Differences in Thromboembolic Complications Between Paroxysmal and Persistent Atrial Fibrillation Patients Following Electrical Cardioversion (From the ENSURE-AF Study)

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It is unclear if patients with paroxysmal atrial fibrillation (AF) and persistent AF have different outcomes following electrical cardioversion (ECV). ENSURE-AF—a multicenter, prospective, randomized, open-label, blinded-endpoint evaluation trial—compared once-daily edoxaban 60 mg with enoxaparin−warfarin in 2,199 subjects undergoing ECV of nonvalvular AF (NCT02072434). Patients received ≥3 weeks of proper anticoagulation or transesophageal echocardiogram before ECV paroxysmal AF was defined as AF with spontaneous conversion of duration of <7 days; persistent AF was defined as AF lasting ≥7 days without spontaneous conversion. Clinical characteristics and outcomes were compared between subjects based on type of AF present at baseline. In total, 415 subjects had paroxysmal AF; 1,777 had persistent AF. Patients with paroxysmal AF were older (65.8 ± 10.3 vs 63.9 ± 10.5, p = 0.001) with more hypertension (82.7% vs 77.2%, p = 0.01) versus persistent AF patients. Congestive heart failure was more common in persistent AF (46.7%) versus paroxysmal AF (31.3%, p <0.0001). CHA_2DS_2-VASc (score >2: 52.0% vs 49.5%, p = 0.4375) and prior myocardial infarction (6.5% vs 6.8%, p = 0.91) did not significantly differ between groups. After ECV, primary endpoint events were numerically higher in paroxysmal AF versus persistent AF (1.5% vs 0.6%, p = 0.0571), approaching statistical significance. Of note, myocardial infarction was observed in paroxysmal AF (n = 4 vs 0), whereas persistent AF was accompanied by stroke (n = 0 vs 5; p <0.05). In conclusion, patients with paroxysmal AF had more frequent major cardiovascular events than patients with persistent AF. Composite event rates were driven mainly by myocardial infarction in patients with paroxysmal AF and by stroke in those with persistent AF. Overall, the absolute number of events was low after ECV under anticoagulation. **(Am J Cardiol 2020;131:27−32)**

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Preprocedural thromboembolic prevention studies suggest that the duration of atrial fibrillation (AF) may have an impact on outcome.[1] Studies and registries demonstrate that paroxysmal AF may be associated with a better prognosis than persistent AF, but this has not been studied in the setting of cardioversion.[2−5] It is unclear if the type of AF affects stroke and myocardial infarction rates in this clinical setting. Paroxysmal AF often presents with episodes of sudden elevation of heart rate, and this may carry a higher risk of ventricular ischemia compared with persistent AF. The opposite might be true for the occurrence of stroke.[4,5] Persistent AF may also reflect the presence of more pronounced atrial endocardial pathologies, which increases the risk of atrial thrombogenesis, and thereby, the risk of stroke in persistent AF.[6−8] It is unknown whether this may result in different outcomes following electrical cardioversion (ECV) despite proper anticoagulation at the time of the procedure. In the EdoxabaN vs wafarin in subjectS UndeRgoing cardiovErsion of Atrial Fibrillation (ENSURE-AF) trial (NCT02072434), a multicenter, prospective, randomized, open-label, blinded-endpoint evaluation trial, the oral factor Xa inhibitor edoxaban demonstrated a comparable efficacy and safety profile versus enoxaparin-warfarin in nonvalvular AF patients undergoing ECV.[3] This analysis

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investigated the primary endpoint (composite of stroke, systemic embolic event [SEE], myocardial infarction [MI], and cardiovascular [CV] mortality) following ECV in patients with paroxysmal versus patients with persistent AF. The aim of the present post hoc analysis of the ENSURE-AF trial was to investigate the differences in outcomes in patients with paroxysmal and persistent AF after ECV.

