Niklas Kiuru

Trends in Polypharmacy Among Patients with Atrial Fibrillation – A report from the Finnish AntiCoagulation in Atrial Fibrillation (FinACAF) Nationwide Cohort Study

Syventävien opintojen kirjallinen työ

Kevätlukukausi 2026

Niklas Kiuru

Trends in Polypharmacy Among Patients with Atrial Fibrillation – A report from the Finnish AntiCoagulation in Atrial Fibrillation (FinACAF) Nationwide Cohort Study

Kliininen laitos

Kevätlukukausi 2026

Vastuuhenkilö: Konsta Teppo

TURUN YLIOPISTO

Lääketieteellinen tiedekunta

KIURU, NIKLAS: Trends in Polypharmacy Among Patients with Atrial Fibrillation – A report from the Finnish AntiCoagulation in Atrial Fibrillation (FinACAF) Nationwide Cohort Study

Syventävien opintojen kirjallinen työ, 25 sivua

Kardiologia

Tammikuu 2026

Atrial fibrillation (AF) is the most common long-standing arrhythmia, and its prevalence increases with aging of the population. Patients with AF frequently have multiple comorbidities, which predisposes them to polypharmacy, which is commonly defined as the concurrent use of five or more medications. Polypharmacy has been associated with an increased risk of adverse outcomes; however, population-level data on its prevalence and temporal trends among patients with AF have been limited. The aim of this study was to assess the prevalence of polypharmacy, associated factors, and temporal trends among Finnish AF patients between 2007 and 2018.

This study was based on the FinACAF registry cohort, which included all patients diagnosed with AF in Finland during the study period. The study population comprised 229,565 patients with a newly diagnosed AF. Medication data were retrieved from national healthcare and prescription registers over a 120-day period before and after the AF diagnosis. Medications were classified according to the Anatomical Therapeutic Chemical (ATC) classification system.

Following AF diagnosis, the mean number of medications used per patient was 6.0. After diagnosis, 63.1% of patients used five or more medications, and 17.7% used ten or more medications. In temporal analyses, the mean number of medications after AF diagnosis increased from 5.5 to 6.2 during study period. Medication use increased across all subgroups regardless of age, sex, prior stroke, or stroke risk scores. These findings underscore the need for holistic, patient-centered management strategies to optimize outcomes in this multimorbid population.

Keywords: atrial fibrillation, polypharmacy, comorbidity.

Trends in Polypharmacy Among Patients with Atrial Fibrillation – A report from the Finnish AntiCoagulation in Atrial Fibrillation (FinACAF) Nationwide Cohort Study

Niklas Kiuru[a], Sanni Reinilä, MD[b], Ville Langén, MD, PhD[c], Jussi Jaakkola, MD, PhD[d, e], K.E. Juhani Airaksinen, MD, PhD[d], Olli Halminen, MSc[f], Jukka Putaala, MD, PhD[g], Pirjo Mustonen, MD, PhD[d], Jari Haukka, PhD[h], Juha Hartikainen, MD, PhD[i, j], Alex Luojus, MD[h, k], Mikko Niemi, MD, PhD[l, m, n], Miika Linna, PhD[f, i], Mika Lehto, MD, PhD[h, k, o], Gregory Y. H. Lip, MD[p, q], Konsta Teppo, MD, PhD[d]

[a] Cardiology Department, Turku University, Turku, Finland

[b] Internal Medicine Department, Turku University Hospital, Turku, Finland

[c] Division of Medicine, Turku University Hospital and University of Turku, Turku, Finland

[d] Heart Center, Turku University Hospital, and University of Turku, Turku, Finland

[e] Heart Unit, Satakunta Central Hospital, Pori, Finland

[f] Aalto University, Espoo, Finland

[g] Neurology, Helsinki University Hospital, and University of Helsinki, Helsinki, Finland

[h] University of Helsinki, Helsinki, Finland

[i] University of Eastern Finland, Kuopio, Finland

[j] Heart Center, Kuopio University Hospital, Kuopio, Finland

[k] Heart and Lung Center, Helsinki University Hospital, Helsinki, Finland

[l] Department of Clinical Pharmacology, University of Helsinki, Helsinki, Finland

[m] Individualized Drug Therapy Research Program, University of Helsinki, Helsinki, Finland

[n] Department of Clinical Pharmacology, HUS Diagnostic Center, Helsinki University Hospital, Helsinki, Finland

[o] Lohja Hospital, Department of Internal Medicine, Lohja, Finland

[p] Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom

[q] Department of Clinical Medicine, Aalborg University, Aalborg University Hospital, Denmark

Correspondence to:

Niklas Kiuru

npkiur@utu.fi

+358400193164

Abstract

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 Finnish AntiCoagulation in Atrial Fibrillation (FinACAF) cohort, including all patients with incident AF between 2007 and 2018. Data were retrieved from national healthcare 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. Associations between baseline characteristics and drug use were analysed using logistic regression, and temporal trends were assessed across subgroups defined by age, comorbidities and stroke risk.

