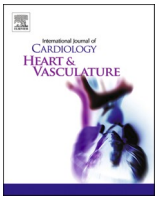
IJC Heart & Vasculature 56 (2025) 101572

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature



Atrial fibrillation does not equal atrial fibrillation: The important prognostic implications of new-onset atrial fibrillation

For practical reasons, clinical atrial fibrillation (AF) is usually subdivided into paroxysmal, persistent and permanent forms [1]. Although such subdivision may assist clinical care decisions, recent studies have shown that first-diagnosed new-onset AF is associated with less favourable outcomes compared to recurrent paroxysmal and persistent AF forms, both in outpatients as in critically ill patients [2,3]. Patients with new-onset AF more often suffer from serious cardiovascular complications, including acute heart failure, stroke and myocardial infarction, and exhibit increased cardiovascular and all-cause mortality, compared to patients with established AF [1–3]. Thus, the first detection of new-onset AF might serve as a novel marker to assess prognosis, and could have important implications for the treatment of AF in various clinical settings.

1. The prognosis of new-onset AF is worse compared other AF forms

Patients with new-onset AF were older than those with recurrent paroxysmal and persistent AF, but younger than those with permanent AF in the EORP-AF pilot general registry of 2,119 patients [4]. Yet, the risk of all-cause death was higher in new-onset AF compared to recurrent paroxysmal or persistent AF and not different from permanent AF [4]. Similarly, hospital admissions for cardiovascular events occurred significantly more often in new-onset (24 %) and permanent AF (20 %) than in recurrent paroxysmal or persistent (15 %). Of note, oral anticoagulants were less frequently prescribed in new-onset compared to other AF forms, after 3 years of follow-up [4].

Recently, a sub-analysis of the randomized EAST-AFNET 4 trial clearly showed in 2,785 AF patients that new-onset AF was associated with a 50 % increased hospitalization for acute coronary syndrome (ACS, IRR: 1.50; 95 % CI: 0.83–2.69) during follow-up compared to paroxysmal or persistent forms of AF [2]. Epidemiological studies also showed that patients with new-onset AF have a higher mortality, and an increased risk to develop heart failure and ACS [2–5]. Although the impact of paroxysmal versus persistent AF on outcome is generally appreciated, the EAST AFNET-4 trial provided the first evidence that differences between first-diagnosed new-onset AF and common AF forms also exist [2]. Similarly, risk of myocardial infarction (mostly NSTEMI), but not of ischemic stroke, is higher in individuals with first-diagnosed paroxysmal compared to non-paroxysmal AF treated with anticoagulants [5].

These observations also hold true for critically ill patients with new-onset AF. From insurance claims data in the setting of severe sepsis in 49,082 ICU admitted patients, new-onset AF was associated with an increased risk of (in-hospital) stroke (2.6 %, 95 % CI 2.0–3.6 %) compared to patients with known AF (0.57 %, 95 % CI 0.43–0.74 %) and those without AF (0.69 %, 95 % CI 0.61–0.78 %). Ischemic stroke occurred in 2.6 % versus 0.6 % in patients with new-onset AF compared to patients without AF (OR = 2.70, 95 % CI 2.07–3.57). Mortality rate was also higher in patients with new-onset AF versus no AF (56 % versus 39 %, OR 1.07, 95 % CI 1.04–1.11) [3]. Similarly, new-onset AF in the intensive care unit is also associated with worse outcome in sepsis and other life-threatening conditions. Meta-analyses showed that new-onset AF and not the presence of AF *per se* is associated with impaired outcome in ICU patients [3]. Thus, new-onset AF is powerful biomarker for poor prognosis in ICU patients as well as in high-risk patients for stroke.

2. New-onset AF may engage different proarrhythmic mechanisms

The observations on outcome of new-onset AF could be clearly, at least in part, explained by a treatment bias. New-onset AF is per definition unrecognized before its first manifestation and detection, which has important implications for the treatment of cardiovascular comorbidities such as hypertension, heart failure, obesity and diabetes, and the prevention of ischemic stroke. Indeed, oral anticoagulants are less frequently prescribed in patients with new-onset AF [4].

