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Atrial Fibrillation: Risk and Prognosis in Critical Illness

PhD dissertation

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PREFACE

This PhD thesis is based on studies carried out during my employments at the Department of Clinical Epidemiology and at Aalborg University Hospital during the period 2011–2014.

This work could not have been accomplished without the support and guidance from a number of people, to whom I am indebted. Firstly, I would like to express my sincere gratitude to my supervisors: Reimar W. Thomsen for his never-failing enthusiasm, for patiently introducing me to the world of clinical epidemiology, and for being a superb scientific mentor in all aspects; Christian F. Christiansen for his always constructive feedback and invaluable help with methodological challenges; and Bodil S. Rasmussen and Lars H. Rasmussen for their encouragement, inspiration, and for generously sharing their great knowledge of critical care medicine and cardiology with me.

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Jacob Gamst, Aalborg, October 2014

This PhD thesis is based on the following studies:

1. Impact of acute infections and influenza vaccination on the risk of atrial fibrillation: a population–based case–control study. *Submitted*.

2. Pre-existing atrial fibrillation and risk of arterial thromboembolism and death following pneumonia: a population-based cohort study. *BMJ Open 2014;4:e006486*.

3. Pre–existing atrial fibrillation and risk of arterial thromboembolism and death in intensive care unit patients: a population–based cohort study. *Manuscript in preparation.*

LIST OF ABBREVIATIONS

AF: Atrial fibrillation

ATE: Arterial thromboembolism

AUPD: Aarhus University Prescription Database

CI: Confidence interval

CRR: Cumulative risk ratio

CRS: Civil registration system

DNPR: Danish National Patient Register

DID: Danish Intensive Care Database

GP: General practitioner

HR: Hazard ratio

ICD-8: International classification of diseases, 8th revision

ICD-10: International classification of diseases, 10th revision

ICU: Intensive care unit

OR: Odds ratio

RR: Relative risk

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1. INTRODUCTION

1.1 Introduction to atrial fibrillation

Atrial fibrillation (AF) is an arrhythmia in which the normal, regular electrical activity of the atria is replaced by a chaotic electrical pattern. Consequently, atrial systole is lost and the heart rate becomes irregular, often times rapid [1]. Symptoms of AF may vary considerably from patient to patient; some being asymptomatic (so called "silent AF"), while others experience palpitations, irregular pulse, dyspnoea, chest pain, or fatigue [2]. Thus, the severity of AF symptoms may range from unnoticeable to invalidating [3]. The clinical signs of AF was well characterized by Mackenzie in 1904 as *"that most puzzling of all the forms of irregularity of the heart, where the heart is never regular in its action, where seldom or never two beats of the same character follow one another"* [4], but AF may have been described in medical literature as early as in the 12th century in the writings of Moses Maimonides [5]. The invention of electrocardiography in the early 20th century allowed for further insights in the electrophysiological properties of AF and the electrocardiographic pattern of AF as we know it today (i.e. ventricular activity at irregular intervals and a number of irregular waves in between) was described by Lewis in 1909 [6].

1.1.1 The epidemic of AF

AF is considered the most common sustained cardiac arrhythmia and by extrapolating data from the Rotterdam Heart Study, it is estimated that prevalence of AF in the European Union is nearly 2% [7, 8]. AF is seldom among young individuals with a reported prevalence below 0.5% in individuals younger than 55 years. The prevalence rises with advancing age to well above 10% in individuals aged 80 or older [7, 9, 10]. The incidence rate of AF has been reported to be approximately 4/1,000 person-years [11]. As with the prevalence, the incidence rate of AF is also dependent on age spanning from 1-3/1,000 person years in individuals aged 55-59 to 18-31/1,000 person-years in individuals aged 85+ [10, 11]. Rising incidence rates of AF have been reported globally, most pronounced in industrialized

countries, and in Denmark the incidence rate of AF increased by 5% annually from 1980 to 2009 [12, 13]. As the demographic composition of the population changes, with an increasing number of elderly citizens, the burden of AF is expected to rise considerably. Thus, the prevalence of AF in the EU is projected to increase to 3.5% by 2060 [7]. Further illustrating the "epidemic of AF", a study from Iceland estimated a 202% increase in the number of individuals with AF by 2050 as compared to a 39% increase of the total adult Icelandic population in the same period [14]. It has been estimated that the lifetime risk of developing AF is nearly 25% [10, 15].

1.1.2 Mechanisms and natural history of AF

AF is believed to be triggered by foci of rapidly depolarising cells [16]. These are most often located in the pulmonary veins near the left atrium, but may be located elsewhere in the atria [16, 17]. AF may also be initiated by other supraventricular arrhythmias such as atrial flutter, atrial premature beats, or atrioventricular nodal re-entrant tachycardia [16]. Once induced, AF may be maintained by sustained activity of rapidly firing ectopic foci or by electric wavelets wandering in the atria. The propensity of forming these wandering wavelets is increased by structural abnormalities such as fibrosis in the atrial myocardium. AF usually starts as short, self-limiting attacks, so-called paroxysmal AF [18]. Overtime, episodes of AF increases in numbers and duration, and may require interventions to be terminated (persistent AF) [19]. The end-stage is permanent AF, in which AF is an uninterrupted arrhythmia. During AF, electrical alterations and structural alterations occur in the myocardium which perpetuates the ongoing AF episode and increases the future likelihood of AF [18, 20].

1.2 Risk factors for AF

Other than age, several diseases and conditions have been associated with development of AF. Cardiovascular diseases such as ischemic heart disease, congestive heart failure, and valvular heart disease have been recognised as AF risk factors in several cohort studies [21–24]. The risk of AF is also increased in patients with diabetes, renal failure, and thyrotoxicosis [24–27]. Further, development of AF has been linked to lifestyle factors such as obesity, alcoholism, and tobacco use [24, 28, 29].

1.2.1 Infections as risk factor for AF

It is commonly observed among clinicians, that patients with infections often have or develop AF. Despite, neither guidelines from Europe nor USA mention infections as a possible initiator of AF [8, 30]. To identify articles studying infections as a risk factor for AF, I conducted a systematic literature search using *PubMed* with the search terms:

```
(("Bacterial Infections and Mycoses"[Mesh] NOT "Rheumatic
Fever"[Mesh]) OR ("Virus Diseases"[Mesh])) AND "atrial
fibrillation"[mesh]
```

and *Embase* with the search terms:

```
1. *heart atrium fibrillation/
2. exp infection/
3. 1 AND 2.
```

The searches yielded a total of 663 articles. After sorting on titles and removal of duplicate findings, 44 articles remained. After reviewing the abstracts of these articles, 31 were found of possible interest. These articles were reviewed in full-text of which those listed in **Table 1** were found to provide insight in the association between infections and development of AF. One additional reference was found incidentally and included in **Table 1**.

Table 1: Previous studies on infections and risk of AF

Author, year	Design, setting	Study subjects	Outcomes of interest
Bunch, 2008 [31]	Cross-sectional study, single-center, USA	Patients undergoing coronary catheterization for chest pain (n=743, of which 83 had AF)	Patients with AF more likely to be helicobacter pylori seropositive than non-AF patients (65 vs. 55%)
Chiang, 2013 [32]	Cohort study, sample from the National Health Insurance, Taiwan	Patients with herpes simplex virus infection (n=15,810) and matched control group (n=73,197).	During follow-up (3 y)1.6% of the exposed patients developed AF compared to 1.1% of the controls; adjusted hazard ratio 1.4 (95%CI 1.2 – 1.6)
Christian, 2008 [33]	Cohort study, Single-centre ICU, USA	General ICU patients, n=1948	Incidence of new-onset AF: Overall: 1%, ICU patients with sepsis: 6%
Hanson, 2004 [34]	Cross-sectional study, single-centre, Sweden	100 patients with paroxysmal AF	20% of the patients believed an infection had caused their AF paroxysm
Hsu, 2013 [35]	Cohort study, Veterans Affairs, USA	Patients with HIV-infection (n=30,533)	2.6% developed AF during follow-up (median 6.8 y). Increased risk of AF in patients with low CD4-count (HR 1.4 (95%CI 1.1 – 1.8) and high viral load (HR 1.7 (95%CI 1.2 – 2.4)
Ichiki, 2009 [36]	Cross-sectional study, single-centre, Japan	Patients with AF scheduled for ablation (n=48) and controls (n=24)	Toll-like receptor 2 (indicative of recent infection) up-regulated in AF patients compared to controls
Ki, 2010 [37]	Cross-sectional study, single-centre, Korea	AF patients with unclear selection criteria (n=66) and controls (n=36)	Elevated inflammatory markers in AF patients as compared to controls
Kindem, 2008 [38]	Cohort study, single-centre, Norway	Patients with bacteremia (n=672)	15% developed new-onset AF. CRP-levels did not predict AF
Lindberg, 2012 [39]	Cross-sectional study, single-centre, Denmark	Patients with admitted with first AF (n=374)	Preceding infection in 61 patients
Lunetta, 2009 [40]	Cohort study, single-centre, Italy	Helicobacter pylori positive patients (n=120) and controls (n=60), unclear inclusion criteria	During 7-y follow-up 21% of the helicobacter pylori positive group developed AF compared to 18% of the controls.

Table 1 continued

Makrygiannis, 2014 [41]	Cohort study, single-centre, Greece	General ICU patients, n=133	15% developed AF, increased risk of AF in patients with sepsis OR 6.5 (95% CI: 2.0–21.1)
Meierhenrich, 2010 [42]	Cohort study, single-centre, Germany	General ICU patients, n=687	Incidence of new-onset AF: Overall: 8%, ICU patients with septic shock: 46%
Montenero, 2005 [43]	Case-control study, single-centre, Italy	AF patients undergoing cardioversion or electrophysiological examination/intervention (n=59) and non-AF controls (n=45). Unclear inclusion criteria for controls.	Higher titres of helicobacter pylori antibodies and C-reactive protein in AF patients than controls
Musher, 2007 [44]	Cohort study, single-centre, USA	Patients with pneumococcal pneumonia (n=170)	7 developed AF
Platonov, 2008 [45]	Case-control study, single-centre, Sweden	Patients with AF (n=72) and controls (n=72)	Higher CRP in AF patients. No difference in titers of Chlamydia pneumonia and helicobacter pylori antibodies
Salman, 2008 [46]	Cohort study, single centre, USA	ICU patients with sepsis (n=81)	31% developed new-onset AF
Spodick, 1976 [47]	Cohort study, single-centre, USA	Patients with pericarditis (n=100)	7 developed atrial arrhythmias
Syed, 2012 [48]	Cohort study, 4 hospitals, South Africa	Patients with TB-pericarditis (n=80)	AF in 25% at admission declining to 0% at 6 months.
Walkey, 2013 [49]	Cohort study, Medicare sample, USA	Patients with sepsis N=60,209	26% had AF during admission of which 18% had pre-existing AF and 7% new-onset AF. ”Acute factors”, e.g. ICU admission, organ failure, was associated with greater risk of AF than ”chronic factors”
Walkey, 2011 [50]	Cohort study, California State Inpatient Database, USA	Patients with sepsis N=49,082	New-onset AF occurred in 6.5% of patients with severe sepsis, 0.7% in patients with non-severe sepsis

CI: confidence interval; HR: hazard ratio; OR: odds ratio

It appears from **Table 1**, that AF is common in severe infections such as bacteraemia, sepsis, and hospitalized infections. Also, increased levels of biomarkers indicative of infection seems related to higher risk of AF. However, most of the studies are conducted in either selected patient populations or have a small sample size. Of the studies listed in **Table 1**, all but one lacks a group of individuals unexposed to infection, and the study that does have a control group focuses on the role of a chronic infection, i.e. Herpes Simplex virus types 1 and 2. Thus, it seems that no population-based estimates on the role of acute infections as a risk factor for AF have been reported to date.

1.2.2 Inflammation: a potential mechanism leading from infection to AF

It has been proposed that inflammation might have a role in the development of AF. This hypothesis became popular following a widely cited study from 1997 that demonstrated inflammatory changes in biopsies of atrial tissue from patients with chronic AF [51]. Since, several studies have associated elevated biomarkers of inflammation such as C-reactive protein, ceruloplasmin, and YKL-40 with increased incidence and prevalence of AF [52–55]. Because infections lead to inflammation, an association between infections and development of AF could potentially be facilitated via the inflammatory response. An association between acute inflammation and AF remains yet to be established, however. Also, it has been questioned whether or not the association between inflammation and AF is driven by inflammation itself or if the inflammation is a marker of other underlying disease. One study demonstrated that genetically elevated levels of C-reactive protein was not associated with increased risk of AF, thus C-reactive protein *per se* does not seem to cause AF [56].

1.2.3 Vaccinations and risk of AF

If the inflammatory response to infections leads to AF, then the transient increase in systemic inflammatory activity following vaccinations could also have the potential to initiate AF. As vaccinations are given with the purpose of preventing disease and often times are given to fragile

individuals, such an association would have major public health implications. To identify any previous literature on the risk of AF following vaccinations, I performed a systematic search of *PubMed* with the terms

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(("Vaccination"[Mesh]) OR "Vaccines"[Mesh]) AND "Atrial
Fibrillation"[Mesh]
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and *Embase* with the terms

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1. *heart atrium fibrillation/
2. exp vaccinations/
3. 1 AND 2.
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The search yielded 6 hits, of which none were found of relevance after reviewing titles and abstracts.

1.3 Prognosis of AF

For many years, AF was not recognized as an important, individual disease entity; rather, AF was considered an artefact or a manifestation of other cardiac disease such as heart failure or valvular heart disease. This perception changed in the 1990s with the publication of two legendary cohort studies from The Framingham Heart Study that associated AF with a 2-fold increased risk of all-cause mortality and a 5-fold increased risk of stroke even after controlling for the effect of age and coexisting diseases [57, 58]. These findings of substantially increased risk of death and stroke have since been confirmed in other major cohort studies [59–62]. Suggested mechanisms for the increased risk of stroke if AF patients include blood stasis in the fibrillating atria and altered structure of the endocardium [63]. Also, increased activity of platelets and the coagulation system has been observed in AF patients [63]. The risks of stroke and death does not seems to differ between paroxysmal, persistent, and permanent AF [64, 65]. Other than cerebral infarcts, AF may also cause embolisation in the peripheral arteries, although these do properly account for less than 10% of the total number of arterial thromboembolisms associated with AF [66, 67]. AF have been associated with a more than 3-

fold increase in the risk of developing congestive heart failure [59, 68]. Also, inefficient diastolic function due to irregular heart rate and lacking atrial systole may further impair left ventricular function in AF patients [69, 70]. It has further been reported that AF patients are at increased risk of developing cognitive dysfunction and that AF patients have reduced quality of life [71–73].

1.3.1 AF in acute disease

Because of the high prevalence of AF it is likely that many patients admitted to hospital with acute disease have AF as a coexisting condition. As previously noted, AF is associated with grim outcomes *quoad vitam*. Potentially, AF could have important prognostic influence in acute disease as patients with AF could be at higher risk of hemodynamic instability and at higher risk of developing arterial thromboembolic complications as compared to patients without AF. However, the role of AF in acute disease is poorly understood.

1.3.2 Pneumonia: definition and epidemiology

Pneumonia can be defined as *inflammation and consolidation of lung tissue due to an infectious agent* [74]. According to the World Health Organization, pneumonia is the 3rd leading cause of death in high-income countries, accountable for 4% of all deaths [75]. Advanced age is a major risk factor for pneumonia. Other risk factors include chronic heart disease, chronic respiratory disease, chronic renal disease, diabetes, obesity, alcoholism, and tobacco use [76–80]. In Denmark, the incidence rate of hospitalized pneumonia rose from 4.96/ 1.000 population-years in 1997 to 8.09/ 1.000 population-years in 2011, assumedly due to increasing numbers of elderly and more fragile individuals [81]. The prognosis for pneumonia patients does not seem to have improved and the 30-day mortality of hospitalized pneumonia in Denmark remained at approximately 13% between 1997 and 2011 [81]. The increasing burden of comorbidity in pneumonia patients is likely to be an important part in the explanation of their unaltered prognosis. Indeed, pre-existing diseases have been shown to be important predictors of pneumonia outcome [82–86].

1.3.3 AF in pneumonia

Because AF and pneumonia share many risk factors, pre-existing AF is likely to be common in pneumonia patients, and it has previously been reported that pre-existing cardiac diseases are present in half of the patients with hospitalized pneumonia [87]. Pre-existing AF may have influence on the prognosis for pneumonia patients, as illustrated by cohort study of 2,287 patients with community-acquired pneumonia that found a history of cardiac arrhythmias associated with an 80% increase in the 30-day risk of cardiac complications [88]. Several pathophysiologic alterations occur during pneumonia which may be of particular importance for AF patients. Firstly, shifting in the balance of the coagulation system in the pro-coagulant direction may increase the risk of thrombus formation [89]. In patients with pneumonia, it has been demonstrated that the degree of coagulation abnormality on admission is correlated to the 90-day mortality and the risk of stroke is temporarily 3-fold increased [89, 90]. These effects may have a more severe impact in AF patients because of the patophysiological changes with AF that leads to increased likelihood of thrombus formation. Secondly, pneumonia affects the cardiovascular system through several mechanisms which may lead to hemodynamic instability. The release of inflammatory mediators leads to peripheral vasodilatation, which must be met by a compensatory increase in the cardiac output in order to insure adequate tissue perfusion [91]. The contractility of the myocardium may also be negatively affected by the acute inflammation process [91, 92]. Consolidation of lung tissue may lead to increased pulmonary vessel resistance, thereby increasing cardiac workload and oxygen demand, as well as shunting leading to hypoxemia. Moreover, activation of the sympathetic nervous system leads to tachycardia which both increases myocardial oxygen consumption and also shortens the diastole, during which coronary blood flow occurs, thereby reducing the amount of oxygen offered for the myocardium. Considering that AF patients often have impaired diastolic and systolic cardiac function as well as chronotropic dysfunction, it is likely that pneumonia patients with AF are more susceptible to these hemodynamic changes than pneumonia patients without AF. To find evidence on the influence of pre-existing AF on

the risk of arterial thromboembolism and death in pneumonia patients, I search *PubMed* using the search terms:

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"atrial fibrillation" [mesh] AND "pneumonia" [mesh]
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and *Embase* with the terms:

```
1. heart atrium fibrillation/
2. exp *pneumonia/
3. 1 AND 2.
```

The searches yielded 194 hits. After removing duplicate findings and screening titles, 10 articles were found of potential interest. After reading abstracts, 4 articles were evaluated in full text. None of these articles, however, answered the research question. Consequently, it seems that there are no previously published studies examining the impact of pre-existing AF on the risk of arterial thromboembolism and death in pneumonia patients.

