Thromboembolism and death in patients with atrial flutter

Vadmann, Henrik

DOI (link to publication from Publisher):
10.5278/vbn.phd.med.00055

Publication date:
2016

Document Version
Publisher's PDF, also known as Version of record

THROMBOEMBOLISM AND DEATH IN PATIENTS WITH ATRIAL FLUTTER

BY
HENRIK VADMANN

DISSERTATION SUBMITTED 2016

AALBORG UNIVERSITY
DENMARK

THROMBOEMBOLISM AND DEATH IN PATIENTS WITH ATRIAL FLUTTER

by

Henrik Vadmann

AALBORG UNIVERSITY
DENMARK

Dissertation submitted 2016

Dissertation submitted: 15 April 2016

PhD supervisor: Associate Prof. Torben Bjerregaard Larsen
MD, PhD, FESC
Thrombosis Research Unit, Department of Cardiology, Atrial Fibrillation Study Group, Aalborg University Hospital
Department of Clinical Medicine, Aalborg University

Assistant PhD supervisors: Associate Prof. Søren Pihlkjær Hjortshøj, MD, PhD
Research Director
Aalborg University Hospital

Associate Prof. Sam Riahi, MD, PhD
Department of Cardiology, Atrial Fibrillation Study Group, Aalborg University Hospital

PhD committee: Clinical Prof. Bodil Steen Rasmussen, MD, PhD (Chair.)
Department of Anesthesia and Intensive Care Medicine, Aalborg University Hospital

Associate Prof. Håkan Walfridsson, MD, PhD
Linköping University Hospital

Associate Prof. Axel Brandes, MD, DMSc
Department of Cardiology, Odense University Hospital

PhD Series: Faculty of Medicine, Aalborg University

ISSN (online): 2246-1302
ISBN (online): 978-87-7112-555-9

Published by:
Aalborg University Press
Skjernvej 4A, 2nd floor
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk

Printed in Denmark by Rosendahls, 2016

ENGLISH SUMMARY

The incidence of atrial flutter is higher in patients with obesity, hypertension and diabetes mellitus and increases with age. With the aging of the general population and the increased prevalence of lifestyle disease, such as obesity, hypertension and diabetes mellitus, the prevalence of atrial flutter is expected to increase in the years to come. Contrary to atrial fibrillation (AF), the thromboembolic and mortality risks associated with atrial flutter are sparsely investigated.

The overall aim of this PhD dissertation was to examine the thromboembolic and mortality risks associated with atrial flutter compared with those of AF. First, we conducted a systematic review of the current literature investigating the thromboembolic risk associated with atrial flutter, and second, we investigated the thromboembolic and mortality risks in atrial flutter compared with AF after an ablation procedure in a Danish nationwide cohort. Third, we investigated the risk of death and development of heart failure and new arrhythmia after an atrial flutter ablation procedure.

The systematic review included both retrospective and prospective studies. From this review, we could conclude that patients with atrial flutter had a high risk of thromboembolic events. In the nationwide cohort studies, we found 1,096 (33%) patients with an incident atrial flutter and 2,266 with an incident AF ablation procedure between 1 January 2000 and 31 December 2013. We found a non-significant increase in the risk of thromboembolic events (hazard ratio (HR) 1.34, 95% confidence interval (CI) 0.71-2.41), heart failure (HR 1.14, 95% CI 0.76-1.71) and development of a new arrhythmia. However, there is a significantly higher mortality risk (HR 1.85, 95% CI 1.29-2.66) in patients with atrial flutter than in AF patients after an ablation procedure. In patients who developed heart failure there was a significant increase in mortality risk in patients with atrial flutter (HR 2.97, 95% CI 1.11-7.91).

In conclusion, in the literature we found an elevated risk of thromboembolic events in patients with atrial flutter. In a Danish cohort, we found a higher all-cause mortality in patients with atrial flutter than in AF patients after an ablation procedure. The risk of developing heart failure or a new arrhythmia was similar between atrial flutter and AF.

DANSK RESUME

Patienter med overvægt, forhøjet blodtryk og sukkersyge har øget risiko for at udvikle atrieflagren, og forekomsten stiger med alderen. Med højere levealder og øget forekomst af livsstilssygdomme som overvægt, forhøjet blodtryk og sukkersyge forventes forekomsten af atrieflagren at stige de næste mange år. Modsat atrieflimren (AF) er risikoen for apopleksi og død ved atrieflagren sparsomt undersøgt.

Hovedformålet med denne ph.d.-afhandling, der er baseret på tre studier, var at undersøge risikoen for apopleksi og død hos patienter med atrieflagren og at foretage en sammenligning overfor patienter med AF. Det første studie var en systematisk gennemgang af den tilgængelige litteratur med henblik på at undersøge sammenhængen mellem apopleksi og atrieflagren. Det andet studie undersøgte risikoen for apopleksi og død efter ablation for atrieflagren og AF i en dansk kohorte. Det tredje studie undersøgte udviklingen i død, hjertesvigt og risikoen for ny arytmi, baseret på data fra det andet studie.

Den systematiske litteraturgennemgang indeholdt både pro- og retrospektive studier. Ud fra gennemgangen kunne vi konkludere, at patienter med atrieflagren har en relativt høj risiko for apopleksi. I de danske kohortestudier identificerede vi 1096 patienter med atrieflagren (33%) og 2266 patienter med AF patienter behandlet med ablation i perioden mellem 1. januar 2000 og 31. december 2013. Vi fandt en ikke-signifikant stigning i risikoen for apopleksi mellem atrieflagren og AF (hazard ratio (HR) 1,34, 95% konfidens interval (CI) 0,71-2,41), hjertesvigt (HR 1,14 95% CI 0,76-1,71) og ny arytmi, men en signifikant øget risiko for død (HR 1,85 95% CI 1,29-2,66) hos patienter med atrieflagren. Hos de der udviklede hjertesvigt efter ablation, havde patienter med atrieflagren en signifikant øget risiko for at dø (HR 2,97, 95% CI 1,11-7,91).

Samlet set viste litteraturgennemgangen en øget risiko for apopleksi hos patienter med atrieflagren, og i de danske kohorte studier fandt vi større risiko for død efter ablation hos patienter ablateret for atrieflagren sammenlignet med AF ablation. Vi fandt en ikke-signifikant stigning mellem atrieflagren og AF i risikoen for apopleksi, hjertesvigt og ny arytmi efter ablation.

ACKNOWLEDGEMENTS

It has been a long journey

This PhD dissertation is based on the work conducted at the Department of Cardiology, Aalborg University Hospital, during my employment from 2010 to 2015.

It all began in the summer of 2010, when a random conversation with Søren Hjortshøj lead to a more formal meeting with him and Sam Riahi. They introduced me to Erik Berg Schmidt, and two months later, I was employed at the Department of Cardiology, Aalborg University Hospital, as part of the Aalborg Atrial Fibrillation Study Group. The aim of the employment was to conduct a clinical research project (FAST II) as a PhD project. Unfortunately, this project was prematurely closed in 2013 due to lack of sufficient data for a PhD dissertation. In the spring of 2013, Torben Bjerregaard Larsen offered his help to conduct an epidemiologic project. This project started in the fall of 2013. Time was sparse, but we were optimistic and hoped that I could submit my PhD dissertation in spring 2015. Now, in the spring of 2016, it is finally ready.

First, I would like to thank Sam Riahi; you are a great inspiration, and I greatly appreciate your opinion and thought on both clinical and scientific matters. Søren Pihlkjær Hjortshøj, despite your busy calendar you somehow always find the time to discuss scientific matters, and your clinical skills are a great inspiration. Erik Berg Schmidt, thank you for believing in me and engaging me in the Atrial Fibrillation Study Group. Torben Bjerregaard Larsen, this PhD dissertation would not have been possible without your invaluable help and guidance. Further thanks go to Gregory Lip who is a co-author on all my papers.

Søren Lundbye-Christensen, thank you for the introduction to statistics and your teaching skills, which actually made me understand some statistics. Furthermore, Flemming Skjøth, I owe you big thanks; you have participated in this PhD project on and off, but you have taught me so much on data management and statistics.

Special thanks goes to my fellow PhD students in the cardiologist PhD room at the Science and Innovation Centre of Aalborg University Hospital, Jakob Stegger, Thomas Rix, Michael René Skjelbo Nielsen, Vibeke Høgh, Jacob Moesgaard Larsen, Anders Gammelmark, Anette Arbjerg Højen, Line Melgaard, Thure Filskov Overvad, Stine Venø, Christian Bork and Pia Dinesen; it has been great fun to meet and work alongside you all.

Jan Jesper Andreasen and Albert Marni Joensen, thank you for involving me in your projects. It has been of great educational value to work with you on other projects beside my PhD.

Finally, I would like to thank Peter Brønnum Nielsen and Hanne Madsen who both have contributed on this PhD project.

