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RESEARCH ARTICLE

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The use of antiarrhythmic drugs for atrial fibrillation in Finland 2007–2018

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ABSTRACT

Background: Patients with atrial fibrillation (AF) are often treated with antiarrhythmic drugs (AADs) to maintain sinus rhythm and with heart rate-lowering drugs to achieve the optimal rate control. In this study, we investigated trends in the use of AADs and rate control drugs in Finnish patients with AF. **Methods and results:** The Finnish AntiCoagulation in Atrial Fibrillation (FinACAF) study is a nationwide study including all patients with AF in Finland from 2007 to 2018. The number of AAD purchases and the proportions of all prevalent AF patients in a certain year of interest were calculated. In total, 391030 AF patients were identified between 2007 and 2018, and 39,816 (10.2%) of them had purchased either class I or III AADs. The proportion of patients using classes I and III AADs decreased from 8.6% to 6.3%. Flecainide and amiodarone were the most often used AADs. The use of flecainide and amiodarone decreased from 4.9% to 3.9% and 1.9% to 1.5%, respectively. The proportion of patients on beta-blockers remained stable at 75%. Dronedarone became available in 2011 when it also was the most used (0.8% of patients), but the use decreased thereafter. The use of sotalol and digoxin decreased from 1.5% to 0.6% and 24.6% to 11.0% over the study period. **Conclusion:** The number of AAD purchases increased alongside with the increasing prevalence of AF, whereas the proportion of AF patients on classes I and III AADs and digoxin decreased between 2007 and 2018. Flecainide remained the most used AAD followed by amiodarone.

KEYWORDS
Atrial fibrillation; antiarrhythmic drugs; rhythm control; rate control

Introduction

Atrial fibrillation (AF) is the most frequent sustained arrhythmia and the number of AF patients is estimated to increase due to the ageing population and more pragmatic screening [1]. In 2018, there were approximately 227 000 patients with AF in Finland, corresponding the prevalence of AF 5.2% in the adult population and 23.4% among the elderly [2].

Comprehensive treatment of AF includes anticoagulation therapy in most patients, maintaining adequate heart rate, and management of cardiovascular risk factors and concomitant diseases [3]. The management of AF-related symptoms is divided into rhythm control and rate control strategies [3]. Rhythm control strategy attempts to restore and/or maintain sinus rhythm, and consists of cardioversion, antiarrhythmic drugs (AADs), and catheter ablation [3]. The primary target of rhythm control strategy is to relieve symptoms, improve quality of life, and, in some cases, to improve prognosis [3–5]. Balancing the use of long-term AADs involves considering both the alleviation of symptoms and the potential adverse effects associated with the drugs, including extracardiac side effects and proarrhythmia [3].

AADs are classified by Miles Vaughan Williams in the 1970s by their pharmacological effects: class I for sodium channel blockers, class II for adrenergic antagonism, class III for action potential prolongation, and class IV calcium channel blockers (CCBs) [6]. Recently, a proposal of modernized classification including all the known groups of pharmacotherapies having antiarrhythmic properties was introduced [7]. In addition to classes I–IV AADs, this classification includes class V, digoxin, and class VII drugs, such as renin–angiotensin–aldosterone inhibitors and statins, targeting tissue remodeling process alleviating the development of AF.

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Cather ablation is increasingly used in the treatment of AF. In the early days, ablation was considered as a second-line therapy if adequate rhythm control was not achieved with AADs. According to the more recent guidelines, ablation can be used as first-line therapy in AF rhythm control [3]. Whether this and the increasing AF prevalence have impacted the use of AADs has remained elusive. The trends of AADs have been investigated in Australia, England, Denmark, and the United States [8–11]. However, only the Australian study investigated AAD use solely in AF patients, whereas the other three studied AAD use in the treatment of all arrhythmias. In addition, nationwide studies including all levels of AF treatment (specialist care, primary care, and private care) are lacking. In this nationwide study, we evaluated the use and temporal trends of the use of the AAD drugs with antiarrhythmic and rate control properties as well as drugs targeting the tissue structure remodeling for AF in all levels of healthcare system in Finland from 2007 to 2018.