1.3.4. Intensive care therapy: definition and epidemiology

The specialty of intensive care therapy was conceived on 25 august 1952 when Dr. Bjørn Ibsen, an anaesthesiologist, was summoned to The Epidemiological Hospital of Copenhagen (Blegdams Hospital) [93]. At the time a polio epidemic was raging Copenhagen; 50 new patients were admitted daily with polio of whom 10% had respiratory insufficiency [94]. The means of treating respiratory insufficiency were far from adequate and the mortality was 87% [94]. By principals familiar to him from his every day work at the operation theatres, Ibsen devised a treatment protocol for polio patients with respiratory insufficiency that emphasised the securing of an unobstructed airway by placing a cuffed tube in the trachea, providing adequate airshift through positive pressure ventilation, and resuscitating circulatory shock with infusion of fluids [95]. Ibsen further organized that these patients were treated at specialized wards equipped with advanced monitoring systems and a high staff-to-patient ratio [95]. Over the following fortnight, the mortality for polio with respiratory failure fell to 50% and by new-year it was down to 20%. Elaborating on the lessons learned during the polio

epidemic, Ibsen opened what was the properly the world's first intensive care unit (ICU) at Copenhagen Municipal Hospital (Kommunehospitalet) in 1953 [96]. Since, intensive care therapy has evolved to become an integrated part of the health care system and the Danish ICUs are now seeing more than 30,000 yearly admissions [97]. Modern ICUs treat critically ill patients from all clinical specialties with manifest or threatening organ failure [98]. ICUs also receive patients following major surgery (e.g. cardiac or intracranial surgery) for close monitoring in order prevent and detect organ failure in the peri-operative period [98]. Thus the ICU patient population is heterogeneous, not being defined by a particular disease category; rather the common denominator is the need for advanced monitoring and life supportive therapy.

In-hospital mortality for ICU patients in western countries is approximately 15% [93]. The mortality varies markedly with the cause of ICU admission, with very low mortality rates in pre-planned ICU admissions following scheduled surgery, to 60% mortality for patients in septic shock [98]. Previous studies have identified the degree of physiologic deterioration during ICU admission, as evaluated by scoring systems such as *the simplified acute physiology scores* and *the acute physiology and chronic health evaluations*, and pre-ICU-admission factors, such as advanced patient age and burden of comorbidity, as important predictors of patient outcome [99–103].

1.3.5 AF in ICU patients

The prevalence of pre-existing AF in Danish ICUs has not been reported previously, but it is likely to be a substantial number, considering a median age of 63 years and a prevalence of prior myocardial infarction and congestive heart failure of approximately 7% in Danish ICU patients [102]. Moreover, the prevalence of ICU patients with pre-existing AF will expectedly rise in the future owing to an increasing proportion of elderly ICU patients [103].

As discussed in relation to pneumonia, patients with AF may vulnerable to complications during hemodynamic instability and in states of high inflammatory activity. These are common conditions in the ICU setting. About one-third of Danish ICU patients are treated with inotropes and/or

vasopressors and in ICU patients aged 65–79 years this figure is nearly 50% [103, 104]. The systemic inflammatory response syndrome—which can be activated by factors such as severe infections, surgical stress, severe injuries, haemorrhage, and ischemia—is present in up to 80% of patients admitted to the ICU [105, 106]. It is therefore plausible, that pre-existing AF has an important prognostic role among ICU patients. Thus, I performed a systematic literature search to find previous studies reporting on the prognostic effect —namely in terms of risk of arterial thromboembolism and death—of pre-existing AF in ICU patients using *PubMed* with the search terms:

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"atrial fibrillation" [mesh] AND ("intensive care" [mesh] OR
"intensive care units" [mesh] or "critical illness" [mesh])
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and *Embase* with the terms:

```
1. *intensive care/
2. *intensive care unit/
3. heart atrium fibrillation/
4. 1 OR 2
5. 3 AND 4.
```

The searches yielded 152 hits. After removal of duplicate findings and screening of titles, 33 articles were found of possible interest. After reading abstracts of these, 8 articles were retrieved for full-text evaluation. Two of these articles—listed in **table 2**— provided estimates on the impact of pre-existing AF on the prognosis for ICU patients.

Table 2: Previous studies the effect of pre-existing AF on the prognosis for ICU patients

Author, year	Design, setting, patients	Outcomes of interest
Goodman, 2006 [107]	Single-centre cohort study, 11-bed general ICU, Israel (n=611)	In-ICU mortality: · No supraventricular arrhythmia: 18% · New-onset supraventricular arrhythmia: 54% · Pre-existing supraventricular arrhythmia: 32% · Mortality rates compared by non-parametric methods: $p<0.05$ Type of supraventricular arrhythmia not specified.
Kanji, 2012 [108]	Cohort-study, 3 general ICUs, Canada (n=325)	In-ICU mortality: · Pre-existing AF: 27% · New-onset AF: 22%

As can be seen from **Table 2**, ICU patients with pre-existing AF seem to have high mortality. The two studies have several limitations. One study addressed supra-ventricular arrhythmias and did not specify subtypes, even though AF is likely to be the numerically dominating subtype. Further, the study did not provide mortality estimates adjusted for confounding factors. The scope of the other study was to examine in-ICU treatment patterns for AF; the reported mortality rates were merely descriptive, the authors did not attempt to compare the mortality in ICU patients with pre-existing AF to ICU patients without AF, and no statistical analyses of the mortality difference between patients with new-onset and pre-existing AF were performed. The literature search revealed 6 studies that showed increased mortality in ICU patients with new-onset AF as compared to ICU patients without AF. All these studies, however, excluded patients with pre-existing AF [42, 109–113]. The authors of a cohort study of 49,082 patients with severe sepsis (not necessarily admitted to the ICU, therefore not included in the table), conducted using the *2007 California Instate Patient Database,* concluded that pre-existing AF was not associated to increased risk of stroke (adjusted odds ratio (OR) = 0.74 (95% confidence interval (CI): 0.55 – 1.01) [50].

1.4 Treatment of AF

As described previously, severe outcomes are associated to AF. Several treatment strategies have been developed in order to alleviate the consequences of AF. The prevention of stroke and other arterial thromboembolisms (ATE) forms a cornerstone in the management of AF. Several randomized clinical trials have shown that anticoagulant therapy with vitamin K antagonist can reduce the risk of stroke by two-thirds, which has been confirmed by observational studies [66, 114, 115]. Also, among AF patients who develop stroke, pre-admission users of vitamin K antagonists seem to have less severe strokes and lower 30-day mortality [116]. The risk of stroke in AF patients is dependent on patient age and prevalence of coexisting disease. To help clinicians identify AF patients who are at truly low risk of developing stroke, and thus do not need anticoagulant treatment, a risk stratification

scheme – the CHA_2DS_2-VASc-score – has been developed [117]. The elements of the CHA_2DS_2-VASc-score include congestive heart failure, hypertension, age>75 years, diabetes, previous stroke, vascular disease, age >65 years (<75 years), and sex category; 2 points are given for a history of stroke or TIA, or age ≥75; and 1 point is assigned for each of the elements age 65–74 years, hypertension, diabetes, congestive cardiac failure, vascular disease, and female sex. In the original paper, a CHA_2DS_2-VASc-score ≤1 conferred a <1% annual risk of ATE [117]. The ability of the CHA_2DS_2-VASc-score to predict development of stroke has been validated using Danish registries, finding an annual stroke rate of 0.66% in AF patients with CHA_2DS_2-VASc-score = 0 and 1.45% with CHA_2DS_2-VASc-score = 1 in patients with AF who were not treated with vitamin K antagonists [118]. Current European guidelines for the management of AF recommends that patients with a CHA_2DS_2-VASc-score≥2 are treated with oral anticoagulants (i.e. vitamin K antagonists or one of the novel oral anticoagulants) whereas prophylactic treatment for ATE is not needed in patients with CHA_2DS_2-VASc-score=0; patients with a CHA_2DS_2-VASc-score=1 can be offered oral anticoagulants, aspirin, or no treatment [8]. The current AF guidelines are more inclusive in recommending anticoagulant treatment than previous guidelines; indeed the purpose of developing the CHA_2DS_2-VASc-score was to extend the existing $CHADS_2$-score in order to identify more AF patients who could benefit from anticoagulant treatment [117, 119]. Aspirin has previously been considered an acceptable choice for prevention of ATE, but as clinical trials have proven aspirin much less efficient than vitamin K antagonists in preventing ATE—with equal rates of adverse effects—current guidelines deemphasises the role of aspirin [8, 114, 115, 120].

Two different treatment strategies are available with regard to controlling the action of the heart. One strategy—called “rhythm control”—relies on restoring sinus rhythm by means such as electric cardioversion, use of antiarrhythmic drugs such as Amiodarone and Flecainide, or invasive procedures such as catheter-based ablation or the Cox-Maze operation [8]. The alternative strategy—“rate control”—accepts the presences of AF; rather the focus is to reduce the ventricular rate to an acceptable level (< 110 beats per minute) using medications such as beta-blockers, cardiac acting calcium channel blockers, or digoxin [8]. Clinical trials comparing rate control to rhythm control has

not proven one superior to the other; one interpretation of these findings is that it is better for the patient to be in sinus rhythm, but this benefit is outweighed by side effects to the means of achieving and maintaining sinus rhythm [121–125].

1.4.1 Preadmission treatment for AF and prognosis in acute disease

The treatment strategies for AF instituted before admission with acute disease, such as pneumonia or in patients admitted to the ICU, may influence the prognosis for the patients. In example, AF patients taking vitamin K antagonists before admission may be less likely to suffer thromboembolic complications, whereas the heart rhythm modifying medications may protect against adverse effects stemming from uncontrolled heart rate. I therefore conducted a systematic literature search to find previous studies on the prognostic effect of preadmission drug therapy for AF in patients with pneumonia and in patients admitted to the ICU. The search was limited to the most commonly prescribed therapies for AF, i.e. vitamin K antagonists, aspirin, beta-blockers, nondihydropyridine calcium-channel blockers, amiodarone, and digoxin [126]. Statins were also included in the search as they are often prescribed to patients with cardiovascular disease and previous studies have associated preadmission statin use to favourable outcome in pneumonia and in ICU patients [127, 128]. The searches regarding pneumonia patients were conducted in *PubMed* with terms:

```
("pneumonia" [mesh]) AND ("Adrenergic beta-Antagonists"[mesh]
OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[mesh] OR
"Aspirin" [mesh] OR "Calcium Channel Agonists"[mesh] OR
"Coumarins"[mesh] OR "Amiodarone" [mesh] OR "Digoxin" [mesh])
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and *Embase* with the terms

