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Original Article

Comorbidity patterns and the risk of injurious falls in older people with atrial fibrillation: Findings from a Swedish nation-wide population-based study

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ABSTRACT

Background: Atrial fibrillation (AF) is associated with an increased fall risk, partly due to AF-related comorbidities. We investigated the impact of different comorbidity patterns on fall risk in older adults with AF.
Methods: Using the Swedish National Patient Register, we identified 203,042 adults (45 % females) with AF and at least one comorbidity, aged 65 years or older, on 01/01/2017. The primary study outcome was any fall requiring medical attention. Secondary outcomes were falls with fractures, falls with hip fractures, and falls with head trauma. Comorbidity patterns were identified through latent class analysis, and their association with 3-year fall risk was tested through Cox regressions.
Results: The sample mean age was 79.6 (SD: 7.9) years, and the mean number of chronic diseases was 6.6 (SD 3.2). We identified one unspecific (34.2 %) and six specific comorbidity patterns characterized by neuropsychiatric (6.6 %), eye (17.4 %), musculoskeletal (7.2 %), metabolic (15.8 %), cardiovascular (7.4 %), and complex (11.3 %) chronic conditions coexisting with AF. Older adults with AF and complex (HR=1.63, 95 %CI: 1.56–1.70), neuropsychiatric (HR=1.48, 95 %CI: 1.41–1.56), cardiovascular (HR=1.21, 95 %CI: 1.15–1.27), eye (HR=1.16, 95 %CI: 1.12–1.20), and musculoskeletal (HR=1.07, 95 %CI: 1.01–1.13) comorbidity had an increased fall risk compared to those with unspecific comorbidity. The highest risk of falls with fractures or head trauma was found in older adults displaying a complex or neuropsychiatric disease pattern, respectively. Higher estimates emerged in males and those aged <80 years.
Conclusions: Evaluating comorbidity patterns in older AF patients could help stratify the risk of falls in this population and support targeted preventive interventions.

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1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the general population, increasing by 30 % over the last 20 years primarily as a result of the better diagnostics and ageing population [1], with a prevalence that peaks at 28.5 % in older adults [2]. The impact of AF on individuals' quality of life and functional status is mainly due to its symptoms, the risk of AF-related complications such as stroke, and the possible adverse effects of its pharmacological treatments [3]. Patients with AF often have various cardiovascular and non-cardiovascular risk factors, and these usually do not occur in isolation, leading to multimorbidity, polypharmacy and frailty [4,5]. Indeed, AF is a classic prototype of a comorbid condition since >90 % of patients present AF and at least one additional disease [6,7]. Such clinical complexity associated with AF patients has major implications for treatments and outcomes [8,9].

Given the heterogeneous complexity of AF patients, integrated care approaches to AF management based on the Atrial fibrillation Better Care (ABC) Pathway [10] and, most recently, the derived AF-CARE framework, are advocated [11–13]. Stroke prevention with oral anticoagulants (OAC) is the cornerstone of such holistic management and only few clinical conditions may contraindicate this treatment [13]. However, the frequency of OAC underprescription can still reach 50 %, especially in advanced age [14], and one of the reasons for underprescription is the perceived risk of falls given the possible serious bleeding risks [15].

Falls represent a crucial issue for older adults living with AF. Indeed, as mentioned in the recent world guidelines for falls prevention and management in older adults [16], AF is one of the main cardiovascular causes of falls, but an increased risk of falls can make physicians less likely to prescribe OAC [17]. Although the current evidence suggests that AF *per se* is a risk factor for falls, due mainly to haemodynamic changes, most of the increased risk of falls in older adults living with AF can be attributed to coexisting comorbidities and related treatments [18,19]. More than 90 % of patients with AF have at least one additional disease [6,7], and the burden of comorbidities at AF diagnosis is increasing over time [1]. Although recent evidence suggests that specific combinations of chronic diseases are associated with higher fall risk in the general population [20], knowledge of how different comorbidity patterns may impact the risk of falls in older adults with AF is lacking. Exploring this issue could allow us to disentangle the clinical heterogeneity among older adults with AF and to detect AF patients at higher risk of falls early to apply tailored preventive interventions.

We hypothesized that the risk of falls may be differently distributed among older adults with AF according to their pattern of coexisting comorbidities. To test this hypothesis, we conducted the present study to assess the association between different comorbidity patterns and the risk of falls in older adults living with AF.

2. Materials and methods

2.1. Study design and population

This study is part of the "Atrial fibrillation integrated approach in frail, multimorbid and polymedicated older people" (AFFIRMO) project funded by the European Union (Horizon 2020, grant agreement no. 899,871). AFFIRMO aims to improve the management of older adults with AF and co-occurring chronic conditions by enlarging the current evidence through observational studies and testing the effectiveness of an integrated approach in clinical practice.

