Intern Emerg Med (2010) 5:91–94
DOI 10.1007/s11739-010-0352-2

IM - EDITORIAL

The risk of myocardial infarction in patients with atrial fibrillation: an unresolved issue

Licia Polimeni · Ludovica Perri · Mirella Saliola · Stefania Basili · Francesco Violi

Received: 11 January 2010 / Accepted: 20 January 2010 / Published online: 3 March 2010

Atrial fibrillation (AF) is the most common sustained dysrhythmia encountered in clinical practice in North America and Europe, accounting for approximately one-third of all hospitalizations for a cardiac rhythm abnormality [1]. The presence of AF markedly increases the patient's risk for developing arterial embolism and stroke, depending on the presence of other clinical conditions, such as hypertension and diabetes [2]. AF is associated with a fivefold increased risk for stroke, and is estimated to cause 15% of all strokes. The rate of ischemic stroke among patients with non-valvular AF averages 5% per year, 2–7 times that of people without AF. Additionally, when transient ischemic attacks (TIAs) and clinically "silent" strokes are considered, the rate of brain ischemia accompanying non-valvular AF exceeds 7% per year. Patients with AF frequently have several risk factors for atherosclerosis, including hypertension, diabetes, and dyslipidemia [3, 4]. Accordingly, systemic signs of atherosclerosis can be detected in AF patients, and these likely account for an enhanced risk of coronary heart disease (CHD).

In addition to cerebrovascular disease, patients with AF may suffer from coronary events including myocardial infarction (MI), but the rate of MI in AF patients seems to be variable, but often underestimated. Surprisingly few studies with antithrombotic drug therapy include MI as an end-point.

We reasoned that analysis of the MI rate in AF could be useful for future interventional trials with anti-thrombotic drugs. Thus, we evaluated the rate of MI in the clinical trials where this clinical end-point was taken into account, and tried to relate it with the common atherosclerotic risk factors.

Searches were conducted in computerized publication database (Medline) with hand searches of publications from January 1995 to September 2008. Bibliographies of all selected articles and review articles were reviewed for other relevant articles.

We used search terms including "atrial fibrillation" and "cardiovascular risk", "atrial fibrillation" and "myocardial infarction", "atrial fibrillation" and "coronary heart disease", "atrial fibrillation" and "mortality", "atrial fibrillation" and "cardiovascular events". The search was confined to human studies and English language restricted.

We obtained 278 articles**.** A trial was included if the overall study population included AF patients, it was published in a peer-reviewed journal, and major adverse coronary events (MACE) were recorded through the follow-up. A trial was excluded from our analysis if the AF population was lower than 150 subjects. Thus, 13 studies were selected according to the above-mentioned inclusion and exclusion criteria [5–17] (Table 1). In only two of these, MACE were included as primary end-points [5, 6] (Table 1A).

In the first study, a very high incidence of new MACE was found in AF patients (74% during a mean follow-up of 30 months) compared with patients with a sinus rhythm (42%) or a supraventricular tachycardia (43%) [5]. These patients had a mean age of 81 years, and a clinical history complicated by CHD in >50% of cases. After controlling

L. Polimeni and L. Perri equally contributed to the study.

L. Polimeni · L. Perri · M. Saliola · S. Basili · F. Violi
Divisione di I Clinica Medica, University of Rome "La Sapienza" , Rome, Italy