My last thoughts and gratitude go to my family, all of whom have supported me in each your way.

Funding

This study was financially supported by the Atrial Fibrillation Study Group, Aalborg University Hospital and Aalborg Thrombosis research Unit.

Henrik Vadmann

April, 2016

TABLE OF CONTENTS

LIST OF PAPERS

This PhD dissertation is based on the following papers:

1. **Atrial flutter and thromboembolic risk: a systematic review**
   Vadmann H, Nielsen PB, Hjortshøj SP, Riahi S, Rasmussen LH, Lip GY, Larsen TB. Heart. 2015 Sep;101(18):1446-55

2. **Death and thromboembolic risk after ablation of atrial flutter compared to atrial fibrillation: A nationwide cohort study**
   Vadmann H, Gorst-Rasmussen A, Hjortshøj S, Riahi S, Lip GY, Larsen TB. Europace 2006 (doi:10.1093/europace/euw107).

3. **The risk of death and adverse outcomes after an ablation procedure in patients with atrial flutter compared to patients with atrial fibrillation**
   Vadmann H, Skjøth F, Hjortshøj S, Riahi S, Lip GY, Larsen TB (submitted).

ABBREVIATIONS

AF: Atrial fibrillation

TIA: Transient ischemic attack

Bpm: Beats per minute

ICD: Internationale Classification of Disease

ATC: Anatomical Therapeutic Chemical

HR: Hazard ratio

CI: Confidence interval

CHA_2DS_2-VASc: Congestive heart failure, Hypertension, Age >75 (double), Diabetes mellitus, previous Stroke/transient ischemic attack/systemic embolism (double), Vascular disease, age 65-74, Sex category (female)

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia with an incidence rate of 4.3 per 1,000 person-years (1) with a lifetime risk of development of approximately 25 percent in people ≥40 years of age (2). AF is an independent risk factor for stroke, thromboembolism and death (3,4). However, less is known about the related supraventricular arrhythmia, atrial flutter and thromboembolic risk. Atrial flutter is the second most common cardiac arrhythmia (5) with an overall incidence of 88 cases per 100,000 person-years in the general population (6). The age-specific incidence rate increases with age, to 587 per 100,000 person-years among individuals above 80 years (7). While no data have been published on atrial flutter prevalence in Denmark, the estimated number of US inhabitants with atrial flutter was 0.07 million in 2005. With approximately 200,000 incident cases per year in the US (8), the prevalence is expected to increase to 0.15 million by 2050 (9).

Increasing age and obesity are associated with the risk of development of atrial flutter (10). Furthermore, male sex, heart failure, chronic obstructive pulmonary disease, diabetes mellitus, and myocardial infarction also increase the risk of atrial flutter (7,8,11). Large population-based studies have demonstrated that patients with atrial flutter have a high burden of cardiovascular co-morbidity, and that these patients are often hospitalized with cardiovascular as well as non-cardiovascular diseases (12). The most commonly related admission diagnoses are major bleeding, stroke or transient ischemic attack (TIA), congestive heart failure, and other cardiac complications (13,14).

As the general population gets older, with increasing co-morbidity, the optimal treatment with the lowest risk of adverse outcomes should be pursued. However, there are no large studies investigating the association of atrial flutter with the risk of thromboembolism and mortality compared with AF.

BACKGROUND

HISTORICAL PERSPECTIVE

In the late 19th century, the first description of atrial flutter, or auricular flutter as it was termed, was published. McWilliam (15), who conducted animal experiments, stated that *"The movements are regular; they seem to consist of a series of contractions originating in the stimulated area and hence spreading over the rest of the tissue"*. Later in the early 20th century, when primitive electrocardiograms evolved, the sawtooth waves in the inferior electrocardiographic leads, later known as classical type I atrial flutter, were described (16). These observations were complemented in 1913 by Lewis et al. (17) who, by a combination of epicardial maps and electrocardiogram recordings, stated that *"the activation sequence was orderly, i.e., the wavefront circulated in either a cranial-caudo or a caudo-cranial direction in the right atrium"*. They stated that atrial flutter was due to an electrical intra-atrial circus movement around the vena cavae. Indeed, in 1947 Rosenbleuth and Garcia-Ramos (17) demonstrated that creation of a lesion between the vena cavae induced a re-entry loop arrhythmia circulating around this lesion. An additional lesion from the inferior vena cava to the atrioventricular groove could terminate the arrhythmia, suggesting that the true atrial flutter circuit involves the cavotricuspid isthmus. However, this intra-atrial re-entry theory was not widely accepted, and several publications supported another theory in which a local ectopic focus was responsible for atrial flutter (18–21).

In the following three decades, both re-entry and ectopic focus theories were widely investigated (17,22), but it was not until 1970 that the first classification of atrial flutter appeared. Puech el al. (22) proposed that atrial flutter should be classified as; (I) typical atrial flutter, (II) atypical atrial flutter and (III) impure atrial flutter. This classification marked a new era, and in the following two decades, various experimental models and small clinical studies confirmed the general mechanism of atrial flutter (17,22). Waldo et al. (22) later modified this classification into two subgroups; Type I attributed to movement around an anatomic obstacle, and type II based on functionally determined re-entry. This classification was valid until 2001, when the Working Group of Arrhythmias of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (23) together published the current and still accepted classification. In the latest joint guideline from 2003 (23), atrial flutter is now divided into two major groups; "isthmus-dependent atrial flutter" and "non-cavotricuspid isthmus-dependent atrial flutter".

DEFINITION AND PATHOPHYSIOLOGY

Cavotricuspid isthmus-dependent atrial flutter

Isthmus-dependent atrial flutter, or typical atrial flutter, is by far the most frequent type (24) and includes a macro-re-entrant counterclockwise or clockwise electrical rotation around the cavotricuspid isthmus. An area of relatively slow conduction velocity exists in the low right atrium, restricted by the tricuspid annulus as the anterior barrier and the crista terminalis as the posterior barrier (6,24).

Non-cavotricuspid isthmus-dependent atrial flutter

This type is also known as atypical atrial flutter. Atypical atrial flutter is primarily caused by macro-entry circuits around barriers such as atrial scars, crista terminalis, the mitral annulus or pulmonary veins (23).

Atrial fibrillation

It is well known that there is a clinical similarity between atrial flutter and AF, and it has even been proposed that there is a pathophysiological similarity (25). However, the mechanisms of AF are not fully established, but contrary to atrial flutter, AF is not a macro-re-entrant arrhythmia but characterized by chaotic, uncoordinated contractions of the atria with rates above 300 bpm. Local micro-re-entry with fibrillatory activity, focal electrical activity, multiple propagating wavelets, and the autonomic nervous system all seem to interact in the development and perpetuation of AF (26,27).

CLINICAL PRESENTATION

The clinical presentation of atrial flutter shares the same characteristics as other arrhythmias, e.g. dyspnoea, chest pain, palpitations and fatigue, and can also be asymptomatic. The acute presentation of atrial flutter may cause impaired cardiac function, heart failure, hypotension, and tachycardia-induced myocardial ischemia. Untreated persistent atrial flutter may lead to tachycardia-mediated cardiomyopathy (28).

ELECTROCARDIOGRAM

As tachycardia-related symptoms are often non-specific for the underlying arrhythmia, characteristic electrocardiographic findings are mandatory for the diagnosis of common atrial flutter. Common atrial flutter typically appears as an inverted sawtooth flutter wave pattern, observed in the inferior electrocardiogram leads (II, III, and aVF). The atrial rate is from 240 to 340 bpm (29,30). Often, no distinct isoelectric period is visible between the flutter ´F´waves. Other types of atrial

flutter can be more difficult to determine as the electrocardiographic patterns are uncharacteristic, and some have even proposed that "*Atypical atrial flutter is defined as continuous baseline activity with anything other than typical atrial flutter F-wave morphology*" (30). Invasive electrophysiology studies are therefore often required to confirm the subtype.

TREATMENT OPTIONS

Until the 1960s, the only treatment option for atrial flutter was pharmacologic with quinidine, digitalis and procainamide (31,32). In 1962, Lown et al. (33) introduced the first non-pharmacologic treatment. They described their initial experience of direct-current cardioversion in the treatment of atrial flutter. Pharmacological and direct-current cardioversion remained the only treatment options until 1986, when Klein et al. (34) reported their results of two patients treated with cryosurgical ablation in the right atrium, preventing atrial flutter recurrence. This observation led to several publications on the technique and results of radiofrequency ablation of typical atrial flutter (6,35–37). Peri-procedural complications during atrial flutter ablations are rare (<4%), with the most frequent being haematomas, atrioventricular block, pericardial effusion and, more rare, as ventricular arrhythmia, cerebral vascular events, myocardial infarction and pulmonary embolism (38–42). Radiofrequency catheter ablation is now considered first-line treatment with a high acute and chronic efficacy and a low complication rate (29,40,43–45). Besides ablation, other treatment options include pharmacologic drugs for either rhythm control (procainamide, propafenone, flecainide, sotalol, ibutilide and amiodarone) or rate control (beta-blockers, digoxin, verapamil, diltiazem and amiodarone) (23,46) and direct-current cardioversion. However, ablation is documented to reduce healthcare utilization with fewer hospitalizations, better quality of life (23,29,43) and to be superior to pharmacologic drugs and direct-current cardioversion in the prevention of recurrent atrial flutter (40).

