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Pre-existing atrial fibrillation and risk of arterial thromboembolism and death following pneumonia: a population-based cohort study

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ABSTRACT

Objectives: To examine the effect of pre-existing atrial fibrillation (AF) and associated therapy on the risk of arterial thromboembolism (ATE) and death following pneumonia.

Design, setting and participants: Population-based cohort study (1997–2012) of 88 315 patients with first-time hospitalisation with pneumonia in Northern Denmark.

Results: Of the included patients (median age 73.4 years), 8880 (10.1%) had pre-existing AF. The risk of ATE within 30 days of admission was 5.2% in patients with AF and 3.6% in patients without AF. After adjustment for higher age and comorbidity, the adjusted HR (aHR) with AF was 1.06 (95% CI 0.96 to 1.18). Among patients with AF, reduced risk of ATE was observed in vitamin-K antagonist users compared with non-users (aHR 0.74 (95% CI 0.61 to 0.91)). Thirty-day mortality was 20.1% in patients with AF and 13.9% in patients without AF. Corresponding 1-year mortalities were 43.7% and 30.3%. The aHRs for 30-day and 1-year mortality with AF were 1.00 (95% CI 0.94 to 1.05) and 1.01 (95% CI 0.98 to 1.05). In patients with AF, reduced mortality risk was observed in users of vitamin-K antagonists (aHR 0.70 (95% CI 0.63 to 0.77)) and β-blockers (aHR 0.77 (95% CI 0.70 to 0.85). Increased mortality was found in digoxin users (aHR 1.16 (95% CI 1.06 to 1.28)).

Conclusions: Pre-existing AF is frequent in patients hospitalised with pneumonia and a marker of increased risk of ATE and death, explained by higher patient age and comorbidity. Prognosis is closely related to preadmission medical treatment for AF.

Strengths and limitations of this study

- Large cohort including 88 315 consecutive patients with first pneumonia hospitalisation.
- Complete follow-up data and reliable end points.
- Conduct within an equal access healthcare system.
- Use of detailed, high-quality registries allowed for extensive confounder adjustment.
- As in all observational studies, the presence of residual or unmeasured confounding cannot be excluded.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia. This condition affects 1.0–1.8% of the adult population in western countries and >10% of individuals ≥80 years of age.[1 2] Since the prevalence of AF increases with age, the numbers of patients with AF are expected to increase dramatically in the future.[1 2] While AF has been recognised as a major risk factor for all-cause death and stroke in the general population,[3–5] very little is known regarding the effect of AF on the prognosis of other acute disease, including severe infections.

Pneumonia remains a leading cause of death globally.[6] Survival has not improved and increasing incidence rates have been reported in recent years, probably because of the ageing population and increasing prevalence of comorbid conditions.[7 8] New onset of AF during pneumonia has been linked to poor prognosis,[9] but the prognostic effect of pre-existing AF on mortality and complications in patients with pneumonia has not been investigated. The pathophysiological alterations that occur during pneumonia may provoke complications (eg, haemodynamic instability and thromboembolic events) in patients with AF. A worsening of pre-existing cardiac diseases often occurs during pneumonia,[10] and the risk of stroke temporarily increases threefold in patients with pneumonia.[11] While AF might lead to increased mortality and complications following pneumonia, medications frequently prescribed to patients with AF such as vitamin-K antagonists and β-blockers might alter these associations.

Since both AF and pneumonia incidence rates are increasing, a negative prognostic impact of AF on the clinical course of pneumonia has important clinical and public health implications. We conducted a large population-based cohort study to examine the effects of pre-existing AF and concomitant drug therapy on the risk of arterial thromboembolism and death in patients with pneumonia.

METHODS

Setting

This cohort study was conducted using prospectively collected data obtained from medical registries within the North and Central Denmark Regions. This geographic area includes approximately 1.8 million inhabitants. Every Danish citizen is assigned a unique personal identification number that allows unambiguous cross-linking of registry data at the individual level. Tax-funded, unrestricted healthcare is provided for all Danish citizens through a national health insurance programme.

Identification of the study cohort

We included all first-time cases of hospitalised pneumonia (1 January 1997 to 31 December 2012) in patients aged ≥15 years in the study cohort. We used the Danish National Patient Register (DNPR) to identify the cohort members. The DNPR includes all hospital admissions and hospital outpatient clinic contacts from 1977 and 1995, respectively. The registry maintains data on admission and discharge dates, surgical procedure codes and diagnostic codes.[12]

Identification of patients with AF

Using DNPR data, we identified all cohort members who had received a diagnosis of AF within 5 years before the date of hospital admission for pneumonia. We included AF diagnoses given during previous hospitalisations and previous hospital outpatient clinic visits. Since very few cardiologists practise outside the Danish public hospital system, most patients with known AF are likely to be registered in the DNPR.

Comorbidity data

Adjustment for comorbidities in the mortality analyses was performed using data retrieved from the DNPR. These data included the 19 conditions in the Charlson Index, which has been validated for prediction of mortality following hospital admission.[13 14] We also noted previous diagnoses of valvular heart disease, alcoholism and obesity. We included the specific thromboembolism risk factors included in the CHA_2DS_2-VASc score (ie, congestive heart failure, hypertension, age, diabetes and previous stroke/transient cerebral ischaemic attack, vascular disease and sex) in the thromboembolism risk analyses. This scoring system has been validated for prediction of stroke risk in patients with AF.[15] We also summarised data on previous episodes of gastrointestinal bleeding and head injuries because these conditions could contraindicate anticoagulant treatment.

