

Atrial fibrillation pharmacotherapy after hospital discharge between 1995 and 2004: a shift towards beta-blockers

Morten Lock Hansen^{1*}, Niels Gadsbøll², Gunnar H. Gislason³, Steen Z. Abildstrom^{3,4}, Tina K. Schramm¹, Fredrik Folke¹, Jens Friberg⁵, Rikke Sørensen³, Søren Rasmussen⁴, Henrik E. Poulsen⁶, Lars Køber⁵, Mette Madsen⁷, and Christian Torp-Pedersen¹

¹Department of Cardiology, Bispebjerg University Hospital, Bispebjerg Bakke 23, DK-2400 Copenhagen, Denmark;

²Department of Medicine, Sygehus Øst Køge, Denmark; ³Department of Cardiology, Gentofte University Hospital, Hellerup, Denmark; ⁴National Institute of Public Health, Copenhagen, Denmark; ⁵Department of Cardiology, The Heart Centre, Rigshospitalet-Copenhagen University Hospital, Denmark; ⁶Department of Pharmacology, Rigshospitalet-Copenhagen University Hospital, Denmark; and ⁷Department of Public Health, University of Copenhagen, Copenhagen, Denmark

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KEYWORDS

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Aims To study evolution in pharmacotherapy of atrial fibrillation from 1995 to 2004.

Methods and results All Danish patients were discharged following first-time atrial fibrillation and their pharmacotherapy was identified by individual-level-linkage of nationwide registers of hospitalization and drug dispensing from pharmacies. A total of 108 791 patients survived 30 days after discharge and were included. In 1995–1996, 7.4% of the patients received beta-blockers, increasing to 44.3% in 2003–2004. The corresponding figures for amiodarone were 2.9 and 5.4%. In contrast, use of nondihydropyridine calcium-channel blockers, digoxin, sotalol, and class 1C antiarrhythmics decreased from 20.6, 63.9, 21.3, and 4.0% in 1995–1996 to 12.6, 43.8, 4.2, and 1.3% in 2003–2004, respectively. Notably, patients receiving anticoagulants increased from 29.8 to 43.5%. Multivariate logistic regression analysis revealed females to be associated with more use of digoxin, but less use of amiodarone and oral anticoagulants than males. Patients above 80 years received less pharmacotherapy, apart from digoxin treatment that was more commonly used in elderly.

Conclusion Pharmacotherapy of atrial fibrillation has changed towards increased beta-blocker use with a coincident decrease in the use of other rate-limiting drugs and sotalol. Treatment with amiodarone or class 1C antiarrhythmics remained very low. Oral anticoagulant therapy increased considerably, but women and elderly were apparently undertreated.

Introduction

For many clinicians treatment of atrial fibrillation has focused on restoration and maintenance of sinus rhythm with direct-current cardioversion and administration of antiarrhythmic drugs. However, several recent trials have led to this strategy being questioned.^{1–5} In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, there was an unexpected poor outcome in the rhythm-control arm which could partly be explained by the adverse effects of antiarrhythmic therapy and the less frequent use of anticoagulation therapy.¹ The extent to which

daily clinical practice in the treatment of atrial fibrillation has evolved during recent years remains unknown. Therefore, we performed a nationwide study, using individual-level-linkage hospital registries and prescriptions dispensed from pharmacies to explore trends from 1995 to 2004 in the medical treatment of all 108 791 Danish patients surviving first-time admission for atrial fibrillation.

Methods

Population

All permanent residents in Denmark have a unique civil registration number that enables linkage between national registers on an individual basis. Patients aged 30 years or older with first hospitalization

* Corresponding author. Tel: +45 35 31 33 28; fax: +45 39 75 18 03.
E-mail address: mlh@heart.dk

with atrial fibrillation [International Classification of Diseases 10th revision (ICD-10) code I48] between 1995 and 2004 were identified from the Danish National Patient Registry—a nationwide registry of all hospitalizations in Denmark since 1978. Atrial fibrillation as the main condition, primary diagnosis, or as a coexisting condition, secondary diagnoses, was also identified. The database was systematically screened to ensure that any transfer of patients between hospitals was registered as a single admission. Patients who died within 30 days of discharge were excluded to ensure that all the remaining patients had at least 30 days to obtain the prescribed medicine from the pharmacy.

