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Depression, antidepressants, and the risk of non-valvular atrial fibrillation: A nationwide Danish matched cohort study

Morten Fenger-Grøn[1], Mogens Vestergaard[1], Henrik S Pedersen[1], Lars Frost[2], Erik T Parner[3], Anette R Ribe[1] and Dimitry S Davydow[4]

Abstract

Background: Depression is associated with an increased risk of a series of cardiovascular diseases and with increased symptom burden in patients with atrial fibrillation. The aim of this study was to determine the association between depression as well as antidepressant treatment and the risk of *incident* atrial fibrillation.

Design: A nationwide register-based study comparing the atrial fibrillation risk in all Danes initiating antidepressant treatment from 2000 to 2013 ($N = 785{,}254$) with that in a 1:5-matched sample from the general population.

Methods: Cox regression was used to estimate adjusted hazard ratios (aHRs) and associated 95% confidence intervals (95% CIs), both after initiation of treatment and in the month before when patients were assumed to have medically untreated depression.

Results: Antidepressant treatment was associated with a three-fold higher risk of atrial fibrillation during the first month (aHR = 3.18 (95% CI: 2.98–3.39)). This association gradually attenuated over the following year (aHR = 1.37 (95% CI: 1.31–1.44) 2–6 months after antidepressant therapy initiation, and aHR = 1.11 (95% CI: 1.06–1.16) 6–12 months after). However, the associated atrial fibrillation risk was even higher in the month before starting antidepressant treatment (aHR = 7.65 (95% CI: 7.05–8.30) from 30 to 15 days before, and aHR = 4.29 (95% CI: 3.94–4.67) the last 15 days before). Overall, 0.4% of patients were diagnosed with atrial fibrillation from 30 days before to 30 days after antidepressant treatment.

Conclusions: Antidepressant users had a substantially increased atrial fibrillation risk, particularly before treatment initiation. Whether this mirrors a causal relation between depression and atrial fibrillation may have large consequences for public health and should be discussed.

Keywords

Atrial fibrillation, depression, antidepressive agents, cardiac arrhythmias, mental health, cardiovascular disease

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Introduction

Atrial fibrillation is the most common cardiac arrhythmia, affecting up to an estimated one in three persons over their lifetime, and the incidence is increasing.[1] Atrial fibrillation is associated with reduced health-related quality of life,[2] increased healthcare costs and higher risks of developing dementia, heart failure, stroke and death.[3] Therefore, a public health imperative to identify modifiable risk factors for atrial fibrillation is gaining ground.

[1]Research Unit for General Practice and Section for General Medical Practice, Department of Public Health, Aarhus University, Denmark
[2]Department of Clinical Medicine, Aarhus University, Silkeborg Hospital, Silkeborg, Denmark
[3]Section for Biostatistics, Department of Public Health, Aarhus University, Denmark
[4]CHI Franciscan Health System, St. Joseph Medical Center, Tacoma, WA, USA

Corresponding author:
Morten Fenger-Grøn, Research Unit for General Practice, Bartholins Allé 2, 8000 Aarhus C, Denmark.
Email: mfgr@ph.au.dk

Depression is a highly prevalent psychiatric disorder and is the leading cause of disability worldwide.[4] Importantly, depression has been found to be associated with increased risk for,[5] as well as increased morbidity and mortality following onset of, cardiovascular diseases.[6,7]

Previous studies have found associations between depression and both increased symptom burden and increased mortality in patients with atrial fibrillation,[8] and between depressive symptoms and increased risk of atrial fibrillation recurrence after cardioversion.[9] Yet, while associations with elevated atrial fibrillation risk have been documented for a variety of indicators of psychological stress, such as work strain[10] or partner bereavement,[11] little is known as to whether depression increases the risk of developing atrial fibrillation. A recent systematic review identified only two previous studies of the association between depression and incident atrial fibrillation.[12] Neither of the two studies reported a clear association, but both had substantial limitations. The first study included only women, a population known to have lower risk of developing atrial fibrillation than men,[1] used self-report measures of depression and studied only the long-term risk.[13] The second study was conducted in a small cohort undergoing cardiac surgery and explored a potential association with short-term risk of post-operative atrial fibrillation.[14] In light of these limitations, additional research examining whether depression could be a risk factor for developing atrial fibrillation is warranted.

