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# Selecting the right anticoagulant for stroke prevention in atrial fibrillation

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**Abstract. – OBJECTIVE: The embolization of thrombi formed within the atria can occur in any form of atrial fibrillation (AF), i.e., paroxysmal, persistent, or permanent. Although ischemic stroke is the most frequent embolic event associated with AF, embolization to other sites in the pulmonary and systemic circulations may occasionally occur. To avert the risk of embolization, long-term oral anticoagulation therapy is recommended for all AF patients if the CHA2DS2-VASC score is at least 1 for men and at least 2 for women. Since anticoagulant therapy is associated with an increased risk of bleeding, the choice of oral anticoagulant agent should be made by careful consideration of the benefit-to-risk ratio. The use of a newer class of direct oral anticoagulants (DOACs) as an alternative to the anti-vitamin K (AVK) anticoagulants (warfarin, acenocumarol, etc.) can help mitigate the need for periodic monitoring of International Normalized Ratio (INR) and adverse bleeding events that are commonly associated with the use of AVK anticoagulants. Though the use of DOACs (dabigatran, rivaroxaban, edoxaban, apixaban, etc.) is gaining ground due to their relative safety profile and the low overall cost, quite a few clinicians remain skeptical about their use.**

**PATIENTS AND METHODS: Our objective was to evaluate the risk of thromboembolism, stroke, neuropsychiatric illness, depression, and dementia, in patients with non-valvular atrial fibrillation who have been treated with either acenocumarol or apixaban, as well as to see the inflammatory status (ESR) and levels of fibrinogen. Our team at Municipal Emergency University Hospital, Timisoara, Romania, conducted a retrospective study using the medical records of AF patients who were treated with either apixaban or acenocumarol between 2016-2019. We divided the patients into two groups and compared the groups for the aforementioned outcomes.**

**RESULTS: AF patients who were prescribed apixaban had a lower rate of stroke and psychiatric illness compared to those on acenocumar-**

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**ol. No significant correlation was found in terms of risk of developing depression or dementia between the groups.**

**CONCLUSIONS: Non-valvular AF patients on apixaban had lower rates of thromboembolic events than the patients on acenocumarol. This article will serve as a reminder of the positive health and financial outcomes of apixaban use, especially to those healthcare systems that are still oblivious to the decrease in economic burden and gain in quality-adjusted life years (QALY) by the long-term use of NOACS/ DOACS instead of the AVK anticoagulants.**

*Key Words:*
Non-valvular atrial fibrillation, Apixaban, Acenocumarol, Systemic embolism, Stroke, Bleeding.

## Introduction

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia entailing uncoordinated atrial activity and ineffective atrial contraction[1]. In addition to the disturbances of rate and rhythm, the risk of thromboembolic events also increases in patients with AF. The combination of factors such as platelet activation, endothelial dysfunction, and sluggish blood flow in the left atrium and left atrial appendage tend to augment coagulation activity and the risk of stroke in AF patients[2,3].

Endothelial dysfunction results in increased stickiness of the endothelia to the leukocytes and the subsequent production of vasoactive and procoagulant factors, growth factors, and cytokines[4]. The Von Willebrand factor (VWF) is a multimeric plasma glycoprotein that plays a crucial role in hemostasis post vascular injury, with subendothelial VWF mediating platelet adhesion to form thrombus at the injured site. The VWF is also secreted from the atrial endocardium in response to vascular disease and or injury. Many studies[5,6] have reported the increased level of VWF in response to widespread endothelial damage/ dysfunction (including atrial endothelium damage), atherothrombosis, and left atrial appendage thrombosis. The link between inflammation and thrombosis has been observed; interleukin-6 (IL-6), which is a circulating cytokine, is released from monocytes, T-lymphocytes, macrophages, and endothelial cells in response to inflammation. IL-6 induces a pro-thrombotic state by increasing the expression of tissue factor, factor VIII, VWF, fibrinogen, and activating platelets and endothelial cells[7-9]. Similarly, elevated levels of high-sensitivity C-reactive protein (HS-CRP) have been reported in AF patients, indicating an inflammatory state with the potential to promote persistent AF in patients[10]. Furthermore, the enhanced hemostatic activation is deemed responsible for the thromboembolic event in cardiogenic stroke[11], and the D-dimer assay can be used to identify the hyperactive coagulation process[12]. The increased fibrin turnover and thrombin generation markers such as d-dimers and prothrombin fragment 1+2 (F1+2), respectively, are increased in AF patients. These markers can be reduced by warfarin administration[8,13]. Another marker, CD40 ligand, stored in the alpha- granules of platelets is expressed by the activated platelets. The level of the soluble CD40 ligand (sCD40L) receptor complex, shed by the activated platelets, is also elevated in patients with AF[13,14]. Ota et al[15] demonstrated that the plasma concentrations of F1+2, D-dimer, soluble fibrin, and thrombin-antithrombin complex are all increased in patients with thrombosis, and therefore, all these markers possess similar diagnostic ability[15].