We conducted the current observational prospective analysis using integrated data from the Swedish National Patient Register (SNPR), the Swedish Prescribed Drug Register, the Swedish Cause of Death Register, the Swedish Total Population Register, and the Swedish Register of Education. Linkage of these registries was carried out by using pseudonymised identifiers. The SNPR gathers national healthcare data regarding hospital visits and admissions since 1987 and specialist outpatient visits since 2001. The Swedish Prescribed Drug Register gathers data on prescribed and pharmacy-dispensed drugs in Sweden since 2005, coded through the Anatomical Therapeutic Chemical (ATC) classification system. The Swedish Total Population Register collects basic sociodemographic information about Swedish residents (e.g., birth, name/sex change, marital status, migration, and death), the Swedish Register of Education records their educational attainment, and the Swedish Cause of Death Registry includes data on the causes of death.

In line with the purpose of the AFFIRMO trial, the study population included all adults aged 65 years or older on 01/01/2017 (index date), who had received an AF diagnosis between 01/01/2012 and 31/12/2016 (based on the ICD-10 code I48) and who had at least one additional disease beyond AF. We obtained a total sample of 206,069 individuals, from which we finally included 203,042 older adults with complete data on sociodemographic characteristics.

The present study was developed in keeping with the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) guidelines (**S1 Table**) and was approved by the Regional Ethical Review Board of Stockholm (dnr: 2016/1001–31/4, 2020–03525; 2021–02004).

2.2. Exposures and outcomes

For each of the study participants, we derived information on sex, age, educational level (categorized as 0–9, 10–12, and 13+ years, based on the schooling years for elementary, high school, or above in Sweden), individual income (categorized in quintiles; mean annual income of the cohort 229,759.5 Swedish krona) and civil status (categorized as married vs. not married [unmarried/divorced/widowed]). For this study, the medications dispensed over three months before the index date were assessed. In particular, we considered the total number of medications to identify the presence of polypharmacy (5–9 drugs/day) and excessive polypharmacy (10 or more drugs/day), and the use of specific drug classes, including antiarrhythmics (ATC codes C01AA02, C01AA52, C01AA05, C01AA08, C01BD01, C07A), antiplatelets (ATC codes starting with B01AC), direct oral anticoagulants (DOAC; ATC codes B01AE07, B01AF01, B01AF02, and B01AF03) and vitamin K antagonist (VKA; ATC codes starting with B01AA).

Chronic diseases and comorbidity patterns. The main study exposure was represented by comorbidity patterns derived as detailed in the statistical analysis section. Information on disease diagnoses, coded according to the International Classification of Diseases system 10th revision (ICD-10), was derived from the SNPR. In agreement with the current literature and guidelines, we considered a disease as chronic based on its prolonged duration and either the need for long-term treatment (pharmacological or nonpharmacological) or consequences (impact on functional status and quality of life) [21]. Four-digit ICD-10 codes corresponding to chronic diseases were identified and grouped into 60 homogeneous disease categories, as described elsewhere [21].

Injurious falls. The main study outcome was incident falls leading to hospital admission with at least an overnight stay, as derived from the SNPR. Incident falls were identified utilizing the following ICD-10 codes: W00, W01, W05-W10, W17-W19 [22]. Additional study outcomes were: 1) falls with subsequent fractures or head trauma, defined by the ICD-10 codes S02, S06, S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T12; 2) falls with subsequent head trauma, defined by the ICD-10 code S06; 3) falls with subsequent hip fracture, defined by the ICD-10 code S72. In order to evaluate recurrent fallers, we also considered the total number of falls leading to hospital admission over the entire observation period. Moreover, for each participant, history of falls was defined as having experienced at least one injurious fall in the year preceding the index date.

2.3. Statistical analysis

The main sociodemographic and clinical characteristics of the total population and by each comorbidity pattern were described using the mean and standard deviation (SD) for continuous variables and the count and percentages for categorical variables. Comparison among different comorbidity patterns were performed through the Student *t*-test and Chi-squared test, as appropriate.

The identification of groups of individuals with similar diseases patterns at the index date was explored through latent class analysis (LCA). For this analysis, out of the 60 disease categories, we only considered 42 conditions with a prevalence >2 % in the study population, to reduce statistical noise [23]. The best number of latent classes was detected by comparing the Bayesian Information Criterion (BIC) and the adjusted BIC of different models, where the lowest values indicate the highest fitness. The latent classes identified were described based on the observed/expected ratios of diseases and by comparing the frequency of chronic conditions in each class with that in the study population. In particular, disease exclusivity was computed as the ratio between the number of disease cases in a class and the total number of individuals with that disease in the population. Chronic conditions with an exclusivity ≥25 % and an observed/expected ratio ≥2 were considered to characterize a given pattern [23].

