

## Not All Types of Atrial Fibrillation Carry the Same Stroke Risk, but Most Benefit From Oral Anticoagulation

Stefan H. Hohnloser, MD; Mate Vamos, MD

Atrial fibrillation (AF) is the most commonly encountered arrhythmia worldwide, with an estimated prevalence of  $\approx 3\%$  in adults  $\geq 20$  years of age<sup>1</sup> and with an even greater prevalence in subjects with conditions such as hypertension, valvular heart disease, or chronic kidney disease. AF is classified according to its pattern of occurrence, and recent guidelines have proposed a consensus definition of the temporal occurrence of AF. Paroxysmal AF is self-terminating and lasts no longer than 7 days; AF episodes lasting longer than 7 days or necessitating termination by cardioversion are defined as persistent AF; and permanent AF is defined as AF without intercurring sinus rhythm, which is accepted by the patient and the physician.<sup>1</sup>

### See Article by Link et al

An often debated issue is whether the type and the duration of AF affect stroke risk. Early findings from the SPAF trials (Stroke Prevention in Atrial Fibrillation)<sup>2</sup> and an analysis of the ACTIVE W study (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events)<sup>3</sup> suggested a similar stroke risk in all types of AF. However, these studies were limited by methodological issues such as moderate sample sizes with relatively low event rates. More recently, subanalyses from the large phase III trials of non-vitamin K oral anticoagulants (NOAC) yielded lower incidences of stroke and systemic embolism in patients with paroxysmal as compared with persistent or permanent AF.<sup>4-7</sup>

In this issue of the journal, similar data are presented from the large ENGAGE AF-TIMI 48 trial (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48), which compared the effects of the NOAC edoxaban to warfarin in patients with AF and stroke risk factors.<sup>8</sup> This trial is the largest of all NOAC trials comprising 21 105 patients, has the longest follow-up period, and provides data on >650 primary outcome events of stroke and systemic embolism. The present well-conducted substudy provides information on 3 important issues: (1) After adjusting for important baseline confounders,

paroxysmal AF was associated with a lower stroke risk of 1.49% per year compared with persistent AF (1.83% per year;  $P=0.015$ ) and permanent AF (1.95% per year;  $P=0.004$ ). Of note, these numbers were observed in subjects who were all undergoing oral anticoagulation therapy. (2) All-cause mortality was also lower in paroxysmal than in persistent or permanent AF, probably foremost reflecting the fact that patients with permanent AF have more advanced heart disease and more comorbidities.<sup>6,7</sup> (3) There was no effect modification by AF pattern on the efficacy and the safety of edoxaban.

These observations are in line with those made in other NOAC trials.<sup>4-7</sup> Although the risk for stroke or systemic embolism is lower in patients with paroxysmal AF as compared with patients with persistent/permanent AF; it still warrants anticoagulation therapy. This need is underpinned if one considers stroke incidences according to AF pattern in patients who are not undergoing oral anticoagulation. There is one retrospective, yet comprehensive study that assessed stroke risk in 6563 patients enrolled in the ACTIVE A and in the AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trials.<sup>9</sup> By study protocol, all of these patients were not receiving anticoagulation but were only treated with aspirin.<sup>9</sup> Yearly ischemic stroke rates were 2.1%, 3.0%, and 4.2% for subjects with paroxysmal, persistent, or permanent AF, substantially higher than those observed in the NOAC trials including ENGAGE AF-TIMI 48.<sup>9</sup> In this large population of nonanticoagulated patients, AF pattern turned out to be a strong independent predictor of stroke risk. All aforementioned analyses of the recent NOAC trials emphasize the fact that the effects of these new anticoagulants compared with warfarin are preserved in all AF patterns.<sup>4-7</sup> Particularly, the safety profile of these compounds (ie, generally lower bleeding risks compared with vitamin K antagonists) allows the treating physician to protect patients with all types of AF from thromboembolic complications.

One important remaining research question at present is whether the above-described observations apply also to patients with subclinical AF.<sup>10,11</sup> Recent studies in patients with permanent pacemakers or implantable cardioverter defibrillators have demonstrated an increased stroke risk even in patients with short-lasting episodes of subclinical AF.<sup>10,11</sup> However, there remain unresolved issues: what is the minimum duration of subclinical AF constituting an increased stroke risk? A subanalysis of the ASSERT trial (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial) indicated that AF episodes lasting 24 hours or longer were associated with a hazard ratio of >3.0 for stroke compared to subjects without any AF, whereas shorter

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Division of Clinical Electrophysiology, Department of Cardiology, J. W. Goethe University, Frankfurt, Germany.