Standardization of a stable therapeutic dosing regimen of vitamin k antagonists (VKA) such as warfarin or acenocumarol is difficult to achieve because several environmental and genetic factors tend to influence the inter and intra patient's variability[16]. A diet rich in vitamin K is one such component that has the potential to counteract the anticoagulant effects of acenocumarol[17,18].

## Patients and Methods

Our team sifted through the database of 450 permanent AF patients (aged between 50-70 years) with CHA2DS2VasC of at least 2 who either received acenocumarol (target international normalized ratio (INR) was 2.0-3.0) or apixaban (5 mg BID), during 2015-2019. We divided the AF patients into two groups based on the type of anticoagulation agent they received. The following were the inclusion criteria: 1) Non-valvular AF patients, 2) AF patients with at least 1 comorbidity of 3 (type 2 diabetes mellitus, hypertension, or heart failure). The patients receiving other types of anticoagulation therapy and patients presenting with a history of stroke or thromboembolic events were excluded, as well as those diagnosed with psychiatric illnesses, dementia, or depression before the initiation of therapy.

The physicians used the International normalized ratio (INR) to monitor the anticoagulant status and evaluate for bleeding risk. Group 1 (N

= 163; 79 males and 84 females) received 5 mg apixaban BID and group 2 (N= 287; 124 males and 163 females) received acenocumarol based on INR value with the purpose to keep it between 2-3. We compared the AF patients for their serum markers of inflammation (erythrocyte sedimentation rate [ESR]) and coagulation (fibrinogen) at the presentation and every six months thereafter.

The patients underwent six-monthly psychiatric evaluations. For the evaluations, treating physicians used tools such as a mini mental state exam (MMSE) and revised symptom checklist (SCL-90-R). Data regarding the appearance of depression, dementia, stroke or thromboembolic event, or neuropsychiatric diseases after initiating anticoagulation therapy were recorded and statistically analyzed.

Statistical analysis was performed with SPSS software (version 17, SPSS Inc., Chicago, USA). The data were electronically stored using Microsoft Excel (version 2013, MS Corp., Redmond, Washington, USA). A $p$-value of $\leq 0.05$ was regarded as statistically significant.

### Ethics Approval and Informed Consent Statement

Prior to the commencement of the study, ethics approval and informed written consent were obtained from all the relevant persons or authorities. The study was approved by the *'Comisia de Etica a Cercetarii Stiintifice'* (Ethics Committee for Scientific Research) of the University of Medicine and Pharmacy "Victor Babes", Timisoara, in accordance with the Helsinki Declaration– Recommendations Guiding Medical Doctor in Biomedical Research Involving Human Subjects. All the steps of the study were conducted in accordance with the above guidelines, conforming to the standard operating procedures for clinical studies approved for Spitalul Municipal (Municipal Emergency University Hospital, Romania).

This retrospective study was conducted in our university hospital and as a part of routine procedure informed each patient signed written consent forms stating that the data can be used for future medical research purposes at the time of admission in the hospital.