The incidence rate of each fall-related outcome was computed for the total study population and by comorbidity pattern, and expressed as the number of events per 100 person-years. The comparison of fall risk between comorbidity patterns, considering the unspecific pattern as the reference, was performed through Kaplan-Meier analysis and Cox proportional hazards regression models. The follow-up period consisted of the time from the index date to the date of the fall-related outcome, date of death, or end of follow-up (3 years from the index date), whichever occurred first. Two different models were implemented: Model 1, adjusted for age, sex, education, income, and civil status; and Model 2, further adjusted for previous falls, polypharmacy, use of antiarrhythmics (which may influence AF-related hemodynamic changes), use of oral anticoagulants (vitamin K antagonists or direct oral anticoagulants, which may influence bone mineralization [VKA] and could capture some aspects of clinical complexity leading to underprescribe these drugs). The covariates included in the models were chosen in light of their potential role as confounders in the association between comorbidity patterns and fall risk. The strength of the association between comorbidity patterns and fall risk was expressed as hazard ratios (HRs) and 95 % confidence intervals (CIs). Interactions of comorbidity patterns with age (≤ vs >80 years), sex, use of antiarrhythmic drugs (in light of their possible effects on AF hemodynamic changes, which may influence fall risk [18]), and polypharmacy were tested and, in case of significant multiplicative interactions ($p < 0.10$), stratified analyses were performed. Furthermore, we performed stratified analysis by the presence of polypharmacy in light of the well-known increased risk of falls linked with this condition (due to drug adverse effects, drug-drug or drug-disease interactions) and since it could indirectly be a proxy of higher clinical complexity or diseases' severity [24,25].

To analyze the association between comorbidity patterns and the number of incident falls over the observation period, we performed multivariable Poisson regression analysis, obtaining Incidence Rate Ratios (IRRs) with 95 %CIs that correspond to the extent to which different comorbidity patterns experienced a higher/lower number of falls compared with the unspecific pattern.

Moreover, as a sensitivity analysis to test whether our results were confirmed over a shorter timeframe (to limit the possible influence of incident clinical conditions on the risk of falls), we repeated all analyses considering incident falls in 1-year follow-up.

In all analyses, a p-value <0.05 was considered statistically significant. Statistical analyses were performed using the statistical software R (version 4.2.0 and poLCA package from version 1.4.1 for the LCA).

2.4. Role of the funding source

The study sponsor had no role in study design, data collection, analysis, and interpretation, and writing of the report.

3. Results

3.1. Sample characteristics

The main characteristics of the study population are shown in Table 1. The mean age was 79.6 years, 44.8 % were women, and 59.3 % had at least a high school or university degree. The mean number of chronic conditions was 6.6 (SD 3.2) overall, being slightly higher in women than in men (6.74 [SD: 3.16] vs 6.48 [3.13], $p < 0.001$). Over one-fourth of the population had polypharmacy (25.5 %) or excessive polypharmacy (8 %). Overall, 64.5 % of study participants were taking oral anticoagulants, either VKA (32.6 %) or DOAC (31.9 %); most of them used antiarrhythmic drugs (55.3 %), while 6.6 % were on antiplatelets.

The following seven comorbidity patterns were identified through LCA: 1) unspecific disease pattern ($n = 69,470$, 34.2 %); 2) neuropsychiatric disease pattern ($n = 13,457$, 6.6 %); 3) cardiovascular disease pattern ($n = 15,073$, 7.4 %); 4) eye disease pattern ($n = 35,418$, 17.4 %); 5) musculoskeletal (MSK) disease pattern ($n = 14,646$, 7.2 %); 6) metabolic disease pattern ($n = 31,990$, 15.8 %); and 7) complex disease pattern ($n = 22,988$, 11.3 %). For the prevalence of single conditions within each disease pattern, please see the **S2 Table**. Briefly, across all patterns hypertension was one of the most prevalent conditions. While no prevalent diseases emerged in the unspecific pattern, the neuropsychiatric disease one had a higher frequency of cerebrovascular diseases, dementia, and neurologic and psychiatric behavioral disorders. The most prevalent conditions in the cardiovascular disease pattern were bradycardias conduction disease and ischemic heart disease, while in the eye pattern were cataract lens diseases. Concerning the MSK disease pattern, the most prevalent condition was osteoarthritis, while in the metabolic disease pattern, patients were more likely to present diabetes, dyslipidemia, and ischemic heart disease. The complex pattern was characterized by a combination of multisystemic disorders, including heart failure, ischemic heart disease, anemia, eye diseases, and colitis-related disease, and reported the highest prevalence of solid neoplasms.

When comparing study participants according to their comorbidity patterns (Table 1), individuals displaying the neuropsychiatric, eye, and complex disease patterns were more likely to be older, less educated, and married, and to have a lower income, as compared with those within the unspecific disease pattern. Individuals within the neuropsychiatric, complex, and cardiovascular disease patterns had a higher mean number of comorbidities, and the first two groups also showed the highest prevalence of polypharmacy or excessive polypharmacy. Concerning the use of specific medications, individuals in the complex and neuropsychiatric disease patterns were less likely to be on oral anticoagulants; in particular, VKAs were prescribed less frequently in the neuropsychiatric pattern, while DOACs less so in the complex group.

3.2. Associations with fall risk

A total of 24,411 falls leading to medical attention occurred over the three years of follow-up (9600 of these falls happened in the first year; **S3 Table**), corresponding to an incidence rate of 4.95 per 100 person/years. The incidence rates of falls with fractures or head trauma, hip fractures, and head trauma were 3.89, 1.57, and 0.69 per 100 person/years, respectively, with the highest rates observed among study participants displaying a complex, neuropsychiatric, or eye diseases comorbidity pattern (Table 2). The Kaplan-Meier curves are shown in Fig. 1.