Medical treatment

The Danish Registry of Medicinal Product Statistics includes information of all prescriptions dispensed from Danish pharmacies since 1995. Each prescribed drug is coded according to the Anatomical Therapeutic Chemical (ATC) classification. The registry also includes information about date of dispensing, strength and formulation, quantity dispensed, and the affiliation of the doctor issuing the prescription. This registry has been found to be accurate and has been described in more detail previously.^{6,7} We identified all prescriptions of beta-blockers (ATC code C07) including the most frequently prescribed brands (atenolol ATC code C07AB03, bisoprolol C07AB07, carvedilol ATC code C07AG02, metoprolol ATC code C07AB02, and propranolol C07AA05), nondihydropyridine calcium-channel blockers [verapamil and diltiazem (ATC code C08D)], digoxin (ATC code C01A), sotalol (ATC code C07AA07), amiodarone (ATC code C01BD01), Class 1C antiarrhythmics [propafenone (ATC code C01BC03), and flecainide (ATC code C01BC04)], and oral anticoagulant therapy [warfarin and phenprocoumon (ATC code B01AA03 and B01AA04)]. All first prescriptions filled within 90 days from discharge were included in our analyses.

Vital status

Information about each patient's vital status (dead or alive) by the end of December 2004 was obtained from the Central Population Registry through Statistics Denmark, which records all cases of death within 2 weeks.

Co-morbidity

To identify a possible influence of co-morbidity on choice of treatment, we identified all patients with a present or previous (5 years before index admission) diagnosis of: myocardial infarction (ICD-10 code I21–22 and ICD-8 code 410), congestive heart failure (ICD-10 code I50 and ICD-8 code 427.0 and 427.1), or ischaemic stroke (ICD-10 code I63–66, I69.3, I69.4 and G65 and ICD-8 code 432–438). These diagnoses have been validated and have high positive predictive values.^{8–10} Furthermore, we identified the patients admitted with atrial fibrillation exclusively and without a previous diagnosis of the aforementioned co-morbidities. These patients were classified as 'atrial fibrillation without the pre-specified co-morbidities'.

Statistical analysis

Multiple logistic regression was used to identify covariates associated with prescription of each of the aforementioned drugs. The models were adjusted for calendar year (1995–1996 as reference), age (30–59 years as reference), gender (women as reference), and co-morbidity (no co-morbidity as reference). The age-related prescription pattern was determined by dividing the patients into four age groups: 30–59, 60–69, 70–79, and ≥ 80 years of age. A level of 5% was considered statistically significant including when testing for interactions. All statistical calculations were performed using the SAS statistical software package, version 9.1 for UNIX servers (SAS Institute Inc., Cary, NC, USA).

Ethics

The Danish Data Protection Agency approved the study. Retrospective register-based studies do not require ethical approval in Denmark.

Results

From 1995 to 2004, a total of 120 964 patients were hospitalized with a first-time diagnosis of atrial fibrillation in Denmark. A total of 108 791 (89.9%) were alive 30 days after discharge and were included in the analysis. The mean age was 73.0 (± 12.1) years and, on average, women were significantly older than men (*Table 1*).

Prescription pattern over time

Antiarrhythmic and rate-limiting drugs

During the 10-year study period, the proportion of atrial fibrillation patients treated with beta-blockers increased from 7.4 to 44.3% (*Figure 1*). Of all beta-blockers ($n = 25\,479$) metoprolol was most frequently used, accounting for 19 488 (76.5%), atenolol 1701 (6.7%), bisoprolol 1534 (6.0%), carvedilol 1290 (5.1%), propranolol 860 (3.4%), and other beta-blockers 606 (2.4%). In contrast, a considerable decrease occurred in the use of digoxin, nondihydropyridine calcium-channel blockers, and sotalol. The use of class 1C antiarrhythmics and amiodarone remained low throughout the study period, although there was an increase in the use of amiodarone, from 2.9 to 5.4%, and a decrease in

