

# The Cumulative Incidence of Stroke, Myocardial Infarction, Heart Failure and Sudden Cardiac Death in Patients with Atrial Fibrillation

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## Abstract

**Introduction:** Atrial fibrillation is considered as a main cause of cardiovascular morbidity worldwide. A lot of progress was made to avoid the fatal complications of this type of cardiac arrhythmia. In Bosnia and Herzegovina there is no accurate published data on how much this arrhythmia is represented and how much is responsible for death and disability in our population.

**Research Objectives:** The objective of our study is to determine the cardiac and cerebrovascular events (myocardial infarction, heart failure, stroke, sudden cardiac death) and their cumulative incidence during 11 years follow up period.

**Patients and methods:** This study includes 2352 ambulant and hospitalized patients with atrial fibrillation (AF) who were enrolled during the follow up period. All patients underwent clinical evaluation in order to determine cardiac and cerebrovascular events (myocardial infarction, heart failure, stroke, sudden cardiac death) and their cumulative incidence.

**Results:** The results of cumulative incidence for sudden cardiac death were 1.71%, for stroke 2.56%, for myocardial infarction 1.20% and for heart failure was 5.73%. In our study the age-adjusted incidence and prevalence of AF was slightly lower in women. The study shows that the risk of death was higher in females than in males with AF.

**Conclusion:** Despite good progress in the management of patients with atrial fibrillation (AF), this arrhythmia remains one of the major causes of stroke, heart failure, sudden death. Effective treatment of patients with atrial fibrillation includes not only rate control, rhythm control, and prevention of stroke, but also management of cardiovascular risk factors and concomitant diseases.

## Introduction

According to the recent data, in the world 20.9 million men and 12.6 million women are suffering from this type of cardiac arrhythmia, in the next 15 years the number of patients with atrial fibrillation will be significantly increased due to the aging of population in developed parts of the world. Atrial fibrillation is considered as a main cause of cardiovascular morbidity worldwide. A lot of progress was made to avoid the fatal complications of this type of cardiac arrhythmia. In Bosnia and Herzegovina there is no accurate published data on how much this arrhythmia is represented and how much is responsible for death and disability in our population [1,2,3].

## Research Objectives

The first objective of our study is to determine the cardiac and cerebrovascular events (myocardial infarction, heart failure, stroke, sudden cardiac death) and their cumulative incidence during median follow up period  $9.7 \pm 1.8$  years (September 2006-September 2016).

## Patients and Methods

This study includes 2352 ambulant and hospitalized patients with atrial fibrillation (AF) who were enrolled during median  $9.7 \pm 1.8$  follow up period (September 2006 until September 2016). A complete medical

history was taken and all patients underwent clinical evaluation which includes thorough assessment for concomitant conditions, establishing the AF pattern, estimation of stroke, myocardial infarction, heart failure and sudden death risk. The AF was documented by 12-lead ECG or ambulatory ECG Holter recording. All patients were subjected to echocardiography to assess left atrial diameter and volume. In this study the following types of AF were included: newly diagnosed, paroxysmal, persistent and permanent AF. During the follow up period, cardiac and cerebrovascular events were evaluated (myocardial infarction, heart failure, stroke, sudden death) and their cumulative incidence.

Statistical analysis was conducted using statistical package IBM Statistics SPSS V23.0 (Chicago, Illinois USA), Baseline characteristics were summarized by mean and SD or frequency percents and assessed for trends across the calendar years of AF diagnosis, considered as a continuous variable. Cumulative incidence is calculated by the number of new cases during a period divided by the number of subjects at risk in the population, or all registered cases with AF during the observed ten-year period (N=2352).

## Results

During the follow up period, we analyzed and follow up 2352 patients with ECG documented different type of atrial fibrillation in order to

evaluate the cumulative incidence of sudden death, stroke, myocardial infarction and heart failure. The demographic data, risk factors, clinical and comorbidity characteristics for all patients are shown on Table 1. The cumulative incidence of sudden death, stroke, myocardial infarction and heart failure is shown on Figure 1. The cardiovascular drugs used for rhythm control are shown on Table 2.