Methods

Study population

The Finnish AntiCoagulation in Atrial Fibrillation (FinACAF) Study (ClinicalTrialsIdentifier:NCT04645537; ENCePP Identifier: EUPAS29845) is a nationwide retrospective cohort study including all patients with documented AF in Finland from 2004 to 2018 [12]. Patients were identified using all national healthcare registers, including hospitalizations and outpatient specialist visits (HILMO), primary healthcare (AvoHILMO), and 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 encompassed permanent emigration abroad before December 31, 2018, and age below 20 years at the time of AF diagnosis [12]. All dispensary of antiarrhythmics from pharmacies is by prescription only (i.e. no over-the counter sale is allowed).

In this study, the focus was to evaluate the use of classes I and III AADs, but additionally also other drugs with antiarrhythmic properties in patients with AF from 2007 to 2018. In class I, we assessed the trends of flecainide, disopyramide, procainamide, propafenone, and quinidine. In Class II, we investigated the trends of beta-blockers. In Class III, we assessed the trends of amiodarone, dofetilide, dronedarone, and sotalol, and in Class IV, the use of diltiazem and verapamil. In addition to beta-blockers and CCBs, we assessed the use of class V digoxin as a rate-controlling agent. Also, Class VII, that is renin–angiotensin–aldosterone system (RAAS) inhibitors, including spironolactone and statins was evaluated. The complete list of the studied medications with their anatomical therapeutic chemical codes (ATC) is provided in the Supplementary Table S1. Spironolactone is included in the diuretics group and not included in the "RAAS inhibitor" group. Also, the "Any Beta-blocker" group includes sotalol as well as non-selective and selective beta-blocking agents, while combinations with diuretics and calcium channel blockers are not included in this group.

We defined a patient as a user of medication if one or more drug purchases were made during the studied year. The proportion of drug users were calculated in relation to all prevalent AF patients in each year of interest. Baseline characteristics were obtained at the time the patient entered the study cohort.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics software version 28.0 (SPSS, Inc., Chicago, Illinois, USA) and R version 4.0.5 (R Core Team, Vienna, Austria; https://www.R-project.or).

Study ethics

The ethical permission for the study was permitted by the ethical committee of the Medical Faculty of Helsinki University (nr. 15/2017 and 15/2024). The study permission was granted by the Helsinki University Hospital (HUS/46/2018 and HUS/217/2024). The data permits have been requested from the Social Insurance Institute (SII), the National Institute for Health and Welfare (THL), and Population Register Centre and Statistics Finland. All patient data were pseudonymized to ensure full data protection and anonymity, and no individuals can be identified. Patients were not contacted in any phase of the study and patient consents were not needed according to Finnish legislation.

Results

In total, between 2007 and 2018, there were 391 030 prevalent patients with AF. During the study period, the number of patients with AF increased from 113 394 in 2007 to 243 802 in 2018 in Finland (Supplementary Table S2). Of all prevalent AF patients 39 816 (10.2%) used either class I or III AADs.

Baseline characteristics

Most of the flecainide and dronedarone purchases were clustered in the youngest age groups (20–64 years) (Table 1). In addition, purchases of amiodarone were also observed among younger age groups. Conversely, the purchases of sotalol were more evenly distributed to all three age groups (20–64, 65–74, and ≥75 years). Flecainide was seldom (0.9%–4.3%) used in patients with comorbidities such as heart failure, coronary artery disease (CHD), and post-myocardial infarction (Table 1).

Classes I and III

Alongside the increasing prevalence of AF, also the number of patients on either class I or class III AADs increased

Table 1. Baseline characteristics at the time of diagnosis of atrial fibrillation.

