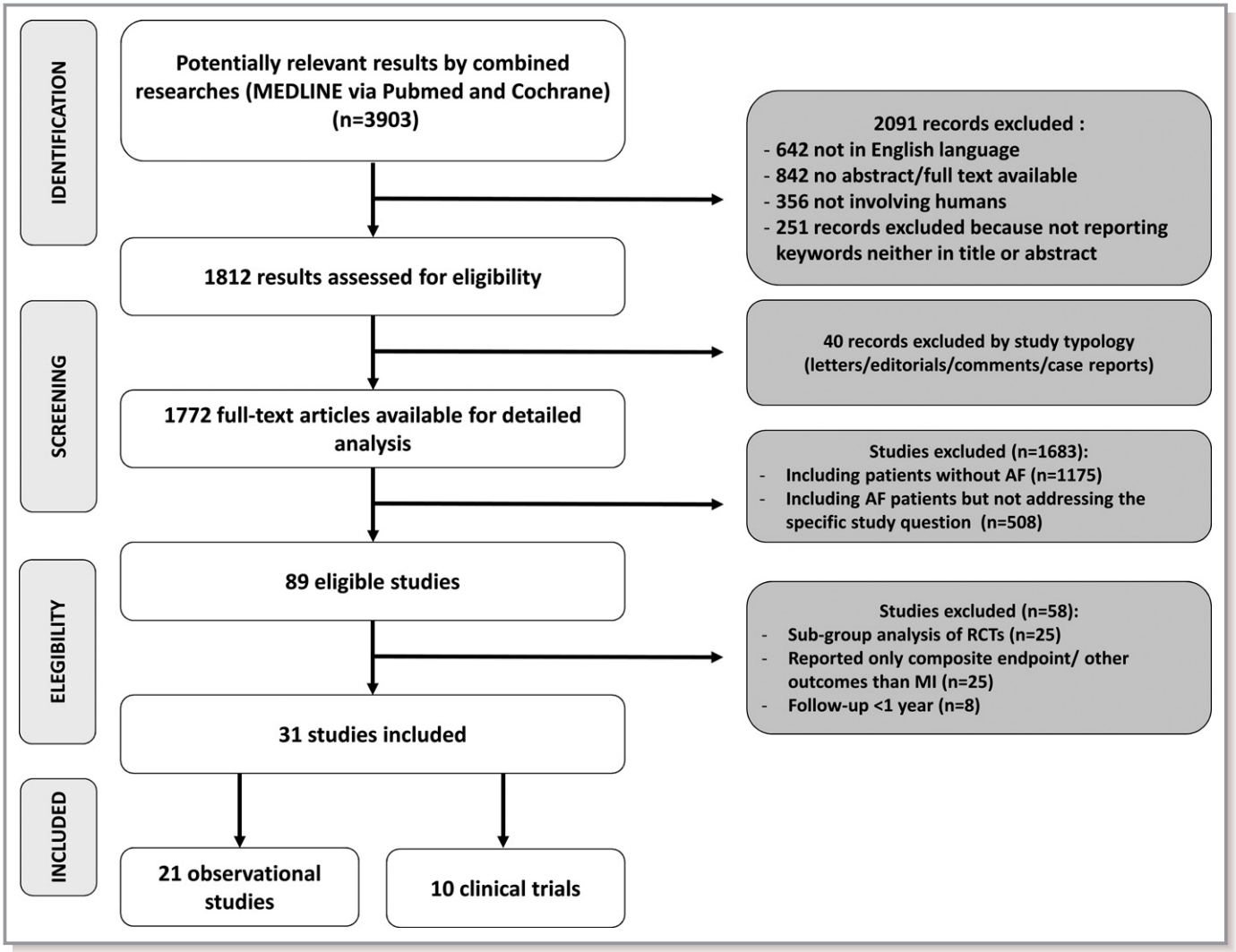

Figure 1. Flow diagram of search strategy. AF indicates atrial fibrillation; MI, myocardial infarction; RCTs, randomized controlled trials.

demonstrated that AF increases the risk of MI by 2-fold during a median follow-up of 4.5 years.

Further support to this finding was provided by other reports indicating that the annual rate of MI in AF patients is close to or over 1%/year, with the exception of the Xantus study where MI incidence was 0.4%.[22] Thus, as reported in Table 1, the annual rate of MI in observational studies of AF patients ranges from 0.4% to 2.5%.

Higher rates of MI were found in AF patients with stable coronary artery disease,[20] peripheral vascular disease,[8] heart failure,[10] or in those undergoing coronary artery intervention[15] (Table 1).

