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Clinical consequences of hospital variation in use of oral anticoagulant therapy after first-time admission for atrial fibrillation

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Abstract. Hansen ML, Gadsbøll N, Rasmussen S, Gislason GH, Folke F, Andersen SS, Schramm TK, Sørensen R, Fosbøl EL, Abildstrøm SZ, Madsen M, Poulsen HE, Køber L, Torp-Pedersen C (Gentofte University Hospital, Hellerup; Sygehus Nord, Køge; National Institute of Public Health; Rigshospitalet-Copenhagen University Hospital; Glostrup Hospital; Rigshospitalet-Copenhagen University Hospital; University of Copenhagen; Copenhagen, Denmark). Clinical consequences of hospital variation in use of oral anticoagulant therapy after first-time admission for atrial fibrillation. *J Intern Med* 2009; **265**: 335–344.

Objective. To analyse how hospital factors influence the use of oral anticoagulants (OAC) in atrial fibrillation (AF) patients and address the clinical consequences of hospital variation in OAC use.

Design and subjects. By linkage of nationwide Danish administrative registers we conducted an observational study including all patients with a first-time hospitalization for AF between 1995 and 2004 as well as prescription claims for OAC. Multivariable logistic regression analysis was used to evaluate hospital factors associated with prescription of OAC therapy. Cox proportional-hazard models were used to estimate the risk of re-hospitalization for thromboembolism and haemorrhagic stroke with respect to discharge from a low, intermediate, or high OAC use hospital.

Results. Overall 40 133 (37%) out of 108 504 patients received OAC; ranging from 17% to 50% between the hospitals with the lowest and highest OAC use, respectively. Cardiology departments had the highest use of OAC, but neither tertiary university hospitals nor high volume hospitals had higher OAC use than local community hospitals and low volume hospitals. Risk of a thromboembolic event was significantly increased amongst patients from hospitals with a low OAC use (hazard ratio 1.16, confidence interval 1.10–1.22). Notably, higher OAC use was not associated with a higher risk of haemorrhagic stroke.

Conclusion. In Denmark between 1995 and 2004, there was a major hospital variation in AF patients receiving OAC, and consequently, more thromboembolic events were observed amongst patients from low OAC use hospitals. Our study emphasizes the need for a continued vigilance on implementation of international AF management guidelines.

Keywords: atrial fibrillation, epidemiology, hospital quality measurement, oral anticoagulant therapy, thromboembolism.

Introduction

Protecting patients with atrial fibrillation (AF) from ischaemic stroke and embolic manifestations is the main challenge for physicians treating patients with this increasingly common arrhythmia. Several clinical trials have demonstrated oral anticoagulation (OAC) therapy as the most effective way to prevent embolic manifestations, and as a consequence OAC is recommended to AF patients who have additional risk factors for stroke[1, 2]. Nevertheless, The Euro Heart Survey on Atrial Fibrillation, recently demonstrated that stroke risk assessment only marginally drives the decision to anticoagulate AF patients [3]. Whether small hospitals with few cardiologist and low degree of specialization perform equally well with regard to prescribing OAC therapy compared with larger institutions is uncertain. The purpose of the present observational study was to test two hypotheses. First, there is a considerable hospital variation in the prescribing of OAC for patients with AF. This variation can be linked to the degree of specialization and other hospital characteristics. Secondly, a low OAC prescription rate within a hospital has consequences for the occurrence of thromboembolic events. Therefore, we sought to analyse how hospital factors influenced the use of OAC in all 108 504 Danish patients surviving first-time admission for AF between 1995 and 2004. Furthermore, we addressed the clinical consequences of hospital variation in prescribing of OAC therapy.