Data on preadmission prescriptions

The Aarhus University Prescription Database receives information on filled prescriptions from all pharmacies in the study area. We acquired data on filled prescriptions for the most commonly prescribed drugs in AF treatment (ie, vitamin K antagonists, aspirin, β-blockers, non-dihydropyridine calcium-channel blockers, amiodarone and digoxin) from this database.[16 17] We also included data on prescriptions for statins, which have been associated with favourable outcome in pneumonia.[18]

Markers of frailty and health awareness

We used data obtained from the National Health Service Register to further control for potential differences in patient frailty and health awareness. This registry of information on contacts with general practitioners (GPs) supplied data on preventive consultations, social-medicine-related consultations, conversational therapy at the GP within 1 year preceding pneumonia admission, influenza vaccination and application for reimbursement due to chronic or terminal illness.[19]

Outcomes

Outcomes were any hospitalised episodes of arterial thromboembolism within 30 days (index admission included), and death within 30 days and 1 year following the hospital admission date for pneumonia. Information on arterial thromboembolism was obtained from the DNPR. We defined arterial thromboembolism as an in-hospital diagnosis of non-haemorrhage stroke, or thrombosis or embolism in arteries of the extremities, the mesenteric arteries or in unspecified arteries. We assessed the vital statistics of each cohort member using the Civil Registration System (CRS). This database includes information on all individuals who have lived in Denmark at any time since 1968. The CRS is updated daily and records the date of birth and exact date of death or emigration.[20]

Statistical analyses

Follow-up began at hospital admission with pneumonia and continued until 1 January 2013, or until death or migration, whichever occurred first. We computed the cumulative incidence (risk) of arterial thromboembolism within 30 days of admission in patients with and without pre-existing AF and accounted for the competing risk of death in the analysis.[21] Further comparisons were performed using Cox regression analyses to estimate crude HRs, and HRs adjusted for the thromboembolism risk factors in the CHA_2DS_2-VASc score. We also performed an analysis stratified by the presence or absence of previously diagnosed arterial thromboembolism to examine whether an association between pre-existing AF and development of arterial thromboembolism was related to repeated events. Among patients with and without AF,

the effect of preadmission treatment with vitamin K antagonists or aspirin on risk of arterial thromboembolism was evaluated by comparing users to non-users. We repeated the analyses for patients without contraindications for anticoagulant therapy. All diagnoses coded during a given admission were assigned to the same discharge date in the DNPR. Consequently, we were unable to assess the actual temporal relationship between pneumonia onset and arterial thromboembolism in patients treated for the two conditions during the same admission. Arterial thromboembolism might have preceded pneumonia in some patients. Thus, we reassessed the 30-day risk of arterial thromboembolism, and only considered diagnoses assigned after discharge from the index pneumonia admission.

Cumulative mortality risks at 30 days and 1 year after admission with pneumonia in patients with and without AF were assessed using the Kaplan-Meier method and compared using Cox regression. The HRs were adjusted for sex and age. Further adjustments were performed for the conditions included in the Charlson Index, and for valvular heart disease, alcoholism and obesity, and GP contacts regarding preventive consultations, social-medicine-related consultations, conversational therapy, vaccination for influenza and reimbursement due to chronic or terminal illness. To examine whether the association between AF and pneumonia mortality was related to coexisting cardiovascular diseases or pneumonia severity, the analyses were repeated using stratification by previous myocardial infarction, congestive heart failure, treatment with mechanical ventilation, and admission to the intensive care unit during the index admission.

We also stratified the data by AF status and compared mortality at 30 days and 1 year in users and non-users of vitamin K antagonists, aspirin, β-blockers, calcium-channel blockers, digoxin, amiodarone and statins using the Kaplan-Meier method and Cox regression analyses. Crude HRs and HRs adjusted for the potential confounders described above were estimated from the Cox regression analyses.

All Cox analyses were preceded by a graphical verification of the proportional hazards assumption. Statistical analyses were performed using Stata V.11.2 software (StataCorp, College Station, Texas, USA).

Ethics

The study protocol was approved by the Danish Data Protection Agency (record numbers 2009-41-3866 and 2013-41-1924). Informed consent from the participants was not required.

RESULTS

Of the 88 315 patients hospitalised for pneumonia between 1997 and 2012, 8880 (10.1%) had a previous diagnosis of AF (table 1). Follow-up data were incomplete for 149 individuals. Patients with AF were older than patients without AF (median age 80.0 vs 72.3 years), yet the proportion of males was higher among patients with AF than among patients without AF (58.0% vs 52.5%). Compared with patients without AF, patients with AF had a substantially higher burden of comorbidity and were more likely to have coexisting cardiac diseases (eg, previous myocardial infarction (18.6% vs 8.3%) and congestive heart failure (34.8% vs 7.2%)). Patients with AF were as likely to be admitted to the intensive care unit (ICU; 7.5% vs 7.0%) and to be treated with mechanical ventilation (4.9% vs 5.3%) as patients without AF.

Risk of arterial thromboembolism

Within 30 days from admission, the cumulative incidence of arterial thromboembolism was 3.6% in patients without AF and 5.2% in patients with AF (table 2). The HR for arterial thromboembolism was 1.61 (95% CI 1.46 to 1.78). After adjustment for prevalence of the risk factors in the CHA_2DS_2-VASc-score, the HR decreased substantially to 1.06 (95% CI 0.96 to 1.18). In patients without previous stroke, the HR for arterial thromboembolism adjusted for the CHA_2DS_2-VASc risk factors was 0.97 (95% CI 0.83 to 1.14), and the adjusted HR for patients who had a previous stroke was 1.17 (95% CI 1.02 to 1.35). The incidence for episodes of arterial thromboembolism recorded after discharge from the index pneumonia admission was 0.8% in patients with AF and 0.5% in patients without AF (aHR=1.13 (95% CI 0.87 to 1.47).

Effect of preadmission drug use on risk of arterial thromboembolism

In patients with AF, users of vitamin K antagonists had a markedly lower risk of arterial thromboembolism compared with non-users (aHR=0.74 (95% CI 0.61 to 0.91; table 2). Users of aspirin had an adjusted HR of 0.83 (95% CI 0.68 to 1.01). The exclusion of patients with potential contraindications for anticoagulant therapy did not change the results (see online supplementary table S2).

In patients with AF without and with previous stroke, users of vitamin K antagonists had similar adjusted HRs for arterial thromboembolism (HR=0.74 (95% CI 0.54 to 1.01) and HR=0.74 (95% CI 0.57 to 0.96), respectively), compared with non-users of vitamin K antagonists. Users of aspirin had adjusted HRs for arterial thromboembolism of 0.89 (95% CI 0.66 to 1.20) and 0.78 (95% CI 0.61 to 1.01), compared with non-users of aspirin.

