Mechanisms of cardioembolic stroke revisited. Atrial cardiopathy

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INTRODUCTION

Atrial fibrillation (AF) represents a mounting public health burden with a great social and economic significance. It is the most common sustained cardiac arrhythmia, affecting 33 million people worldwide and 400–500 thousand people in Poland [1]. These numbers are estimated to almost triple during the next several decades given the expected aging of populations [2]. AF significance derives largely from high thromboembolic risk expressed as a five-fold increase in the risk of ischaemic stroke [3]. Stroke is yet another important public health issue, leading to diminished quality of life and disability as well as being the second cause of death worldwide, just after heart disease. The Framingham Heart Study showed that AF contributes to 23.5% of strokes in persons aged above 80 years [4]. Despite growing incidence and importance, there has been surprisingly little progress in our understanding of arrhythmia-related stroke over the years. Our approach is still based on a long-lived hypothesis that atrial contractile dysfunction due to fibrillation causes blood stasis, which, accompanied by other factors acting together as Virchow's triad, generates thrombus and the subsequent embolism to the brain. A growing body of evidence indicates a more complex relationship, with dysrhythmia itself as one of the players. In everyday practice, evaluation of thromboembolic risk and subsequent treatment decisions in patients with AF are based mainly on the CHA_2DS_2-VASc score, which involves clinical features but has only limited predictive value. What is more — we are still incapable of predicting and preventing one third of ischaemic strokes, which remain cryptogenic, and with unknown aetiology. According to the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria — their radiographic manifestations resemble of cardioembolic background; however, no embolic source has been determined and extensive diagnostic evalu-
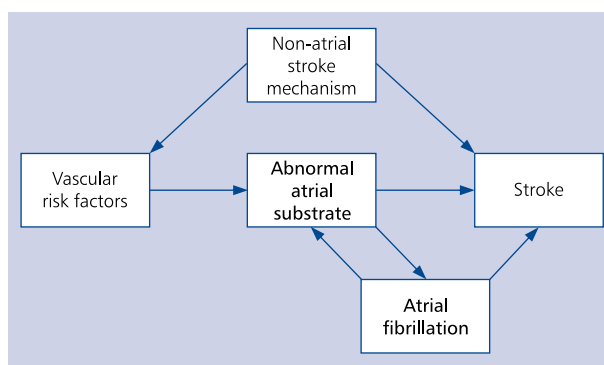
Figure 1. Potential mechanisms of stroke: time for a new model based on a concept proposed by Hooman Kamel and co-workers [9]

ation has revealed no explicit cause [5]. Regarding emerging evidence, we probably need a new approach and a new model explaining the relation between arrhythmia, including AF, and ischaemic stroke.

In this review, we discuss a relatively new concept of atrial cardiopathy (Fig. 1) [6–9]. It assumes that the risk of thromboembolism is increased regardless of atrial rhythm, being largely driven by atrial tissue abnormalities such as fibrosis, endothelial cell and myocyte dysfunction, and atrial dilatation. Once set up, atrial cardiopathy is always present, permanently thrombogenic, and might periodically present as AF. This new perspective considers both AF and thromboembolism as concomitant manifestations and consequences of underlying atrial tissue abnormalities. In consequence AF is a potential warning sign but no longer a cause of thromboembolism. Atrial cardiopathy may cause thromboembolism even in the absence of AF. This concept has several clinical implications.