Table 1 Baseline characteristics of the study sample

Characteristic	<i>n</i>	%
Total patients (mean age \pm SD, years)	108 791 (73.0 \pm 12.1)	100.0
Women (mean age \pm SD, years)	50 890 (76.5 \pm 10.8)	46.8
Men (mean age \pm SD, years)	57 901 (69.9 \pm 12.3)	53.2
Atrial fibrillation primary diagnosis	54 809	50.4
Atrial fibrillation without pre-specified co-morbidities	20 980	19.1
Year of atrial fibrillation		
1995–1996	19 003	17.5
1997–1998	19 997	18.4
1999–2000	22 483	20.7
2001–2002	24 478	22.5
2003–2004	22 830	21.0
Age (years)		
30–59	15 531	14.3
60–69	20 908	19.2
70–79	36 420	33.5
≥ 80	35 932	33.0
Co-morbidity		
Prior or concurrent myocardial infarction	9896	14.0
Prior or concurrent congestive heart failure	23 950	23.9
Prior or concurrent ischaemic stroke	16 708	15.4
Prior or concurrent haemorrhagic stroke	5778	5.3

SD indicates standard deviation.

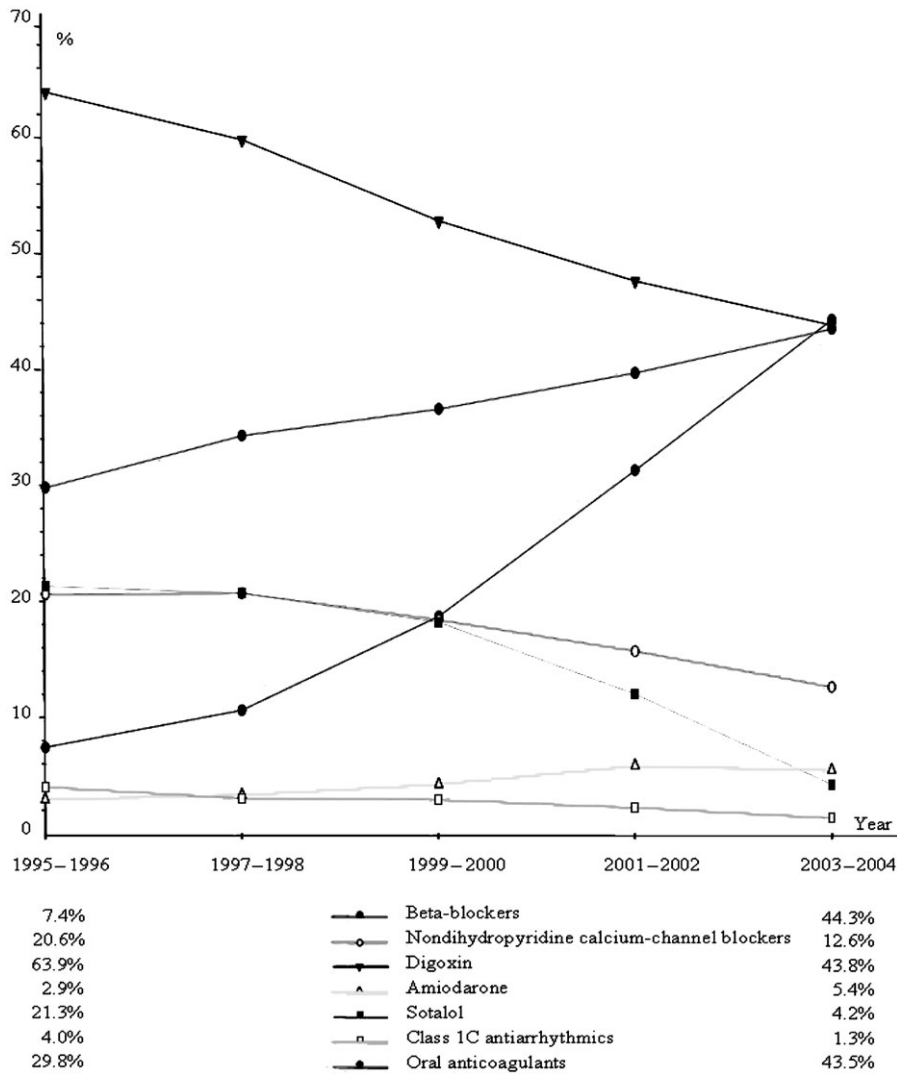


Figure 1 Proportion of atrial fibrillation patients who claimed a prescription of beta-blockers, nondihydropyridine calcium channel blockers, digoxin, sotalol, amiodarone, class 1C-antiarrhythmics, or oral anticoagulants within 90 days of discharge.

