

UNDERGRADUATE ARTICLE

The Burden of Atrial Fibrillation in Unselected Acute Medical Admissions

AC Cameron¹, SMM Jenkins², FG Dunn²

¹University of Glasgow Medical School, Wolfson Medical School Building, University Avenue, Glasgow, G12 8QQ

²Department of Cardiology, Stobhill Hospital, Balornock Road, Glasgow, G21 3UW

Correspondence to

Alan C Cameron

Intercalated Third Year Medical Student, Faculty of Medicine, Wolfson Medical School Building, University Avenue, Glasgow G12 8QQ UK

Tel: + 44 0141 330 5921 e.mail: alan.c.cameron@hotmail.com

Abstract

Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is of increasing prevalence. The presence of AF complicates the management of patients presenting as medical emergencies.

Objective

To assess the prevalence of AF and current investigation and management strategies in unselected acute medical admissions.

Design

Prospective survey of all acute medical admissions over 22 days.

Setting

Stobhill Hospital – district general hospital in north Glasgow.

Subjects

Consecutive acute medical admissions.

Results

Of the 507 patients, 47 (9.3%) had AF. AF was a new diagnosis in five patients (11.0%). The most common presenting features were dyspnoea and chest pain. The principal underlying medical conditions were hypertension and ischaemic heart disease. AF was the primary reason for admission in six patients (12.8%) and a documented reason for admission in 11 patients (23.4%). Thyroid function tests were or had previously been performed in 45 patients (95.7%). Twenty-four patients (51.1%) underwent echocardiography or had done so previously. Twenty-two patients (46.8%) received anticoagulation with warfarin. Ten patients (21.3%) should have received warfarin by standard guidelines but did not. No patient received warfarin inappropriately. Rate control was used in 40 patients (85.1%). Rhythm control was attempted in four patients (8.5%).

Conclusion

AF is common amongst emergency admissions to district general hospitals and has significant resource implications. Improvements are needed both in the use of echocardiography and in the administration of anticoagulant therapy.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is of increasing prevalence.¹ It affects 2% of the general population.² Prevalence and incidence of AF increase with age, affecting around 5% of those aged over 65 years and around 10% of those aged over 80 years.³ AF accounts for 0.97% of NHS expenditure in the United Kingdom.⁴ AF is a significant risk factor for stroke, thromboembolism, heart failure and impaired quality of life.⁵ Strokes associated with AF tend to be more severe and cause greater mortality, greater disability, greater duration of hospital stay and reduced discharge to the patient's own home.^{3,5,6} With an increasingly ageing population, AF (and its significant complications) will become an increasing burden on health care resources.³

AF is classified according to its clinical subtype: "paroxysmal AF" (terminates spontaneously within seven days), "persistent AF" (does not self-terminate); and "permanent AF" (established AF that has not terminated, has terminated but recurred, or for which cardioversion has not been attempted).^{1,2,5}

The presence of AF complicates the management of patients presenting as medical emergencies. It must be ascertained whether AF is the principal cause of admission, or an associated feature, which also requires to be addressed. Rate control therapy may have to be adjusted or in some situations discontinued, depending on the patient's clinical status. Furthermore, decisions regarding additional anticoagulant therapy and thrombolytic treatment must take into consideration the patient's existing anticoagulant status.

Opinions on the optimal management of atrial fibrillation have previously varied considerably, both with regards to the most appropriate form of thromboprophylaxis and whether to adopt a rate or rhythm control strategy.^{7,8,9} However, recently published guidelines by the American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC)¹ and the National Institute for Health and Clinical Excellence (NICE)⁵ have assisted in moving towards a consensus position. We report an audit relating to the prevalence, aetiology, investigation and management of AF in consecutive patients admitted as emergencies to a district general hospital, for a 22 day period between 24 May 2007 and 14 June 2007.

Methods

The hospital is a 440 bed district general hospital in north Glasgow. All consultants participating in acute medical receiving were informed that an audit would take place.

Thereafter, information was collected from patients' medical records and no further discussions were held with the physicians involved.

Patients from the acute medical receiving unit and coronary care unit were studied. All patients admitted to these units undergo electrocardiography and this was the case in our patient population. Patients were prospectively included in the study if found to be in established AF on admission electrocardiogram or if they had a history of AF documented in their medical records.