A lower annual rate has been described in patients from Eastern countries. For example, in the J-TRACE study, which included 2056 Japanese AF patients, the rate of MI was 0.2%/year.[7] Similarly, a large nationwide cohort on 12 114 subjects from Taiwan found a rate of MI of 0.29%/year.[11]

Clinical trials reported a lower annual rate of MI in AF[26–36] (Table 2). Overall, 46 923 AF patients were treated with NOACs, 34 800 with VKAs, and 14 725 with antiplatelets. In particular, MI incidence in AF patients treated with NOACs ranged from 0.53%/year for apixaban to 1.1%/year for ximelagatran, which was similar to that in patients treated with VKAs (from 0.44%/year in the SIFA study to 1.1%/year of ROCKET trial). Finally, for the group of patients treated with antiplatelets, the rate of MI ranged from 0.43%/year in the SIFA study to 1.3%/year in the CHARISMA (Table 2).

The reason for these differences is unclear. Differences in the populations and the distribution of atherosclerotic risk factors and comorbidities are possible explanations for some of these differences. Moreover, another aspect to be considered is that patients included in clinical trials may have been monitored more closely than patients in observational studies, resulting in an improved treatment of comorbid conditions and atherosclerotic risk factors, and, thereby, in lower rates of MI.

Finally, many patients included in the observational cohorts were not treated with oral anticoagulants, suggesting that in the real world of AF, a significant proportion of patients

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Table 1. Incidence of Myocardial Infarction in Observational Studies Including Atrial Fibrillation Patients

Author/Study (y)	Antithrombotic Agent	Participants (n)	Female (%)	Age, y	$CHADS_2$/CHA_2DS_2-VASc Scores	Number of MI, n (%)	Follow-Up (y)	Rate of MI (%/y)
LIFE study (2005)[4]	Not reported	342	43.3	70.3	Not reported	19 (5.6%)	4	1.13
Goto et al/REACH Registry (2008)[5]	Warfarin (53.1%)	6814	35.6	72.8	$CHADS_2$ 0 to 1=17.6%; $CHADS_2$ ≥2=82.4%	Not reported	1	1.36
Winkel et al/REACH Registry* (2010)[6]	Warfarin (60.7%)	392	25.6	71.6	Not reported	18 (4.6%)	2	2.30
Goto et al/J-TRACE (2011)[7]	Warfarin (70.0%)	2056	31.3	70.0	Not reported	Not reported	1	0.20
ADHERE Registry† (2012)[8]	Warfarin	537	45.1	78.1	$CHADS_2$ ≥2=93.3	15 (2.8)	1	2.80
	No warfarin	2049	46.3	80.0	$CHADS_2$ ≥2=96.6	60 (2.9)		2.90
Soliman et al/REGARDS study (2014)[9]	Warfarin (19.9%) Aspirin (41.2%)	1631	61.6	66.5	$CHADS_2$ ≤1=983 $CHADS_2$ >1=648	78 (4.8) $CHADS_2$ ≤1=30 (3.0) $CHADS_2$ >1=48 (7.4)	4.5	1.20
Andersson et al (2014)[10]	Not reported	9519	31.0	Women: 67.7	CHA_2DS_2-VASc: <55 years and 55 to 64=1 65 to 74=2 75 to 85=3	Not reported	>10	<55: 0.20%, 55 to 64: 0.40%, 65 to 74: 0.80% 75 to 85: 1.40%
				Men: 54.9	CHA_2DS_2-VASc: <55 years and 55 to 64=0 65 to 74=1 75 to 85=2			<55: 0.20%, 55 to 64: 0.50%, 65 to 74: 1.20% 75 to 85: 1.90%
Chao et al (2014)[11]	Not reported	12 114	40.0	—	Men: CHA_2DS_2-VASc=0 Women: CHA_2DS_2-VASc=1	258	5.7	0.29
Senoo et al (2014)[12]	Warfarin (47.2%) Aspirin (39%)	1835	24.6	63.2	$CHADS_2$ 0 to 1=69.4%; $CHADS_2$ ≥2=30.6%	51‡ (2.78)	1.46	1.90 (3.60 for $CHADS_2$ ≥2)
Shore et al (2014)[13]	Dabigatran	5376	1.7	71.3	$CHADS_2$=2.38 CHA_2DS_2-VASc=3.22	20 (0.4)	1	0.40
AFCAS Registry§ (2014)[14]	DAPT+warfarin	679	29.0	73.0	$CHADS_2$=2.3	43 (6.3)	1	6.30
	DAPT	162	35.0	73.0	$CHADS_2$=2.1	4 (2.5)		2.50
	Warfarin+ clopidogrel	73	29.0	74.0	$CHADS_2$=2.4	4 (5.5)		5.50
Lamberts et al‖ (2014)[15]	Prevalent AF: warfarin (20.7%) antiplatelet (29.2%) both (6%)	7804	35.7	76.8	CHA_2DS_2-VASc=5.3	Not reported	3	4.47**