the use of class 1C antiarrhythmics, from 4.0 to 1.3%. Female gender was associated with significantly more frequent use of beta-blockers, nondihydropyridine calcium-channel blockers, and digoxin than by males [the gender difference increased with increasing age (age and gender interaction, $p < 0.001$)], and less frequent use of amiodarone (Table 2). Increasing age was positively associated with increased digoxin treatment, but negatively associated with the use of any other antiarrhythmic drug treatment (Table 2). A total of 9896 (9.1%) and 23 950 (22.0%) patients were identified with a current or prior admission for myocardial infarction or congestive heart failure. Treatment in atrial fibrillation patients with and without the specified co-morbidities is illustrated in Figure 2. Similar trends in treatment over time were observed for all subgroups, but treatments with beta-blockers or digoxin were consistently most common among myocardial infarction and congestive heart failure patients (Table 2). Likewise, amiodarone was most frequently prescribed to patients with a diagnosis of myocardial infarction or congestive heart failure (Table 2). Finally, treatment with nondihydropyridine calcium-channel blockers, sotalol, and class 1C antiarrhythmics were most

common among atrial fibrillation patients without the specified co-morbidities (Table 2). The incidence of the specified co-morbidities was stable throughout the period of observation. Thus, the changes in prescription pattern were not related to baseline co-morbidities as illustrated in Figure 2.

Oral anticoagulants

The proportion of patients receiving oral anticoagulants increased from 29.8 in 1995–1996 to 43.5% in 2003–2004 (Figure 1). The greatest increase was among patients older than 80 years of age (age and calendar year interaction, $P < 0.001$), but nevertheless they remained less likely to receive treatment than those in younger age groups (Figure 3A and Table 3). Female gender was associated with significantly less frequent use of anticoagulants than by males, although the gender difference declined with increasing age (age and gender interaction, $P < 0.001$; Figures 3B and 4 and Table 3). Treatment with anticoagulants was most common among patients with current or prior ischaemic stroke ($n = 13\ 034$, 12.0%) (Figure 3C and Table 3).

Table 2 Multivariate logistic regression analysis of factors associated with use of beta-blockers, nondihydropyridine calcium-channel blockers, digoxin, amiodarone, sotalol, and class 1C antiarrhythmics in atrial fibrillation patients

Variable	%	Beta-blockers		Nondihydropyridine calcium-channel blockers		Digoxin		Amiodarone		Sotalol		Class 1C antiarrhythmics	
		OR		%	OR	%	OR	%	OR	%	OR	%	OR
Gender													
Women	23.2	1.00		18.7	1.00	57.1	1.00	3.1	1.00	13.1	1.00	2.3	1.00
Men	23.6	0.89 (0.87–0.92)		16.2	0.83 (0.81–0.86)	49.4	0.85 (0.83–0.87)	5.5	1.45 (1.36–1.54)	16.5	0.97 (0.94–1.01)	3.0	0.96 (0.88–1.03)
Age													
30–59	26.5	1.00		14.9	1.00	34.0	1.00	5.7	1.00	25.8	1.00	5.5	1.00
60–69	27.5	1.03 (0.98–1.09)		18.5	1.30 (1.23–1.38)	47.7	1.65 (1.58–1.73)	6.5	1.08 (0.98–1.18)	22.1	0.89 (0.85–0.94)	4.2	0.83 (0.76–0.92)
70–79	23.8	0.85 (0.81–0.89)		19.5	1.37 (1.30–1.44)	56.1	2.18 (2.09–2.27)	4.9	0.81 (0.74–0.88)	14.9	0.55 (0.53–0.59)	2.4	0.59 (0.45–0.55)
≥80	19.3	0.59 (0.56–0.62)		15.7	1.04 (0.99–1.10)	61.0	2.54 (2.43–2.65)	2.1	0.33 (0.30–0.36)	5.9	0.21 (0.20–0.23)	0.7	0.16 (0.12–0.17)
Co-morbidity													
Myocardial infarction	38.1	2.38 (2.27–2.50)		13.3	0.72 (0.68–0.77)	48.4	0.67 (0.65–0.71)	9.4	2.17 (2.01–2.35)	14.5	1.27 (1.19–1.35)	1.3	0.59 (0.49–0.71)
Congestive heart failure	24.2	1.13 (1.09–1.18)		17.2	1.01 (0.97–1.05)	68.4	2.03 (1.96–2.09)	6.7	1.89 (1.77–2.02)	8.2	0.57 (0.54–0.60)	1.1	0.52 (0.46–0.60)
Ischaemic stroke	20.6	0.82 (0.78–0.86)		14.5	0.80 (0.75–0.84)	54.2	0.92 (0.88–0.95)	2.8	0.62 (0.55–0.69)	8.5	0.67 (0.63–0.72)	1.3	0.67 (0.57–0.79)
Atrial fibrillation without the pre-specified co-morbidities	20.6	1.00 (0.96–1.04)		19.4	1.07 (1.03–1.12)	44.8	0.78 (0.75–0.80)	3.3	0.73 (0.67–0.80)	25.8	1.65 (1.58–1.72)	5.0	1.49 (1.37–1.63)