```
1. exp *pneumonia/
2. exp beta adrenergic receptor blocking agent/
3. exp hydroxymethylglutaryl coenzyme A reductase inhibitor/
```

4. acetylsalicylic acid/

5. Antivitamin K/

6. exp Calcium channel blocking agent/

7. Amiodarone/

8. Digoxin/

9. 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8

10. 1 AND 9.

These searches yielded a total of 1427 hits. After limiting to studies concerning humans, sorting on titles and removal of duplicate findings 47 articles remained. After reading abstracts of these, 21 articles were reviewed in full-text. After the final screening, 14 articles were found to provide estimates on the prognostic role of preadmission use of statins, vitamin K antagonists, aspirin, beta-blockers, nondihydropyridine calcium-channel blockers, amiodarone, and digoxin. These articles are listed in **Table 3**.

The searches regarding ICU patients were conducted in *PubMed* with terms:

("intensive care" [mesh] or "intensive care units" [mesh] or "critical illness" [mesh]) AND ("Adrenergic beta-Antagonists"[mesh] OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[mesh] OR "Aspirin" [mesh] OR "Calcium Channel Agonists"[mesh] OR "Coumarins"[mesh] OR "Amiodarone" [mesh] OR "Digoxin" [mesh])

and *Embase* with the terms:

1. *intensive care/

2. *intensive care unit/

3. 1 OR 2

4. exp beta adrenergic receptor blocking agent/

5. exp hydroxymethylglutaryl coenzyme A reductase inhibitor/

6. acetylsalicylic acid/

7. Antivitamin K

8. exp Calcium channel blocking agent/

9. Amiodarone/

10. Digoxin/

11. 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10

12. 3 AND 11.

The searches yielded 1679 hits. Limiting to human studies and English language, sorting on titles and removal of duplicates, 17 titles were selected for review of abstracts as well as full-text review, of which 13 articles were relevant according to the research question. The selected articles are listed in **Table 4**.

As can be seen from **Tables 3 and 4**, several studies have examined the role of statins in both ICU patients and patients with pneumonia, and most of these studies have found statin use associated to favourable outcome. Beta blocker use in pneumonia patients was examined by 2 studies, one concluding no effect and the other finding increased mortality in users as compared to none-users. In ICU patients, 4 studies found preadmission use of beta blockers associated to improved mortality. One study found aspirin use associated to improved outcome in pneumonia patients and 2 studies found aspirin use associated to lower mortality in ICU patients. Also supporting a protective effect of aspirin in pneumonia, the literature search revealed 1 clinical trial of 198 patients hospitalized with community acquired pneumonia randomized to 300 mg of aspirin or no aspirin in an open-labelled design [129]. At 1 month following admission, acute coronary syndrome had occurred in 10 persons in the control group and 1 in the interventions group (relative risk RR 0.10 (95%CI: 0.01 – 0.75) and death in 9 individuals in the control group and 3 in the intervention group (RR 0.34 (95%CI: 0.07 – 1.33). No studies were found concerning calcium channel blockers, amiodarone, or vitamin K antagonists.

1.5 Conclusion of the literature review

AF affects a large proportion of the population and is a major cause of patient morbidity and mortality. The burden of AF is likely to increase in the coming years due to increasing numbers of elderly citizens. Even though AF is often seen preceded by infections, there is no epidemiologic evidence on this association to date. There is no evidence on the consequences of pre-existing AF in patients with hospitalized pneumonia nor in patients admitted to the ICU. Medications prescribed for AF can potentially have prognostic importance in other acute disease.

Table 3: Impact of preadmission cardiovascular drug use on pneumonia prognosis

Author, year	Drug	Design and setting	N	Outcome measures of interest	Results
Wu, 2014‡ [130]	Statins Beta blockers	Cohort study based on registries, Veteran Affairs, USA	21,985	90 day mortality	Statins: Adjusted OR 0.70, 95% CI 0.63–0.77 Beta blockers Adjusted OR 0.98, 95% CI 0.89–1.09
Doshi, 2013 [131]	Statins	Single-centre cohort study based on registries, Veteran Affairs, USA	347	30 day mortality	Adjusted HR 0.39 (95%CI: 0.16 – 0.92)
Mortensen, 2012‡ [132]	Statins	Cohort study based on registries, Veteran Affairs, USA	22,996	30 day mortality	OR 0.74 (95%CI: 0.68 – 0.82) propensity matched
Rothberg, 2012 [133]	Statins	Cohort study based on registries, Premier's Perspective, USA	121,254	30 day mortality	OR 0.90 (95%CI: 0.82 – 0.99) propensity matched
Nielsen, 2012* [127]	Statins	Cohort study based on registries, National Registry of Patients, Denmark	70,914	30 day mortality	Adjusted HR 0.73 (95%CI: 0.67 – 0.79)
Yende, 2011 [134]	Statins	Prospective cohort study, USA	1,895	90 day mortality	Adjusted OR 0.74 (95%CI: 0.48 – 1.24)
Douglas, 2011† [135]	Statins	Cohort study based on registries, THIN database (Primary care), UK	9,073	½ year mortality	Adjusted HR 0.67 (95%CI: 0.49 – 0.91)
Myles, 2009† [136]	Statins	Cohort study based on registries, THIN database (Primary care), UK	3,681	30 day mortality	Adjusted HR 0.33 (95%CI: 0.19 – 0.58)
Mortensen, 2008 [137]	Statins	Cohort study based on registries, Veteran Affairs, USA	8,652	30 day mortality	Adjusted HR: 0.54 (95%CI: 0.42 – 0.70)
Thomsen, 2008* [138]	Statins	Cohort study based on registries, National Registry of Patients, Denmark	29,900	30 day 90 day mortality	30-day: Adjusted HR 0.69 (95%CI: 0.58 – 0.82) 90-day: Adjusted HR 0.75 (95%CI: 0.65 – 0.86)

Table 3 continued

Chalmers, 2008 [139]	Statins Aspirin Beta blockers	Single-centre prospective cohort study, Edinburgh, UK	1,007	30 day mortality	Statins Adjusted OR 0.46 (95%CI: 0.25 – 0.85) Aspirin Adjusted OR 0.63 (95%CI: 0.36 – 1.11) Beta blockers Adjusted OR 1.97 (95%CI: 1.03 – 3.78)
Frost, 2007 [140]	Statins	Cohort study based on registries, Lovelace Patient Database, USA	76,232	In-hospital mortality	Adjusted OR 0.73 (95%CI: 0.47 - 1.33)
Majumdar, 2006 [141]	Statins	Cohort study based on chart review and interview, Capital Health, Edmonton, Alberta, Canada	3,415	Composite: 30 day mortality and/or ICU admission	Adjusted OR 1.10 (95%CI: 0.76 – 1.60)
Mortensen, 2005‡ [142]	Statins	2 centre cohort study based on registries and chart reviews, Tx, USA	787	30 day mortality	Adjusted OR 0.36 (95%CI: 0.14 – 0.92)

*: Overlapping cohorts; †: Overlapping cohorts; ‡: Overlapping cohorts; HR: Hazard ratio; OR: Odds ratio; CI: confidence interval

Table 4: Impact of preadmission cardiovascular drug use on the prognosis for ICU patients

Author, year,	Drug	Design and setting	Patients	N	Outcome measures of interest	Results
Macchia, 2012 [143]	Beta blockers	Cohort study based on registries, Italy	ICU patients with sepsis	9,465	30 day mortality	Adjusted OR 0.81 (95%CI 0.68 – 0.97)
Bukur, 2012 [144]	Beta blockers	Single-centre cohort study based on registries, USA	ICU patients with severe head injury	663	In hospital mortality	Adjusted OR 0.37 (95%CI 0.21 – 0.58)
Bajwa, 2012 [145]	Statins	Single-centre cohort study based on registries, USA	ICU patients with adult respiratory distress syndrome	738	60-day mortality	OR 0.88 (95%CI 0.49 – 1.60), Propensity matched
Eisen, 2012 [146]	Aspirin	Single-centre cohort study based on registries, Australia	ICU patients with systemic inflammatory response syndrome	5,523	In hospital mortality	Risk difference -6.2% (95%CI -9.5% – -3.5%), Propensity matched
Christensen, 2011 [147]	Beta blockers	Cohort study based on registries, Denmark	Mixed surgical/medical ICU patients	8,087	30 day mortality	Adjusted OR 0.82 (95%CI 0.71 – 0.94)
Al Harbi, 2011 [148]	Statins	Single-centre nested case-control study, Saudi Arabia	Mixed surgical/medical ICU patients	763	In hospital mortality	Adjusted OR 0.60 (95%CI 0.36 – 0.99)
Terblanche, 2011 [149]	Statins	Single-centre cohort study based on registries, UK	Mixed surgical/medical ICU patients	1,397	Organ failure during ICU admission	Adjusted OR 1.22 (95%CI 0.92 – 1.62)
Noveanu, 2010 [150]	Beta blockers	Cohort study in a clinical trial population, Switzerland	ICU patients with respiratory failure	314	30 day mortality 1 year mortality	30-day mortality Adjusted HR 0.33 (95%CI 0.14 – 0.74) One year mortality Adjusted HR 0.29 (95%CI 0.16 – 0.51)
Christensen, 2010 [128]	Statins	Cohort study based on registries, Denmark	Mixed surgical/medical ICU patients	12,483	30-day mortality	Adjusted MMR 0.76 (95%CI 0.69 – 0.86)
Winning, 2010 [151]	Asprin	Cohort study based on chart review, Germany	Mixed surgical/medical ICU patients	615	In hospital mortality	Adjusted OR 0.19 (95%CI 0.12 – 0.33)

Table 4 continued

Kor, 2009 [152]	Statins	Single-centre cohort study based on chart review, USA	ICU patients with acute lung injury or adult respiratory distress syndrome	178	In hospital mortality	Crude OR 0.62 (95%CI 0.29 – 1.32)
Fernandez, 2006 [153]	Statins	Single-centre cohort study based on chart review, Spain	Mixed surgical/medical ICU patients	438	In hospital mortality	Statin users: 61% Non-users: 42% Mortality rates compared by non-parametric methods: p= 0.03
Schmidt, 2006 [154]	Statins	Single-centre cohort study based on chart review, Germany	ICU patients with multiple organ dysfunction syndrome	120	28-day mortality	Adjusted HR 0.53 (95%CI 0.29 – 0.99)

HR: Hazard ratio; OR: Odds ratio; CI: confidence interval

2. AIMS OF THE THESIS

The aims of the thesis were:

1) To assess the extend and duration of any increased risk of incident AF following acute infections and influenza vaccinations (study 1)

2) To examine the effect of pre-existing AF and associated preadmission medication on the risk of arterial thromboembolism and death in patients with hospitalized pneumonia (study 2)

3) To examine the effect of pre-existing AF and associated preadmission medication on the risk of arterial thromboembolism and death in patients admitted to the ICU (study 3)

3. METHODS

3.1 Research field

This dissertation was performed within the research field of clinical epidemiology. The word epidemiology derives from the Greek words *epi* and *demos* meaning among the people, and epidemiology can be defined as "*the study of how often diseases occur in different groups of people and why*" [155]. The prefix "clinical" denotes a relationship with clinical medicine and a focus on patients and clinical outcomes, as opposed the population epidemiology, which focuses on the general population [156]. Clinical epidemiological research may by based on data obtained by many different means such as examination of patients, review of patient charts, interview of patient relatives, or by using clinical registries. The latter is particularly efficient because the epidemiologist is relieved of the cumbersome job of collecting data, thus speeding up the research process and allowing substantially larger datasets than what would be feasible if data where to be gathered "by hand" [157]. Denmark is particularly well suited for registry based research because of a long lasting tradition of registration of citizens (dating back to 1645) and use of clinical databases, and not the least, because citizens can be uniquely identified via their so-called CPR-number [158]. All 3 studies in the present dissertation were conducted by cross-linking of administrative and clinical registries, which will be described in detail below.

3.2 Data sources

3.2.1 The Civil Registration System

The Civil Registration System (CRS) was established in 1968 as an electronic successor to the paper based personnel registries that were being maintained by the local municipalities [159]. The principal purpose of establishing the CRS was to aid in taxation of Danish residents. All individuals who live or have lived in Denmark are registered in the CRS. The CRS holds information on vital status

(exact date of birth, migration, and death) and place of abode. The CRS also records place of birth, parents, siblings and twins, citizenship and marital status. Any changes in the variables coded in the CRS are updated daily without deleting old data. Importantly, the CRS assigns each resident a CPR-number (CPR is an abbreviation of Centrale Person Register, which is Danish for CRS). The CPR-number consists of 10 digits; the first 6 digits encode the individual's date of birth (format ddmmyy), the following 3 digits are serial numbers and encode the century of birth, while the final digit encodes gender (even for female, odd for male) and serves as a control digit. As mentioned, the CPR-number is a unique personal identifier. The CPR-number is used in all public (and many private) registries, thereby enabling cross-linking of data at the individual level. As such, the CRS can be considered the mother of all Danish registries.

3.2.2 The Danish National Patient Register

The Danish National Patient Register (DNPR) holds data on all admissions to public hospitals in Denmark from 1977 and onward [160]. It records date and time of hospital admission and discharge, diagnostic codes, and procedural codes. Diagnostic codes – 1 primary and up to 20 secondary - are assigned by the treating physician according to the 8th edition of World Health Organization's International Classification of Diseases (ICD-8) until 1993, thereafter according to the ICD-10 (ICD-9 was never used). Procedural codes are assigned according to the Nordic Medico-Statistical Committee's Classification of Surgical Procedures since 1996; prior to 1996 a classification system developed by the Danish National Board of Health was used. The DNRP was extended to include contacts to emergency rooms and hospital specialist outpatient clinics in 1995, and in 2003 it became mandatory for private hospitals to report to the DNPR.

3.2.3 The Danish Intensive Care Database

The Danish Intensive Care Database (DID) records data on all ICU admissions in Denmark and was established in 2005 [161, 162]. Variables in the DID include timing of admission and discharge from the ICU, use of ICU treatment modalities such as invasive mechanical ventilation, non-

invasive mechanical ventilation, renal replacement therapy, and treatment with inotropes. Recently, the DID has also begun the record New Simplified Acute Physiology Score (SAPS II score). All data in the DID stems from the DNPR with an interposed validation step that excludes procedural codes of intensive care therapy or observation assigned from non-ICUs.

3.2.4 The Aarhus University Prescription Database

The Danish National Health Services offers partial reimbursement for most prescription pharmaceuticals [163]. The size of reimbursement that the patient is entitled for, is dependent on the patient's annual expenditure on prescription drugs. To calculate correct reimbursement, all pharmacies therefore record prescription sales at the time of dispensing and submit these data to a central database. A copy of the data from the pharmacies in the North Denmark Region and the Central Denmark Region (before the municipality reform of 2007 the counties of North Jutland, Viborg, Ringkjøbing, and Aarhus) are transferred to a research database located at the Department of Clinical Epidemiology at Aarhus University called the Aarhus University Prescription Database (AUPD). This database has had complete coverage since 1998. The AUPD records the patient's CPR-number, anatomic therapeutic chemical (ATC) classification code of the prescribed drug, and the date of dispensing. Non-reimbursable pharmaceuticals, which are not registered in the AUPD, include contraceptives and over-the-counter drugs, e.g. non-narcotic analgesics and motion-sickness medications.

3.2.5 The Danish National Prescription Registry

Like the AUPD, the Danish National Prescription Registry is a registry of expedited prescriptions and records patient CPR-numbers, ATC-codes, and date of expedition. The Danish National Prescription Registry covers entire Denmark and also includes non-reimbursable pharmaceuticals; over-the-counter medications are not included however. The Danish National Prescription Registry was established in 1994.

3.2.6 The Danish National Health Service Register

This register holds data from 1990 and onwards on consultations and treatments performed by primary health care providers such as general practitioners (GP), dentists, and physiotherapists [164]. The data in the National Health Service Register is based on invoices sent to the Regional Health Administrations by the primary health care providers. The data includes dates and codes for the specific services performed along with patient CPR-numbers. Importantly, the primary health care providers do not record diagnostic codes.

3.3 Study design

An overview of the study designs used in this thesis is presented in **Table 5**, and explained in further detail in the following.

Table 5: Design of the studies in the thesis

Study	Setting, period	Design	Participants	Exposures	Outcomes
1	North Denmark and Central Denmark Regions 1999-2010	Case-control	All incident cases of AF and population controls	· Infections treated at the hospital · Infections treated in the community · Seasonal influenza vaccinations	· Incident AF
2	North Denmark and Central Denmark Regions 1997-2012	Cohort	All patients with first-time pneumonia hospitalization	· AF · Pre-admission use of cardiovascular medications	· 30-day ATE risk · 30-day and 365-day mortality
3	Denmark 2005-2011	Cohort	All patients with first-time ICU admission	· AF · Pre-admission use of cardiovascular medications	· 30-day and 365-day ATE risk · 30-day and 365-day mortality

AF: atrial fibrillation; ATE: arterial thromboembolism

3.3.1 Study 1

To examine the risk of incident AF following infections and influenza vaccinations, we conducted a population-based case-control study in the North Denmark and Central Denmark Regions from 1999 through 2010. All incident cases of AF in the study area were identified in the DNPR. We used the CRS to include up to 5 control persons for each case. Cases and controls were matched on age,

sex, and index date (i.e. date of first hospital contact with AF in the case person). Controls had to be alive and in risk of incident AF on the index date. We retrieved data on hospital contacts with infections (admission, out-patient specialist clinic, and emergency room) from the DNPR. Infections treated in the community were ascertained by filled prescriptions for antibiotics or anti-viral agents recorded in the AUPD. The Danish National Health Service Registry provided information reimbursement for seasonal influenza vaccinations given at the GPs; seasonal influenza vaccinations have been universally reimbursed since 2003 to all citizens ≥65 years old and those with chronic diseases [165]. All exposures were ascertained within a 90 day time-period before the index date.

Conditions that we assumed could confound our estimates included ischemic heart disease, congestive heart failure, valvular heart disease, cerebral arteriosclerosis, peripheral arteriosclerosis, arterial hypertension, diabetes types 1 and 2, thyrotoxicosis, uraemia, chronic pulmonary disease, obesity, alcoholism, and prior cardiac surgery. We therefore searched the DNPR for occurrences of these conditions before the index date. Because uncomplicated arterial hypertension, diabetes type 2, and thyrotoxicosis are often managed by the GPs without hospital referral, these conditions are likely underreported in the DNPR. We therefore supplemented with AUPD data to extend the category of thyrotoxicosis to include persons prescribed anti-thyroid drugs, the category of diabetes type 2 to include noninsulin glucose-lowering drugs users, and the category of hypertension to include users of two or more classes of the most common antihypertensive drugs (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta-blockers, vasodilating calcium channel blockers, thiazide diuretics).

Even though guidelines recommend referring patients with newly diagnosed AF to specialist evaluation [166], we cannot rule out that some GPs may chose to manage AF patients without referral. This could lead to inclusion of cases with prevalent rather than incident atrial fibrillation or inclusion of individuals with atrial fibrillation in the control group. To estimate the size of this issue, we used the AUPD to identify participants with filled prescriptions for digoxin or vitamin K antagonists.

3.3.2 Study 2 and 3

To examine the impact of pre-existing AF and associated preadmission mediation on the prognosis for patients hospitalized with pneumonia and patients admitted to the ICU we conducted two cohort studies (study 2 and study 3). Study 2 included all patients with first hospitalized pneumonia episode in the North Denmark and Central Denmark Regions from 1997 through 2012. Study 3 included all first-time ICU admissions in entire Denmark from 2005 through 2011. The participants in study 2 were identified using the DNPR, whereas the DID was used to include participants for study 3. In both studies 2 and 3, cohort members with a diagnosis of AF recorded in the DNPR within 5 years before the index pneumonia/ ICU admission were indentified. The outcomes in study 2 were risk of arterial thromboembolism at 30 days following admission, and mortality at 30 days and 365 days following admission. In study 3, the outcomes were risk of arterial thromboembolism and mortality, both at 30 days and 365 days following admission. Episodes of arterial thromboembolism were noted in the DNPR whereas the CRS provided data on vital status.