INTERNATIONAL GUIDELINES

There are no separate guidelines for the management of patients with atrial flutter, and numerous published articles and current international guidelines do not discriminate between the two arrhythmias. In the 2010 European Society of Cardiology (27) guideline for AF it is stated that "*Antithrombotic therapy is recommended for patients with atrial flutter as for those with atrial fibrillation"*, but with a low level of evidence. Due to the high procedural success rate, around 95%, and a low annual recurrence rate, atrial flutter ablation is often considered a curative treatment (47), and some even suggest that anticoagulant treatment could be stopped four to six weeks after ablation (28,48,49). However, no large randomized controlled trials have addressed the long-term thromboembolic risk associated with atrial flutter, and most data are derived from case reports as well as echocardiographic and cohort studies, and the true thromboembolic and mortality risk thereby remains uncertain.

AIMS AND HYPOTHESISES

The overall aim of this PhD dissertation was to examine the thromboembolic and mortality risk associated with atrial flutter compared to AF.

The specific aims and hypotheses for papers I-III are:

Paper I

Aims: To perform an up-to-date systematic review of the literature to investigate the association between atrial flutter and thromboembolic events.

Hypothesis: Patients with atrial flutter have a similar risk of thromboembolic events as patients with AF.

Paper II

Aims: To investigate whether there is a similar mortality and thromboembolic risk following an atrial flutter ablation procedure, compared with an AF ablation procedure.

Hypothesis: There is a similar mortality and thromboembolic risk following stand-alone atrial flutter ablation compared with an AF ablation.

Paper III

Aims: To compare the risk of death and development of new/recurrent arrhythmia and/or subsequent heart failure after an atrial flutter and an AF ablation procedure, respectively.

Hypothesis: There is a similar or lower risk of adverse outcomes after an atrial flutter ablation procedure than after an AF ablation procedure.

MATERIAL AND METHODS

The following is a brief description of paper I-III. Paper II and III are based on the same data sources and study population and are therefore described together. A more detailed description is presented in each paper.

PAPER I

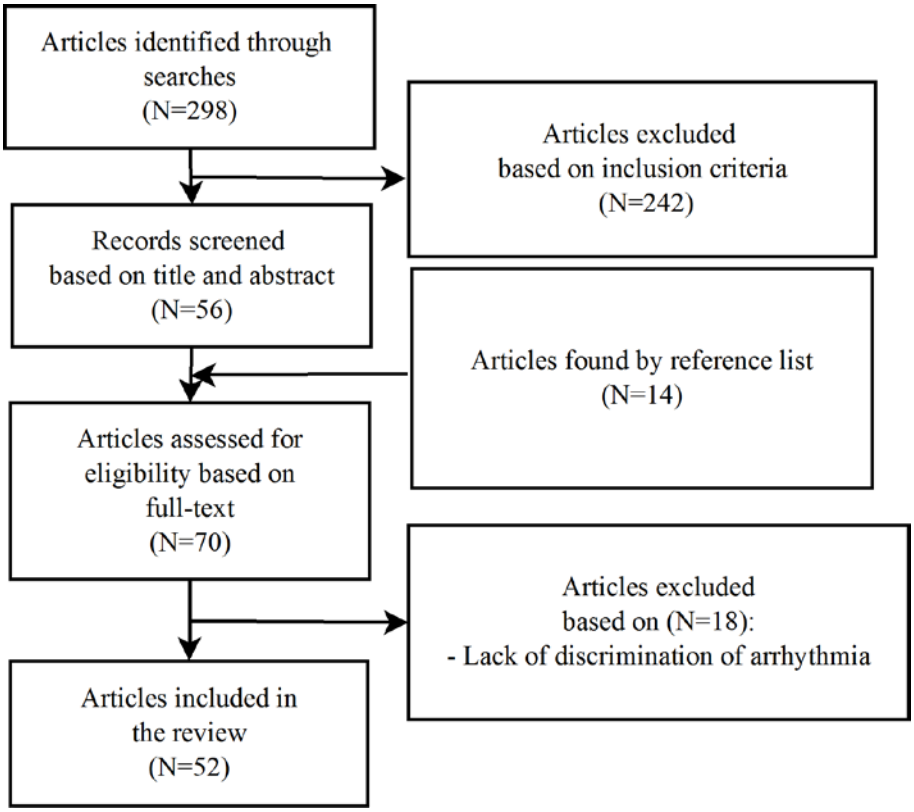
Study eligibility and data collection

Articles included in this review were identified by searching EMBASE and MEDLINE databases using MeSH terms such as “atrial flutter” and “stroke”. In addition, a manual search was made of references listed in included articles. International guidelines and retro- and prospective studies were included, and eligibility was assessed based on the PICO components (population, intervention, comparator, outcomes) (50). Inclusion criteria were restricted to age >18 years and a clear differentiation between atrial flutter and AF. Author, year of publication, study design, sample size, distribution of patients with atrial flutter and AF, type (if any) of anticoagulant treatment, length of follow-up, results of transthoracic and transoesophageal echocardiography, co-morbidities, and thromboembolic events were extracted to further analyses. Quality assessment of each study was performed by using context-specific methodological aspects with five predefined parameters (51). Due to large heterogeneity, a meta-analysis of the included studies was not conducted.

Study characteristics

Two hundred and ninety-eight articles were identified by a structured as well as an unstructured search, and 52 articles were included in the final review (Figure 1). Included articles comprise case-reports, international guidelines and observational, echocardiographic, cardioversion and ablation studies.

Figure 1: Flowchart explaining the exclusion process



PAPER II+III

Data sources (Paper II+III)

Study data were obtained by merging data from three Danish Nationwide registries: the Danish Civil Registration System, the Danish National Patient Registry and the National Prescription Registry. All three registries hold information on all Danish inhabitants and were linked by the patients' personal and unique identification number, given to all Danish inhabitants. The Danish Civil Registration System (52,53) contains data on date of birth, sex, vital status, migration, and date of death. Since 1977, the Danish National Patient Registry (54–57) has registered all hospital admissions with a discharge diagnose code and surgical procedure code according to the 10th revision of the Internationale Classification of Disease (ICD) since 1995 (54). The National Prescription Registry (58) has recorded all prescription medication

redeemed from Danish pharmacies since 1995 and onwards. Prescribed medication is coded according to the Anatomical Therapeutic Chemical (ATC) Classification System (57,58).

Study population (Paper II+III)

All Danish inhabitants between 18 and 75 years, with an incident atrial flutter or AF ablation code between 1 January 2000 and 31 December 2013 were included in the study. Patients with a prior ablation procedure code, or diagnose code for heart failure, ischemic heart disease, pacemaker, valvular heart disease and/or prior thromboembolic events were excluded. In addition, patients regarded as not on anticoagulant treatment at the time of ablation were excluded (defined as no warfarin prescription redeemed 90 days before ablation. Co-morbidity was obtained at baseline defined as the date of the ablation procedure.

Outcomes (Paper II)

All-cause mortality was the primary endpoint with the combined thromboembolic event (ischemic stroke, TIA, or pulmonary embolism) as secondary endpoint. Outcomes were measured from ablation until the occurrence of endpoints, emigration or end of study period, whichever came first.

Outcomes (Paper III)

Outcomes were defined as all-cause mortality, heart failure, or the combined arrhythmia management endpoint (new atrial flutter or AF procedure and/or pacemaker implantation).

Statistical analyses (Paper II)

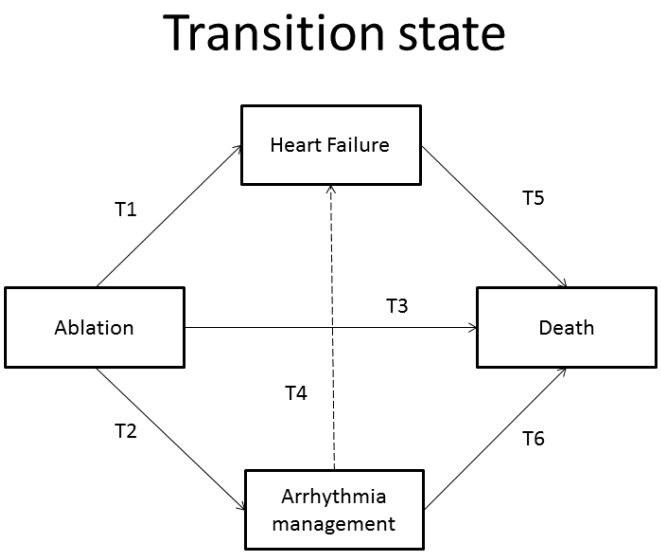
We used Kaplan-Meier curves to display survival. Cox proportional hazards regression models were used to calculate event rates and hazard ratio (HR). HR were reported as crude and adjusted estimates.