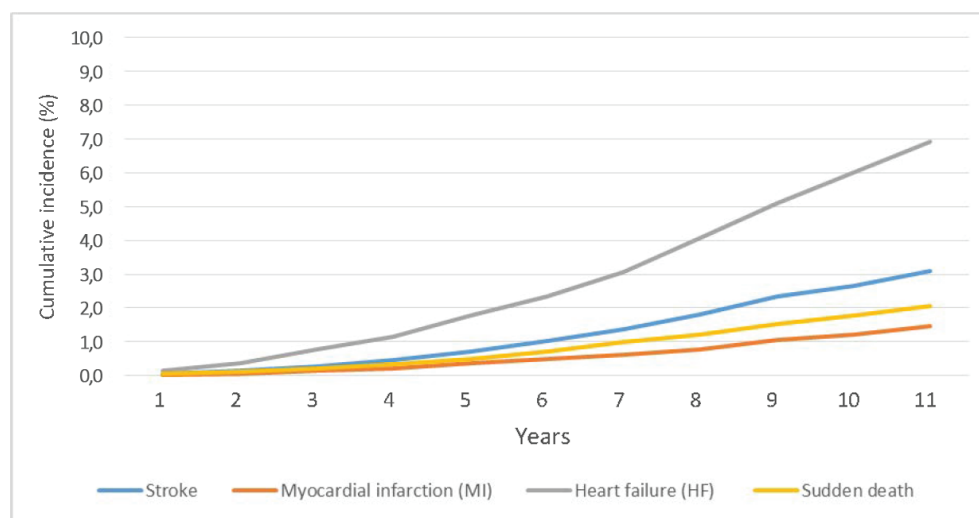
In our study among 2352 patients, AF was reported to be first detected in 352, paroxysmal in 194, persistent in 728, and permanent in 1078 patients. Concomitant diseases were present in 84% of all patients. Oral anticoagulation with VKA<sub>s</sub> was prescribed in 35% and NOAC<sub>s</sub> in 44% of patients, respectively. A rhythm control strategy was applied in 63% of currently symptomatic patients and in 47% of patients who never experienced symptoms according to the ESC guidelines.

In our study the age-adjusted incidence and prevalence of AF were slightly lower in women. The study shows that the risk of death was higher in females than that in males with AF, the risk of stroke was higher also in women with AF. The risk of myocardial infarction in our study was higher in men, the study shows that the risk of heart failure was almost same in both gender.

During median follow up period 9.7 ± 1.8 years, the cumulative incidence for sudden cardiac death was 1.71%, for stroke 2.56%, for myocardial infarction 1.20 and for heart failure was 5.73%. Our study shows that the majority of patients with atrial fibrillation have mild to moderate enlargement of left atrium; more than half of patients have mildly-moderately reduced LV EF.