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, while 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 (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, polypharmacy, comorbidity.

Clinical Perspective

What Is New?

- Among patients with AF, polypharmacy is increasing, with approximately two-thirds using more than five medications and one-fifth using ten or more different drugs concurrently.

What Are the Clinical Implications?

- Given the high prevalence of polypharmacy in patients with AF, 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.

Introduction

Atrial fibrillation (AF) is the most common long-standing arrhythmia, affecting approximately 5% of the adult population and as many as one in four over the age of 75.[1] The prevalence of AF is estimated to double over the next four 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 (NCBI) as the concurrent, regular use of five or more 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, while 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

Study cohort

The Finnish AntiCoagulation in Atrial Fibrillation (FinACAF) 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 healthcare registers, including hospitalizations and outpatient specialist visits (HILMO), primary healthcare (AvoHILMO), and the National Reimbursement Register maintained by the Social Insurance Institute (KELA). 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 31 December 2018 and age below 20 years at AF diagnosis. The present sub-study 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 healthcare registers from all levels of care. The definitions of baseline comorbidities are presented in Supplementary Table 1.

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 (KELA). 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 four characters (level 3), and the main pharmacological groups based on the first letter (level 1) of the ATC code. 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 (nr. 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; 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 one-way analysis of variance were used to compare baseline variables as well as differences between the medication categories. Temporal trends in the number

of medications were evaluated overall and within subgroups defined by age, history of stroke, and a CHA_2DS_2-VA score of 4 or more. Logistic regression was used to assess the association between the baseline variables and number of medications. 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, standard deviation (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 five different drug compounds, and 17.7% redeemed ten or more different drug compounds. Patients with higher numbers of medications were on the average older, more often women and were 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). All studied baseline variables showed statistically significant associations with drug count in the multivariable model. Hypertension and diabetes had the strongest positive associations, while 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 ($p < 0.001$). 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. This trend reflects an overall increase in the intensity of pharmacological management among patients with AF (Figure 2).

There was a substantial increase in the use of certain drug classes over the study period. Notably, the utilization 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% ($p < 0.001$). 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 usage patterns of drugs across all therapeutic classes during the study period are presented in Supplementary Table 2.

Medication use before and after diagnosis of AF

The mean number of medications per patient increased significantly from 5.0 (SD 3.8) prior to 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 classes. The most notable increases were in the use of cardiovascular system drugs from 75.8% to 85.2% ($p < 0.001$) and blood and blood forming organ agents, from 19.0% to 61.4% ($p < 0.001$). Conversely, the use of medications for the musculoskeletal system declined from 21.5% to 14.2% ($p < 0.001$). Most other drug classes only showed minor shifts.

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 (Supplementary Figure 1). Similarly, patients with a CHA_2DS_2-VASc score of 4 or higher were prescribed a greater mean number of drug compounds (mean 7.3, SD 4.2) compared with those with scores below 4 (mean 5.3, SD 3.5; $p < 0.001$). An upward trend in medication use was evident in both risk categories (Supplementary Figure 2). Patients with a history

of ischemic stroke had a slightly lower mean number of drug compounds (mean 6.0, SD 3.8) compared with those without prior stroke (mean 6.2, SD 4.2; $p < 0.001$). Nevertheless, temporal increases in medication use were observed in both groups (Supplementary Figure 3).

Discussion

This nationwide retrospective cohort study found that polypharmacy was common among AF patients, with over 60% using more than five medications and nearly one-fifth using ten or more. 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 has 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 (more than 5 medication) among AF patients was slightly over 60%. While this finding aligns with the wide prevalence range reported in previous studies, it likely provides a more reliable estimate for real-world AF patients, owing to the comprehensive nationwide coverage across all levels of healthcare. Importantly, these data extend existing knowledge by quantifying polypharmacy in a contemporary, unselected AF population 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 healthcare 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, indicating a shift toward more intensive pharmacological management of this patient group, although the magnitude of this increase was relatively modest. Of note, the observation period spans both the pre-DOAC and DOAC 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 U.S. adults, the prevalence of polypharmacy rose from 8.2% in 1999–2000 to 17.1% in 2017–2018, 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, national 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 ABC pathway, higher medication counts may indicate adherence to guideline-directed therapy for stroke prevention, symptom control, and comorbidity management.

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 anticoagulant therapy, since 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 recognised that AF management is more than just anticoagulation for stroke prevention, and a holistic care approach is needed[18], 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 healthcare 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 healthcare system, and additional studies in other ethnic groups from different healthcare settings are needed given the recognised 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.

Conclusion

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.