## Results

Apixaban was associated with a reduced risk of stroke or systemic embolism when compared with acenocumarol (Chi-squared Test, $p$=0.005), OR=0.426, 95% CI [0.232, 0.782]. It is noteworthy that the overall rate of development of psychiatric diseases was lower (Chi-squared Test, $p$=0.006), OR=0.431, 95% CI [0.239, 0.775] in patients treated with apixaban than the ones receiving Vitamin K antagonists. Insignificant correlation was noted while comparing the benefits of apixaban *vs.* acenocumarol with regard to depression and dementia, the statistical results being (Chi-squared Test, $p$=0.203), OR=0.338, 95% CI [0.079, 1.453] and Chi-squared Test, $p$=0.275, OR=0.377, 95% CI [0.087, 1.627] respectively. There was no significant correlation found between ESR levels and stroke; Chi-squared test, $p$=0.729, OR=1.098, 95%CI= [0.699, 1.989725]. While high ESR levels were positively linked with the occurrence of psychiatric illness Chi-squared test, $p$<0.001, OR=0.493, 95% CI= [0.323, 0.751]. There was no significant correlation found between high levels of fibrinogen and stroke: Chi-squared test, $p$=0.242, OR=1.306, 95% CI [0.857, 1.989] and correlation with psychiatric illness was also not significant Chi-squared test, $p$=0.622, OR=0.896, 95% CI [0.609, 1.318]. At the same time, it was noticed that patients having high fibrinogen levels and receiving treatment with Apixaban, had no stroke events, while 64% of the ones having high fibrinogen and receiving acenocumarol, presented with stroke during the study period. No mortality was noted in either group during the study period (Figures 1 and 2).

## Discussion

In our retrospective study involving anticoagulant treatment of non-valvular AF patients, we aimed at assessing the effectiveness and safety of apixaban in comparison to acenocumarol. Our findings indicated that apixaban was associated

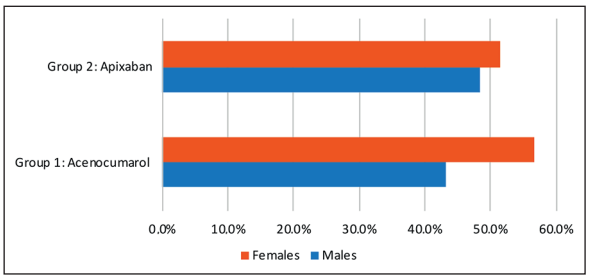


**Figure 1.** Patients receiving acenocumarol or apixaban and their gender.

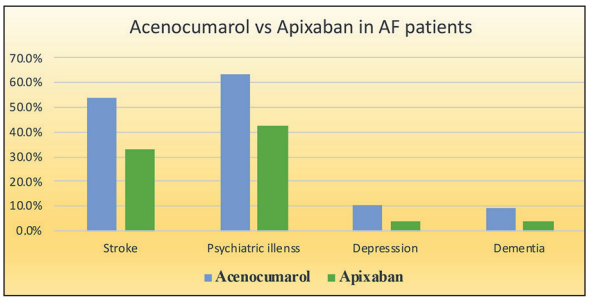


**Figure 2.** Incidence of health issues in AF patients kept on acenocumarol *vs.* apixaban.

with better anticoagulation and safety. Our study provides an estimate of anticipated clinical outcomes, which may help patients and clinicians to make an informed choice between apixaban and acenocumarol.

Many studies[19] have compared the effectiveness and safety of dabigatran and rivaroxaban with warfarin, but very few have compared these parameters of apixaban with that of acenocumarol. For instance, the RE-LY analyses have demonstrated that the use of dabigatran increases the risk of major bleed in patients aged ≥ 75; however, the risk is lower in patients aged < 75[19].

Following the ROCKET-AF trial, which involved prescribing rivaroxaban to the high-risk elderly population, clinicians gravitated to prescribing rivaroxaban to the elderly population, reflecting the tendency of clinicians to prescribe drugs similar to ones used in studies/ trials.

The study conducted by Nakase et al[20], clearly stated the beneficial effects of apixaban in reducing the inflammatory response, and similar results were seen in our study where none of the patients despite having high levels of fibrinogen, had stroke. Hijazi et al[21] stated that in AF patients, the biomarkers of inflammation are significantly associated with a high risk of developing stroke or mortality, but in our study, we found no significant correlation between high levels of ESR or fibrinogen and stroke, and mortality was nil during the study period. Unfortunately, we were unable to evaluate and factor in HS-CRP and VWF levels to draw precise conclusions, which can be stated as the limitation of the study.

