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LETTERS

RESEARCH LETTER

Atrial Fibrillation and Takotsubo Syndrome

A Propensity-Matched Analysis From the GEIST and ATHERO-AF Registries

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Atrial fibrillation (AF) is one of the most common arrhythmias worldwide, with increasing prevalence driven by aging and comorbidities.[1] Chronic diseases, including heart failure (HF), are known to influence both AF onset and outcomes. Takotsubo syndrome (TTS) is an HF phenotype characterized by transient impairment of left ventricular ejection fraction (LVEF) and relevant rates of short- and long-term adverse events.[2] AF is a marker of worse prognosis in TTS.[3] However, it remains unclear how a previous recovered TTS episode may have an impact on the natural history of patients with AF.

In this study, we compared 386 AF patients discharged alive after a TTS-related hospitalization and enrolled in the GEIST (GErman Italian Spanish Takotsubo) registry (NCT04361994) with 826 AF

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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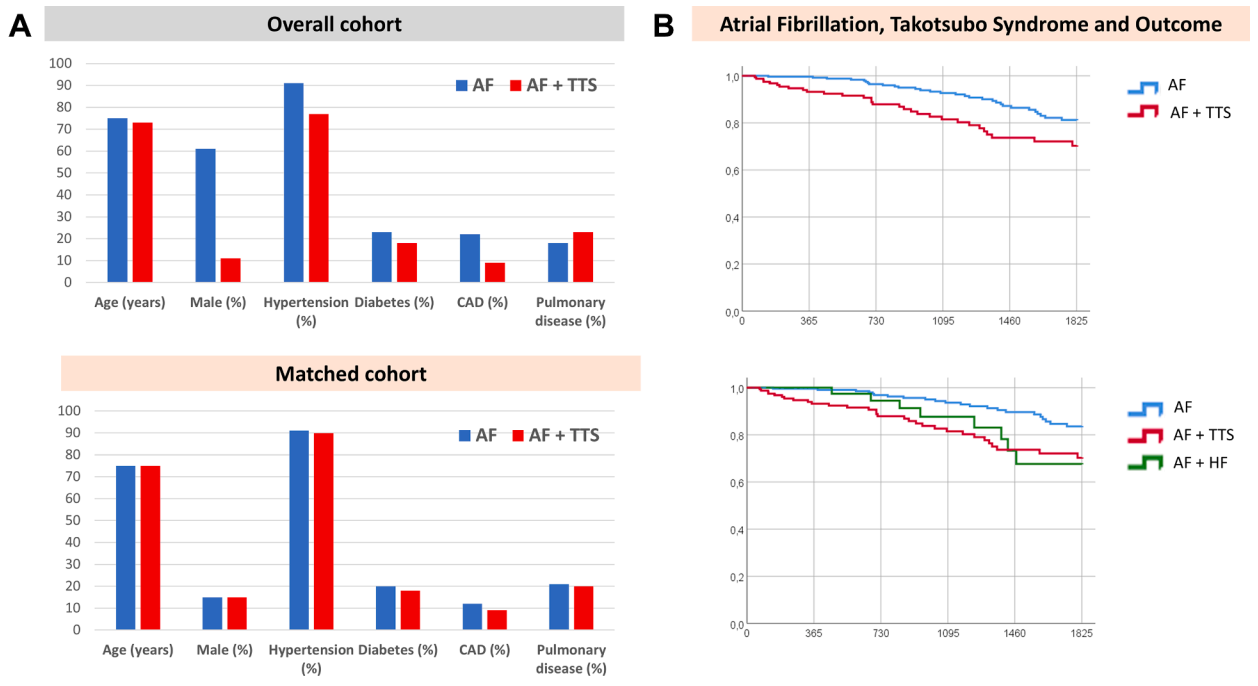
FIGURE 1 Histograms Reporting Main Differences Between Groups



(A) Overall cohort (above). (B) Matched cohort (below). Kaplan-Meier curves for long-term mortality in the matched group for AF-TTS patients and AF (B, above) and then splitting the latter for the presence/absence of heart failure (B, below). AF = atrial fibrillation; HF = heart failure; TTS = Takotsubo syndrome.

