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ORIGINAL RESEARCH

Trends in Polypharmacy Among Patients With Atrial Fibrillation: A Report From the Finnish AntiCoagulation in Atrial Fibrillation Nationwide Cohort Study

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BACKGROUND: Polypharmacy, commonly defined as the concurrent use of ≥5 medications, is associated with adverse outcomes, but comprehensive data on its prevalence and temporal trends in patients with atrial fibrillation (AF) are limited.

METHODS: We conducted a nationwide retrospective cohort study using FinACAF (Finnish AntiCoagulation in Atrial Fibrillation) cohort, including all patients with incident AF between 2007 and 2018. Data were retrieved from national health care and prescription registers, covering all levels of care. Medication use was assessed within 120 days before and after AF diagnosis. Polypharmacy was defined as the use of ≥5 medications. Temporal trends and associations between baseline characteristics and drug count were analyzed using linear regression.

RESULTS: Among 229 565 patients with incident AF (mean age 72.7 years, SD 13.2; 50% women), the mean number of medications after diagnosis was 6.0 (SD 3.9). Overall, 63.1% of patients were exposed to polypharmacy, and 17.7% used ≥10 medications. Polypharmacy was more common among older patients and those with comorbidities, especially hypertension and diabetes. From 2007 to 2018, the mean number of drugs increased modestly (from 5.5 to 6.2, $P<0.001$). The most pronounced increases were seen in anticoagulant and cardiovascular drug use.

CONCLUSIONS: Polypharmacy is highly prevalent among patients with AF in Finland and has increased over time. These findings underscore the need for holistic, patient-centered management strategies to optimize outcomes in this multimorbid population.

Key Words: atrial fibrillation ■ comorbidity ■ polypharmacy

Atrial fibrillation (AF) is the most common long-standing arrhythmia, affecting ~5% of the adult population and as many as 1 in 4 over the age of 75.[1] The prevalence of AF is estimated to double over the next 4 decades, driven by increased longevity, enhanced detection of undiagnosed AF, and improved survival from other cardiac conditions.[2] Concurrently, along with the global population aging, the prevalence of numerous chronic diseases continues to rise. Given the high burden of comorbidities in patients with AF, an integrated management approach is important and strongly emphasized in contemporary international AF guidelines.[3,4]

The term polypharmacy is defined by the National Center for Biotechnology Information as the concurrent,

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CLINICAL PERSPECTIVE

What Is New?

- Among patients with atrial fibrillation, polypharmacy is increasing, with approximately two thirds using ≥5 medications and one fifth using ≥10 different drugs concurrently.

What Are the Clinical Implications?

- Given the high prevalence of polypharmacy in patients with atrial fibrillation, a holistic, integrated treatment approach is important.
- Guidelines and clinical practice should acknowledge the rising prevalence of polypharmacy in this population and encourage efforts to minimize potential harms associated with it.

Nonstandard Abbreviations and Acronyms

ATC	Anatomical Therapeutic Chemical

regular use of ≥5 medications. The excessive and cumulative use of multiple medications is associated with an increased risk of adverse outcomes, including falls, frailty, functional decline, and mortality. Polypharmacy is common in older adults and at-risk younger individuals, with prevalence increasing steadily in recent years, particularly among those aged 75 and older.[5,6]

However, there are limited comprehensive data on drug use and prevalence of polypharmacy in patients with AF. Furthermore, although much has changed in medicine over the past decades, it remains unknown whether the prevalence of polypharmacy has changed over time. Therefore, this study aimed to investigate the prevalence, associated factors, and especially the temporal trends of polypharmacy in Finnish patients with AF.

METHODS

Data Availability Statement

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the Finnish national register holders (Social Insurance Institution of Finland, Finnish Institute for Health and Welfare, Population Register Center and Tax Register) through Findata (https://findata.fi/en/). In the interest of research transparency and reproducibility, the analysis code used in this study has been made publicly available on GitHub and permanently archived on Zenodo under DOI 10.5281/zenodo.17227609. These resources can also be accessed directly at https://doi.org/10.5281/zenodo.17227609.