**Table1:** Baseline demographics and clinical characteristics

Variable	Overall	Cox and sex adjusted P-value	Hazard Ratio (± 95% CI)
No. of patients (n = 2352)			
Age, years	68 ± 13	< 0.001	1.028 (1.021 - 1.035)
Male, n (%)	1223 (52)	0.3562	1.074 (0.902 - 1.253)
BMI, kg/m <sup>2</sup>	26 ± 7	0.0266	1.009 (1.004 - 1.014)
Normal BMI, n (%)	729 (31)	0.0031	0.764 (0.637 - 0.894)
Overweight, n (%)	1035 (44)	0.2253	0.847 (0.702 - 0.990)
Obesity, n (%)	588 (25)	0.0054	1.314 (1.071 - 1.561)
Sedentary lifestyle	1082 (46)	0.2184	1.503 (1.252 - 1.754)
Family history of AF	643 (27)	< 0.001	1.465 (1.287 - 1.682)
Family history of CAD	729 (31)	< 0.001	1.543 (1.359 - 1.746)
Current or past smoker, n (%)	1341 (57)	0.1464	1.240 (1.188 - 1.296)
Alcohol consumption acute/chronic, n (%)	635 (27)	0.1546	1.206 (1.094 - 1.319)
Hypertension, n (%)	1788 (76)	0.0027	1.352 (1.151 - 1.553)
Angina/CAD, n (%)	917 (39)	0.6842	0.916 (0.763 - 1.069)
Heart Failure	641 (27)	0.1603	1.425 (1.293 - 1.557)
Valvular heart disease, n (%)	258 (11)	< 0.001	1.280 (1.057 - 1.505)
Diabetes mellitus, n (%)	517 (22)	0.1761	1.170 (0.898 - 1.379)
Dyslipidemia, n (%)	1388 (59)	0.4892	1.082 (0.862 - 1.304)
Chronic obstructive pulmonary disease, n (%)	612 (26)	0.0468	1.194 (0.586 - 1.857)
Peripheral vascular disease, n (%)	376 (16)	0.6852	1.054 (0.792 - 1.312)
Thyroid disease, n (%)	78 (3)	0.1583	1.206 (0.995 - 1.417)
Open heart surgery, n (%)	282 (12)	0.5124	1.240 (1.045 - 1.435)
Chronic kidney disease, n (%)	240 (10)	0.4981	1.165 (0.917 - 1.410)
Obstructive sleep apnea, n (%)	47 (2)	0.1573	1.521 (0.861 - 2.181)



**Figure 1:** The cumulative incidence of stroke, MI, HF and SD during the follow up period

**Table 2:** Pharmacological therapy n (%)

Amiodarone	1324 (56)
Beta blockers	631 (27)
Calcium channel blockers	511 (22)
Digoxin	725 (31)
ACE-I/ARB	1084 (46)
Diuretics	1284 (55)
Alpha blockers	420 (18)
Nitrates	752 (32)
Statins	1657 (70)
Antiplatelet agents (Aspirin/Clopidogrel)	514 (22)
Anticoagulants (VKAs)	588 (25)
NOACs	447 (19)
Antidiabetics- oral	346 (15)
Insulin	171 (7)
Number of cardiovascular drugs (mean)	2,62 ± 1,84

## Discussion

Atrial fibrillation is the most common arrhythmia in the general population, with a prevalence of 1.5-2%, which increases with age. In addition, it occurs more frequently in males, with a male to female ratio of 1.2:1. In 2010, the estimated numbers of men and women with AF worldwide were 20.9 million and 12.6 million, respectively, with higher incidence and prevalence rates in developed countries. One in four middle-aged adults in Europe and the US will develop AF. By 2030, 14-17 million AF patients are anticipated in the European Union, with 120 000-215 000 newly diagnosed patients per year. Given that AF is associated with significant morbidity and mortality, this increasing number of individuals with AF will have major public health implications [1,2,4-8].

In our study, the mean age of the patients was  $68 \pm 13$  years; the males represent 52% of patients with AF. The published studies also have reported a predominance of males (generally around 60%), the mean age of the patients in most reports is between 65 and 70 years, which is comparable to the mean age of our population [9,10].

In our study, family history of CAD was present in 31% of patients with AF, [HR 1.543 (CI 1.359-1.746)], also CAD was found in 39% of patients [HR 0.916 (CI 0.763-1.069)], which is in consistent with the results of published studies. Viola F et al. In their investigation they 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. The main conclusion was that AF patients had a significant residual risk of MI despite anticoagulant treatment [11].

Echocardiography provides vital information about cardiac chambers and function, complications, and prognosis in patients with AF. This information may be helpful in determining the conditions associated with AF, the risk for recurrent AF following cardioversion, and the hemodynamic benefit of maintaining sinus rhythm, also identification of patients at increased risk for thromboembolic complications of AF before cardioversion and in patients with chronic AF [3,12-15].