Yet, studying the relationship between depression and atrial fibrillation is methodologically challenging. Difficulties in assessing the exact onset of both conditions could lead to detection bias and reverse causation. Additionally, antidepressant medication treatment may constitute an independent risk factor for developing atrial fibrillation since some antidepressants may hold risk of other arrhythmias.[15–17]

We aimed to determine the association between depression as well as antidepressant treatment and risk of incident atrial fibrillation. Therefore, we conducted a nationwide study comparing the atrial fibrillation risk in all Danish men and women initiating antidepressant treatment with that in the general background population. We assessed the risk after initiation of treatment as well as in the month before, during which the patients were assumed to have been depressed and medically untreated.

Methods

Study design and setting

We performed a nationwide register-based matched cohort study comparing all patients initiating antidepressant treatment from 2000 to 2013 with a reference group matched 1:5 on sex and birth month. The reference group was randomly sampled among all Danish citizens.

Matching was performed on the day of the first antidepressant initiation for exposed persons (index date). At the index date, both exposed and reference persons were required to be aged 18–100 years, to have lived in Denmark for at least five years, to have no history of antidepressant treatment before the index date, and to have no history of atrial fibrillation before the inclusion date, which was set at 30 days before the index date to quantify atrial fibrillation incidence within the month before initiation of antidepressant treatment. All participants were followed until the day of atrial fibrillation diagnosis, death, emigration or 31 December 2013, whichever came first. Additionally, persons were excluded if diagnosed with valve disease (ICD-8: 394, 395, 396 or ICD-10: I05, I06, I08, I34, I35).

Details of the data sources have been extensively described elsewhere and are summarised in the online Supplementary Material. The chosen study population and period ensured a register history of at least five years before index date for all participants.

Exposure

The exposure of interest was depression and subsequent antidepressant treatment as identified by first-time antidepressant prescription redemption in the registered period. In this study, we defined depression as the condition in the last 30 days before antidepressant treatment. In order to balance the statistical power with homogeneity regarding chemical structure, indication and cardiac risk classification according to applicable guidelines, antidepressants were categorised as follows: citalopram (ATC code: N06AB04), escitalopram (N06AB10), other selective serotonin reuptake inhibitors (SSRIs) (remaining N06AB), mirtazapine (N06AX11), venlafaxine (N06AX16) and other antidepressants (remaining N06AX and monoamine oxidase inhibitors, N06AF and N06AG). Tricyclic antidepressants (TCAs) (N06AA) were not included in our analyses because Danish treatment guidelines do not recommend TCAs as the primary treatment option for depression, and this medication class is commonly used for neuropathic pain. Likewise, bupropion (N06AX12) was not included as this medication was approved only for smoking cessation in Denmark during the study period.

Outcomes

Our primary outcome was incidence of atrial fibrillation or flutter (AF) as defined by an inpatient or

outpatient contact registered with ICD-8 code 427.93 or 427.94 or ICD-10 code I48. AF diagnoses based on emergency room visits were not included due to insufficient validity.[18]

Covariates

Besides marital status (married/single), sex and age, we obtained information on the following comorbid medical and psychiatric diagnoses: diabetes, ischaemic heart disease, dyslipidaemia, hypertension, heart failure, stroke, peripheral artery disease, anaemia, thyroid disorder, chronic kidney disease, schizophrenia or schizoaffective disorder, bipolar affective disorder, dementia, alcohol abuse and/or other substance abuse. All comorbid diagnoses were assessed at inclusion date by previously developed algorithms (Supplementary Table E1 online).

