CHEST

# Incidence of Myocardial Infarction and Vascular Death in Elderly Patients With Atrial Fibrillation Taking Anticoagulants

## Relation to Atherosclerotic Risk Factors

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**BACKGROUND:** Recent findings suggest that patients with atrial fibrillation (AF), in addition being at thromboembolic risk, are at risk of myocardial infarction (MI). Our aim was to investigate predictors of MI and cardiovascular death in a cohort of patients with AF who were taking anticoagulants.

**METHODS:** We prospectively followed up 1,019 patients with AF for a median of 33.7 months (3,223 person-years). All patients were treated with oral vitamin K antagonists. Primary outcome was a composite end point of cardiovascular events (CVEs) including fatal/nonfatal MI, cardiac revascularization, and cardiovascular death.

**RESULTS:** The mean age of the patients was 73.2 years, and 43.8% were women. At follow-up, 111 CVEs (3.43%/y) had occurred: 47 fatal-nonfatal MI/revascularization and 64 cardiovascular deaths. In addition, 31 stroke/transient ischemic attacks (0.96%/y) were recorded. Patients experiencing CVEs were older ($P < .001$) and had a higher prevalence of metabolic syndrome (MetS) ($P = .005$), heart failure ($P = .001$), and prior cardiac ($P < .001$) and cerebrovascular events ($P < .001$). On a Cox proportional hazard analysis, age (hazard ratio [HR], 1.083; 95% CI, 1.053-1.113; $P < .001$), smoking (HR, 2.158; 95% CI, 1.193-3.901; $P = .011$), history of cerebrovascular (HR, 1.704; 95% CI, 1.119-2.597; $P = .013$) and cardiac (HR, 1.658; 95% CI, 1.105-2.489; $P = .015$) events, MetS (HR, 1.663; 95% CI, 1.107-2.499; $P = .014$), heart failure (HR, 1.584; 95% CI, 1.021-2.456; $P = .040$), and male sex (HR, 1.499; 95% CI, 1.010-2.223; $P = .044$) predicted CVEs.

**CONCLUSIONS:** Patients with AF still experience a high rate of CVEs despite receiving anticoagulant treatment. MetS is a common clinical feature in patients with AF, which increases the risk of CVEs. A holistic approach is needed to reduce the cardiovascular risk in patients with AF.

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**ABBREVIATIONS:** AF = atrial fibrillation; CVE = cardiovascular event; HF = heart failure; HR = hazard ratio; MetS = metabolic syndrome; MI = myocardial infarction; NOAC = non-vitamin K antagonist oral anticoagulant; TIA = transient ischemic attack; VKA = vitamin K antagonist

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Atrial fibrillation (AF) is the most common cause of cardiac arrhythmia and is known to be associated with a high risk of thromboembolic stroke.[1] Current evidence also suggests that patients with AF are at higher risk of experiencing myocardial infarction (MI),[2,3] with a rate ranging from 0.5% to 4%/y.[2] The relationship between AF and MI has been investigated recently in a cohort of approximately 1,600 patients with AF in whom the age-adjusted incidence rate of MI was 1.2 per 100 person-years,[3] which was significantly higher than in patients without AF. However, the real impact of cardiovascular events (CVEs) in AF cannot be fully deduced by the study by Soliman et al[3] because < 50% of the AF population were taking an anticoagulant (warfarin). Furthermore, the relatively young population (66 years of age on average) suggests that the incidence of MI could be even higher among the elderly AF population.

Common atherosclerotic risk factors are observed in the majority of elderly patients with AF, the most frequent being represented by arterial hypertension, diabetes, and dyslipidemia.[4] Thus, patients with AF show early signs of atherosclerosis, which has been detected in > 20% of elderly patients with AF, as assessed by an altered ankle/brachial index.[5] Some of these factors, which are used to identify patients at high risk of stroke, are also associated with incident MI.

Until now, the impact of MI in elderly patients with AF receiving oral anticoagulation treatment has been unknown. Based on this, we prospectively investigated the rate of MI and cardiovascular death in the elderly AF population established on oral anticoagulation treatment. Furthermore, we assessed whether the classic risk factors of atherosclerosis are associated with MI, including the metabolic syndrome (MetS), whose prevalence in the white AF population is still poorly defined.