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

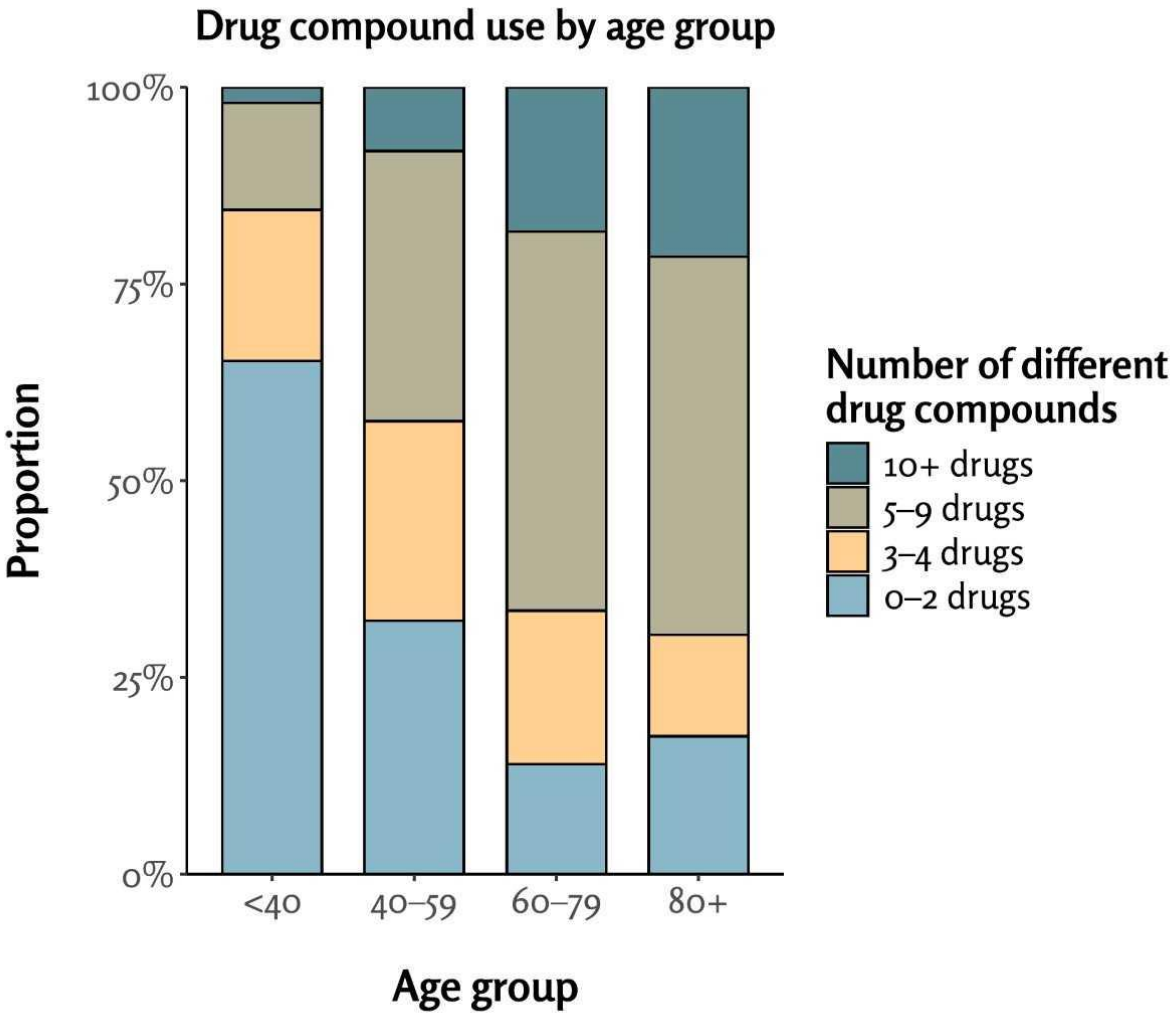


Figure 2. Drug use during the first 120 days after diagnosis of AF according to the year of AF diagnosis.