Statistical analyses (Paper III)

We used Cox proportional hazards regression to compare event rates and HR between atrial flutter and AF. Kaplan-Meier survival curves display disease-free survival, and the Aalen-Johansen estimator was used to calculate the cumulative incidence rates under competing risks of arrhythmia management or heart failure. We used a semi-Markov transition model to compare event rates between atrial flutter and AF and the different transition states (Figure 2), and each state and transition were analysed separately.

Data were analysed using Stata (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Figure 2: Transition states from index ablation procedure

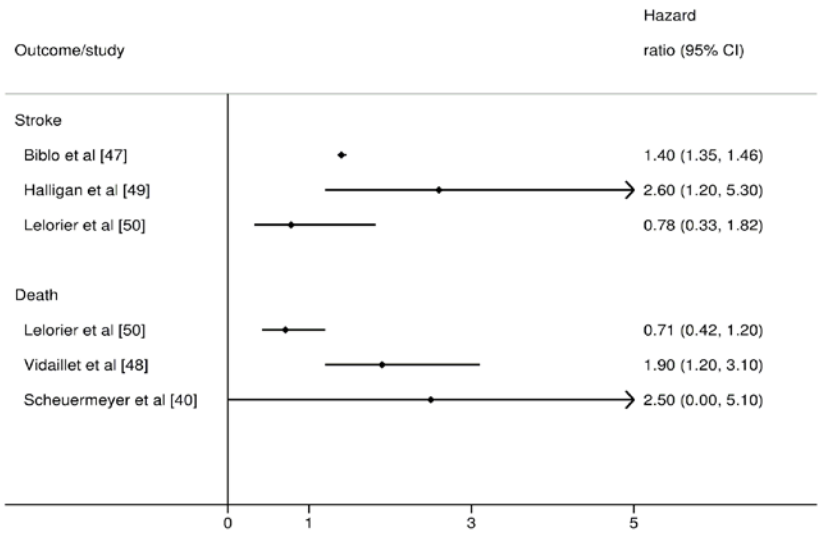


MAIN RESULTS

PAPER I

Fifty-two articles were included in the review: six observational, 15 echocardiographic, 14 cardioversion, three ablation studies, two case-reports and twelve international guidelines. Publication dates span from 1962 to 2014, with the majority published after 1990. The six observational studies revealed a trend towards an increased risk of thromboembolic events and death in patients with atrial flutter (Figure 3). The highest reported thromboembolic risk was reported in echocardiographic studies (0% to 6.8%). There was a high prevalence of thrombus in the left atrial appendage (0-38%), and all studies reported the prevalence of spontaneous echo contrast (21%-28%). Cardioversion studies had the greatest publication date span, stretching from 1962 to 2011. The highest incidence of thromboembolic events (0-6%) occurred 1-2 days after the procedure. The ablation studies reported that the rate of thromboembolic events was reduced from 17.9 per 1,000 person-years to 13.1 per 1,000 person-years after an ablation procedure. Furthermore, the development of AF after atrial flutter ablation nearly doubled the risk of thromboembolic events (0.6 vs. 1.1 per 100 person-years).

Figure 3: Forest plot of associations between atrial flutter and stroke and/or all-cause mortality (Paper I)



PAPER II

A total of 8,170 patients with either an incident atrial flutter or AF ablation procedure were identified by the registries. The study population consisted of 1,096 (33%) patients with an atrial flutter and 2,266 (67%) patients with an AF ablation procedure. The main reasons for exclusion were the lack of anticoagulant treatment at baseline (n=2,044) and heart failure (n=963) (Figure 4). Baseline characteristics (Table 1) were nearly similar between the two groups; however, there was an overweight of patients with chronic obstructive pulmonary disease, prior heart valve surgery and congenital heart disease in the atrial flutter group. After an atrial flutter ablation procedure there was a higher mortality risk than after an AF ablation (Figure 5). The mortality rate was almost two-fold higher (crude HR 1.92, 95% confidence interval (CI) 1.22-3.03) in the atrial flutter group during 5 years of follow-up. After multivariable adjustment, the higher risk among atrial flutter patients persisted (HR 1.68, 95% CI 1.05-2.69). The thromboembolic event rate for atrial flutter was 0.35 per 100 person-years, and the risk was similar to that of AF (crude HR 1.34, 95% CI 0.71-2.41).

Figure 4: Flowchart of study population exclusion (Paper II and III)

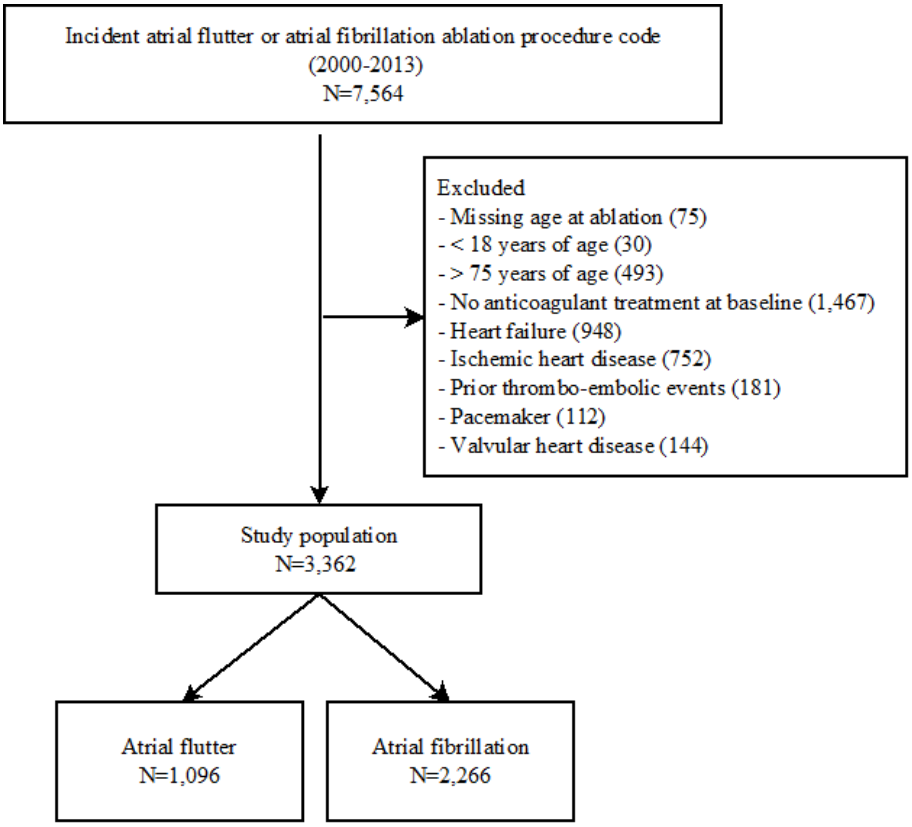
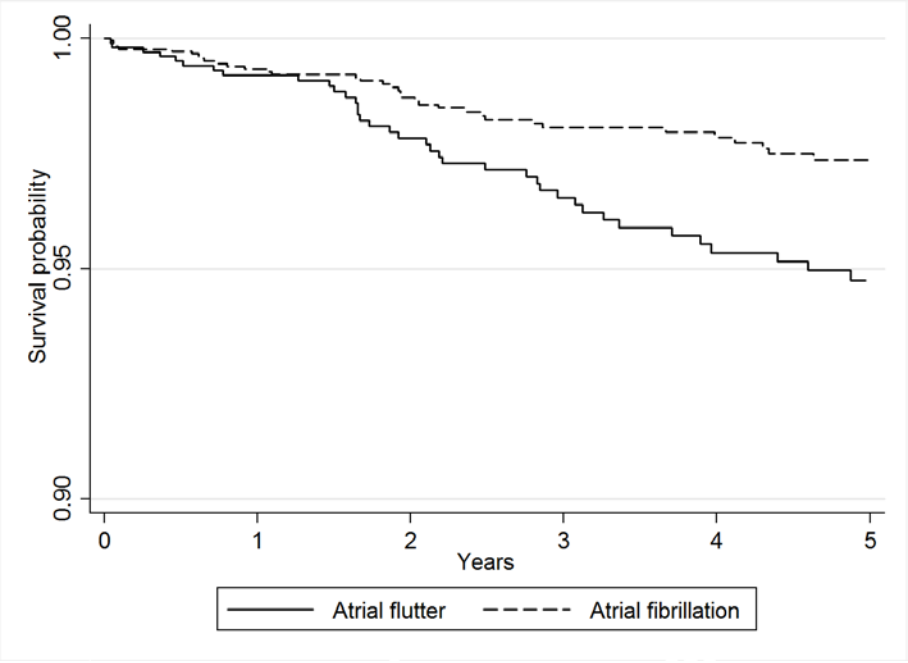