Continued

Table 1. Continued

Author/Study (y)	Antithrombotic Agent		Participants (n)	Female (%)	Age, y	$CHADS_2$/CHA_2DS_2-VASc Scores	Number of MI, n (%)	Follow-Up (y)	Rate of MI (%/y)
	Incident AF: warfarin (25.0%) antiplatelet (30.3%) both (8.0%)		6432	34.9		CHA_2DS_2-VASc=5.2	Not reported		4.37**
Martinez et al (2014)[16]	Not reported		5555	38.4	70.9	CHA_2DS_2-VASc=2.5	Not reported	3	0.90
Larsen et al (2014)[17]	Naive	Dabigatran 110	2124	55.5	82.0	$CHADS_2$=1.90 CHA_2DS_2-VASc=3.70	29/97¶	16 months	1.20/4.10¶
		Dabigatran 150	2694	37.6	68.0	$CHADS_2$=0.98 CHA_2DS_2-VASc=2.19	30/134¶		0.91/4.15¶
		Warfarin	8133	42.2	72.0	$CHADS_2$=1.29 CHA_2DS_2-VASc=2.74	142/481¶		1.37/4.75¶
	Warfarin experienced	Dabigatran 110	1554	54.6	82.0	$CHADS_2$=2.07 CHA_2DS_2-VASc=3.89	26/73¶		1.33/3.82¶
		Dabigatran 150	1825	35.9	69.0	$CHADS_2$=1.30 CHA_2DS_2-VASc=2.63	21/85¶		0.81/3.34¶
		Warfarin	49 868	37.9	75.0	$CHADS_2$=1.58 CHA_2DS_2-VASc=3.05	2564/8968¶		0.72/2.55¶
Piccini et al/ Medicare (2014)[18]	Not reported		186 461	55.4	79.5	$CHADS_2$=2.8 CHA_2DS_2-VASc=5.0	2272 (1.2)	1	1.20
O'Neal et al (2014)[19]	Aspirin (31%)		434	55.0	65 to 70 y=35% 71 to 74 y=25% ≥75=40%	Not reported	Overall (AF+non-AF) 797 (17.3)	12.2	2.55
Lamberts et al# (2014)[20]	Aspirin: 3273 Clopidogrel: 417 DAPT: 1767		5457	37 to 46	73.0 to 76.1	CHA_2DS_2-VASc 0=1% to 2%; CHA_2DS_2-VASc 1=4% to 8%; CHA_2DS_2-VASc ≥2=89% to 95%	Aspirin: 1048 (32) Clopidogrel: 55 (13.2) DAPT: 119 (6.7)	3.3	Aspirin: 8.40 Clopidogrel: 9.0 DAPT: 11.50
	VKAs:950 VKA+aspirin:1471 VKA+Clopidogrel:322 VKA+DAPT: 500		3243	20 to 38	71.0 to 73.6	CHA_2DS_2-VASc 0=0% to 1%; CHA_2DS_2-VASc 1=4% to 8%; CHA_2DS_2-VASc ≥2=91% to 95%	VKAs: 188 (14.5) VKA+Aspirin: 339 (23) VKA+Clopidogrel: 17 (5.3) VKA+DAPT: 16 (3.2)		VKAs: 4.70 VKA+aspirin: 4.70 VKA+Clopidogrel: 4.40 VKA+DAPT: 7.80
Pastori et al (2015)[21]	Warfarin		1019	43.8	73.2	CHA_2DS_2-VASc=4.0	29 (0.9)	2.8	0.90

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Table 1. Continued

Author/Study (y)	Antithrombotic Agent	Participants (n)	Female (%)	Age, y	$CHADS_2/CHA_2DS_2$-VASc Scores	Number of MI, n (%)	Follow-Up (y)	Rate of MI (%/y)
XANTUS (2015)[22]	Rivaroxaban	6784	41.0	71.5	$CHADS_2$=2.0 CHA_2DS_2-VASc=3.4	27 (0.4)	1	0.40
Soliman et al/ARIC cohort (2015)[23]	Warfarin (1.3%) Aspirin (48.4%)	1545	49.9	56.6	Not reported	107 (6.9)	21.6	1.16
Vermond et al (2015)[24]	Not reported	265	30.0	62.0	Not reported			2.06

ADHERE indicates acute decompensated heart failure national registry; AFCAS, atrial fibrillation undergoing coronary artery stenting; ARIC, Atherosclerosis Risk in Communities; DAPT, dual antiplatelet therapy; J-TRACE, Japan Thrombosis Registry for Atrial Fibrillation, Coronary, or Cerebrovascular Events; LIFE, Losartan Intervention for End Point Reduction in Hypertension; MI, myocardial infarction; REACH, REduction of Atherothrombosis for Continued Health; REGARDS, REasons for Geographic and Racial Differences in Stroke; VKA, vitamin K antagonists; XANTUS, Xarelto (®) for Prevention of Stroke in Patients with Atrial Fibrillation.