Materials and methods

Hospital structure in Denmark

The Danish hospital sector is almost entirely public funded with free and equal access for all citizens. We classified public hospitals as tertiary hospitals, main regional hospital and local community hospitals. University-affiliated, highly specialized hospitals with cardiac care centers were defined as tertiary hospitals ($n = 5$), main regional hospitals ($n = 38$) were the district hospitals of the 15 Danish counties and local community hospitals ($n = 41$) were small hospitals with a low degree of specialization typically covering areas with a lower population-density. Hospital AF volume were defined as the total number of AF hospitalizations between 1995 and 2004 at each hospital and hospitals with a volume less than 100 AF hospitalizations were excluded from analysis ($n = 7$). The hospitals were classified into low, intermediate and high AF hospital volume tertiles. In total, 77 hospitals providing care for AF patients were included and of those 22 were closed or had stopped admitting AF patients by 2004. Hospital departments were classified as departments/divisions of cardiology or department/division of internal medicine. Noncardiology/internal medicine departments were categorized as 'other' departments.

Population

The Danish National Patient Registry contains administrative data for all hospitalizations in the country since 1978. From the registry we identified all Danish residents with a first-time hospitalisation for AF as primary or secondary diagnosis [International Classification of Diseases 10th revision (ICD-10) code I48] between January 1, 1995 and December 31, 2004. All patients aged 30 years or older were included. Those with a prior hospital diagnosis of AF were excluded. Only patients alive 30 days after discharge were included in the analysis. The identification of the study population has been described in more detail previously [4].

Pharmacotherapy

The Danish Registry of Medicinal Product Statistics includes information of all prescriptions dispensed from Danish pharmacies on the individual level since 1995. The pharmacies are required through Danish legalization to provide this information which ensures complete registration. Each prescribed drug is coded according to the Anatomical Therapeutical Chemical (ATC) classification. The registry also includes information about date of dispensing, strength, quantity dispensed and affiliation of the issuing physician. The registry has been found to be accurate and has been described in more detail previously [5, 6].

Oral anticoagulants therapy

By cross-linkage of the Danish National Patient Registry and The Danish Registry of Medicinal Product Statistics via the patient's unique civil registration number, patients with a first hospital diagnosis of AF and the proportion of these patients receiving OAC therapy [warfarin or phenprocoumon (ATC code B01AA03 and B01AA04, respectively)] after discharge were identified. Patients were defined as having OAC treatment initiated by the hospital if they had claimed at least one prescription of OAC within 90 days of discharge. Persistence to therapy was analysed by identifying subsequent prescriptions claims. The proportion of patients alive who were still receiving treatment 1, 2, 3, 4 and 5 years after their first prescription claim of OAC therapy was calculated. These methods have been described in details previously [7].

Concomitant medical therapy

Prescription claims of beta-blockers (ATC code C07), nondihydropyridine calcium-channel blockers (CCBs) [verapamil and diltiazem (ATC code C08D)], digoxin (ATC code C01A), sotalol (ATC code C07AA07), amiodarone (ATC code C01BD01) and Class 1C antiarrhythmics [propafenone (ATC code C01BC03) and flecainide (ATC code C01BC04)] within 90 days of discharge were identified and classified as concomitant medical therapy.

Co-morbidity

Co-morbidity is a potential confounder for initiation of preventive OAC therapy. We used ICD-10 discharge codes (Table 1) from prior hospitalizations up to 1 year before index hospitalization to define co-morbidity.

Outcome measures

The proportion of patients who claimed a prescription for OAC was analyzed according to clinical risk factors for thromboembolism as specified in the $CHADS_2$ index (heart failure, hypertension, age 75 or older, diabetes and ischaemic stroke) [8] and hospital factors (hospital AF volume, hospital type and type of department). Risk of re-hospitalization for thromboembolism, combined ischaemic stroke (ICD-10 code I63-I66) and systemic embolism (ICD-10 code I26 and I74), haemorrhagic stroke (ICD-10 code I60-62) and all-cause mortality were analysed separately with respect to whether the hospital had a low, intermediate or high (OAC hospital-tertiles) prescription rate of OAC. The ICD codes of ischaemic and haemorrhagic stroke in The Danish National Patient Registry have a positive predictive value of 97% and 74%, respectively [9].