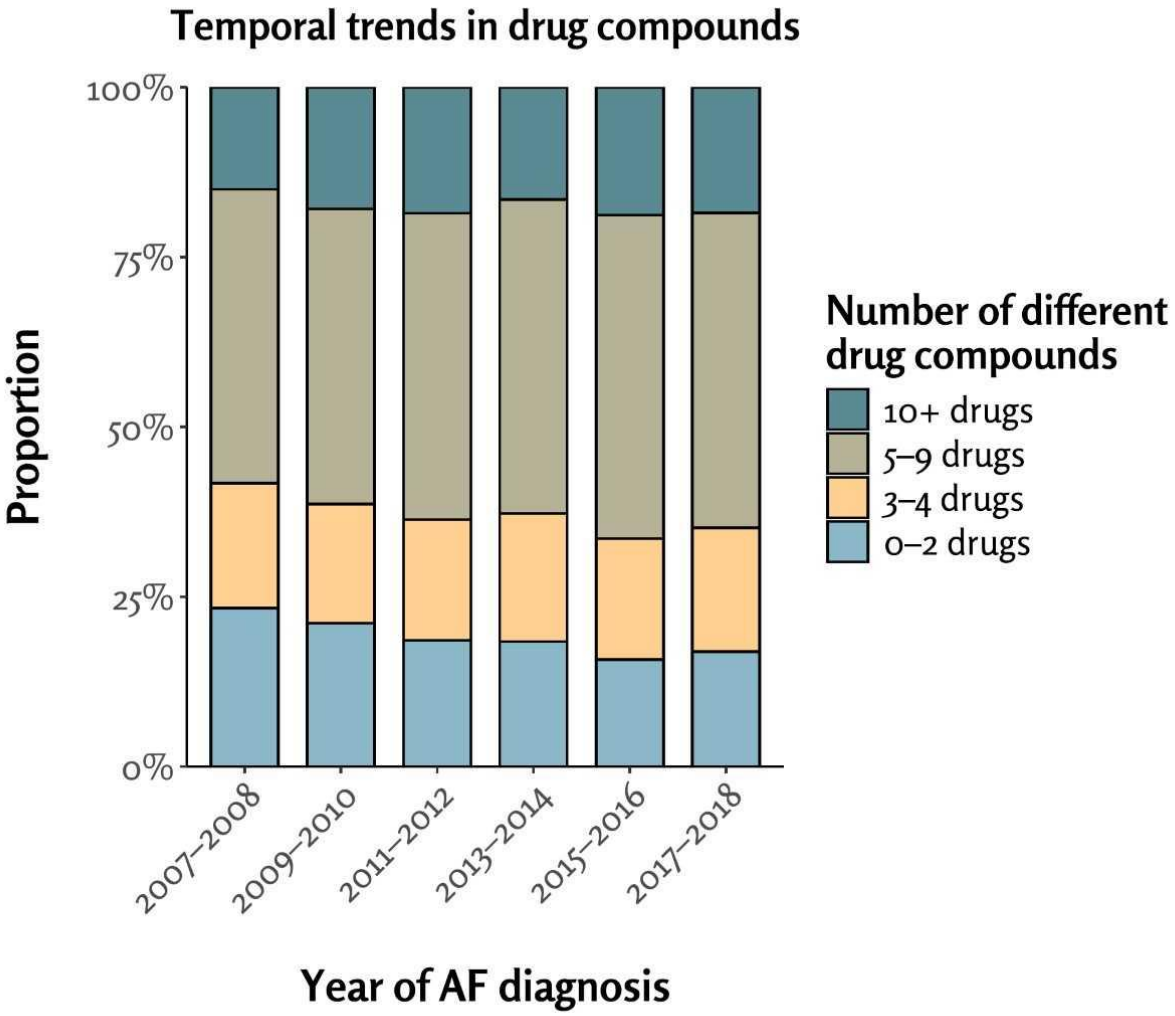


Table 1. Characteristics of the study cohort by number of distinct drug compounds used after atrial fibrillation diagnosis

Number of different drug compounds	0-2	3-4	5-9	10 or more
	n=43018	n=41601	n=104447	n=40499
Demographics				
Mean age, years	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				
1st (lowest)	31.8	25.7	34.9	43.0
2nd	25.7	32.1	34.4	35.3
3rd (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 (standard deviation). All differences between $p < 0.001$. Abbreviations: 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 TIA (2 points), vascular disease (1 point), age 65-74 years (1 point), sex category (female) (1 point); IS, ischemic stroke; 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 INR, max score 8).

Table 2. Univariate and multivariate models of factors associated with drug count

	Univariate model		**Multivariate model**	
Variable	Beta coefficient	p-value	Beta coefficient	p-value
Age (per 10 years)	0.58 (0.56–0.59)	<0.01	0.17 (0.16–0.18)	<0.01
Female sex	0.84 (0.80–0.87)	<0.01	0.45 (0.42–0.48)	<0.01
Hypertension	2.35 (2.31–2.38)	<0.01	1.36 (1.33–1.4)	<0.01
Heart failure	1.59 (1.55–1.63)	<0.01	0.90 (0.86–0.94)	<0.01
Hyperlipidemia	2.20 (2.17–2.23)	<0.01	1.14 (1.11–1.17)	<0.01
Diabetes	2.54 (2.51–2.58)	<0.01	1.62 (1.59–1.66)	<0.01
Any vascular disease	1.96 (1.93–1.99)	<0.01	0.91 (0.87–0.94)	<0.01
Stroke	0.14 (0.09–0.19)	<0.01	-0.62 (-0.67–-0.58)	<0.01
Bleedings	0.74 (0.69–0.79)	<0.01	0.22 (0.18–0.27)	<0.01
Alcohol use disorder	-0.26 (-0.34–-0.18)	<0.01	-0.57 (-0.65–-0.48)	<0.01
Dementia	0.04 (-0.03–0.11)	0.29	-0.77 (-0.84–-0.7)	<0.01
Psychiatric diseases	0.73 (0.69–0.78)	<0.01	0.83 (0.78–0.88)	<0.01
Income tertiles (lowest as reference)	-0.93 (-0.95–-0.90)	<0.01	-0.22 (-0.24–-0.19)	<0.01

95% confidence intervals are shown in parentheses. Multivariate models included all variables displayed in the univariate model results.