		NoAAD	Flecainide	Disopyramide, propafenone, or quinidine	Amiodarone	Dronedarone	Sotalol
Age	20-64	74161 (20.5)	14512 (61.3)	783 (38.2)	7087 (44.7)	1699 (56.2)	2853 (33.1)
	65-74	94063 (26.0)	6975 (29.4)	623 (30.3)	5154 (32.6)	1014 (33.5)	2698 (31.3)
	75 and older	193333 (53.5)	2204 (9.3)	647 (31.5)	3587 (22.7)	311 (10.3)	3072 (35.6)
Sex	Male	181956 (50.3)	13080 (55.2)	1174 (57.2)	10065 (63.6)	1611 (53.3)	4947 (57.4)
	Female	179601 (49.7)	10611 (44.8)	879 (42.8)	5763 (36.4)	1413 (46.7)	3676 (42.6)
Hypertension		267300 (73.9)	15474 (65.3)	1240 (60.4)	10877 (68.7)	2156 (71.3)	6867 (79.6)
Diabetes		78154 (21.6)	1728 (7.3)	184 (9.0)	2610 (16.5)	347 (11.5)	1458 (16.9)
Prior IS or TIA		54379 (15.0)	1071 (4.5)	139 (6.8)	1158 (7.3)	148 (4.9)	803 (9.3)
Heart failure		70086 (19.4)	447 (1.9)	100 (4.9)	3201 (20.2)	118 (3.9)	862 (10.0)
Coronary heart disease		84022 (23.2)	1017 (4.3)	42(2.0)	4139 (26.1)	424 (14.0)	1553 (18.0)
Myocardial infarction		28633 (7.9)	207 (0.9)	243 (11.8)	1585 (10.0)	108 (3.6)	404 (4.7)

Values denote patients with common comorbidities of atrial fibrillation with antiarrhythmic drug purchases. The values denote n (%). Abbreviations: IS, ischemic stroke; NoAAD, not purchases of any of the following drugs: amiodarone, disopyramide, dronedarone, flecainide, quinidine, propafenone, sotalol; TIA, transient ischemic attack.

during the study period (Table S2). However, the proportion of AF patients using classes I and III AADs decreased from 8.6% to 6.3% between 2007 and 2018 (Figure 1(a)). In addition, the classes I and III AADs were most used among individuals aged between 60–69 and 70–79 years (Figure S1). The most notable decline was observed in patients aged 50–69 years (Figure S1).

Class I

Flecainide was the most often used classes I and III AAD. The number of flecainide purchases increased during the observation period 2007–2018 (Figure S2). However, the proportion of AF patients on flecainide decreased from 4.9% to 3.9% between 2007 and 2018 (Figure 1(b)). The use of disopyramide, propafenone, and quinidine decreased from very low (0.3%, 0.2% and 0.1%, respectively) in 2007 to zero by year 2015 (Figure 1(c)). Procainamide was not used in Finland during the study period.

Class II

Beta-blockers were used frequently, by approximately 75% of patients throughout the study period, with bisoprolol being the most often used beta-blocker (Figure 2(a)). The use of bisoprolol increased from 48.7% to 60.4%, whereas the use of metoprolol more than halved from 23.4% to 10.8%. The use of atenolol decreased from 2.3% to 1.5% and the use of carvedilol from 2.0% to 1.0% (Figure S3).

Class III

The proportion of AF patients on class III AADs decreased from 3.4% to 2.5% (Figure 3). Amiodarone was the most often prescribed class III AAD and the second most prescribed AAD (after flecainide) among classes I and III. The purchases of amiodarone increased during 2007–2018 (Figure S2). However, the proportion of AF patients using amiodarone decreased from 1.9% to 1.5%. Dronedarone became available in 2011 when it also reached its highest sale with 0.8% and thereafter decreased to 0.4% in 2018. The use of sotalol constantly decreased from 1.5% to 0.6%. Dofetilide was not used in Finland.

Class IV

The total use of class IV AADs, that is non-dihydropyridine calcium channel blockers, decreased from 3.5% to 2.0% (Figure 2(b)). The use of verapamil decreased from 1.8% to 1.0%, and the use of diltiazem from 1.7% to 1.0% over the study period.