Mortality

The 30-day mortality rate was 20.1% in patients with AF and 13.9% in patients without AF (table 3). The effect of AF differed little between men and women. The presence or absence of previous myocardial infarction had limited effect on the estimates. Mortality rates were substantially higher in patients with congestive heart failure compared with patients without heart failure, but coexisting AF and heart failure in patients only resulted in a minor increase in mortality rate compared with patients with heart

Table 1 Characteristics of 88 315 patients admitted to hospital with pneumonia according to pre-existing atrial fibrillation

	No AF, n (%)	AF, n (%)	Total, n (%)
All patients	79 435 (89.9)	8880 (10.1)	88 315 (100.0)
Age, median (IQR), years	72.3 (59.2–81.5)	80.0 (73.3–85.4)	73.4 (60.6–82.1)
Female	37 751 (47.5)	3738 (42.1)	41 489 (47.0)
Male	41 684 (52.5)	5142 (58.0)	46 826 (53.0)
Admission period			
1997–2001	20 555 (25.9)	1730 (19.5)	22 285 (25.2)
2002–2006	26 552 (33.4)	2839 (32.0)	29 391 (33.3)
2007–2012	32 328 (40.7)	4311 (48.6)	36 639 (41.5)
Comorbidities, Charlson Index			
Myocardial infarction	6605 (8.3)	1654 (18.6)	8259 (9.4)
Congestive heart failure	5724 (7.2)	3090 (34.8)	8814 (9.98)
Peripheral vascular disease	6496 (8.2)	1365 (15.4)	7861 (8.9)
Cerebrovascular disease	11 234 (14.1)	2434 (27.4)	13 668 (15.5)
Dementia	1764 (2.2)	346 (3.9)	2110 (2.4)
Chronic pulmonary disease	15 101 (19.0)	2305 (26.0)	17 406 (19.7)
Connective tissue disease	4165 (5.2)	624 (7.0)	4789 (5.4)
Ulcer disease	6542 (8.2)	1013 (11.4)	7555 (8.6)
Mild liver disease	1540 (1.9)	132 (1.5)	1672 (1.9)
Diabetes, types I and II	6159 (7.8)	1315 (14.8)	7474 (8.5)
Hemiplegia	545 (0.7)	47 (0.5)	592 (0.7)
Moderate to severe renal disease	2885 (3.6)	790 (8.9)	3675 (4.2)
Diabetes with end-organ failure	3224 (4.1)	791 (8.6)	3985 (4.5)
Any tumour	12 536 (15.8)	1743 (19.6)	14 279 (16.2)
Leukaemia	855 (1.1)	87 (1.0)	942 (1.1)
Lymphoma	1561 (2.0)	178 (2.0)	1.739 (2.0)
Moderate to severe liver disease	463 (0.6)	47 (0.5)	510 (0.6)
Metastatic solid tumour	2.649 (3.3)	267 (3.0)	2916 (3.3)
AIDS	105 (0.1)	2 (0.0)	107 (0.1)
Comorbidities, other types			
Valvular heart disease	2798 (3.5)	1309 (14.7)	4107 (4.7)
Hypertension	13 905 (17.5)	3623 (40.8)	17 528 (19.8)
Transient cerebral ischaemic attack	3101 (3.9)	732 (8.2)	3833 (4.3)
Obesity	3144 (4.0)	577 (6.5)	3721 (4.2)
Alcoholism	3865 (4.9)	301 (3.4)	4166 (4.7)
Frailty and health awareness markers			
Influenza vaccination given	13 456 (16.9)	2506 (28.2)	15 962 (18.1)
Preventive GP consultation	13 148 (16.6)	2065 (23.3)	15 213 (17.2)
Social medicine GP consultation	9908 (12.5)	1722 (19.4)	11 630 (13.2)
GP conversational therapy	4610 (5.8)	452 (5.1)	5062 (5.7)
Reimbursement for chronic illness	2097 (2.6)	294 (3.3)	2391 (2.7)
Reimbursement for terminal illness	281 (0.4)	34 (0.4)	315 (0.4)
CHA_2DS_2-VASc score*			
0	11 420 (14.4)	183 (2.1)	11 603 (13.1)
1	17 576 (22.1)	580 (6.5)	18 156 (20.6)
2+	50 439(63.5)	8117 (91.4)	58 556 (66.3)
Admission variables			
Intensive care unit admission	5588 (7.0)	669 (7.5)	6257 (7.1)
Mechanical ventilation	4189 (5.3)	438 (4.9)	4627 (5.2)
Non-invasive ventilation	1666 (2.1)	197 (2.2)	1863 (2.1)
Preadmission cardiovascular drug use			
Statins	10 145 (12.8)	2097 (22.6)	12 242 (13.9)
Aspirin	14 944 (18.8)	3251 (36.6)	18 195 (20.6)
Vitamin K-antagonists	2207 (2.8)	3396 (38.2)	5603 (6.3)
β-Blockers	11 967 (15.1)	3878 (43.7)	15 845 (17.9)
Non-dihydropyridine CCBs†	2415 (3.0)	859 (9.7)	3274 (3.7)
Digoxin	3307 (4.2)	3622 (40.8)	6929 (7.9)
Amiodarone	319 (0.4)	685 (7.7)	1004 (1.1)

*Disease categories in the CHA_2DS_2-VASc score include congestive heart failure, hypertension, age >75 years (double weight), diabetes, previous stroke (double weight), vascular disease, age >65 years, and sex category (female=1, male=0).
†Non-dihydropyridine calcium-channel blockers.
AF, atrial fibrillation; CCBs, calcium-channel blockers; GP, general practitioner.