*AF in patients with symptomatic peripheral arterial disease.

†AF patients with heart failure and atrial fibrillation and a cardiovascular implantable electronic device.

‡Coronary events.

§AF patients undergoing coronary artery stenting.

‖Heart failure and vascular disease Plus AF.

¶Considering all myocardial ischemic events.

#Patients with AF and stable coronary artery disease.

**Refers to all group.

do not receive an adequate prevention for thromboembolism. This is in keeping with findings from recent surveys reporting that at least 15% to 30% of AF patients are treated only with aspirin, or do not receive any antithrombotic treatment.[37,38] MI rate is also influenced by sex, with females being at higher risk of MI compared to men, as shown in the REGARDS study.[9] Of note, the percentage of females included in the interventional trials is typically lower than that in the observational studies (30–40% versus about 50%; Tables 1 and 2).

Synthesis of Results

The annual rate of MI in observational studies including AF patients ranges from 0.4% to 2.5%. Higher rates of MI were reported in AF patients with stable coronary artery disease (11.5%/year), vascular disease (4.47%/year), heart failure (2.9%/year), or in those undergoing coronary artery intervention (6.3%/year). A low annual rate has been described in AF patients from Eastern countries (0.2–0.3%/year). Overall, a lower rate has been described in clinical trials (from 0.4% to 1.3%/year).

Discussion

Mechanisms of Cardiovascular Disease in AF

AF is associated with systemic signs of inflammation that could promote a pro-thrombotic state and eventually MI.[39] Systemic inflammation may depend on AF per se or on the concomitant presence of the classic atherosclerotic risk factors, which are typically associated with AF.[40] In this context, it is worth noting that hypertension, diabetes, and dyslipidemia are associated with platelet activation,[41] a key step in the pathogenesis of MI. This has been evidenced by studies showing that aspirin, which irreversibly acetylates COX1, thus inhibiting the formation of the pro-aggregating molecule thromboxane (Tx) A_2,[42] significantly reduces the risk of cardiovascular outcomes in patients at risk of or with MI.[43] Several biomarkers of platelet activation such as plasma levels of P-selectin, β-thromboglobulin, and soluble CD40L (sCD40L)[44] have been found to be elevated in AF, suggesting a role for platelets in precipitating vascular disease. This hypothesis is supported by an observational prospective study performed in 231 patients with AF, where high plasma levels of sCD40L discriminated patients who experienced MI during a follow-up of 28 months.[45] Further support to the role of platelets in favoring MACE is provided by a prospective single-center study in which the predictive value of 11-dehydro-TxB_2, a marker of in vivo platelet activation, was examined in 837 AF patients followed up to 30 months. During the follow-up, 99 patients experienced fatal and nonfatal MACE. Patients who were in the top tertile of 11-dehydro-TxB_2 showed the

Table 2. Incidence of Myocardial Infarction in Clinical Trials Including Patients With Atrial Fibrillation

Author/Study	Antithrombotic Agent	Participants (n)	Female (%)	Age, y	$CHADS_2/CHA_2DS_2$-VASc Scores	Number of MI (n/%)	Follow-Up (y)	Rate of MI (%/y)
SIFA (1997)[26]	Indobufen	462	54.5	72.8	Not reported	2 (0.43)	1.0	0.43
	Warfarin	454	51.5	72.2	68% with ≥2 risk factors	2 (0.44)		0.44
SPORTIF III (2003)[27]	Ximelagatran	1704	32.0	70.3	70% with ≥2 risk factors	24	1.4	1.10
	Warfarin	1703	30.0	70.1	68% with ≥2 risk factors	13		0.60
ACTIVE W (2006)[28]	Clopidogrel+aspirin	3335	33.0	70.2	$CHADS_2$=2.0	36 (1.1)	1.28	0.86
	Warfarin	3371	34.0			23 (0.7)		0.55
CHARISMA (2008)[29]	Clopidogrel+aspirin	298	19.0	70.0	Not reported	9 (3.0)	2.3	1.30
	Aspirin	285	24.0			6 (2.1)		0.91
ACTIVE (2009)[30]	Clopidogrel+aspirin	3772	41.4	70.9	$CHADS_2$=2.0	90 (2.4)	3.6 median	0.70
	Aspirin	3782	42.4	71.1		115 (3.0)		0.90
RE-LY (2009)[31]	Dabigatran 150 mg	6076	36.8	71.5	$CHADS_2$ 0 to 1=32.2%; $CHADS_2$ 2=35.2%; $CHADS_2$ >2=32.6%	89 (1.5)	2.0	0.74
	Dabigatran 110 mg	6015	35.7		$CHADS_2$ 0 to 1=32.6%; $CHADS_2$ 2=34.7%; $CHADS_2$ >2=32.7%	86 (1.4)		0.72
	Warfarin	6022	36.7		$CHADS_2$ 0 to 1=30.9%; $CHADS_2$ 2=37.0%; $CHADS_2$ >2=32.1%	63 (1.0)		0.53
ARISTOTLE (2011)[32]	Apixaban	9120	35.5	70.0	$CHADS_2$=2.1	90 (1.0)	1.8	0.53
	Warfarin	9081	35.0			102 (1.1)		0.61
AVERROES (2011)[33]	Apixaban	2808	41.0	70.0	$CHADS_2$=2.0	24	1.1	0.80
	Aspirin	2791	42.0	70.0	$CHADS_2$=2.1	28		0.90
ROCKET AF (2011)[34]	Rivaroxaban	7131	39.7	73.0	$CHADS_2$=3.48	101 (1.4)	1.9	0.90 (overall) (0.57 AF without prior MI; 2.77 AF with prior MI)[36]
	Warfarin	7133	39.7		$CHADS_2$=3.46	126 (1.8)		1.10 (overall) (0.77 AF without prior MI; 2.80 AF with prior MI)[36]
ENGAGE AF TIMI 48 (2013)[35]	Edoxaban 60 mg	7035	37.9	72.0	$CHADS_2$ ≤3=77.1%; $CHADS_2$ 4 to 6=22.9%.	133 (1.9)	2.8	0.70
	Edoxaban 30 mg	7034	38.8		$CHADS_2$ ≤3=77.8%; $CHADS_2$ 4 to 6=22.2%	169 (2.4)		0.89
	Warfarin	7036	37.5		$CHADS_2$ ≤3=77.4%; $CHADS_2$ 4 to 6=22.6%	141 (2.0)		0.65