Multiple logistic regression analysis adjusted for calendar year, age, gender, and co-morbidity.

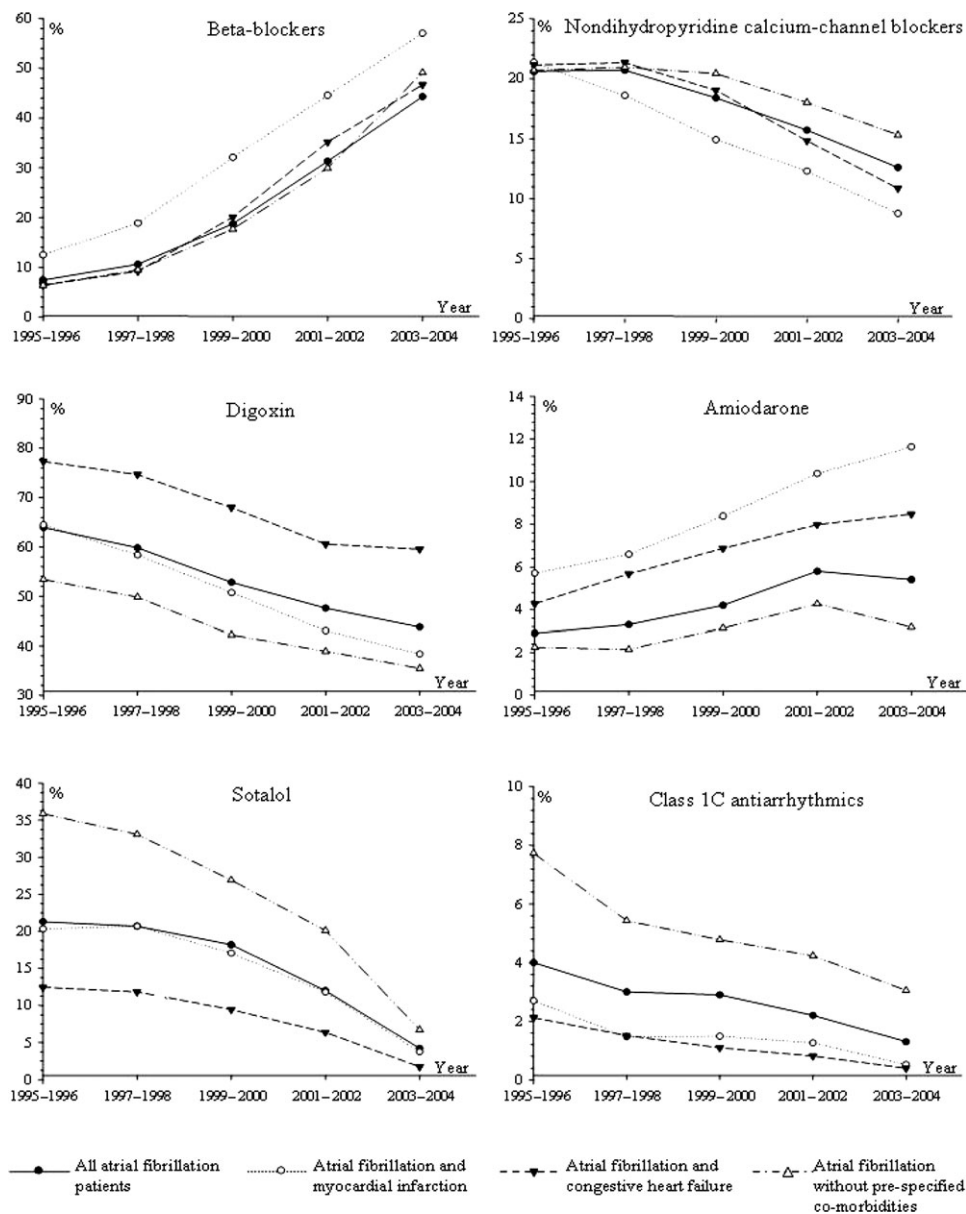


Figure 2 Proportion of atrial fibrillation patients initiating antiarrhythmic and rate-lowering therapy according to co-morbidity.

Discussion

The present study addresses the temporal trends in prescription pattern of seven drugs frequently used in patients following first-time hospitalization for atrial fibrillation. Our main findings were: (1) from 1995 to 2004 there was a six-fold increase in the use of beta-blockers at the expense of digoxin, nondihydropyridine calcium-channel blockers, and sotalol; (2) sotalol, once the second most commonly used drug for treating atrial fibrillation (21.3% of cases in 1995-1996), was used in only 4.2% of patients in 2003-2004; (3) treatment with amiodarone and class 1C antiarrhythmics remained infrequent throughout the period of observation; (4) there was a considerable increase in the use of oral anticoagulants; and (5) there was a systematic gender and age difference, with elderly patients most likely to receive digoxin, and with women more frequently receiving digoxin, and less frequently amiodarone and anticoagulation therapy than their male counterparts.

Prescription pattern over time

In 2001, the first AHA/ACC/ESC guidelines for the treatment of atrial fibrillation were published, based on a comprehensive review of the literature from 1980 to 2001.¹¹ These guidelines describe various therapeutic options for the treatment of patients with atrial fibrillation, but do not recommend any particular therapeutic strategy or drug choice. Therefore it is difficult to explain the substantial changes in prescription pattern in the present series of 108 791 unselected patients with a first-time diagnosis of atrial fibrillation. Notably, changes in prescription pattern took place from the very start of the study period, many years before the AFFIRM, the Rate Control vs. Electrical Cardioversion for Persistent Atrial Fibrillation (RACE) and other large trials questioned the use of antiarrhythmic drugs in atrial fibrillation patients.¹⁻⁵

One explanation for the increase in the use of beta-blockers could be a 'carry-over effect' from beta-blocker