F. Violi (✉)
Prima Clinica Medica, Viale del Policlinico 155, Rome 00161, Italy
e-mail: francesco.violi@uniroma1.it

Table 1 Studies characteristics

Ref. #	*N*	Population	FU (years)	Age	Diabetes (%)	AH (%)	Dysl (%)	History of stroke (%)	History of CHD (%)	Smoke (%)	Stroke (%/year)	MI (%/year)	CV mortality (%/year)
(a)													
Aronow et al. [5]	184	Patients with HD and AF, PSVT or SR	2.5	83 ± 7	–	–	–	–	54	–	–	28.4	–
Miyasaka et al. [6]	2,768	Adult with first documented AF and without prior CHD	6	71	12.8	73.6	29.7	4.44	0	52	–	2.8	–
(b)													
Krahn et al. [7]	299	AF patients	4.5	66 ± 9	11.7	53	–	CerVD: 8.7	36.4	74.2	2.4	1.4	5.7
Kaarisalo et al. [8]	642	Patients with first ischemic stroke	1	67.4 ± 6.3	22.7	48	–	100	19.6	–	45.5	28.6	29.9
Wachtell et al. [9]	342	Patients with AH and LVH + AF or history of AF	1.4	70.3 ± 6.4	24.3	100	–	CerVD: 7.7	25.7	14.3	11.7	4	12
Miyasaka et al. [10]	4,618	Adult with first documented AF	5.3	73 ± 14	18	80	37	9.5	21	56	1.88	4.15	–
Hohnloser et al. [11]	4,628	AF patients with additional risk factors for death	1.75	71.6 ± 9	–	85.8	–	–	31.7	–	0.6	0.4	2.2
Haywood et al. [12]	423	AF patients with AH and at least 1 additional CVD risk factor	6	≥55	31.2	100	27.9[a]	–	35.9	14.2	3.3	2.8	–
Morocutti et al. [13]	916	AF patients with a recent ischemic stroke	1	72.2 ± 8.1	15.4	54.6	18.9	48.7	7.9	20.5	2.8	3.3	6.4
Olsson et al. [14]	3,410	AF patients with 1 or more stroke risk factors	1.4	70 ± 9	–	72	–	24	–	–	1.9	0.5	–
Executive Steering Committee for the SPORTIF V Investigators [15]	3,922	AF patients with 1 or more stroke risk factors	1.6	72 ± 9.0	–	81	–	18	–	–	1.3	1.4	–
Mant et al. [16]	973	AF patients	2.7	81.5 ± 4.2	13	54	–	12	10.5	–	3.4	1.1	–
Connolly et al. [17]	18,113	AF patients with previous stroke/TIA/EF < 40%/ HF NYHA II/ >75 year/65-74 year and DM or AH or CHD	2.0	71.6 ± 8.6	23.4	78.9	–	19.8	16.1	–	1.57	0.53	2.69

FU follow-up, *HD* Heart Disease, *PSVT* Parossistic Sopraventricular Tachycardia, *SR* Sinus Rhythm, *MI* Myocardial Infarction, *Dysl* Dyslipidemia, *AH* Arterial Hypertension, *CerVD* Cerebrovascular Disease, *LVH* Left Ventricular Hypertrophy, *CVD* cardiovascular disease, *CHD* Coronary Heart Disease, *TIA* Transient Ischemic Attack, *EF* Ejection Fraction, *HF* Heart Failure, *DM* Diabetes Mellitus

[a] Defined as HDL <35 mg/dl

for other prognostic variables, patients with AF and CHD showed 2.2 times higher probability of developing new coronary events than other patients with CHD and no AF. The second study was performed on AF patients with no clinical history of CHD [6]. Of the 2,768 patients included, 17% had a first MACE during a mean follow-up of 6 years on average. The unadjusted incidence was 3.1% person-years. In these patients of advancing age, male gender, higher systolic blood pressure, history of systemic hypertension, diabetes mellitus and PAD were significant independent predictors of a first MACE.

Among the remaining 11 studies [7–17], in which MACE had been recorded during the follow-up, we observed a high variability (Table 1B). In fact, the rate of fatal and non-fatal MI ranged from 0.5 to 4%/year.

We analyzed if there were a clinical history of CHD that could account for such variability. A cut-off of 19% (median) of a positive history for previous CHD was used to analyze the data. This value is in agreement with the prevalence of CHD reported in the general population. In fact, the NHANES III study [18], conducted on American adults, reports an incidence of CHD of 18.7% in subjects aged 65 years or older. In the six studies in which more than 19% of patients had previous CHD, the average incidence of MI was 6.9% [7–12]. In contrast, in the remaining 5 studies in which a clinical history of CHD was detected in <19% of cases, MI occurred significantly less frequently(1.4%; *Test for difference between two proportions*: $P < 0.0001$) [13–17].

