ESC European Society of Cardiology

Europace (2023) **25**, 249–250
https://doi.org/10.1093/europace/euac197

EDITORIAL

New-onset atrial fibrillation during critical illness: another piece of the puzzle

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Online publish-ahead-of-print 10 November 2022

This editorial refers to 'Critical illness associated new onset atrial fibrillation: subsequent atrial fibrillation diagnoses and other adverse outcomes', by D. Lancini *et al.*, https://doi.org/10.1093/eupace/euac174.

Atrial fibrillation (AF) is associated with chronic underlying cardiovascular conditions such as hypertension, diabetes, heart failure, atherosclerosis, obesity, valvular disease, and senescence. These risk factors can lead to the onset of AF and promote the formation of an arrhythmogenic atrial substrate, which leads to the perpetuation of AF for longer periods. The short- and long-term risks of AF-related complications such as stroke, heart failure, and mortality are mainly driven by the extensiveness of these concomitant conditions.

The current guidelines recommend that the clinical risk factor–based CHA_2DS_2-VASc score [congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years, sex category (female)] be used in patients with AF to guide the decision-making regarding long-term anticoagulation.[1,2]

However, in situations where a temporary trigger for AF is observed (e.g. after surgery or infection), or when asymptomatic AF is only detected by a cardiac implantable electronic device or smartwatch, the evidence for anticoagulation is less well established. In line with this, the current ESC AF guidelines offer limited recommendations to the approach to patients with transient AF episodes during a period of critical illness.[2]

In this issue of the *Journal*, Lancini *et al.*[3] studied a large group of patients in Australia with critical illness–associated new-onset AF (CI-NOAF) in order to determine factors associated with subsequent AF diagnoses and other adverse outcomes. A total of 309 patients (5.0%) without previous AF were diagnosed with CI-NOAF out of 6219 unique patients admitted to a tertiary general intensive care unit (ICU). They were screened for AF episodes through an hourly analysis of continuous electrocardiogram (ECG) monitoring. At discharge, 21% of CI-NOAF patients were treated with anticoagulation. After a median follow-up of 413 days post-discharge, approximately one-third of patients were identified with subsequent AF, and the rate of anticoagulation increased to 27.2%.

The strongest independent predictor of AF recurrence was increased AF burden at ICU stay, with a 63% risk of subsequent AF diagnosis in the highest quartile of AF burden (>25% of ICU stay). Increased left atrial size was also strongly and independently associated with AF recurrence during follow-up. The other factors investigated were not independently associated with AF recurrence. Patients with high AF burden had higher rates of mortality (28.8 vs. 12.8%, $P = 0.003$) and major adverse cardiovascular events (MACE) (35.6 vs. 21.4%, $P = 0.016$) post-discharge. However, in this observational cohort, the numbers of individual MACE components were insufficient to undertake valid statistical analysis.

First of all, the authors are to be commended for this research that works towards answering the clinically relevant but largely unexplored area that is CI-NOAF. No previous studies have investigated the incidence of subsequent AF diagnoses or identified an independent association between CI-NOAF burden and long-term outcomes.

A retrospective study published in 2014 using Medicare claims data reported 7% new-onset AF in patients (mean age 80 years and mean CHA_2DS_2-VASc score 6) hospitalized in the USA for sepsis between 1999 and 2010.[4] They reported a higher 5-year risk of AF recurrence after discharge among patients with new-onset AF during hospitalization for sepsis (54.9%) than in patients without AF during hospitalization for sepsis (15.5%). Patients with new-onset AF during sepsis also had higher 5-year risks of heart failure, stroke, and mortality, compared with patients without AF during sepsis. The current study of Lancini *et al.* shows us that, in a far younger patient population (mean age 67 years) with a significantly lower mean CHA_2DS_2-VASc score of 2.6, these patients with CI-NOAF are also at high risk for the development of recurrent AF. Thus, despite the lower risk category of these patients, the event that has caused the ICU hospitalization exposes the presence of an underlying atrial substrate in some, suggesting a selection of patients especially prone to cardiovascular events, as also shown by Lancini *et al.*[3] These patients may, therefore, benefit from active monitoring for recurrent AF and more aggressive cardiovascular risk factor management, as it seems particularly in those with high AF burden during critical illness and/or left atrial dilation.

Think ahead, be more aggressive on risk factor management

Treatment of AF-related cardiovascular risk factors remains the cornerstone of adequate AF management, reducing the risk of both AF recurrences and AF-related complications.[2] Adequate management

The opinions expressed in this article are not necessarily those of the Editors of *Europace* or of the European Society of Cardiology.