Methods

The design and trial results of the ENSURE-AF trial (NCT 02072434) were reported elsewhere.[9,10] The ENSURE-AF trial was a multicenter, prospective, randomized, open-label, blinded-endpoint evaluation, parallel group phase 3b clinical trial, in which patients with non-valvular AF were randomized to edoxaban or warfarin after ECV. Patients with an international normalized ratio (INR) <2.0 at randomization received enoxaparin and daily warfarin until the INR was ≥2.0, and those with INR ≥2.0 at the time of randomization did not require enoxaparin and were treated with warfarin alone. Patients were stratified by anticoagulation strategy (transesophageal echocardiography [TEE] or non-TEE strata, or whether previously anticoagulation naïve or experienced, selected edoxaban dose, and region, as defined at randomization; Figure 1).

ENSURE-AF study was done in compliance with the protocol, the ethical principles as outlined in the Declaration of Helsinki, the International Conference on Harmonisation consolidated Guideline E6 for Good Clinical Practice (CPMP/ICH/135/95), and applicable regulatory requirements. The protocol and its amendments were approved by ethics committees or institutional review boards. All patients provided written informed consent prior to participation in the study.

In this trial, paroxysmal and persistent AF were defined in accordance to the definitions of the European Society of Cardiology guidelines at the time of the study.[11] Paroxysmal AF patients were defined as such when they had prior AF episodes with spontaneous conversion to sinus rhythm without using pharmacological or direct current cardioversion in <7 days and presenting at the time of ECV of the study with continuous AF for <7 days. Persistent AF patients were defined as such if they had prior history of pharmacological or ECV or had spontaneous AF cardioversion more than 7 days after the episode onset.

All subjects were followed for safety for 30 days (day 58) after completing treatment in the respective arms. If thrombi were identified during TEE, subjects were not eligible for ECV. Subjects with unsuccessful ECV or relapse of AF could be cardioverted again at the investigator's discretion.