patients without a history of TTS enrolled in the ATHERO-AF (Atherosclerosis in Atrial Fibrillation; NCT01882114) registry. Afterward, we performed propensity score matching (PSM) with a 1:1 ratio including age, sex, hypertension, diabetes, history of malignancies, history of pulmonary disease, and history of coronary artery disease. Matched cohorts consisted of 277 patients each, for whom additional comparisons for long-term outcome were carried out. Approval of the local ethics committee was obtained at all participating sites (1092/CEAp1IT/19), all patients were treated in accordance with the Declaration of Helsinki, and all signed informed consent. Categorical variables were compared using a chi-square analysis or Fisher exact test. The Student's *t*-test for independent samples or Mann-Whitney *U* test was used to compare continuous variables. Univariable and multivariable Cox regression analyses were performed to assess factors independently associated with long-term mortality. Kaplan-Meier curves and log-rank test were used to assess survival function at follow-up. The proportional hazards assumption was checked and met in the matched cohort. The matched cohort of AF without TTS patients was further dichotomized according to the presence or absence of HF. In comparison with those without TTS, AF patients with previous TTS had a lower prevalence of male sex (11% vs 61%, $P < 0.001$), hypertension (77% vs 91%, $P < 0.001$), and coronary artery disease, (9% vs 22%, $P < 0.001$), whereas the prevalence of pulmonary disease was higher (23% vs 18%, $P = 0.031$). After matching, the main variables were similarly represented in both groups. The prevalence of HF in the AF without TTS cohort was 21% and 16% in the overall and matched subgroups, respectively; patients with AF and HF had lower LVEF than did those without (whole population: 40% ± 11% vs 55% ± 7%; $P < 0.05$; matched cohort: 38% ± 9% vs 55% ± 7%; $P < 0.05$) (Figure 1A). Patients with AF-TTS had worse prognosis than those with AF alone both before (log-rank test $P < 0.001$) and after matching (log-rank test $P = 0.003$) (Figure 1B). Patients with AF-TTS were found to have similar prognosis to that of AF patients without TTS but with a

history of HF both in the whole ($P = 0.253$) and matched cohort ($P = 0.723$) (Figure 1B). At multivariable Cox regression analysis, including all AF patients with or without TTS, previous TTS (HR: 2.11; 95% CI: 1.46-3.03; $P < 0.001$) was independently associated with long-term mortality.

The main findings of the present study are as follows: 1) AF-TTS patients have a higher female and pulmonary disease prevalence but lower rates of coronary artery disease and hypertension; 2) a history of TTS has long-term prognostic relevance in AF patients; and 3) AF-TTS patients have similar impaired prognosis as those with AF and history of HF. The fact that hypertension and coronary artery disease, known factors associated with AF, were less prevalent in the AF-TTS group suggests that in this setting the arrhythmia can be partly explained by other variables. The excessive sympathetic activity that underlines TTS, and the inflammatory activation with increased interleukin-6 and interleukin-10.[4] could induce atrial electrical remodeling, facilitating the new onset of AF. In this study we demonstrated that in stable outpatient individuals with a diagnosis of AF, a previous episode of TTS is associated with a poorer long-term prognosis even after matching for baseline differences; hence, it constitutes a relevant risk marker mandating more intensive monitoring. Interestingly, we observed that the prognosis of AF-TTS patients was similar to that of AF patients with a history of HF. Patients with TTS examined long after the acute event might be characterized by an HF phenotype, including diffuse myocardial fibrosis, altered myocardial deformation, and impaired cardiopulmonary functional capacity.[5] Whether these abnormalities are a consequence of the TTS event or, alternatively, pre-existing features of a vulnerable phenotype prone to develop the syndrome is unknown, but they can help explain our outcome findings. Some limitations apply to the study: no cause-and-effect relationships between the index TTS event and increased long-term mortality can be established, the mode of death was not systematically assessed, despite PSM unmeasured confounders might have been present, and also differences in survival times between different populations.

In conclusion, we found different clinical characteristics and prognosis of AF patients with and without TTS, suggesting that in patients with AF a history of TTS should be investigated and a more intensive monitoring offered, potentially like that provided in the presence of HF.

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