Sensitivity analysis

To ensure that our results were not influenced by time changes in patient characteristics and medical care we analysed hospital variation in OAC use in five different time periods. From each time period the crude hospital variation between the low and high hospital OAC tertiles was estimated.

Statistical analysis

Multivariable logistic regression analysis was used to evaluate clinical risk factors for thromboembolism and hospital factors associated with prescription of OAC therapy. We used generalized estimating equations (GEE) models with robust standard errors to adjust for clustering of patients at hospitals. Cox proportional-hazard models were used to compare the risk between patients in the OAC hospital-tertiles of re-hospitalization for thromboembolism, haemorrhagic stroke and all-cause mortality, separately. Both models were adjusted for calendar year of index AF (1995–1996 as reference), age (30–59 years as reference), gender (women as reference), co-morbidity (no co-morbidity as reference), concomitant pharmaceutical treatment (none as reference) and the cluster effects of hospitals. Model assumptions – linearity of continuous variables, the proportional-hazard assumption and lack of interactions – were tested and found valid unless otherwise indicated. Patients were censored at the end of the study period (31 December 2004). 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 windows servers (SAS Institute Inc., Cary, NC, USA).

Table 1 Baseline characteristics of the study population

Characteristics	Total	Patients from low OAC hospital-tertile	Patients from intermediate OAC hospital-tertile	Patients from high OAC hospital-tertile
Total patients	108 504	23 195 (21.4%)	46 472 (42.8%)	38 837 (35.8%)
Females	50 755 (46.8%)	11 386 (49.1%)	21 789 (46.9%)	17 580 (45.3%)
AF primary diagnosis	54 766 (50.5%)	10 045 (47.2%)	23 905 (51.4%)	19 916 (51.3%)
Mean age at presentation (±SD, years)	73.0 (±12.1%)	74.0 (±11.9%)	72.5 (±12.2%)	72.8 (±11.9%)
Co-morbidity				
Ischaemic heart disease	19 867 (18.3%)	3 904 (16.8%)	8 891 (19.3%)	7 072 (18.2%)
Heart failure	21 010 (21.4%)	4 884 (21.1%)	8 861 (19.3%)	7 165 (18.5%)
Valvular heart disease	5 075 (4.7%)	775 (3.3%)	2 404 (5.2%)	1 896 (4.9%)
Hypertension	14 633 (13.5%)	2 936 (12.8%)	6 383 (13.7%)	5 287 (13.6%)
Ischaemic stroke	9 938 (9.2%)	2 286 (9.9%)	4 074 (8.8%)	3 578 (9.2%)
Systemic embolism	1 327 (1.2%)	289 (1.3%)	571 (1.2%)	467 (1.2%)
Haemorrhagic stroke	540 (0.5%)	113 (0.5%)	224 (0.5%)	203 (0.5%)
Peptic ulcer disease	1 929 (1.8%)	496 (2.1%)	799 (1.7%)	634 (1.7%)
Chronic pulmonary disease	9 388 (8.7%)	2 145 (9.3%)	3 874 (8.3%)	3 369 (8.7%)
Diabetes	9 227 (8.5%)	2 043 (8.8%)	3 969 (8.5%)	3 215 (8.3%)
Hyperthyroidism	2 820 (2.6%)	536 (2.3%)	1 111 (2.4%)	1 173 (3.0%)
Malignancy	3 401 (3.1%)	808 (3.5%)	1 525 (3.4%)	1 068 (2.8%)
$CHADS_2$ score ≥1	72 782 (67.1%)	16 420 (70.8%)	30 689 (66.0%)	25 673 (66.1%)
Therapy dispensed within 90 days of discharge				
Oral anticoagulants (OAC)	40 133 (37.0%)	7 061 (30.4%)	16 515 (35.5%)	16 557 (42.6%)
Beta-blockers	25 424 (23.4%)	3 979 (17.2%)	11 059 (23.8%)	10 386 (26.7%)
Nondihydropyridine CCBs	18 875 (17.4%)	4 772 (20.6%)	7 857 (16.9%)	6 246 (16.1%)
Digoxin	57 457 (53.0%)	13 478 (58.1%)	24 263 (52.2%)	19 716 (50.8%)
Sotalol	16 136 (24.9%)	2 739 (11.8%)	6 609 (14.2%)	6 788 (17.5%)
Amiodarone	4 778 (4.4%)	527 (2.3%)	2 128 (4.6%)	2 123 (5.5%)
Class 1C antiarrhythmics	2 869 (2.6%)	514 (2.2%)	1 359 (2.9%)	996 (2.6%)