However, despite this potential lagging behind of appropriate therapy, the inflammatory and oxidative stress induced damage to the atrium and other organs appears different in new-onset AF compared to established AF (Fig. 1). Aside from extensive atrial changes [6,7], inflammatory signaling and oxidative stress have been implicated in the evolution of AF-induced changes in solid organs including the ventricles, the kidneys and the brain [8]. In addition, in a gene set enrichment analysis of proteins present in LA tissue from patients with persistent AF, biological processes associated with oxidative stress were upregulated compared to patients without AF [9]. In patients without AF who developed AF during follow-up, genes associated with extracellular matrix production were upregulated, whereas fatty acid respiration and cellular respiration were downregulated in comparison to atrial tissue of patients who did not develop AF [10] The oxidative stress during acute AF is mainly mediated by peroxynitrite. Similarly, rapid *in vitro* pacing of atrial tissue slices also induced oxidative modifications of proteins, along with mitochondrial dysfunction [11]. Key components of excitation–contraction coupling are also impaired by these mechanisms [8]. Similarly, *in vitro* AF-simulation reconstituted the impaired Ca^{2+} handling phenotype and uncovered APD prolongation and an enhancement of late Na^{+} current as in human left ventricular

https://doi.org/10.1016/j.ijcha.2024.101572

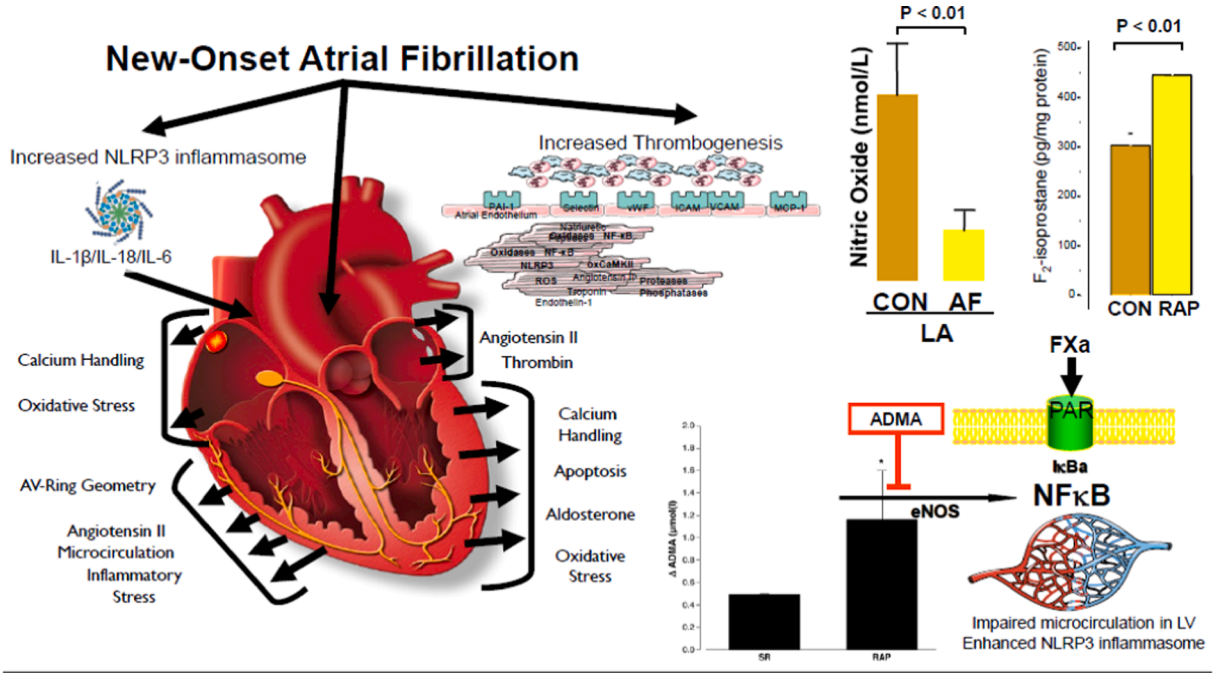


Fig. 1. Putative molecular mechanisms of new-onset atrial fibrillation. For further details see main text. Abbreviations: ADMA, asymmetric dimethylarginine; CON, control; eNOS, endothelial nitric oxide synthase; FXa, factor Xa; ICAM, intracellular adhesion molecule 1; IL-1β, interleukin 1-beta; IL-6, interleukin 6; IL-18, interleukin 18; LA, left atrium; NFκB, nuclear factor kappa B; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; NO, nitric oxide; PAI-1, plasminogen activator inhibitor-1; PAR, protease activated receptor; RAP, rapid atrial pacing; ROS, reactive oxidative species; VCAM, vascular cel adhesion protein 1; vWF, von Willebrabd factor-1.

cardiomyocytes and iPSC-cardiomyocytes [12]. While myocardial fibrosis and apoptosis were unchanged, ROS-dependent activation of Ca^{2+}/calmodulin-dependent protein kinase IIδc contributed to adverse remodeling of the left ventricle during AF [12]. This study suggests that acute AF causes distinct functional and molecular remodeling of the human left ventricle and provides mechanistic insights into the negative impact of acute AF on the human ventricle. Furthermore, several experimental results show that oxidative stress is not restricted to the atrial myocardium but also extends to ventricular tissue during AF. Lack of nitric oxide (NO) in the ventricles cause microcirculatory flow impairment and may cause moderate ventricular ischemia (type 2 myocardial infarctions) in many patients. Of note, the acute onset of AF appears to be of particular importance since ischemic events encompassing the ventricles are less frequent in patients with other AF forms. A shift from NADPH oxidase to other cellular sources of reactive oxygen species (ROS), which include xanthine oxidase, monoamine oxidase, and uncoupled eNOS also occurs during AF [11,13]. Reduced expression of eNOS contributes to the reduced plasma levels of NO, which were detected during acute AF [14]. In addition, AF is associated with increased levels of ADMA, an endogenous inhibitor of eNOS [11–15]. In summary, altered NO generation due to oxidative stress during new-onset AF occurs not only in the atria, but also impairs the ventricles during acute AF [13–15]. In addition, it impairs microcirculatory flow and the mechanical performance of the ventricles by causing abnormalities in Ca^{2+} handling and related contractility [12,15]. Most important, during acute AF impaired blood flow has been shown to occur in various organs. Due to counterregulatory adaptive mechanisms, these acute AF-induced changes appear to occur mainly during the first 1 week of AF, and disappear when AF continues to persists thereafter.

3. Treatment efficacy is different in new-onset AF

As indicated above, the emerge of new-onset AF confers an increased risk of vascular thromboembolic events, including ischemic stroke and myocardial infarction, increased rates of hospitalization and increased risk of mortality, not only in comparison with patients without AF, but also compared to patients in whom AF is established [1].

From observational studies it is clear that the initiation of oral anticoagulation lags behind, which may in part be the explanation for the increased risk of stroke. Hence, we suggest that an aggressive approach toward anticoagulation needs to be pursued once the diagnosis of new-onset AF is made. Due to the increased risk of vascular thromboembolism and type-2 myocardial infarction in particular, rate control should be the primary approach because antiarrhythmic therapy appears to be less effective in new-onset AF. Of note, the recent sub-study of the EAST trial showed even negative effects of rhythm control in this setting [2]. Whether the temporary increase in inflammatory and oxidative stress is responsible for this, and whether they should become a treatment target in new-onset AF needs to be established.

Overall, these considerations support the notion that patient with new-onset AF should not be treated as just another AF patient, but require thorough assessment of cardiovascular risks and prompt introduction of rate control and initiation of anticoagulation for stroke prevention.