In the Cox regression analyses (Table 3), after adjusting for potential confounders and compared with subjects within the unspecific diseases

Table 1
Characteristics of the total sample and by comorbidity pattern.

	All	Unspecific	Neuro-psychiatric	Cardio-vascular	Eye	MSK	Metabolic	Complex	p
n	203,042	69,470	13,457	15,073	35,418	14,646	31,990	22,988	
Sex (female)	91,027 (44.8)	29,980 (43.2)	6437 (47.8)	6460 (42.9)	18,788 (53.0)	7493 (51.2)	10,659 (33.3)	11,210 (48.8)	<0.001
Age (y)	79.63 (7.88)	78.12 (8.01)	81.09 (7.83)	80.63 (7.71)	82.68 (7.19)	77.92 (7.09)	77.98 (7.60)	81.39 (7.47)	<0.001
Age > 80 y	95,896 (47.2)	26,740 (38.5)	7459 (55.4)	7937 (52.7)	22,945 (64.8)	5543 (37.8)	12,075 (37.7)	13,197 (57.4)	<0.001
Education (y)									<0.001
0–9	82,743 (40.8)	25,859 (37.2)	5858 (43.5)	6156 (40.8)	15,360 (43.4)	5303 (36.2)	13,641 (42.6)	10,566 (46.0)	
10–12	76,122 (37.5)	26,278 (37.8)	4908 (36.5)	5683 (37.7)	12,643 (35.7)	5759 (39.3)	12,211 (38.2)	8640 (37.6)	
13+	44,177 (21.8)	17,333 (25.0)	2691 (20.0)	3234 (21.5)	7415 (20.9)	3584 (24.5)	6138 (19.2)	3782 (16.5)	
Civil status (not married)	105,690 (52.1)	33,983 (48.9)	7926 (58.9)	7974 (52.9)	19,875 (56.1)	6985 (47.7)	15,344 (48.0)	13,603 (59.2)	<0.001
Income									<0.001
Quintile 1	39,726 (19.6)	13,206 (19.0)	2734 (20.3)	2770 (18.4)	7448 (21.0)	2852 (19.5)	6051 (18.9)	4665 (20.3)	
Quintile 2	40,622 (20.0)	12,540 (18.1)	3026 (22.5)	3045 (20.2)	7757 (21.9)	2626 (17.9)	6234 (19.5)	5394 (23.5)	
Quintile 3	40,880 (20.1)	12,606 (18.1)	2873 (21.3)	3267 (21.7)	7472 (21.1)	2872 (19.6)	6430 (20.1)	5360 (23.3)	
Quintile 4	40,888 (20.1)	14,054 (20.2)	2649 (19.7)	3176 (21.1)	6888 (19.4)	3028 (20.7)	6690 (20.9)	4403 (19.2)	
Quintile 5	40,926 (20.2)	17,064 (24.6)	2175 (16.2)	2815 (18.7)	5853 (16.5)	3268 (22.3)	6585 (20.6)	3166 (13.8)	
N. diseases	6.60 (3.15)	3.94 (1.49)	8.00 (2.25)	7.96 (2.18)	7.21 (2.07)	7.66 (2.25)	6.14 (1.75)	11.91 (2.68)	<0.001
N. drugs/day									<0.001
5–9	95,212 (46.9)	32,030 (46.1)	6289 (46.7)	7693 (51.0)	17,860 (50.4)	7199 (49.2)	17,164 (53.7)	6977 (30.4)	
10+	52,887 (26.0)	7652 (11.0)	5187 (38.5)	3753 (24.9)	9853 (27.8)	3909 (26.7)	7982 (25.0)	14,551 (63.3)	
Use of VKA	66,119 (32.6)	22,184 (31.9)	3020 (22.4)	5402 (35.8)	12,222 (34.5)	4514 (30.8)	11,773 (36.8)	7004 (30.5)	<0.001
Use of DOAC	64,782 (31.9)	23,625 (34.0)	4651 (34.6)	4353 (28.9)	11,057 (31.2)	5309 (36.5)	9653 (30.2)	6134 (26.7)	<0.001
Use of antiplatelets	13,389 (6.6)	2936 (4.2)	1789 (13.3)	1172 (7.8)	2182 (6.2)	555 (3.8)	2467 (7.7)	2288 (10.0)	<0.001
Use of antiarrhythmic	112,276 (55.3)	35,590 (51.2)	7809 (58.0)	8693 (57.7)	19,365 (54.7)	7595 (51.9)	18,765 (58.7)	14,459 (62.9)	<0.001

Notes: Numbers are mean (standard deviation) or count (%) for continuous and categorical variables, respectively. *Abbreviations*: DOAC, direct oral anticoagulant; y, years; MSK, musculoskeletal; VKA, vitamin K antagonist.