We considered the elements included in the CHA_2DS_2-VASc-score (congestive heart failure, hypertension, diabetes, previous stroke, vascular disease, age, and sex) to be potential confounders in the thromboembolism analyses and we retrieved data on these disease categories from the DNPR. For the mortality analyses, we included data from the DNPR on the disease categories included in the Charlson Index, which has been shown to predict mortality following admission the hospital and admission to the ICU [101, 167, 168]. We further regarded valvular heart disease, angina pectoris and chronic ischemic heart disease, hypertension, smoking, alcoholism, and obesity as potentially confounding factors in the mortality analyses and these were conditions were consequently also included. To correct the mortality estimates for imbalances in frailty or health awareness, not controlled for by previously diagnosed disease, we retrieved data from the Danish National Health Service Registry on preventive consultations, social-medicine related consultations, conversational therapy, and influenza vaccination at the GP within one year preceding index admission, and further included applications for reimbursement due to chronic or terminal illness. In study 2, the DNPR

further provided data on use of mechanical ventilation during pneumonia admission, and in study 3, the DID supplied information on use of invasive mechanical ventilation, non-invasive ventilation, renal replacement therapy, and use of inotropes and vasopressors.

Data on pre-admission treatments for AF included prescriptions for statins, vitamin K antagonists, aspirin, beta-blockers, nondihydropyridine calcium-channel blockers, amiodarone, and digoxin filled within 100 days of index admission. In study 2, prescription data was obtained from the AUPD, whereas the Danish National Prescriptions Registry provided data for study 3.

3.4 Statistical analyses

3.4.1 Study 1

We first calculated frequencies and proportions of the study variables among cases and controls. We used conditional logistic regression analysis to compute odds ratios (OR) with 95% confidence intervals (CI) for the association between infections with hospital contact, infections treated in the community, and seasonal influenza vaccinations. These ORs can be considered unbiased estimates of the incidence rate ratio because cases and controls were matched on the index date. ORs were presented both as unadjusted estimates and estimates adjusted for the potential confounders (ischemic heart disease, congestive heart failure, valvular heart disease, cerebral arteriosclerosis, peripheral arteriosclerosis, arterial hypertension, diabetes types 1 and 2, thyrotoxicosis, uraemia, chronic pulmonary disease, obesity, alcoholism, and prior cardiac surgery). We further produced estimates within subgroups of the most common types of hospitalized infections (bacterial pneumonia, other lower airway infections, gastroenteritis, abdominal infections, urinary tract infections, cutaneous infections, blood stream infections) and the most commonly prescribed antibiotics and antiviral agents (penicillin V, antistaphylococcal penicillins, extended-spectrum penicillins, sulfonamides and/or trimethoprim, macrolides, nitrofurantoin, acyclovir). To investigate if these associations was different in individuals free of other cardiovascular disease, we excluded all

study participants with previously or coincidentally diagnosed ischemic heart disease, congestive heart failure, valvular heart disease, cerebral arteriosclerosis, peripheral arteriosclerosis, hypertension, and prior cardiac surgery. Because these restrictions depleted many of the case-control pairs, we chose not to uphold matching in the restricted analyses. Instead we used logistic regression analyses to estimate crude and adjusted ORs, including the matching criteria (age and gender) in the adjusted analyses along with the other confounders, thereby yielding adjusted estimates similar to those that would have been obtained from conditional logistic regression analyses, had it been feasible [169]. To assess the effect of time from exposure to onset of AF, we produced estimates within post-exposure periods of 0-14, 15-30, 31-60, and 61-90 days. We performed sensitivity analyses, in which we repeated the previously performed analyses in a restricted study population that excluded participants with prescriptions for vitamin K antagonists or digoxin because this could indicate previously diagnosed AF. We also excluded children (age<18) from the restricted population because AF in childhood could indicate congenital heart disease. Further, we investigated whether estimates differed if AF was diagnosed during hospitalization, at the hospital specialist outpatient clinic, or in the emergency department. To assess the possibility of AF being prevalent before onset of infection, we computed estimates for AF diagnosed at 1–14 and 1–90 days after hospital contact with infection, incorporating that the patient had to be discharged from the hospital contact with infection at least the day before the hospital contact with AF. Owing to the reimbursement rules, all analyses concerning seasonal influenza vaccinations were limited to atrial fibrillation diagnosed from 2003–2010 in individuals >65 years old.

3.4.2 Study 2

Follow-up began at hospital admission with pneumonia and continued until 1 January 2013, or until death or migration, whichever occurred first. The risk of arterial thromboembolism was estimated as the cumulative incidence of arterial thromboembolism within 30 days of admission in patients with and without pre-existing AF. Death was a competing risk for the outcome of arterial

thromboembolism, which we accounted for in the analysis [170]. To further compare the risk of arterial thromboembolism in patients with pre-existing AF to that in patients without, we estimated crude hazard ratios (HRs), and HRs adjusted for the thromboembolism risk factors in the CHA2DS2-VASc score using Cox regression analyses. To investigate whether an association between pre-existing AF and development of arterial thromboembolism was related to repeated events, we also performed an analysis according to presence or absence of previously diagnosed arterial thromboembolism. We examined if preadmission treatment with vitamin K antagonists or aspirin had influence on the risk of arterial thromboembolism by comparing users to non-users in patients with and without AF separately. We repeated the analyses for patients without contraindications for anticoagulant therapy (previous cranial trauma and gastro-intestinal bleeding episode). Because all diagnoses coded during a given admission were assigned to the same discharge date in the DNPR, 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. In some patients, arterial thromboembolism might have preceded pneumonia. We therefore performed supplementary analyses in which we assessed the 30-day risk of arterial thromboembolism, only considering diagnoses assigned after discharge from the index pneumonia admission.

We estimated the mortality following pneumonia admission in patients with and without pre-existing AF by using the Kaplan-Meier method to produce cumulative mortality risks at 30 and 365 days. We further compared the mortality in patients with and without pre-existing AF by computing hazard ratios (HR) for death, using Cox regression analysis. We computed crude HRs, HRs adjusted for age and sex, and HRs adjusted for age, sex, the conditions included in the Charlson Index, valvular heart disease, alcoholism, 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 by stratification on previous myocardial infarction, congestive heart failure, treatment with

mechanical ventilation, and admission to the intensive care unit during the index pneumonia admission. The effect of preadmission medication on the risk of death was evaluated by comparing users to non-users of vitamin K antagonists, aspirin, beta-blockers, calcium-channel blockers, digoxin, amiodarone, and statins, in patients with and without pre-existing AF separately, using Kaplan-Meier methods and Cox regression.

Preceding all Cox regression analyses, we verified the assumption of proportional hazards graphically.

3.4.3 Study 3

Follow-up began at ICU admission and continued until 1 January 2013. We estimated the cumulative risk of arterial thromboembolism at 30 days and 365 days following ICU admission in patients with and without pre-existing AF by computing pseudo values for each observation, which we analyzed in a generalized linear regression model, accounting for the competing risk of death in the analyses [171, 172]. Likewise, we estimated the cumulative risk ratio (CRR) comparing the risk of arterial thromboembolism at 30 days and 365 days in patients with AF to that in non-AF patients. We calculated both crude CRRs and CRRs adjusted for prevalence of the risk factors in the CHA_2DS_2-VASc-score. The effect of preadmission use of vitamin-K antagonists and aspirin on the risk of arterial thromboembolism was examined by comparing users to non-users among patients with and without pre-existing AF. As described in relation to study 2, the actual time of arterial thromboembolism onset during an admission cannot be determined by the DNPR data and some episodes of arterial thromboembolism may have occurred before the patient was admitted to the ICU. We therefore performed supplementary analyses in which we estimated the cumulative risk and CRR of arterial thromboembolism at 30 days and 365 days following ICU admission, only considering arterial thromboembolisms diagnosed at a later hospital admission than the hospital admission during which the patient was treated at the ICU.

We started the mortality analyses by computing the Kaplan-Meier mortality estimates in patients with and without pre-existing AF at 30 days and 365 days following ICU admission. We then compared the mortality risk in ICU patients with pre-existing AF to that in ICU patients without pre-existing AF by computing relative risks (RR) through generalized linear regression analyses of pseudo values for each observation [172, 173]. We computed crude RRs and RRs adjusted for age, sex, co-morbidities, and frailty markers as defined by GP services. To examine if any effect of AF was different across subgroups of ICU patients, we divided the cohort into 3 age groups of equal size (15–55, 55–71, 71–103 years) and repeated the analyses within each age group. We also performed analyses among men and women separately. We investigated if the effect of AF was dependent of coexisting cardiovascular diseases by conducting analyses in ICU patients with and without previous myocardial infarction and previously diagnosed congestive heart failure. To address any influence of the disease severity during ICU admission and the type of ICU admission on the effect of AF, we also performed stratified analyses defined by use of mechanical ventilation and renal replacement therapy during the ICU admission, and type of surgery performed in relation to the ICU admission. To examine the effect of preadmission treatment for AF, we assessed absolute and relative risks of death in users of statins, vitamin K antagonists, aspirin, beta-blockers, cardiac acting calcium-channel blockers, amiodarone, and digoxin as compared to non-users in patients with and without AF separately.

3.5 Software

All analyses were performed using Stata 11.2 software (StataCorp, College Station, Texas, USA). In study 2, the cumulative incidence of arterial thromboembolism was computed using the `stcompet` command included in the user-written `st0059` package [174]. In study 3, pseudo values were generated using the `stpci` and `stpsurv` commands as appropriate, which are included in the user-written `st0202` package [172].

3.6 Ethics

In concordance with Danish legislation, we did not obtain informed consent from the study participants because all studies were conducted using registry data. The studies were approved by the Danish Data Protection Agency, record numbers 2013-41-1924, 2009-41-3987, and 2009-41-3866.

4. RESULTS

The main results of the 3 studies are presented in the following.

4.1 Study 1

In study 1, we included 51,491 cases of incident AF and 253,112 matched control persons. We were unable to find matching control persons for 701 cases and the unmatched cases did not participate in the matched analyses. The median age of the case persons was 75 years (inter quartile range: 65–83 years) and was 74 years (inter quartile range 65–82 years) in the controls. The prevalence of co-existing diseases was higher among the cases than the controls; in example 12% of the cases had previously diagnosed myocardial infarction as opposed to 7% if the controls, and 36% of the cases had hypertension compared with 22% of the controls.

As compared to individuals who did not have infections, the risk of incident AF was markedly increased following infections with hospital contact (adjusted OR 15.56 (95% CI: 14.88–16.27)) and following infections treated in the community (adjusted OR 1.92 (95% CI: 1.88–1.97). There was substantial variation in the risk of AF dependent of the type of infection. In infections with hospital contact, high ORs was observed with pneumonia (adjusted OR 20.76 (95% CI: 19.43–22.19)) and bloodstream infections (adjusted OR 19.19 (95% CI: 16.31–22.57)) and relatively lower ORs with abdominal infections (adjusted OR 6.86 (95% CI: 6.13–7.69)) and cutaneous infections (adjusted OR (95% CI: 6.49–8.86)). In infections treated in the community, treatments with penicillin-V and macrolides were associated with higher ORs for incident AF (adjusted OR 2.13 (95% CI: 2.05–2.21) and 2.22 (95% CI: 2.11–2.34), whereas lower ORs were seen with sulphonamides and/or trimethoprim and nitrofurantoin (adjusted OR 1.22 (95% CI: 1.15–1.29) and 1.16 (95% CI: 1.04–1.28)). A prescription for acyclovir was not associated with incident AF (adjusted OR 0.99 (95% CI: 0.81–1.21). Individuals who had been given seasonal influenza vaccinations did not have a higher risk of incident AF than those who had not been vaccinated (adjusted OR 1.02 (95%CI: 0.97–1.07)). The

interpretation of the estimates did not change when focussing on associations in individuals free of other cardiovascular disease. The association between infections and incident AF was clearly dependent on the time from exposure to diagnosis of AF with strong associations in the first 14 days following exposure, thereafter rapidly diminishing ORs. **Table 5** illustrates the effect of increasing time from exposure on the estimates for selected types of infections with hospital contact and antibiotics. Infections with hospital contact and infections treated in the community remained strongly associated with incident AF in the sensitivity analyses.

Table 5: Relationship between incident atrial fibrillation and selected infections with hospital contact and filled prescriptions for antibiotics in the community setting, by time from exposure to diagnosis

	0–14 days Adjusted OR * (95% CI)	15–30 days Adjusted OR * (95% CI)	31–60 days Adjusted OR * (95% CI)	61–90 days Adjusted OR * (95% CI)
No infection	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Any infection	65.16 (59.97–70.80)	1.94 (1.68–2.24)	1.55 (1.38–1.74)	1.05 (0.92–1.20)
Bacterial pneumonia	82.14 (72.65–92.88)	2.42 (1.94–3.00)	1.86 (1.20–2.89)	1.21 (0.98–1.48)
Bloodstream infections	71.51 (52.90–96.65)	5.24 (3.09–8.90)	3.56 (2.40–5.28)	1.40 (0.85–2.29)
No antibiotic or antiviral agent	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Any antibiotic or antiviral agent	2.84 (2.73–2.95)	1.83 (1.74–1.91)	1.52 (1.46–1.58)	1.34 (1.29–1.39)
Penicillin V	3.77 (3.53–4.03)	2.16 (1.99–2.34)	1.74 (1.64–1.85)	1.47 (1.37–1.57)
Sulfonamides and/or trimethoprim	1.29 (1.16–1.43)	1.23 (1.10–1.38)	1.08 (0.99–1.18)	1.09 (1.00–1.19)
Macrolides	3.95 (3.60–4.35)	2.42 (2.16–2.72)	1.88 (1.72–2.06)	1.49 (1.35–1.63)

CI = confidence interval; OR = odds ratio

* Conditional on age and sex. Adjusted for prevalence of ischemic heart disease, congestive heart failure, valvular heart disease, cerebral arteriosclerosis, peripheral arteriosclerosis, hypertension, diabetes types 1 and 2, thyrotoxicosis, uremia, obesity, alcoholism, and prior cardiac surgery.

4.2 Study 2

Study 2 included 88,315 patients with first pneumonia hospitalization of which 8,880 (10%) had pre-existing AF. The median age of the pneumonia patients with pre-existing AF was 80 years (inter quartile range: 73–85) and the median age in non-AF patients was 72 (inter quartile range: 59–81). Compared to patients without AF, patients with pre-existing AF had more coexisting diseases such as congestive heart failure (38.4% vs. 7.2%) and previous myocardial infarction (18.6% vs. 8.3%), diabetes (14.8% vs. 8.2%), and renal failure (8.9% vs. 3.6%). Patterns of ICU admission and treatment with mechanical ventilation were fairly similar among patients with and without AF (7.5% vs. 7.0% and 4.9% vs. 5.3%, respectively).

The cumulative incidence of arterial thromboembolism at 30 days following admission was 5.2% in patients with AF and 3.6% in non-AF patients. Comparing patients with and without AF, the crude HR for arterial thromboembolism was 1.61 (95% CI: 1.46–1.78), but after controlling for the risk factors in the CHA_2DS_2-VASc-Score an adjusted HR of 1.06 (95% CI: 0.96–1.18) was yielded. Among AF patients, preadmission use of vitamin K antagonists was associated to reduced risk of arterial thromboembolism as compared to non-users (adjusted HR 0.74 (95% CI: 0.61–0.91)). Comparing AF patients who were preadmission users of aspirin to AF patients who did not use aspirin, the adjusted HR for arterial thromboembolism at 30 days following pneumonia admission was 0.83 (95% CI: 0.68–1.01).

The mortality at 30 days following pneumonia admission was 20.1% in AF patients and 13.9% in patients without AF. Comparing pneumonia patients with and without AF, the crude HR for 30-day mortality was 1.49 (95%CI: 1.42–1.57). When accounting for differences in age, sex distribution, and burden of comorbidity, the adjusted HR was 1.00 (95% CI: 0.94–1.05). The adjusted HR estimates varied little over strata defined by sex, previous myocardial infarction, congestive heart failure, ICU admission, and treatment with mechanical ventilation. Mortality at 365 days following pneumonia admission was 43.7% in patients with AF and 30.3% in patients without AF. The

corresponding crude HR was 1.57 (95% CI: 1.52–1.63) and the adjusted HR was 1.01 (95%CI: 0.98–1.05). As with the 30-day estimates, little variation was observed in the adjusted HRs in the stratified analyses (sex, previous myocardial infarction, congestive heart failure, ICU admission, mechanical ventilation).

In pneumonia patients with AF, reduced mortality was observed in preadmission users of vitamin K antagonists, beta-blockers, and statins as compared to non users; increased mortality was observed with amiodarone and digoxin use. Estimates are summarized in **Table 6**.

Table 6. Impact of preadmission medication on mortality following pneumonia admission in patients with AF

Medication	30-day mortality Adjusted HR (95% CI)*	365-day mortality Adjusted HR (95% CI)*
Vitamin K antagonists	0.70 (0.63–0.77)	0.72 (0.67–0.77)
Aspirin	0.98 (0.89–1.08)	0.98 (0.91–1.05)
Beta-blockers	0.77 (0.70–0.85)	0.83 (0.78–0.89)
Calcium-channel blockers	1.17 (1.00–1.36)	1.03 (0.93–1.15)
Statins	0.70 (0.61–0.80)	0.72 (0.66–0.79)
Amiodarone	1.18 (1.00–1.42)	1.15 (1.02–1.30)
Digoxin	1.16 (1.06–1.28)	1.15 (1.08–1.23)

AF: Atrial fibrillation; HR: Hazard ratio; CI: Confidence interval *: Reference group: non-users

4.3 Study 3

For study 3, we included 57,110 patients with first ICU admission, of which 5,065 (9%) had pre-existing AF. The median age for ICU patients with pre-existing AF was 75 years (inter quartile range: 67–81) and 62 year (inter quartile range 47–73) in ICU patients without AF. The proportion of males was higher among ICU patients with pre-existing AF than non-AF patients (62% vs. 55%). The burden of coexisting diseases was substantially higher in patients with pre-existing AF as compared to patients without AF. In example, the prevalence of previously diagnosed myocardial infarction was 20.1% vs. 9.8%, congestive heart failure 33.8% vs. 6.2%, hypertension 48.5% vs. 21.1%, and chronic pulmonary disease 26.4% vs. 14.9% in ICU patients with and without pre-existing AF respectively. ICU

patients with pre-existing AF were more often treated with mechanical ventilation (42% vs. 35%), renal replacement therapy (5% vs. 3%), and inotropes or vasopressors (41% vs. 29%) than did non-AF patients.

The 30-day risk of arterial thromboembolism in ICU patients with and without pre-existing AF was 2.8% (95% CI: 2.4–3.3) and 2.0% (95% CI: 1.9–2.2) respectively. The corresponding crude CRR was 1.41 (95% CI: 1.19–1.67). After adjusting for the risk factors included in the CHA_2DS_2-VASc-score the estimate fell to 1.14 (95% CI: 0.93–1.40). At 365 days following ICU admission, the risk of arterial thromboembolism was 4.3% (95% CI: 3.7–4.9) in patients with AF and 2.9% (95% CI: 2.7–3.0) in patients without AF. The crude CRR comparing these figures was 1.50 (95% CI: 1.31–1.73) and the adjusted CRR was 1.20 (1.02–1.41). In AF patients, the adjusted CRR for arterial thromboembolism comparing preadmission users of vitamin K antagonists to non-users was 0.57 (95% CI: 0.26–1.25) at 30 days following admission and 0.76 (95% CI: 0.50–1.16) at 365 days. Comparing preadmission users of aspirin to non-users, among ICU patients with pre-existing AF, the adjusted CRR for 30-day arterial thromboembolism was 1.05 (95% CI: 0.64–1.75) and 1.13(95% CI: 0.81–1.59) at 365 days.