Study Cohort

The FinACAF (Finnish AntiCoagulation in Atrial Fibrillation) study (ClinicalTrials Identifier: NCT04645537; ENCePP Identifier: EUPAS29845) is a nationwide retrospective cohort study that includes patients diagnosed with AF at all levels of care in Finland from 2004 to 2018. Patients were identified using all available national health care registers, including hospitalizations and outpatient specialist visits (HILMO [Finnish Care Register for Health Care]), primary health care (AvoHILMO [Finnish Primary Health Care Register]), and the National Reimbursement Register maintained by the Social Insurance Institute of Finland. The cohort inclusion criterion was an *International Classification of Diseases, Tenth Revision* (*ICD-10*), diagnosis code of I48, encompassing AF and atrial flutter, collectively referred to as AF, recorded between 2004 and 2018. Exclusion criteria were permanent emigration abroad before December 31, 2018, and age <20 years at AF diagnosis. The present substudy was conducted within a cohort of patients with incident AF from 2007 to 2018, established in previous studies of the FinACAF cohort.[7] Data on baseline comorbidities at the time of AF diagnosis were obtained from the aforementioned health care registers from all levels of care. The definitions of baseline comorbidities are presented in Table S1–S3.

Data on Medication Use

Medication use was assessed using pharmacy claims data obtained from the National Reimbursement Register maintained by the Social Insurance Institution of Finland. This nationwide register captures all prescription medication claims, but it does not include over-the-counter drugs. Medication use was considered from drug purchases made on the date of AF diagnosis and during the subsequent 120 days. The 120-day window was selected because, under the Finnish reimbursement system, patients can purchase medication for up to 90 days at a time, with an additional 30-day grace period. Therefore, patients on continuous pharmacotherapy would be expected to have at least one prescription claim within this interval. The study focused on the overall number of medications used rather than on specific individual drugs. Medications were classified according to the Anatomical Therapeutic Chemical (ATC) classification system. We calculated the number of unique chemical substances based on the complete ATC code (7 characters), the number of therapeutic drug classes based on the first 4 characters (level 3), and the main pharmacological groups based on the first letter (level

1) of the ATC code. We evaluated both the total drug count and categorized drug classes, using previously established definitions of polypharmacy, with ≥5 drugs considered polypharmacy. In addition to analyzing medication use following AF diagnosis, we assessed medication use during the 120-day period preceding the diagnosis, using the same methodology.

Study Ethics

The study protocol was approved by the Ethics Committee of the Medical Faculty of Helsinki University, Helsinki, Finland (no. 15/2017), and received research permission from the Helsinki University Hospital (HUS/46/2018). Respective permissions were obtained from the Finnish register holders (KELA 138/522/2018; Finnish Institute for Health and Welfare THL 2101/5.05.00/2018; Population Register Centre VRK/1291/2019-3; Statistics Finland TK-53-1713-18/u1281; and Tax Register VH/874/07.01.03/2019). Patients' personal identification numbers were pseudonymized, and the research group received individualized but unidentifiable data. Informed consent was waived due to the retrospective registry nature of the study. The study conforms to the Declaration of Helsinki as revised in 2024.

Statistical Analysis

The χ^2 test, the Student's *t* test, and the 1-way ANOVA were used to compare baseline variables as well as differences between the medication categories. The number of medications and temporal trends were evaluated separately in subgroups defined by age, history of stroke, and a CHA_2DS_2-VA score ≥4. Linear regression was used to assess the temporal trends and associations between baseline variables and the number of medications in both unadjusted and adjusted analyses. Trends in ordered drug use categories across calendar periods were evaluated using linear regression with ordinal coding of medication category. In subgroup analyses, we focused on crude trends in mean drug count, assessing differences across subgroups using linear models that included the subgroup, calendar period, and their interaction. McNemar and Wilcoxon signed-rank tests were used to assess changes in drug use before and after AF diagnosis. Statistical analyses were performed with the IBM SPSS Statistics software version 28.0 (SPSS, Inc., Chicago, IL, USA) and R version 4.0.5 (R Core Team, Vienna, Austria; https://www.R-project.org).

RESULTS

Cohort Characteristics

We identified 229 565 patients with new-onset AF (50.0% women; mean age 72.7 years, SD 13.2). Mean number of different drug compounds during the first 120 days after AF diagnosis was 6.0 (SD 3.9), and the mean number of different drug classes used was 3.4 (SD 1.9). Overall, 63.1% of the patients used at least 5 different drug compounds, and 17.7% used ≥10 different drug compounds. Patients with higher numbers of medications were on average older, more often women, and characterized by a greater burden of comorbidities (Table 1).