pattern, the risk of falls increased by 63 % for the complex disease pattern (95 %CI: 1.56 1.70), by 48 % for the neuropsychiatric disease pattern (95 %CI: 1.41, 1.56) and by 21 % for the cardiovascular diseases pattern (95 %CI: 1.15, 1.27), followed by the eye disease (HR=1.16, 95 %CI: 1.12, 1.20) and MSK disease (HR=1.07, 95 %CI: 1.01, 1.13) patterns. The risk of falls with fractures or head trauma and falls only with head trauma was higher for the complex disease pattern (with HRs increasing by 54 % and 60 %, respectively), followed by the neuropsychiatric one (with HRs increased by 43 % and 54 %, respectively), while these two patterns had similar estimates for the risk of falls with hip fractures (ranging between 40 and 46 % increased risk). Weaker but still significant results were observed for the cardiovascular and eye disease patterns, with HRs increasing by 17–25 % and 9–17 %, respectively, for the said fall-related outcomes. The MSK disease pattern was associated with 21 % (95 %CI: 0.71, 0.88) lower risk of falls with hip fractures compared with the unspecific one, while no significant results emerged for the metabolic pattern (Table 3). Similar trends were found when, in sensitivity analyses, we restricted the follow-up time to one year (**S4 Table**).

Significant interactions were found when considering age and sex and the neuropsychiatric, complex, and cardiovascular patterns, whereby associations with an increased risk of falls were stronger for men and those younger than 80 years (**S5–6 Tables**). One exception was the association between the cardiovascular and eye disease patterns with the risk of falls with head trauma, which was higher among females. As regards the use of antiarrhythmics (**S7 Table**), we found that fall risk was more marked among individuals with a complex disease pattern who were not using antiarrhythmic drugs. Considering polypharmacy, the associations between comorbidity patterns and the risk of falls with or without fractures or head trauma seemed to be more marked among individuals taking 0–4 or 5–9 drugs/day, while they were attenuated in those with excessive polypharmacy. This picture slightly changed for the association between cardiovascular, eye and MSK patterns and incident falls with head trauma, whose risk was stronger among people taking 5 to 9 drugs/day (**S8 Table**).

Finally, as regards recurrent falls, the results of the Poisson regression showed that individuals in the complex and neuropsychiatric disease patterns experienced an 77 % and 50 % higher number of falls than the unspecific group. Smaller but still significant increased number of falls were observed for the cardiovascular (IRR= 1.25, 95 %CI: 1.17, 1.33), eye (IRR= 1.18, 95 %CI: 1.12, 1.23), and MSK (IRR= 1.13, 95 % CI: 1.06, 1.21) patterns (**S9 Table**).

4. Discussion

In this nation-wide Swedish study, our principal findings are as follows: (i) the risk and number of falls experienced by older adults with AF are influenced by their comorbidity patterns; (ii) adults with AF within the complex comorbidity pattern, as well as those within the neuropsychiatric pattern, showed the highest risk of experiencing falls leading

Table 2
Incidence rate of injurious falls by comorbidity pattern over a 3-year follow-up.

	Incidence rate per 100 person/years (95 % confidence interval)			
	All falls	Falls with fracture or head trauma	Falls with hip fracture	Falls with head trauma
All	4.95 (4.89, 5.02)	3.89 (3.84, 3.95)	1.57 (1.54, 1.61)	0.69 (0.67, 0.71)
Comorbidity pattern				
Unspecific	3.61 (3.53, 3.70)	2.96 (2.88, 3.04)	1.20 (1.15, 1.25)	0.53 (0.50, 0.56)
Neuropsychiatric	7.55 (7.23, 7.88)	5.82 (5.54, 6.10)	2.50 (2.32, 2.68)	1.01 (0.90, 1.13)
Complex	9.01 (8.74, 9.29)	6.77 (6.53, 7.01)	2.59 (2.45, 2.74)	1.12 (1.03, 1.22)
Eye	6.19 (6.02, 6.36)	4.70 (4.55, 4.85)	2.00 (1.91, 2.10)	0.79 (0.74, 0.86)
MSK	4.18 (3.98, 4.39)	3.22 (3.05, 3.40)	1.02 (0.93, 1.13)	0.60 (0.52, 0.68)
Metabolic	3.66 (3.53, 3.79)	2.99 (2.88, 3.12)	1.16 (1.09. 1.24)	0.57 (0.52, 0.62)
Cardiovascular	5.53 (5.29, 5.78)	4.31 (4.10, 4.53)	1.86 (1.73, 2.01)	0.79 (0.70, 0.88)

Abbreviations: MSK, musculoskeletal.

to medical attention (including those with consequent fractures) and recurrent falls; (iii) the complex, neuropsychiatric, and cardiovascular patterns were associated with an increased risk of falls with head trauma. These findings suggest the prognostic value of specific comorbidity patterns in older adults affected by AF.

The complex diseases pattern in our population included a combination of anaemia, cardiovascular diseases, chronic kidney diseases, diabetes, eye disorders, and, in one-third of cases, solid neoplasms. This group of study participants had the highest number of chronic diseases and prevalence of polypharmacy. Overall, these characteristics might have made them more vulnerable and prone to experience adverse events such as falls, whose risk is increased not only by the consequences of the single conditions but also by the interactions between different diseases and/or medications affecting physical performance [20,26,27].