Conflict of Interest Disclosures: Niklas Kiuru: none. Sanni Reinilä: none. Konsta Teppo: Research Grants: The Finnish Foundation for Cardiovascular Research, Aarne and Aili Turunen Foundation, The Finnish Medical Foundation, The Finnish Foundation for Alcohol Studies and the Finnish State Research Funding. Jussi Jaakkola: none. Ville Langén: Research grants: The State Research Funding of the wellbeing services county of Southwest Finland; Speaker: Boehringer-Ingelheim. Olli Halminen: none. Jukka Putaala: Speaker: Bayer, Boehringer-Ingelheim, BMS-Pfizer, Abbott; Advisory board: Portola, Novo Nordisk, Herantis Pharma; Visiting editor: Terve Media; Stock ownership: Vital Signum. Pirjo Mustonen: Consultant: Roche, BMS-Pfizer-alliance, Novartis Finland, Boehringer Ingelheim, MSD Finland. Jari Haukka: Consultant: Research Janssen R&D; Speaker: Bayer Finland. Miika Linna: Speaker: BMS-Pfizer-alliance, Bayer, Boehringer-Ingelheim. Juha Hartikainen: Research grants: The Finnish Foundation for Cardiovascular Research, EU Horizon 2020, EU FP7. Advisory Board Member: BMS-Pfizer-alliance, Novo Nordisk, Amgen. Speaker: Cardiome, Bayer. K.E. Juhani Airaksinen: Research grants: The Finnish Foundation for Cardiovascular Research; Speaker: Bayer, Pfizer and Boehringer-Ingelheim. Mika Lehto: Consultant: BMS-Pfizer-alliance, Bayer, Boehringer-Ingelheim, and MSD; Speaker: BMS-Pfizer-alliance, Bayer, Boehringer Ingelheim, MSD, Terve Media and Orion Pharma. Research grants: Aarne Koskelo Foundation, The Finnish Foundation for Cardiovascular Research, and Helsinki and Uusimaa Hospital District research fund, Boehringer-Ingelheim.

Funding/Support: This work was supported by the Aarne Koskelo Foundation, The Finnish Foundation for Cardiovascular Research, and Helsinki and Uusimaa Hospital District research fund (TYH2019309).

Data Availability Statement

Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the Finnish national register holders (KELA, 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.

References

1. Lehto M, Haukka J, Aro A, Halminen O, Putaala J, Linna M, Mustonen P, Kinnunen J, Kouki E, Niiranen J, Luojus A, Tiili P, Itäinen-Strömberg S, Hartikainen J, Airaksinen JKE. Comprehensive nationwide incidence and prevalence trends of atrial fibrillation in Finland. *Open Heart*. 2022;9:e002140.
2. Kornej J, Börschel CS, Benjamin EJ, Schnabel RB. Epidemiology of Atrial Fibrillation in the 21st Century: Novel Methods and New Insights. Circ Res. . 2020;127. doi:10.1161/CIRCRESAHA.120.316340.
3. Van Gelder IC, Rienstra M, Bunting K V, Casado-Arroyo R, Caso V, Crijns HJGM, De Potter TJR, Dwight J, Guasti L, Hanke T, Jaarsma T, Lettino M, Løchen M-L, Lumbers RT, Maesen B, Mølgaard I, Rosano GMC, Sanders P, Schnabel RB, Suwalski P, Svennberg E, Tamargo J, Tica O, Traykov V, Tzeis S, Kotecha D, Group ESCSD. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): Developed by the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC), with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Endorsed by the European Stroke Organisation (ESO). *Eur Heart J*. 2024;:ehae176.
4. Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, Deswal A, Eckhardt LL, Goldberger ZD, Gopinathannair R, Gorenek B, Hess PL, Hlatky M, Hogan G, Ibeh C, Indik JH, Kido K, Kusumoto F, Link MS, Linta KT, Marcus GM, McCarthy PM, Patel N, Patton KK, Perez M V, Piccini JP, Russo AM, Sanders P, Streur MM, Thomas KL, Times S, Tisdale JE, Valente AM, Van Wagoner DR. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2023;0. doi:10.1161/CIR.0000000000001193.
5. Varghese D, Ishida C, Patel P, et al. Polypharmacy. [Updated 2024 Feb 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532953/.
6. Finnish Medicines Agency (Fimea). Significant Polypharmacy in the elderly. Available from: https://fimea.fi/en/significant-polypharmacy-in-the-elderly. .
7. Teppo K, Airaksinen KEJ, Jaakkola J, Halminen O, Salmela B, Kouki E, Haukka J, Putaala J, Linna M, Aro AL, Mustonen P, Hartikainen J, Lip GYH, Lehto M. Ischaemic stroke in women with atrial fibrillation: temporal trends and clinical implications. *Eur Heart J*. 2024;45:1819–1827.
8. Wang J, Yang Y-M, Zhu J, Zhang H, Shao X-H. Multimorbidity and Polypharmacy in Chinese Emergency Department Patients With Atrial Fibrillation and Impacts on Clinical Outcomes. *Front Cardiovasc Med*. 2022;9:806234.
9. Tsagkaris C, Papazoglou AS, Kartas A, Samaras A, Moysidis D V, Vouloagkas I, Baroutidou A, Bekiaridou A, Patsiou V, Chatzisolomou A, Panteris E, Karagiannidis E, Karvounis H, Tzikas A, Giannakoulas G. Polypharmacy and Major Adverse Events in Atrial Fibrillation. *J Cardiovasc Pharmacol*. 2022;80:826–831.
10. Wang Y, Singh S, Bajorek B. Old age, high risk medication, polypharmacy: a "trilogy" of risks in older patients with atrial fibrillation. *Pharm Pract (Granada)*. 2016;14:706.
11. Proietti M, Raparelli V, Olshansky B, Lip GYH. Polypharmacy and major adverse events in atrial fibrillation: observations from the AFFIRM trial. *Clin Res Cardiol*. 2016;105:412–20.
12. Wang X, Liu K, Shirai K, Tang C, Hu Y, Wang Y, Hao Y, Dong JY. Prevalence and trends of polypharmacy in U.S. adults, 1999–2018. *Glob Health Res Policy*. 2023;8. doi:10.1186/s41256-023-00311-4.