Table 1: Baseline characteristics of study population (Paper II and III)

	Atrial flutter (N=1,096)	**Atrial fibrillation** (N=2,266)
Sex (male)	868 (79.2%)	1,645 (72.6%)
Age at ablation, median IQR	61.0 (52.4 - 66.5)	58.9 (51.5 - 64.7)
Years with diagnosis[1], mean (sd)	2.0 (2.9)	2.8 (3.5)
Hypertension	290 (26.5%)	612 (27.0%)
Diabetes	61 (5.6%)	82 (3.6%)
Obesity	51 (4.6%)	86 (3.8%)
Hyperthyreosis	29 (2.6%)	76 (3.3%)
Alcoholism	13 (1.2%)	15 (0.7%)
Renal disease	13 (1.2%)	15 (0.7%)
Chronic obstructive pulmonary disease	35 (3.2%)	38 (1.7%)
Cancer diagnosis	87 (7.9%)	134 (5.9%)
Heart arrhythmia surgery	25 (2.3%)	32 (1.4%)
Congenital heart disease	36 (3.3%)	19 (0.8%)
Beta-blocker[2]	842 (76.8%)	1,685 (74.2%)
Anti-arrhythmic medication[2]	506 (46.2%)	1,134 (50.0%)
Digoxin	313 (28.5%)	520 (22.9%)
Amiodarone	170 (15.5%)	452 (19.9%)
Other[3]	311 (28.4%)	960 (42.4%)

IQR: Interquartile range
[1]Atrial flutter or atrial fibrillation diagnose
[2]At least one redeemed prescription < 1 year before ablation
[3]Verapamil, sotalol, dronedarone and flecainide

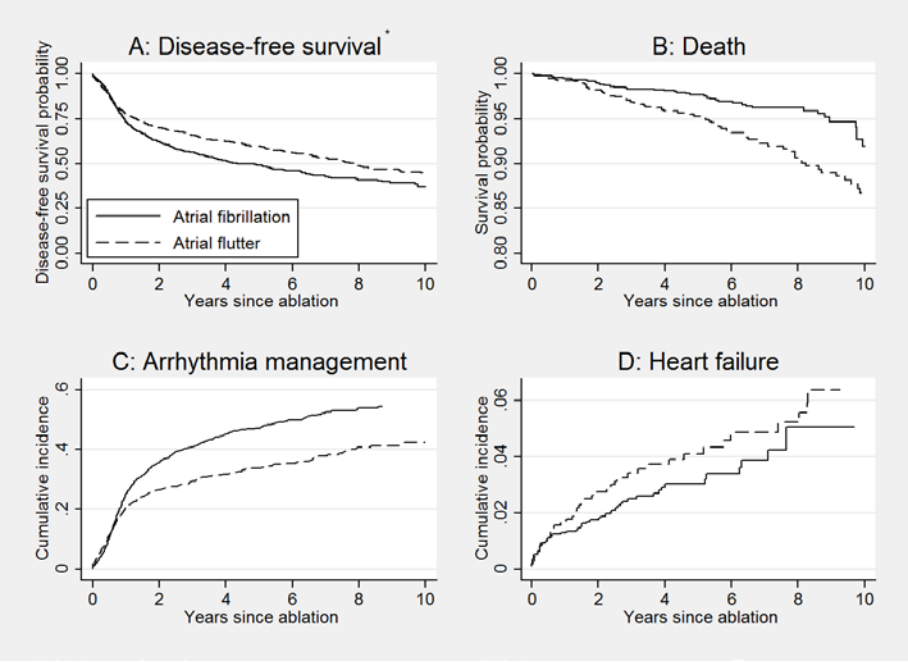
Figure 5: Kaplan-Meier survival plot (Paper II)



PAPER III

Using the same study population (Table 1) as paper II, we included 3,362 patients, 1,096 (33%) with an incident atrial flutter ablation procedure. There was a lower disease-free survival but a higher risk of heart failure and death in the atrial flutter group compared with AF (Figure 6). The observed differences between the ablation groups occurred after approximately one year following the initial ablation. With an average follow-up of 4.6 years, there was an almost two-fold higher all-cause mortality risk after an atrial flutter ablation procedure (HR 1.85, 95% CI 1.29-2.66). In the atrial flutter group, the event rate for pacemaker implantation was 1.56 per 100 person-years, and higher compared with the AF group. However, the risk of subsequent death after pacemaker implantation was similar between the two groups (HR 4.29, 95% CI 0.82-22.4). The transition to heart failure was similar between the atrial flutter and the AF group (HR 1.14, 95% CI 0.76-1.71), but a subsequent transition from heart failure to death was higher in patients who had an atrial flutter ablation as the index procedure (HR 2.97, 95% CI 1.11-7.91).

Figure 6: Kaplan-Meier survival plot (Paper III)



METHODOLOGICAL CONSIDERATIONS

Some considerations about the methods and limitations of the three studies should be acknowledged. In the following, various sources of bias that can affect the interpretation of the studies will be discussed.

Selection issues

Selection bias may be defined as any aspect of the way subjects are included in the study, creating a systematic difference between the compared populations that is not attributable to the associations. In an observational study, selection criteria therefore mainly affect the generalisability of the results. In studies II and III, we should therefore ask ourselves if any systematic difference exists, I) Do Danish patients differ from patients ablated in, for instance, other Western countries? II) Is there a systematic difference between patients ablated for atrial flutter and patients ablated for AF? Regarding the latter, no comparative data exist, but patients ablated for atrial flutter in the Danish cohort (paper II and III) were slightly older, included more males and had higher co-morbidity and a shorter mean time with the diagnosis (2.0 versus 2.8 years, respectively) compared with those ablated for AF. This could reflect presence of selection bias in the study. Using Cox proportional hazards models gives us the possibility of exploring the relationship between the survival of a patient and several explanatory variables. This method also takes into account time to event and time to censoring. The study populations in studies II and III included all Danish patients with an incident atrial flutter or AF ablation procedure in a restricted time-period. In order to eliminate competing arrhythmias we excluded patients with a prior ablation procedure code. Atrial flutter and AF often co-exist and in the earlier ICD-10 codes classification even shared the same code. In order to separate the two arrhythmias for this study, the study populations were included by the ablation procedure codes for atrial flutter and AF, respectively, as these represent two different ablation procedures. The ICD-10 codes for atrial flutter in the Danish National Patient Registry have previously been validated with a positive predictive value of 57.5% in men and 29.6% in women (59).

Publication bias

Sometimes biases apply to a population of studies, rather than to one study, as in publication bias (tendency to publish papers showing positive results). We did not find any large randomized trials on atrial flutter ablation in our systematic review. Some proclaim that randomized trials are the gold standard for treatment efficacy and safety assessments. While randomized controlled trials are indeed the gold standard in the sense of providing "fair" comparisons, they may not always provide the most

relevant comparisons. Well-designed observational studies can address the question whether a treatment is beneficial in daily clinical practice, not just whether the treatment by itself is beneficial in ideal settings. Furthermore, bias related to the selective reporting of outcomes has also been characterized as a serious problem in meta-analyses of clinical trials (60,61). The same is true for meta-analyses of cohort studies that can be subject to serious bias (62).

In paper I, a systematic review was conducted, but it is possible that the exclusion criteria - such as foreign language - could lead to additional (selection) bias. Furthermore, the data in the included articles were dominated by high heterogeneity and low quality in terms of follow-up, methodological methods and endpoints. Due to the high heterogeneity in study characteristics, it was not feasible to conduct a meta-analysis. Nevertheless, in order to minimize bias, we conducted the review according to the PRISMA statement (50) and assessed the eligibility of the included studies based on the PICO components. We applied strict inclusion criteria with predefined components, but a major challenge was the lack of differentiation between atrial flutter and AF. This could lead to an underestimation of the presence of AF. Finally, the publication date span from 1964 to 2014, a period with great progress in the understanding, diagnosing, and treatment of atrial flutter.

There can be other explanations for the discrepancies between outcome data from observational studies and those seen in randomized studies (63). For example, differences in length of follow-up may result in different conclusions. In addition, randomized controlled trials are externally valid only for the type of patients included in that trial, and there is a tendency to publish studies with “interesting” and positive outcomes. However, this is probably even truer for observational studies.