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EVALUATING AF AS A CAUSE
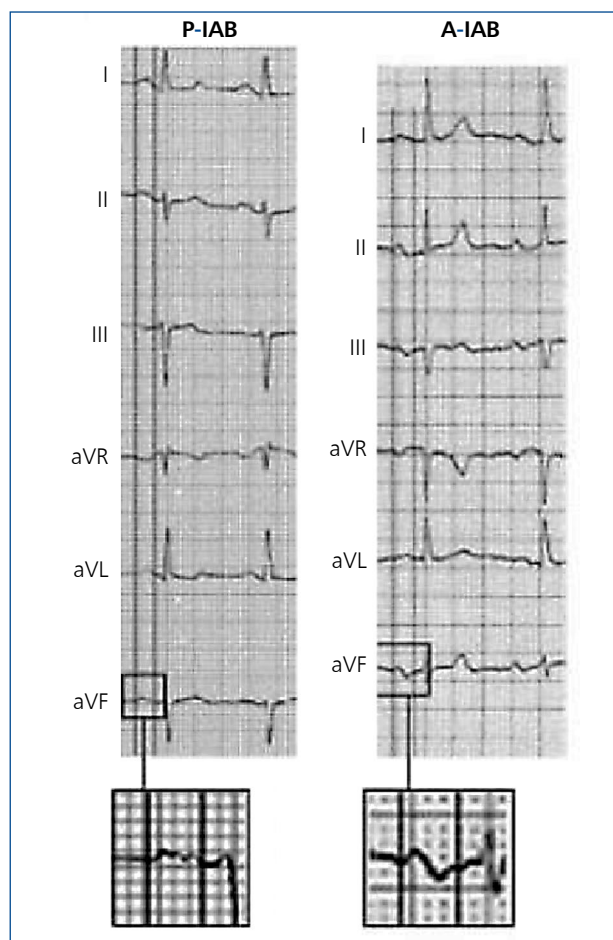## OF CRYPTOGENIC STROKE

As long as the causes of cryptogenic strokes remain unknown, we do not know how to prevent them. Since AF is an acknowledged risk factor for stroke, it often occurs asymptomatically and can be undetected before stroke, it has been considered a potential cause of cryptogenic ischaemic events. This view led to prolonged ambulatory heart rhythm monitoring among patients with unexplained stroke using electrocardiogram (ECG) long-term Holter monitoring or insertable cardiac monitors. Evidence coming from numerous studies shows that an exact relation between subclinical AF and thromboembolic events is hard to establish [10]. A meta-analysis of several surveys demonstrated that the procedure of long-term rhythm monitoring after stroke or transient ischaemic attack (TIA) detected a new AF in only 11.5% of patients; however the timing, duration, and means of monitoring differed among studies [11]. Thereby AF probably fails to explain the vast majority of cryptogenic strokes, principally if temporal relation is considered. Data from the TRENDS study of patients with at least one risk factor for stroke and an implanted dual-chamber cardiac pacemaker revealed that as few as 25% of patients manifested AF within 30 days before stroke [12]. Only 17% of participants followed in the Veterans Administration Health Care System had device-detected AF in 30 days of stroke event [13]. In the ASSERT trial this number equalled 8% [14]. Data on the relationship between the pattern or duration of AF and the risk of stroke are also discrepant. AF is defined as paroxysmal if it lasts < 7 days; persistent when lasting > 7 days; longstanding persistent, which lasts > 12 months, and permanent — an ongoing long-term one [15]. Several studies (e.g. ROCKET-AF, AMADEUS) and meta-analyses showed that paroxysmal AF is related more to lower risk of stroke, death, and bleeding than persistent or permanent type of arrhythmia, although the reason for this phenomenon remains uncertain [16–18]. Could it be due to a less diseased atrial substrate in a shorter-lasting arrhythmia? The TRENDS trial results suggest that AF lasting more than 5.5 h daily in 30 days prior to stroke doubles its risk [12]. However none of the studies has been sufficient to prove a "safe" burden of AF, which does not increase the risk of stroke so far. Episodes as brief as six minutes seemed to increase the risk of thromboembolic complications more than two-fold among patients aged over 65 years with established vascular risk factors, according to the ASSERT trial [14]. On the other hand, evidence from the ASSERT-2 trial demonstrates that patients over 65 years of age have similar risk of subclinical AF (lasting longer than 5 min) — regardless of history of prior stroke, systemic embolism, or transient ischaemic events [19]. Occurrence of lone AF probably does not increase the risk of stroke in younger people. Young patients with documented AF but without known vascular risk factors had the same rates of stroke as healthy controls [20]. These data suggest that thromboembolic risk may be triggered by something more than just the arrhythmia. There is yet another puzzling issue: why successful and sustained restoration of sinus rhythm is not sufficient to reduce the risk of stroke, which is a conclusion from a meta-analysis of several trials [21]. However, recent evidence from large cohorts of AF patients treated with catheter ablation has shown a significant reduction of stroke or transient ischaemic events in comparison with a well-matched general AF population, also including patients after cardioversion [22].