## Materials and Methods

### *Study Design and Patient Selection*

This prospective single-center study included 1,105 patients with nonvalvular AF who were referred to our center at the Department of Internal Medicine and Medical Specialties of Sapienza University of Rome for monitoring and management of antithrombotic therapies. All patients were treated with vitamin K antagonists (VKAs) (warfarin/acenocumarol) after appropriate thrombotic risk stratification, initially according to $CHADS_2$ (congestive heart failure, hypertension, age ≥ 75 years, diabetes, prior stroke or transient ischemic attack [doubled]) score,[6] and afterward according to the $CHA_2DS_2$-VASc (congestive heart failure, hypertension, age ≥ 75 years [doubled], diabetes, stroke [doubled], vascular disease, age 65 to 74 years, sex category [female]) score,[7] when the new score was recommended by international guidelines. International normalized ratio values were maintained in an intended range of between 2.0 and 3.0, and the time in therapeutic range was calculated to assess the quality of anticoagulation.[8] Exclusion criteria were prosthetic heart valves or the presence of any severe valvulopathies, severe cognitive impairment, chronic infections (HIV infection, hepatitis C virus, hepatitis B virus), or systemic autoimmune diseases. Subjects were also excluded from the study if they had active cancer or liver insufficiency (eg, cirrhosis).

Based on these criteria, 86 patients (7.5%) were excluded, and 1,019 patients with AF were included in the prospective study cohort. Forty-seven patients (4.6%) were lost to follow-up (13 cancer, one hepatic cirrhosis, one fatal hemorrhage, one mitral valvuloplasty, and 31 noncardiovascular death). At baseline, each patient provided written informed consent and the patient's medical history was recorded. Anthropometric data were collected, as well as data regarding concomitant diseases and drug therapies. At baseline, ECG and transthoracic echocardiography were performed. Cardiovascular risk factors were defined as follows. Arterial hypertension: repeated elevated BP (≥ 140/≥ 90 mm Hg) or taking antihypertensive drugs[9]; diabetes: a casual plasma glucose ≥ 200 mg/dL (11.1 mmol/L), or fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L), or 2-h plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test or taking antidiabetic drugs[10]; and heart failure (HF): presence of signs and symptoms typical of HF or reduced ejection fraction (≤ 40%).[11]

MetS was defined according to modified Adult Treatment Panel III criteria: elevated waist circumference (men, > 102 cm [> 40 in]; women, > 88 cm [> 35 in]); elevated triglycerides ≥ 150 mg/dL (1.7 mmol/L) or receiving drug treatment of elevated triglycerides; reduced high-density lipoprotein cholesterol (men, < 40 mg/dL [1.03 mmol/L]; women, < 50 mg/dL [1.3 mmol/L]) or receiving drug treatment of reduced high-density lipoprotein cholesterol; elevated BP ≥ 130 (≥ 85 mm Hg); and elevated fasting glucose ≥ 100 mg/dL or receiving drug treatment of elevated glucose.[12]

### *Outcome Events*

The primary outcome of the study was a combined end point of CVEs, including fatal/nonfatal MI, cardiac revascularization (stent or coronary artery bypass surgery), and cardiovascular death. A diagnosis of MI was made according to the definition proposed by the Joint European Society of Cardiology, American College of Cardiology Foundation, American Heart Association, and the World Heart Federation Task Force.[13] If a patient died within 4 weeks of MI, this event was recorded as fatal MI.

Death was classified as vascular unless the central adjudication committee (see later discussion) confirmed an unequivocal noncardiovascular cause of death. Cardiovascular death included sudden death; progressive congestive HF; procedure-related death (surgical or percutaneous revascularization); and presumed cardiovascular deaths (ie, those for which a noncardiovascular cause had not been clearly established). Only the first event that occurred during follow-up was used in the analysis. In addition, the occurrence of any ischemic stroke or transient ischemic attack (TIA) was recorded. Ischemic stroke was determined on clinical manifestations and confirmed by radiologic findings. TIA was defined according to the *Classification of Cerebrovascular Diseases III*.[14]

### *Validation of End Points*

Data on CVEs were collected prospectively during follow-up. When a CVE occurred, a standardized form was filled in by the investigators.

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