On the other hand, the neuropsychiatric disease pattern was mainly composed of cerebrovascular diseases and dementia in combination with hypertension, cardiovascular diseases, colitis, and anaemia. Our results align with recent studies in the general population that observed a higher risk of falls and worse physical performance linked to multimorbidity patterns including neurological and psychiatric conditions [20,27]. The impact of these conditions on patients with AF is substantial due to the well-known relationship of AF with cognitive decline, primarily through vascular damage to the brain micro- and macrovascular system [28], and considering that deficits in cognitive domains, like processing speed and executive function, have been shown to predict injurious falls in the long-term [29].

Approximately, a 20 % increased risk of falls requiring medical attention emerged for the cardiovascular and eye disease patterns. Considering the former, the coexistence of AF with other cardiovascular conditions, in particular heart failure and sinus node dysfunction, could exacerbate the negative impact of AF on the risk of falls due to blood pressure unbalances and multiorgan hypoperfusion. Hemodynamic changes may decrease cardiac output, leading to an increased incidence of falls in older people [18]. Eye diseases and visual impairment are other common causes of falls [30,31], and a benefit for reducing the falling rate has been shown after the correction of these disorders [32]. Of note, not only cataract but also other eye diseases, such as binocular vision disorders, could predispose to falls [33] by hampering the avoidance of environmental risk factors (e.g. disconnectedness in the ground) and developing balance deficits [34].

Finally, a weak positive association with the risk of any fall was observed for the musculoskeletal diseases pattern, which mainly included people with osteoarthritis and, in 10 % of cases, osteoporosis. Conversely, the risk of falls with hip fractures seemed to be reduced in the presence of musculoskeletal comorbidities, especially among women. A recent systematic review found an overall increased risk of recurrent falls for symptomatic knee or hip osteoarthritis [35], but the association was attenuated when considering the radiographically-assessed disease, with an opposite trend emerging for radiographic hip osteoarthritis [35]. Interestingly, these results, primarily driven by studies involving older women [36], were also observed in our study. Although the impact of osteoarthritis on fall risk may be mediated by limitations in physical activity and deficits in muscle strength, proprioception, and balance [37], such an effect is still unclear when considering incident fractures and should be better elucidated [38].

Of note, the metabolic disease pattern was not associated with fall risk. This result may be linked to the fact that this pattern included more cardiovascular risk factors, like dyslipidemia and hypertension, than overt diseases, such as diabetes, ischemic heart disease, and heart failure. This issue could explain our findings, along with the fact that individuals in this group had lower chronic diseases than most of the other patterns.

We found that the impact of comorbidity patterns on fall risk was generally more marked in male patients with AF, those younger than 80 years, and taking no more than 9 drugs/day. Although we cannot rule out the possibility that these categories of study participants had more severe comorbidities than their counterparts, previous studies suggest that the burden of AF and related comorbidities could more strongly affect physical performance in male and younger patients [39,40]. In addition, it is possible that older people, as well as those taking excessive polypharmacy, could be more clinically complex and have more limited mobility, which reduce the chance of falls. Considering the differences between sexes, our results differ from the current literature that, despite some conflicting data [26], found a stronger detrimental impact of multimorbidity on physical performance [41] and fall risk [42] in women. Moreover, women with AF are generally older, have more comorbidities, worse quality of life, and poorer clinical and cognitive outcomes of AF at disease onset compared to men [43]. However, when interpreting our data, we should consider that the unspecific comorbidity pattern was chosen as the reference category. Therefore, we could be less likely to capture the additional burden of comorbidity patterns among those patients (e.g., females or older ones) who already have an intrinsically higher risk of falls.

Interesting results emerged when evaluating the interplay between comorbidity patterns and some medications commonly used in AF. In particular, study participants with AF and a complex disease pattern showed an increased risk of falls compared with those displaying an unspecific pattern, which was attenuated in those using antiarrhythmic drugs. Although this result could be linked to the buffering of haemodynamic changes of AF by antiarrhythmics [18], some drugs (e.g., amiodarone) have also been associated with an increased risk of syncope and injurious falls in other large cohorts of older adults, especially during the first months of treatment [44].

Our findings contribute to clinical practice by supporting the evaluation not just of single chronic diseases but also their combinations to optimize patients' stratification for the risk of fall. This could be facilitated by the development of informatic supporting tools that suggest which comorbidity patterns the patient belongs to based on the list of comorbidities recorded by the physician. Incorporating this assessment into routine clinical practice can also help identify the best strategies to prevent falls in these patients. In a recent study on hospitalized older