EVALUATING ATRIAL
CARDIOPATHY UNDERLYING AF

The current approach regarding AF as a direct cause of stroke requires prolonged heart rhythm monitoring in order to detect subclinical arrhythmia, evaluation of the ischaemic stroke risk, and finally the use of anticoagulation, if indicated. Nevertheless, emerging data provide evidence for a substantial association between left atrial (LA) abnormalities and ischaemic stroke even in the absence of AF. Atrial tissue abnormalities including fibrosis, endothelial cell and cardiomyocyte dysfunction, and chamber dilation may cause thromboembolism instead of arrhythmia, especially regarding lack of evidence for the consistent temporal and causative link between AF and cryptogenic stroke. Rhythm control strategies seem to be insufficient to reduce the risk of stroke. Growing evidence shows that atrial arrhythmias other than apparent AF are also linked to elevated risk of ischaemic stroke. Investigators from the Copenhagen Holter Study demonstrated an association between supraventricular ectopic activity and higher risk of death and stroke even after adjustment for cardiovascular risk factors [23]. Results of another study showed an independent association between paroxysmal supraventricular tachycardia and cryptogenic stroke among a large group of patients with no overt AF [24]. Furthermore, thromboembolic risk is increased in the absence of any atrial arrhythmia, but due to the presence of electrocardiographic features of LA abnormalities. P-wave terminal force in lead V_1 ($PTFV_1$), P-wave duration and maximum P-wave area are electrocardiographic parameters used to assess LA abnormalities related to the risk of developing AF (Fig. 2) [25–29]. $PTFV_1$ and advanced interatrial block are considered markers of LA derangements including fibrosis, elevated pressure, and dilatation; hence, they may be markers of atrial cardiopathy development, a further basis for subsequent thromboembolism and AF. However, we must consider several limitations of the citied studies, such as lack of long-term heart rhythm monitoring, so that subclinical AF cannot be ruled out in individual cases as a mediator of the relationship between $PTFV_1$ and thrombotic brain injury. Despite limitations, non-AF atrial arrhythmias and ECG markers of atrial derangements might comprise a clinical sign of atrial cardiopathy and a promising novel potential marker for the risk of thromboembolism stratification.

Besides ECG abnormalities, several imaging techniques may be useful in the assessment of atrial cardiopathy in its sub-

Figure 2. Partial interatrial block (P-IAB, P wave duration ≥ 120 ms, positive in leads II, III, and aVF) and advanced interatrial block (A-IAB, P wave duration ≥ 120 ms with biphasic morphology in leads II, III, and aVF [28]

in cardiac magnetic resonance imaging reveals the area of fibrosis in vivo, and the extent of fibrosis was demonstrated to correlate with $CHADS_2$ score and a history of stroke, as well as to anticipate the outcomes of catheter ablation in AF [32].

CLINICAL IMPACT OF ATRIAL CARDIOPATHY EVALUATION

Assuming that fibrosis is one of the pathogenic pathways in AF development, it is conceivable that it develops over some period of time. In the beginning, normal atrium changes under the influence of some well-known factors promoting fibrosis (such as LA overload, shear stress, oxidative stress, inflammation) and slowly moves into stages of more and more advanced myopathy. If we are capable of identifying signs of atrial cardiopathy in its early stages before thromboembolism or AF may occur, some early preventive treatments and upstream therapies should be considered in order to stop, reverse, or retard further pathologies and their consequences. In fact, beneficial effects of various upstream therapies have been already evaluated in primary prevention as well as in established AF, to start with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists (MRA), statins, or omega-3 polyunsaturated fatty acids. MRA and statins seem to be the most prognostically effective. The renin-angiotensin-aldosterone system hyperactivity is well-documented in the AF pathology. Angiotensin II and aldosterone strongly promote fibroblast activity, which leads to structural changes in the cardiac tissue, such as fibrosis, and they induce inflammatory processes, oxidative stress, cardiomyocyte hypertrophy, and necrosis. The EMPHASIS-HF study demonstrated an essential reduction in new-onset AF among patients with heart failure (New York Heart Association Class II, ejection fraction < 35%) treated with eplerenone [33]. Use of MRA in patients with hypertension or heart failure has been demonstrated to reduce LA fibrosis and remodelling and to be successful in primary as well as in secondary prevention of AF [34, 35]. Statins were proven to substantially reduce the risk of AF incidence or recurrence and were more beneficial in secondary than primary prevention of arrhythmia, based on a meta-analysis of 20 studies [36].