In Romania, the staple diet consumed by the rural population is quite rich in Vitamin K, due to which the management of patients on acenocumarol becomes challenging, but whether the diet consisting of vitamin K interferes with VKA therapy is debatable, and requires in-depth research, as stated by Violi et al[22]. Furthermore, VKA therapy increases the financial burden on the health care system and or patients, as patients' INR values have to be monitored at frequent intervals for therapeutic dose adjustments, ensuring effective anticoagulation while avoiding bleeding risk.

Although clinically diagnosed stroke garners all the attention, AF-induced brain ischemia and silent cerebral microinfarcts also have the potential of causing cognitive impairment and dementia[23]. Evidence from meta-analyses of many prospective epidemiological studies has shown that AF, with or without a history of stroke, could be a predictor of cognitive impairment and increased risk of dementia (hazard ratio (HR) range 1.3-2.3)[24-29]. It is noteworthy that the risk of dementia associated with AF appeared to be stronger with a follow-up period of > 5 years[24]. The data of the Whitehall II study has demonstrated that AF patients reach thresholds of cognitive impairment or dementia sooner than individuals with no history of AF, and AF patients with longer exposure to AF (5-15 years) experience a rapid cognitive decline[30]. The association between AF and dementia is stronger when AF starts in middle age[31]. Apart from the clinical stroke, the suggested mechanism of this association is covert embolism to the brain[32,33]. Additionally, atrophy of brain volume has been associated with AF[34]. Existing data suggest that the NOACs/ DOACs are a better choice for the prevention of dementia than a VKA[35,36] due to a comparatively lower rate of intracerebral bleeding[36].

The relationship between AF and psychological stress is a bidirectional one, wherein both have the potential to exacerbate each other[31]. The psychological distress caused by anxiety, depression, and preoccupation with symptoms is high (25% -50 %) in AF patients[37]. A cross-sectional comparison of two large clinical trials showed that depression was significantly more common in permanent AF patients when compared with paroxysmal AF patients[38]. Similarly, a study comprising 170 patients with permanent AF reported depressed mood and substantial anxiety in 20 % and 35% patients, respectively[39]. To quite an extent, both these conditions were associated with "interactions with medical staff"[31]. Therefore, efforts should be made to implement a therapeutic strategy that limits the patient-staff interactions required for periodic monitoring. Unlike the use of VKA (like Acenocumarol), the judicious use of NOACs/

DOACs (like Apixaban) could help patients and clinicians minimize the frequency of INR monitoring and bleeding episodes.

## Conclusions

Non-valvular AF patients on apixaban had lower rates of thromboembolic events than the patients on acenocumarol. Our study revealed that constantly high levels of ESR can be an early predictor for the likelihood of psychiatric disease development, and further studies should be performed to understand the mechanism behind it. On the other hand, we found that despite high levels of fibrinogen, apixaban reduces risk of stroke in comparison to acenocumarol treatment. This article will serve as a reminder of the positive health and financial outcomes of apixaban use, especially to those healthcare systems that are still oblivious to the decrease in economic burden and gain in QALY by the long-term use of NOACS/ DOACS instead of the AVK anticoagulants.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

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## References

1) January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline 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 Heart Rhythm Society. J Am Coll Cardiol 2014; 21: 2246-2280.
2) Breitenstein A, Glanzmann M, Falk V, Maisano F, Stämpfli SF, Holy EW, Finlay M, Ling L-H, Schilling RJ, Lüscher TF, Steffel J, Camici GG. Increased prothrombotic profile in the left atrial appendage of atrial fibrillation patients. Int J Cardiol 2015; 185: 250-255.
3) Sohara H, Amitani S, Kurose M, Miyahara K. Atrial fibrillation activates platelets and coagulation in a time-dependent manner: a study in patients with paroxysmal atrial fibrillation. J Am Coll Cardiol 1997; 29: 106-112.
4) Blann AD. Endothelial cell activation, injury, damage and dysfunction: separate entities or mutual terms? Blood Coagul Fibrinolysis 2000; 11: 623-630.
5) Conway DS, Pearce LA, Chin BS, Hart RG, Lip GY. Prognostic value of plasma von Willebrand factor and soluble P-selectin as indices of endothelial damage and platelet activation in 994 patients with nonvalvular atrial fibrillation. Circulation 2003; 107: 3141-3145.
6) Roldán V, Marín F, García-Herola A, Lip GY. Correlation of plasma von Willebrand factor levels, an index of endothelial damage/dysfunction, with two point-based stroke risk stratification scores in atrial fibrillation. Thromb Res 2005; 116: 321-325.
7) Kumagai K, Fukunami M, Ohmori M, Kitabatake A, Kamada T, Hoki N. Increased intracardiovascular clotting in patients with chronic atrial fibrillation. J Am Coll Cardiol 1990; 16: 377-380.
8) Lip G, Lowe G, Rumley A, Dunn. Increased markers of thrombogenesis in chronic atrial fibrillation: effects of warfarin treatment. Br Heart J 1995;73: 527-533.
9) Lip GY. Does atrial fibrillation confer a hypercoagulable state? Lancet 1995; 346: 1313-1314.
10) Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A, Carnes CA, Bauer JA, Tchou PJ, Niebauer MJ, Natale A, Van Wagoner DR. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. Circulation 2001; 104: 2886-2891.
11) Feinberg WM, Erickson LP, Bruck D, Kittelson J. Hemostatic markers in acute ischemic stroke. Association with stroke type, severity, and outcome. Stroke 1996; 27: 1296-1300.
12) Lip GY, Lowe GD. Fibrin D-dimer: a useful clinical marker of thrombogenesis? Clin Sci (Lon) 1995; 89: 205-214.