Mortality at 30 days following ICU admission was 26.8% (95% CI: 25.6–28.0) in ICU patients with pre-existing AF and 16.0% (95% CI: 15.7%–16.4%) in ICU patients without AF. The corresponding crude RR was 1.67 (95% CI: 1.59–1.76) and the confounder adjusted RR was 1.04 (95% CI: 0.99–1.10). In the analyses stratified on age, a substantially higher mortality risk was observed in patients with pre-existing AF in the youngest third of the cohort (age 15–55 years) as compared to patients without AF (13.6% (95% CI: 10.0–18.5) vs. 6.1% (95% CI: 5.7–6.4)). This effect of AF persisted after controlling for confounders (adjusted RR 1.73 (95% CI: 1.29–2.32)). In the two older age groups (age 55–71 and 71–105 years), the adjusted RRs for 30-day mortality were close to 1. Among ICU patients treated with mechanical ventilation, the adjusted RR for 30 day mortality was 1.12 (95% CI: 1.05–1.20) comparing ICU patients with and without pre-existing AF, whereas the estimate in ICU patients not treated with mechanical ventilation was 1.00 (95% CI: 0.93–1.08).

Adjusted RR estimates were close to 1 over strata defined by sex, previous myocardial infarction, congestive heart failure, and surgery in relation to the ICU admission.

Mortality at 365 days following ICU admission was 40.9% (95% CI: 40.0–42.3) in patients with pre-existing AF and 25.4% (95% CI: 25.0–25.8) in ICU patients without AF, with a crude RR of 1.61 (95% CI: 1.55–1.67) and an adjusted RR of 1.03 (95% CI: 1.00–1.07). As observed with the 30-day estimates, higher mortality with AF was observed in the age group 15–55 years (adjusted RR 1.34 (95% CI: 1.06–1.69) whereas the estimates for the age groups 55–71 years and 71–105 years were close 1. Also in concordance with the 30-day findings, pre-existing AF was associated to increased mortality among ICU patients treated with mechanical ventilation (adjusted RR 1.09 (95% CI: 1.04–1.15). As opposed to the 30-day estimates, increased risk with AF was observed at 365 days in patients who had undergone surgery in relation to the ICU admission (adjusted RR 1.07 (95% CI: 1.02–1.13)) and in females (adjusted RR 1.07 (95% CI: 1.01–1.13)). The results from the remaining stratified analyses were in line with the 30-day estimates.

In ICU patients with AF, preadmission users of vitamin K antagonists had reduced mortality as compared to non-users; increased mortality was seen in users of amiodarone. Estimates for the effect of preadmission medications on the mortality are given in **Table 7**.

Table 7. Impact of preadmission medication on mortality following ICU admission in patients with AF

Medication	30-day mortality Adjusted RR (95% CI)*	365-day mortality Adjusted RR (95% CI)*
Vitamin K antagonists	0.91 (0.82–1.00)	0.91 (0.85–0.97)
Aspirin	0.99 (0.91–1.09)	1.00 (0.94–1.06)
Beta-blockers	1.07 (0.98–1.18)	1.00 (0.95–1.07)
Calcium-channel blockers	0.86 (0.71–1.03)	0.93 (0.82–1.05)
Statins	0.93 (0.84–1.04)	0.95 (0.88–1.02)
Amiodarone	1.15 (0.98–1.34)	1.12 (1.01–1.25)
Digoxin	0.97 (0.88–1.07)	1.01 (0.95–1.08)

AF: Atrial fibrillation; RR: Relative risk; CI: Confidence interval; *: Reference group: non-users

5. METHODOLOGICAL CONSIDERATIONS

5.1 Selection bias

Selection biases occur if procedures used to select study participants result in a different relationship between exposure and outcome among the study participants than that in those who should have been able to participate in the study [175]. To illustrate how selection bias might have affected our **case-control study**, I would like to derive how the odds ratios yielded in a case-control study estimate the incidence rate ratio (IRR) in the source population. The IRR is the ratio between the incidence rate in the exposed (IR_1) and the incidence rate in the unexposed (IR_0), which can be written as:

$$IRR = \frac{IR_1}{IR_0} = \frac{A/PT_1}{B/PT_0}$$

where A is the number of diseased individuals who were exposed, B the number of diseased individuals who were unexposed, PT_1 the exposed person-time, and PT_0 the unexposed person-time in the source population. Assuming the numbers of cases sampled for the study that were exposed (a) and the numbers of cases sampled for the study that were unexposed (b) equals the numbers of exposed and unexposed diseased individuals in the source population, we can formulate the IRR as:

$$IRR = \frac{A/PT_1}{B/PT_0} = \frac{a/PT_1}{b/PT_0} = \frac{a}{b} \times \frac{PT_0}{PT_1}.$$

If controls are sampled from the source population at random and at the same time as their corresponding case, then the number of exposed controls (c) seen relative to the amount exposed person-time in the source population should be equal to the number of unexposed controls (d) as seen relative to the amount of unexposed person-time in the source population:

$$\frac{c}{PT_1} = \frac{d}{PT_0} \Leftrightarrow \frac{c}{d} = \frac{PT_1}{PT_0}$$

Thus, we can express the IRR as

$$IRR = \frac{a}{b} \times \frac{PT_0}{PT_1} = \frac{a}{b} \times \frac{d}{c},$$

the latter term being the cross-product of the case-control study's two-by-two table, which is the odds ratio. Are the assumptions made above valid in our case-control study? Cases were identified using hospital diagnoses of AF. Validation studies have estimated the positive predictive value of AF diagnoses in the DNPR to be within the range 92–99% [28, 176, 177]. We can therefore reasonably assume that the vast majority of cases included in the study do in fact have AF. The negative predictive value of AF in the DNPR is unknown, however. Indeed, it is very unlikely that we included all incident cases of AF in the population, due to the fact that a substantial part of AF patients are not diagnosed, because their AF is without symptoms. As can be seen from the equations above, this will only result in a bias if the quantity $\frac{a}{b}$ do not equal $\frac{A}{B}$, in other words, if the selection of cases (=first hospital diagnosis of AF) is dependent on exposure status (=infections treated at the hospital, infections treated in the community, or influenza vaccinations). Because patients who are hospitalized with infections or receive a prescription for antibiotics necessarily have been in contact with the health care services, they will have a greater chance of having any silent AF diagnosed, as compared to individuals in the population without infections. A selection bias on this account is therefore possible and would lead to an inflation of the estimates. Our finding of a null-association between incident AF and influenza vaccinations—which also involves health care contact—does provide some methodological reassurance in this context. Also, the sensitivity analyses focussing on AF diagnoses recorded at a later admission than the admission with infection further addresses this potential problem, still demonstrating a substantial association between infections and incident AF. Controls were sampled using detailed population registries and selection bias is this process is unlikely. In our study design, we only allowed individuals to be sampled as controls once. Consequently—and owing to the

prevalence of AF—there were times during the study period when numbers of eligible controls persons in the source population were limited and 701 cases were unmatched. The loss of the unmatched cases from the matched analyses reduces the precision of the estimates, but selection bias is only introduced if the lacking controls (i.e. missing information on person-time) is dependent on exposure status, which we have no reason to believe. In hindsight, we could have avoided this issue by allowing controls to be sampled multiple times. This would have given no disadvantages—rather it would have improved the precision of the estimates—as long as exposure status was updated at each sampling. We chose, however, to adhere to our pre-planned analyses.

In **the cohort studies**, we defined the study participants by a first-time pneumonia diagnosis in the DNPR, respectively a first-time entry in the DID. The positive predictive value of pneumonia in the DNPR has been reported to be 90% (95% CI: 82–95%) [178]. The positive predictive value of a procedural code of ICU therapy or ICU observation recorded in the DNPR is 87.2% (95% CI: 75.6–94.5) [179]. This figure is probably higher in the DID, because the DID only accepts procedural codes of ICU therapy or observation assigned from an ICU; concerning procedural codes of ICU therapy or ICU observation assigned in patients also treated with mechanical ventilation, the positive predictive value is 100% (95% CI: 95.1–100)[179]. It is assumed that the DID has 95% coverage and the negative predictive value of pneumonia coding has been reported to be 91.3% (95% CI: 90.4–92.1%) in patients admitted to the emergency department [162, 180]. Thus, well-defined populations constitute the two cohorts. Any coding errors leading to erroneous inclusion or exclusion into/ out of the cohorts is unlikely to be related to exposure (=AF status) and will therefore not give rise to selection bias. Loss to follow-up could cause selection bias in the cohort studies if exits from the study were related to the exposure. However, the completeness of the used registries eliminated this concern in both cohorts; in fact, the follow-up data was virtually complete.

5.2 Information bias

Information bias is a distortion of study estimates induced by erroneous measuring of study variables (exposure, confounders, and outcomes) [181]. Measurement errors in variables of discrete data are also called misclassification [175]. Any misclassification of a variable that is dependent on the value of other variables is referred to as differential misclassification, whereas misclassification that is independent of other variables is called non-differential misclassification. This distinction is important because bias induced by non-differential misclassification will be towards the null, whereas the direction a bias caused by differential misclassification is unpredictable [175].

All studies in this thesis were conducted on prospectively sampled registry data which eliminated the risk of "recall bias"—a common type of information bias in observational studies where the researcher has to ascertain exposures and confounders retrospectively. An obvious prerequisite for yielding meaningful estimates from registry-based studies is a high validity of the data recorded in the registries. As discussed above, a diagnostic code of AF—defining cases in our case-control study, defining exposure status in our cohort studies—has a high positive predictive value in the DNPR. Diagnostic codes of infection, which we used as exposure variables in our case-control study, have only been validated in a few studies, reporting the positive predictive value for pneumonia to be 90% (95% CI: 82–95%), for pleural empyema to be 91% (95% CI: 86.0–94.1%), and for various infections treated at an emergency department to be 78% (95% CI: 76.6–79.9) [178, 180, 182]. We ascertained infections treated in the community as filled prescriptions for antibiotics, thereby assuming that patients are only prescribed antibiotics if they actually have an infection. Because Danish doctors have a conservative approach concerning prescription of antibiotics this may be a fair assumption [183]. Any misclassification of the exposure in our case-control study is unlikely to be dependent on case-status and would therefore be non-differential. We considered the day of hospitalization with infection, or the day of filling a prescription for antibiotics, to be the day of exposure, but the actual onset of infection may have occurred at an earlier time. We could thereby underestimate period of

increased risk of AF following infections. Because most patients contact their physician soon after symptoms of infection appear, this underestimation is likely limited to a few days [184]. In our cohort studies, we examined the impact of preadmission medications on the risk of arterial thromboembolism and mortality. In these analyses, we relied on filled prescriptions as a proxy measure for actual use of the given medication, which implies that any non-adherence or discontinuation of the medication after the prescription was filled, would bias the estimate of the drug effect towards the null.

For both our case-control study and the cohort studies, we included data on a wide range of variables that could potentially confound the estimates. The disease categories included in the Charlson Index—which we used in the mortality analyses—is coded with a mean positive predictive value of 98% (95% CI: 96.9–98.8%) [185]. Because there is a substantial overlap between the disease categories included the Charlson Score and the disease categories included in the thromboembolism analyses and in the case-control study was also expect a high validity of these variables. Because most patients with AF are examined by a cardiologist, it is possible that AF patients are more likely to be diagnosed with other cardiovascular diseases, e.g. heart failure or valvular heart disease, than non-AF patients which could lead to differential misclassification of confounders in our cohort studies. This is, however, only likely to concern asymptomatic—thus less severe—stages of co-existing cardiac diseases. Concerning other variables included for confounder analyses, we do not consider that there is an appreciable association between any misclassification and exposure status.

In our cohort studies, the outcomes were arterial thromboembolism and death. The coding of the latter outcome is virtually flawless in the civil registration system, vulnerable only to emigration. Validation studies have reported a positive predictive value of a diagnostic code for ischemic stroke in the range 87.6% (95% CI: 80.1–93.1%)–100% (97.5% CI: 89.4–100%) and the majority of patients coded with unspecified stroke have ischemic stroke [186, 187]. The validity of diagnostic codes for peripheral arterial thromboembolisms is unknown. Likewise, the negative predictive value for arterial

thromboembolism is unknown. It is unlikely that major episodes of arterial thromboembolisms are unnoticed because these are associated with severe symptoms and require interventions and/or rehabilitation. Treating physicians may forget to code minor, self-resolving episodes of arterial thromboembolism, however, namely in patients with lengthy and complicated admission. Also, diagnostic codes assigned in an admission, during which the patient dies, may be less comprehensive. Thus, underassessment of the outcome arterial thromboembolism is possible. Ascertainment of arterial thromboembolism is unlikely to be dependent on preadmission AF status *per se*, but because AF patients have higher mortality in both cohort studies than non-AF patients, there may still be a risk of non-differential misclassification of this outcome.

5.3 Confounding

Confounding—also called confounding bias—is a distortion of the estimates induced by a factor that is associated with both the outcome and exposure, but not being interposed between exposure and outcome on the causal path [181]. As described in the methods section, we considered age, sex, a range of co-existing diseases to be potential confounding factors in our studies. In the cohort studies we further included certain services at the GPs to act as proxy variables for social marginalisation (conversational therapy, social medicine related consultation), advanced stage chronic disease (reimbursements for chronic and terminal disease), and frailty and health awareness (preventive consultation, influenza vaccination). We controlled for the effect of these variables by including them in multivariate models. In matched analyses in the case-control study, we controlled for age and sex by matching cases and controls on these factors. Despite the extensive adjustment procedures, estimates may still be under influence of uncontrolled confounding, stemming from either unmeasured or residual confounding. Unmeasured confounding—confounding from diseases or conditions not included in the data—is unlike to be a major issue in these studies owing to the large number covariates representing all major disease categories. Residual confounding, occurring when included data on the confounding variable is inadequate in describing the effect of the confounder in

the study population, cannot be ruled out. Residual confounding may be a problem in particular, concerning the variable congestive heart failure. In our data, congestive heart failure was described only by a dichotomous variable (present/ not present). In clinical practice, however, the diagnosis congestive heart failure spans from an asymptomatic echocardiographic finding to a severely disabling and life threatening disease. The severity of congestive heart failure seems of prognostic importance. Thus, had quantitative measures of cardiac performance—say ejection fraction, b-natriuretic peptide, or New York Heart Association Score—been available, we would have been able to control better for congestive heart failure. Concerning the analyses of preadmission medications and outcome in our cohort studies, two special types of bias—confounding by indication and healthy user bias—needs to be addressed. Patients who receive treatment with a given medication often differ from non-users, because users will have an indication for the treatment whereas non-users typically will not. Confounding by indication occurs when the indication for treatment is also related to the study outcome [188]. The prescribing physician will often have a greater picture of the patient's disease than what can be reflected in charts and registries; confounding by indication can therefore persist even after thorough confounder control. In our cohort studies, the finding of increased mortality with preadmission use of amiodarone may be ascribed confounding by indication, because amiodarone—being without negative inotropic properties—is often preferred for AF patients with substantially reduced ejection fraction, which we were not able to control for as discussed above. A healthy user bias occurs if users of a medication have a healthier life style and greater awareness of own health than non-users. Our ability to control for lifestyle factors was limited due to underreporting of elements such as smoking, alcohol overuse, and obesity in our dataset, and other important factors of health such as dietary habits, exercise, and mental wellbeing are completely lacking. Healthy users bias is probably more likely to occur with the prophylactic medications—e.g. statins—than medications prescribed for manifest disease [189]. The structure of the Danish healthcare system, with medical care free at the point of delivery and partial reimbursement of prescription drugs, minimises these

effects and, in fact, it does seem that statin users in Denmark have a more unhealthy lifestyle than non-users [190].

5.4 Reverse causation

The term reverse causation refers to a confusion concerning the temporal relations of the elements on the causal path, such that the researcher misinterprets what in reality is an exposure for being the outcome, and mistakes the real outcome for being an exposure. In our case-control study, AF may have been present in some cases before onset on infection. This is not reverse causation proper, however, because we do not believe that AF caused the infection; rather the temporal confusion in this instance could lead to a selection bias as previously discussed. In our cohort study of pneumonia patients (study 2), the outcome of arterial thromboembolism may be vulnerable to reverse causation because we could not determine the sequence of arterial thromboembolisms and pneumonia diagnosed during the same admission. Occurring in some 9% of patients admitted with stroke, pneumonia is a well recognised complication in stroke. Consequently, our absolute estimates of risk of arterial thromboembolism are likely inflated by reverse causation. If reverse causation also has influence on the relative estimates, comparing pneumonia patients with and without AF, depends on whether or not stroke patients with AF are more likely to develop pneumonia than stroke patients without AF, which we could not find information on in the literature. We performed sensitivity analyses, in which we only considered diagnoses of arterial thromboembolism assigned at a later admission than the pneumonia admission, in order to minimize the influence of potential reverse causation. The drawback of this approach is that the absolute risk estimates are likely to diminish as the time from the exposure to outcome is increased. Considering the magnitude of reverse causation in the pneumonia cohort, it should be noted, that the proportion of study participants expected to have nosocomial pneumonia is approximately 12% [178]. Similarly, reverse confounding may have had influence in the arterial thromboembolism analyses in the ICU cohort (study 3), but probably to a