Class V—digoxin

The use of digoxin decreased from 24.6% to 11.0% from 2007 to 2018 (Figure 2(c)). There was a change in digoxin reimbursement policy in 2013, and the data from 2013 is incomplete. For this reason, the use of digoxin was interpolated based on the years 2012 and 2014.

Class VII

The proportion of AF patients using RAAS acting drugs increased from 51.0% to 56.1% (Figure 2(d)). The use of ACEIs decreased from 28.1% to 23.5%, whereas the use of ARBs increased from 16.1% to 24.1%. Similar trends were observed in the combinations of ACEIs and ARBs with diuretics (Supplementary Table 2). The use of spironolactone and statins constantly increased over the study period (Figure S4).

Discussion

In this nationwide study including all the patients with AF in Finland, the use of classes I and III AADs decreased, use of beta-blockers remained stable, and the use of RAAS acting drugs and statins increased.

The purchases of classes I and III AADs increased alongside the increasing prevalence of AF, but the percentage of AF patients on classes I and III AADs decreased from 8.6% to 6.3% between 2007 and 2018. We also noticed that despite very congruent international guidelines, the use of AADs differs between countries. Our results are in line with the studies from Australia, Denmark, and England reporting that the prescriptions of classes I and III AADs peaked between 2004 and 2009 and thereafter have been on the constant decline [8–10]. On the contrary, in the United States the total prescriptions of AADs increased 184%