The classification of AF, mode of presentation, past medical history, investigations carried out, treatment before and after admission, duration of hospital stay and inpatient mortality were all noted. Data were stored in a Microsoft Access 2003 database. Investigation and treatment were assessed against key indicators from published clinical guidelines.^{1,5} Key aspects of investigation assessed included the use of electrocardiography, transthoracic echocardiography (TTE) and blood tests of thyroid, renal and hepatic function.^{1,5} Electrocardiography confirms the diagnosis of AF.¹ TTE identifies associated valvular heart disease and assesses left ventricular systolic function.¹ These parameters may influence treatment strategies. Assessment of thyroid, renal and hepatic function is essential to identify any reversible underlying precipitants of AF and also as a baseline prior to the commencement of medication. Treatment was assessed on the basis of the thromboprophylaxis decision and the choice to adopt a rate control or rhythm control strategy.^{1,5} The success of rate control was assessed against a target resting heart rate of less than 90 bpm.⁵

Results

During the 22 days of the study there were 507 emergency admissions to the acute medical receiving unit and coronary care unit. Forty-seven patients (9.3%) had AF: 19 (40.4%) male and 28 (59.6%) female. The mean (SD, range) age was 75.5 (9.7, 57-97) years. AF was a new diagnosis in 5 patients (10.6%). Forty-two patients (89.4%) had a history of AF: 17 (40.5%) paroxysmal AF and 25 (59.5%) persistent or permanent AF. AF was the primary reason for admission in six patients (12.8%) and a documented reason for admission in 11 patients (23.4%). Table I summarises key aspects of investigation and management in the 47 patients with AF.

Table I Key Aspects of Investigation and Management in 47 Patients with AF

	New Diagnosis AF	Paroxysmal AF	Persistent or permanent AF
	Number (%) (Total n = 5)	Number (%) (Total n = 17)	Number (%) (Total n = 25)
Echocardiography performed/planned	3 (60.0)	11 (64.7)	12 (48.0)
Thyroid function tests performed	5 (100.0)	17 (100.0)	23 (92.0)
Warfarin prescribed	2 (40.0)	8 (47.1)	11 (44.0)
Rate control implemented or continued	4 (80.0)	14 (82.4)	22 (88.0)
Rhythm control attempted	1 (20.0)	3 (17.6)	0 (0.0)

Relevant Medical History

Table II details the underlying medical conditions identified. The principal conditions were hypertension (24 patients (51.1%)), ischaemic heart disease (21 patients (44.7%)) and cerebrovascular disease (19 patients (40.4%)).

Table II Relevant Medical History

	Number (%) (total n = 47)
Hypertension	24 (51.1)
Ischaemic heart disease	21 (44.7)
Cerebrovascular disease	19 (40.4)
Heart failure or left ventricular systolic dysfunction	16 (34.0)
Diabetes mellitus	14 (29.8)
Chronic obstructive pulmonary disease	9 (19.1)
Previous myocardial infarction	8 (17.0)
Thyroid disease	8 (17.0)
Rheumatic heart disease	4 (8.5)

Presenting Features on Admission

Table III details the most common presenting features. The principal features were dyspnoea (21 patients (44.7%)), chest pain (15 patients (31.9%)) and sepsis (11 patients (23.4%)). The most common presenting features in the six patients in whom AF was the primary reason for admission were dyspnoea (four patients (66.7%)) and palpitations (three patients (50.0%)). Two of the patients presenting with dyspnoea also had palpitations.

Table III Presenting Features on Admission

	Number (%) (total n = 47)
Dyspnoea	21 (44.7)
Chest pain	15 (31.9)
Sepsis	11 (23.4)
Palpitations	5 (10.6)
Syncope	4 (8.5)
Cerebrovascular event	3 (6.4)
Dizziness	3 (6.4)
Asymptomatic	1 (2.1)

Investigations

All patients had an electrocardiogram, full blood count, liver function tests and measurement of urea and electrolytes on admission. Thyroid function tests were or had previously been performed in 45 patients (95.7%) and were performed in all of the patients in whom AF was a new diagnosis. C-reactive protein (CRP) was measured in 45 patients (95.7%) and chest radiography was performed in 42 patients (89.4%). Troponin-I was measured in 26 patients (55.3%). Twenty-four patients (51.1%) underwent transthoracic echocardiography (TTE) or had done so previously. Two (4.0%) of the patients in whom AF was a new diagnosis underwent TTE and this was planned in one patient (20.0%).