THE NEED FOR AN UPDATED MODEL OF STROKE RISK ASSESSMENT

Once AF is diagnosed, treatment must consider causative approach, choice of rhythm versus rate control strategy, and appropriate prevention of thromboembolic events. There is no place for a one-size-fits-all scheme. Treatment decisions require a precise stroke risk evaluation, whereas currently recommended tools do not provide fully reliable discrimination. CHA_2DS_2-VASc score (heart failure, hypertension, age 65–74 [1 point] or ≥ 75 years [2 points], diabetes mellitus, stroke, TIA or thromboembolism [2 points], vascular disease, sex category — female) is effective in identifying low-risk

clinical phase. These include transthoracic echocardiography (TTE), which nowadays is an imaging tool of choice and a crucial part of clinical evaluation of a patient presenting with AF. Left atrial enlargement in TTE is widely considered as a marker of increased risk of thromboembolism among patients with apparent AF, but what is more — extended LA dimension or volume are predictive of elevated risk of stroke even after adjustment for AF or in the absence of AF [30, 31]. There are several novel echocardiographic techniques currently not included in everyday clinical practice but revealing more than just the atrial size. Assessment of LA ejection fraction, LA function index, tissue Doppler imaging, speckle-tracking strain analysis, and three-dimensional echocardiography allow us to measure LA dysfunction and myocardial deformation. They offer new insights into pathophysiological processes underlying AF and thromboembolism and are assumed to predict development of AF or even stroke (although existing data remain limited). Atrial late gadolinium enhancement

patients. However, its c-statistic (probability that a randomly selected patient who had experienced stroke had a higher risk score than a patient who had not experienced the event, where 1.0 means a perfect discrimination) remains suboptimal (ranging from 0.55 to 0.67 among various cohorts) [8]. An updated model of stroke risk assessment may improve discrimination of patients with truly low risk of thromboembolism, who do not benefit from anticoagulation. Furthermore, it should potentially comprise a screening tool in the general population without documented AF. Therefore, introducing novel markers of increased stroke risk is necessary.

Various serum biomarkers have already been evaluated, and even though they seem not to be specific to atrial myopathy, several agents might be predictive of AF and its complications. The most promising biomarkers are natriuretic peptides and troponins. Data from the subanalysis of the RE-LY and ARISTOTLE trials have demonstrated that elevated levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) correlated with increased risk of stroke or systemic embolism; however, added to the CHA_2DS_2-VASc score they only modestly improved its c-statistics [37, 38]. Similar results were obtained for cardiac troponin I levels [37]. Recently, subanalysis of the ENGAGE AF-TIMI 48 trial demonstrated that elevated levels of troponin I, NT-proBNP and D-dimers taken together among patients with AF corresponded with more than 15-fold gradient of risk of stroke, systemic embolic events, or death after adjustment for CHA_2DS_2-VASc score. When added to the CHA_2DS_2-VASc score, they significantly improved its prognostic value with c-statistic elevated from 0.586 to 0.708 [39].

A number of studies show that chronic kidney disease also contributes to elevated risk of thromboembolic complications in AF. Subanalyses of the ROCKET-AF and ATRIA studies have demonstrated that in patients with nonvalvular AF at a moderate to high risk of stroke, reduced creatinine clearance is an independent predictor of stroke and systemic embolism, and it modestly improved c-statistic of CHA_2DS_2-VASc score [40]. Impaired renal function has been found to be a predictive factor of stroke risk also in a cohort of low-risk AF patients (with CHA_2DS_2-VASc score 0–1), as shown by Lin et al. [41]. It supports a moderate value of CHA_2DS_2-VASc-based stroke risk assessment. Bayes de Luna et al. [28] suggest new steps in the prevention of ischaemic stroke by using anticoagulation therapy in sinus rhythm patients if they are at high risk of AF and stroke, even without documentation of AF. The subgroup of high risk patients may be identified by advanced interatrial block, structural heart disease, CHA_2DS_2-VASc score ≥ 3, and frequent premature atrial contractions. Prospective validation of this approach in controlled interventional studies should be performed. Two of the proposed criteria are not precisely defined: structural heart disease and frequent premature atrial contractions, which can have a temporal character (Table 1) [28].