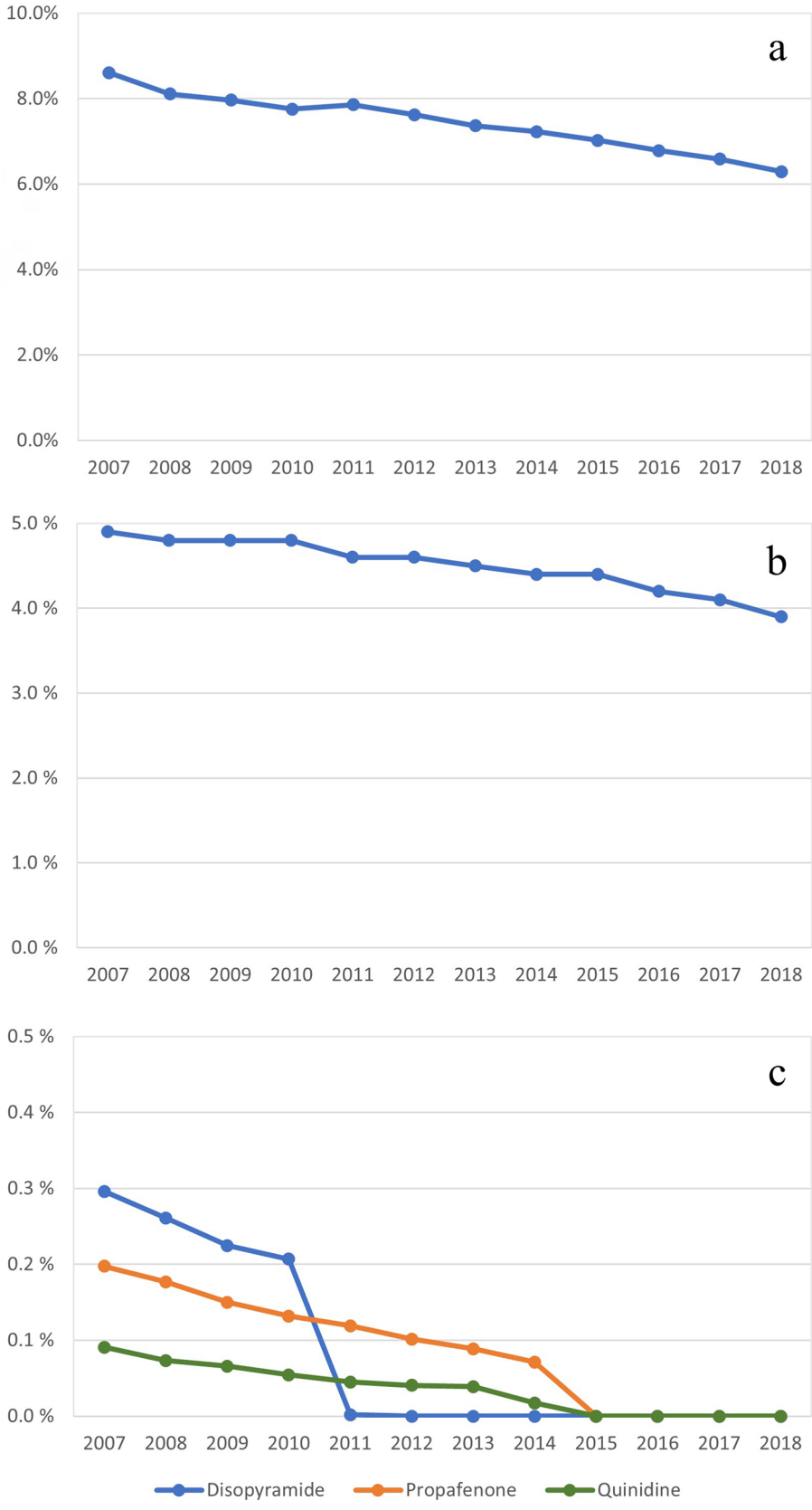

Figure 1. The use of (a) class I and III antiarrhythmic drugs, (b) flecainide, (c) disopyramide, propafenone and quinidine 2007–2018.

between 2004 and 2016 [11]. However, it is difficult to compare the trend of AADs use between the countries, because some studies report the total number of AADs prescriptions, and some report the proportion of total population on AADs and some the proportion of arrhythmia patients on AADs. In addition, only the Australian study investigated AAD use solely in AF patients, whereas in the other three studies AAD use in the treatment of all arrhythmias was