SD, standard deviation; Nondihydropyridine CCBs, nondihydropyridine calcium channel blockers; AF, atrial fibrillation.
$CHADS_2$ score of 1 or more includes those patients with at least one of the following baseline characteristics; heart failure, hypertension, age more than 75 or ischaemic stroke.

Ethics

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

Results

Between 1995 and 2004 a total of 120 964 patients were hospitalized for first-time AF in Denmark. Excluding patients from hospitals with less than 100 AF admissions, 108,504 (89.7%) patients were alive 30 days after discharge and included into the study. Baseline characteristics of the population are shown in Table 1.

OAC therapy was mainly initiated early after discharge. Within 90 days 40 133 (37.0%) patients claimed a prescription of OAC. Only 5 023 (4.6%) patients claimed their first prescription between day 91 and 1 year after AF. The majority (80.3%) of first prescription of OAC therapy filled within 90 days was

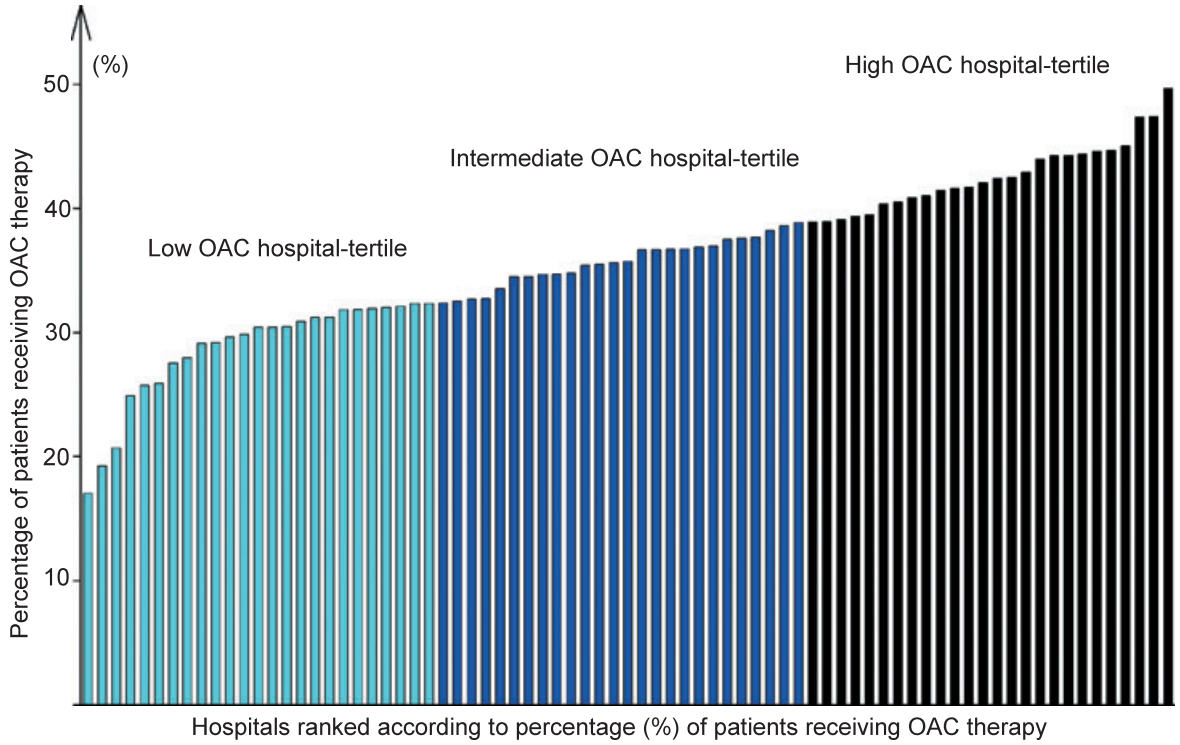

Fig. 1 The percentage of patients receiving oral anticoagulant (OAC) therapy in 77 Danish hospitals (ranked in tertiles according to use of OAC).