Supplementary analysis

To assess the magnitude of potential detection bias, we conducted a supplementary analysis calculating the number of electrocardiograms (ECGs) registered in general practice (remuneration codes 7155 and 7156).

Statistical methods

We used Cox regression models to estimate adjusted hazard ratios (aHRs) for the association between depression/antidepressant treatment and AF. These models were stratified on match groups and adjusted for marital status and each of the above-mentioned comorbidities in addition to the intrinsic correction for matched characteristics (i.e. sex, age and calendar time). The time scale was time since study inclusion. To distinguish between the potential effects of depression and of antidepressant treatment, the study period started 30 days prior to the index date. The proportionality assumption was assessed graphically by log-minus-log plots and by allowing for an interaction between time and the relevant covariates. Clear non-proportionality was revealed for the exposure effect, which was consequently studied in sufficiently short time spans for results obtained under an assumption of piecewise proportionality to appear informative.

In the supplementary analyses of ECGs, we used Poisson regression to estimate adjusted incidence rate ratios (aIRRs) in order to accommodate that some persons could have multiple ECGs in the period; in rare cases, these could even be registered on the same date. These analyses allowed for the same characteristics as outlined above, but they also accounted for individual risk time.

References were sampled with replacement between strata in order to prevent immortality bias while facilitating sampling of a reference group even for persons who were exposed in the last part of the study period.[19] To account for dependence between observations on the same person in different strata (or, for Poisson analyses, in subsequent time periods), we estimated 95% confidence intervals (CIs) for all aHRs and aIRRs using cluster robust variance estimation with person as the unit of clustering.

The crude absolute proportion receiving an AF diagnosis (and at least one ECG in general practice) within the first months of the study was calculated by the Nelson–Aalen estimator considering death (and, when studying ECG, AF) as a competing risk.

In the sensitivity analyses, we considered four alternative outcome definitions: inpatient AF contacts only and/or only contacts with AF as the primary diagnosis or outpatient contacts only. Furthermore, we considered four different restrictions of our data. First, we excluded persons treated with TCAs within four months before study inclusion due to lack of clarity in their depression status. Second, we excluded persons who had received vitamin K antagonists (ATC code: B01AA), Xa inhibitors (B01AF) or dabigatranetexilate (B01AE07) as these treatments could be markers of AF diagnosed and treated in general practice. Third, we included only persons with a registered ECG in the 18–6 months before index date as they could represent a subgroup with a low prevalence of undiagnosed AF. Fourth, we excluded AF events that were registered before index date as secondary diagnoses at a hospital contact with stroke (ICD-10: I60-I64, I69) as the primary diagnosis, since this combination was quite frequent, and the use of SSRIs to aid post-stroke recovery of motor functioning has been suggested.[20]

All analyses were performed using Stata version 13, College Station, Texas, USA.

Approvals

The study was approved by the Danish Data Protection Agency, the Danish Health Data Authority, and Statistics Denmark. According to Danish law, no further ethical approval or informed consent from the participants is required for register-based studies.

Results

Patients initiating antidepressant treatment ($N = 785{,}254$) were more often single and had more comorbid conditions compared with the reference group (Table 1).

Adjusted for baseline characteristics, antidepressant use was associated with a 218% greater risk of AF during the first month after treatment initiation (aHR = 3.18; 95% CI: 2.98–3.39). This association

Table 1. Baseline characteristics of study participants.