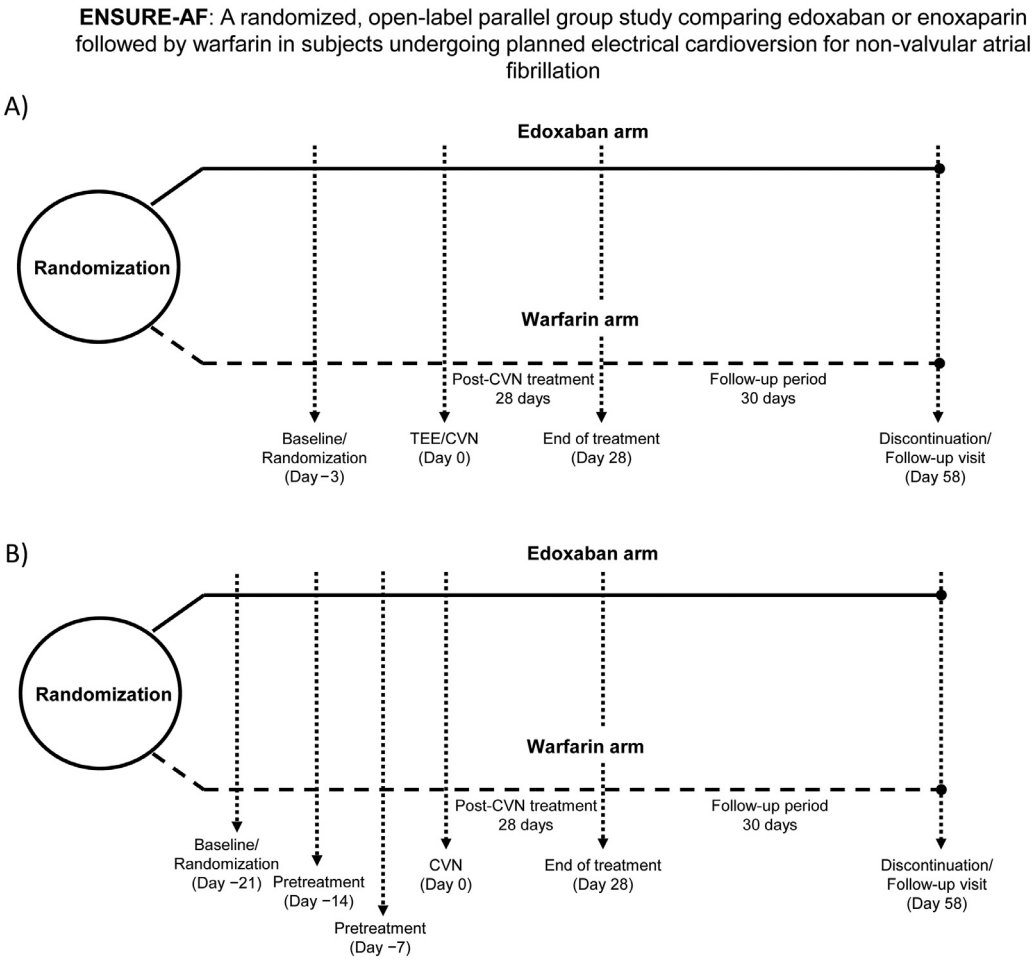

Figure 1. Study flow diagram for (a) TEE-guided stratum and (b) non-TEE-guided stratum. CVN, cardioversion; TEE, transesophageal echocardiogram.

The primary efficacy endpoint was a composite of stroke, SEE, MI, and CV death. The primary safety endpoint was the composite of major and clinically relevant nonmajor bleeding. All endpoints were reviewed, classified, and adjudicated by a blinded adjudication committee.

The primary efficacy analysis was performed on the intent-to-treat population, which included all randomized, enrolled patients. Efficacy outcomes were analyzed during the overall study period, 28 days on study drug after cardioversion + 30 days follow-up. The primary safety analysis was carried out on the safety population, which included all patients who took ≥1 dose of the study drug. Safety outcomes were analyzed during the on-treatment period from the time of first dose to the last dose of the study drug taken plus 3 days. Clinical characteristics and outcomes were compared between patients based on type of AF present at baseline.

A logistic regression analysis was performed to identify predictors for MI, or the composite endpoint of stroke, SEE, MI, and CV death. Age, gender, region, CHA_2DS_2-VASc score, type of AF, medical histories of ischemic stroke/transient ischemic attack, hypertension, diabetes, congestive heart failure, valvular heart disease, MI, and peripheral arterial disease are included as variables in the analysis. Due to likely correlations among these variables, a stepwise approach is applied. A significance level of 0.1 is required to allow a variable into the model and for a variable to stay in the model.

Results

Overall, 2,199 patients were enrolled in the study; 415 had paroxysmal AF and 1,777 had persistent AF (Table 1). Patients with paroxysmal AF were significantly older and

