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Drug use in patients with atrial fibrillation in Swedish primary health care: a comparison 5 years apart

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Abstract *Objective*: A study of the utilization of drugs, particularly antithrombotic agents and anti-arrhythmic agents, in patients with atrial fibrillation (AF) with changes over time in primary health care.
Methods: Surveys were done of patients with AF over 1-year periods, 1992–1993 (n = 135) and 1997–1998 (n = 144), respectively, at a community health centre in Stockholm County. Information on the prescription of drugs was obtained from the computerized medical records.
Results: The rate of antithrombotic treatment increased from 62.2% to 79.2% (P = 0.001), owing to an increased use of antiplatelet agents from 36.3% to 47.9% (P = 0.037), while the use of anticoagulant agents was on an equal level (25.9% vs 31.3%). The use of any antithrombotic agent in the primary prevention of thromboembolic events in AF increased from 20.0% to 41.0% (P = 0.000). The mean doses of aspirin, when used, increased from 123 to 142 mg (P = 0.036, one-tailed student's t-test). The use of sotalol also increased, from 14.2% to 25.2% (P = 0.024).
Conclusions: Despite the increased use of antithrombotic agents, there is still an under-prescription of anticoagulant agents and of doses of aspirin.

Key words Anticoagulants · Atrial fibrillation · Primary health care

Introduction

Atrial fibrillation (AF) is a common heart disorder, with an estimated prevalence in Sweden of around 1% of the overall population, which increases with age [1, 2]. The stroke rate in patients with AF is around 5% per year, and also increases with age [3, 4]. Treatment with warfarin has been shown to decrease the risk of stroke by 68% in published, randomized, controlled trials concerning primary stroke prevention and has been found to be cost-effective [3, 5]. This would call for a more active treatment with warfarin than is actually found [6].

Treatment with aspirin is an alternative, with a relative risk reduction of 21% in a meta-analysis [7], but with a relative risk reduction of up to 44% with a dose of 325 mg in the Stroke Prevention in Atrial Fibrillation 1 Study [3]. Aspirin is recommended in low-risk patients, i.e. those without prior transient ischaemic attack (TIA) or stroke, systemic hypertension and diabetes, younger than 65 years of age, at a dose of 325 mg per day, and in patients 65 years of age and older with contra-indications for warfarin, by Koefoed et al. [4]. The dose of 325 mg per day of aspirin was also recommended by the Swedish Medical Products Agency in their guidelines in 1992 [2].

Anti-arrhythmic drug therapy is also a matter of interest. In their guidelines in 1992, the Swedish Medical Products Agency recommended that sotalol or disopyramide could be used as prophylaxis in cases of paroxysmal or electroconverted AF, and digoxin, β-adrenergic blocking agents or some calcium antagonists (e.g. verapamil and diltiazem), for ventricular rate control [2].

The aim of this study was to compare AF patients in 1992–1993 and 1997–1998 with regard to drug use, particularly antithrombotic and anti-arrhythmic agents, with an expected change in pattern involving more patients on antithrombotic agents and, if on aspirin, at higher doses, and a greater use of sotalol.

Materials, methods and subjects

The community health centre (CHC) at Åkersberga in 1992 served the total population of the Österåker community (30 200 inhabitants). In 1997, it served the subjects listed at the CHC, as well as

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unlisted subjects in a defined area, i.e. around 24 000 out of a total of 32 000 in the entire community. Medical records were computerized from 1 October 1992.

Subjects with a diagnosis of AF at the CHC from October 1992 to September 1993, and from October 1997 to September 1998, were registered. Data were extracted from medical records regarding treatment, co-morbidity, cardiovascular drugs and complications. AF was classified as paroxysmal, i.e. episodes of AF which are self-terminating, persistent, i.e. an episode of AF which has not reverted spontaneously to sinus rhythm, or permanent, i.e. when attempts at restoration of sinus rhythm have failed or where the probability of successful cardioversion is considered so low that no attempt is made [8].

Chi-square analysis was used for comparison, as well as Fisher's exact test, Student's *t*-test and the Mann-Whitney U-test. As the mean doses of aspirin were presumed to increase, the Student's *t*-test was one-tailed. Multiple logistic regression was performed with the use of antithrombotic agents, anticoagulant agents and antiplatelet agents as dependent variables, and age, sex, heart disease, active AF, thromboembolic events related to AF and other conditions predisposing to thromboembolism as predicting factors.