In the reviewed literature, the prescription of oral anticoagulation on hospital discharge was also lower in patients with paroxysmal vs. permanent AF (51 vs. 80%, 55 vs. 74%, 78 vs. 91%). In a Swiss registry of outpatients with AF seen by cardiologists, prescription of anticoagulants reached 88% in patients with a CHADS2 score  $\geq 1$ . However, 57% of the patients with a score of zero also received anticoagulants [16-27].

During median follow up period  $9.7 \pm 1.8$  years, the cumulative incidence for sudden cardiac death was 1.71%, for stroke 2.56%, for

myocardial infarction 1.20 and for heart failure was 5.73%. The cumulative incidences of stroke, myocardial infarction, heart failure and sudden cardiac death are similar to those in published studies and meta-analysis [28,29]. The published studies shows the following cumulative incidence for stroke 5-7.5%, MI 0.4 - 2.5%, heart failure 6 - 35% [1,2,4,5,8,9,11,24,30].

In our study, the most prescribed and used drugs for rhythm control were Amiodarone 56%, followed by digitalis 31% and beta-blockers 27%. The same drugs were used in other published studies. Lafuente-Lafuente C et al. They performed a systematic review to determine the effect of long-term treatment with those drugs on death, embolisms, adverse effects, and atrial fibrillation recurrence. Forty-four trials were included, with a total of 11 322 patients. They conclude that Class IA, IC, and III drugs are effective in maintaining sinus rhythm but increase adverse effects, and class IA drugs may increase mortality [31].

Krijthe BP et al. they calculate projections on the number of individuals with AF in the European Union from 2010 to 2060 using the information collected in the community-based prospective cohort study: The Rotterdam Study. They estimate that the number of adults 55 years old and over with AF in the European Union will be more than double. As AF is associated with significant morbidities and mortality, this increasing number of individuals with AF may have major public health implications [32-36]. In other systematic review by Wolowacz S.E. et al. for the economic burden of AF, hospitalizations consistently represented the major cost driver. In the USA, AF hospitalizations alone cost \$6.65 billion in 2005. Costs and hospitalizations attributable to AF have increased markedly over recent decades and are expected to increase in future due to ageing populations [37].

## Conclusion

Despite good progress in the management of patients with atrial fibrillation (AF), this arrhythmia remains one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world. AF is associated with a 4-fold increase in the risk of stroke, 3-fold increase in the risk of heart failure, and 1.5-1.9 increased risk of death. AF is known to have a significant impact on healthcare costs, with the major cost drivers being hospitalizations, stroke, and loss of productivity. Atrial fibrillation should be considered as a manifestation of hypertensive heart disease. Effective treatment of patients with atrial fibrillation includes not only rate control, rhythm control, and prevention of stroke, but also management of cardiovascular risk factors and concomitant diseases.

## Study limitations

1. We didn't have IBR approval or patient's consents; the data was collected from outpatient's medical records and regular visits to the cardiologist and from hospital discharge reports and hospitals data base.
2. Unfortunately, in the last 2 decades despite several attempts to establish the laboratory for electrophysiological studies (EPS) and AF ablation, until now we don't have such one. So, we are not able to perform AF ablation. In the last 2 years, several medical centers have cooperation with experts in EPS from Norway and neighbor countries for education and training of young cardiologists for EPS and we hope that we will have soon our lab for EPS.
3. During this study we didn't have subgroup analysis to compare all the outcomes in rate control vs rhythm control due to the reason mentioned above, also we don't have data about difference in outcomes between VKA and NOCA drugs. The NOCA drug Rivaroxaban was registered in Bosnia and Herzegovina before several years.