Table 1. Proposed criteria of high stroke risk patients with indications for anticoagulation therapy [28]

Advanced interatrial block (P wave ≥ 120 ms, positive in leads II, III, aVF)
Structural heart disease
CHA_2DS_2-VASc score ≥ 3
Frequent premature atrial contractions

CONCLUSIONS AND FUTURE DIRECTIONS

Current pathophysiology of AF and thromboembolism appears to be unclear, as experimental and clinical evidence has failed to establish any clear causative or temporal association between arrhythmia and ischaemic stroke so far. A new approach considering LA tissue abnormalities as a real cause of thromboembolism rather than atrial arrhythmia is more consistent with present data. Although the concept of atrial cardiopathy is not yet widely accepted and its clinical significance still needs to be established, a detailed report by the European Heart Rhythm Association (EHRA), the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLAECE) working committee in collaboration with the American Heart Association (AHA) and the American College of Cardiology (ACC) has been published lately in order to discuss the issue of "atrial cardiomyopathy". On the base of current reports the term "atrial cardiopathy" occurs more often in the context of stroke, whereas "atrial cardiomyopathy" covers a larger area of potential pathologies. The authors of the statement define atrial cardiomyopathy as "any complex of structural, architectural, contractile, or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestation" [42]. They precisely characterise atrial cardiomyopathy considering atrial anatomy, electrophysiology, structural properties, functions, imaging, and causes of atrial pathologies. They make a first attempt to develop a new classification of atrial cardiomyopathy based on histological features. Moreover, the document has several therapeutic implications [43]. It is an attempt to establish the effect of atrial cardiomyopathy on arrhythmogenesis and efficacy of AF ablation. The statement indicates the need for optimal selection of patients referred to ablation or rate control therapy, depending on atrial cardiomyopathy features. Experts also discuss potential implications of atrial cardiomyopathy diagnosis for stroke prevention. Reducing rates of stroke constitutes the most important therapeutic aim. Incorporating novel markers of atrial derangements into stroke risk scoring strategies is likely to improve future outcomes. Detecting atrial pathology before diagnosis of AF may facilitate and precipitate usage of

upstream therapies, thus making primary prevention of AF more successful. Yet another question arises. Is anticoagulation advisable for patients with atrial cardiopathy or multiple stroke risk factors with no AF documented in spite of the application of current diagnostic methods? A study of patients with heart failure revealed that incidence of stroke, thromboembolism, or death was similar regardless of AF presence, and the c-statistic for the CHA_2DS_2-VASc score was 0.67 in a group with AF and 0.64 without AF [44]. The prevalence of stroke is independent of AF for patients beyond a score value of 6. The risk of stroke is particularly high in patients with the presence of arrhythmic symptoms, previous myocardial infarction, or heart failure even in the absence of documented arrhythmias [45]. Future trials are needed to shed more light on a concept of atrial cardiopathy and its contribution to ischaemic stroke. Finally, AF is a complex condition and its possible consequences in an individual patient are hard to predict.