Table 2 Risk of arterial thromboembolism* within 30 days following admission for pneumonia, by atrial fibrillation status

	No AF	AF
Overall		
Cumulative incidence, %	3.6 (3.1 to 3.4)	5.2 (4.7 to 5.7)
HRs		
Crude	1.00 (ref)	1.61 (1.46 to 1.78)
Adjusted for CHA_2DS_2-VASc†	1.00 (ref)	1.06 (0.96 to 1.18)
Vitamin K antagonists		
Cumulative incidence, %		
Non-users	3.2 (3.1 to 3.4)	5.7 (5.1 to 6.4)
Users	4.2 (3.4 to 5.0)	4.3 (3.7 to 5.0)
HRs		
Non-user	1.00 (ref)	1.00 (ref)
Users, Crude	1.29 (1.05 to 1.59)	0.74 (0.61 to 0.90)
Adjusted for CHA_2DS_2-VASc†	0.97 (0.79 to 1.20)	0.74 (0.61 to 0.91)
Aspirin		
Cumulative incidence, %		
Non-users	2.9 (2.8 to 3.0)	5.3 (4.8 to 5.9)
Users	4.8 (4.5 to 5.2)	5.0 (4.3 to 5.8)
HRs		
Non-users	1.00 (ref)	1.00 (ref)
Users, crude	1.69 (1.55 to 1.84)	0.94 (0.78 to 1.14)
Adjusted for CHA_2DS_2-VASc†	0.96 (0.88 to 1.06)	0.83 (0.68 to 1.01)

Cumulative incidence values were computed with non-stroke associated death as a competing risk.
95% CIs are presented in parentheses.
*Defined as a diagnostic code for ischaemic stroke, unspecified stroke, thrombosis, or embolism in arteries of the extremities, mesenteric arteries, or unspecified arteries assigned during index admission or subsequent admissions.
†Adjusted for prevalence of the risk factors included in the CHA_2DS_2-VASc-score (ie, congestive heart failure, hypertension, age, diabetes, previous stroke, vascular disease and sex).
AF, atrial fibrillation; HR, hazard ratio.

failure only (23.7% vs 21.2%). In patients treated with mechanical ventilation, 30-day mortality was 34.6% in patients with AF and 27.8% in patients without AF.

The overall HR for death at 30 days following admission was 1.49 (95% CI 1.42 to 1.57) (table 3). After controlling for the effect of age and sex, the estimate decreased to 1.08 (95% CI 1.03 to 1.14). Further adjustment for comorbid conditions and lifestyle factors resulted in an HR of 1.00 (95% CI 0.94 to 1.05). Likewise, analyses comparing patients with and without AF and stratified by sex, previous myocardial infarction, congestive heart failure, ICU admission and mechanical ventilation yielded HRs close to a value of one in the fully adjusted model.

One-year mortality was 43.7% in patients with AF and 30.3% in patients without AF. The corresponding fully adjusted HR was 1.01 (95% CI 0.98 to 1.05). Similar estimates were obtained when the analyses were stratified according to sex, previous myocardial infarction, heart failure and ICU admission (table 3).

Effect of preadmission drug use on mortality

At 30 days of follow-up in patients with AF, the adjusted HR for death comparing users to non-users of vitamin K antagonists was 0.70 (95% CI 0.63 to 0.77) (table 4). Similarly, reduced mortality was observed in patients with AF who used β-blockers (aHR=0.77 (95% CI 0.70 to 0.85)) and statins (aHR=0.70 (95% CI 0.61 to 0.80)). No difference in mortality was observed in users compared with non-users of aspirin (aHR=0.98 (95% CI 0.89 to 1.08)). The values for the estimates changed very little when the follow-up period was extended to 1 year (table 4).

Increased 30-day mortality was observed in patients with AF who were users of amiodarone (aHR=1.18 (95% CI 1.00 to 1.42)) and users of digoxin (aHR=1.16 (95% CI 1.06 to 1.28)) (table 4). Uses of amiodarone and digoxin were also associated with increased 1-year mortality. Also, the use of calcium-channel blockers was associated with an increased 30-day mortality (aHR=1.17 (95% CI 1.00 to 1.36)), but no difference was observed for 1-year mortality (aHR=1.03 (95% CI 0.93 to 1.15) (table 4).

DISCUSSION

In this population-based study of 88 315 patients hospitalised with pneumonia, we found that compared with patients without AF, patients with pre-existing AF had a 60% higher risk of arterial thromboembolism within 30 days of admission and 50% higher mortality after 30 days and 1 year. However, after controlling for other prognostic factors associated with AF, the excess risk of arterial thromboembolism and mortality was found to be related to major differences in age and coexisting diseases, rather than to AF directly.

There was a robust association between preadmission use of vitamin K antagonists and reduced risk of arterial

Table 3 Mortality rates and HRs at 30 and 365 days following admission, by atrial fibrillation status