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of, for example, hypertension and diabetes mellitus is well known, but it is often under-recognized that obesity is also an important and modifiable risk factor for both AF and stroke while new therapies are emerging.[5–7] The mean body mass index (BMI) of patients with new-onset CI-NOAF was 29.4 kg/m^2, and among those who developed subsequent AF after discharge, more than half of the patients were obese (mean BMI 31.6 kg/m^2) and almost one-third of patients suffered from diabetes mellitus.[3] In the SUSTAIN-6 study in patients with Type 2 diabetes who were at high cardiovascular risk, the rate of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke was significantly lower among patients receiving semaglutide than among those receiving placebo, accompanied by a significant weight loss in the semaglutide group compared with the placebo one.[5] Obesity is associated with atrial enlargement and ventricular diastolic dysfunction and appears to be an important, potentially modifiable risk factor for AF.[6] Adequate treatment of overweight will thereby kill two birds with one stone. Besides, follow-up for optimizing cardiovascular risk factors provides a feasible opportunity to screen for AF recurrence.

Not all types of atrial fibrillation carry the same stroke risk

The question remains, however, whether CI-NOAF patients have a comparable stroke risk after discharge compared with patients with new-onset clinical AF not triggered by critical illness. For patients after non-cardiac surgery, the 2020 ESC guidelines recommend, given the currently available evidence, that long-term oral anticoagulation therapy should be considered to prevent thrombo-embolic events (Class IIa, Level of evidence B).[2] However, the same guidelines do not comment on the management of AF first diagnosed after a non-surgery temporary trigger such as CI-NOAF, but, for instance, also not for uncomplicated infections, as studies hereon are lacking despite the frequency of this therapeutic dilemma encountered in daily clinical practice. The authors of this article have provided an important new insight into CI-NOAF, but it is clear that further research on cardiovascular event rates and the benefit of anticoagulation is much needed.

Complicating matters further is that, given the fact that new-onset AF was identified through continuous ECG monitoring, probably at least a part of these CI-NOAF episodes may be classified as subclinical AF. Previously, the ASSERT study showed that in patients with device-detected subclinical AF (mean age 77 years and mean $CHADS_2$ score 2.2), there is an increased risk of stroke, but this risk is still approximately half the risk when compared with clinical AF.[8] Moreover, the observation that the strongest independent predictor of AF recurrence in patients with CI-NOAF appeared to be increased AF burden at ICU stay is also in line with a sub-analysis of ASSERT, which showed that subclinical AF duration of >24 h was associated with a significant increased risk of clinical AF and subsequent stroke or systemic embolism.[9]

Therefore, the next step should be randomized clinical trials investigating the efficacy and safety of long-term anticoagulation after hospital discharge in patients with CI-NOAF.

Reappraisal of left atrial size in weighing stroke risk in critical illness–associated new-onset atrial fibrillation patients?

Before the introduction of the clinical risk factor–based $CHADS_2$ and CHA_2DS_2-VASc scores, left atrial enlargement was graded as a moderate risk factor for stroke in previous guidelines. However, controversy exists regarding whether left atrial enlargement is still an important independent predictor of stroke in patients with AF not associated with mitral valve stenosis. In 2016, the large prospective Fushimi AF Registry showed a significantly increased risk of stroke/systemic embolism (hazard ratio: 1.74, 95% confidence interval: 1.25–2.42; $P < 0.01$) independent of the components of the CHA_2DS_2-VASc score or anticoagulation use.[10]

In addition, in the prospective Tromsø study, long-term follow-up of 2844 patients showed that patients with higher CHA_2DS_2-VASc scores and left atrial enlargement had an approximately nine times increased odds of stroke irrespective of AF status.[11] Also, left atrial size was strongly and independently associated with AF recurrence during follow-up in the current study of Lancini *et al.*[3] It is tempting to speculate that the role of atrial size—as a surrogate for arrhythmic atrial substrate and/or atrial cardiomyopathy—may also play a role in the risk assessment and perhaps management of recurrent AF and stroke in patients with CI-NOAF.

In conclusion, patients with critical illness–associated new-onset AF have a substantially increased risk of subsequent clinical AF and often have clinical risk factors associated with stroke, heart failure, and mortality. Adequate treatment of modifiable risk factors seems mandatory to reduce the risk of recurrent AF and cardiovascular complications. Future randomized clinical trials should be done to investigate the efficacy and safety of long-term anticoagulation and follow-up after hospital discharge in this patient population.

Conflict of interest: None declared.

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