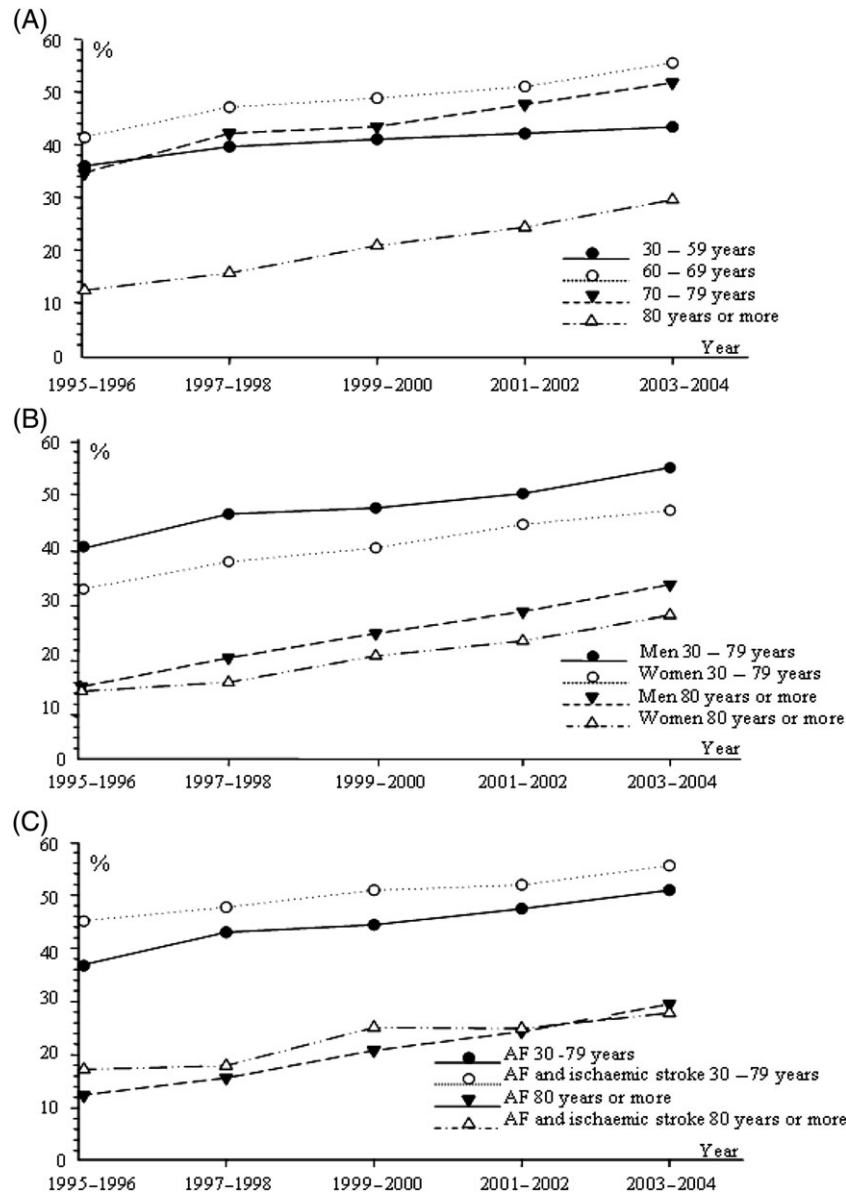


Figure 3 Proportion of atrial fibrillation patients initiating treatment with oral anticoagulants from 1995 to 2004, by (A) age, (B) gender, and (C) ischaemic stroke.

studies in non-atrial fibrillation patients. In the 1980s, the use of beta-blockers as a means of secondary prevention following myocardial infarction was shown to improve survival by 20–25% and to reduce the risk of reinfarction.¹² Also, during the 1990s, evidence of the benefit of beta-blockade in heart-failure patients accumulated.^{13–15} This may have influenced clinicians treating atrial fibrillation patients, many of whom had ischaemic heart disease or heart failure, although nondihydropyridine calcium-channel blockers in many ways are considered interchangeable with beta-blockers in the treatment of atrial fibrillation.¹⁶ Furthermore, beta-blocker treatment is not restricted to specific types of atrial fibrillation, as illustrated in The Euro Heart Survey on Atrial Fibrillation, where the frequency of beta-blocker use was 29–30% regardless of whether the patients had first-detected, paroxysmal, persistent, or permanent atrial fibrillation.¹⁷

In 1995–1996, almost two-thirds of all atrial fibrillation patients received treatment with digoxin, and although its use declined considerably during the 10-year study period, it continued to be frequently used. In agreement with current guidelines, digoxin was most often prescribed to congestive heart failure and elderly patients.¹⁶ Notably, digoxin was more often used in female than in male patients. This is a matter of concern, since female patients may have a greater susceptibility to the adverse effects of digoxin.¹⁸

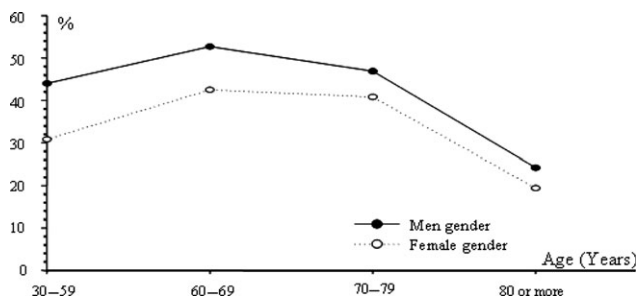
Sotalol use decreased substantially during the study period. This probably reflects the increased risk of death and proarrhythmia associated with this drug^{19–22} and the fact that sotalol is hardly more efficient than conventional beta-blockers for maintaining sinus rhythm.²³