4. Conclusions

New-onset AF is a distinct entity than paroxysmal or persistent AF [2,5]. Patients with new-onset AF have an increased risk of vascular thromboembolic complications, and stroke and myocardial infarction in particular, and are at a higher risk of death [2–5]. This applies to both outpatient and critically ill patients. Aside from less optimal treatment and control of cardiovascular comorbidities, a possible explanation for this unique outcome may be the temporary increase in inflammatory and oxidative stress that affects not only the atrium, but also the microcirculation of the ventricles, the kidneys and the brain [8,12,15]. Therefore, we suggest each patient with new-onset AF should be carefully assessed and monitored, with stroke prevention with oral anticoagulation and rate control being immediately initiated, aside from proper management of cardiovascular comorbidities and risk factors.

Funding

The European Union (large-scale network project MAESTRIA No. 965286 to AG and DD), Deutsche Forschungsgemeinschaft (Research Training Group 2989, project 517043330 to DD), and National Institutes of Health (R01HL136389, R01HL163277, R01HL131517, R01HL160992, R01HL165704, and R01HL164838 to DD).

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: "AG discloses honoraria and speaker fees from Astra Zeneca, Bayer Health Care, Berlin-Chemie, Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, Boston Scientific, Daiichi Sankyo, Medtronic, Novartis, and Omeicos. JRdG received research grant through his institution from Atricure, Bayer, boston Scientific, Daiichi Sankyo, Johnson&Johnson, Medtronic. JRdG received honoraria, speakers and consultancy fees from AtrianMedical, Atricure, bayer, Biotronik, Daiichi Sankyo, Medtronic, Novartis, and Servier. DD received speaker's/consultancy honoraria from Daiichi Sankyo and AbbVie.".

References

[1] I.C. Van Gelder, M. Rienstra, K.V. Bunting, R. Casado-Arroyo, V. Caso, H.J.G. M. Crijns, T.J.R. De Potter, J. Dwight, L. Guasti, T. Hanke, T. Jaarsma, M. Lettino, M.L. Løchen, R.T. Lumbers, B. Maesen, I. Mølgaard, G.M.C. Rosano, P. Sanders, R. B. Schnabel, P. Suwalski, E. Svennberg, J. Tamargo, O. Tica, V. Traykov, S. Tzeis, D. Kotecha, ESC Scientific Document Group, 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS), Eur Heart J. 45 (36) (2024) 3314–3414.

[2] A. Goette, K. Borof, G. Breithardt, A.J. Camm, H. Crijns, K.H. Kuck, K. Wegscheider, P. Kirchhof, Presenting pattern of atrial fibrillation and outcomes of early rhythm control therapy, J. Am. Coll. Cardiol. 80 (2022) 283–295.

[3] A.J. Walkey, R.S. Wiener, J.M. Ghobrial, L.H. Curtis, E.J. Benjamin, Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis, JAMA 306 (2011) 2248–2254.

[4] G. Boriani, M. Proietti, C. Laroche, I. Diemberger, M.I. Popescu, S. Riahi, A. Shantsila, G.A. Dan, L. Tavazzi, A.P. Maggioni, G.Y.H. Lip, Changes to oral anticoagulant therapy and risk of death over a 3-year follow-up of a contemporary cohort of European patients with atrial fibrillation final report of the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) pilot general registry, Int. J. Cardiol. 271 (2018) 68–74.

[5] G. Ntaios, D. Sagris, B.J.R. Buckley, S.L. Harrison, A. Abdul-Rahim, P. Austin, G.Y. H. Lip, L Risk of myocardial infarction and ischemic stroke in individuals with first-diagnosed paroxysmal vs. non-paroxysmal atrial fibrillation under anticoagulation, Europace 25 (2023) 1–6.

[6] D. Dobrev, J. Heijman, R. Hiram, N. Li, S. Nattel, Inflammatory signalling in atrial cardiomyocytes: a novel unifying principle in atrial fibrillation pathophysiology, Nat. Rev. Cardiol. 20 (3) (2023) 145–167.