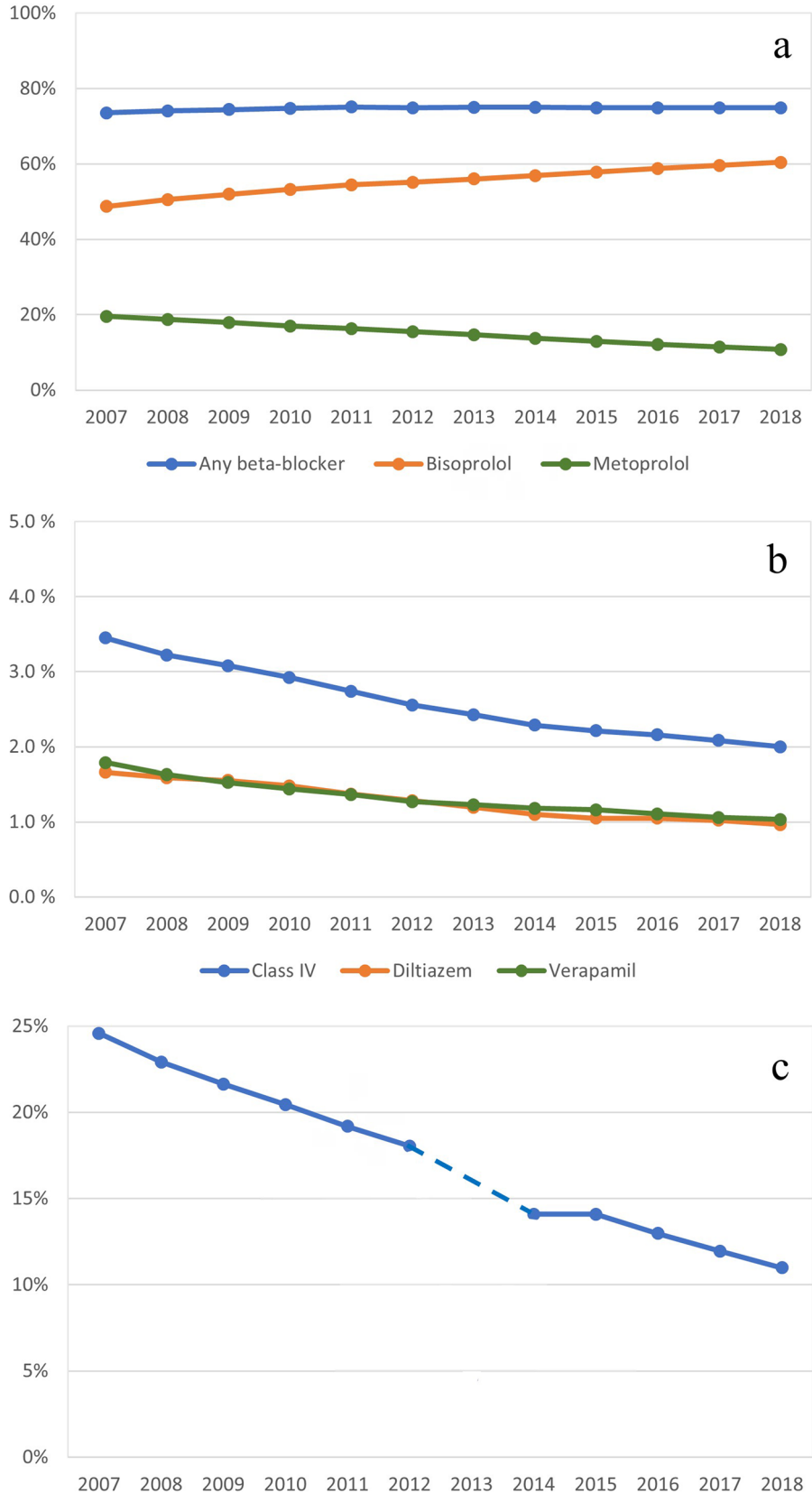

Figure 2. The use of (a) beta-blockers, (b) calcium channel blockers, (c) digoxin, and (d) renin–angiotensin–aldosterone–system inhibitors 2007–2018.

examined. However, since nowadays AF is the major indication for AADs, we can conclude, that except for United States, the use of classes I and III AADs have decreased during the last decade [8–11]. Given the continuously increasing trend in the AF prevalence, the decrease in the use of classes I and II AADs is counterintuitive [2]. What is of note is the decreasing trend in the purchases of classes I and III AADs particularly in the 50–69-year-old patients in

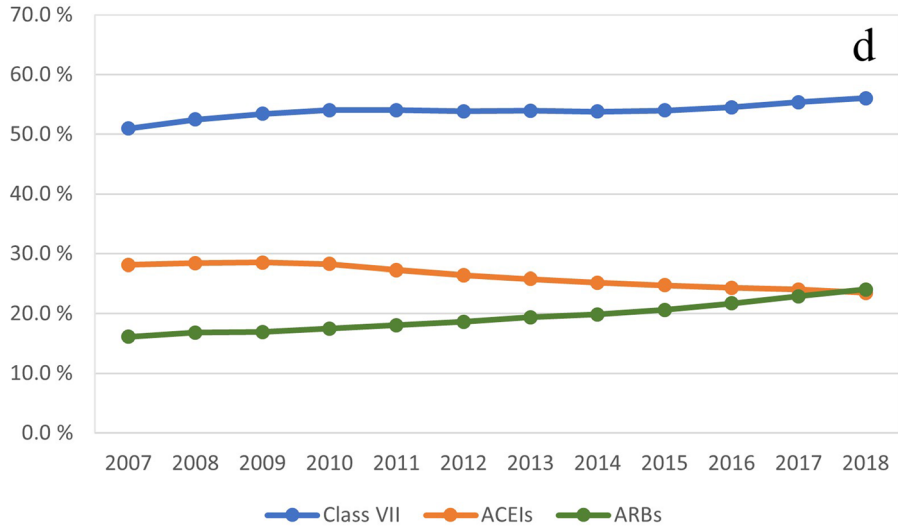

Figure 2. Continued.