Table 1
Baseline demographics and clinical characteristics by AF type

Parameter	Paroxysmal (n = 415)	Persistent (n = 1,777)	p value
Age (years), mean ± SD	66 ± 10	64 ± 11	0.0010
Men	256 (62%)	1183 (67%)	0.0661
Weight (kg), mean ± SD	89 ± 18	92 ± 19	0.0049
Body mass index, mean ± SD	30 ± 6	31 ± 6	0.1119
Geographical distribution			
Eastern Europe	223 (54%)	1074 (60%)	<0.0001
Middle East and North Africa	45 (11%)	37 (2%)	
North America	31 (8%)	63 (4%)	
Western Europe	116 (28%)	603 (34%)	
Anticoagulant naive	193 (47%)	406 (23%)	<0.0001
Current non-vitamin k antagonist oral anticoagulant user	45 (11%)	259 (15%)	0.0487
International normalized ratio at randomization, mean ± SD	1.3 ± 0.7	1.6 ± 0.7	<0.0001
Transesophageal echocardiogram stratum	270 (65%)	909 (51%)	<0.0001
Creatinine clearance, mean ± SD	91 ± 37	95 ± 35	0.1062
CHA_2DS_2-VASc score			
0-1	82 (20%)	401 (23%)	0.4375
2	117 (28%)	494 (28%)	
>2	216 (52%)	879 (50%)	
HAS-BLED score, mean ± SD	1.0 ± 0.8	0.9 ± 0.8	0.0208
Hypertension	343 (83%)	1371 (77%)	0.0145
Congestive heart failure	130 (31%)	830 (47%)	<0.0001
Diabetes disease	87 (21%)	327 (18%)	0.2366
Peripheral arterial disease	16 (4%)	78 (4%)	0.6885
Valvular heart disease	95 (23%)	395 (22%)	0.7936
Myocardial infarction	27 (7%)	120 (7%)	0.9136
Hepatic disease	21 (5%)	95 (5%)	0.9033
Ischemic/embolic stroke or transient ischemic attack	33 (8%)	101 (6%)	0.0879
Non-intracranial bleeding	15 (4%)	63 (4%)	0.8840
Intracranial bleeding	2 (0.5%)	3 (0.2%)	0.2409
Life-threatening bleed	3 (0.7%)	3 (0.2%)	0.0859
Drug therapies			
Aspirin	126 (30%)	286 (16%)	<0.0001
ACE inhibitor / angiotensin II receptor blocker	261 (63%)	1116 (63%)	1.0000
Beta blocker	327 (79%)	1380 (78%)	0.6461
Statin	191 (46%)	646 (36%)	0.0003
Amiodarone	84 (20%)	455 (26%)	0.0227
Diuretic	151 (36%)	744 (42%)	0.0458
Time to achieve therapeutic range			
Days, mean ± SD	8 ± 6	8 ± 5	0.5823
% of time, mean ± SD	67 ± 29	72 ± 27	0.0226
Time in therapeutic range (% of time), mean ± SD	55 ± 29	61 ± 31	0.0109
Successful/spontaneous cardioversion	305 (84%)	1273 (81%)	0.1752
Spontaneous cardioversion	63 (15%)	104 (6%)	<0.0001

Data are presented as n (%). AF, atrial fibrillation

Table 2
Efficacy endpoint events by AF type and treatment group

Endpoint	Edoxaban		Enoxaparin-Warfarin		Overall	
	Paroxysmal AF (n = 208)	Persistent AF (n = 887)	Paroxysmal AF (n = 207)	Persistent AF (n = 890)	Paroxysmal AF (n = 415)	Persistent AF (n = 1777)
Stroke, Systemic embolic events, Myocardial infarction or Cardiovascular Death (primary endpoint)	2 (1.0%)	3 (0.3%)	4 (1.9%)	7 (0.8%)	6 (1.5%)	10 (0.6%)
Stroke	0%	2 (0.2%)	0%	3 (0.3%)	0%	5 (0.3%)
Systemic embolic events	1 (0.5%)	0%	0%	1 (0.1%)	1 (0.2%)	1 (0.1%)
Myocardial infarction	1 (0.5%)	1 (0.1%)	3 (1.5%)	0%	4 (1.0%)	1 (0.1%)
Cardiovascular death	0%	1 (0.1%)	2 (1.0%)	3 (0.3%)	2 (0.5%)	4 (0.2%)
Intracranial hemorrhage	0%	0%	0%	0%	0%	0%

Data are presented as n (%). AF, atrial fibrillation

more frequently hypertensive compared with persistent AF patients (Table 1). Congestive heart failure was more common in patients with persistent AF versus paroxysmal AF (Table 1). The distribution of CHA_2DS_2-VASc scores and rate of prior MI did not significantly differ between patients with paroxysmal versus persistent AF (Table 1). At enrollment, more patients with paroxysmal AF were anticoagulant-naïve, taking aspirin or statins, and had lower INR relative to patients with persistent AF (Table 1). There was a significantly greater proportion of patients with paroxysmal versus persistent AF in the TEE-guided stratum, and significantly more paroxysmal AF patients experienced a spontaneous cardioversion than occurred in persistent AF patients (Table 1), consistent with previous reports.[4]

During the study (before ECV and at 58 days follow-up), the primary composite endpoint event rate was numerically higher—approaching statistical significance—in patients with paroxysmal versus persistent AF (1.5% vs 0.6%, $p = 0.0571$; individual events shown in Table 2).