issued by a hospital physician. Nevertheless, the percentage of patients receiving OAC therapy ranged from 17.1% in the hospital with fewest patients receiving OAC to 49.7% in the hospital with the highest OAC-prescription rate (Fig. 1). OAC therapy was associated with a co-morbidity diagnosis of ischaemic stroke, heart failure and hypertension. In contrast, elderly patients were less likely to receive OAC than did those younger patients (Table 2). There was no association between AF hospital volume and the proportion of patients receiving therapy (Table 2). From tertiary hospitals, main regional hospitals and local community hospitals, 35.5%, 36.5% and 39.3% of the patients received OAC therapy, respectively (Tables 2 and 3). Patients admitted to cardiology departments were more frequently treated with OAC than patients discharged from departments of internal medicine and 'other' departments (Tables 2 and 3). The persistence to OAC therapy is illustrated in Fig. 2. Discontinuation of therapy was mainly observed within the first year after the first prescription claim of OAC (34% of those patients alive). After the first year the persistence to OAC therapy was stable and did not differ between the OAC hospital-tertiles.

In the low OAC hospital-tertile the patients (n = 23 195) were slightly older and more often females but did not differ with respect to co-morbidity (Table 1). Beta-blockade, sotalol, amiodarone and Class 1C antiarrhythmic therapy were also less frequent prescribed for these patients. In contrast, they more often received nondihydropyridine CCBs and digoxin therapy than patients in the high OAC hospital-tertile (Table 1).

Re-hospitalization for thromboembolism and haemorrhagic stroke

Results from the Cox proportional-hazard analysis for re-hospitalization for thromboembolism and haemorrhagic stroke between patients in the OAC hospital-tertiles are shown in Table 4. A total of

Table 2 Multivariate regression analysis of patient characteristics and hospital factors associated with atrial fibrillation patients receiving oral anticoagulant (OAC) therapy post discharge

Variable	Percentage (%) receiving OAC therapy	Adjusted odds ratio
$CHADS_2$ index		
Heart failure	38.6%	1.28 (1.23–1.32)
Hypertension	40.8%	1.11 (1.06–1.15)
Age 75 years or older	27.3%	0.50 (0.49–0.52)
Diabetes mellitus	35.3%	0.83 (0.79–0.87)
Stroke–ischaemic	41.3%	1.41 (1.35–1.48)
Hospital AF volume		
Low volume tertile	33.9%	0.97 (0.92–1.02)
Intermediate volume tertile	37.8%	1.06 (1.03–1.10)
High volume tertile	37.0%	1.00 (reference)
Type of hospital		
Tertiary University hospital	35.5%	0.83 (0.78–0.89)
Main regional hospitals	36.5%	0.91 (0.87–0.96)
Local community hospital	39.3%	1.00 (reference)
Type of Department		
Cardiology	40.1%	1.48 (1.40–1.56)
Medicine	37.1%	1.47 (1.40–154)
'Other'	29.2%	1.00 (reference)

AF, atrial fibrillation; OR, odds ratio; 95% CI, 95% confidence interval.
Multivariate logistic regression adjusted for calendar year, age, gender, co-morbidity, concomitant pharmaceutical treatment and clustering at the hospital level.