**References**

1. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, et al. (2016) 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur J Cardiothorac Surg* 50: e1-e88.
2. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, et al. Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J* 37: 3232-3245.
3. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, et al. (2011) 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 123: e269-e367.
4. Masic I, Dilic M, Rajjevic E, Vulic D, Mott D (2010) Trends in cardiovascular diseases in Bosnia and Herzegovina and perspectives with heartscore programme. *Med Arh* 64: 260-263.
5. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, et al. (2014) Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 129: 837-847.
6. Nguyen TN, Hilmer SN, Cumming RG (2013) Review of epidemiology and management of atrial fibrillation in developing countries. *Int J Cardiol* 167: 2412-2420.
7. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S (2014) Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol* 6: 213-220.
8. Vermond RA, Geelhoed B, Verweij N, Tieleman RG, Van der Harst P, et al. (2015) Incidence of Atrial Fibrillation and Relationship With Cardiovascular Events, Heart Failure, and Mortality: A Community-Based Study From the Netherlands. *J Am Coll Cardiol* 66: 1000-1007.
9. Le Heuzey JY, Breithardt G, Camm J, Crijns H, Dorian P, et al. (2010) The RecordAF study: design, baseline data, and profile of patients according to chosen treatment strategy for atrial fibrillation. *Am J Cardiol* 105: 687-693.
10. Zubaid M, Rashed WA, Alsheikh-Ali AA, Almahmeed W, Shehab A, et al. (2011) Gulf Survey of Atrial Fibrillation Events (Gulf SAFE): design and baseline characteristics of patients with atrial fibrillation in the Arab Middle East. *Circ Cardiovasc Qual Outcomes* 4: 477-482.
11. Violi F, Soliman EZ, Pignatelli P, Pastori D (2016) Atrial Fibrillation and Myocardial Infarction: A Systematic Review and Appraisal of Pathophysiologic Mechanisms. *J Am Heart Assoc* 5 pii: e003347.
12. Ellinor PT, Lunetta KL, Albert CM, Glazer NL, Ritchie MD, et al. (2012) Meta-analysis identifies six new susceptibility loci for atrial fibrillation. *Nat Genet* 44: 670-675.
13. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, et al. (2016) Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. *BMJ* 354.
14. Tae-Seok K, Ho-Joong Y (2011) Role of Echocardiography in Atrial Fibrillation. *J Cardiovasc Ultrasound* 19: 51-61.
15. Nieuwlaar R, Capucci A, Camm AJ, Olsson SB, Andresen D, et al. (2005) Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. *Eur Heart J* 26: 2422-2434.
16. Lip GY, Laroche C, Ioachim PM, Rasmussen LH, Vitali-Serdoz L, et al. (2014) Prognosis and treatment of atrial fibrillation patients by European cardiologists: one year follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase (EORP-AF Pilot registry). *Eur Heart J* 35: 3365-3376.
17. Medjedovic S, Deljo D, Sukalo A, Masic I (2015) Clinical-epidemiological study on stroke presence in the population of Herzegovina -Neretva canton influenced by investigated risk factors. *Mater Sociomed* 27: 314-317.
18. Dilic M, Begic A, Sabanovic-Bajramovic N, Bico A, Terzic O (2013) Antithrombotic therapy for the secondary prevention of ischemic stroke related to atrial fibrillation: ESC/ACC/ACCP Guidelines. *Cardiologia CROATICA* 8: 299.
19. Kirchhof P, Ammentorp B, Darius H, De Caterina R, Le Heuzey JY, et al. (2014) Management of atrial fibrillation in seven European countries after the publication of the 2010 ESC Guidelines on atrial fibrillation: primary results of the PREvention of thromboembolic events--European Registry in Atrial Fibrillation (PREFER in AF). *Europace* 16: 6-14.