13) Christersson C, Wallentin L, Andersson U, Alexander JH, Alings M, De Caterina R, Gersh BJ, Granger CB, Halvorsen S, Hanna M, Huber K, Hylek EM, Lopes RD, Oh BH, Siegbahn A. Effect of apixaban compared with warfarin on coagulation markers in atrial fibrillation. Heart 2019; 105: 235-242.

14) Choudhury A, Chung I, Panja N, Patel J, Lip GY. Soluble CD40 ligand, platelet surface CD40 ligand, and total platelet CD40 ligand in atrial fibrillation: relationship to soluble P-selectin, stroke risk factors, and risk factor intervention. Chest 2008; 134: 574-581.

15) Ota S, Wada H, Abe Y, Yamada E, Sakaguchi A, Nishioka J, Hatada T, Ishikura K, Yamada N, Sudo A, Uchida A, Nobori T. Elevated Levels of Prothrombin Fragment 1 + 2 Indicate High Risk of Thrombosis. Clin Appl Thromb Hemost 2008; 14: 279-285.

16) Pop TR, Vesa ŞC, Trifa AP, Buzoianu AD, Crişan S. An acenocoumarol dose algorithm based on a South-Eastern European population. Eur J Clin Pharmacol 2013; 69: 1901-1907.

17) Rombouts EK, Rosendaal FR, Meer FJ. Influence of dietary vitamin K intake on subtherapeutic oral anticoagulant therapy. Br J Haematol 2010; 149: 598-605.

18) Pignatelli P, Pastori D, Vicario T, Bucci T, Del BM, Russo R, Tanzilli A, Nardoni ML, Bartimoccia S, Nocella C, Ferro D, Saliola M, Cangemi R, Lip GY, Violi F. Relationship between Mediterranean diet and time in therapeutic range in atrial fibrillation patients taking vitamin K antagonists. Europace 2015; 17: 1223-1228.

19) Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, Yang S, Alings M, Kaatz S, Hohnloser SH, Diener HD, Franzosi MG, Huber K, Reilly P, Varrone J, Yusuf S. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation 2011; 123: 2363-2372.

20) Nakase T, Moroi J, Ishikawa T. Anti-inflammatory and antiplatelet effects of non-vitamin K antagonist oral anticoagulants in acute phase of ischemic stroke patients. Clin Transl Med 2018; 7: 2.

21) Hijazi Z, Aulin J, Andersson U, Alexander JH, Gersh B, Granger CB, Hanna M, Horowitz J, Hylek EM, Lopes RD, Siegbahn A, Wallentin L. Biomarkers of inflammation and risk of cardiovascular events in anticoagulated patients with atrial fibrillation. Heart 2016; 102: 508-517.

22) Violi F, Lip GY, Pignatelli P, Pastori D. Interaction Between Dietary Vitamin K Intake and Anticoagulation by Vitamin K Antagonists: Is It Really True?: A Systematic Review. Medicine (Baltimore) 2016; 95: e2895.