lesser extent because most ICU admissions were surgery related. Reverse confounding is obviously not an issue in the mortality analyses in the two cohort studies.

5.5 Random error

Random errors are inevitable in research. We therefore presented all estimates accompanied by 95% confidence interval, which has the interpretation, that if the study was repeated an indefinite number of times, then the point estimate would be located within the limits of the confidence interval 95% of the times [191]. A prerequisite for this interpretation is that the test hypothesis is true and the study unbiased. Owing to the large sample sizes of our studies, most estimates had high statistical precision (i.e. narrow confidence intervals), but in some of the stratified analyses numbers of participants were reduced to an extent, that interpretation of point estimates was difficult due to broad confidence intervals. The definition of the confidence interval implies that true associations occasionally will not be "statistically significant"; conversely, "statistically significant" findings may be due to random error. In example, we found a "significant" association between seasonal influenza vaccinations and risk of AF at 2–3 months following exposure. Because this finding was in conflict with the other estimates for influenza vaccination, was not robust to sensitivity analyses, and exerted an illogical behaviour with concern to time from exposure to outcome, we concluded that this association was not a manifestation of a causal relation between influenza vaccinations and AF.

6. DISCUSSION IN RELATION TO THE EXISTING LITERATURE

6.1 Study 1

As can be seen from table 1, there are to our knowledge no previous studies examining the risk of AF following infections in a population-based setting and the results presented in the present dissertation are therefore completely novel. Our finding of markedly increased risk of AF following both infections treated at the hospital and infections treated in the community are in line with two small cross-sectional studies reporting preceding infections in 10–16% of patients with incident AF [34, 39]. Our literature searched showed that new-onset AF apparently is particularly common with severe infections. This is in concordance with our results for infections with hospital contact, showing higher odds ratios for incident AF with infections such as pneumonia and bloodstream infections as compared to less severe infections such as cutaneous infections and urinary tract infections. Consistently, the risk for AF with infections with hospital contact was much higher than infections treated in the community which are likely less severe.

We stated in the introduction, that an associated between infections and incident AF could be mediated via the inflammatory response to infection. From our results it clearly does seem that the severity of infection, and thereby following the degree of inflammatory activity, has an important impact on the subsequent risk of AF. We cannot from this observational study, however, clarify the underlying mechanisms in our findings. Plausibly, activation of the sympathetic nervous system by the inflammatory response, leading to tachycardia, shortened refractory period, myocardial strain, and provocation of rapidly depolarizing cells, could trigger AF. Inflammatory mediators could potentially also have direct effects on the myocardium. In infections with hospital contact we saw a high risk of AF with pneumonia, and among infections treated in the community penicillins and macrolides—preferred choices for respiratory tract infection—were associated with the highest risk of AF. In

patients with chest infections, AF could also be brought on by hypoxemia and increased pulmonary vessel resistance leading to myocardial ischemia and atrial stretching.

6.2 Study 2

We are not aware of other studies reporting estimates of the prognostic effect of pre-existing AF in patients with hospitalized pneumonia. In consistence with the previous literature, we found a high risk of thromboembolic complications and high mortality in pneumonia patients [81, 90]. While new-onset AF during pneumonia previously has been associated to increased mortality [192], we found similar relative mortality risk estimates in pneumonia patients with and without AF after accounting for confounding factors. One possible explanation for this discrepancy between new-onset and pre-existing AF could be that, 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, contemporary treatment strategies for AF can outweigh the potentially deleterious effects of the arrhythmia. As our results show, preadmission medication for AF appears to have great prognostic impact. Alternatively, new-onset AF during pneumonia may not be associated with worse prognosis in it self, but rather be a marker of clinically more severe pneumonia.

Because of the lacking previous literature on pneumonia patients with pre-existing AF, we can only relate our findings concerning effects of preadmission treatments, to studies of pneumonia patients in general. Our finding of reduced mortality with preadmission statin use is in concordance with several previous studies, as shown in table 3. It has been suggested that the beneficial effect of statins in pneumonia is related to statin's ability to modulate the inflammatory response and to prevent endothelia dysfunction [127].

Preadmission beta-blocker use was associated with reduced mortality in our study. This conflicts with a previous study (n=1,007, 188 beta-blocker users) reporting increased 30-day mortality in beta-blocker users compared with non-users (adjusted OR, 1.97 (95% CI, 1.03 – 3.78))

[139]. More extensive confounder control in our study may explain some of this difference. Mechanisms by which beta-blockers improve the prognosis for pneumonia patients may include protection against uncontrolled tachycardia, reduction of myocardial oxygen consumption, and possible also by dampening the metabolic shift towards catabolism that occur during critical illness [193].

We found both pneumonia patients with AF who were users of amiodarone, and pneumonia patients with AF who were digoxin users, to have higher mortality than non-users. The impact of these medications in pneumonia patients have not been investigated previously. While the increased mortality with amiodarone could be explained by residual confounding or confounding by indication, as previously discussed, the finding of increased mortality with digoxin is alarming because digoxin was used by 41% of the pneumonia patients with AF. Whether or not digoxin is associated with increased mortality in AF patients in the general population has been debated and observational studies have come to conflicting results [194]. During acute, severe disease it may be of importance that digoxin is a relatively difficult drug to manage clinically due to its narrow therapeutic window, multiple drug interactions, and susceptibility to disturbances in electrolyte concentrations [195]. Digoxin can induce severe arrhythmias, even with minor deviations from the target plasma concentration. This could be an explanation for the observed excess mortality among digoxin users in our cohort.

The role of vitamin K antagonists in pneumonia has not been investigated to date. We found that pre-admission use of vitamin K antagonists was associated with both reduced risk of arterial thromboembolism and improved survival. Previous studies have shown that the activity of the coagulation system is increased during infections and the degree of coagulation abnormality at hospital admission is correlated with the outcome of community-acquired pneumonia [89, 196]. Protection against hypercoagulation induced by infection is a plausible mechanism for the beneficial effect of vitamin K antagonists.

We did not find aspirin to be associated with neither reduced risk of arterial thromboembolism nor reduced mortality. Our findings are in line with clinical trials and present guidelines which—as discussed in the introduction—deemphasises the beneficial effect of aspirin in AF patients. Of note, we found reduced mortality with pre-admission use of in non-AF patients, which is in line with a previous study [139].

6.3 Study 3

Before ours, the risk of arterial thromboembolic complications has not been investigated in ICU patients with pre-existing AF and only two studies have, as far as we know, reported mortality rates in this patient group (**Table 2**). Our study is far larger than the previous, the first to provide estimates concerning arterial thromboembolic complications, and the first to provide confounder adjusted estimates concerning mortality with pre-existing AF in ICU patients. As previously mentioned, a large cohort study of patients admitted to hospital with sepsis (not necessarily to the ICU) did not find pre-existing AF associated with increased risk of stroke; in fact the point estimate was indicative of a "protective" effect. As opposed, our estimates points towards increased risk of arterial thromboembolism with pre-existing AF. The reason for this difference is unclear, but may represent the differences in cohort composition or differences in treatment of AF, both preadmission and in-hospital. As in study 2, our overall finding of no increased mortality with pre-existing AF conflicts with findings of increased risk of death with new-onset AF in the ICU patients. The arguments for this difference presented in relation to study 2 (influence of preadmission treatments, new-onset AF possible marker of disease severity) also apply in this setting. In contrast to study 2, however, we did find pre-existing AF associated with increased risk of mortality in ICU patients younger than 55 years. One explanation for this finding may be that other diseases and conditions overshadow the effect of AF in the older ICU patients and that the true effect of AF is unmasked in the younger ICU patients, who have lower absolute mortality and lower burden of co-existing diseases. Alternatively, AF in individuals younger than 55 years is seldom; it could possibly be associated with more severe

underlying structural heart disease, than what was reflected in our confounding variables. We also found increased mortality with pre-existing AF in ICU patients treated with mechanical ventilation, even after confounder adjustment. We suggest the following mechanisms could explain this finding. Mechanical ventilation results in positive intra-thoracic pressure, which can reduce cardiac filling. In AF patients, the diastolic phase may also be inefficient due to tachycardia and irregular heart rate. These effects combined could lead to hemodynamic instability in the mechanically ventilated patient. Alternatively, the use of mechanical ventilation may not be directly linked to increased mortality in AF patients, rather mechanical ventilation being a marker of greater disease severity during which pre-existing AF could have an impact on mortality in patients with severe hemodynamic instability due to diminished cardiac performance caused by AF itself.

In the thromboembolism analyses, point estimates with preadmission vitamin K antagonist use were indicative of a protective effect, but the interpretation was difficult due to confidence intervals ranging well above 1. In the mortality analyses, preadmission use of vitamin K antagonists was associated with reduced mortality at both 30 and 365 days following admission and estimates with amiodarone were indicative of increased risk at 30 and 365 days. The mechanisms behind these findings are likely the same as discussed in relation to study 2. In the cohort of ICU patients, it was noteworthy, that preadmission use of statins and beta-blockers did not seem to improve the prognosis for patients with pre-existing AF as opposed to previous studies (**Table 4**). Reasons for this are unclear, but—of note—our estimates for ICU patients without pre-existing AF were compatible to those reported by others. In our ICU cohort, the prognostic effect of preadmission medications was much less pronounced than in our cohort of pneumonia patients. As opposed to pneumonia patients, ICU patients often receive nutrition via a feeding tube and it is not seldom for ICU patients to have bowel dysfunction [197]. It is therefore plausible that ICU patients are more likely to have their pre-admission oral medications paused or altered than patients with pneumonia.

7. MAIN CONCLUSIONS

Reflecting on the yielded results and the possible limitations of the studies, we drew the following conclusions:

7.1 Study 1

The risk of AF was markedly increased following infections with hospital contact and infections treated in the community setting, whereas seasonal influenza vaccinations was not associated with increased risk of AF. The risk of AF was most pronounced in the first 14 days following the infection. The risk fell rapidly thereafter and little excess risk remained at 61–90 days following the exposure.

7.2 Study 2

In patients with hospitalised pneumonia, pre-existing AF was a marker of increased risk of both arterial thromboembolism and death. This was explained by more advanced ages and higher burdens of coexisting disease in patients with pre-existing AF than in patients without AF. We found preadmission use of vitamin K antagonists, statins, and beta blockers associated with favourable outcome, whereas increased mortality was observed in preadmission users of amiodarone and digoxin.

7.3 Study 3

In ICU patients, patients with pre-existing AF had higher risk of arterial thromboembolism and death than non-AF patients. After adjusting for confounding factors, no increased mortality was seen with AF and only a modestly increased risk of arterial thromboembolism. In stratified analyses, we found AF associated with increased mortality in ICU patients aged <55 years and in ICU patients treated with mechanical ventilation even after confounder control. Preadmission use of vitamin K antagonists was associated with reduced mortality risk.

8. PERSPECTIVES

The three studies contained in this PhD dissertation provide complete novel data on the risk of AF following infections and on the prognosis for patients with AF following pneumonia and ICU admission. Based on the findings in study 1 (the case-control study), health care professionals should be aware of the substantially increased risk of AF following infections, namely in the first two weeks. Also, we have identified that the risk of AF is increased in particular with chest infections and blood stream infections. It is tempting to recommend screening for AF in patients with these infections, but that would be stretching our results too far, because we could not provide estimates on the absolute risk of AF owing to the case-control design of our study. Our results raise several new research questions. It would be of great value to examine whether the prognosis for patients with incident AF associated with infections is similar to that of incident AF without preceding infections. It is possible that the short term prognosis is worse for patients with infection related incident AF because of increased pro-coagulant activity induced by inflammation as discussed earlier in this dissertation. On the other hand, it is possible that incident AF related to infections is a temporary phenomenon that was induced by the infection and will resolve once the infection is cured. It would also be tempting to investigate if the association between infections and incident AF is modifiable by immunomodulating or sympatholytic medications; such a study we shed further light on the mechanism behind the association. From a public health perspective, it was reassuring that seasonal influenza vaccinations did not increase the risk of AF. On the other hand, it was also somewhat disappointing that influenza vaccinations offered no protection against incident AF. However, viral pneumonias did only account for a small proportion of the included infections. Also, a beneficial effect of influenza vaccination is likely to most pronounced in years with influenza epidemics by virus types covered by the vaccination, whereas the influenza vaccination would be of little help in years with influenza epidemics not covered by that season's vaccination. Such information was included in our study and our findings

should not discourage researchers to further explore the potential of vaccinations to reduce the risk of incident AF.

Based on the findings in our cohort studies, clinicians should recognise patients with pre-existing AF represent a high-risk group when hospitalized with pneumonia or admitted to the ICU. At present, there are no guidelines for the management of AF during severe infections like pneumonia or in ICU patients. Our findings emphasises the urgent need for evidence-based treatment protocols in these settings. Our consistent findings of better outcomes in preadmission users of vitamin K antagonists suggests that further research in optimised anticoagulant treatment during critical illness may aid in improving the prognosis for AF patients. We found increased mortality with preadmission use of amiodarone, in ICU patients younger than 55 years, and in ICU patients treated with mechanical ventilation and better insights in the mechanisms behind these associations are warranted. Studies with detailed clinical data may contribute with valuable knowledge on these issues.

9. SUMMARY

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is expected to affect 2% of the population is the European Union. Being associated with a 5-fold increased risk of stroke and 2-fold increased mortality, AF is a major clinical and public health problem. Because the incidence and prevalence of AF increases with advancing age, the burden of AF is expected to grow considerably in the coming years owing to the changing demographic composition of the population with increasing numbers of elderly citizens. A greater understanding of risk factors for development of AF and of the prognosis for patients with AF is therefore of great importance.

The aims of the thesis were to examine extend and duration of increased risk of incident AF following acute infections and influenza vaccinations (study 1), and to examine the impact of pre-existing AF and associated pre-admission drug therapy on the risk of arterial thromboembolism and mortality in patients with hospitalised pneumonia (study 2) and in patients admitted to the intensive care unit (study 3). All studies were conducted using prospectively sampled data from Danish clinical and administrative registries.

Study 1 was a case-control study and included all 51,491 patients with incident AF in the North– and Central Denmark Regions from 1999 through 2010, matched to 253,112 population-based control persons. As compared to individuals without infections, the risk of incident AF was substantially increased in patients with infections with hospital contact (adjusted odds ratio (OR) 15.56 (95% confidence interval (CI): 14.88–16.27) and in individuals with infections treated in the community (adjusted OR 1.92 (95% CI: 1.88–1.97). The risk of AF was highest in the first two weeks following infection, thereafter diminishing rapidly. Influenza vaccinations were not associated with increased risk of AF.

Study 2 was a cohort study and included all patients with first time pneumonia admission in the North– and Central Denmark Regions in the period 1997–2012, n=88,315. Pneumonia patients

with pre-existing AF had substantially higher risk of arterial thromboembolism and death than pneumonia patients without pre-existing AF, but after controlling for confounders no different prognosis were observed. Among pneumonia patients with pre-existing AF, preadmission use of vitamin K antagonists, beta-blockers, and statins was associated to improved outcome, whereas increased mortality was observed in users of amiodarone and digoxin.

Study 3 was a cohort study of all 57,110 patients with first-time ICU admission in Denmark between 2005 and 2011. Patients with pre-existing AF had higher risk of arterial thromboembolism and death than patients without AF. After confounder adjustment, only a modest association between pre-existing AF and risk of arterial thromboembolism remained (adjusted relative risk (RR) 1.14 (95% CI: 0.93–1.40) at 30 days, 1.20 (95% CI: 1.02–1.41) at 365 days)), and no increased mortality was observed. In subgroup analyses, pre-existing AF was associated with a substantial increase in mortality risk in ICU patients aged <55 years (adjusted RR 1.73 (95% CI: 1.29–2.32) at 30 days and 1.34 (95% CI: 1.06–1.69) at 365 days) and in ICU patients treated with mechanical ventilation adjusted RR 1.12 (95% CI: 1.05–1.20) at 30 days; 1.09 (95% CI: 1.05–1.15) at 365 days). In ICU patients with pre-existing AF, preadmission use of vitamin K antagonists was associated to improved prognosis, whereas increased mortality was observed with preadmission users of amiodarone.

In conclusion, we found that the risk of AF was substantially increased in the time shortly after infections. Pre-existing AF was a marker of increased risk of arterial thromboembolism and death in patients with hospitalised pneumonia and in ICU patients, but apart from ICU patients treated with mechanical ventilation and ICU patients aged <55 years, these findings were explained by differences in age and burden of comorbidity, rather than an independent effect of AF. Preadmission treatment for AF had important prognostic impact, namely in pneumonia patients.