Factors Associated With Polypharmacy

The number of drugs increased substantially with rising age (Table 1 and Figure 1; *P* value for trend <0.001). All studied baseline variables, except for calendar year period, showed statistically significant associations with drug count in the adjusted model. Hypertension and diabetes had the strongest positive associations, whereas higher income, prior stroke, dementia, and alcohol use disorder were linked to lower medication use (Table 2).

Temporal Trends in Polypharmacy

The mean count of different drug compounds during the first 120 days from AF diagnosis increased from 5.5 to 6.2 during the study period (*P* value for trend <0.001). Over time, medication use patterns shifted toward greater polypharmacy, with a decline in minimal drug use (0–2 compounds) and moderate use (5–9 compounds) remaining most prevalent (*P* value for trend in drug categories <0.001; Figure 2). However, in the adjusted analysis, calendar period was not significantly associated with the mean number of drugs 120 days after AF diagnosis (Table 2, *P*=0.29).

There was a substantial increase in the use of certain drug classes over the study period. Notably, the use of drugs related to the blood and blood-forming organs, classified under the ATC system with the first letter B, increased from 46.9% to 72.4% (*P* value for trend <0.001). Significant increases were also observed in the use of medications within the alimentary tract and metabolism, cardiovascular system, and nervous system drug classes. In contrast, the most pronounced decrease was seen in the use of drugs associated with the musculoskeletal system. The composition and usage patterns of drugs across main pharmacological groups during the study period are presented in Table S2.

Medication Use Before and After Diagnosis of AF

The mean number of medications per patient increased significantly from 5.0 (SD 3.8) before AF diagnosis to 6.0 (SD 3.9) following the diagnosis (*P*<0.001). Following a diagnosis of AF, significant changes were observed in medication use across multiple drug

Table 1. Characteristics of the Study Cohort by Number of Distinct Drug Compounds Used After Atrial Fibrillation Diagnosis

Number of different drug compounds	0–2	3–4	5–9	≥10
	n=43 018	n=41 601	n=104 447	n=40 499
Demographics				
Mean age, y	68.2 (17.5)	69.9 (13.1)	74.4 (11.4)	76.3 (10.1)
Female sex	41.9	44.6	52.4	58.1
Income tertiles				
First (lowest)	31.8	25.7	34.9	43.0
Second	25.7	32.1	34.4	35.3
Third (highest)	42.5	42.2	30.7	21.7
Comorbidities				
Any vascular disease	18.7	15.6	29.5	46.9
Cancer	17.5	16.8	21.3	25.9
Diabetes	11.1	9.9	22.7	41.8
Hyperlipidemia	25.9	36.2	53.6	67.9
Hypertension	52.8	66.4	80.3	88.9
Heart failure	14.4	7.8	17.7	29.7
Prior ischemic stroke	12.7	7.8	11.5	12.9
Abnormal renal function	3.9	1.7	3.5	7.7
Alcohol use disorder	5.2	4.0	3.8	4.1
Dementia	6.9	3.0	4.8	6.3
Prior bleeding	10.0	8.0	10.4	14.8
Risk scores				
Mean modified HAS-BLED score	1.7 (1.2)	1.8 (1.0)	2.2 (1.0)	2.6 (1.0)
Mean CHA_2DS_2-VASc score	2.7 (2.2)	2.7 (1.6)	3.6 (1.7)	4.4 (1.7)
Mean CHA_2DS_2-VA score	2.3 (2.0)	2.2 (1.5)	3.1 (1.5)	3.9 (1.6)

Values denote proportions (%) or means±SD. All differences between $P<0.001$. CHA_2DS_2-VA(Sc) score, congestive heart failure (1 point), hypertension (1 point), age≥75 years (2 points), diabetes (1 point), history of stroke or transient ischemic attack (2 points), vascular disease (1 point), age 65 to 74 years (1 point), sex category (female) (1 point); modified HAS-BLED score, hypertension (1 point), abnormal renal or liver function (1 point each), prior stroke (1 point), bleeding history (1 point), age>65 years (1 point), alcohol abuse (1 point), concomitant antiplatelet/NSAIDs (1 point) (no labile international normalized ratio, max score 8).

classes. The most notable increases were in the use of cardiovascular system drugs from 75.8% to 85.2% (*P* value for trend <0.001) and blood and blood-forming organ agents, from 19.0% to 61.4% (*P* value for trend <0.001). Conversely, the use of medications for the musculoskeletal system declined from 21.5% to 14.2% (*P* value for trend <0.001). Most other drug classes showed only minor shifts. The composition of drug use across the main pharmacological groups before and after AF diagnosis is presented in Table S3.