There were no differences in all bleeding (2.9% vs 3.1%, $p = 0.83$), major bleeding (0.5% vs 0.3%, $p = 0.65$), and the composite of major and clinically relevant nonmajor bleeding events (1.5% vs 1.2%, $p = 0.66$) between patients with paroxysmal versus persistent AF.

A stepwise logistic regression analysis was performed to identify predictors for MI or the composite endpoint of stroke, SEE, MI, and CV death. AF type and CHA_2DS_2-VASc score emerged as independent predictors of MI ($p = 0.0152$ and 0.0276, respectively; patients with high CHA_2DS_2-VASc score or paroxysmal AF had higher probability of MI). Region and CHA_2DS_2-VASc score emerged as independent predictors of composite endpoint of stroke, SEE, MI, and CV death ($p = 0.0058$ and 0.0007, respectively), but AF type did not. However, there are limitations with a stepwise approach. The p values may be underestimated.

Discussion

In this ancillary analysis from ENSURE-AF, our principal findings are: (1) patients with paroxysmal AF may have more frequent major cardiovascular events than those with persistent AF following ECV, despite proper anticoagulation at time of procedure; (2) Composite event rates were driven mainly by MIs in patients with paroxysmal AF and by stroke among those with persistent AF; (3) patients with paroxysmal AF were more frequently anticoagulant-naïve despite similar CHA_2DS_2-VASc scores compared with persistent AF patients; and (4) of note, all patients were treated with adequate full dose of anticoagulant therapy encompassing edoxaban or enoxaparin/warfarin in the present trial after ECV.

Recent results from the GARFIELD-AF registry showed that persistent and permanent AF are associated with a higher risk of stroke/systemic embolism, death, and new or worsening heart failure than paroxysmal AF, even after adjustment for a large variety of clinical features.[12] Another finding of the GARFIELD-AF registry is that differences between types of AF were apparent in the subgroup of patients only were was not prescribed anticoagulant therapy.[12] In anticoagulated patients, difference in the risks of stroke/systemic embolism and new or worsening heart failure were absent.[12] This finding is in contrast to the findings in the ENSURE-AF trial since all included patients were fully anticoagulated throughout the follow up.[3] However, ECV may carry a particular and more specific risk compared with data from registries. Therefore, some differences might be explained by the different durations of follow-up. Nevertheless, outcome data are more rigorously assessed in randomized prospective trials compared with registries.

Risks of stroke/systemic embolism in different AF types are not captured by the values of CHA_2DS_2-VASc score. As proposed, AF types, biomarker measurements, P-wave analyses, and imaging modalities, in addition to the clinical risk profile, may further refine the predictive value of risk scores.[10,13–16] This may help to define the extent of the underlying atrial cardiomyopathy and degree of endocardial remodeling, which defines the risk for atrial clot formation at a molecular level.[6] In addition, trial results already suggest that taking AF pattern into consideration could aid the decision to anticoagulate, particularly in patients with a low stroke risk (i.e., a CHA_2DS_2-VASc score of ≤ 2).[16–18] A recent study by Kaplan et al analyzed 21,768 nonanticoagulated patients with implanted devices, and found that an increased AF duration and increasing CHA_2DS_2-VASc score were both significantly associated with annualized risk of stroke and systemic embolism.[17] Importantly, stroke and systemic embolism rates were low in AF patients with

CHA_2DS_2-VASc 0 to 1 regardless of AF duration. This is in accordance with the present data set that showed that paroxysmal AF was associated to a lesser extent with stroke than with MI. In that study, however, stroke risk crossed a threshold defined as >1%/year in CHA_2DS_2-VASc 2 patients with >23.5 hours of AF, CHA_2DS_2-VASc 3 to 4 patients with >6 minutes of AF.[16] A remarkable finding of that study is that in CHA_2DS_2-VASc ≥5 patients stroke rates were increased even in the absence of AF.[17] The exact duration of AF was not assessed in the ENSURE-AF trial; therefore, no comment can be made regarding different AF duration on stroke and MI after ECV.