The principal findings identified on chest radiography were cardiomegaly (14 patients (33.3%)), pulmonary congestion (six

patients (14.3%)) and consolidation (five patients (11.9%)). Carcinoma was present in one patient (2.4%).

The findings identified on TTE are detailed in table IV. Principal findings were mitral regurgitation (10 patients (41.7%)) and left ventricular hypertrophy (10 patients (41.7%)).

Troponin-I was negative in 19 patients (73.1%). In seven patients (26.9%), troponin-I was positive: mean (SD, range) value 2.3 (4.7, 0.09-12.80) ng/mL.

CRP was negative in 16 patients (35.6%). In 29 patients (64.4%), CRP was positive: mean (SD, range) value 58.7 (86.9, 6-334) mg/L.

Table IV Transthoracic Echocardiogram Findings

	Number (%) (total n = 24)
Mitral regurgitation	10 (41.7)
Left ventricular hypertrophy	10 (41.7)
Aortic regurgitation	6 (25.0)
Normal echocardiogram	5 (20.8)
Tricuspid regurgitation	4 (16.7)
Left ventricular systolic dysfunction	3 (12.5)
Aortic stenosis	1 (4.2)

Diagnoses

Table V details the main diagnoses recorded. The principal diagnoses were acute coronary syndrome (11 patients (23.4%)) and infection (nine patients (19.1%)). In three patients (6.4%), the diagnosis was gastrointestinal (GI) bleeding. Two of these three patients (66.7%) were taking warfarin prior to admission and one patient (33.3%) had alcohol-related liver disease but was not taking warfarin. AF was the main diagnosis in four (80.0%) of the five patients presenting with new AF.

Table V Principal Admission Diagnosis

	Number (%) (total n = 47)
Acute coronary syndrome	11 (23.4)
Infection	9 (19.1)
Atrial fibrillation	6 (12.8)
Unspecified/other	6 (12.8)
Cardiac failure	3 (6.4)
Cerebrovascular event	3 (6.4)
Gastrointestinal bleed	3 (6.4)
Asthma/chronic obstructive pulmonary disease	2 (4.3)
Renal failure	2 (4.3)
Uncontrolled INR	2 (4.3)

Treatment

Of the 42 patients with a history of AF, 12 patients (28.6%) received aspirin 75mg alone and four patients (9.5%) received clopidogrel 75mg alone. Two patients (4.8%) received both aspirin 75mg and clopidogrel 75mg. Thirteen patients (31.0%) received warfarin alone, whilst six patients (14.3%) received both antiplatelet and anticoagulant therapy. Five patients (11.9%) were not on an antiplatelet agent or warfarin.

Of the five patients with a new diagnosis of AF, two patients (40.0%) were commenced on warfarin alone whilst one patient (20.0%) was commenced on warfarin in addition to antiplatelet therapy. Two patients (40.0%) were not given an antiplatelet agent or warfarin. In one of these patients, AF was likely secondary to pneumonia and resolved prior to discharge. The other patient was anaemic on admission (haemoglobin 8g/dL) and endoscopy showed gastritis. This patient's haemoglobin later increased to 11.5g/dL but no antiplatelet agent or warfarin was prescribed.

The thromboprophylaxis decision accorded with NICE guidelines in 30 patients (63.8%) and did not in 17 patients (36.2%).⁵ Had the guidelines been followed, 10 of these 17 patients (58.8%) should have received warfarin. A reason for warfarin not being prescribed was recorded in four patients (40.0% of 10). Three patients did not receive warfarin because of a GI bleed. One patient declined warfarin, despite it being advised. No patient received warfarin inappropriately.

Rate control was implemented or already in operation in 40 patients (85.1%). Twelve patients (30.0%) received digoxin, 10 patients (25.0%) received a beta-blocker and six patients (15.0%) received a rate-limiting calcium channel blocker. Dual therapy with digoxin and a beta-blocker or rate-limiting calcium channel blocker was used in 12 patients (30.0%). Excluding nine patients with sepsis, rate control (based on admission electrocardiogram heart rate) was successful (rate < 90 beats/minute)⁵ in 22 (71.0%) of the 31 patients. Six (27.2%) of these 22 patients received digoxin, four (18.2%) received a beta-blocker, three (13.6%) received a rate-limiting calcium channel blocker and nine (40.1%) received dual therapy with digoxin and a beta-blocker or rate-limiting calcium channel blocker. The reason for choosing rate control was not documented in any patient.