Subgroup Analyses

The mean number of different drug compounds prescribed during the first 120 days after AF diagnosis was higher among patients aged 75 years or older (mean 6.6, SD 3.9) compared with those younger than 75 years (mean 5.5, SD 3.7; *P*<0.001). In both age categories, medication use increased over time (beta coefficient, 0.10 [95% CI, 0.09–0.12]; *P*<0.001 for <75; beta coefficient, 0.13 [95% CI, 0.12–0.14]; *P*<0.001 for ≥75), with a significant interaction term indicating a slightly steeper increase among older patients (beta coefficient, 0.026; *P*=0.005; Figure S1–S3).

Similarly, patients with a CHA_2DS_2-VASc score ≥4 were prescribed more drugs (mean 7.3, SD 4.2) than those with scores <4 (mean 5.3, SD 3.5; *P*<0.001). Increasing trends were observed in both groups (beta coefficient, 0.06, 95% CI, 0.05–0.07; *P*<0.001 for <4; beta coefficient, 0.13, 95% CI, 0.11–0.15; *P*<0.001 for ≥4), with a significant interaction term reflecting faster increases in those with higher scores (beta coefficient, 0.073; *P*<0.001; Figure S2).

Patients with prior ischemic stroke had a slightly lower mean drug count (mean 6.0, SD 3.8) than those without (mean 6.2, SD 4.2; *P*<0.001). Medication use increased in both groups over time (beta coefficient, 0.10, [95% CI, 0.09–0.11]; *P*<0.001 for no stroke; beta coefficient, 0.26, [95% CI, 0.23–0.29]; *P*<0.001 for stroke), with a significant interaction indicating a more pronounced increase among patients with prior stroke (beta coefficient, 0.156; *P*<0.001; Figure S3).

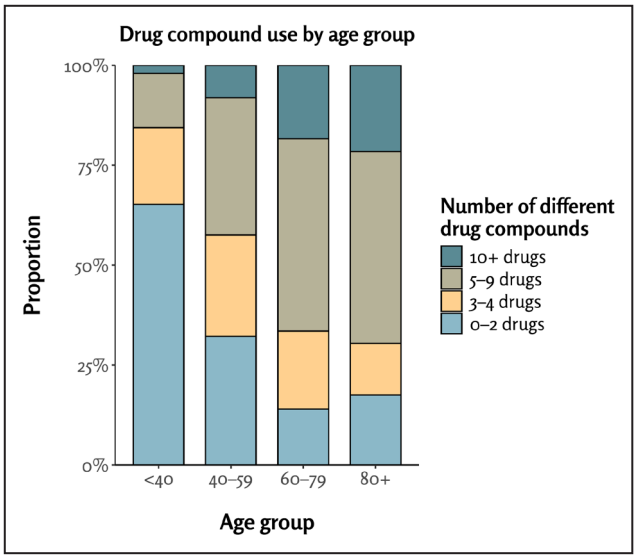

Figure 1. Drug use during the first 120 days after diagnosis of AF according to age.
AF indicates atrial fibrillation.

DISCUSSION

This nationwide retrospective cohort study found that polypharmacy was common among patients with AF, with approximately two thirds using >5 medications and one fifth using ≥10. Polypharmacy was particularly prevalent among older adults and was strongly associated with comorbidities such as hypertension and diabetes. The number of different medications after AF diagnosis increased during the study period from 2007 to 2018.