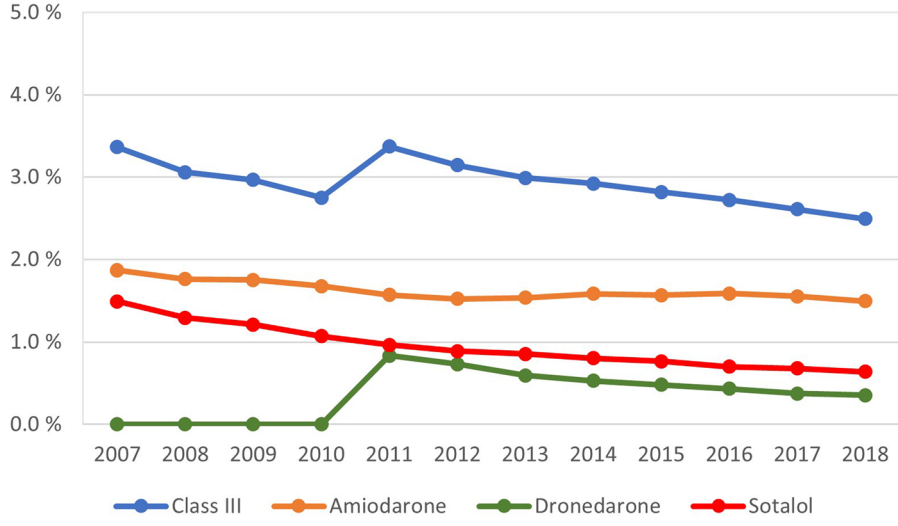

Figure 3. The use of class III antiarrhythmic drugs.

Finland. In Finland, the initiation of class I AADs and amiodarone is restricted to cardiologists and internists. This may contribute to rapid implementation of ESC guidelines leading to increased use of catheter ablation, and correspondingly, declined use of AADs in the treatment of AF [3,13]. The number of first-time catheter ablation procedures for AF and AFL more than doubled from 2012 to 2018 in Finland [14].

In our study, flecainide was the most used AAD for AF rhythm control out of classes I and III, and the number of patients on flecainide increased together with the increase in the prevalence of AF. However, the proportion of AF patients on flecainide therapy constantly decreased. In all reference countries, the use of flecainide has increased but it has not been the most used AAD in any of them. In Australia and Denmark, flecainide was the second most prescribed AAD [8,10], and in England and in the United States, it was the third most prescribed AAD [9,11] According to the recent ESC 2020 guidelines, flecainide is the first-line AAD in the prevention of AF in patients without structural heart disease [3].

Three quartiles of AF patients were on beta-blockers throughout the study period. The use of bisoprolol constantly increased, and it was the most used beta-blocker. In Australia, the proportion of patients using beta-blockers in patients with AF was markedly lower compared to Finland, but slightly increased from 35,0% to 38,0% between 2009 and 2018 [8]. In Denmark, the prescriptions of beta-blockers increased 117% from 1999 to 2017 [9]. In fact, metoprolol was the most used beta-blocker in Denmark accounting for 67% of total beta-blocker use in 2017 [9]. However, in addition to rate control in AF, beta-blockers are indicated also for the treatment of coronary artery disease, heart failure and hypertension, all common comorbidities in AF patients [3,15,16].

Amiodarone is the most effective AAD to maintain sinus rhythm. However, its use is limited by extracardiac adverse effects including pulmonary toxicity and hyper-/hypothyroidism [17,18]. As a result, amiodarone has been the second most prescribed AAD in Finland. The proportion of AF patients on amiodarone decreased in Finland, and in

Australia and England [8,9]. In contrast, in Denmark and in the USA, amiodarone dispense has increased and amiodarone has become the most prescribed AAD [10,11]. Whether genetic variation in drug response and tolerability contributes to the differences in the use of amiodarone between the countries deserves to be studied.