Results

The number of patients with AF at the CHC increased between 1992 to 1993 and 1997 to 1998 from 135 to 144, despite a lower number of listed subjects. There were no significant differences in age or sex distribution (Table 1). Results regarding the type of AF and co-morbidity are also shown in Table 1, with no significant differences between the two occasions.

The use of antithrombotic agents increased between 1992 to 1993 and 1997 to 1998, both at ages below and above 75 years of age (Table 2). The increase was due to an increased use of antiplatelet agents in subjects above 75 years of age. There was an insignificant increase in the use of anticoagulant agents in patients below 75 years of age. The mean doses of aspirin increased somewhat. The number of subjects on antithrombotic treatment with the AF as the main or only indication increased from 27 (20.0%) to 59 (41.0%; $P = 0.000$), the number on anticoagulants increased from 6 (4.4%) to 16 (11.1%; $P = 0.039$) and the number on antiplatelet agents increased from 21 (15.6%) to 43 (29.2%; $P = 0.005$).

The use of anti-arrhythmic agents is shown in Table 3, where the only difference was an increased use of sotalol. In 1992–1993, one patient with ventricular arrhythmia was treated with amiodarone (in combination with metoprolol) and one with quinidine. In 1997–1998, one patient was treated with disopyramide (in combination with digoxin), after cardioversion, owing to recurrent AF. As regarded digoxin, in 1992–1993 it was used in 74 out of 110 patients (67.3%) on AF rhythm versus 5 out of 24 (20.8%) on sinus rhythm (SR; $P = 0.000$), and in 1997–1998 in 67 out of 109 patients (61.5%) on AF rhythm versus 11 out of 34 (32.4%) on SR ($P = 0.003$). Regarding sotalol, in 1992–1993 it was used in 9 out of 110 patients (8.2%) on AF rhythm versus 10 out of 24 (41.7%) on SR ($P = 0.000$), and in 1997–1998 in 20 out of 109 patients (18.3%) in AF rhythm versus 16 out of 34 (47.1%) on SR ($P = 0.001$).

Diuretic agents were used by 90 out of 134 patients (67.2%) in 1992–1993 versus by 79 out of 143 (55.2%) in 1997–1998 ($P = 0.042$), and ACE inhibitors by 21 out of 134 patients (15.7%) in 1992–1993 versus by 41 out of 143 (28.7%) in 1997–1998 ($P = 0.009$); in the latter period, angiotensin II inhibitors were used by 7 out of 143 patients (7.9%). The results of logistic regression are shown in Table 4, in which different patterns regarding the use any antithrombotic agent and anticoagulant agents between 1992–1993 and 1997–1998 can be seen.

Table 1 Patients with atrial fibrillation (*AF*) at a community health centre in Stockholm County. The figures are numbers, with standard deviations in parentheses, unless otherwise stated

	1992–1993 ($n = 135$)	1997–1998 ($n = 144$)	Difference 1992–1997
Demography			
Men	79 (58.5%)	87 (60.4%)	–
Women	56 (41.5%)	57 (39.4%)	–
Men [mean age (years)]	73.2 (8.9)	72.9 (9.4)	−0.3 ($P = 0.85$)
Women [mean age (years)]	77.7 (9.2)	76.5 (10.1)	−1.3 ($P = 0.48$)
All [mean age (years)]	75.2 (9.3)	74.7 (9.8)	−0.8 ($P = 0.51$)
Type of AF			$P = 0.04$
Paroxysmal	20 (14.8%)	14 (9.7%)	
Persistent, converted	4 (3.0%)	20 (13.9%)	
Persistent	1 (0.7%)	4 (2.8%)	
Permanent	110 (81.5%)	106 (73.6%)	
Co-morbidity			
Hypertension	36 (26.7%)	49 (34.0%)	$P = 0.182$
Ischaemic heart disease	40 (29.6%)	49 (34.0%)	$P = 0.431$
Heart failure	56 (41.8%)	61 (42.4%)	$P = 0.882$
Valvular disease	8 (5.9%)	9 (6.3%)	$P = 0.910$
Other heart disease	6 (4.4%)	7 (4.9%)	$P = 0.869$
Diabetes	21 (15.6%)	25 (17.4%)	$P = 0.685$
Previous AF-related thromboembolism	28 (20.7%)	36 (25.0%)	$P = 0.398$
Peripheral-artery disease	8 (5.9%)	6 (4.2%)	$P = 0.501$
Previous non-AF thromboembolism	9 (6.7%)	8 (5.6%)	$P = 0.698$
Earlier bleeding event	2 (1.5%)	4 (2.8%)	$P = 0.443$