ACTIVE indicates Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events; AF, atrial fibrillation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; AVERROES, Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; ENGAGE AF-TIMI 48, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48; MI, myocardial infarction; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; SIFA, studio italiano fibrillazione atriale; SPORTIF III, Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation.

highest risk of experiencing ischemic events, including cardiac complications. The relationship between platelet activation and cardiovascular disease has been also confirmed by another prospective observational study in which the predictive value of prostaglandin PGF2alpha was analyzed in 1002 AF patients on treatment with VKAs and followed up for 25.7 months.[46] Prostaglandin PGF2alpha is a chemically stable eicosanoid stemming from arachidonic acid oxidation by superoxide anion, which activates platelets via TxA_2 receptors.[47] During the follow-up, 125 patients experienced a MACE

including 44 (35.2%) cardiac complications, such as fatal and nonfatal MI (n=31) and cardiac revascularization (n=13). Patients in the highest tertile of prostaglandin PGF2alpha were at higher risk of experiencing MACE, suggesting again a role for platelets in precipitating cardiac complications.

In addition to atherosclerosis, MI may occur in AF by other mechanisms. For example, episodes of AF with high ventricular rates may yield type 2 MI, which is characterized by an imbalance between demand and blood supply, and is usually associated with non-ST elevation MI.[48] Another possibility is direct thromboembolization from left atrium into the coronary arteries.[49] In 1776 patients with new-onset MI, Shibata et al[50] showed that 52 were due to coronary embolism and most of them (n=38, 73%) were observed in patients with AF, suggesting that AF may cause thromboembolism not only to the cerebral but also to the coronary circulation.

Together these findings suggest that at least 3 mechanisms may account for MI in AF: (1) atherosclerosis and its associated inflammatory process, yielding a pro-thrombotic state; (2) direct coronary thromboembolism from left atrial appendage; and (3) tachyarrhythmia episodes resulting in supply–demand mismatch (Figure 2).

Predictors of MI in AF

Instrumental and clinical variables have been investigated as predictors of MI in AF patients. Ankle-brachial index (ABI) and brachial flow-mediated dilation (FMD), two markers of systemic atherosclerosis,[51] have been prospectively studied to assess their predictive value against cardiovascular disease in AF.[52,53]

ABI is a simple, inexpensive, and noninvasive marker of peripheral artery disease, which is recommended as a first-line screening tool to assess the presence of a peripheral artery disease in asymptomatic adults at moderate risk.[54] Low ABI (ie, <0.90) indicates ≥50% stenosis between the aorta and the distal leg arteries and is associated with an increased risk of cardiovascular events.[55] Prior studies have reported that AF patients had a low ABI compared to controls,[56] and that an ABI ≤0.90 is detectable in about 20% of the AF population.[57] Low ABI is associated with ischemic events also in AF patients, as shown by the "Ankle-brachial index Prevalence Assessment-Collaborative Italian Study" (ARAPACIS) registry, which followed 2027 AF patients for a median of 35 months. The study showed that a low ABI ≤0.90 was more prevalent in patients with, compared to those without, a vascular event (32.2% versus 20.2%, $P<0.05$). During follow-up, 176 vascular events occurred (3.81%/year) and, at multivariate analysis, low ABI was an independent predictor of MI.[53]