Rhythm control was attempted in four patients (8.5%). In three patients (75.0%), pharmacological cardioversion was attempted with intravenous amiodarone. One patient (25.0%) was scheduled to undergo elective direct current cardioversion. Cardioversion to sinus rhythm was achieved in one (33.3%) of the three patients in whom pharmacological cardioversion was attempted. The reason for choosing rhythm control was not documented in any patient.

Five patients (10.6%) received no rate control or rhythm control. The reason for this was not documented in any patient. In these five patients, the mean (SD, range) heart rate on admission electrocardiogram was 73.6 (7.8, 66-83) beats per minute.

The decision to adopt a rate control or rhythm control strategy accorded with NICE guidelines in 41 patients (87.2%) and did not in six patients (12.8%).⁵ Five of these six patients (83.3%) received no rate or rhythm control. One patient (16.7%) received rate control when NICE guidelines recommended they receive rhythm control.

Duration of Hospital Stay and Inpatient Mortality

The mean (SD, range) inpatient stay was 10.64 (12.98, 1-74) days. There were no inpatient deaths among our patients.

Discussion

Of the 507 patients admitted as emergencies, 9.3% (47) had AF. This compares to 6.3% (170/2686) and 6.1% (25/407) in previous studies conducted in a similar setting.^{10,11} Thus, our study reaffirms AF as being a common finding amongst patients presenting as emergency admissions to district general hospitals.

Indeed, the prevalence of AF amongst such patients is increasing. The presence of AF complicates the overall management of such patients. The mean duration of hospital stay was 10.64 days, which is three times the mean duration of stay in unselected medical admissions at Stobhill Hospital.

Patients presenting with AF should undergo formal clinical assessment, including a history and clinical examination.¹ Potential precipitating factors (e.g. alcohol and infection) should be identified.^{1,10} Successful treatment of such factors often eliminates AF.¹ Routine blood tests (including full blood count, thyroid, renal and hepatic function tests) and electrocardiography should be performed.¹ Most cardiologists would consider echocardiography essential.² A chest radiograph is often useful.¹

Our study shows a satisfactory use of most of these investigations. However, there was suboptimal use of echocardiography. Twenty-four patients (51.1%) underwent TTE or had done so previously. TTE was not performed or planned in two (40.0%) of the five patients in whom AF was a new diagnosis. TTE identified mitral regurgitation in 10 patients (41.7%) and left ventricular hypertrophy in 10 patients (41.7%). Thus, TTE can yield valuable information and should be performed.

TFTs were or had previously been performed in 45 (95.7%) of the 47 patients with AF. This represents an improvement on our previous audit.¹⁰ All of the five patients in whom AF was a new diagnosis received TFTs. This is an essential investigation since hyperthyroidism can cause and may present with AF.^{10,12,13,14} Furthermore, successful treatment of hyperthyroidism can restore sinus rhythm in up to 60% of patients with hyperthyroid AF.¹⁵

The most common underlying medical conditions were hypertension, ischaemic heart disease and cerebrovascular disease. Compared to previous studies, there was a relatively high prevalence of hypertension and cerebrovascular disease amongst our patients.^{10,11} This could be attributed to increased prevalence of these conditions in the general population.^{16,17}

The most common presenting features were dyspnoea and chest pain. Palpitations were present in a relatively small proportion of our patients compared to previous studies.^{10,11} This illustrates the fact that AF can be relatively asymptomatic and requires a high index of suspicion amongst physicians in patients presenting with non-specific cardiac features. Furthermore, whilst AF was a documented reason for admission in only 11 patients (23.4%), it may have been a contributing factor towards admission in more patients. For example, chest pain and dyspnoea are both recognised clinical manifestations of AF.¹

Sepsis was a presenting feature in 11 of our patients (23.4%) and CRP was elevated in 29 patients (64.4%). Infection can precipitate AF^{1,3,10,18} and successful treatment of this may restore sinus rhythm.¹ Furthermore, attempting cardioversion and maintenance of sinus rhythm without correcting an underlying precipitant is unlikely to be successful.¹⁵