Table 2 Antithrombotic treatment of patients with atrial fibrillation at a community health centre in Stockholm County. The figures are numbers, with percentages or standard variations (*SD*) in parentheses. Only significant *P* values are given

	1992–1993 (n = 135)	1997–1998 (n = 144)	Difference 1992–1997 (P value)
All patients			
Anticoagulant agent	35 (25.9%)	45 (31.3%)	–
Any antiplatelet agents	49 (36.3%)	69 (47.9%)	0.037
Dipyridamole	2[a]	2[b]	–
Aspirin	47	67	–
Any antithrombotic agent	84 (62.2%)	114 (79.2%)	0.001
Mean dose of aspirin (mg)	123 (SD: 46)	142 (SD: 67)	0.036*
Patients <75 years	(n = 58)	(n = 68)	
Anticoagulant agent	15 (25.9%)	26 (38.2%)	–
Antiplatelet agent	24 (41.4%)	31 (45.6%)	–
Any antithrombotic agent	39 (67.2%)	57 (83.8%)	0.029
Patients ≥75 years	(n = 77)	(n = 76)	
Anticoagulant agent	20 (26.0%)	19 (25.0%)	–
Antiplatelet agent	25 (32.5%)	38 (50.0%)	0.028
Any antithrombotic agent	45 (58.4%)	57 (75.0%)	0.030

[a] + One patient in whom dipyridamole is combined with anticoagulant agent or aspirin
[b] + Four patients in whom dipyridamole is combined with anticoagulant agent or aspirin
* One-tailed Student's *t*-test

Table 3 Anti-arrhythmic treatment of patients with atrial fibrillation at a community health centre in Stockholm County. The figures are numbers, with percentages in parentheses, unless otherwise stated. Significant *P* values in the χ^2 test are shown

	1992–1993 (n = 134)	1997–1998 (n = 143)	Difference 1992–1997
Digoxin	79 (59.0%)	78 (54.5%)	
β-*adrenergic blocking agents*	42 (31.3%)	63 (44.1%)	P = 0.025
Sotalol	19 (14.2%)	36 (25.2%)	P = 0.024
Selective β-1	20 (14.9%)	22 (15.4%)	
Unselective	3 (2.2%)	5 (3.5%)	
Calcium antagonists	19 (14.2%)	14 (9.8%)	
Verapamil	19 (14.2%)	13 (9.1%)	
Diltiazem	0	1 (0.7%)	
Other drugs	2 (1.5%)	1 (0.7%)	
Quinidine	1 (0.7%)	0	
Amiodarone	1 (0.7%)	0	
Disopyramide	0	1 (0.7%)	
Any anti-arrhythmic agent	111 (82.8%)	124 (86.7%)	

Table 4 Patients with atrial fibrillation (AF) at a community health centre in Stockholm County in 1992–1993 and 1997–1998. Logistic regression model with antithrombotic treatment and anticoagulant treatment as dependent factors, and sex, age, heart disease, AF rhythm (i.e. non-regular rhythm) AF-related thromboembolic complications and other, non-AF-related, thromboembolic disorders as dependent factors. Only significant figures are given; as regarded the use of antiplatelet agents, no significance was found. Age is per year. *CI* confidence interval

	1992–1993 (n = 135)			1997–1998 (n = 144)		
	Odds ratio	(95% CI)	P value	Odds ratio	(95% CI)	P value
Antithrombotic agent						
Age				0.91	(0.85–0.96)	0.002
Concomitant heart disease	5.05	(1.91–13.33)	0.001			
In AF rhythm				3.58	(1.27–10.03)	0.015
AF-related, thromboembolic events				14.68	(1.81–118.90)	0.012
Anticoagulant						
Age				0.90	(0.86–0.95)	0.000
Concomitant heart disease	8.60	(2.57–28.83)	0.000	2.75	(1.07–7.09)	0.037
AF-related, thromboembolic events	12.08	(3.80–38.43)	0.000	7.26	(2.72–19.33)	0.000
Non-AF, thromboembolic conditions	8.18	(1.80–37.13)	0.006			

Discussion

The percentage of AF patients on anticoagulation treatment (31%) is similar to that in an American study, (32%) conducted in 1992 and 1993 [9] and twice as high as that in a Spanish study (14%) [6], conducted from 1991 to 1993, and in a British study (18%) [10]. The frequency of treatment with antiplatelet agents was much higher in the British study, and increased during the 5-year period from 36 to 48% versus 10% in the American study [9] and 17% in the Spanish [6]. However, when comparing the age- and sex-standardized frequencies of warfarin treatment of AF in the Österåker community in Sweden with data from a Finnish study [11], the rate was found to be 35% lower [12].