An impaired FMD has been described in many cardiovascular diseases.[58,59] An increased risk of cardiovascular events seems to be present for a value of FMD <10%, further rising for a value <5%.[60] A meta-analysis by Inaba et al showed how 1% increase of FMD is associated with 13% reduction of risk of cardiovascular event.[61]

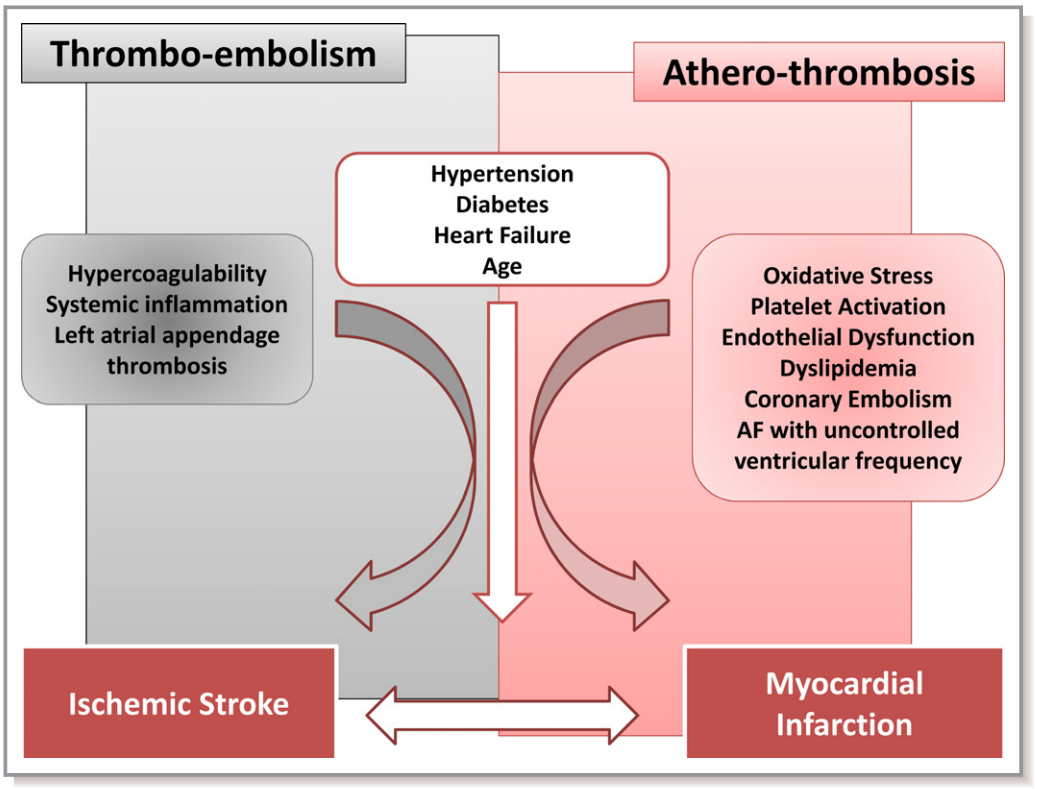

Figure 2. Mechanisms of thromboembolism and atherothrombosis in atrial fibrillation (AF).

In a cohort of 514 AF patients, a reduced value of FMD was detected (median 4.6%), with an increase of cardiovascular events in patients with FMD below the median value (3.06% [interquartile range 0.00–6.00] versus 4.67% [interquartile range 1.58–8.22], P=0.027).[62]

In addition to ABI and FMD, other atherosclerotic risk factors have been studied in AF. Metabolic syndrome (MetS) represents a worldwide challenge, with a widespread prevalence that appears to be increasing in parallel with the prevalence of obesity.[63] MetS encloses a cluster of cardiometabolic alterations including visceral adiposity and atherogenic dyslipidemia. It is estimated that about 40% of the population aged 60 years old have MetS in the United States.[64] Subjects with MetS have an excess risk for subsequent cardiovascular events and death, as confirmed by a recent meta-analysis including 951 083 patients.[65] Moreover, a higher risk to develop AF has been well recognized in patients with MetS,[66] and the prevalence of MetS in AF ranges from 18.8% to 52.1%.[67]

In accordance with data from the general population without AF, the association between MetS and cardiovascular events was also evident in the AF population. For example, in a cohort of 1019 AF patients followed for a median of 33.7 months, the prevalence of MetS was 52.1%, conferring an increased risk of MACE (hazard ratio, 1.663; 95% CI, 1.107–2.499; P=0.014).[21]

In an attempt to improve cardiovascular risk stratification, a new simple score to identify AF patients at higher risk to experience MACE has been proposed.[68] The 2MACE score (Figure 3) assigning 2 points for Metabolic Syndrome and Age ≥75, 1 point for MI/revascularization, Congestive heart failure (ejection fraction ≤40%), thromboembolism (stroke/transient ischemic attack) was developed and validated in >2000 AF patients in a multicenter study; a