Table 3 The percentage of atrial fibrillation patients receiving oral anticoagulant therapy (OAC) according to type of hospital and department

Type of hospital	Tertiary hospital	Main regional hospital	Local community hospital
Type of department			
Cardiology	40.6%	39.7%	–
Medical	33.5%	36.7%	40.0%
'Other'	29.9%	29.0%	28.5%
Total	35.5%	36.5%	39.3%

14 579 (13.4%) patients were re-admitted for a thromboembolic event. The risk of thromboembolism was significantly higher amongst patients in the low OAC hospital-tertile. After dividing the patients into those receiving OAC and those not receiving OAC, risk was similar amongst patients receiving OAC therapy across the hospital-tertiles. However, in patients not receiving OAC therapy, a significantly higher risk of thromboembolism was observed in patients from the low OAC hospital-tertile compared with corresponding patients from the high OAC hospital-tertile. A total of 1 848 (1.7%) patients were re-hospitalized for haemorrhagic stroke. There was a small trend towards an increased risk of haemorrhagic stroke amongst patients in the high OAC hospital-tertile. A total of 44 229 (40.7%) patients in the cohort died. Mortality risk was slightly increased amongst patients in the low OAC hospital-tertile (Table 4).

Time-trend in OAC therapy

Use of OAC therapy increased over the period of observation, but the hospital variation persisted (Fig. 3). By 2003–2004, the risk of thromboembolism was still higher amongst patients from the lowest OAC hospital-tertile (hazard ratio 1.18, 95% confidence limits 1.04–1.36 using patients from the highest OAC hospital-tertile as reference).

Discussion

This nationwide study of 108 504 patients discharged after first-time hospitalization for AF between 1995 and 2004 demonstrated a considerably hospital variation with respect to OAC therapy practices. Furthermore, patients discharged from hospitals with low rates of OAC prescribing had higher risk of thromboembolic events and higher mortality, which could not be explained by higher co-morbidity or other patient characteristics. If OAC was prescribed early after discharge, persistence to therapy was stable and did not differ between hospitals with low or high OAC prescribing rates.

High versus low use of oral anticoagulants

The value of OAC therapy in AF patients with risk for stroke has been demonstrated in several

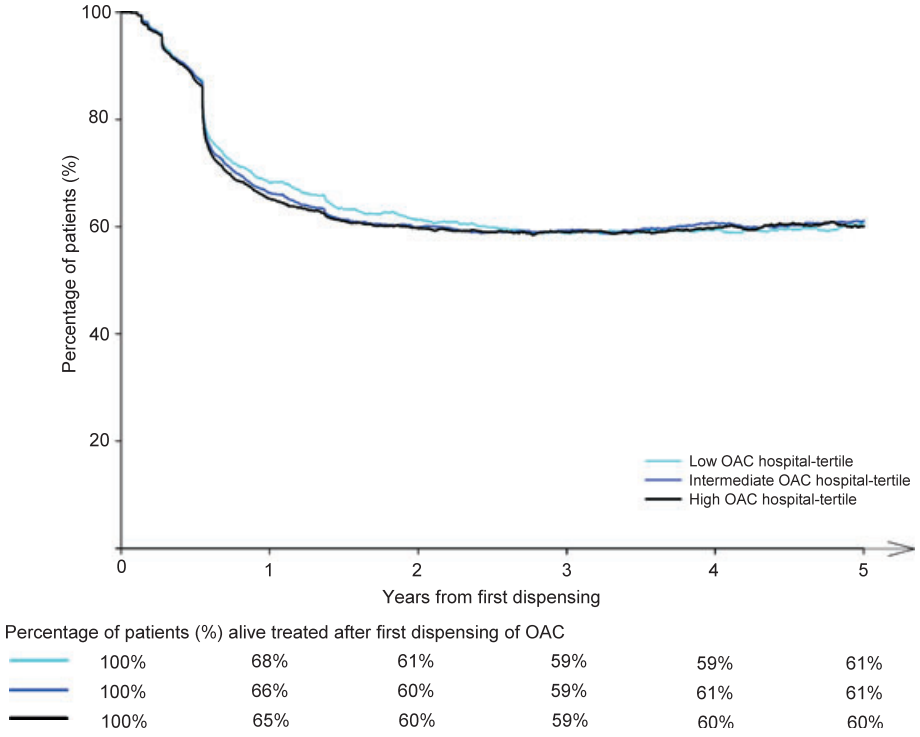

Fig. 2 Persistence of oral anticoagulant therapy (OAC) in atrial fibrillation patients from hospitals with low (low OAC hospital-tertile) intermediate (intermediate OAC hospital-tertile) and high (high OAC hospital-tertile) use of OAC therapy.