It is also important that antithrombotic drugs are used in the right way, i.e. that patients with the highest risk of stroke are effectively treated [13]. The occurrence of concomitant heart disease and of an earlier, AF-related, thromboembolic event were significant factors in both 1992–1993 and 1997–1998 for warfarin treatment, i.e. for patients at the highest risk of stroke. However, according to the guidelines, more patients should be treated with anticoagulant agents and the doses of aspirin, when used, should be higher. In this regard, the situation is not satisfactory.

In a study by Monette et al. [14] of prescribing decisions, it was found that the doctor's concerns about the risk of bleeding appear to prevail over stroke prevention in patients over 75 years of age. In a cost-benefit analysis by Lightowlers and McGuire [5], the anticoagulant treatment of AF patients was found to be cost-effective, despite the higher risk of adverse events, as the incidence of stroke is higher. However, this is not generally accepted. Green et al. [15] performed a meta-analysis, in which they found that the margin between benefit and harm for warfarin prophylaxis in patients with non-valvular AF was uncomfortably thin, as the number of intracranial haemorrhages exceeded the number of embolic events prevented. Gustafsson et al. [16] stated that patients aged over 80 years of age were not eligible for treatment with anticoagulants, because the risk of cerebral haemorrhage was similar to the gain with treatment. The mean age of patients in the randomized trials was 69 years, while the median age for all patients with AF is approximately 75 years [1]. Independent risk factors for stroke in AF are advanced age, hypertension, previous stroke or TIA and diabetes [4], while among the risk factors for bleeding complications with warfarin are advanced age (>75 years), hypertension and previous cerebrovascular disease [17–20]. The rate of fatal and major bleedings has been estimated at 0.5% and 1.6%, respectively, in a review of ten studies [17]. The rate of bleeding complications may have been underestimated in these studies, and in the studies of the rates of fatal and major haemorrhages of 1.5% and 5.6%, respectively [20] and of 2.1% and 4.4%, respectively [21] in clinical patient populations.

The reluctance of general practitioners to initiate anticoagulant treatment in AF patients, especially in older patients, is thus understandable. Since half or more of the AF patients are above 75 years of age, this is a matter of great concern. There is a need for more studies regarding the safety of anticoagulant agents in older AF patients.

As regards the use of anti-arrhythmic agents, the extensive use of digoxin may be somewhat surprising, although it is the most common drug in this class. Digoxin was the only available drug for the control of ventricular rates in cases of chronic AF for many years, but its efficacy has been questioned [22]. Cobbe published an algorithm for treatment with β-adrenergic blocking agents or propafenone or flecainide in cases of paroxysmal AF or in maintaining SR post-cardioversion, and digoxin with the addition of a β-adrenergic blocking agent or verapamil/diltiazem for ventricular-rate control in cases of established AF [8]. Thus, digoxin could be claimed as the drug of first choice in cases of permanent AF, and most of the digoxin prescriptions in this study concern this indication. The use of sotalol increased, and it was mostly used in patients for SR, while the use of more potent anti-arrhythmic drugs, such as the class IA agents quinidine and disopyramide and the class II agent amiodarone, was limited to only a few patients. Sotalol combines the electrophysiological features of a β-adrenergic blocking agents (class II anti-arrhythmic) with those of a class III anti-arrhythmic agent, and thus holds an exceptional position among β-adrenergic blocking agents [23]. The use of the most effective drugs, amiodarone and quinidine, is limited by their adverse effects, including an increased mortality [22, 24]. Sotalol has been found to be as effective as quinidine and better tolerated [24], and therefore Cobbe [8] recommends it (or another β-adrenergic blocking agent) as the first choice in the management of paroxysmal AF or the prophylaxis of recurrence after cardioversion in patients with significant heart disease. However, sotalol is also accompanied by adverse effects, such as the risk of torsades de pointes, bradycardia and exacerbation of sick sinus syndrome [24]. Thus, there is as yet no ideal anti-arrhythmic drug for cases of AF.

The final conclusion is that there is an increase in the use of antithrombotic drugs, particularly aspirin, in stroke prevention in AF. However, more patients could benefit from anticoagulant treatment, and the doses of aspirin are lower than what has been found to be effective. However, there is still a lack of information regarding the safety of anticoagulant treatment for older patients, i.e. those over 75 or 80 years of age, and therefore the caution with regard to this treatment is justified.