10. DANSK RESUMÉ

Atrieflimren er den hyppigste hjerterytmeforstyrrelse og antages at påvirke 2 % af befolkningen i Den Europæiske Union. Atrieflimren er forbundet med en 5 gange øget risiko for apopleksi og fordoblet mortalitet, og udgør derved en betydelig klinisk og folkesundhedsmæssig problemstilling. Da både incidens og prævalens af atrieflimren stiger med alderen, forventes antallet af individer med atrieflimren at stige betydeligt i de kommende på grund af demografiske ændringer med et stigende antal ældre medborgere. En større forståelse af risikofaktorer for udvikling af atrieflimren samt prognosen for patienter med atrieflimren er derfor af stor betydning.

Formålene med denne afhandling var at undersøge omfanget og varigheden af øget risiko for atrieflimren efter infektioner og influenzavaccinationer (studie 1), samt at undersøge betydningen af forudbestående atrieflimren og behandlingen af denne, for risikoen for arteriel thromboemboli og død blandt patienter med hospitaliseret pneumoni (studie 2), samt blandt patienter indlagt på intensiv afdeling (studie 3). Alle studier i afhandlingen er gennemført på baggrund af prospektivt registrerede data fra kliniske og administrative registre.

Studie 1 var et case-kontrolstudie og indbefattede samtlige 51.491 patienter med incident atrieflimren i Region Nord- og Midtjylland samt 253.112 befolkningsbaserede kontrolpersoner i perioden 1999-2010. Sammenlignet med individer uden infektion var risikoen for atrieflimren betragteligt øget blandt patienter med infektioner med hospitalskontakt (justeret odds ratio (OR) 15,56 (95 % konfidensinterval (KI): 14,88–16,27)) og blandt individer med samfundsbehandlede infektioner (justeret OR 1,92 (95 % KI: 1,88–1,97)). Risikoen for atrieflimren var højeste i de første to uger efter infektion og aftog betydeligt derefter. Influenzavaccinationer var ikke forbundet med øget risiko for atrieflimren.

Studie 2 var et kohortestudie og inkluderede alle patienter med førstegangs hospitalsindlæggelse med pneumoni i Region Nord- og Midtjylland i perioden 1997–2012 (n=88.315).

Pneumonipatienter med atrieflimren havde betydeligt højere risiko for arteriel thromboemboli og død end patienter uden atrieflimren, men efter at der var justeret for effekten af confoundere, observeredes der ingen forskel. Blandt pneumonipatienter med atrieflimren var prognosen bedre for patienter der var i behandling med vitamin K antagonister, betablokkere og statiner forud for indlæggelsen, mens der blev observeret øget dødelighed blandt brugere af amiodarone og digoxin.

Studie 3 var et kohortestudie af alle 57.110 patienter med førstegangsindlæggelse på en dansk intensiv afdeling mellem 2005 og 2011. Patienter med forudbestående atrieflimren havde højere risiko for arteriel thromboemboli og død end patienter uden atrieflimren. Efter confounderjustering fandtes kun en beskeden sammenhæng mellem forudbestående atrieflimren og risiko for arteriel thromboemboli (justeret relativ risiko (RR) 1,14 (95 % KI: 0,93–1,40) efter 30 dage og 1,20 (95 % KI: 1,02–1,41) efter 365 dage) og der blev ikke observeret forskel i dødelighed. I subgruppeanalyser var forudbestående atrieflimren forbundet med betydeligt øget dødelighed blandt intensiv patienter der var yngre end 55 år (justeret RR 1,73 (95 % KI: 1,29–2,32) efter 30 dage, 1,34 (95 % KI: 1,06–1,69) efter 365 dage) og blandt intensiv patienter der blev behandlet med mekanisk ventilation (justeret RR 1,12 (95 % KI: 1,05–1,20) efter 30 dage, 1,09 (95 % KI: 1,04–1,15) efter 365 dage). Blandt intensiv patienter med forudbestående atrieflimren var forudgående behandling med vitamin K antagonister associeret med bedre prognose, mens dødelighed var højere blandt patienter der før indlæggelsen var i behandling med amiodarone.

Sammenfattende fandt vi at risikoen for atrieflimren var betydeligt forøget i perioden kort efter infektioner. Forudbestående atrieflimren var en markør for øget risiko for arteriel thromboemboli og død blandt patienter indlagt på hospital med pneumoni og blandt patienter indlagt på intensiv afdeling, men fraset intensiv patienter behandlet med mekanisk ventilation og intensiv patienter yngre end 55 år, kunne disse fund forklares ved forskelle i alder og komorbiditet fremfor en selvstædig effekt af atrieflimren. Forudbestående behandling for atrieflimren havde væsentlig prognostisk betydning, særligt blandt pneumonipatienter.

11. REFERENCES

1. Marchlinski F: **The Tachyarrhythmias**. In *Harrison's Princ Intern Med*. 12th edition. Edited by Longo DL, Fauci AS, Kasper DL, Hauser SL, J J, J L. New York, N.Y.: McGraw-Hill; 2012.

2. Lip GYH, Beevers DG, Singh SP, Watson RDS: **ABC of atrial fibrillation. History, epidemiology, and importance of atrial fibrillation.** *BMJ* 1995, **311**:1361–3.

3. Kirchhof P, Auricchio A, Bax J, Crijns H, Camm J, Diener H-C, Goette A, Hindricks G, Hohnloser S, Kappenberger L, Kuck K-H, Lip GYH, Olsson B, Meinertz T, Priori S, Ravens U, Steinbeck G, Svernhage E, Tijssen J, Vincent A, Breithardt G: **Outcome parameters for trials in atrial fibrillation: executive summary.** *Eur Heart J* 2007, **28**:2803–17.

4. Mackenzie J: **Observations on the Inception of the Rhythm of the Heart by the Ventricle: As the cause of Continuous Irregularity of the Heart.** *Br Med J* 1904, **1**:529–36.

5. Prystowsky EN: **The history of atrial fibrillation: the last 100 years.** *J Cardiovasc Electrophysiol* 2008, **19**:575–82.

6. Lewis T: **REPORT CXIX. AURICULAR FIBRILLATION: A COMMON CLINICAL CONDITION**. *BMJ* 1909, **2**:1528–1528.

7. Krijthe BP, Kunst A, Benjamin EJ, Lip GYH, Franco OH, Hofman A, Witteman JCM, Stricker BH, Heeringa J: **Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060.** *Eur Heart J* 2013, **34**:2746–51.

8. Camm a J, Kirchhof P, Lip GYH, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey J-Y, Ponikowski P, Rutten FH: **Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC).** *Eur Heart J* 2010, **31**:2369–429.

9. Wilke T, Groth A, Mueller S, Pfannkuche M, Verheyen F, Linder R, Maywald U, Bauersachs R, Breithardt G: **Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients.** *Europace* 2013, **15**:486–93.

10. Heeringa J, van der Kuip DAM, Hofman A, Kors JA, van Herpen G, Stricker BHC, Stijnen T, Lip GYH, Witteman JCM: **Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study.** *Eur Heart J* 2006, **27**:949–53.

11. Wilke T, Groth A, Mueller S, Pfannkuche M, Verheyen F, Linder R, Maywald U, Bauersachs R, Breithardt G: **Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients.** *Europace* 2013, **15**:486–93.

12. Christensen AL, Rasmussen LH, Baker MG, Lip GYH, Dethlefsen C, Larsen TB: **Seasonality, incidence and prognosis in atrial fibrillation and stroke in Denmark and New Zealand.** *BMJ Open* 2012, **2**:1–9.

13. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim Y-H, McAnulty JH, Zheng Z-J, Forouzanfar MH, Naghavi M, Mensah G a, Ezzati M, Murray CJL: **Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study.** *Circulation* 2014, **129**:837–47.

14. Stefansdottir H, Aspelund T, Gudnason V, Arnar DO: **Trends in the incidence and prevalence of atrial fibrillation in Iceland and future projections.** *Europace* 2011, **13**:1110–7.

15. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ: **Lifetime risk for development of atrial fibrillation: the Framingham Heart Study**. *Circulation* 2004, **110**(1524-4539 (Electronic)):1042–1046.

16. Schotten U, Verheule S, Kirchhof P, Goette A: **Pathophysiological mechanisms of atrial fibrillation: a translational appraisal.** *Physiol Rev* 2011, **91**:265–325.

17. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Métayer P, Clémenty J: **Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins.** *N Engl J Med* 1998, **339**:659–66.

18. Allessie M a., Boyden P a., Camm a. J, Kleber a. G, Lab MJ, Legato MJ, Rosen MR, Schwartz PJ, Spooner PM, Van Wagoner DR, Waldo a. L: **Pathophysiology and Prevention of Atrial Fibrillation**. *Circulation* 2001, **103**:769–777.

19. De Vos CB, Pisters R, Nieuwlaat R, Prins MH, Tieleman RG, Coelen R-JS, van den Heijkant AC, Allessie M a, Crijns HJGM: **Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis.** *J Am Coll Cardiol* 2010, **55**:725–31.

20. Wijffels MCEF, Kirchhof CJHJ, Dorland R, Allessie MA: **Atrial Fibrillation Begets Atrial Fibrillation : A Study in Awake Chronically Instrumented Goats**. *Circulation* 1995, **92**:1954–1968.

21. Benjamin EJ: **Independent Risk Factors for Atrial Fibrillation in a Population-Based Cohort**. *JAMA* 1994, **271**:840.

22. Stewart S, Hart CL, Hole DJ, McMurray JJ: **Population prevalence, incidence, and predictors of atrial fibrillation in the Renfrew/Paisley study.** *Heart* 2001, **86**:516–21.

23. Friberg J, Scharling H, Gadsbøll N, Jensen GB: **Sex-specific increase in the prevalence of atrial fibrillation (The Copenhagen City Heart Study).** *Am J Cardiol* 2003, **92**:1419–23.

24. Smith JG, Platonov PG, Hedblad B, Engström G, Melander O: **Atrial fibrillation in the Malmö Diet and Cancer study: a study of occurrence, risk factors and diagnostic validity.** *Eur J Epidemiol* 2010, **25**:95–102.

25. Alonso A, Lopez FL, Matsushita K, Loehr LR, Agarwal SK, Chen LY, Soliman EZ, Astor BC, Coresh J: **Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study.** *Circulation* 2011, **123**:2946–53.

26. Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, Tracy RP, Ladenson PW: **Thyroid Status, Cardiovascular Risk, and Mortality in Older Adults**. *JAMA J Am Med Assoc* 2006, **295**:1033–1041.

27. Frost L, Vestergaard P, Mosekilde L: **Hyperthyroidism and risk of atrial fibrillation or flutter: a population-based study.** *Arch Intern Med* 2004, **164**:1675–8.

28. Frost L, Vestergaard P: **Alcohol and risk of atrial fibrillation or flutter: a cohort study.** *Arch Intern Med* 2004, **164**:1993–8.

29. Frost L, Hune LJ, Vestergaard P: **Overweight and obesity as risk factors for atrial fibrillation or flutter: the Danish Diet, Cancer, and Health Study.** *Am J Med* 2005, **118**:489–95.

30. January CT, Wann LS, Alpert JS, Calkins H, Cleveland JC, Cigarroa JE, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW: **2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society.** *Circulation* 2014.

31. Bunch TJ, Day JD, Anderson JL, Horne BD, Muhlestein JB, Crandall BG, Weiss JP, Lappe DL, Asirvatham SJ: **Frequency of helicobacter pylori seropositivity and C-reactive protein increase in atrial fibrillation in patients undergoing coronary angiography.** *Am J Cardiol* 2008, **101**:848–51.

32. Chiang C-HH, Huang C-CC, Chan W-LL, Huang P-HH, Chen Y-CC, Chen T-JJ, Lin S-JJ, Chen J-WW, Leu H-BB: **Herpes simplex virus infection and risk of atrial fibrillation: a nationwide study.** *Int J Cardiol* 2013, **164**:201–4.

33. Christian SA, Schorr C, Ferchau L, Jarbrink ME, Parrillo JE, Gerber DR: **Clinical characteristics and outcomes of septic patients with new-onset atrial fibrillation**. *J Crit Care* 2008, **23**(1557-8615 (Electronic)):532–536.

34. Hansson A, Madsen-Härdig B, Olsson SB: **Arrhythmia-provoking factors and symptoms at the onset of paroxysmal atrial fibrillation: a study based on interviews with 100 patients seeking hospital assistance.** *BMC Cardiovasc Disord* 2004, **4**:13.

35. Hsu JC, Li Y, Marcus GM, Hsue PY, Scherzer R, Grunfeld C, Shlipak MG: **Atrial fibrillation and atrial flutter in human immunodeficiency virus-infected persons: incidence, risk factors, and association with markers of HIV disease severity.** *J Am Coll Cardiol* 2013, **61**:2288–95.

36. Ichiki H, Orihara K, Hamasaki S, Ishida S, Oketani N, Iriki Y, Ninomiya Y, Okui H, Kuwahata S, Fujita S, Matsushita T, Yoshifuku S, Oba R, Hirai H, Nagata K, Tei C: **The role of infection in the development of non-valvular atrial fibrillation: Up-regulation of Toll-like receptor 2 expression levels on monocytes**. *J Cardiol* 2009, **53**:127–135.

37. Ki M-R, Shin D-G, Park J-S, Hong K-S, Hong I-H, Park J-K, Jeong K-S: **Frequency of vacuolating cytotoxin A (VacA)-positive Helicobacter pylori seropositivity and TGF-β1 decrease in atrial fibrillation.** *Int J Cardiol* 2010, **145**:345–6.

38. Kindem IA, Reindal EK, Wester AL, Blaasaas KG, Atar D: **New-onset atrial fibrillation in bacteremia is not associated with C-reactive protein, but is an indicator of increased mortality during hospitalization.** *Cardiology* 2008, **111**:171–80.

39. Lindberg S, Hansen S, Nielsen T: **Spontaneous conversion of first onset atrial fibrillation.** *Intern Med J* 2012, **42**:1195–9.

40. Lunetta M, Fazio G, Avena V, Corrado E, Loredana S, Arnone E, Novo G, Novo S: **Helicobacter pylori and atrial fibrillation: absence of correlations.** *J Cardiovasc Med (Hagerstown)* 2009, **10**:4–5.

41. Makrygiannis SS, Margariti A, Rizikou D, Lampakis M, Vangelis S, Ampartzidou OS, Katsifa K, Tselioti P, Foussas SG, Prekates A a: **Incidence and predictors of new-onset atrial fibrillation in noncardiac intensive care unit patients.** *J Crit Care* 2014, **29**:697.e1–5.

42. Meierhenrich R, Steinhilber E, Eggermann C, Weiss M, Voglic S, Bögelein D, Gauss A, Georgieff M, Stahl W: **Incidence and prognostic impact of new-onset atrial fibrillation in patients with septic shock: a prospective observational study.** *Crit Care* 2010, **14**:R108.

43. Montenero a S, Mollichelli N, Zumbo F, Antonelli A, Dolci A, Barberis M, Sirolla C, Staine T, Fiocca L, Bruno N, O'Connor S: **Helicobacter pylori and atrial fibrillation: a possible pathogenic link.** *Heart* 2005, **91**:960–1.

44. Musher DM, Rueda AM, Kaka AS, Mapara SM: **The Association between Pneumococcal Pneumonia and Acute Cardiac Events**. *Clin Infect Dis* 2007, **45**:158–165.

45. Platonov P, Ekesbo R, Hansson A, Andsberg E, Meurling CJ, Nilsson I, Ljungh A, Wadström T, Olsson SB: **Permanent atrial fibrillation in patients without structural heart disease is not associated with signs of infection by Chlamydia pneumoniae and Helicobacter pylori.** *Acta Cardiol* 2008, **63**:479–84.

46. Salman S, Bajwa A, Gajic O, Afessa B: **Paroxysmal atrial fibrillation in critically ill patients with sepsis.** *J Intensive Care Med* 2008, **23**:178–83.

47. Spodick DH: **Arrhythmias during acute pericarditis. A prospective study of 100 consecutive cases.** *JAMA* 1976, **235**:39–41.

48. Syed FF, Ntsekhe M, Wiysonge CS, Badri M, Oh JK, Mayosi BM: **Atrial fibrillation as a consequence of tuberculous pericardial effusion.** *Int J Cardiol* 2012, **158**:152–4.

49. Walkey AJ, Greiner M a, Heckbert SR, Jensen PN, Piccini JP, Sinner MF, Curtis LH, Benjamin EJ: **Atrial fibrillation among Medicare beneficiaries hospitalized with sepsis: incidence and risk factors.** *Am Heart J* 2013, **165**:949–955.e3.

50. Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ: **Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis.** *JAMA* 2011, **306**:2248–54.

51. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A: **Histological Substrate of Atrial Biopsies in Patients With Lone Atrial Fibrillation**. *Circulation* 1997, **96**:1180–1184.

52. Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, Kronmal RA, Tracy RP, Van Wagoner DR, Psaty BM, Lauer MS, Chung MK: **Inflammation as a risk factor for atrial fibrillation.** *Circulation* 2003, **108**:3006–10.

53. Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A, Carnes CA, Bauer JA, Tchou PJ, Niebauer MJ, Natale A, Van Wagoner DR: **C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation.** *Circulation* 2001, **104**:2886–91.

54. Henningsen KM, Therkelsen SK, Johansen JS, Bruunsgaard H, Svendsen JH: **Plasma YKL-40, a new biomarker for atrial fibrillation?** *Europace* 2009, **11**:1032–1036.

55. Adamsson Eryd S, Smith JG, Melander O, Hedblad B, Engström G: **Inflammation-sensitive proteins and risk of atrial fibrillation: a population-based cohort study.** *Eur J Epidemiol* 2011, **26**:449–55.

56. Marott SCW, Nordestgaard BG, Zacho J, Friberg J, Jensen GB, Tybjaerg-Hansen A, Benn M: **Does elevated C-reactive protein increase atrial fibrillation risk? A Mendelian randomization of 47,000 individuals from the general population.** *J Am Coll Cardiol* 2010, **56**:789–95.

57. Wolf P a., Abbott RD, Kannel WB: **Atrial fibrillation as an independent risk factor for stroke: the Framingham Study**. *Stroke* 1991, **22**:983–988.

58. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D: **Impact of Atrial Fibrillation on the Risk of Death : The Framingham Heart Study**. *Circulation* 1998, **98**:946–952.

59. Stewart S, Hart CL, Hole DJ, McMurray JJ V: **A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study.** *Am J Med* 2002, **113**:359–64.

60. Andersson T, Magnuson A, Bryngelsson I-L, Frøbert O, Henriksson KM, Edvardsson N, Poçi D: **All-cause mortality in 272,186 patients hospitalized with incident atrial fibrillation 1995-2008: a Swedish nationwide long-term case-control study.** *Eur Heart J* 2013, **34**:1061–7.

61. Conen D, Chae CU, Glynn RJ, Tedrow UB, Everett BM, Buring JE, Albert CM: **Risk of death and cardiovascular events in initially healthy women with new-onset atrial fibrillation.** *JAMA* 2011, **305**:2080–7.

62. Miyasaka Y, Barnes ME, Bailey KR, Cha SS, Gersh BJ, Seward JB, Tsang TSM: **Mortality trends in patients diagnosed with first atrial fibrillation: a 21-year community-based study.** *J Am Coll Cardiol* 2007, **49**:986–92.

63. Watson T, Shantsila E, Lip GYH: **Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited.** *Lancet* 2009, **373**:155–66.

64. Friberg L, Hammar N, Pettersson H, Rosenqvist M.: **Increased mortality in paroxysmal atrial fibrillation: report from the Stockholm Cohort-Study of Atrial Fibrillation (SCAF)**. *Eur Heart J* 2007, **28**:2346–2353.

65. Friberg L, Hammar N, Rosenqvist M: **Stroke in paroxysmal atrial fibrillation: report from the Stockholm Cohort of Atrial Fibrillation.** *Eur Heart J* 2010, **31**:967–75.

66. Go AS, Hylek EM, Chang Y, Phillips KA, Henault LE, Capra AM, Jensvold NG, Selby J V, Singer DE: **Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice?** *JAMA* 2003, **290**:2685–92.

67. Singer DE, Chang Y, Fang MC, Borowsky LH, Pomernacki NK, Udaltsova N, Go AS: **The net clinical benefit of warfarin anticoagulation in atrial fibrillation.** *Ann Intern Med* 2009, **151**:297–305.

68. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf P a, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ: **Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study.** *Circulation* 2003, **107**:2920–5.

69. Samet P, Bernstein W, Levine S: **SIGNIFICANCE OF THE ATRIAL CONTRIBUTION TO VENTRICULAR FILLING.** *Am J Cardiol* 1965, **15**(February):195–202.

70. Daoud EG, Weiss R, Bahu M, Knight BP, Bogun F, Goyal R, Harvey M, Strickberger SA, Man KC, Morady F: **Effect of an irregular ventricular rhythm on cardiac output.** *Am J Cardiol* 1996, **78**:1433–6.

71. Ott A, Breteler MMB, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A: **Atrial Fibrillation and Dementia in a Population-Based Study: The Rotterdam Study**. *Stroke* 1997, **28**:316–321.

72. Knecht S, Oelschläger C, Duning T, Lohmann H, Albers J, Stehling C, Heindel W, Breithardt G, Berger K, Ringelstein EB, Kirchhof P, Wersching H: **Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy.** *Eur Heart J* 2008, **29**:2125–32.

73. Thrall G, Lane D, Carroll D, Lip GYH: **Quality of life in patients with atrial fibrillation: a systematic review.** *Am J Med* 2006, **119**:448.e1–19.

74. Marrie TJ: **Community-Acquired Pneumonia**. *Clin Infect Dis* 1994, **18**:501–515.

75. World Health Organization: *The Global Burden of Disease: 2004 Update*. Geneva; 2008.

76. Torres A, Peetermans WE, Viegi G, Blasi F: **Risk factors for community-acquired pneumonia in adults in Europe: a literature review.** *Thorax* 2013, **68**:1057–65.

77. Mor A, Thomsen RW, Ulrichsen SP, Sørensen HT: **Chronic heart failure and risk of hospitalization with pneumonia: a population-based study.** *Eur J Intern Med* 2013, **24**:349–53.

78. Kornum JB, Nørgaard M, Dethlefsen C, Due KM, Thomsen RW, Tjønneland A, Sørensen HT, Overvad K: **Obesity and risk of subsequent hospitalisation with pneumonia.** *Eur Respir J* 2010, **36**:1330–6.

79. Kornum JB, Due KM, Nørgaard M, Tjønneland A, Overvad K, Sørensen HT, Thomsen RW: **Alcohol drinking and risk of subsequent hospitalisation with pneumonia.** *Eur Respir J* 2012, **39**:149–55.

80. Kornum JB, Thomsen RW, Riis A, Lervang H-H, Schønheyder HC, Sørensen HT: **Diabetes, glycemic control, and risk of hospitalization with pneumonia: a population-based case-control study.** *Diabetes Care* 2008, **31**:1541–5.

81. Søgaard M, Nielsen RB, Schønheyder HC, Nørgaard M, Thomsen RW: **Nationwide trends in pneumonia hospitalization rates and mortality, Denmark 1997-2011.** *Respir Med* 2014, **108**:1214–22.

82. Kornum JB, Thomsen RW, Riis A, Lervang H-H, Schønheyder HC, Sørensen HT: **Type 2 diabetes and pneumonia outcomes: a population-based cohort study.** *Diabetes Care* 2007, **30**:2251–7.

83. Thomsen RW, Kasatpibal N, Riis A, Nørgaard M, Sørensen HT: **The impact of pre-existing heart failure on pneumonia prognosis: population-based cohort study.** *J Gen Intern Med* 2008, **23**:1407–13.