Confounding

A simple definition of confounding is *confusion of effects*. This is a phenomenon resulting from the fact that one feature of study subjects has not been separated from a second feature, and has thus been confounded with it, producing bias. Bias creates an association that is erroneous, but confounding describes an association that may be correct, but potentially misleading. For example: are patients admitted for atrial flutter ablation confounded by a risk factor that is not present in patients admitted for AF ablation? The factor that creates the bias, or the confounding variable, must be associated with both the independent and dependent variables (i.e. with the exposure and the disease). Confounding is primarily a parameter related to studies of causality and therefore not a major issue in paper II focusing on outcome. However, as this study is based on registry data, it leaves open the possibility of residual and unmeasured confounding, in addition to misclassification and ascertainment error. As an example, atrial flutter ablation was offered to an older and possibly sicker population for which the relevant comorbidities are not necessarily captured by the registries.

In cohort studies like studies II and III, various analytical techniques exist that provide ways of adjusting for confounding in the analysis, e.g. stratification and multiple variable regression analysis. To minimize the risk of confounding, Cox proportional hazards models were used to account for known explanatory variables and time to event and censoring. However, where there is confounding, there is also the possibility of residual confounding. If measured or unmeasured heterogeneous key risk factors are a possible explanation for the association, then 'possible' does not always mean 'plausible'. Therefore, a cautious choice of methods and principles can ease confounding concerns in observational studies using linked healthcare databases (64). Based solely upon electrocardiogram findings, atrial flutter diagnosing seems challenging and, in some cases, only 55% of the diagnoses are correct (65). In studies II and III, arrhythmia management was defined as renewed ablation (atrial flutter or AF) and/or pacemaker implantation. Ablation and pacemaker procedure codes were used to investigate arrhythmia management. However, this approach does not take into account that patients may have various arrhythmias that are not treated by ablation. Asymptomatic AF may be underestimated and undertreated leading to a higher mortality and thromboembolic risk, but contrary to the results from paper II, this should lead to a more similar mortality risk in the atrial flutter group compared with the AF group and cannot explain the higher mortality. In conclusion, paper II was a study of associations between exposure and outcomes, and the study did not fulfil the requirements to answer questions regarding causality (66). In addition, the results from paper III should be interpreted very cautiously in terms of causality, and prospective follow-up studies, e.g. with loop-recorders, are needed.

Limitations of the Danish registries

In the two cohort studies (papers II and III), data were extracted from three Danish Nationwide registries which implies some limitations. Main factors affecting the value of data from the used registries are: I) completeness of registration of individuals, II) the accuracy and degree of completeness of the registered data, III) data accessibility and availability, and IV) possibilities of linkage with other data sources (record linkage) (67). First, not all patients diagnosed with atrial flutter or AF are registered in the Danish National Patient Register, as some cases are managed at the general practice level. The diagnoses of atrial flutter and/or AF in Danish registries have previously been validated with a combined positive predictive value of 92.6% (59); however, by the use of ablation procedure codes, the risk of arrhythmia misclassification is reduced due to the nature of the ablation procedure. The primary endpoint, all-cause mortality, is somehow an unspecific endpoint and non-informative about causation. Data availability and accessibility may also be a problem when using registry-based data as the data collection has already been performed.

DISCUSSION

The aim of this PhD dissertation was to investigate the thromboembolic and mortality risk associated with atrial flutter compared with AF. The PhD dissertation is based upon three sub-studies, and in the following sections, each sub-study will be discussed separately.

Paper I: Atrial flutter and thromboembolic risk: a systematic review

This systematic review confirms that there is a risk of thromboembolic events, and that the presence of left atrial thrombus and spontaneous echo contrast is highly prevalent in patients with atrial flutter. The majority of articles included in this review were published before 2001, at a time when the use of anticoagulant treatment was almost non-existing. It was not until 2001 that international guidelines addressed the issue of anticoagulant treatment in atrial flutter patients (68). The recommendation was based upon echocardiographic studies revealing low blood flow velocities in the left atrial appendage during atrial flutter compared with sinus rhythm, but higher than during AF. The elevated risk of thrombus formation with low blood flow velocities is supported by the Virchow triad theory (changes in blood flow, changes in the vessel wall and changes in the properties of blood) (69). However, as the formation of thrombus associated with atrial flutter seems explicable, the thromboembolic risk is multifactorial as demonstrated by Arnold et al. (70) who reported no thromboembolic events in 122 patients with atrial flutter who underwent a cardioversion procedure without anticoagulant treatment. Moreover, the multifactorial cause of thromboembolic events is well recognized in AF patients, where the use of different risk scores for thromboembolic risk stratification is well-validated (26). No randomized trials were included in paper I, and due to the large heterogeneity and low quality of the data, it was not possible to make an exact estimate of the thromboembolic risk. Only papers published until October 2014 were included, and subsequently seven articles focusing on the risk of thromboembolic events in patients with atrial flutter have been published (48,71–75), but still no randomized studies. It is noticeable that a recent Framingham substudy (11) identified a higher risk of stroke, mortality and myocardial infarction in patients with atrial flutter compared with healthy controls. As emphasized in the latest guideline from the European Society of Cardiology (27), the recommendation of anticoagulant treatment is based on a low level of evidence due to the non-existence of high quality studies. Nevertheless, this systematic review, based on observational, echocardiographic and cardioversion studies, and later published articles, supports the current recommendation that atrial flutter should be treated according to the same risk profile as AF.

Paper II: Death and thromboembolic risk after ablation of atrial flutter compared with atrial fibrillation: A nationwide cohort study

Following an ablation procedure, patients with atrial flutter had a higher mortality risk than patients with AF. Atrial flutter patients had a mortality rate of 1.08 per 100 person-years and compared with AF, there was nearly a two-fold higher mortality risk (crude HR 1.92, 95% CI 1.22-3.03). The higher mortality risk was not due to a higher risk of thromboembolic events, as there was no difference between the two groups (HR 1.22, 95% CI 0.62-2.41). The stroke rate of 0.46 per 100 person-years was comparable with that of the general population (76) but lower than in other studies (77). In comparison, the Framingham Heart study (11) found a stroke rate of 2.8 per 100 person-years in atrial flutter patients, which is equal to the rate in AF patients. Compared with other studies (7,78,79), we included a relatively healthy population, and although there were no large differences between the atrial flutter and AF groups at baseline, it cannot be dismissed that the atrial flutter group might be older and more ill. Indeed, chronic pulmonary disease and heart failure have been found to be predictive factors for death in patients with atrial flutter (80). There was a higher prevalence of chronic obstructive pulmonary disease in the atrial flutter group (3.2% vs. 1.7%), but the mortality risk remained elevated after adjustment for chronic obstructive pulmonary disease (HR 1.66, 95% CI 1.01-2.73). The higher mortality risk after an atrial flutter ablation observed in our study, differs from similar studies that have reported an equal or even lower risk among atrial flutter patients, indeed an annual risk of one third of the risk in patients with AF has been reported, (80,81). Seara et al. (80) found that the development of AF after an atrial flutter ablation increases the subsequent risk of death nearly threefold (HR 2.82, 95% CI 1.88-4.70). The development of AF after atrial flutter is well known and documented to be as high as 23.1% in a meta-analysis (40), and this could therefore be an explanation for the observed higher mortality risk. It could be speculated that atrial flutter patients' co-morbidity is multifactorial and not easily captured by a simple regression analysis. Moreover, as some clinicians consider atrial flutter ablation to be a curative treatment, this may cause an insufficient follow-up.

Paper III: The risk of death and adverse outcomes after an ablation procedure in patients with atrial flutter compared to patients with atrial fibrillation

This study confirms an increased overall mortality risk in atrial flutter compared with AF patients (HR 1.85, 95% CI 1.29-2.66). The difference in HR between paper II and III is that paper II follow-up is stopped at 5 years, whereas in paper III, there is a full available follow-up. The mortality rate without transition to other states was 1.10 per 100 person-years. There was a markedly higher risk of pacemaker implantation among atrial flutter patients (HR 1.66, 95% CI 1.14-2.41) but no difference in the transition to heart failure (HR 1.14, 95% CI 0.76-1.71) compared with AF patients. A similar study by Seara et al. (80) found a nearly two-fold higher mortality rate than in our study (2.2 per 100 person-years), but contrary to our study, they included patients

with ischemic heart disease, prior thromboembolic events and heart failure, which are all independent mortality risk factors. Vidaillet et al. (78) found that with a follow-up of more than 13 months, there is a similar mortality risk when comparing an atrial flutter ablation, AF ablation procedure and matched controls. This contrasts our results, where there is a similar mortality risk until one year after ablation. Whether this delayed mortality risk is due to new arrhythmias is speculative, but it has been shown that the incidence of AF after atrial flutter ablation seems to be time dependent, with reported rates of 17-22% after 6 months increasing to 50% after 2 years, and 60-80% after 4 years (48). In our study, only 155 patients (14.1%) underwent an AF ablation after an index atrial flutter ablation procedure. However, asymptomatic or subclinical atrial tachyarrhythmia is found to be eight times more common than clinical AF in patients without previous atrial arrhythmia after pacemaker implantation (82). Furthermore, an AF ablation is a far more complex procedure with an inherent higher procedural risk, and physicians may therefore choose not to refer elderly, frail patients with comorbidities for ablation.