Table 4 Hazard ratios for thromboembolic event, haemorrhagic stroke and death in patients from hospitals with low (low OAC hospital-tertile) versus high (high OAC hospital-tertile) use of oral anticoagulant (OAC) therapy

	Patients from low OAC hospital-tertile	Patients from intermediate OAC hospital-tertile	Patients from high OAC hospital-tertile[a]
Hazard ratio with 95% confidence interval.			
Thromboembolism (combined ischaemic stroke and nonCNS systemic embolism)			
All AF patients	1.12 (1.07–1.17)	1.02 (0.98–1.06)	1.00
AF patients receiving OAC therapy	1.03 (0.96–1.11)	0.95 (0.88–1.01)	1.00
AF patients not receiving OAC therapy	1.16 (1.10–1.22)	1.06 (1.01–1.11)	1.00
Haemorrhagic stroke			
All AF patients	0.97 (0.85–1.09)	0.87 (0.79–0.97)	1.00
AF patients receiving OAC therapy	1.06 (0.88–1.28)	0.86 (0.74–1.05)	1.00
AF patients not receiving OAC therapy	0.96 (0.81–1.13)	0.92 (0.79–1.05)	1.00
Death			
All AF patients	1.04 (1.01–1.06)	1.00 (0.98–1.03)	1.00

CNS, central nervous system.
Cox proportional hazard analysis adjusted for calendar year, age, gender, co-morbidity, concomitant pharmaceutical treatment and clustering at the hospital level.
[a]Reference group.

studies [10–15]. Still, appropriate anticoagulation of AF patients remains a challenge. Several reports have demonstrated that use of OAC therapy is not consistent with an accurate assessment of the risks and benefits associated with treatment [16–24].

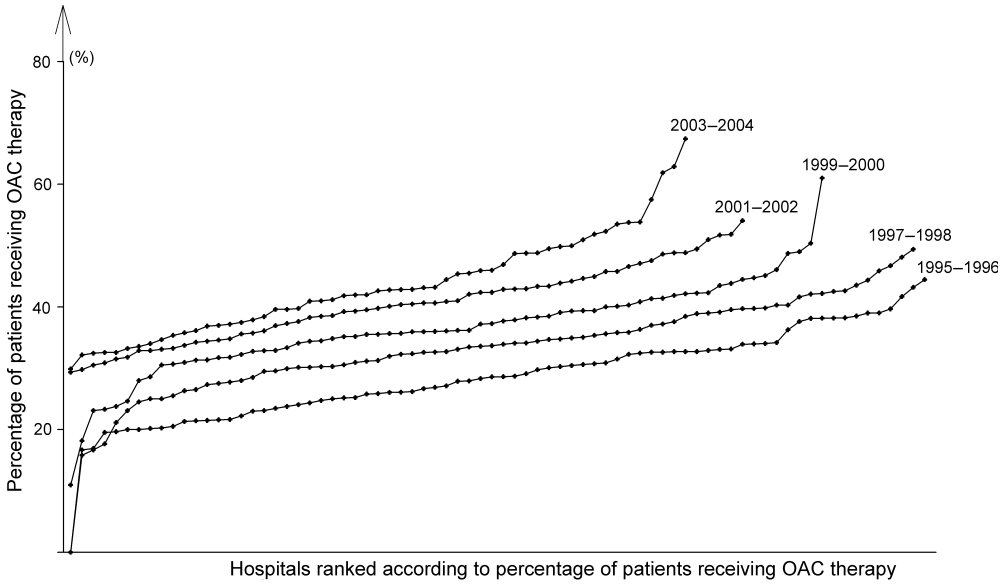

Fig. 3 The proportion of first-time hospitalized atrial fibrillation patients receiving oral anticoagulant therapy (OAC) between 1995–1996 and 2003–2004.