Atherosclerotic risk factors may be another important variable explaining the large variability of MI, but, as shown by the Table, data analysis is difficult because of incomplete report of risk factors prevalence. However, from the data of the two trials with adequate analysis of risk factors [9, 14], a relation seems to exist because MI occurs more frequently in groups of patients with a higher prevalence of risk factors such as diabetes and hypertension.

There are also anatomic and clinical studies suggesting a true link between AF and the risk of CHD. In a recent study, a correlation between coronary artery calcification, a marker of coronary atherosclerosis and MACE, and enlarged left atrium (LA), left atrial appendage (LAA) and pulmonary veins (PVs) was observed [19]. The coexistence of systemic atherosclerosis is documented by anatomical changes typical of atherosclerotic damage in the vascular tree. Thus, complex aortic plaque identified by transoesophageal echocardiography (TEE) is common and occurs in up to 57% of patients with AF, of whom about 25% have complex plaque (i.e., thicker than 4 mm and with ulceration, pedunculation, or mobile elements) [20]. The presence of complex plaque on the descending aorta is a risk factor for stroke [21]. Aortic plaque aids identification of patients who are at high stroke risk by virtue of the presence of associated vascular risk factors or atherothrombotic disease, in addition to AF. Coexistence of peripheral arterial disease (PAD) is a relevant clinical sign of systemic atherosclerosis. Thus, two large studies in patients with AF document the existence of PAD in about 3–5% of patients [22, 23]. It is possible, however, that such an incidence has been underestimated as only symptomatic patients were considered as affected by PAD. As PAD is an important marker of systemic atherosclerosis, its association with AF reinforces the concept that patients with AF have systemic atherosclerosis that potentially account for coronary complications.

AF is also associated with biomarkers that are typically observed in patients with atherosclerotic disease [24–27]. In particular, we recently reported that sCD40L, a marker of platelet activation, is elevated in AF patients, and predicts the recurrence of both stroke and MI [28]. These findings are likely to account for the small but significant reduction of vascular events with aspirin in this setting [29].

Based on these considerations, we believe that MI may have an important impact in the clinical progression of AF depending on the type of AF patients. The clinical history of CHD may be a simple approach to identify patients at high risk, but an analysis of other laboratory and clinical variables including the coexistence of PAD, could provide more information to stratify the atherosclerotic risk. This may help to explain the large variability of MI rate so far reported in an AF population, and to better evaluate the atherothrombotic risk in this clinical setting. In the era of new antithrombotic agents, exclusion or poor consideration of MI in the end-points of AF trials cannot fully reveal information from the clinical history of AF.

Conflict of interest None.

References

1. Fuster V, Rydén LE, Cannom DS et al (2006) 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 27:1979–2030
2. Singer DE, Albers GW, Dalen JE et al (2004) Antithrombotic therapy in atrial fibrillation: the Seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 126(suppl):429S–456S
3. Benjamin EJ, Levy D, Vaziri SM et al (1994) Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA 271:840–844