	No AF, %	AF, %	Crude HR*	Adjusted HR, step 1*†	Adjusted HR, step 2*‡
30-day mortality					
Overall	13.9 (13.7 to 14.1)	20.1 (19.3 to 21.0)	1.49 (1.42 to 1.57)	1.08 (1.03 to 1.14)	1.00 (0.94 to 1.05)
Sex					
Male	14.5 (14.2 to 14.9)	20.4 (19.3 to 21.5)	1.45 (1.36 to 1.55)	1.09 (1.02 to 1.16)	1.01 (0.95 to 1.09)
Female	13.3 (12.9 to 13.6)	19.7 (18.5 to 21.0)	1.53 (1.42 to 1.66)	1.07 (0.99 to 1.16)	0.97 (0.90 to 1.06)
Previous myocardial infarction					
Not present	13.7 (13.4 to 13.9)	20.1 (19.1 to 21.0)	1.52 (1.44 to 1.60)	1.08 (1.02 to 1.14)	0.98 (0.93 to 1.04)
Present	16.8 (15.9 to 17.7)	20.4 (18.5 to 22.4)	1.24 (1.09 to 1.40)	1.12 (0.99 to 1.27)	1.06 (0.93 to 1.20)
Congestive heart failure					
Not present	13.4 (13.1 to 13.6)	18.2 (17.2 to 19.2)	1.40 (1.31 to 1.49)	1.01 (0.95 to 1.08)	0.98 (0.92 to 1.05)
Present	21.2 (20.1 to 22.2)	23.7 (22.2 to 25.2)	1.13 (1.03 to 1.24)	1.06 (0.97 to 1.16)	1.04 (0.95 to 1.14)
ICU admission					
No	13.1 (12.9 to 13.4)	19.1 (18.3 to 20.0)	1.50 (1.43 to 1.59)	1.08 (1.02 to 1.14)	0.99 (0.93 to 1.04)
Yes	24.8 (23.7 to 25.9)	32.1 (28.7 to 35.8)	1.38 (1.20 to 1.59)	1.05 (0.91 to 1.22)	1.05 (0.90 to 1.22)
Mechanical ventilation					
No	13.2 (12.9 to 13.4)	19.4 (18.5 to 20.2)	1.52 (1.44 to 1.60)	1.08 (1.03 to 1.14)	0.99 (0.94 to 1.05)
Yes	27.8 (26.5 to 29.2)	34.6 (30.4 to 39.3)	1.33 (1.12 to 1.58)	1.05 (0.89 to 1.25)	1.06 (0.89 to 1.27)
365-day mortality					
Overall	30.3 (30.0 to 30.6)	43.7 (42.7 to 44.7)	1.57 (1.52 to 1.63)	1.14 (1.10 to 1.18)	1.01 (0.98 to 1.05)
Sex					
Male	31.8 (31.3 to 32.2)	43.9 (41.8 to 45.0)	1.50 (1.43 to 1.57)	1.12 (1.07 to 1.17)	1.01 (0.96 to 1.06)
Female	28.7 (28.2 to 29.1)	43.4 (42.5 to 45.3)	1.66 (1.58 to 1.75)	1.17 (1.11 to 1.24)	1.01 (0.96 to 1.07)
Previous myocardial infarction					
Not present	29.5 (29.2 to 29.9)	43.6 (42.4 to 44.7)	1.61 (1.55 to 1.68)	1.15 (1.10 to 1.19)	1.02 (0.98 to 1.06)
Present	38.7 (37.5 to 39.9)	44.3 (41.9 to 46.7)	1.20 (1.10 to 1.30)	1.09 (1.01 to 1.19)	0.99 (0.91 to 1.08)
Congestive heart failure					
Not present	29.0 (28.7 to 29.4)	40.6 (39.3 to 41.9)	1.50 (1.44 to 1.57)	1.08 (1.04 to 1.13)	1.02 (0.98 to 1.07)
Present	46.7 (45.4 to 47.9)	49.5 (47.7 to 51.3)	1.09 (1.02 to 1.16)	1.03 (0.97 to 1.10)	1.01 (0.95 to 1.08)
ICU admission					
No	29.5 (29.2 to 29.7)	42.3 (41.9 to 44.1)	1.58 (1.53 to 1.65)	1.14 (1.10 to 1.18)	1.00 (0.97 to 1.04)
Yes	40.5 (39.2 to 41.8)	52.3 (48.6 to 56.2)	1.43 (1.27 to 1.60)	1.09 (0.97 to 1.22)	1.07 (0.95 to 1.20)
Mechanical ventilation					
No	29.6 (29.27 to 29.9)	43.1 (42.0 to 44.2)	1.59 (1.54 to 1.65)	1.14 (1.10 to 1.18)	1.01 (0.97 to 1.04)
Yes	42.8 (41.3 to 44.3)	54.9 (50.2 to 59.7)	1.41 (1.24 to 1.62)	1.10 (0.96 to 1.26)	1.11 (0.96 to 1.28)

*Reference group: patients without AF.
†Step 1: adjusted for age and sex.
‡Step 2: adjusted for age, sex, the 19 individual disease categories in the Charlson Index, hypertension, heart valve disease, transient cerebral ischaemic attack, obesity, alcoholism, and contacts with the general practitioner regarding preventive consultations, social-medicine-related consultations, conversational therapy, vaccination for influenza, and reimbursement due to chronic or terminal illness.
AF, atrial fibrillation; HR, hazard ratio; ICU, intensive care unit.
95% CIs are presented in parentheses.

thromboembolism following pneumonia in patients with AF. We also observed markedly reduced risks of death in patients with AF who were treated with statins, β-blockers or vitamin K antagonists. However, compared with non-users, there was an increased risk of death in users of amiodarone and digoxin.

Strengths and limitations

The risk of selection bias was minimal in this study because we used population-based data with virtually complete follow-up. A positive predictive value of 90% has been estimated for the pneumonia diagnoses recorded in the DNPR; 87% of the cases represent community-acquired infections.[22] Atrial fibrillation is also accurately coded in the DNPR. Positive predictive value estimates range from 93% to 99%.[23–25] Since AF and atrial flutter share the same code in the DNPR, we were unable to distinguish between these arrhythmias. However, of patients coded with atrial fibrillation/flutter, only 5–6% have atrial flutter.[23–25] The coding system also did not allow for differentiation between paroxysmal, persistent and permanent AF. Finally, the DNPR's positive predictive value for ischaemic stroke is 88–100%. Of the patients coded with unspecified stroke, 57–70% have ischaemic stroke.[26 27]

Since we used filled prescriptions as a measure of actual drug intake, non-adherence or treatment discontinuation before admission could have biased the effect of any given drug towards the null value. However, we concluded that this source of bias was a low concern for

Table 4 Effects of preadmission drug use on mortality at 30 and 365 days, by atrial fibrillation status