Somewhat surprisingly our study showed that small hospitals with few cardiologist and a low degree of specialization performed equally well with regard to prescribing OAC therapy compared with larger institutions. This is in contrast, to a large population-based study from Canada of elderly AF patients, which found that teaching hospital status were associated with a higher OAC use [25]. Munschauer *et al.* also found that discharge from a tertiary hospital in western New York was associated with a high prescription rate of OAC [26]. Therefore, person-related factors at the attending physician level or local tradition seem to play a role in Danish hospitals. This was emphasized by the finding that hospitals with low use of OAC also differed from hospitals with high use of OAC with respect to the antiarrhythmic treatment of patients with AF. Thus, low-OAC use hospitals used more digoxin and nondihydropyridine CCBs and less beta-blockers and Class I and III antiarrhythmics than hospitals with a high use of OAC, which could indicate a generally less individualized pharmacotherapy of AF in low OAC use hospitals.

Clinical consequences

Patients treated with OAC had the same persistence to therapy and the same risk of thromboembolism and haemorrhagic stroke irrespectively of whether they were discharged from a hospital with high or low use of OAC leaving no indication of a difference in quality of care once OAC was instituted. However, amongst those patients who did not receive OAC, risk of thromboembolism was higher in patients from hospitals with a low OAC use (Table 4) suggesting that hospitals with a high OAC use were better to select appropriate patients for thromboembolic prophylaxis.

An important finding in this respect was the vital role of the attending hospital physician, since the vast majority of patients who claimed their first prescription of OAC had their prescription issued by a

hospital physician. Thus, if the patient was not discharged with a prescription of OAC there was a small chance that the patient's general practitioner would initiate treatment. On the other hand we cannot rule out that all patients with an indication for OAC prophylaxis indeed received treatment at discharge or shortly after. Importantly, as illustrated in Fig. 2 the majority of patients receiving therapy after discharge continued OAC long-term, which is reassuring indicating that patients follows physicians instructions once therapy is started. This finding appears to be part of a general pattern where the long-term persistence to cardiac medication is high. We have provided similar findings with therapy specific for patients with acute myocardial infarction or heart failure [7, 27].

Limitations of the study

Due to the observational nature of this study there are important limitations that need to be acknowledged. Although the ICD codes in The Danish National Patient Registry have a very high positive predictive value for the diagnosis of AF, differences in coding praxis between the hospitals may have influenced the results [28]. Also, the sensitivity of a diagnosis of AF is unknown. Secondly, the study is based on administrative registries that do not include clinical data. Thus, precise indications and contraindications for OAC treatment of the individual AF patient are not available.

Clinical implications

A continuous focus on educating physicians to tailor OAC therapy according to the patient's risk profile is needed. In our study OAC use was associated with important risk factors for thromboembolism but awareness that advanced age is not a contraindication for OAC is needed [29]. A useful instrument to facilitate this could be one uniform and easy to use risk stratification scheme. Also, establishment of anticoagulation clinics might ensure higher rates of prescribing OAC therapy and safe follow up once therapy is instituted. Finally, to heighten patients' awareness of risks and benefits of OAC therapy education on this topic may help to further improve appropriate AF management.

Conclusion

In Denmark between 1995 and 2004, there was a major hospital variation in the prescription of OAC therapy to patients with AF. Surprisingly, local community hospitals with a low degree of specialization and a low AF volume were not associated with a low OAC use. Furthermore, the hospital variation had important clinical consequences with more thromboembolic events amongst patients from hospitals with a low OAC prescription rate. Our study emphasizes the need for an improved implementation of international guidelines for the management of patients with AF.

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Conflict of Interest statement

None declared.

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