	Exposed group		Reference group[a]
	Number	Col %	Col %
Total	785,254		
ATC group			
Citalopram	366,571	46.7	46.7
Escitalopram	83,707	10.7	10.7
Other SSRI	153,306	19.5	19.5
Mirtazapine	114,741	14.6	14.6
Venlafaxine	31,961	4.1	4.1
Other antidepressants	34,968	4.4	4.4
Year, index date			
2000–2004	293,874	37.4	37.4
2005–2009	292,812	37.2	37.2
2010–2013	198,568	25.3	25.3
Sex			
Male	320,496	40.8	40.8
Female	464,758	59.2	59.2
Age group, years			
18–40	277,153	35.3	35.3
40–60	254,439	32.4	32.4
60–80	173,551	22.1	22.1
80–100	80,111	10.2	10.2
Marital status			
Single	425,531	54.2	50.2
Married	359,723	45.8	49.8
Comorbidities			
Hypertension	158,738	20.2	16.4
Dyslipidaemia	38,231	4.9	4.1
Ischaemic heart disease	30,637	3.9	2.6
Heart failure	7810	1.0	0.6
Peripheral artery occlusive disease	18,198	2.3	1.3
Stroke	36,244	4.6	1.7
Thyroid disorder	24,331	3.1	2.4
Diabetes	47,479	6.0	4.4
Chronic kidney disease	4449	0.6	0.3
Anaemias	18,833	2.4	1.1
Schizophrenia or schizoaffective disorder	6294	0.8	0.3
Bipolar affective disorder	2949	0.4	0.1
Dementia	17,707	2.3	0.5
Alcohol problems	11,239	1.4	0.2
Substance abuse	4680	0.6	0.1

[a]In total, 2,442,393 unique persons were included in the reference group in at least one period. Persons who are included more than once contribute to the stated percentages with their characteristics at each inclusion date.
Col %: Column percentages; SSRI: selective serotonin reuptake inhibitor

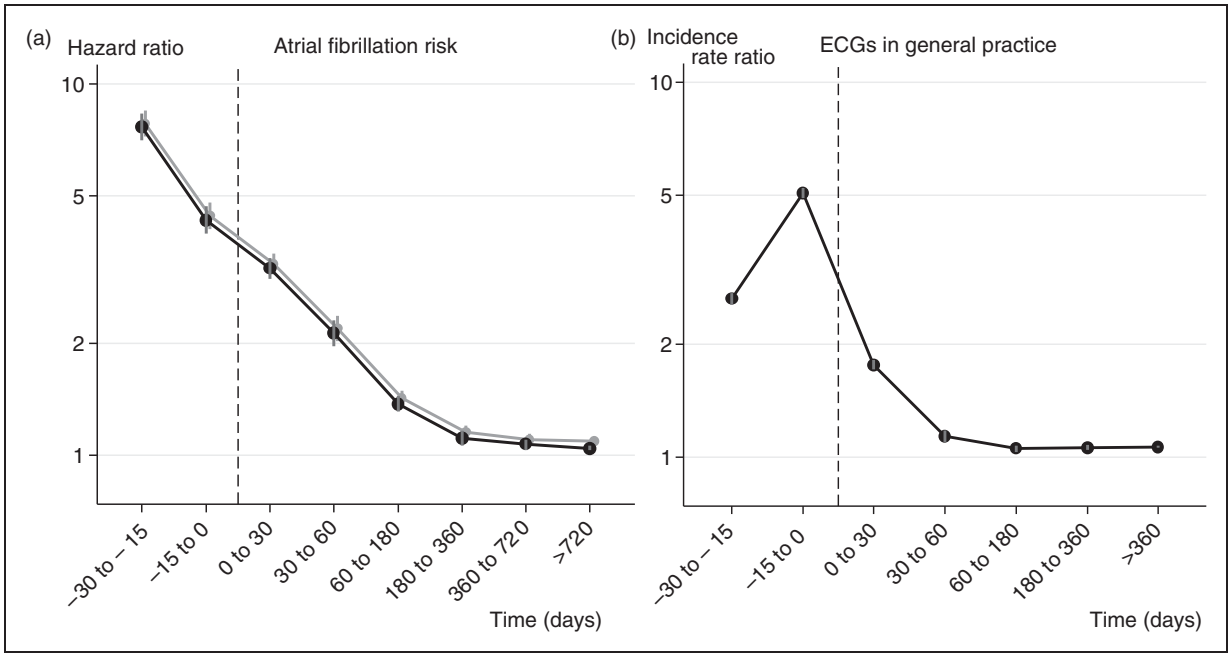

Figure 1. (a) Risk of atrial fibrillation before and after initiation of antidepressant treatment. Crude (grey) and adjusted (black) hazard ratios representing the incidence of atrial fibrillation in persons initiating antidepressant treatment (exposed) compared with a matched antidepressant-free background population as a function of time since treatment. (b) Adjusted incidence rate ratios of ECGs in general practice before and after initiation of antidepressant treatment compared with a matched antidepressant-free background population. (Widths of confidence intervals are smaller than the marked points.)
ECG: electrocardiogram.