	Non-users, %	Users, %	Crude HR*	Adjusted HR, step 1*†	Adjusted HR, step 2*‡
30-day mortality					
Vitamin K antagonists					
No AF	13.9 (13.7 to 14.2)	13.8 (12.4 to 15.3)	0.99 (0.88 to 1.11)	0.87 (0.77 to 0.97)	0.83 (0.74 to 0.93)
AF	23.2 (22.1 to 24.3)	15.2 (14.0 to 16.4)	0.62 (0.56 to 0.69)	0.69 (0.62 to 0.76)	0.70 (0.63 to 0.77)
Aspirin					
No AF	13.2 (13.0 to 13.5)	17.0 (16.4 to 17.6)	1.31 (1.25 to 1.37)	0.95 (0.90 to 0.99)	0.89 (0.85 to 0.93)
AF	19.6 (18.6 to 20.7)	21.0 (19.6 to 22.4)	1.07 (0.97 to 1.18)	0.99 (0.89 to 1.08)	0.98 (0.89 to 1.08)
β-Blockers					
No AF	13.7 (13.5 to 14.0)	15.0 (13.3 to 15.6)	1.09 (1.04 to 1.15)	0.93 (0.88 to 0.97)	0.90 (0.86 to 0.96)
AF	22.4 (21.2 to 23.6)	17.2 (16.0 to 18.4)	0.74 (0.68 to 0.82)	0.78 (0.71 to 0.86)	0.77 (0.70 to 0.85)
Calcium-channel blockers					
No AF	13.8 (13.6 to 14.1)	16.7 (15.27 to 18.2)	1.23 (1.11 to 1.36)	1.00 (0.91 to 1.11)	1.05 (0.95 to 1.16)
AF	20.0 (19.2 to 20.9)	20.1 (18.4 to 23.9)	1.06 (0.90 to 1.23)	1.10 (0.95 to 1.29)	1.17 (1.00 to 1.36)
Statins					
No AF	14.3 (14.0 to 14.6)	11.3 (10.7 to 12.0)	0.78 (0.73 to 0.83)	0.75 (0.70 to 0.80)	0.69 (0.64 to 0.73)
AF	21.67 (20.7 to 22.7)	15.0 (13.5 to 16.6)	0.67 (0.59 to 0.75)	0.75 (0.66 to 0.84)	0.70 (0.61 to 0.80)
Amiodarone					
No AF	13.9 (13.7 to 14.1)	19.8 (15.8 to 24.6)	1.46 (1.14 to 1.87)	1.25 (0.98 to 1.60)	1.23 (0.96 to 1.58)
AF	20.1 (19.2 to 21.0)	20.3 (17.5 to 23.5)	1.02 (0.86 to 1.21)	1.21 (1.02 to 1.44)	1.18 (1.00 to 1.42)
Digoxin					
No AF	13.5 (13.2 to 13.7)	24.0 (22.5 to 25.5)	1.90 (1.76 to 2.04)	1.26 (1.17 to 1.36)	1.23 (1.15 to 1.33)
AF	18.4 (17.4 to 19.5)	22.5 (21.2 to 23.9)	1.25 (1.14 to 1.37)	1.19 (1.08 to 1.31)	1.16 (1.06 to 1.28)
365-day mortality					
Vitamin K antagonists					
No AF	30.2 (29.9 to 30.6)	34.3 (32.3 to 36.3)	1.15 (1.07 to 1.24)	0.99 (0.92 to 1.07)	0.92 (0.85 to 0.99)
AF	48.9 (47.6 to 50.3)	35.2 (33.4 to 36.9)	0.64 (0.60 to 0.69)	0.70 (0.65 to 0.75)	0.72 (0.67 to 0.77)
Aspirin					
No AF	28.7 (28.3 to 29.0)	37.5 (36.7 to 38.3)	1.38 (1.34 to 1.42)	1.00 (0.97 to 1.03)	0.91 (0.88 to 0.94)
AF	43.1 (41.8 to 44.5)	44.7 (42.3 to 46.4)	1.06 (0.99 to 1.13)	0.98 (0.91 to 1.04)	0.98 (0.91 to 1.05)
β-Blockers					
No AF	29.7 (29.4 to 30.1)	33.5 (32.6 to 34.3)	1.15 (1.11 to 1.19)	0.96 (0.93 to 1.00)	0.91 (0.88 to 0.94)
AF	46.6 (45.2 to 48.0)	39.8 (38.3 to 41.4)	0.80 (0.75 to 0.85)	0.83 (0.78 to 0.89)	0.83(0.78 to 0.89)
Calcium-channel blockers					
No AF	30.1 (29.8 to 30.5)	35.9 (33.4 to 37.8)	1.24 (1.16 to 1.33)	1.01 (0.94 to 1.08)	1.04 (0.97 to 1.11)
AF	43.9 (42.8 to 45.0)	41.7 (38.5 to 45.1)	0.94 (0.85 to 1.05)	0.99 (0.88 to 1.10)	1.03 (0.93 to 1.15)
Statins					
No AF	30.1 (30.3 to 31.0)	27.7 (26.8 to 28.6)	0.88 (0.84 to 0.91)	0.82 (0.79 to 0.86)	0.72 (0.69 to 0.75)
AF	46.3 (45.2 to 47.6)	34.7 (32.69 to 36.9)	0.68 (0.63 to 0.74)	0.76 (0.70 to 0.83)	0.72 (0.66 to 0.79)
Amiodarone					
No AF	30.2 (29.9 to 30.6)	43.8 (38.5 to 49.5)	1.56 (1.32 to 1.85)	1.38 (1.12 to 1.57)	1.26 (1.06 to 1.49)
AF	43.7 (42.6 to 44.8)	43.8 (40.1 to 47.6)	1.01 (0.90 to 1.14)	1.19 (1.06 to 1.34)	1.15 (1.02 to 1.30)
Digoxin					
No AF	29.5 (29.2 to 29.9)	47.9 (46.2 to 49.6)	1.86 (1.77 to 1.96)	1.25 (1.18 to 1.31)	1.21 (1.15 to 1.27)
AF	40.7 (39.6 to 42.1)	48.0 (45.3 to 49.6)	1.24 (1.16 to 1.32)	1.17 (1.10 to 1.25)	1.15 (1.08 to 1.23)

95% CIs are presented in parentheses.
*Reference group: patients in the stratum without the given drug exposure.
†Step 1: adjusted for age and sex.
‡Step 2: adjusted for age, sex, the 19 individual disease categories in the Charlson Index, hypertension, heart valve disease, transient cerebral ischaemic attack, obesity, alcoholism, and contacts with a general practitioner regarding preventive consultations, social-medicine-related consultations, conversational therapy, vaccination for influenza, and reimbursement due to chronic or terminal illness.
AF, atrial fibrillation.

the results of this study. We did not have data on in-hospital medications; thus, we were unable to assess whether pre-admission treatments were continued, discontinued or altered (eg, change of vitamin K antagonists to low-molecular heparins) during admission. Any bias introduced by the discontinuation of a drug during admission would be directed towards the null. Use of the prophylactic drugs (eg, statins and β-blockers) could be markers for unmeasured, but greater, health awareness among the patient population. However, the welfare structure of the Danish society reduces the risk of confounding by differences in socioeconomic status; in Denmark, statin users have unhealthier lifestyles than statin non-users.[28 29]

We adjusted our estimates for a broad range of potentially confounding factors, and the major diseases included in the Charlson Index have a mean positive predictive value of 98%.[30] However, confounding by unmeasured variables and residual confounding might have affected the results of this observational study. Since we were unable to identify conditions managed only by a patient's GP, the prevalence values for hypertension, obesity and alcoholism are most likely underestimated in our study.