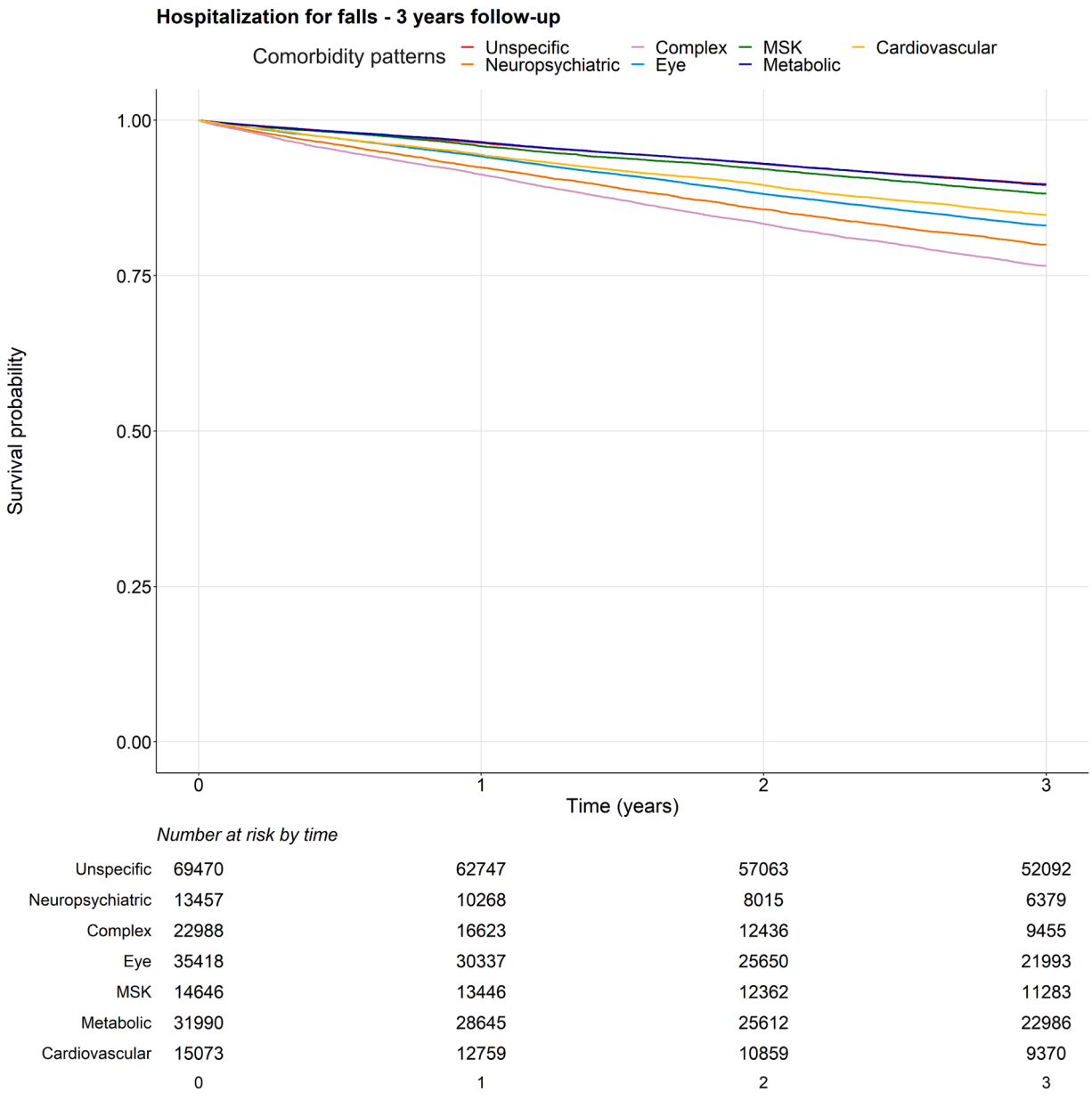

Fig. 1. Kaplan-Meier curve for incident falls over the 3-year follow-up by comorbidity pattern
Abbreviations: MSK, musculoskeletal.

patients, the pattern of chronic diseases modified the effectiveness of an exercise intervention [45]. In the context of our study, we can argue that even among patients with AF, belonging to specific patterns of comorbidities may emphasize the benefits of specific types of interventions, including those based on exercise, balance, or coordination training (for the musculoskeletal, neuropsychiatric, cardiovascular, and complex patterns), on the minimization of modifiable risk factors (for the eye disease pattern) or the medication review (for the neuropsychiatric, cardiovascular, and complex patterns).

4.1. Limitations and strenghts

The main strengths of the present study are the inclusion of a large population and the use of solid register-based data, which support the generalizability of our findings. Among the limitations of our study, we considered only falls leading to hospital medical attention, which could underestimate both the incidence of falls in the study population and the associations between comorbidity patterns and fall risk. Second, since we used administrative data, it was not possible to evaluate factors such as functional and nutritional status, or cognitive and physical performance, which could act as potential confounders or mediators in the studied associations. As well-known, falls derive from the interaction of multiple factors linked to patients' diseases, cognitive and physical performance, functional abilities, and environment [16]. Evaluating how the identified comorbidity patterns interact with such a wide set of factors in older people with AF will be the subject of future investigations based on data from population-based studies. In addition, blood pressure data were not available for the included participants. Therefore, we could not evaluate the specific role of this factor in the association between comorbidity patterns and fall risk, although blood pressure imbalances and vascular damage seem to be crucial pathophysiological mechanisms. Third, the small number of fall-related brain haemorrhages in our study population did not allow us to assess the association between comorbidity patterns and this kind of injurious falls. Fourth, we evaluated the comorbidity patterns at the index date and not possible newly diagnosed chronic diseases or medications'

Table 3
Cox regression for the association between comorbidity patterns and incident falls over the 3-year follow-up.