20. Masic I, Rahimic M, Dilic M, Kadribasic R, Toromanovic S (2011) Socio-medical Characteristics of Coronary Disease in Bosnia and Herzegovina and the World. *Mater Sociomed* 23: 171-183.
21. Huisman MV, Lip GY, Diener HC, Dubner SJ, Halperin JL, et al. (2014) Design and rationale of Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation: a global registry program on long-term oral antithrombotic treatment in patients with atrial fibrillation. *Am Heart J* 167: 329-334.
22. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, et al. (2014) 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation* 130: 2071-2104.
23. Naser N, Dzibur A, Durak A, Kulic M, Naser N (2016) Blood Pressure Control in Hypertensive Patients, Cardiovascular Risk Profile and the Prevalence of Masked Uncontrolled Hypertension (MUCH). *Med Arch* 70: 274-279.
24. Jahangir A, Lee V, Friedman PA, Trusty JM, Hodge DO, et al. (2007) Long-term progression and outcomes with aging in patients with lone atrial fibrillation: a 30-year follow-up study. *Circulation* 115: 3050-3056.
25. Elgendy AY, Mahtta D, Barakat AF, Abuzaid A, Mahmoud A, et al. (2017) Meta-Analysis of Safety and Efficacy of Uninterrupted Non-Vitamin K Antagonist Oral Anticoagulants Versus Vitamin K Antagonists for Catheter Ablation of Atrial Fibrillation. *Am J Cardiol* 120: 1830-1836.
26. Almeida ED, Guimarães RB, Stephan LS, Medeiros AK, Foltz K, et al. (2015) Clinical Differences between Subtypes of Atrial Fibrillation and Flutter: Cross-Sectional Registry of 407 Patients. *Arq Bras Cardiol* 105: 3-10.
27. Wolowacz SE, Samuel M, Brennan VK, Jasso-Mosqueda JG, Van Gelder IC (2011) The cost of illness of atrial fibrillation: a systematic review of the recent literature. *Europace* 13: 1375-1385.
28. M Saad, IY Elgendy, A Mentias, HK Abdelaziz (2017) Incidence, Predictors, and Outcomes of Early Atrial Arrhythmias After Lung Transplant: A Systematic Review and Meta-Analysis. *J Am Coll Cardiol EP* 3: 718-726.
29. Mahmoud AN, Al-Ani M, Saad M, Elgendy AY, Elgendy IY (2016) Development and validation of a simple integer risk score for prediction of in-hospital mortality following Takotsubo syndrome. *Heart Lung* 45: 510-514.
30. Liu Z, Ling Z, Su L, Wu J, Lan X, et al. (2008) The effect of different treatment strategies on left atrial size in patients with lone paroxysmal atrial fibrillation-a prospective cohort study. *J Interv Card Electrophysiol* 23: 167-173.
31. Lafuente-Lafuente C, Mouly S, Longás-Tejero MA, Mahé I, Bergmann JF (2006) Antiarrhythmic drugs for maintaining sinus rhythm after cardioversion of atrial fibrillation: a systematic review of randomized controlled trials. *Arch Intern Med* 166: 719-728.
32. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, et al. (2013) Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J* 34:2746-2751.
33. Vanassche T, Lauw MN, Eikelboom JW, Healey JS, Hart RG, et al. (2015) Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES. *Eur Heart J* 36: 281a-287a.



34. Xu X, Alida CT, Yu B (2015) Administration of antiarrhythmic drugs to maintain sinus rhythm after catheter ablation for atrial fibrillation: a meta-analysis. *Cardiovasc Ther* 33: 242-246.
35. Morseth B, Graff-Iversen S, Jacobsen BK, Jørgensen L, Nyrnes A, et al. (2016) Physical activity, resting heart rate, and atrial fibrillation: the Tromsø Study. *Eur Heart J* 37: 2307-2313.
36. Oduyayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, et al. (2016) Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. *BMJ* 354: i4482.
37. Wolowacz SE, Samuel M, Brennan VK, Jasso-Mosqueda JG, Van Gelder IC (2011) The cost of illness of atrial fibrillation: a systematic review of the recent literature. *Europace* 13: 1375-1385.