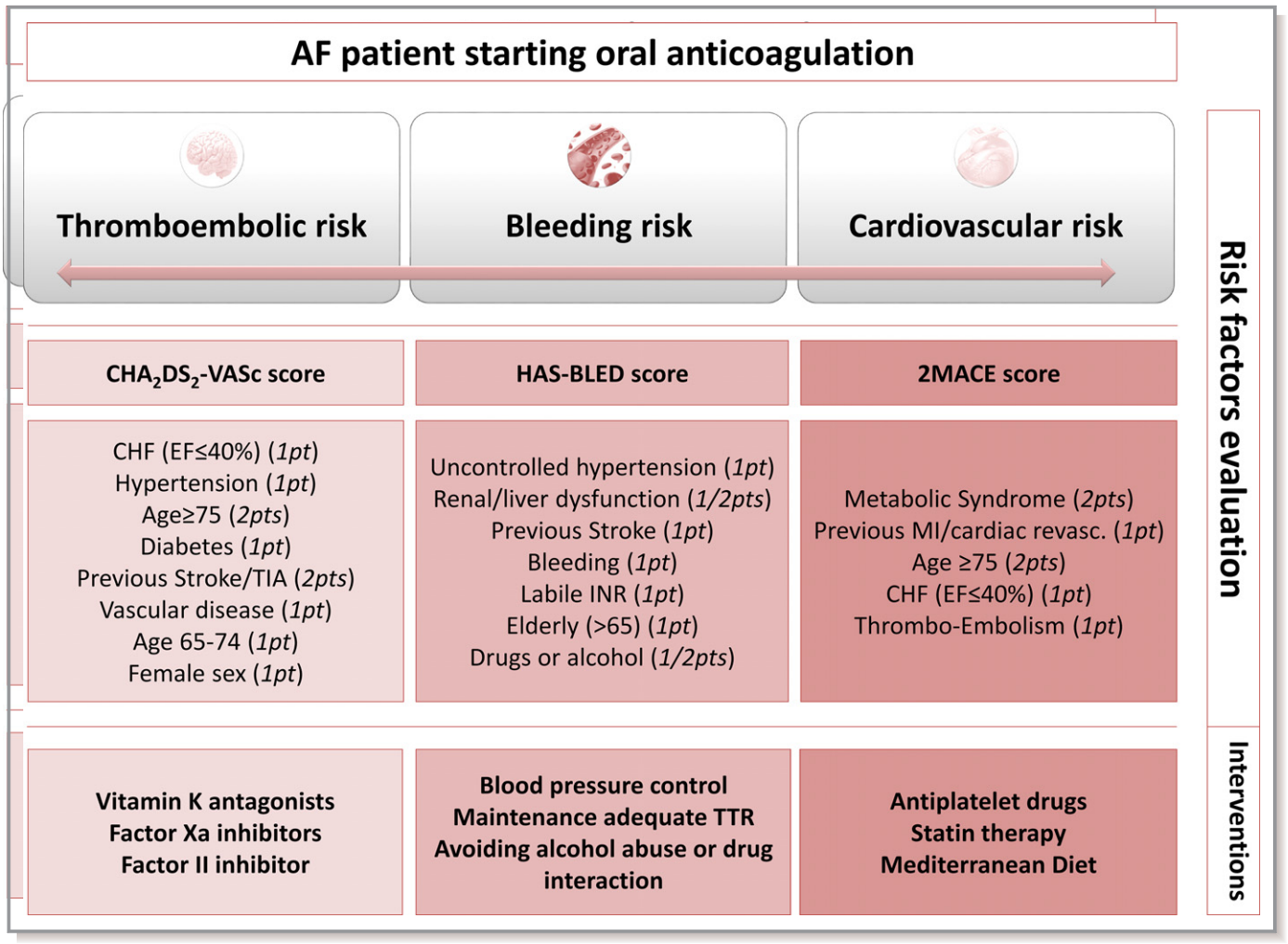

Figure 3. Holistic antithrombotic approach for the management of AF patients starting oral anticoagulation. AF indicates atrial fibrillation; CHF, congestive heart failure; EF, ejection fraction; INR, international normalized ratio; MI, myocardial infarction; TIA, transient ischemic attack; TTR, time in therapeutic range.