	Hazard ratio (95 % confidence interval)					
	Neuro-psychiatric	Cardio-vascular	Eye	MSK	Metabolic	Complex
All falls						
Model 1	1.69	1.28	1.23	1.15	1.04	1.96
	(1.61, 1.77)	(1.22, 1.35)	(1.19, 1.28)	(1.09, 1.21)	(0.99, 1.08)	(1.88, 2.04)
Model 2	1.48	1.21	1.16	1.07	0.99	1.63
	(1.41, 1.56)	(1.15, 1.27)	(1.12, 1.20)	(1.01, 1.13)	(0.94, 1.03)	(1.56, 1.70)
Falls with fracture or head trauma						
Model 1	1.61	1.24	1.17	1.07	1.04	1.83
	(1.53, 1.71)	(1.17, 1.31)	(1.12, 1.22)	(1.01, 1.14)	(0.99, 1.09)	(1.75, 1.91)
Model 2	1.43	1.17	1.10	1.00	0.99	1.54
	(1.35, 1.51)	(1.11, 1.24)	(1.06, 1.15)	(0.94, 1.07)	(0.94, 1.04)	(1.46, 1.61)
Falls with hip fracture						
Model 1	1.65	1.28	1.15	0.84	1.00	1.65
	(1.52, 1.79)	(1.17, 1.39)	(1.07, 1.22)	(0.76, 0.94)	(0.93, 1.08)	(1.54, 1.77)
Model 2	1.46	1.21	1.09	0.79	0.95	1.40
	(1.34, 1.59)	(1.11, 1.32)	(1.02, 1.16)	(0.71, 0.88)	(0.88, 1.03)	(1.30, 1.51)
Falls with head trauma						
Model 1	1.68	1.31	1.22	1.14	1.07	1.84
	(1.48, 1.92)	(1.15, 1.49)	(1.11, 1.35)	(0.99, 1.32)	(0.96, 1.19)	(1.66, 2.05)
Model 2	1.54	1.25	1.17	1.09	1.03	1.60
	(1.35, 1.76)	(1.09, 1.42)	(1.06, 1.29)	(0.94, 1.25)	(0.92, 1.15)	(1.42, 1.79)

Notes: The unspecific diseases cluster is the reference category. Model 1 is adjusted for age, sex, education, income, and civil status; Model 2 is also adjusted for previous falls, polypharmacy, use of vitamin K antagonists, use of direct oral anticoagulants, and use of antiarrhythmics. *Abbreviations*: MSK, musculoskeletal.

changes during the study period. As the literature suggests, multimorbidity is a dynamic condition that can modify over time [23]. However, the sensitivity analysis considering a one-year follow-up, which makes possible changes in comorbidity patterns less likely, substantially confirmed our main findings. Fifth, we could not distinguish whether the presence of paroxysmal or permanent AF modifies the impact of comorbidity patterns on the risk of falls. Indeed, both types of AF seem to be associated with a higher fall risk and may be characterized by different clinical profiles [46]. However, the frequent conversion from paroxysmal to permanent AF, especially in older age, would make it challenging to categorize individuals without being subjected to misclassification bias [47]. Finally, as mentioned above and as done in previous studies [23,48], the reference category was the unspecific disease pattern, which did not include healthy controls but people with fewer chronic diseases than the other groups.

5. Conclusions

Our findings support the need for personalizing the therapeutic approach in older adults with AF based not just on single comorbidities but also on their combinations. Indeed, our study shows that comorbidity patterns may influence the risk of falls, which have substantial functional and clinical complications. Of note, our study does not suggest that AF patients with certain comorbidity patterns should not be treated with anticoagulants because of their higher risk of falls. Instead, evaluating comorbidities and developing novel informatic supporting tools that may provide the physician with information about the patients' more likely comorbidity pattern – based on their list of ascertained chronic diseases – can help stratify the risk of falls. This would facilitate addressing specific subgroups of AF patients to targeted fall preventive actions, such as regular medication review (reconsidering fall-risk-increasing drugs) and multicomponent interventions, including exercise and balance training.

Contributor ship

CT, CD, ACL, AM, MP, RP, GL, SJ and DLV contributed to the conceptualization of the study. RP, CT, DLV, MP, GL, SJ contributed to the funding acquisition. CT, DLV, and CD defined the methodology of the study. SJ and GL provided to the project administration. JW and KJ contributed to data curation. CD performed the formal analyses. CT, CD, and DLV wrote the original draft. LD, ACL, JW, KJ, CA, GO, AM, RP, GL, SJ, and MP contributed to the supervision of the work, and to the review and editing of the manuscript. All authors approved the final version of the manuscript.

Data availability statement: Data are available upon request to DLV.

Ethics approval statement

The study protocol was approved by the Regional Ethical Review Board of Stockholm (dnr: 2016/1001–31/4, 2020–03,525; 2021–02,004).

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Conflict of interest disclosure

The authors declare they have no conflict of interest.

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Supplementary materials

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