Pathophysiologically, there are substantial differences between paroxysmal and persistent AF with regard to molecular atrial and ventricular biology.[6,19–21] Short periods of AF instantaneously induce microcirculatory flow abnormalities in the heart.[19] This is associated with occurrence of angina pectoris in some patients, followed by release of troponin T and a type 2 MI in the absence of coronary artery disease.[19] If coronary artery disease is present, increased and irregular rate after initiation of AF may impair flow across coronary artery stenoses causing myocardial ischemia. The main mechanisms during the initial phase of AF have been identified as the lack of nitric oxide due to generation of reactive oxygen species and oxidative stress in the ventricular tissue.[20,21] Thus, short duration of AF prior to ECV might have increased vulnerability of ventricular myocardium periprocedurally, which may have contributed to increased rate of MI in this particular subgroup despite the presence of adequate anticoagulation.[6] Interestingly, in persistent AF, oxidative stress is counterbalanced by downregulation of oxidative stress enzymes and signaling pathways.[6] In addition, paroxysmal AF often presents with high heart rate episodes, which may potentiate ischemic events. This is generally the case for persistent AF patients who have less dramatic heart rate changes, but, in contrast, may have higher average heart rate eventually leading to different degrees of tachycardia-induced cardiomyopathy and heart failure. Therefore, persistent AF carries a lower risk of AF-related myocardial ischemia in comparison with paroxysmal AF. Importantly, many AF patients remain in their category of AF for longer periods of time. Thus, the pattern of AF encompassing the already established atrial pathology is unlikely to have changed in the present trial with a short follow-up of 58 days.[6] Development of atrial thrombi is related to the Virchow's Triad including endocardial damage, reduced blood flow, and activation of the clotting system. Persistent AF much better characterizes such prothrombotic atrial pathologies.[4,5] Histologic studies have revealed more pronounced atrial tissue changes after longstanding AF episodes compared with AF of short duration.[6] Of note, these atrial changes persist even after successful restoration of sinus rhythm in patients with persistent AF, which may help to understand the increased stroke rate in persistent AF patients. However, the overall burden of AF might be a more useful and a better way for characterization of stroke risk compared with the general classification of paroxysmal and persistent AF.[16–18] Thus, the effects of AF burden on stroke rates need to be further elucidated. Nevertheless, ENSURE-AF was not designed to assess recurrences of AF after ECV. Therefore, it remains speculative if relapses of AF have contributed directly to the observed ischemic events. Outcome differences between patients with paroxysmal versus persistent AF could also be due to more frequent changes in thromboprophylaxis regimen in the former or to longer exposure to anticoagulants in the latter.

There are a number of limitations to this analysis, which may limit its generalizability. True duration of AF recurrence and AF burden was not assessed in the ENSURE-AF trial. Therefore, no comment can be made regarding the impact of AF duration on stroke and MI. The follow-up in the ENSURE-AF trial encompassed a total of 58 days, only. Thus, no comment can be made regarding longer follow up periods. Although our trial is the largest ECV trial so far, the absolute number of ischemic events was low. However, sufficiently powered trials to assess ischemic endpoints after ECV appear unrealistic since such a trial would need more than 10,000 patients.[9] Nevertheless, previous studies have shown that successful ECV is accompanied by substantial intraindividual changes of neurohormones, stem cells and organ perfusion despite adequate anticoagulation.[22–24] However, lack of sufficient anticoagulation after ECV might provide better answers regarding pathophysiological outcomes, but such an approach is considered unethical, and therefore, not feasible.