gradually attenuated to a 37% (95% CI: 31–44) higher risk 2–6 months after initiation of antidepressant therapy and an 11% (95% CI: 6–16) higher risk 6–12 months after (Figure 1(a)).

However, the associated AF risk was even higher in the month before starting antidepressant treatment (aHR = 7.65; 95% CI: 7.05–8.30 from 30 to 15 days before, and aHR = 4.29; 95% CI: 3.94–4.67 from ≤ 15 days before) (Figure 1(a)).

These results were essentially unchanged in the sensitivity analyses with varied definitions of AF. Yet, the relative incidence of AF in the first two weeks of the study (i.e. 30–15 days before index date) was particularly high when the secondary diagnoses were included (aHR = 4.47; 95% CI: 3.95–5.07 for primary diagnoses only), and it was higher for inpatient (aHR = 8.63; 95% CI: 7.90–9.44) than outpatient (aHR = 3.44; 95% CI: 2.75–4.31) contacts (online Supplementary Figure 1(a)).

Likewise, the pattern was remarkably consistent across different antidepressants (online Figure 1(b) and (c)), sex (online Figure 1(d)) and study period (online Figure 1(e)), but some age-related differences were observed. Among people aged 60 + years, the observed relative incidence of AF was highest in the first two weeks of the study period (aHR = 7.47; 95% CI: 6.56–8.51 from 30 to 15 days before index date for persons aged 60–80 years, and aHR = 8.72; 95% CI: 7.80–9.75 for people aged 80+). For persons aged 40–60 years, the relative incidence was significantly lower in these first weeks (aHR = 2.77; 95% CI: 1.99–3.86), although it was more similar to that found in older individuals over the rest of the study period (online Figure 1(f)). The results were unchanged in the sensitivity analyses, where data restrictions were applied (online Figure 2).

Accompanying these findings, the number of ECGs performed in general practice peaked in the two weeks prior to antidepressant initiation (aIRR = 5.07; 95% CI: 4.92–5.22) (Figure 1(b)). The frequencies of ECGs performed in general practice were similar, regardless of antidepressant type (online Figure 3).

In absolute numbers, 3.8 (95% CI: 3.7–3.9) per 1000 persons were diagnosed with AF between one month before and one month after antidepressant initiation compared with 0.8 (95% CI: 0.8–0.9) per 1000 reference persons. In the same period, 20.1 (95% CI: 19.7–20.4) per 1000 persons who initiated antidepressant treatment had at least one ECG in general practice versus 4.4 (95% CI: 4.3–4.4) per 1000 reference persons (Table 2).

Discussion

In this nationwide matched cohort study, we found that initiation of non-tricyclic antidepressant treatment was

Table 2. Cumulated proportion of persons with an AF diagnosis or an ECG in general practice relative to the date of treatment initiation (index date).