13. Jandu JS, Mohanaselvan A, Dahal R, et al. Strategies to Reduce Polypharmacy in Older Adults. [Updated 2024 Aug 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK574550/. .
14. Darrow JJ, Avorn J, Kesselheim AS. FDA Approval and Regulation of Pharmaceuticals, 1983-2018. *JAMA*. 2020;323:164.
15. Teppo K, Airaksinen KEJ, Jaakkola J, Halminen O, Linna M, Haukka J, Putaala J, Mustonen P, Kinnunen J, Hartikainen J, Aro AL, Lehto M. Trends in treatment and outcomes of atrial fibrillation during 2007–17 in Finland. *Eur Heart J Qual Care Clin Outcomes*. 2023;9:673–679.
16. Lip GYH. The ABC pathway: an integrated approach to improve AF management. *Nat Rev Cardiol*. 2017;14:627–628.
17. Romiti GF, Guo Y, Corica B, Proietti M, Zhang H, Lip GYH. Mobile Health-Technology-Integrated Care for Atrial Fibrillation: A Win Ratio Analysis from the mAFA-II Randomized Clinical Trial. *Thromb Haemost*. 2023;123:1042–1048.
18. Treewaree S, Lip GYH, Krittayaphong R. Non-vitamin K Antagonist Oral Anticoagulant, Warfarin, and ABC Pathway Adherence on Hierarchical Outcomes: Win Ratio Analysis of the COOL-AF Registry. *Thromb Haemost*. 2023;124:69–79.
19. Chu M, Zhang S, Gong J, Yang S, Yang G, Sun X, Wu D, Xia Y, Jiao J, Peng X, Peng Z, Hong L, Wang Z, Li M, Lip GYH, Chen M, Guo Y, Liu X, Lu S, Investigators on behalf of the M-A. Telemedicine-based integrated management of atrial fibrillation in village clinics: a cluster randomized trial. *Nat Med*. 2025;31:1276–1285.
20. Sund Reijo. Quality of the Finnish Hospital Discharge Register: A systematic review. *Scand J Public Health*. 2012;40:505–515.
21. https://www.worldbank.org/en/programs/statistical-performance-indicators. .
22. Kim M-H, Yang P-S, Kim D, Jang E, Yu HT, Kim T-H, Sung J-H, Pak H-N, Lee M-H, Lip GYH, Joung B. Racial differences and similarities in atrial fibrillation epidemiology and risk factors in UK Biobank and Korean NHIS-HEALS cohort studies. *Heart Rhythm*. 2025;22:e277–e284.
23. Kang D-S, Yang P-S, Kim D, Jang E, Yu HT, Kim T-H, Sung J-H, Pak H-N, Lee M-H, Lip GYH, Joung B. Racial Differences in Ischemic and Hemorrhagic Stroke: An Ecological Epidemiological Study. *Thromb Haemost*. 2024;124:883–892.

Supplemental material

Supplementary Table 1. Medication use among AF patients before and after diagnosis according to the main pharmacological groups. Values are shown as counts (%).