Interpretation

To the best of our knowledge, this study was the first to examine the effect of pre-existing AF and its treatment on the prognosis for pneumonia patients. This study added to previous studies reporting a high risk of thromboembolic complications and mortality in pneumonia patients.[7 11] Our results indicated that there was a similar adjusted risk of arterial thromboembolism and an equal adjusted mortality in hospitalised pneumonia patients with and without AF, after confounders were accounted for. We also did not find that there were different rates in ICU admission or treatment with mechanical ventilation for patients with AF compared with patients without AF. Our finding of similar prognosis in pneumonia patients with and without pre-existing AF conflicts with previous findings of increased mortality in pneumonia patients with new-onset AF.[9] We can only speculate on the mechanisms behind this difference, yet as opposed to patients with new-onset AF, patients with pre-existing AF are more likely to receive well-balanced treatment for AF at the time of pneumonia; possibly, current management approaches can counterbalance the potentially deleterious effects of AF. Indeed, we have shown that preadmission medical treatment for AF appears to have great prognostic impact in pneumonia patients with this condition. Alternatively, new-onset AF during pneumonia may not be associated with worse prognosis per se, but rather is a marker of clinically more severe pneumonia.

Our study adds to the growing number of observational studies that support a protective role for the preadmission use of statins in hospitalised pneumonia patients. Our findings for the prognostic effect measures of statin therapy are comparable to previously published findings.[18 31–34]

We also found that there was a substantial beneficial effect of β-blocker therapy in pneumonia patients with AF. β-blockers may improve the prognosis for pneumonia patients with AF by protecting against uncontrolled tachycardia and reducing myocardial oxygen consumption. In patients with paroxysmal AF, β-blockers could protect against AF relapse provoked by increased sympathetic tonus. β-blockers can also dampen the metabolic changes towards catabolism that occur during critical illness.[35] Pre-admission β-blocker use was also related to improved prognosis in patients without AF indicating that the beneficial effects of β-blockers are not exclusive to patients with AF. This result conflicts, however, with the results of a previous study of 1007 patients hospitalised with pneumonia (including 188 β-blocker users) that reported an increased 30-day mortality in β-blocker users, compared with non-users (aOR=1.97 (95% CI 1.03 to 3.78)).[34] Explanations for this discrepancy are unclear but may include more extensive control for confounding factors in the present study.

The observed excess mortality related to amiodarone use should be interpreted within the context that only 7.7% of patients with AF are users of this drug. In this study cohort, prescription of amiodarone may have been reserved for special circumstances, such as for patients with impaired left ventricular function who poorly tolerate drugs with negative inotrope properties. Even though we adjusted for diagnosed heart failure, the mortality difference between amiodarone users and non-users could be related to differences in cardiac performance because the data set did not include quantitative measures of heart failure severity. A well-described side effect of amiodarone treatment is the development of pulmonary fibrosis,[36] which may have been a factor that contributed to the excess mortality observed among amiodarone users.

The finding of increased mortality in patients with AF using digoxin was alarming. Since digoxin was the single most used AF drug in our cohort, it seems unlikely that digoxin users represent a selected sample of patients with particularly severe AF.

The effect of cardiac-acting calcium-channel blockers on the prognosis of acute disease has not been investigated. We found that there was a slightly increased 30-day mortality in patients with AF using calcium-channel blockers, but there were no mortality differences 1 year after admission.

We found that compared with non-users, patients with AF treated with vitamin K antagonists had a markedly reduced mortality rate and risk of arterial thromboembolism. The role of preadmission treatment with vitamin K antagonists has not been investigated previously in patients with pneumonia. However, severe and uncomplicated infections induce increased activity of the coagulation system and the degree of coagulation abnormality at hospital admission is correlated with the outcome of community-acquired pneumonia.[37 38] Thus, we speculate that the beneficial effect of vitamin K antagonist treatment may be related to protection from hypercoagulation induced by systemic inflammation. This may also explain the finding of favourable prognosis with preadmission use of vitamin K antagonists in patients without AF.

We did not find that mortality of aspirin users was reduced in patients with pneumonia with AF. Furthermore, aspirin use by patients with AF was associated with only a modest risk reduction from arterial thromboembolisms. Our findings agree with the findings of clinical studies that indicate that aspirin use in patients with AF has little benefit for prevention of stroke.[39] Of note, we found preadmission use of aspirin

to be associated with reduced mortality in patients without AF, which is in line with a previous study.[34]

Finally, the results of our study indicated that there was an increased risk of thromboembolism in patients with AF not taking anticoagulants, even after controlling for the established risk factors for stroke (ie, the risk factors included in the CHA_2DS_2-VASc-score). Our study results indicate that severe infection should be considered to be a novel risk factor for stroke in patients with AF.

CONCLUSION

In conclusion, pre-existing AF is a frequent condition in patients admitted to the hospital with pneumonia, and marks increased risk of death and arterial thromboembolism. This effect is attributable to the more advanced ages and higher burdens of coexisting disease that are present in patients with AF. Our results also showed that the prognosis for patients with AF with pneumonia was substantially influenced by preadmission drug treatment, which suggests that treatment protocols could be improved.