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References

1. Pruszczyk P, Stępińska J, Banasiak W, et al. [New oral anticoagulants in the prevention of embolic complications in patients with atrial fibrillation. Polish Cardiac Society, Polish Neurological Society and Working Group on Haemostasis of the Polish Society of Haematologists and Transfusiologists consensus statement]. Kardiol Pol. 2012; 70(9): 979–988, indexed in Pubmed: 22993019.
2. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001; 285(18): 2370–2375, doi: 10.1001/jama.285.18.2370, indexed in Pubmed: 11343485.
3. Albers GW, Bernstein RA, Brachmann J, et al. Heart Rhythm Monitoring Strategies for Cryptogenic Stroke: 2015 Diagnostics and Monitoring Stroke Focus Group Report. J Am Heart Assoc. 2016; 5(3): e002944, doi: 10.1161/JAHA.115.002944, indexed in Pubmed: 27068633.
4. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991; 22(8): 983–988, doi: 10.1161/01.str.22.8.983, indexed in Pubmed: 1866765.
5. Marnane M, Duggan CA, Sheehan OC, et al. Stroke subtype classification to mechanism-specific and undetermined categories by TOAST, A-S-C-O, and causative classification system: direct comparison in the North Dublin population stroke study. Stroke. 2010; 41(8): 1579–1586, doi: 10.1161/STROKEAHA.109.575373, indexed in Pubmed: 20595675.
6. Calenda BW, Fuster V, Halperin JL, et al. Stroke risk assessment in atrial fibrillation: risk factors and markers of atrial myopathy. Nat Rev Cardiol. 2016; 13(9): 549–559, doi: 10.1038/nrcardio.2016.106, indexed in Pubmed: 27383079.
7. Kamel H, Okin PM, Longstreth WT, et al. Atrial cardiopathy: a broadened concept of left atrial thromboembolism beyond atrial fibrillation. Future Cardiol. 2015; 11(3): 323–331, doi: 10.2217/fca.15.22, indexed in Pubmed: 26021638.
8. Goldberger JJ, Arora R, Green D, et al. Evaluating the Atrial Myopathy Underlying Atrial Fibrillation: Identifying the Arrhythmogenic and Thrombogenic Substrate. Circulation. 2015; 132(4): 278–291, doi: 10.1161/CIRCULATIONAHA.115.016795, indexed in Pubmed: 26216085.
9. Kamel H, Okin PM, Elkind MSV, et al. Atrial Fibrillation and Mechanisms of Stroke: Time for a New Model. Stroke. 2016;
10. 47(3): 895–900, doi: 10.1161/STROKEAHA.115.012004, indexed in Pubmed: 26786114.
10. Majos E, Dabrowski R. Significance and Management Strategies for Patients with Asymptomatic Atrial Fibrillation. J Atr Fibrillation. 2015; 7(5): 1169, doi: 10.4022/jafib.1169, indexed in Pubmed: 27957147.
11. Kishore A, Vail A, Majid A, et al. Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. Stroke. 2014; 45(2): 520–526, doi: 10.1161/STROKEAHA.113.003433, indexed in Pubmed: 24385275.
12. Glotzer TV, Daoud EG, Wyse DG, et al. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. Circ Arrhythm Electrophysiol. 2009; 2(5): 474–480, doi: 10.1161/CIRCEP.109.849638, indexed in Pubmed: 19843914.
13. Turakhia MP, Ziegler PD, Schmitt SK, et al. Atrial Fibrillation Burden and Short-Term Risk of Stroke: Case-Crossover Analysis of Continuously Recorded Heart Rhythm From Cardiac Electronic Implanted Devices. Circ Arrhythm Electrophysiol. 2015; 8(5): 1040–1047, doi: 10.1161/CIRCEP.114.003057, indexed in Pubmed: 26175528.
14. Healey JS, Connolly SJ, Gold MR, et al. ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med. 2012; 366(2): 120–129, doi: 10.1056/NEJMoa1105575, indexed in Pubmed: 22236222.
15. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016; 37(38): 2893–2962, doi: 10.1093/eurheartj/ehw210, indexed in Pubmed: 27567408.
16. Steinberg BA, Hellkamp AS, Lokhnygina Y, et al. ROCKET-AF Steering Committee and Investigators. Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF Trial. Eur Heart J. 2015; 36(5): 288–296, doi: 10.1093/eurheartj/ehu359, indexed in Pubmed: 25209598.
17. Senoo K, Lip GYH, Lane DA, et al. Residual Risk of Stroke and Death in Anticoagulated Patients According to the Type of Atrial Fibrillation: AMADEUS Trial. Stroke. 2015; 46(9): 2523–2528, doi: 10.1161/STROKEAHA.115.009487, indexed in Pubmed: 26205373.
18. Ganesan AN, Chew DP, Hartshorne T, et al. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. Eur Heart J. 2016; 37(20): 1591–1602, doi: 10.1093/eurheartj/ehw007, indexed in Pubmed: 26888184.
19. Healey JS, Alings M, Ha A, et al. ASSERT-II Investigators. Subclinical Atrial Fibrillation in Older Patients. Circulation. 2017; 136(14): 1276–1283, doi: 10.1161/CIRCULATIONAHA.117.028845, indexed in Pubmed: 28778946.
20. Chao TF, Liu CJ, Chen SJ, et al. Atrial fibrillation and the risk of ischemic stroke: does it still matter in patients with a CHA2DS2-VASc score of 0 or 1? Stroke. 2012; 43(10): 2551–2555, doi: 10.1161/STROKEAHA.112.667865, indexed in Pubmed: 22871677.
21. Al-Khatib SM, Allen LaPointe NM, Chatterjee R, et al. Rate- and rhythm-control therapies in patients with atrial fibrillation: a systematic review. Ann Intern Med. 2014; 160(11): 760–773, doi: 10.7326/M13-1467, indexed in Pubmed: 24887617.
22. Jarman JWe, Hunter TD, Hussain W, et al. Mortality, stroke, and heart failure in atrial fibrillation cohorts after ablation versus propensity-matched cohorts. Pragmat Obs Res. 2017; 8: 99–106, doi: 10.2147/POR.S134777, indexed in Pubmed: 28615986.
23. Binici Z, Intzilakis T, Nielsen OW, et al. Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke. Circulation. 2010; 121(17): 1904–1911, doi: 10.1161/CIRCULATIONAHA.109.874982, indexed in Pubmed: 20404258.
24. Kamel H, Elkind MSV, Bhave PD, et al. Paroxysmal supraventricular tachycardia and the risk of ischemic stroke. Stroke.