Dronedarone was designed to be a better version of amiodarone for AF rhythm control without extracardiac adverse effects, and it became available in 2009. However, the Pallas study reported that dronedarone was associated with increased risk of heart failure, stroke, and cardiovascular mortality in patients with permanent AF [19]. This, and the lower-than-expected efficacy in AF rhythm control and laborious laboratory monitoring have been responsible for low uptake of dronedarone in many countries [20]. Indeed, in Finland and in other countries the dronedarone purchases have declined since 2011 [9,11].

The use of sotalol gradually decreased and it has been the third most used AAD among classes I and III in Finland. In Australia and in England, sotalol has been the most prescribed AAD for AF rhythm control [8,9]. However, in Finland as well as in Australia, England, and Denmark the use of sotalol has been on the decline, whereas in the USA sotalol use continues to increase and was the second most prescribed AAD in 2016 [8–11]. Importantly, the Cochrane Database Systematic Review suggested that the use of sotalol is associated with increased mortality in AF patients [21].

The declining use of digoxin in Finland is in line with reports from Australia and Denmark [8,10]. Digoxin has a narrow therapeutic index and it is used as a rate-controlling drug next to beta-blockers in AF patients with heart failure or left ventricular dysfunction [3]. In a recent study, no difference in quality of life was observed in patients with permanent AF when either digoxin or bisoprolol was used as a rate-controlling drug [22]. Furthermore, a systematic review and meta-analysis demonstrated that the use of digoxin was associated with all-cause and cardiovascular mortality in patients with AF [23].

The proportion of patients on RAAS acting drugs and statins increased. Among the RAAS drugs the proportion of patients using ARBs increased, whereas the proportion of patients on ACEIs decreased. To best of our knowledge, the trends of ACEIs, ARBs, and statins have not been assessed in patients with AF. In Denmark, the use of ARBs significantly increased in patients with hypertension between 1999 and 2015 [24]. The Losartan Intervention For End Point Reduction in Hypertension (LIFE) study published in 2005 demonstrated that losartan reduced the incidence of new-onset AF compared to atenolol in patients with hypertension [25]. The increase in the use of RAAS acting drugs and statins is associated with overall improved control of cardiovascular risk factors in patients with AF in Finland [13].

The strength of this study is based on the large cohort size. The nationwide cohort eliminates selection bias, and our study includes patients from all levels of care: primary, secondary, and tertiary care. Compared to earlier studies, our study includes all rhythm and rate control AADs used for the treatment of AF. Furthermore, we also demonstrate the trends of ACEIs, ARBs, diuretics, spironolactone, and statins that have not been included in the previous studies [8–11].

Our study is limited by the retrospective design and could also be limited by information bias due to inaccuracies in the register data. However, AADs or rate control drugs are not sold over the counter in Finland, and thus, the available pharmacy claims data covers virtually all filled prescriptions. Moreover, all health care visits must be registered in the nationwide registers which is directed by the Finnish law. In addition, Finnish registers have been found especially reliable in registering cardiovascular diseases, and recently The World Bank assessed the Finnish registers having the highest performance of statistical systems in the world [26,27]. However, we cannot differentiate patients with different types of AF (paroxysmal, persistent, or permanent). Our data covers the years 2007–2018. Thus, it lacks the most recent years. However, AF guidelines from 2010 to 2020 have not changed their recommendations as regards the selection of AADs, but the major update has been the increasing role of catheter ablation in the treatment of AF [3]. Accordingly, it is likely that the total use of AADs has continued to decrease during the last 6 years. However, despite very congruent international guidelines, the differences in the use of AADs persisted between the examined countries during the years 2007–2018 and most probably this has continued until now [8–11].

Conclusions

In conclusion, our nationwide cohort study revealed that although the number of classes I and III AAD purchases increased, the proportion of AF patients on classes I and III AADs and digoxin decreased between 2007 and 2018. The use of beta-blockers remained stable and the use of RAAS acting medications and statins increased.

Disclosure statement

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