23) van Veluw SJ, Shih AY, Smith EE, Chen C, Schneider JA, Wardlaw JM, Greenberg SM, Biessels GJ. Detection, risk factors, and functional consequences of cerebral microinfarcts. Lancet Neurol 2017; 16: 730-740.

24) Islam M, Poly TN, Walther BA, Yang HC, Wu CC, Lin MC, Chien SC, Li YC. Association between atrial fibrillation and dementia: a meta-analysis. Front Aging Neurosci 2019; 11: 305.

25) Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with atrial fibrillation: a meta-analysis. Ann Intern Med 2013; 158: 338-346.

26) Liu DS, Chen J, Jian WM, Zhang GR, Liu ZR. The association of atrial fibrillation and dementia incidence: a meta-analysis of prospective cohort studies. J Geriatr Cardiol 2019; 16: 298-306.

27) Saglietto A, Matta M, Gaita F, Jacobs V, Bunch TJ, Anselmino M. Stroke-independent contribution of atrial fibrillation to dementia: a meta-analysis. Open Heart 2019; e000984.

28) Santangeli P, Di Biase L, Bai R, Mohanty S, Pump A, Cereceda Brantes M, Horton R, Burkhardt JD, Lakkireddy D, Reddy YM, Casella M, Dello Russo A, Tondo C, Natale A. Atrial fibrillation and the risk of incident dementia: a meta-analysis. Heart Rhythm 2012; 9: 1761-1768.

29) Stefanidis KB, Askew CD, Greaves K, Summers MJ. The effect of non-stroke cardiovascular disease states on risk for cognitive decline and dementia: a systematic and meta-analytic review. Neuropsychol Rev 2018; 28: 1-15.

30) Singh-Manoux A, Fayosse A, Sabia S, Canonico M, Bobak M, Elbaz A, Kivimäki M, Dugravot A. Atrial fibrillation as a risk factor for cognitive decline and dementia. Eur Heart J 2017; 38: 2612-2618.

31) Ladwig KH, Goette A, Atasoy S, Johar H. Psychological aspects of atrial fibrillation: A systematic narrative review: Impact on incidence, cognition, prognosis, and symptom perception. Curr Cardiol Rep 2020; 22: 137.

32) Kalantarian S, Ay H, Gollub RL, Lee H, Retzepi K, Mansour M, Ruskin JN. Association between atrial fibrillation and silent cerebral infarctions: a systematic review and meta-analysis. Ann Intern Med 2014; 161: 650-658.

33) Wang Z, Veluw VSJ, Wong A, Liu W, Shi L, Yang J, Xiong Y, Lau A, Biessels GJ, Mok VC. Risk factors and cognitive relevance of cortical cerebral microinfarcts in patients with ischemic stroke or transient ischemic attack. Stroke 2016; 47: 2450-2455.

34) Stefansdottir H, Arnar DO, Aspelund T, Sigurdsson S, Jonsdottir MK, Hjaltason H, Launer LJ, Gudnason V. Atrial fibrillation is associated with reduced brain volume and cognitive function independent of cerebral infarct. Stroke 2013; 44: 1020-1025.

35) Cheng W, Liu W, Bin L, Dongfang L. Relationship of anticoagulant therapy with cognitive impairment among patients with atrial fibrillation: A meta-analysis and systematic review. J Cardiovasc Pharmacol 2018; 71: 380-387.

36) Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko AJ, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014; 383: 955-962.

37) Patel D, Mc Conkey ND, Sohaney R, Mc Neil A, Jedrzejczyk A, Armaganijan L. A systematic review of depression and anxiety in patients with atrial fibrillation: the mind-heart link. Cardiovasc Psychiatry Neurol 2013; 2013.

38) Rothe AFE, Goette A, Kirchhof P, Breithardt G, Limbourg T, Calvert M, Baumert J, Ladwig KH. Depression in paroxysmal and persistent atrial fibrillation patients: a cross-sectional comparison of patients enroled in two large clinical trials. Europace 2014; 16: 812-819.

39) Polikandrioti M, Koutelekos I, Vasilopoulos G, Gerogianni G, Gourni M, Zyga S, Panoutsopoulos. Anxiety and depression in patients with permanent atrial fibrillation: prevalence and associated factors. Cardiol Res Pract 2018; 2018.