[7] M.J. Mihm, F. Yu, C.A. Carnes, P.J. Reiser, P.M. McCarthy, D.R. Van Wagoner, J. A. Bauer, Impaired myofibrillar energetics and oxidative injury during human atrial fibrillation, Circulation 104 (2001) 174–180.

[8] J. Song, J.A. Navarro-Garcia, J. Wu, A. Saljic, I. Abu-Taha, L. Li, S.K. Lahiri, J. A. Keefe, Y. Aguilar-Sanchez, O.M. Moore, Y. Yuan, X. Wang, M. Kamler, W. E. Mitch, G. Ruiz-Hurtado, Z. Hu, S.S. Thomas, D. Dobrev, X.H. Wehrens, N. Li, Chronic kidney disease promotes atrial fibrillation via inflammasome pathway activation, J. Clin. Invest. 133 (19) (2023) e167517.

[9] M. Kawasaki, E.R. Meulendijks, N.W.E. van den Berg, F.A. Nariswari, J. Neefs, R. Wesselink, S.W.E. Baalman, A. Jongejan, T. Schelfhorst, S.R. Piersma, T. V. Pham, W.J.P. van Boven, A.H.G. Driessen, C.R. Jimenez, J.R. de Groot, Neutrophil degranulation interconnects over-represented biological processes in atrial fibrillation, Sci. Rep. 11 (2021) 2972.

[10] J. Heijman, A.P. Muna, T. Veleva, C.E. Molina, H. Sutanto, M. Tekook, Q. Wang, I. H. Abu-Taha, M. Gorka, S. Künzel, A. El-Armouche, H. Reichenspurner, M. Kamler, V. Nikolaev, U. Ravens, N. Li, S. Nattel, X.H.T. Wehrens, D. Dobrev, Atrial myocyte NLRP3/CaMKII nexus forms a substrate for postoperative atrial fibrillation, Circ. Res. 127 (8) (2020) 1036–1055.

[11] A. Bukowska, L. Schild, G. Keilhoff, D. Hirte, M. Neumann, A. Gardemann, K. H. Neumann, F.W. Rohl, C. Huth, A. Goette, U. Lendeckel, Mitochondrial dysfunction and redox signaling in atrial tachyarrhythmia, Exp. Biol. Med. (Maywood) 233 (2008) 558–574.

[12] S. Pabel, M. Knierim, T. Stehle, F. Alebrand, M. Paulus, M. Sieme, M. Herwig, F. Barsch, T. Körtl, A. Pöppl, B. Wenner, S. Ljubojevic-Holzer, C.E. Molina, N. Dybkova, D. Camboni, T.H. Fischer, S. Sedej, D. Scherr, C. Schmid, C. Brochhausen, G. Hasenfuß, L.S. Maier, N. Hamdani, K. Streckfuss-Bömeke, S. Sossalla, Effects of atrial fibrillation on the human ventricle, Circ. Res. 130 (7) (2022) 994–1010.

[13] T. Minamino, M. Kitakaze, H. Sato, H. Asanuma, H. Funaya, Y. Koretsune, M. Hori, Plasma levels of nitrite/nitrate and platelet cGMP levels are decreased in patients with atrial fibrillation, Arterioscler. Thromb. Vasc. Biol. 17 (1997) 3191–3195.

[14] A. Goette, M. Hammwohner, A. Bukowska, F. Scalera, J. Martens-Lobenhoffer, D. Dobrev, U. Ravens, S. Weinert, S. Medunjanin, U. Lendeckel, S.M. Bode-Boger, The impact of rapid atrial pacing on ADMA and endothelial NOS, Int. J. Cardiol. 154 (2012) 141–146.

[15] A. Goette, A. Bukowska, D. Dobrev, J. Pfeiffenberger, H. Morawietz, D. Strugala, I. Wiswedel, F.W. Röhl, C. Wolke, S. Bergmann, P. Bramlage, U. Ravens, U. Lendeckel, Acute atrial tachyarrhythmia induces angiotensin II type 1 receptor-mediated oxidative stress and microvascular flow abnormalities in the ventricles, Eur. Heart J. 30 (11) (2009) 1411–1420.

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