There are limited reliable data on polypharmacy in patients with AF, particularly regarding its temporal trends. Estimates of polypharmacy prevalence among patients with AF in previous studies have varied greatly, ranging from 28.3% to 94.8%.[8–11] This wide variation likely reflects the limitations of previous studies, particularly substantial selection bias, small sample sizes, and the lack of comprehensive pharmacy claims data. In our study, the prevalence of polypharmacy (>5 medications) among patients with AF was slightly >60%. Although this finding aligns with the wide prevalence range reported in previous studies, it likely provides a more reliable estimate for real-world patients with AF, owing to the comprehensive nationwide coverage across all levels of health care. Importantly, these data extend existing knowledge by quantifying polypharmacy in a contemporary, unselected population with AF and identifying patient characteristics associated with higher medication use. This information can inform clinical management by highlighting patients at risk of potentially inappropriate polypharmacy and support health care policy aimed at optimizing medication review and resource allocation in these high-risk groups.

To our knowledge, no previous study has examined the temporal trend of polypharmacy specifically among patients with AF. Polypharmacy increased during the study period in our study, although the magnitude of this increase was relatively modest. Moreover, drug use was not significantly associated with calendar year in the adjusted analyses, suggesting that other factors, such as older age and higher prevalence of comorbidities, are likely driving the increase in the number of medications among these patients. Of note, the observation period spans both the pre-direct oral anticoagulant and direct oral anticoagulant eras in AF management, reflecting changes in clinical practice across these distinct treatment periods. Corresponding with our results, in the general population, an increasing trend in polypharmacy has been reported; Among US adults, the prevalence of polypharmacy rose from 8.2% in 1999 to 2000 to 17.1% in 2017 to 2018, with significantly higher rates observed among individuals with cardiovascular disease.[12]

Several factors may contribute to this increase. First, population aging leads to a higher burden of comorbidities, which in turn results in increased medication use. Improvements in diagnostic techniques and more sensitive disease screening, including for AF, may have also expanded the number of individuals receiving pharmacological treatment. Moreover, clinical guidelines frequently recommend combination therapy for the management of chronic conditions, further contributing to polypharmacy.[13] Ongoing advances in pharmacotherapy have introduced a growing number of effective medications into clinical practice, which may also drive higher overall drug use.[14] Consistent with these advances, the adoption of oral anticoagulant therapy among patients newly diagnosed with AF in Finland increased substantially from 2007 to 2017, a trend also reflected in the current study by the rise in ATC category B (drugs related to blood and blood-forming organs).[15] Relatedly, some of the observed increase in medication use may reflect comprehensive, evidence-based care rather than inappropriate polypharmacy. Within integrated AF management, including the Atrial Fibrillation Better Care pathway, higher medication counts may indicate adherence to guideline-directed therapy for stroke prevention, symptom control, and comorbidity management. Finally, although our results indicate that calendar year itself is not independently associated with mean drug count, they suggest that higher age and greater clinical complexity are likely the main drivers of drug use patterns.

Our study demonstrates that the diagnosis of new-onset AF is associated with an increase in the overall number of medications used per patient, with the mean rising from 5.0 to 6.0 following AF detection. This increase is likely largely attributable to the initiation of

Table 2. Factors Associated With Drug Count After Atrial Fibrillation Diagnosis

Variable	Unadjusted model		Adjusted model	
	Beta coefficient	*P* value	Beta coefficient	*P* value
Calendar year (per 2 y)	0.12 (0.11 to 0.13)	<0.01	0.00 (−0.01 to 0.00)	0.29
Age (per 10 y)	0.58 (0.56 to 0.59)	<0.01	0.17 (0.16 to 0.19)	<0.01
Female sex	0.84 (0.80 to 0.87)	<0.01	0.45 (0.42 to 0.48)	<0.01
Hypertension	2.35 (2.31 to 2.38)	<0.01	1.36 (1.33 to 1.40)	<0.01
Heart failure	1.59 (1.55 to 1.63)	<0.01	0.90 (0.86 to 0.94)	<0.01
Hyperlipidemia	2.20 (2.17 to 2.23)	<0.01	1.14 (1.11 to 1.17)	<0.01
Diabetes	2.54 (2.51 to 2.58)	<0.01	1.62 (1.59 to 1.66)	<0.01
Any vascular disease	1.96 (1.93 to 1.99)	<0.01	0.91 (0.87 to 0.94)	<0.01
Stroke	0.14 (0.09 to 0.19)	<0.01	−0.62 (−0.67 to −0.58)	<0.01
Bleeding	0.74 (0.69 to 0.79)	<0.01	0.22 (0.18 to 0.27)	<0.01
Alcohol use disorder	−0.26 (−0.34 to −0.18)	<0.01	−0.57 (−0.65 to −0.48)	<0.01
Dementia	0.04 (−0.03 to 0.11)	0.29	−0.77 (−0.84 to −0.70)	<0.01
Psychiatric diseases	0.73 (0.69 to 0.78)	<0.01	0.83 (0.78 to 0.88)	<0.01
Income tertile (per 1 tertile)	−0.93 (−0.95 to −0.90)	<0.01	−0.21 (−0.24 to −0.18)	<0.01