Thromboembolism prophylaxis is central to the management of AF.³ Aspirin reduces incidence of stroke in AF by 22% with no significant increase in haemorrhage.¹⁹ The reduction in risk of ischaemic stroke or systemic embolism is significantly higher with warfarin than with aspirin.^{19,20,21} Bleeding risk must be assessed prior to implementing anticoagulation.³ There is no evidence that combining anticoagulation with antiplatelet therapy reduces stroke risk or all-cause mortality compared with anticoagulation alone.^{1,22}

Furthermore, the most important predictor of bleeding in patients receiving anticoagulation in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial was concomitant aspirin use.²³ The ACC/AHA/ESC and NICE have both recently published guidelines with recommendations for aspirin and warfarin thromboprophylaxis in AF based on the presence or absence of well defined moderate or high risk factors.^{1,5}

The thromboprophylaxis decision was not in accordance with the NICE guidelines in 17 (36.2%) of our patients. Had the guidelines been adhered to, 10 patients (58.8% of 17) should have received warfarin. A reason for warfarin not being prescribed was not documented in any of these 10 patients. The physician may have felt there was a relative contraindication to warfarin. However, suboptimal documentation makes this difficult to assess. Seven (14.9%) of our patients received both antiplatelet and anticoagulant therapy, despite there being no evidence that this is more effective than anticoagulation alone in reducing stroke risk.^{1,22} These patients are at greater risk of major bleeding. Three of these seven patients (42.9%) had coronary artery disease. No patient received warfarin inappropriately. Thus, it can be concluded that there was a bias towards prescribing antiplatelet therapy rather than anticoagulant therapy.

The choice between rate control and rhythm control is a key decision in the management of AF. Rhythm control was traditionally thought to be superior because of a perceived reduction in thromboembolism risk and postulated benefits in morbidity and mortality. However, a number of randomised trials have broadly concluded that a rate control strategy is not inferior to a rhythm control strategy.^{3,23,24,25,26,27,28,29} The decision to adopt a rate control or rhythm control strategy should be based on the patient's age, symptoms, co-morbidities and preference.^{1,5}

The decision to adopt a rate control or rhythm control strategy accorded with NICE guidelines in 41 (87.2%) of our patients. Beta-blockers or rate-limiting calcium channel blockers are recommended as first line therapy for rate control.^{1,5} Digoxin is only recommended as monotherapy in patients with decompensated heart failure or a sedentary lifestyle.^{1,5} Of the 40 patients receiving rate control therapy, 12 (30.0%) received digoxin alone. Excluding nine patients with sepsis, rate control appeared more successful in patients receiving dual therapy with digoxin and a beta-blocker or rate-limiting calcium channel blocker. The success of rate control was not assessed in patients with sepsis which may affect heart rate and thus influence the accuracy of results.³⁰

The limitations in this study include the relatively short duration and therefore small study population. Documentation in the patients' notes was not always complete. An example is the suboptimal documentation of reasons for not prescribing warfarin. It is possible that there were justified reasons for not prescribing warfarin in these patients that simply were not documented.

This study illustrates that AF is a common finding in patients presenting as emergencies to a Scottish district general hospital. While there have been areas of improvement from our previous audits there remains underutilisation of both transthoracic echocardiography and oral anticoagulant therapy in this acute setting. A possible solution could be for all patients with new AF in a hospital setting to be reviewed by a cardiologist. Given the high prevalence of AF amongst medical admissions this is unlikely to be practical, especially in the district hospital setting.

Recently published clinical guidelines should help physicians appropriately investigate patients with AF and instigate treatment. It is important that these guidelines be easily accessible in all acute medical admissions areas. Outpatient cardiology follow-up is worth considering so that all the different therapeutic options may be considered.

Acknowledgements

We would like to thank the staff of Stobhill Hospital for their support and cooperation.