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REFERENCES

1. Go AS, Hylek EM, Phillips KA, *et al*. Prevalence of diagnosed atrial fibrillation in adults. *JAMA* 2001;285:2370–5.
2. Krijthe BP, Kunst A, Benjamin EJ, *et al*. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J* 2013;34:2746–51.
3. Benjamin EJ, Wolf PA, D'Agostino RB, *et al*. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;98:946–52.
4. Friberg L, Hammar N, Pettersson H, *et al*. Increased mortality in paroxysmal atrial fibrillation: report from the Stockholm Cohort-Study of Atrial Fibrillation (SCAF). *Eur Heart J* 2007;28:2346–53.
5. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22:983–8.
6. World Health Organization. *The global burden of disease: 2004 update*. Geneva, 2008.
7. Søgaard M, Nielsen RB, Schønheyder HC, *et al*. Nationwide trends in pneumonia hospitalization rates and mortality, Denmark 1997–2011. *Respir Med* 2014;108:1214–22.
8. Fry AM, Shay DK, Holman RC, *et al*. Trends in hospitalizations for pneumonia among persons aged 65 years or older in the United States, 1988–2002. *JAMA* 2005;294:2712–19.
9. Mandal P, Chalmers JD, Choudhury G, *et al*. Vascular complications are associated with poor outcome in community-acquired pneumonia. *QJM* 2011;104:489–5.
10. Corrales-Medina VF, Musher DM, Wells GA, *et al*. Cardiac complications in patients with community-acquired pneumonia: incidence, timing, risk factors, and association with short-term mortality. *Circulation* 2012;125:773–81.
11. Smeeth L, Thomas SL, Hall AJ, *et al*. Risk of Myocardial Infarction and Stroke after Acute Infection or Vaccination. *N Engl J Med* 2004;351:2611–18.
12. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39(7 Suppl):30–3.
13. Charlson ME, Pompei P, Ales KL, *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
14. De Groot V, Beckerman H, Lankhorst GJ, *et al*. How to measure comorbidity: a critical review of available methods. *J Clin Epidemiol* 2003;56:221–9.
15. Olesen JB, Lip GYH, Hansen ML, *et al*. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ* 2011;342:d124.
16. Ehrenstein V, Antonsen S, Pedersen L. Existing data sources for clinical epidemiology: Aarhus University Prescription Database. *Clin Epidemiol* 2010;2:273–9.
17. Hansen ML, Gadsbøll N, Gislason GH, *et al*. Atrial fibrillation pharmacotherapy after hospital discharge between 1995 and 2004: a shift towards beta-blockers. *Europace* 2008;10:395–402.
18. Nielsen AG, Nielsen RB, Riis AH, *et al*. The impact of statin use on pneumonia risk and outcome: a combined population-based case-control and cohort study. *Crit Care* 2012;16:R122.
19. Andersen JS, Olivarius NDF, Krasnik A. The Danish National Health Service Register. *Scand J Public Health* 2011;39:34–7.
20. Pedersen CB, Gøtzsche H, Møller JO, *et al*. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006;53:441–9.
21. Andersen PK, Geskus RB, de Witte T, *et al*. Competing risks in epidemiology: possibilities and pitfalls. *Int J Epidemiol* 2012;41:861–70.
22. Thomsen RW, Riis A, Nørgaard M, *et al*. Rising incidence and persistently high mortality of hospitalized pneumonia: a 10-year population-based study in Denmark. *J Intern Med* 2006;259:410–17.
23. Rix TA, Riahi S, Overvad K, *et al*. Validity of the diagnoses atrial fibrillation and atrial flutter in a Danish patient registry. *Scand Cardiovasc J* 2012;46:149–53.
24. Frost L, Vestergaard P. Alcohol and risk of atrial fibrillation or flutter: a cohort study. *Arch Intern Med* 2004;164:1993–8.
25. Frost L, Andersen LV, Vestergaard P, *et al*. Trend in mortality after stroke with atrial fibrillation. *Am J Med* 2007;120:47–53.
26. Johnsen SP, Overvad K, Sørensen HT, *et al*. Predictive value of stroke and transient ischemic attack discharge diagnoses in The Danish National Registry of Patients. *J Clin Epidemiol* 2002;55:602–7.
27. Krarup L-H, Boysen G, Janjua H, *et al*. Validity of stroke diagnoses in a National Register of Patients. *Neuroepidemiology* 2007;28:150–4.
28. Thomsen RW, Johnsen SP, Olesen AV, *et al*. Socioeconomic gradient in use of statins among Danish patients: population-based cross-sectional study. *Br J Clin Pharmacol* 2005;60:534–2.
29. Thomsen RW, Nielsen RB, Nørgaard M, *et al*. Lifestyle profile among statin users. *Epidemiology* 2013;24:619–20.
30. Thygesen SK, Christiansen CF, Christensen S, *et al*. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol* 2011;11:83.
31. Thomsen RW, Riis A, Kornum JB, *et al*. Preadmission use of statins and outcomes after hospitalization with pneumonia:

population-based cohort study of 29,900 patients. *Arch Intern Med* 2008;168:2081–7.
32. Douglas I, Evans S, Smeeth L. Effect of statin treatment on short term mortality after pneumonia episode: cohort study. *BMJ* 2011;342:d1642.
33. Mortensen EM, Nakashima B, Cornell J, *et al*. Population-based study of statins, angiotensin II receptor blockers, and angiotensin-converting enzyme inhibitors on pneumonia-related outcomes. *Clin Infect Dis* 2012;55:1466–73.
34. Chalmers JD, Singanayagam A, Murray MP, *et al*. Prior statin use is associated with improved outcomes in community-acquired pneumonia. *Am J Med* 2008;121:1002–1007.e1.
35. Norbury W, Jeschke M, Herndon D. Metabolism modulators in sepsis: propranolol. *Crit Care Med* 2007;35:s616–620.
36. Ernawati DK, Stafford L, Hughes JD. Amiodarone-induced pulmonary toxicity. *Br J Clin Pharmacol* 2008;66:82–7.
37. Milbrandt EB, Reade MC, Lee M, *et al*. Prevalence and significance of coagulation abnormalities in community-acquired pneumonia. *Mol Med* 2009;15:438–45.
38. Amaral A, Opal SM, Vincent J-L. Coagulation in sepsis. *Intensive Care Med* 2004;30:1032–40.
39. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146:857–67.