2MACE score ≥3 identified patients at highest risk for MACE.[68]

Therapeutic Approach to Cardiovascular Risk in AF Patients

Management of AF patients at risk or with previous MI is becoming a hot topic, because of the complexity of antithrombotic treatment in this setting. MI may precede AF, and about one quarter of the AF population has a history of MI; thus, MI is considered a risk factor for AF.[69] This likely explains the reason for the frequent association of oral anticoagulants with aspirin in the AF population, as evidenced by the recent trials with NOACs in which 29% to 41% of patients included have been treated with such a combination. Alternatively, the addition of aspirin to oral anticoagulants may depend on the physician's perception of a high risk of vascular disease. However, this combination therapy is associated with a significant increase of bleeding, while the clinical benefit is dubious.[20] The use of aspirin in combination with oral anticoagulants in patients with or without a history of MI is a critical issue that should be addressed. Previous studies consistently demonstrated that warfarin alone lowers the risk of MI recurrence in patients with previous acute coronary syndromes.[70] In accordance with this hypothesis, a retrospective analysis of the SPORTIF III trial[27] showed that good-quality anticoagulation treatment had a positive impact on MACE occurrence. Also, in the warfarin arm of the RE-LY study including >6000 AF patients, a time in therapeutic range >65% was associated with lower MI risk versus patients with time in therapeutic range <65%. This finding was confirmed in a prospective observational study including 627 AF patients who were followed up for 30 months.[71] The study showed that higher time in therapeutic range (>70%) was associated with lower risk of MI, reinforcing the concept that a good quality of anticoagulation treatment is necessary not only to reduce stroke but also MI. A matter of concern is, however, that the rate of MACE was still elevated with a rate >2%/year, suggesting that oral anticoagulants alone are not enough to lower the risk of MI in AF. In this context, it may be of potential interest to see whether, differently from warfarin, a combination of aspirin with NOACS could be clinically effective. The association between rivaroxaban and aspirin has been tested for patients with recent acute coronary syndrome in the ATLAS ACS 2–TIMI 51 study[72]; 15 526 patients were randomly assigned to twice-daily administration of either 2.5 or 5.0 mg of rivaroxaban or placebo, in addition to standard medical therapy including low dose of aspirin. Rivaroxaban, at both dosages, significantly reduced the rate of death from cardiovascular causes, MI, or stroke, as compared with placebo, but increased major bleeding with the twice-daily 5-mg dose. Furthermore, in the ENGAGE AF-TIMI 48 study,[35] about 30% of patients were treated with aspirin in association with VKAs, edoxaban 60 mg, or edoxaban 30 mg; a positive effect of low-dose edoxaban in association with aspirin in reducing the rate of cardiovascular events was observed.

Due to the complexity of treating AF patients with MI, much effort should be made to come up with cost-effective prevention strategies. Scores identifying AF patients at higher risk, such as the 2MACE score, should be further validated, as a score ≥3 seems to be particularly useful in identifying AF patients at risk of cardiac events.[68] In this context, it would be interesting to investigate whether AF patients with 2MACE ≥3 would benefit from the combination of old or new anticoagulants with aspirin. Another treatment option may be represented by statins, as they have been shown to reduce the risk of MI in primary and secondary prevention trials.[73] Furthermore, statins possess antithrombotic activity including antiplatelet and anticoagulant properties, which may be useful in AF patients, who are characterized by a systemic and local ongoing prothrombotic state. Preliminary data from an observational study demonstrated that statins reduce cardiovascular death in AF patients.[74] In the meantime, correction of atherosclerotic risk factors with a pharmacological approach, or a dietary intervention, could be a reasonable strategy to reduce the atherosclerotic complications. AF patients, for instance, could be advised to adhere to Mediterranean diet, which is known to possess antioxidant property, does not interfere with time in therapeutic range in warfarin-treated patients,[75] and is associated with lower risk of MI and stroke.[76]

Based on these considerations, a holistic approach including management of thromboembolism and MI is proposed (Figure 3). Thus, in addition to the CHA_2DS_2-VASc and HAS-BLED scores to stratify stroke and bleeding risk, respectively, inclusion of a score for MACE risk should be taken into account. This approach could prove useful not only to assess the stroke and bleeding risks, but also to assess the MACE risk, and to drive therapeutic choices. For instance, future clinical trials are needed to examine the usefulness of addition of aspirin or statins to oral anticoagulants in reducing the risk of both MI and stroke in AF patients.

Limitation

A limitation of this systematic review may be represented by the different definitions used to diagnose MI, as these changed over time, and may be responsible for some of the differences in the annual rate of MI observed among studies. In particular, since the first universal definition of MI,[77] which indicated cardiac troponin over creatine kinase as a more specific diagnostic biomarker for MI, the inclusion of electrocardiographic changes other than ST-segment modifications

or Q waves (ie, new-onset left bundle branch block), and availability of new cardiac imaging techniques have improved the diagnosis of MI.[78]

Conclusions

In conclusion, MI and AF are closely related; MI may precede or complicate the clinical course of AF. The presence of MI in AF patients creates a challenge in clinical management, because of the complexity of using anticoagulants and antiplatelet drugs, with the ensuing high risk of bleeding. Reducing the risk of MI in AF should be an objective for future studies.

Disclosures

None.

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