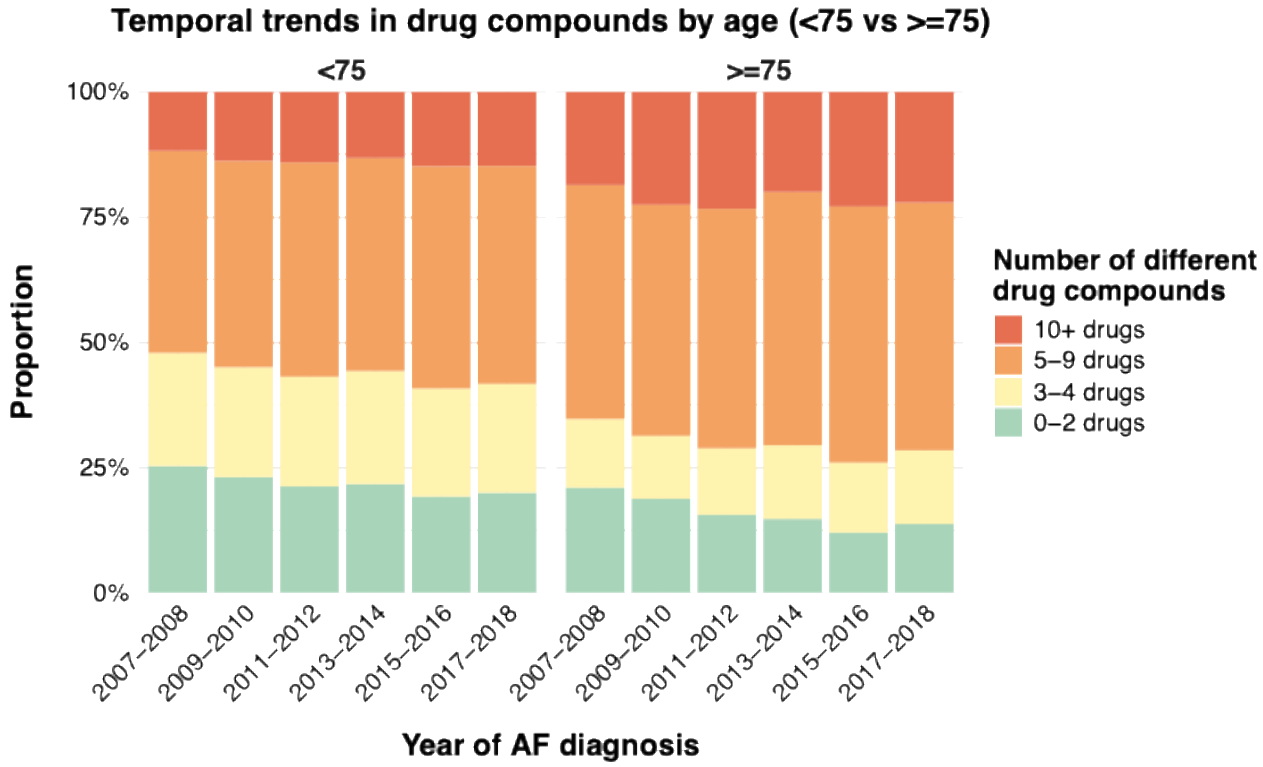
Drug class	Users before AF diagnosis n (%)	Users after AF diagnosis n (%)	p-value (McNemar Test)
Alimentary tract and metabolism	91215 (39.7)	97487 (42.5)	<0.001
Blood and blood forming organs	43698 (19.0)	140902 (61.4)	<0.001
Cardiovascular system	174062 (75.8)	195547 (85.2)	<0.001
Dermatologicals	12122 (5.3)	10623 (4.6)	<0.001
Genitourinary system and sex hormones	36548 (15.9)	33632 (14.6)	<0.001
Systemic hormonal preparations, excl. sex hormones and insulins	37817 (16.5)	37700 (16.4)	0.454
Anti-infectives for systemic use	48869 (21.3)	54486 (23.7)	<0.001
Antineoplastic and immunomodulating agents	10306 (4.5)	9705 (4.2)	<0.001
Musculo-skeletal system	49289 (21.5)	32524 (14.2)	<0.001
Nervous system	92855 (40.4)	101513 (44.2)	<0.001
Antiparasitic products, insecticides and repellents	3409 (1.5)	3408 (1.5)	1.000
Respiratory system	39416 (17.2)	36959 (16.1)	<0.001
Sensory organs	22599 (9.8)	19876 (8.7)	<0.001

Supplementary Table 2. Temporal trends in drug use according to the main pharmacological groups. Values are shown as counts (%).