Patients with paroxysmal AF have more frequent major CV events than those with persistent AF following ECV despite proper anticoagulation at the time of procedure and during follow-up. Of note, composite event rates were driven mainly by MI in patients with paroxysmal AF and by stroke among those with persistent AF. However, the absolute number of ischemic events was low after ECV.

Authors Contribution

Andreas Goette: Conceptualization, Writing - Original Draft, Writing - Review & Editing. Gregory Y.H. Lip: Conceptualization, Writing - Original Draft, Writing - Review & Editing. James Jin: Formal analysis, Writing - Review & Editing. Hein Heidbuchel: Conceptualization, Writing - Original Draft, Writing - Review & Editing. Aron-Ariel Cohen: Conceptualization, Writing - Original Draft, Writing - Review & Editing. Michael Ezekowitz: Conceptualization, Writing - Original Draft, Writing - Review & Editing. Jose Luis Merino: Conceptualization, Writing - Original Draft, Writing - Review & Editing.

Disclosures

The authors have no conflicts of interest to disclose.

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1. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr., Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW,

Members AATF. 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. *Circulation* 2014;130:e199–e267.
2. Hsu JC, Chan PS, Tang F, Maddox TM, Marcus GM. Differences in anticoagulant therapy prescription in patients with paroxysmal versus persistent atrial fibrillation. *Am J Med* 2015;128. 654 e651-654 e610.
3. Goette A, Merino JL, Ezekowitz MD, Zamoryakhin D, Melino M, Jin J, Mercuri MF, Grosso MA, Fernandez V, Al-Saady N, Pelekh N, Merkely B, Zenin S, Kushnir M, Spinar J, Batushkin V, de Groot JR, Lip GY, investigators E-A. Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial. *Lancet* 2016;388:1995–2003.
4. Steinberg BA, Hellkamp AS, Lokhnygina Y, Patel MR, Breithardt G, Hankey GJ, Becker RC, Singer DE, Halperin JL, Hacke W, Nessel CC, Berkowitz SD, Mahaffey KW, Fox KA, Califf RM, Piccini JP, Committee R-AS, 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;36:288–296.
5. Vanassche T, Lauw MN, Eikelboom JW, Healey JS, Hart RG, Alings M, Avezum A, Diaz R, Hohnloser SH, Lewis BS, Shestakovska O, Wang J, Connolly SJ. Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES. *Eur Heart J* 2015;36:281−287a.
6. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, Chugh SS, Corradi D, D'Avila A, Dobrev D, Fenelon G, Gonzalez M, Hatem SN, Helm R, Hindricks G, Ho SY, Hoit B, Jalife J, Kim YH, Lip GY, Ma CS, Marcus GM, Murray K, Nogami A, Sanders P, Uribe W, Van Wagoner DR, Nattel S, Document R. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Europace* 2016;18:1455–1490.
7. Goette A, Bukowska A, Dobrev D, Pfeiffenberger J, Morawietz H, Strugala D, Wiswedel I, Rohl FW, Wolke C, Bergmann S, Bramlage P, Ravens U, Lendeckel U. Acute atrial tachyarrhythmia induces angiotensin II type 1 receptor-mediated oxidative stress and microvascular flow abnormalities in the ventricles. *Eur Heart J* 2009;30:1411–1420.
8. Bukowska A, Felgendreher M, Scholz B, Wolke C, Schulte JS, Fehrmann E, Wardelmann E, Seidl MD, Lendeckel U, Himmler K, Gardemann A, Goette A, Muller FU. CREM-transgene mice: an animal model of atrial fibrillation and thrombogenesis. *Thromb Res* 2018;163:172–179.
9. Lip GYH, Al-Saady N, Ezekowitz MD, Banach M, Goette A. The relationship of renal function to outcome: a post hoc analysis from the EdoxabaN versus warfarin in subjectS UndeRgoing cardiovErsion of Atrial Fibrillation (ENSURE-AF) study. *Am Heart J* 2017;193:16–22.