84. Neupane B, Walter SD, Krueger P, Marrie T, Loeb M: **Predictors of inhospital mortality and re-hospitalization in older adults with community-acquired pneumonia: a prospective cohort study.** *BMC Geriatr* 2010, **10**:22.

85. Feagan BG, Marrie TJ, Lau CY, Wheeler SL, Wong CJ, Vandervoort MK: **Treatment and outcomes of community-acquired pneumonia at Canadian hospitals.** *CMAJ* 2000, **162**:1415–20.

86. Fine MJ: **Prognosis and Outcomes of Patients With Community-Acquired Pneumonia**. *JAMA* 1996, **275**:134.

87. Fry AM, Shay DK, Holman RC, Curns AT, Anderson LJ: **Trends in hospitalizations for pneumonia among persons aged 65 years or older in the United States, 1988-2002.** *JAMA* 2005, **294**:2712–9.

88. Corrales-Medina VF, Musher DM, Wells G a, Chirinos J a, Chen L, Fine MJ: **Cardiac complications in patients with community-acquired pneumonia: incidence, timing, risk factors, and association with short-term mortality.** *Circulation* 2012, **125**:773–81.

89. Milbrandt EB, Reade MC, Lee M, Shook SL, Angus DC, Kong L, Carter M, Yealy DM, Kellum J a: **Prevalence and significance of coagulation abnormalities in community-acquired pneumonia.** *Mol Med* 2009, **15**:438–45.

90. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P: **Risk of Myocardial Infarction and Stroke after Acute Infection or Vaccination**. *N Engl J Med* 2004, **351**:2611–2618.

91. Vincent JL, Zhang H, Szabo C, Preiser JC: **Effects of nitric oxide in septic shock.** *Am J Respir Crit Care Med* 2000, **161**:1781–5.

92. Yetkin O, Hacievliyagil SS, Gunen H: **Assessment of B-type natriuretic peptide in patients with pneumonia.** *Int J Clin Pract* 2008, **62**:488–91.

93. Finfer S, Vincent J-L: **Critical care--an all-encompassing specialty.** *N Engl J Med* 2013, **369**:669–70.

94. Lassen HC: **The epidemic of poliomyelitis in Copenhagen, 1952.** *Proc R Soc Med* 1954, **47**:67–71.

95. Ibsen B: **The anaesthetist's viewpoint on the treatment of respiratory complications in poliomyelitis during the epidemic in Copenhagen, 1952.** *Proc R Soc Med* 1954, **47**:72–4.

96. Berthelsen PG, Cronqvist M: **The first intensive care unit in the world: Copenhagen 1953**. *Acta Anaesthesiol Scand* 2003, **47**:1190–1195.

97. *Dansk Intensiv Database: Årsrapport 2012*. 2013(december 2012).

98. Adhikari NKJ, Fowler R a, Bhagwanjee S, Rubenfeld GD: **Critical care and the global burden of critical illness in adults.** *Lancet* 2010, **376**:1339–46.

99. Le Gall J-R: **A New Simplified Acute Physiology Score (SAPS II) Based on a European/North American Multicenter Study**. *JAMA J Am Med Assoc* 1993, **270**:2957.

100. Knaus WA, Draper EA, Wagner DP, Zimmerman JE: **APACHE II: a severity of disease classification system.** *Crit Care Med* 1985, **13**:818–29.

101. Christensen S, Johansen MB, Christiansen CF, Jensen R, Lemeshow S: **Comparison of Charlson comorbidity index with SAPS and APACHE scores for prediction of mortality following intensive care.** *Clin Epidemiol* 2011, **3**(1179-1349 (Electronic)):203–11.

102. Christiansen CF, Christensen S, Johansen MB, Larsen KM, Tønnesen E, Sørensen HT: **The impact of pre-admission morbidity level on 3-year mortality after intensive care: a Danish cohort study.** *Acta Anaesthesiol Scand* 2011, **55**:962–70.

103. Nielsson MS, Christiansen CF, Johansen MB, Rasmussen BS, Tønnesen E, Nørgaard M: **Mortality in elderly ICU patients: a cohort study.** *Acta Anaesthesiol Scand* 2014, **58**:19–26.

104. Christiansen CF, Johansen MB, Christensen S, O'Brien JM, Tønnesen E, Sørensen HT: **Type 2 diabetes and 1-year mortality in intensive care unit patients.** *Eur J Clin Invest* 2013, **43**:238–47.

105. Neher MD, Weckbach S, Flierl M a, Huber-Lang MS, Stahel PF: **Molecular mechanisms of inflammation and tissue injury after major trauma--is complement the "bad guy"?** *J Biomed Sci* 2011, **18**:90.

106. Brun-Buisson C: **The epidemiology of the systemic inflammatory response**. *Intensive Care Med* 2000, **26**:S064–S074.

107. Goodman S, Shirov T, Weissman C: **Supraventricular arrhythmias in intensive care unit patients: short and long-term consequences.** *Anesth Analg* 2007, **104**:880–6.

108. Kanji S, Williamson DR, Yaghchi BM, Albert M, McIntyre L: **Epidemiology and management of atrial fibrillation in medical and noncardiac surgical adult intensive care unit patients.** *J Crit Care* 2012, **27**:326.e1–326.e8.

109. Knotzer H, Mayr A, Ulmer H, Lederer W, Schobersberger W, Mutz N, Hasibeder W: **Tachyarrhythmias in a surgical intensive care unit: a case-controlled epidemiologic study.** *Intensive Care Med* 2000, **26**:908–14.

110. Seguin P, Laviolle B, Maurice A, Leclercq C, Malledant Y: **Atrial fibrillation in trauma patients requiring intensive care**. *Intensive Care Med* 2006, **32**(0342-4642 (Print)):398–404.

111. Seguin P, Signouret T, Laviolle B, Branger B, Malledant Y: **Incidence and risk factors of atrial fibrillation in a surgical intensive care unit**. *Crit Care Med* 2004, **32**(0090-3493 (Print)):722–726.

112. Artucio H, Pereira M: **Cardiac arrhythmias in critically ill patients: epidemiologic study**. *Crit Care Med* 1990, **18**(0090-3493 (Print)):1383–1388.

113. Reinelt P, Karth G, Geppert A, Heinz G: **Incidence and type of cardiac arrhythmias in critically ill patients: a single center experience in a medical-cardiological ICU**. *Intensive Care Med* 2001, **27**:1466–1473.

114. 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.

115. Segal JB, McNamara RL, Miller MR, Powe NR, Goodman SN, Robinson KA, Bass EB: **Anticoagulants or antiplatelet therapy for non-rheumatic atrial fibrillation and flutter.** *Cochrane database Syst Rev* 2001:CD001938.

116. Johnsen SP, Svendsen ML, Hansen ML, Brandes A, Mehnert F, Husted SE: **Preadmission oral anticoagulant treatment and clinical outcome among patients hospitalized with acute stroke and atrial fibrillation: a nationwide study.** *Stroke* 2014, **45**:168–75.

117. Lip GYH, Nieuwlaat R, Pisters R, Lane D a, Crijns HJGM: **Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation.** *Chest* 2010, **137**:263–72.

118. Olesen JB, Lip GYH, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen A-MS, Gislason GH, Torp-Pedersen C: **Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study.** *BMJ* 2011, **342**:d124.

119. Rasmussen LH, Larsen TB, Due KM, Tjønneland A, Overvad K, Lip GYH: **Impact of vascular disease in predicting stroke and death in patients with atrial fibrillation: the Danish Diet, Cancer and Health cohort study.** *J Thromb Haemost* 2011, **9**:1301–7.

120. Mant J, Hobbs FDR, Fletcher K, Roalfe A, Fitzmaurice D, Lip GYH, Murray E: **Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial.** *Lancet* 2007, **370**:493–503.

121. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD: **A comparison of rate control and rhythm control in patients with atrial fibrillation.** *N Engl J Med* 2002, **347**:1825–33.

122. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJM, Tijssen JGP, Crijns HJGM: **A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation.** *N Engl J Med* 2002, **347**:1834–40.

123. Corley SD, Epstein AE, DiMarco JP, Domanski MJ, Geller N, Greene HL, Josephson R a, Kellen JC, Klein RC, Krahn AD, Mickel M, Mitchell LB, Nelson JD, Rosenberg Y, Schron E, Shemanski L, Waldo AL, Wyse DG: **Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study.** *Circulation* 2004, **109**:1509–13.

124. Opolski G, Torbicki A, Kosior D a, Szulc M, Wozakowska-Kaplon B, Kolodziej P, Achremczyk P: **Rate control vs rhythm control in patients with nonvalvular persistent atrial fibrillation: the results of the Polish How to Treat Chronic Atrial Fibrillation (HOT CAFE) Study.** *Chest* 2004, **126**:476–86.

125. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, Bourassa MG, Arnold JMO, Buxton AE, Camm AJ, Connolly SJ, Dubuc M, Ducharme A, Guerra PG, Hohnloser SH, Lambert J, Le Heuzey J-Y, O'Hara G, Pedersen OD, Rouleau J-L, Singh BN, Stevenson LW, Stevenson WG, Thibault B, Waldo AL:

Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med* 2008, **358**:2667–77.

126. Andersen SS, Hansen ML, Gislason GH, Schramm TK, Folke F, Fosbøl E, Abildstrøm SZ, Madsen M, Køber L, Torp-Pedersen C: **Antiarrhythmic therapy and risk of death in patients with atrial fibrillation: a nationwide study.** *Europace* 2009, **11**:886–91.

127. Nielsen AG, Nielsen RB, Riis AH, Johnsen SP, Sørensen HT, Thomsen RW: **The impact of statin use on pneumonia risk and outcome: a combined population-based case-control and cohort study.** *Crit Care* 2012, **16**:R122.

128. Christensen S, Thomsen RW, Johansen MB, Pedersen L, Jensen R, Larsen KM, Larsson A, Tønnesen E, Sørensen HT: **Preadmission statin use and one-year mortality among patients in intensive care - a cohort study.** *Crit Care* 2010, **14**:R29.

129. Oz F, Gul S, Kaya MG, Yazici M, Bulut I, Elitok A, Ersin G, Abakay O, Akkoyun CD, Oncul A, Cetinkaya E, Gibson MC, Oflaz H: **Does aspirin use prevent acute coronary syndrome in patients with pneumonia: multicenter prospective randomized trial.** *Coron Artery Dis* 2013, **24**:231–7.

130. Wu A, Good C, Downs JR, Fine MJ, Pugh MJ V, Anzueto A, Mortensen EM: **The association of cardioprotective medications with pneumonia-related outcomes.** *PLoS One* 2014, **9**:e85797.

131. Doshi SM, Kulkarni P a, Liao JM, Rueda AM, Musher DM: **The impact of statin and macrolide use on early survival in patients with pneumococcal pneumonia.** *Am J Med Sci* 2013, **345**:173–7.

132. Mortensen EM, Nakashima B, Cornell J, Copeland L a, Pugh MJ, Anzueto A, Good C, Restrepo MI, Downs JR, Frei CR, Fine MJ: **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.

133. Rothberg MB, Bigelow C, Pekow PS, Lindenauer PK: **Association between statins given in hospital and mortality in pneumonia patients.** *J Gen Intern Med* 2012, **27**:280–6.

134. Yende S, Milbrandt EB, Kellum J a, Kong L, Delude RL, Weissfeld L a, Angus DC: **Understanding the potential role of statins in pneumonia and sepsis.** *Crit Care Med* 2011, **39**:1871–8.

135. Douglas I, Evans S, Smeeth L: **Effect of statin treatment on short term mortality after pneumonia episode: cohort study.** *BMJ* 2011, **342**:d1642.

136. Myles PR, Hubbard RB, Gibson JE, Pogson Z, Smith CJP, McKeever TM: **The impact of statins, ACE inhibitors and gastric acid suppressants on pneumonia mortality in a UK general practice population cohort.** *Pharmacoepidemiol Drug Saf* 2009, **18**:697–703.

137. Mortensen EM, Pugh MJ, Copeland L a, Restrepo MI, Cornell JE, Anzueto A, Pugh J a: **Impact of statins and angiotensin-converting enzyme inhibitors on mortality of subjects hospitalised with pneumonia.** *Eur Respir J* 2008, **31**:611–7.

138. Thomsen RW, Riis A, Kornum JB, Christensen S, Johnsen SP, Sørensen HT: **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.

139. Chalmers JD, Singanayagam A, Murray MP, Hill AT: **Prior statin use is associated with improved outcomes in community-acquired pneumonia.** *Am J Med* 2008, **121**:1002–1007.e1.

140. Frost FJ, Petersen H, Tollestrup K, Skipper B: **Influenza and COPD mortality protection as pleiotropic, dose-dependent effects of statins.** *Chest* 2007, **131**:1006–12.

141. Majumdar SR, McAlister F a, Eurich DT, Padwal RS, Marrie TJ: **Statins and outcomes in patients admitted to hospital with community acquired pneumonia: population based prospective cohort study.** *BMJ* 2006, **333**:999.

142. Mortensen EM, Restrepo MI, Anzueto A, Pugh J: **The effect of prior statin use on 30-day mortality for patients hospitalized with community-acquired pneumonia.** *Respir Res* 2005, **6**:82.

143. Macchia A, Romero M, Comignani PD, Mariani J, D'Ettorre A, Prini N, Santopinto M, Tognoni G: **Previous prescription of β-blockers is associated with reduced mortality among patients hospitalized in intensive care units for sepsis.** *Crit Care Med* 2012, **40**:2768–72.

144. Bukur M, Lustenberger T, Cotton B, Arbabi S, Talving P, Salim A, Ley EJ, Inaba K: **Beta-blocker exposure in the absence of significant head injuries is associated with reduced mortality in critically ill patients.** *Am J Surg* 2012, **204**:697–703.

145. Bajwa EK, Malhotra CK, Thompson BT, Christiani DC, Gong MN: **Statin therapy as prevention against development of acute respiratory distress syndrome: an observational study.** *Crit Care Med* 2012, **40**:1470–7.

146. Eisen DP, Reid D, McBryde ES: **Acetyl salicylic acid usage and mortality in critically ill patients with the systemic inflammatory response syndrome and sepsis.** *Crit Care Med* 2012, **40**:1761–7.

147. Christensen S, Johansen MB, Tønnesen E, Larsson A, Pedersen L, Lemeshow S, Sørensen HT: **Preadmission beta-blocker use and 30-day mortality among patients in intensive care: a cohort study.** *Crit Care* 2011, **15**:R87.

148. Al Harbi S a, Tamim HM, Arabi YM: **Association between statin therapy and outcomes in critically ill patients: a nested cohort study.** *BMC Clin Pharmacol* 2011, **11**:12.

149. Terblanche MJ, Pinto R, Whiteley C, Brett S, Beale R, Adhikari NKJ: **Statins do not prevent acute organ failure in ventilated ICU patients: single-centre retrospective cohort study.** *Crit Care* 2011, **15**:R74.

150. Noveanu M, Breidthardt T, Reichlin T, Gayat E, Potocki M, Pargger H, Heise A, Meissner J, Twerenbold R, Muravitskaya N, Mebazaa A, Mueller C: **Effect of oral β-blocker on short and long-term mortality in patients with acute respiratory failure: results from the BASEL-II-ICU study.** *Crit Care* 2010, **14**:R198.

151. Winning J, Neumann J, Kohl M, Claus RA, Reinhart K, Bauer M, Lösche W: **Antiplatelet drugs and outcome in mixed admissions to an intensive care unit.** *Crit Care Med* 2010, **38**:32–7.

152. Kor DJ, Iscimen R, Yilmaz M, Brown MJ, Brown DR, Gajic O: **Statin administration did not influence the progression of lung injury or associated organ failures in a cohort of patients with acute lung injury.** *Intensive Care Med* 2009, **35**:1039–46.

153. Fernandez R, De Pedro VJ, Artigas A: **Statin therapy prior to ICU admission: protection against infection or a severity marker?** *Intensive Care Med* 2006, **32**:160–4.

154. Schmidt H, Hennen R, Keller A, Russ M, Müller-Werdan U, Werdan K, Buerke M: **Association of statin therapy and increased survival in patients with multiple organ dysfunction syndrome.** *Intensive Care Med* 2006, **32**:1248–51.

155. **What is epidemiology? | The BMJ** [http://www.bmj.com/about-bmj/resources-readers/publications/epidemiology-uninitiated/1-what-epidemiology]

156. Sørensen HT: **Clinical Epidemiology - a fast new way to publish important research.** *Clin Epidemiol* 2009, **1**:17–8.

157. Sorensen HT, Sabroe S, Olsen J: **A framework for evaluation of secondary data sources for epidemiological research.** *Int J Epidemiol* 1996, **25**:435–42.

158. Sørensen HT, Christensen T, Schlosser HK, Pedersen L (Eds): *Use of Medical Databases in Clinical Epidemiology*. 2nd edition. Aarhus: Aarhus University; 2009.

159. Pedersen CB: **The Danish Civil Registration System.** *Scand J Public Health* 2011, **39**(7 Suppl):22–5.

160. Lynge E, Sandegaard JL, Rebolj M: **The Danish National Patient Register.** *Scand J Public Health* 2011, **39**(7 Suppl):30–3.

161. Rønholm E, Christensen S, Andersen JS, Jensen RH, Sørensen HT: **[Clinical database for intensive care patients].** *Ugeskr Laeger* 2007, **169**:724–7.

162. Christiansen CF, Rønholm E: **[Danish Intensive Care Database].** *Ugeskr Laeger* 2012, **174**:2544.

163. Ehrenstein V, Antonsen S, Pedersen L: **Existing data sources for clinical epidemiology: Aarhus University Prescription Database.** *Clin Epidemiol* 2010, **2**(1179-1349 (Electronic)):273–9.

164. Andersen JS, Olivarius NDF, Krasnik A: **The Danish National Health Service Register.** *Scand J Public Health* 2011, **39**(7 Suppl):34–7.

165. **Influenzavaccination 2013/2014**. *Epi-Nyt* 2013:1–2.

166. **Atrieflimren og -flagren** [https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/hjerte-kar/tilstande-og-sygdomme/arytmier/atrieflimren-og-flagren/]

167. Charlson ME, Pompei P, Ales KL, MacKenzie CR: **A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.** *J Chronic Dis* 1987, **40**:373–83.

168. De Groot V, Beckerman H, Lankhorst GJ, Bouter LM: **How to measure comorbidity: a critical review of available methods**. *J Clin Epidemiol* 2003, **56**:221–229.

169. Greenland S, Rothman KJ: **Analysis of data from matched studies**. In *Mod Epidemiol*. 3rd edition. Edited by Rothman KJ, Greenland S, Lash TL. Philadelphia: Wolters Kluwer; 2008:283–288.

170. Andersen PK, Geskus RB, de Witte T, Putter H: **Competing risks in epidemiology: possibilities and pitfalls.** *Int J Epidemiol* 2012, **41**:861–70.

171. Klein JP, Andersen PK: **Regression modeling of competing risks data based on pseudovalues of the cumulative incidence function.** *Biometrics* 2005, **61**:223–9.

172. Parner ET, Andersen PK: **Regression analysis of censored data using pseudo-observations**. *Stata J* 2010, **10**:408–422.

173. Klein JP, Logan B, Harhoff M, Andersen PK: **Analyzing survival curves at a fixed point in time.** *Stat Med* 2007, **26**:4505–19.

174. Coviello V, Boggess M: **Cumulative incidence estimation in the presence of competing risks**. *Stata J* 2004, **4**:103–112.

175. Rothman KJ, Greenland S, Lash TL: **Validity in epidemiologic studies**. In *Mod Epidemiol*. 3rd edition. Edited by Rothman KJ, Greenland S, Lash TL. Philadelphia: Wolters Kluwer; 2008:128–147.

176. Rix TA, Riahi S, Overvad K, Lundbye-Christensen S, Schmidt EB, Joensen AM: **Validity of the diagnoses atrial fibrillation and atrial flutter in a Danish patient registry.** *Scand Cardiovasc J* 2012, **46**:149–53.

177. Frost L, Andersen LV, Vestergaard P, Husted S, Mortensen LS: **Trend in mortality after stroke with atrial fibrillation.** *Am J Med* 2007, **120**:47–53.

178. Thomsen RW, Riis A, Nørgaard M, Jacobsen J, Christensen S, McDonald CJ, Sørensen HT: **Rising incidence and persistently high mortality of hospitalized pneumonia: a 10-year population-based study in Denmark.** *J Intern Med* 2006, **259**:410–7.

179. Blichert-Hansen L, Nielsson MS, Nielsen RB, Christiansen CF, Nørgaard M: **Validity of the coding for intensive care admission, mechanical ventilation, and acute dialysis in the Danish National Patient Registry: a short report.** *Clin Epidemiol* 2013, **5**:9–12.

180. Henriksen DP, Nielsen SL, Laursen CB, Hallas J, Pedersen C, Lassen AT: **How well do discharge diagnoses identify hospitalised patients with community-acquired infections?--a validation study.** *PLoS One* 2014, **9**:e92891.

181. Fletcher RH, Fletcher SW: *Clinical Epidemiology - The Essentials*. 4th edition. Baltimore: Lippincott Williams & Wilkins; 2005.

182. Søgaard M, Kornum JB, Schønheyder HC, Thomsen RW: **Positive predictive value of the ICD-10 hospital diagnosis of pleural empyema in the Danish National Registry of Patients.** *Clin Epidemiol* 2011, **3**:85–9.

183. Mölstad S, Lundborg CS, Karlsson A-K, Cars O: **Antibiotic Prescription Rates Vary Markedly Between 13 European Countries**. *Scand J Infect Dis* 2002, **34**:366–371.

184. Little P, Williamson I, Warner G, Gould C, Gantley M, Kinmonth AL: **Open randomised trial of prescribing strategies in managing sore throat**. *BMJ* 1997, **314**:722–722.

185. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT: **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.

186. Johnsen SP, Overvad K, Sørensen HT, Tjønneland A, Husted SE: **Predictive value of stroke and transient ischemic attack discharge diagnoses in The Danish National Registry of Patients.** *J Clin Epidemiol* 2002, **55**:602–7.

187. Krarup L-H, Boysen G, Janjua H, Prescott E, Truelsen T: **Validity of stroke diagnoses in a National Register of Patients.** *Neuroepidemiology* 2007, **28**:150–4.

188. Strom BL, Melmon KL: **The use of pharmacoepidemiology to study beneficial drug effects**. In *Pharmacoepidemiology*. 4th edition. Edited by Strom BL. Chichester: John Wiley & Sons Ltd.; 2005.

189. Thomsen RW: **The lesser known effects of statins: benefits on infectious outcomes may be explained by "healthy user" effect.** *BMJ* 2006, **333**:980–1.

190. Thomsen RW, Nielsen RB, Nørgaard M, Horsdal HT, Stürmer T, Larsen FB, Sørensen HT: **Lifestyle profile among statin users.** *Epidemiology* 2013, **24**:619–20.

191. Rothman KJ, Greenland S, Lash TL: **Precision and statistics in epidemiologic studies**. In *Mod Epidemiol*. 3rd edition. Edited by Rothman KJ, Greenland S, Lash TL. Philadelphia: Lippincott Williams & Wilkins; 2008.

192. Mandal P, Chalmers JD, Choudhury G, Akram AR, Hill AT: **Vascular complications are associated with poor outcome in community-acquired pneumonia.** *QJM* 2011, **104**:489–95.

193. Norbury W, Jeschke M, Herndon D: **Metabolism modulators in sepsis: propranolol**. *Crit Care Med* 2007, **35**:s616–620.

194. Van Veldhuisen DJ, Van Gelder IC, Ahmed A, Gheorghiade M: **Digoxin for patients with atrial fibrillation and heart failure: paradise lost or not?** *Eur Heart J* 2013, **34**:1468–70.

195. Lip GY, Metcalfe MJ, Dunn FG: **Diagnosis and treatment of digoxin toxicity.** *Postgrad Med J* 1993, **69**:337–339.

196. Amaral A, Opal SM, Vincent J-L: **Coagulation in sepsis.** *Intensive Care Med* 2004, **30**:1032–40.

197. Reintam a, Parm P, Kitus R, Kern H, Starkopf J: **Gastrointestinal symptoms in intensive care patients.** *Acta Anaesthesiol Scand* 2009, **53**:318–24.