4. Vizzardi E, Nodari S, Zanini G et al (2009) High sensitivity C-reactive protein: a predictor for recurrence of atrial fibrillation after successful cardioversion. Intern Emerg Med 4:309–313
5. Aronow WS, Ahn C, Mercando AD et al (1995) Correlation of atrial fibrillation, paroxysmal supraventricular tachycardia, and sinus rhythm with incidences of new coronary events in 1,359 patients, mean age 81 years, with heart disease. Am J Cardiol 75:182–184
6. Miyasaka Y, Barnes ME et al (2007) Coronary ischemic events after first atrial fibrillation: risk and survival. Am J Med 120:357–363
7. Krahn AD, Manfreda J, Tate RB et al (1995) The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med 98:476–484
8. Kaarisalo MM, Immonen-Räihä P et al (1997) Atrial fibrillation and stroke. Mortality and causes of death after the first acute ischemic stroke. Stroke 28:311–315
9. Wachtell K, Hornestam B, Lehto M et al (2005) Cardiovascular morbidity and mortality in hypertensive patients with a history of atrial fibrillation: The Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. J Am Coll Cardiol 45:705–711
10. Miyasaka Y, Barnes ME et al (2007) Mortality trends in patients diagnosed with first atrial fibrillation: a 21-year community-based study. J Am Coll Cardiol 49:986–992
11. Hohnloser SH, Crijns HJ, van Eickels M et al (2009) ATHENA Investigators. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med 360:668–678
12. Haywood LJ, Ford CE, Crow RS et al (2009) Atrial fibrillation at baseline and during follow-up in ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial). J Am Coll Cardiol 54:2023–2031
13. Morocutti C, Amabile G, Fattapposta F et al (1997) Indobufen versus warfarin in the secondary prevention of major vascular events in nonrheumatic atrial fibrillation. SIFA (Studio Italiano Fibrillazione Atriale) Investigators. Stroke 28:1015–1021
14. Olsson SB, Executive Steering Committee of the SPORTIF III Investigators (2003) 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 362:1691–1698
15. Executive Steering Committee for the SPORTIF V Investigators (2005) Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. JAMA 293:690–698
16. Mant J, Hobbs FD, Fletcher K et al (2007) BAFTA investigators; Midland Research Practices Network (MidReC). Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet 370:493–503
17. Connolly SJ, Ezekowitz MD et al (2009) Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 361:1139–1151
18. Ford ES, Giles WH et al (2000) Prevalence of nonfatal coronary heart disease among American adults. Am Heart J 139:371–377
19. Pan NH, Tsao HM, Chang NC et al (2009) Dilated left atrium and pulmonary veins in patients with calcified coronary artery: a potential contributor to the genesis of atrial fibrillation. J Cardiovasc Electrophysiol 20:153–158
20. Blackshear JL, Pearce LA, Hart RG et al (1999) Aortic plaque in atrial fibrillation: prevalence, predictors, and thromboembolic implications. Stroke 30:834–840
21. Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography (1998) Transesophageal echocardiographic correlates of thromboembolism in high-risk patients with nonvalvular atrial fibrillation. Ann Intern Med 128:639–647
22. Investigators I-GISSI-AF, Disertori M, Latini R, Barlera S et al (2009) Valsartan for prevention of recurrent atrial fibrillation. N Engl J Med 360:1606–1617
23. Marini C, De Santis F, Sacco S et al (2005) Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. Stroke 36:1115–1119
24. Akar JG, Jeske W, Wilber DJ (2008) Acute onset human atrial fibrillation is associated with local cardiac platelet activation and endothelial dysfunction. J Am Coll Cardiol 51:1790–1793
25. Li-Saw-Hee FL, Blann AD, Gurney D et al (2001) Plasma von Willebrand factor, fibrinogen and soluble P-selectin levels in paroxysmal, persistent and permanent atrial fibrillation. Effects of cardioversion and return of left atrial function. Eur Heart J 22:1741–1747
26. Sohara H, Amitani S, Kurose M et al (1997) Atrial fibrillation activates platelets and coagulation in a time-dependent manner: a study in patients with paroxysmal atrial fibrillation. J Am Coll Cardiol 29:106–112
27. Choudhury A, Chung I, Blann AD et al (2007) Elevated platelet microparticle levels in nonvalvular atrial fibrillation: relationship to p-selectin and antithrombotic therapy. Chest 131:809–815
28. Ferro D, Loffredo L, Polimeni L et al (2007) Soluble CD40 ligand predicts ischemic stroke and myocardial infarction in patients with nonvalvular atrial fibrillation. Arterioscler Thromb Vasc Biol 27:2763–2768
29. Hart RG, Benavente O, McBride R et al (1999) Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med 131:492–501