Throughout the 10-year observation period only a minority of patients received amiodarone and class 1C antiarrhythmic

Table 3 Multivariate logistic regression analysis of factors associated with use of vitamin K-antagonists in atrial fibrillation patients

Variable	Oral anticoagulants	
	%	OR
Gender		
Women	30.8	1.00
Men	42.4	1.40 (1.36–1.44)
Age		
30–59	40.7	1.00
60–69	49.1	1.46 (1.40–1.52)
70–79	44.0	1.22 (1.17–1.27)
≥80	21.2	0.41 (0.39–0.43)
Co-morbidity		
Myocardial infarction	36.6	0.70 (0.67–0.74)
Congestive heart failure	37.6	1.24 (1.20–1.28)
Ischaemic stroke	38.8	1.24 (1.19–1.29)
Atrial fibrillation without the pre-specified co-morbidities	32.3	0.97 (0.93–1.00)

Multiple logistic regression analysis adjusted for calendar year, age, gender, and co-morbidity.

**Figure 4** Proportion of women and men with atrial fibrillation initiating treatment with oral anticoagulants by age group.

drugs, even though these agents can maintain sinus rhythm.^{24,25} The reluctance to use these agents outside the hospital is understandable because of their potential serious side effects.¹⁶ Furthermore, class 1C drugs are restricted to patients without established ischaemic heart disease or left ventricular dysfunction, which limits their use in a population of atrial fibrillation patients.¹⁶ The minor decrease in amiodarone use from 2002 to 2004 could be related to the publication of the findings of the AFFIRM and RACE trials, which failed to show an advantage of rhythm control of atrial fibrillation over rate control.

Oral anticoagulants

The observed increase in atrial fibrillation patients receiving anticoagulant therapy is in accordance with our previous report²⁶ and reflects the impact of the large trials that have proved the value of anticoagulation in high-risk patients with atrial fibrillation.^{27–32} Older age is a well-known predictor of stroke among atrial fibrillation patients^{16,33} and we observed the greatest increase in

anticoagulant therapy among patients above 80 years of age. However, elderly patients still remained less likely to receive anticoagulation treatment than did those in younger age groups, even in patients with a previous or concomitant diagnosis of ischaemic stroke, for whom the indication for anticoagulation treatment is particularly strong. Increasing risk of haemorrhagic complications associated with anticoagulant treatment in elderly patients^{16,34} might restrain many physicians from prescribing this therapy, despite lower complication rates in newer anticoagulation treatment regimes.¹⁶ We also demonstrated that women less frequently received anticoagulant therapy than did men throughout the observation period. The gender-related difference in the anticoagulation therapy was largest in the younger age groups, and might reflect the fact that men acquire more risk factors for stroke early in life than do their female counterparts. Nevertheless, it is a matter of concern since females with atrial fibrillation have a higher risk of stroke than their male counterparts.^{35–37}

Limitations of the study

Due to the observational nature of this study there are some limitations that need to be acknowledged. First, although the diagnosis of atrial fibrillation in the Danish National Patient Registry has been validated,³⁸ we did not have any information on whether the individual cases of atrial fibrillation were paroxysmal, persistent, or permanent. Secondly, the study is based on administrative registries that do not include clinical data. Thus, precise indications for treatment of the individual patient are not available. Thirdly, information about contraindication for treatment and adverse reactions that might have led to the treatment being withheld due to assessment of the patient by the physician in charge is also not included in the registries. Finally, although Denmark generally follows the AHA/ACC/ESC guidelines for the treatment of atrial fibrillation, there may be individual differences between countries in the pharmacotherapy and general strategies of management of atrial fibrillation.

Conclusion

Over the 10-year period there was a dramatic increase in the use of beta-blockers in Danish atrial fibrillation patients at the expense of digoxin, nondihydropyridine calcium-channel blockers, and sotalol. In fact, sotalol, the second most used drug in 1995–1996, is rarely used nowadays, while amiodarone and class 1C antiarrhythmics still play a very modest role. Use of oral anticoagulants has increased considerably, but there is a persistent under-use of anticoagulation treatment in the elderly and in women with atrial fibrillation.

Conflict of interest: none declared.

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