	AF		ECG	
	Cumulated proportion, per 1000 (95% CI)		Cumulated proportion, per 1000 (95% CI)	
Time, days	Exposed	Reference	Exposed	Reference
30 days before	0 (start)	0 (start)	0 (start)	0 (start)
15 days before	1.5 (1.4–1.6)	0.2 (0.2–0.2)	5.1 (4.9–5.2)	1.2 (1.2–1.3)
Treatment initiation	2.4 (2.3–2.5)	0.4 (0.4–0.4)	14.2 (13.9–14.5)	2.3 (2.2–2.3)
15 days after	3.2 (3.1–3.3)	0.6 (0.6–0.7)	17.6 (17.3–18.0)	3.3 (3.2–3.3)
30 days after	3.8 (3.7–3.9)	0.8 (0.8–0.9)	20.1 (19.7–20.4)	4.4 (4.3–4.4)
60 days after	4.7 (4.5–4.8)	1.3 (1.2–1.3)	23.5 (23.1–23.9)	6.6 (6.5–6.7)
180 days after	6.8 (6.7–7.0)	3.0 (2.9–3.0)	34.5 (34.0–34.9)	15.4 (15.2–15.5)

AF: atrial fibrillation; ECG: electrocardiogram

associated with a more than three-fold increased risk of AF shortly after treatment initiation compared with a randomly sampled background population without a history of antidepressant treatment. However, the observed risk of AF was even higher in the weeks before treatment. This pattern was found regardless of calendar time, definition of AF, sex and age of the patients and antidepressant type.

Strengths and limitations

To our knowledge, the present study is the largest study performed that attempts to distinguish between the potential influence of antidepressants and underlying depression on the risk of incident AF.

Utilising data from Danish nationwide registries, which cover a free hospital system, ensured a very complete registration of AF diagnoses with minimal selection bias due to socioeconomic differences in health care-seeking behaviour and virtually no loss to follow-up. Additionally, the risk of recall bias was non-existent due to the prospective data recording. Furthermore, the positive predictive value of the register-based AF diagnoses was above 90%, which suggests high validity.[18] However, our data did not allow us to distinguish between paroxysmal, persistent and permanent atrial fibrillation and atrial flutter, and these conditions might differ in aetiology.

An additional limitation is our reliance on antidepressant medication redemption as a proxy for depression diagnosis. The registers we used lacked information on antidepressant indication and on diagnoses made only in general practice, where the vast majority of antidepressants are prescribed, so for some patients, the primary indication for antidepressant treatment may have been pain or, particularly, anxiety. In principle, this could bias our results both upwards and downwards. However, by excluding TCAs we limited the likelihood that pain was the primary indication for antidepressant prescription, and the extensively documented, close association between depression and anxiety[21] is therefore likely to ensure a very high frequency of depression in the patients initiating antidepressants.

Exposure status was assessed at index date only, and subsequent changes in exposure status for both those treated and those not treated with antidepressants could lead to over-conservative estimates. However, this is unlikely to have much impact on the rather short-term associations of primary interest in this study.

We matched exposed and non-exposed persons on the date of initiated treatment (index date), that is, 30 days after study start. While this approach is legitimate for analyses of AF risk *after* index date, it poses a theoretically problematic conditioning on the future in the analyses of the 30 days *before* the index date. Thus, persons can only be included (in a given stratum) if they survive and do not receive antidepressants in the first 30 days. However, the short-term mortality directly caused by AF must be assumed to be limited and not modified by antidepressant medication to such an extent that it implies a bias of the magnitude of the observed association between antidepressant exposure and AF.

Finally, residual confounding is always a consideration in observational studies. We lacked data on lifestyle characteristics or on socioeconomic status with the exception of marital status. However, although the (vague) long-term differences between people with and without depression could well stem from confounding differences between individuals who develop and seek treatment for depression and those who do not, it is unlikely that the marked changes in AF risk around

the initiation of antidepressant treatment should be caused by factors that are unrelated to depression or antidepressants.

Interpretation and implications of findings

The present study identifies an association between depression and/or antidepressant treatment and increased risk of AF, but the underlying mechanisms remain unclear.