Correspondence to Stefan H. Hohnloser, MD, Division of Clinical Electrophysiology, Department of Cardiology, J. W. Goethe University, Theodor-Stern-Kai 7, 60590 Frankfurt, Germany. E-mail hohnloser@em.uni-frankfurt.de

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lasting subclinical AF episodes carried a much smaller risk.<sup>12</sup> Why is there only a weak temporal relationship between the documented episode and the occurrence of stroke in individuals with subclinical AF?<sup>13</sup> One cannot exclude the possibility that such subclinical AF is simply a risk marker for stroke than a causal factor. And most importantly, can this stroke risk be mitigated by oral anticoagulation? These unanswered questions are currently explored in 2 large-scale prospective trials (ARTESiA [Apixaban for the Reduction of Thrombo-Embolic in Patients With Device-Detected Sub-Clinical Atrial Fibrillation] NCT01938248 and NOAH [Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes] NCT02618577). Until the results of these studies become available, uncertainty will remain as to the issue of minimal AF duration constituting an indication for anticoagulation. However, based on the study by Link et al<sup>9</sup> and other similar reports,<sup>4–8</sup> subjects with clinically documented paroxysmal AF should receive anticoagulation treatment, preferably with a NOAC, similar to subjects with persistent or permanent AF.

### Disclosures

Dr Hohnloser reports receiving consulting fees from Bayer Healthcare, BI, BMS, Boston Scientific, Daiichi Sankyo, Gilead, Johnson & Johnson, Medtronic, Pfizer, Portola, Sanofi Aventis, Servier, SJM, and Zoll. Dr Vamos reports lecture fees from Bayer, Pfizer, and Spectranetics.

### References

- Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella Pericas M, Diener HD, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962.
- Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. *J Am Coll Cardiol*. 2000;35:183–187.
- Hohnloser SH, Pajitnev D, Pogue J, Healey JS, Pfeffer MA, Yusuf S, Connolly SJ; ACTIVE W Investigators. Incidence of stroke in paroxysmal versus sustained atrial fibrillation in patients taking oral anticoagulation or combined antiplatelet therapy: an ACTIVE W Substudy. *J Am Coll Cardiol*. 2007;50:2156–2161. doi: 10.1016/j.jacc.2007.07.076.
- Al-Khatib SM, Thomas L, Wallentin L, Lopes RD, Gersh B, Garcia D, Ezekowitz J, Alings M, Yang H, Alexander JH, Flaker G, Hanna M, Granger CB. Outcomes of apixaban vs. warfarin by type and duration of atrial fibrillation: results from the ARISTOTLE trial. *Eur Heart J*. 2013;34:2464–2471. doi: 10.1093/eurheartj/eh135.
- Inoue H, Atarashi H, Okumura K, Yamashita T, Kumagai N, Origasa H. Thromboembolic events in paroxysmal vs. permanent non-valvular atrial fibrillation. Subanalysis of the J-RHYTHM Registry. *Circ J*. 2014;78:2388–2393.
- 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; 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;36:288–296. doi: 10.1093/eurheartj/ehu359.
- Senoo K, Lip GY, Lane DA, Büller HR, Kotecha D. Residual risk of stroke and death in anticoagulated patients according to the type of atrial fibrillation: AMADEUS trial. *Stroke*. 2015;46:2523–2528. doi: 10.1161/STROKEAHA.115.009487.
- Link MS, Giugliano RP, Ruff CT, Scirica BM, Huikuri H, Oto A, Crompton AE, Murphy SA, Lanz H, Mercuri M, Antman EM, Braunwald E; on behalf of the ENGAGE AF-TIMI 48 Investigators. Stroke and mortality risk in patients with various patterns of atrial fibrillation: results from the ENGAGE AF-TIMI 48 trial (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48). *Circ Arrhythm Electrophysiol*. 2016;10:e004267. doi: 10.1161/CIRCEP.116.004267.
- Vanassche T, Lauw MN, Eikelboom JW, Healey JS, Hart RG, Alings M, Avezum A, Díaz 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. doi: 10.1093/eurheartj/ehu307.
- 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; ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med*. 2012;366:120–129. doi: 10.1056/NEJMoa1105575.
- Glutzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilker C, Miller C, Qi D, Ziegler PD. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. *Circ Arrhythm Electrophysiol*. 2009;2:474–480. doi: 10.1161/CIRCEP.109.849638.
- Van Gelder IC, Healey JS, Crijns HJGM, Wang J, Hohnloser SH, Gold MR, Capucci A, Lau CP, Morillo CA, Hobbelt A, Rienstra M, Connolly SJ; on behalf of the ASSERT Investigators. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. *Eur Heart J*. In press.
- Brambatti M, Connolly SJ, Gold MR, Morillo CA, Capucci A, Muto C, Lau CP, Van Gelder IC, Hohnloser SH, Carlson M, Fain E, Nakamya J, Mairesse GH, Halytska M, Deng WQ, Israel CW, Healey JS; ASSERT Investigators. Temporal relationship between subclinical atrial fibrillation and embolic events. *Circulation*. 2014;129:2094–2099. doi: 10.1161/CIRCULATIONAHA.113.007825.

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