References

1. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text: 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. *Europace* 2006; 8: 651-745.
2. Dewar RI, Lip GYH, on behalf of the Guidelines Development Group for the NICE clinical guideline for the management of atrial fibrillation. Identification, diagnosis and assessment of atrial fibrillation. *Heart* 2007; 93: 25-28.
3. Lip GYH, Tello-Montoliu A. Management of atrial fibrillation. *Heart* 2006; 92: 1177-1182.
4. Stewart S, Murphy N, Walker A, et al. Cost of an emerging epidemic: an economic analysis of atrial fibrillation in the UK. *Heart* 2004; 90: 286-292.
5. NICE. The Management of Atrial Fibrillation. Available from <http://guidance.nice.org.uk/CG36> 2006. (Accessed 10th March 2008)
6. Lip GYH, Edwards SJ. Stroke prevention with aspirin, warfarin and ximelagatran in patients with non-valvular atrial fibrillation: a systematic review and meta-analysis. *Thromb Res* 2006; 118: 321-333.
7. Thomson R, McElroy H, Sudlow M. Guidelines on anticoagulant treatment in atrial fibrillation in Great Britain: variation in content and implications for treatment. *BMJ* 1998; 316: 509-513.
8. Chang HJ, Bell JR, Deroo DB, et al. Physician variation in anticoagulating patients with atrial fibrillation. Dartmouth Primary Care COOP Project. *Arch Intern Med* 1990; 150: 81-4.
9. Markides V, Schilling RJ. Atrial fibrillation: classification, pathophysiology, mechanisms and drug treatment. *Heart* 2003; 89: 939-943.
10. Lip GYH, Tean KN, Dunn FG. Treatment of atrial fibrillation in a district general hospital. *Br Heart J* 1994; 71: 92-95.
11. Personal correspondence: Campbell E. Audit of aetiology, investigations and treatment of atrial fibrillation in a district general hospital (Stobhill Hospital). 2006.
12. Toft AD, Boon NA. General cardiology: thyroid disease and the heart. *Heart* 2000; 84: 455-460.
13. Forfar JC, Miller HC, Toft AD. Occult thyrotoxicosis: a correctable cause of "idiopathic" atrial fibrillation. *Am J Cardiol* 1979; 44: 9-12.
14. Woeber KA. Thyrotoxicosis and the heart. *N Engl J Med*. 1992; 327: 94-8.
15. Brass LM, Krumholz HM, Scinto JM, et al. Warfarin use among patients with atrial fibrillation. *Stroke* 1997; 28: 2382-2389.
16. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988-2000. *JAMA* 2003; 290: 199-206.
17. Orlandi G, Gelli A, Fanucchi S, et al. Prevalence of stroke and transient ischaemic attack in the elderly population of an Italian rural community. *Eur J Epidemiol* 2003; 18: 879-882.
18. Lim HS, Hamaad A, Lip GYH. Clinical review: Clinical management of atrial fibrillation – rate control versus rhythm control. *Crit Care* 2004; 8: 271-279.
19. Hart RG, Benavente O, McBride R, et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999; 131: 492-501.
20. Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation* 1991; 84: 527-539.
21. Lip GY, Edwards SJ. Stroke prevention with aspirin, warfarin and ximelagatran in patients with non-valvular atrial fibrillation: a systematic review and meta-analysis. *Thromb Res* 2006; 118: 321-333.
22. Dentali F, Douketis JD, Lim W, et al. Combined aspirin-oral anticoagulant therapy compared with oral anticoagulant therapy alone among patients at risk for cardiovascular disease: a meta-analysis of randomized trials. *Arch Intern Med* 2007; 167: 117-124.
23. DiMarco JP, Flaker G, Waldo AL, et al. Factors affecting bleeding risk during anticoagulant therapy in patients with atrial fibrillation: observations from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Am Heart J* 2005; 149: 650-656.
24. Lim HS, Hamaad A, Lip GYH. Clinical review: clinical management of atrial fibrillation-rate control versus rhythm control. *Crit Care* 2004; 8: 271-9.

25. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002; 347: 1825-1833.
26. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002; 347: 1834-1840.
27. Hohnloser SH, Kuck KH, Lilienthal J. Rhythm or rate control in atrial fibrillation--Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. *Lancet* 2000; 356: 1789-1794.

28. Carlsson J, Miketic S, Windeler J, et al. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. *J Am Coll Cardiol* 2003; 41: 1690-1696.
29. Opolski G, Torbicki A, Kosior DA, et al. Rate control versus rhythm control in patients with nonvalvular persistent atrial fibrillation: the results of the Polish How to Treat Chronic Atrial Fibrillation (HOT CAFE) Study. *Chest* 2004;126(2):476-486.
30. Napolitano C, Priori SG. Genetics of ventricular tachycardia. *Curr Opin Cardiol* 2002; 17: 222-228.