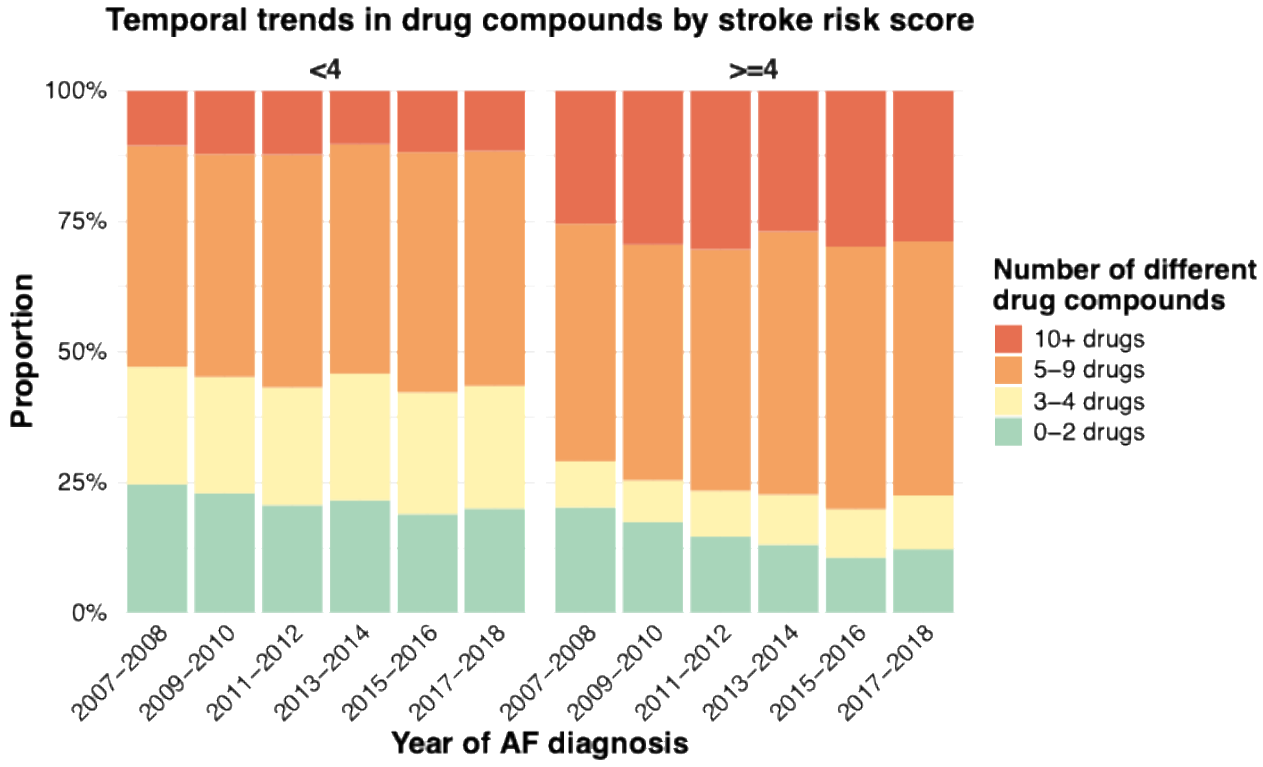
Drug class	Calendar years					
	2007-2008	2009-2010	2011-2012	2013-2014	2015-2016	2017-2018
Alimentary tract and metabolism	12508 (37.9)	13485 (41.5)	16235 (42.7)	16933 (42.8)	18673 (44.8)	19653 (43.9)
Blood and blood forming organs	15490 (46.9)	16291 (50.2)	22876 (60.1)	24990 (63.1)	28829 (69.2)	32426 (72.4)
Cardiovascular system	27011 (81.8)	26902 (82.8)	32324 (85.0)	33900 (85.6)	36442 (87.5)	38968 (87.0)
Dermatologicals	1441 (4.4)	1416 (4.4)	1747 (4.6)	1820 (4.6)	2008 (4.8)	2191 (4.9)
Genitourinary system and sex hormones	4769 (14.4)	5109 (15.7)	6430 (16.9)	5162 (13.0)	5854 (14.1)	6308 (14.1)
Systemic hormonal preparations, excl. sex hormones and insulins	4183 (12.7)	4974 (15.3)	6350 (16.7)	6627 (16.7)	7523 (18.1)	8043 (18.0)
Anti-infectives for systemic use	8156 (24.7)	8026 (24.7)	9513 (25.0)	9453 (23.9)	9753 (23.4)	9585 (21.4)
Antineoplastic and immunomodulating agents	1147 (3.5)	1297 (4.0)	1496 (3.9)	1704 (4.3)	1926 (4.6)	2135 (4.8)
Musculo-skeletal system	6462 (19.6)	5313 (16.4)	5292 (13.9)	4954 (12.5)	5214 (12.5)	5289 (11.8)
Nervous system	12043 (36.5)	14383 (44.3)	17334 (45.6)	18021 (45.5)	19132 (45.9)	20600 (46.0)
Antiparasitic products, insecticides and repellents	483 (1.5)	520 (1.6)	548 (1.4)	568 (1.4)	653 (1.6)	636 (1.4)
Respiratory system	4617 (14.0)	4713 (14.5)	5944 (15.6)	6325 (16.0)	7325 (17.6)	8035 (17.9)
Sensory organs	2442 (7.4)	2581 (7.9)	3232 (8.5)	3427 (8.7)	3927 (9.4)	4267 (9.5)

P value $p < 0.001$ for all variables except Antiparasitic products, insecticides and repellents - category ($p=0.184$).

Supplementary Figure 1. Temporal trends in drug compounds by age



Supplementary Figure 2. Temporal trends in drug compounds by stroke risk score



Supplementary Figure 3. Temporal trends in drug compounds by stroke history