The simplest explanation, that antidepressant medications increase the risk for incident AF, is inconsistent with our finding that the associated risk peaks before antidepressant initiation. Furthermore, this explanation goes against other studies, which conclude that antidepressant use per se is not associated with AF risk.[22,23]

A plausible interpretation could be that depression increases the risk of incident AF. An extensive body of research has reported that depression is associated with dysregulation in the autonomic nervous system, particularly excessive sympathetic activity, which can contribute to cardiovascular morbidity.[24,25] Furthermore, acute emotional stress and anxiety disorders have previously been associated with increased risk of arrhythmias.[11,26,27] At least one study has found that panic disorder is independently associated with increased risk of AF.[28]

In this context, our observation of a decreasing association between AF risk and antidepressant use over time could suggest that treatment might moderate this risk. In a previous study, patients with depression who were treated with sertraline had measurable decreases in plasma norepinephrine over a 12-week period,[24] which suggests that this mechanism is plausible. Still, a potential treatment effect seems unlikely to explain how the association is already substantially decreased in the two weeks before first prescription redemption. Alternatively, the attenuation of the observed association could simply reflect that the risk of depression-related AF is a time-limited event. The rather fast attenuation of the association between depression and AF could explain the earlier null findings from the Women's Health Study,[13] which estimated an average hazard ratio in a setting with a median time to AF of more than 10 years.

However, despite plausibility and statistical significance, we note at least three reasons to recommend that our results be interpreted with a great deal of caution.

First, AF can be largely asymptomatic. A 2013 review of screening studies reported a prevalence of undiagnosed AF in the magnitude of 1% in populations similar to ours,[29] and concordant results were recently reported from a Danish general practice setting.[30] In our study, the excess AF risk is concentrated in the period from 30 days before to 30 days after initiation of antidepressant medication, in which the observed cumulative risk was about 0.4%. Hence, the observed excess risk could reflect that prevalent AF cases are identified in connection with the diagnosis of depression. Since depression can intensify symptoms of AF,[12,31] and ECG screening is recommended prior to starting many types of psychiatric medications, some screening effect is likely. According to our data, only 2% of the exposed patients (compared with 0.4% of the reference persons) had an ECG taken in general practice in the mentioned period, so routine ECG screening appears to be rare. Still, the recent Danish screening study used a two-step procedure in which pulse palpation was followed by ECG in the case of irregular pulse. This approach identified prevalent AF in 1% of all persons aged 65–75 years after ECG screening of only 4.4%.[30] These figures cannot be directly translated into our setting, but they do suggest that increased attention to patients around the time of antidepressant prescription could contribute substantially to the observed excess incidence. This may be particularly true for younger patients, in whom the observed risk of AF peaked at the same time as pre-treatment ECG activity.

Second, an element of reverse causation cannot be ruled out as AF can cause symptoms such as fatigue or anxiety, which could lead to being diagnosed with depression. For this mechanism to have an impact, the AF would need to be present prior to the depression diagnosis and, hence, most likely before the inclusion date at 30 days before antidepressant initiation. Yet, some delayed AF diagnoses could still be registered in the study period.

Third, the particularly high excess incidence of AF seen in the first couple of weeks of the study period seems to be partly driven by secondary inpatient diagnoses. This observation could indicate an influence from other conditions that could cause depression and promote either AF or the diagnosis of prevalent AF, such as stroke, heart failure or myocardial infarction. The analytic models used in our study included traditional regression adjustments for all of these conditions, but initiation of antidepressant treatment could be associated with both the severity and the timing of these conditions in a way that is not accounted for by standard approaches.

In conclusion, patients treated with antidepressants have a substantially elevated AF risk, both in the short term and over more than six months, and our findings suggest a potentially larger impact of the underlying condition than of the treatment. However, there is also evidence that the observed associations may be explained, in part, by informal screening or temporal fluctuations in confounding conditions that may not be fully accounted for by standard analytical methods. In light of the considerable prevalence of depression and

the public health impacts of AF, further investigation is called for to determine whether depression represents a potentially modifiable risk factor for developing AF and related morbidities.

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Author contribution

MFG, MV and DSD conceived the study. MFG and HSP acquired and analysed the data. MFG designed the study and drafted the manuscript. All authors revised the manuscript for important intellectual content and approved of the final version.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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