Moreover, the elevated mortality risk could be considered procedure-related, as there is a higher risk of pacemaker implantation after an atrial flutter ablation procedure (42). Nevertheless, when adjusting for early pacemaker implantation (<30 days after ablation), the risk remains elevated (adjusted HR 1.85, 95% CI 1.09-3.13). Untreated atrial tachyarrhythmia is a known risk factor for the development of heart failure, and in observational studies (11), the event rate is 3.6 per 100 person-years and 5.5 per 100 person-years in a post-ablation population. Although there is no statistically significant difference in the transition from index atrial flutter (4%) or AF (2.6%) ablation to heart failure (HR 1.14, 95% CI 0.76-1.71), patients who develop heart failure after the index atrial flutter ablation had a higher mortality risk (HR 2.97, 95% CI 1.11-7.91). In a newly published paper, Expósito et al. (48) reported a mortality risk of 15.8% with 5 years of follow-up after a cavotricuspid isthmus ablation procedure. Remarkably, the main cause of death was non-cardiovascular in 68.4% (13/19) of cases. Whether adverse effects of anticoagulant treatment drive the observed higher mortality risk in the present study remains unanswered, and only randomized studies can give us a clear answer of that question.

CONCLUSION

This PhD dissertation provides additional information on the association between atrial flutter and mortality from an epidemiological perspective. Based upon the three studies, the main conclusions are summarized below

Paper I

The presence of spontaneous echo contrast and left atrial thrombus is highly prevalent in patients with atrial flutter. The correlation between spontaneous echo contrast, left atrial thrombus and subsequent thromboembolic events is, however, multifactorial. This review confirms that there is an elevated risk of thromboembolic events associated with atrial flutter.

Paper II

In contrast to similar studies, we found a higher mortality risk after an atrial flutter ablation procedure compared with an AF ablation procedure. The higher mortality risk does not seem related to a higher risk of thromboembolic events.

Paper III

Patients with atrial flutter have a higher mortality risk than AF patients after an ablation procedure. There is no difference in the risk of heart failure development. However, a higher mortality was seen in the patients who develop heart failure after atrial flutter ablations compared with AF ablation procedures.

PERSPECTIVES

When and whom to offer anticoagulation, remains a challenge. While the recommendations regarding AF patients seems well supported, the recommendations for atrial flutter patients are unclear. This PhD dissertation has investigated the risk of thromboembolism and death after atrial flutter ablation compared with AF from several angles. Thus, the result of the systematic review supports the current recommendation regarding thromboembolic risk reduction (83). The CHA_2DS_2-VASc stroke risk score has been validated for patients with AF (26) but not for atrial flutter patients. However, in the future these scores may provide guidance for the atrial flutter populations after systematic validation studies in independent populations. The initiation and duration of anticoagulant treatment after atrial flutter ablations therefore remain debatable, especially in medium to high-risk patients. In clinical settings, atrial flutter ablation is generally considered a low risk procedure with a high procedural success rate (28,47,75). Rather surprisingly, studies II and III demonstrate an increased mortality risk after atrial flutter ablations. While adjusting for a number of known mortality risk factors and procedure-related complications, the mortality risk in the atrial flutter group remains increased. This PhD dissertation also indicates that patients who develop heart failure after an atrial flutter ablation have a higher mortality. However, the registry-based design of the studies does not reveal the mechanism as we have no data concerning left ventricular ejection fraction, peri-procedural anticoagulation strategies, the exact cause of death, or other clinical data. Regarding the optimal treatment of atrial flutter, especially following cavotricuspid ablation, a number of questions remain unanswered. Although cavotricuspid isthmus ablation offers a high procedural success rate, many patients will subsequently develop AF and thus possess a renewed – or continued – thromboembolic risk. Furthermore, studies with implantable cardiac monitors have demonstrated that patients have a higher burden of asymptomatic AF following ablation than previously anticipated (84). A study using implantable cardiac monitors after atrial flutter ablation might therefore provide valuable insight into the burden of post ablation arrhythmia and, at the same time, provide information about other types of arrhythmias, e.g. concomitant ventricular arrhythmia in patients with heart failure.

LITERATURE LIST

1. 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 Feb;25(2):95–102.

2. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, et al. Lifetime risk for development of atrial fibrillation: The framingham heart study. Circulation. 2004;110(9):1042–6.

3. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med. 1995 May;98(5):476–84.

4. Benjamin EJ, Wolf P a, 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(10):946–52.

5. Link MS. Clinical practice. Evaluation and initial treatment of supraventricular tachycardia. N Engl J Med. 2012 Oct 11;367(15):1438–48.

6. Bun S-S, Latcu DG, Marchlinski F, Saoudi N. Atrial flutter: more than just one of a kind. Eur Heart J. 2015;36(35):2356–63.

7. Granada J, Uribe W, Chyou PH, Maassen K, Vierkant R, Smith PN, et al. Incidence and predictors of atrial flutter in the general population. J Am Coll Cardiol. 2000 Dec;36(7):2242–6.

8. Mareedu RK, Abdalrahman IB, Dharmashankar KC, Granada JF, Chyou P-H, Sharma PP, et al. Atrial flutter versus atrial fibrillation in a general population: differences in comorbidities associated with their respective onset. Clin Med Res. 2010 Mar;8(1):1–6.

9. Naccarelli G V, Varker H, Lin J, Schulman KL. Increasing prevalence of atrial fibrillation and flutter in the United States. Am J Cardiol. 2009 Dec 1;104(11):1534–9.

10. 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 May;118(5):489–95.

11. Rahman F, Wang N, Yin X, Ellinor PT, Lubitz SA, LeLorier PA, et al. Atrial flutter: Clinical risk factors and adverse outcomes in the Framingham Heart Study. Hear Rhythm. Elsevier; 2015;13(1):233–40.

12. Naccarelli G V, Johnston SS, Dalal M, Lin J, Patel PP. Rates and implications for hospitalization of patients ≥65 years of age with atrial fibrillation/flutter. Am J Cardiol. G.V. Naccarelli, Penn State Heart and Vascular Institute, Milton S. Hershey Medical Center, Penn State University, Hershey, PA, United States. E-mail: gnaccarelli@hmc.psu.edu: Elsevier Inc. (360 Park Avenue South, New York NY 10010, United States); 2012 Feb 15;109(4):543–9.

13. Naccarelli G V, Johnston SS, Dalal M, Lin J, Patel PP. Rates and implications for hospitalization of patients ≥65 years of age with atrial fibrillation/flutter. Am J Cardiol. 2012 Feb 15;109(4):543–9.

14. Patel NJ, Deshmukh A, Pau D, Goyal V, Patel S V, Patel N, et al. Contemporary utilization and safety outcomes of catheter ablation of atrial flutter in the United States: Analysis of 89,638 procedures. Heart Rhythm. 2016 Feb 6;

15. McWilliam JA. Fibrillar Contraction of the Heart. J Physiol. 1887 Oct;8(5):296–310.

16. Jolly W a, Ritchie WT. Auricular flutter and fibrillation. 1911. Ann Noninvasive Electrocardiol. 2003 Jan;8(1):92–6.

17. Lee KW, Yang Y, Scheinman MM. Atrial flutter: a review of its history, mechanisms, clinical features, and current therapy. Curr Probl Cardiol. 2005 Mar;30(3):121–67.

18. SCHERF D. Studies on auricular tachycardia caused by aconitine administration. Proc Soc Exp Biol Med. 1947 Feb;64(2):233–9.

19. Wellens HJ, Janse MJ, van Dam RT, Durrer D. Epicardial excitation of the atria in a patient with atrial flutter. Br Heart J. 1971 Mar;33(2):233–7.

20. Rosen KM, Lau SH, Damato AN. Simulation of atrial flutter by rapid coronary sinus pacing. Am Heart J. 1969 Nov;78(5):635–42.

21. PRINZMETAL M. The nature and treatment of the auricular arrhythmias. Can Med Assoc J. 1952 Jun;66(6):535–40.

22. Mary-Rabine L, Mahaux V, Waleffe A, Kulbertus H. Atrial flutter: historical background. J Cardiovasc Electrophysiol. 1997 Mar;8(3):353–8.

23. Blomström-Lundqvist C, Scheinman MM, Aliot EM, Alpert JS, Calkins H, Camm AJ, et al. ACC/AHA/ESC guidelines for the management of patients

with supraventricular arrhythmias--executive summary. a report of the American college of cardiology/American heart association task force on practice guidelines and the European society of cardiology . J Am Coll Cardiol. 2003 Oct 15;42(8):1493–531.

24. Saoudi N, Cosío F, Waldo a, Chen S a, Iesaka Y, Lesh M, et al. A classification of atrial flutter and regular atrial tachycardia according to electrophysiological mechanisms and anatomical bases; a Statement from a Joint Expert Group from The Working Group of Arrhythmias of the European Society of Cardiology and the . Eur Heart J. 2001 Jul;22(14):1162–82.