References

1. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG (1995) Prevalence, age distribution, and gender of patients

with atrial fibrillation. Analysis and applications. Arch Intern Med 155: 469–473
2. Anonymous (1993) Treatment of atrial fibrillation. Recommendations from a workshop arranged by the Medical Products Agency (Uppsala, Sweden) and the Swedish Society of Cardiology. Eur Heart J 14: 1427–1433
3. Atrial fibrillation investigators (1994) Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. Arch Intern Med 154: 1449–1457
4. Koefoed BG, Gulløv AL, Petersen P (1997) Prevention of thromboembolic events in atrial fibrillation. Thromb Haemost 78: 377–381
5. Lightowlers S, McGuire A (1998) Cost-effectivenes of anticoagulation in nonrheumatic atrial fibrillation in the primary prevention of ischemic stroke. Stroke 29: 1827–1832
6. Llop R, Ferrer A, Agusti A, Vidal X, Arnau JM, Laporte JR (1997) From clinical trials to clinical practice: oral anticoagulation among patients with non-rheumatic, atrial fibrillation. Eur J Clin Pharmacol 53: 1–5
7. The Atrial Fibrillation Investigators (1997) The efficacy of aspirin in patients with atrial fibrillation. Analysis of pooled data from 3 randomized trials. Arch Intern Med 157: 1237–1240
8. Cobbe SM (1997) Using the right drug. A treatment algorithm for atrial fibrillation. Eur Heart J 18 (Suppl C): C33–C40
9. Stafford RS, Singer DE (1996) National patterns of warfarin use in atrial fibrillation. Arch Intern Med 156: 2537–2541
10. Sudlow M, Rodgers H, Kenny RA, Thomson R (1997) Population based study of use of anticoagulants among patients with atrial fibrillation in the community. BMJ 314: 1529–1530
11. Eskola K, Aittoniemi P, Kurunmäki H, Latva-Nevala A, Paloneva M, Wallin A, Viitaniemi M, Virjo I, Ylinen S, Öhman S, Isokoski M (1996) Anticoagulant treatment in health care in Finland. Scand J Prim Health Care 14: 165–170
12. Wändell PE (1998) Anticoagulant patients in Swedish primary health care. A comparison five years apart. Scand J Prim Health Care 16: 183–187
13. Lip GYH, Lowe GDO (1996) Warfarin and aspirin as thromboprophylaxis in atrial fibrillation. Br J Clin Pharmacol 41: 369–379
14. Monette J, Gurwitz JH, Rochon PA, Avorn J (1997) Physician attitudes concerning warfarin for stroke prevention in atrial fibrillation: results of a survey of long-term care practitioners. J Am Geriatr Soc 45: 1060–1065
15. Green CJ, Hadorn DC, Bassett K, Kazanjian A (1997) Anticoagulation in chronic nonvalvular atrial fibrillation: a critical appraisal and meta-analysis. Can J Cardiol 13: 811–815
16. Gustafsson C, Asplund K, Britton M, Norrving B, Olsson B, Marké LÅ (1992) Cost effectiveness of primary stroke prevention in atrial fibrillation: Swedish national perspective. BMJ 305: 1457–1460
17. Gulløv AL, Koefoed BG, Petersen P (1995) The bleeding risk in anticoagulant therapy [in Danish with English summary]. Nord Med 110: 114–118
18. Landefeld CS, Beyth RJ (1993) Anticoagulant-related bleeding: clinical epidemiology, prediction and prevention. Am J Med 95: 315–328
19. Launbjerg J, Egeblad H, Heaf J, Nielsen NH, Fugleholm AM, Ladefoged K (1991) Bleeding complications to oral anticoagulant therapy: multivariate analysis of 1010 treatment years in 551 outpatients. J Intern Med 229: 351–355
20. Sjöberg KH, Ormegard A, Hägglund H, Pettersson T (1995) Complications of anticoagulants. Frequency of fatal bleedings justifies more rigid indications [in Swedish]. Läkartidningen 34: 3006–3010
21. Wändell P (1998) A five-year follow-up of 115 patients treated with anticoagulants. Bleeding complications may be underestimated [English summary]. Läkartidningen 95: 3673–3674
22. Riley RD, Pritchett ELC (1997) Pharmacologic management of atrial fibrillation. J Cardiovasc Electrophysiol 8: 818–829
23. Mackstaller LL, Alpert JS (1997) Atrial fibrillation: a review of mechanism, etiology, and therapy. Clin Cardiol 20: 640–650
24. Ganz LI, Antman EM (1997) Antiarrhythmic drug therapy in the management of atrial fibrillation. J Cardiovasc Electrophysiol 8: 1175–1189