95% CIs are shown in parentheses. Linear regression was used, and adjusted analysis included all variables displayed in the unadjusted model results.

anticoagulant therapy, because the most pronounced increases occurred in the use of drugs affecting blood and blood-forming organs and drugs targeting the cardiovascular system (ATC codes starting with letters B and C, respectively). Polypharmacy was highly prevalent and increased with age, but this should not necessarily be viewed solely negatively, as it may reflect the complex clinical needs of older patients who often present with multiple comorbidities. Indeed, drug use was significantly associated with the comorbidities. In addition, it is increasingly recognized that AF management is more than just anticoagulation for stroke prevention, and a holistic care approach is needed, with additional management (often involving drug therapies) for rate or rhythm control as well as comorbidity management.[16] Such integrated care has been associated with improved clinical outcomes in clinical trials and observational cohorts.[17–19]

The retrospective design of the current study inherently poses some limitations that need to be acknowledged. Mainly, our results may be affected by information bias due to potential inaccuracies in the registry data. However, Finnish health care registers have been found to be particularly reliable in documenting cardiovascular diseases, and recently the World Bank assessed the Finnish registers as having the highest-performing statistical system globally.[20,21] The study covers all prescribed and dispensed medications, which adds to the completeness of the data, but the study does not include medications purchased over the counter. Furthermore, the current study has the central strengths of a large cohort size and complete nationwide coverage encompassing all levels of care, thus reducing the risk of selection bias. These data are from a European population in a well-structured health care system, and additional studies in other ethnic groups from different health care settings are needed, given the recognized differences in the epidemiology of cardiovascular disease risk factors and outcomes.[22,23] Finally, further in-depth research is needed to characterize problematic polypharmacy, evaluate the use of potentially inappropriate or harmful medications, assess clinically significant drug interactions, and determine the impact of polypharmacy on outcomes in patients with AF.

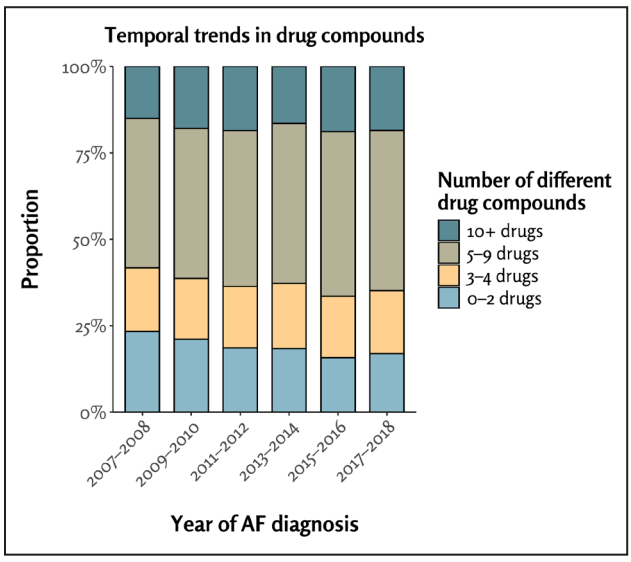

Figure 2. Drug use during the first 120 days after diagnosis of AF according to the year of AF diagnosis.
AF indicates atrial fibrillation.

CONCLUSIONS

This nationwide retrospective cohort study demonstrates that polypharmacy among patients with AF is common, especially among older patients with multiple comorbid conditions. Moreover, the prevalence of polypharmacy has increased over time in patients with AF.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S3
Figures S1–S3
STROBE Checklist

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