2013; 44(6): 1550–1554, doi: 10.1161/STROKEAHA.113.001118, indexed in Pubmed: 23632982.

25. Kamel H, Soliman EZ, Heckbert SR, et al. P-wave morphology and the risk of incident ischemic stroke in the Multi-Ethnic Study of Atherosclerosis. Stroke. 2014; 45(9): 2786–2788, doi: 10.1161/STROKEAHA.114.006364, indexed in Pubmed: 25052322.

26. Kamel H, Bartz TM, Longstreth WT, et al. Association between left atrial abnormality on ECG and vascular brain injury on MRI in the Cardiovascular Health Study. Stroke. 2015; 46(3): 711–716, doi: 10.1161/STROKEAHA.114.007762, indexed in Pubmed: 25677594.

27. Kamel H, Hunter M, Moon YP, et al. Electrocardiographic Left Atrial Abnormality and Risk of Stroke: Northern Manhattan Study. Stroke. 2015; 46(11): 3208–3212, doi: 10.1161/STROKE-AHA.115.009989, indexed in Pubmed: 26396031.

28. Bayés de Luna A, Baranchuk A, Martínez-Sellés M, et al. Anticoagulation in patients at high risk of stroke without documented atrial fibrillation. Time for a paradigm shift? Ann Noninvasive Electrocardiol. 2017; 22(1), doi: 10.1111/anec.12417, indexed in Pubmed: 27982498.

29. He J, Tse G, Korantzopoulos P, et al. P-Wave Indices and Risk of Ischemic Stroke: A Systematic Review and Meta-Analysis. Stroke. 2017; 48(8): 2066–2072, doi: 10.1161/STROKEAHA.117.017293, indexed in Pubmed: 28679858.

30. Barnes ME, Miyasaka Y, Seward JB, et al. Left atrial volume in the prediction of first ischemic stroke in an elderly cohort without atrial fibrillation. Mayo Clin Proc. 2004; 79(8): 1008–1014, doi: 10.4065/79.8.1008, indexed in Pubmed: 15301328.

31. Karas MG, Devereux RB, Wiebers DO, et al. Incremental value of biochemical and echocardiographic measures in prediction of ischemic stroke: the Strong Heart Study. Stroke. 2012; 43(3): 720–726, doi: 10.1161/STROKEAHA.111.631168, indexed in Pubmed: 22207511.

32. Calenda BW, Fuster V, Halperin JL, et al. Stroke risk assessment in atrial fibrillation: risk factors and markers of atrial myopathy. Nat Rev Cardiol. 2016; 13(9): 549–559, doi: 10.1038/nrcardio.2016.106, indexed in Pubmed: 27383079.