10. Merino JL, Lip GYH, Heidbuchel H, Cohen AA, De Caterina R, de Groot JR, Ezekowitz MD, Le Heuzey JY, Themistoclakis S, Jin J, Melino M, Winters SM, Merkely B, Goette A. Determinants of left atrium thrombi in scheduled cardioversion: an ENSURE-AF study analysis. *Europace* 2019;21:1633–1638.
11. European Heart Rhythm A, European Association for Cardio-Thoracic S, Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;31:2369–2429.
12. Atar D, Berge E, Le Heuzey JY, Virdone S, Camm AJ, Steffel J, Gibbs H, Goldhaber SZ, Goto S, Kayani G, Misselwitz F, Stepinska J, Turpie AGG, Bassand JP, Kakkar AK. The association between patterns of atrial fibrillation, anticoagulation, and cardiovascular events. *Europace* 2020;22:195–204.
13. Hall A, Simpson RFG, Mitchell ARJ. Biomarker assays for personalised stroke risk assessment in atrial fibrillation. *Cardiovasc Hematol Disord Drug Targets* 2017;17:58–63.
14. Hijazi Z, Lindback J, Alexander JH, Hanna M, Held C, Hylek EM, Lopes RD, Oldgren J, Siegbahn A, Stewart RA, White HD, Granger CB, Wallentin L, Aristotle, Investigators S. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. *Eur Heart J* 2016;37:1582–1590.
15. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH, Investigators A. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;366:120–129.
16. Overvad TF, Nielsen PB, Lip GY. Treatment thresholds for stroke prevention in atrial fibrillation: observations on the CHA2DS2-VASc score. *Eur Heart J Cardiovasc Pharmacother* 2017;3:37–41.
17. Kaplan RM, Koehler J, Ziegler PD, Sarkar S, Zweibel S, Passman RS. Stroke risk as a function of atrial fibrillation duration and CHA2DS2-VASc score. *Circulation* 2019;140:1639–1646.
18. Van Gelder IC, Healey JS, Crijns H, Wang J, Hohnloser SH, Gold MR, Capucci A, Lau CP, Morillo CA, Hobbelt AH, Rienstra M, Connolly SJ. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. *Eur Heart J* 2017;38:1339–1344.
19. Goette A, Bukowska A, Lillig CH, Lendeckel U. Oxidative stress and microcirculatory flow abnormalities in the ventricles during atrial fibrillation. *Front Physiol* 2012;3:236.
20. Bukowska A, Hammwohner M, Sixdorf A, Schild L, Wiswedel I, Rohl FW, Wolke C, Lendeckel U, Aderkast C, Bochmann S, Chilukoti RK, Mostertz J, Bramlage P, Goette A. Dronedarone prevents microcirculatory abnormalities in the left ventricle during atrial tachypacing in pigs. *Br J Pharmacol* 2012;166:964–980.
21. Cai H, Li Z, Goette A, Mera F, Honeycutt C, Feterik K, Wilcox JN, Dudley SC Jr., Harrison DG, Langberg JJ. Downregulation of endocardial nitric oxide synthase expression and nitric oxide production in atrial fibrillation: potential mechanisms for atrial thrombosis and stroke. *Circulation* 2002;106:2854–2858.
22. Goette A, Hoffmanns P, Enayati W, Meltendorf U, Geller JC, Klein HU. Effect of successful electrical cardioversion on serum aldosterone in patients with persistent atrial fibrillation. *Am J Cardiol* 2001;88:906–909. A908.
23. Goette A, Jentsch-Ullrich K, Lendeckel U, Rocken C, Agbaria M, Auricchio A, Mohren M, Franke A, Klein HU. Effect of atrial fibrillation on hematopoietic progenitor cells: a novel pathophysiological role of the atrial natriuretic peptide? *Circulation* 2003;108:2446–2449.
24. Golaszewska K, Harasim-Symbor E, Polak-Iwaniuk A, Chabowski A. Serum fatty acid binding proteins as a potential biomarker in atrial fibrillation. *J Physiol Pharmacol* 2019;70.