33. Swedberg K, Zannad F, McMurray JJV, et al. EMPHASIS-HF Study Investigators. Eplerenone and atrial fibrillation in mild systolic heart failure: results from the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure) study. J Am Coll Cardiol. 2012; 59(18): 1598–1603, doi: 10.1016/j.jacc.2011.11.063, indexed in Pubmed: 22538330.

34. Dabrowski R, Borowiec A, Smolis-Bak E, et al. Effect of combined spironolactone-β-blocker ± enalapril treatment on occurrence of symptomatic atrial fibrillation episodes in patients with a history of paroxysmal atrial fibrillation (SPIR-AF study). Am J Cardiol. 2010; 106(11): 1609–1614, doi: 10.1016/j.amjcard.2010.07.037, indexed in Pubmed: 21094362.

35. Dąbrowski R, Szwed H. Antiarrhythmic potential of aldosterone antagonists in atrial fibrillation. Cardiol J. 2012; 19(3): 223–229, doi: 10.5603/cj.2012.0043, indexed in Pubmed: 22641540.

36. Fang Wt, Li HJ, Zhang H, et al. The role of statin therapy in the prevention of atrial fibrillation: a meta-analysis of randomized controlled trials. Br J Clin Pharmacol. 2012; 74(5): 744–756, doi: 10.1111/j.1365-2125.2012.04258.x, indexed in Pubmed: 22376147.

37. Hijazi Z, Oldgren J, Andersson U, et al. Cardiac biomarkers are associated with an increased risk of stroke and death in patients with atrial fibrillation: a Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) substudy. Circulation. 2012; 125(13): 1605–1616, doi: 10.1161/CIRCULATIO-NAHA.111.038729, indexed in Pubmed: 22374183.

38. Hijazi Z, Wallentin L, Siegbahn A, et al. N-terminal pro-B-type natriuretic peptide for risk assessment in patients with atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation). J Am Coll Cardiol. 2013; 61(22): 2274–2284, doi: 10.1016/j.jacc.2012.11.082, indexed in Pubmed: 23563134.

39. Ruff CT, Giugliano RP, Braunwald E, et al. Cardiovascular Biomarker Score and Clinical Outcomes in Patients With Atrial Fibrillation: A Subanalysis of the ENGAGE AF-TIMI 48 Randomized Clinical Trial. JAMA Cardiol. 2016; 1(9): 999–1006, doi: 10.1001/jamacardio.2016.3311, indexed in Pubmed: 27706467.

40. Piccini JP, Stevens SR, Chang Y, et al. ROCKET AF Steering Committee and Investigators. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R(2)CHADS(2) index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study cohorts. Circulation. 2013; 127(2): 224–232, doi: 10.1161/CIR-CULATIONAHA.112.107128, indexed in Pubmed: 23212720.

41. Lin WY, Lin YJ, Chung FP, et al. Impact of renal dysfunction on clinical outcome in patients with low risk of atrial fibrillation. Circ J. 2014; 78(4): 853–858, doi: 10.1253/circj.cj-13-1246, indexed in Pubmed: 24521763.

42. Goette A, Kalman JM, Aguinaga L, et al. Document Reviewers. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. Europace. 2016; 18(10): 1455–1490, doi: 10.1093/europace/euw161, indexed in Pubmed: 27402624.

43. Guichard JB, Nattel S. Atrial Cardiomyopathy: A Useful Notion in Cardiac Disease Management or a Passing Fad? J Am Coll Cardiol. 2017; 70(6): 756–765, doi: 10.1016/j.jacc.2017.06.033, indexed in Pubmed: 28774383.

44. Melgaard L, Gorst-Rasmussen A, Lane DA, et al. Assessment of the CHA2DS2-VASc Score in Predicting Ischemic Stroke, Thromboembolism, and Death in Patients With Heart Failure With and Without Atrial Fibrillation. JAMA. 2015; 314(10): 1030–1038, doi: 10.1001/jama.2015.10725, indexed in Pubmed: 26318604.

45. Martínez-Sellés M, García-Izquierdo Jaén E, Fernández Lozano I. Anticoagulation in elderly patients at high risk of atrial fibrillation without documented arrhythmias. J Geriatr Cardiol. 2017; 14(3): 166–168, doi: 10.11909/j.issn.1671-5411.2017.03.004, indexed in Pubmed: 28592958.