25. Waldo AL. The interrelationship between atrial fibrillation and atrial flutter. Prog Cardiovasc Dis. 2005;48(1):41–56.

26. January CT, Wann LS, Alpert JS, Calkins H, Cleveland JC, Cigarroa JE, et al. 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. J Am Coll Cardiol. 2014 Mar 28;

27. Camm AJ, Kirchhof P, Lip GYH, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace. 2010 Oct;12(10):1360–420.

28. Wellens HJJ. Contemporary management of atrial flutter. Circulation. 2002;106:649–52.

29. Sawhney NS, Anousheh R, Chen W-C, Feld GK. Diagnosis and management of typical atrial flutter. Cardiol Clin. Elsevier Inc.; 2009 Feb;27(1):55–67, viii.

30. Anselme F, Saoudi N, Poty H, Douillet R, Cribier A. Radiofrequency catheter ablation of common atrial flutter: significance of palpitations and quality-of-life evaluation in patients with proven isthmus block. Circulation. 1999 Feb 2;99(4):534–40.

31. Pinchin AJ. Auricular Flutter and Fibrillation. Postgrad Med J. 1926 Aug;1(11):155–8.

32. Walker MJA. Antiarrhythmic drug research. Br J Pharmacol. 2006;147 Suppl :S222–31.

33. LOWN B, AMARASINGHAM R, NEUMAN J. New method for terminating cardiac arrhythmias. Use of synchronized capacitor discharge. JAMA. 1962

Nov 3;182:548–55.

34. Klein GJ, Guiraudon GM, Sharma AD, Milstein S. Demonstration of macroreentry and feasibility of operative therapy in the common type of atrial flutter. Am J Cardiol. 1986 Mar 1;57(8):587–91.

35. Cosio FG, López-Gil M, Goicolea A, Arribas F, Barroso JL. Radiofrequency ablation of the inferior vena cava-tricuspid valve isthmus in common atrial flutter. Am J Cardiol. 1993 Mar 15;71(8):705–9.

36. Feld GK, Fleck RP, Chen PS, Boyce K, Bahnson TD, Stein JB, et al. Radiofrequency catheter ablation for the treatment of human type 1 atrial flutter. Identification of a critical zone in the reentrant circuit by endocardial mapping techniques. Circulation. 1992 Oct;86(4):1233–40.

37. Saoudi N, Atallah G, Kirkorian G, Touboul P. Catheter ablation of the atrial myocardium in human type I atrial flutter. Circulation. 1990 Mar;81(3):762–71.

38. Andrew P, Montenero AS. Atrial flutter: a focus on treatment options for a common supraventricular tachyarrhythmia. J Cardiovasc Med (Hagerstown). 2007 Aug;8(8):558–67.

39. Rodgers M, McKenna C, Palmer S, Chambers D, Van Hout S, Golder S, et al. Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation. Health Technol Assess. 2008 Dec;12(34):iii – iv, xi – xiii, 1–198.

40. Pérez FJ, Schubert CM, Parvez B, Pathak V, Ellenbogen K a, Wood M a. Long-term outcomes after catheter ablation of cavo-tricuspid isthmus dependent atrial flutter: a meta-analysis. Circ Arrhythm Electrophysiol. 2009 Aug;2(4):393–401.

41. Walters TE, Kistler PM, Kalman JM. Radiofrequency ablation for atrial tachycardia and atrial flutter. Heart Lung Circ. Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) and The Cardiac Society of Australia and New Zealand (CSANZ); 2012 Jul;21(6-7):386–94.

42. Brembilla-Perrot B, Filali ML, Zinzius P-Y, Sellal J-M, Beurrier D, Schwartz J, et al. Is ablation of atrial flutter always safe? Pacing Clin Electrophysiol. 2012 Oct;35(9):1061–6.

43. Dewland T a, Glidden D V, Marcus GM. Healthcare utilization and clinical outcomes after catheter ablation of atrial flutter. PLoS One. 2014

Jan;9(7):e100509.

44. Verma A, Macle L, Cox J, Skanes AC. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: catheter ablation for atrial fibrillation/atrial flutter. Can J Cardiol. 2011;27(1):60–6.

45. Spector P, Reynolds MR, Calkins H, Sondhi M, Xu Y, Martin A, et al. Meta-analysis of ablation of atrial flutter and supraventricular tachycardia. Am J Cardiol. Elsevier Inc.; 2009 Oct 1;104(5):671–7.

46. Stiell IG, Macle L. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: management of recent-onset atrial fibrillation and flutter in the emergency department. Can J Cardiol. 2010;27(1):38–46.

47. Lee G, Sanders P, Kalman JM. Catheter ablation of atrial arrhythmias: state of the art. Lancet. 2012 Oct 27;380(9852):1509–19.

48. Expósito V, Rodríguez-Entem F, González-Enríquez S, Veiga G, Olavarri I, Olalla JJ. Stroke and Systemic Embolism After Successful Ablation of Typical Atrial Flutter. Clin Cardiol. 2016;n/a – n/a.

49. Voight J, Akkaya M, Somasundaram P, Karim R, Valliani S, Kwon Y, et al. Risk of new-onset atrial fibrillation and stroke after radiofrequency ablation of isolated, typical atrial flutter. Heart Rhythm. Elsevier; 2014 Jul 1;11(11):1884–9.

50. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.

51. Jüni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. BMJ. 2001 Jul 7;323(7303):42–6.

52. Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. Dan Med Bull. 2006 Nov;53(4):441–9.

53. Pedersen CB. The Danish Civil Registration System. Scand J Public Health. 2011 Jul;39(7 Suppl):22–5.

54. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449–90.

55. Andersen TF, Madsen M, Jørgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull. 1999 Jun;46(3):263–8.

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

57. Thygesen LC, Daasnes C, Thaulow I, Brønnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. Scand J Public Health. 2011 Jul;39(7 Suppl):12–6.

58. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health. 2011 Jul;39(7 Suppl):38–41.

59. 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 Jun;46(3):149–53.

60. Chan A-W, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. JAMA. 2004 May 26;291(20):2457–65.

61. Page MJ, McKenzie JE, Kirkham J, Dwan K, Kramer S, Green S, et al. Bias due to selective inclusion and reporting of outcomes and analyses in systematic reviews of randomised trials of healthcare interventions. Cochrane database Syst Rev. 2014;10:MR000035.

62. Dwan K, Gamble C, Williamson PR, Kirkham JJ, Reporting Bias Group. Systematic review of the empirical evidence of study publication bias and outcome reporting bias - an updated review. PLoS One. 2013;8(7):e66844.

63. Sørensen HT, Lash TL, Rothman KJ. Beyond randomized controlled trials: a critical comparison of trials with nonrandomized studies. Hepatology. 2006 Nov;44(5):1075–82.

64. Stürmer T, Jonsson Funk M, Poole C, Brookhart MA. Nonexperimental comparative effectiveness research using linked healthcare databases. Epidemiology. 2011 May;22(3):298–301.

65. Shiyovich A, Wolak A, Yacobovich L, Grosbard A, Katz A. Accuracy of diagnosing atrial flutter and atrial fibrillation from a surface electrocardiogram by hospital physicians: analysis of data from internal medicine departments. Am J Med Sci. 2010 Oct;340(4):271–5.

66. Rothman KJ, Greenland S. Causation and causal inference in epidemiology. Am J Public Health. 2005;95 Suppl 1:S144–50.

67. Sorensen HT, Sabroe S, Olsen J. A framework for evaluation of secondary data sources for epidemiological research. Int J Epidemiol. 1996 Apr;25(2):435–42.

68. Fuster V, Rydén LE, Asinger RW, Cannom DS, Crijns HJ, Frye RL, et al. ACC/AHA/ESC Guidelines for the Management of Patients With Atrial Fibrillation: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee . Circulation. 2001 Oct 23;104(17):2118–50.

69. Chung I, Lip GYH. Virchow's triad revisited: blood constituents. Pathophysiol Haemost Thromb. 33(5-6):449–54.

70. Arnold AZ, Mick MJ, Mazurek RP, Loop FD, Trohman RG. Role of prophylactic anticoagulation for direct current cardioversion in patients with atrial fibrillation or atrial flutter. J Am Coll Cardiol. 1992 Mar 15;19(4):851–5.

71. Roswell RO, Greet B, Shah S, Bernard S, Milin A, Lobach I, et al. Intravenous heparin dosing strategy in hospitalized patients with atrial dysrhythmias. J Thromb Thrombolysis. 2016 Mar 7;

72. Redfearn DP, Furqan MA, Enriquez A, Barber D, Shaw C, Simpson C, et al. Emergency Department Re-Presentation for Atrial Fibrillation and Atrial Flutter. Can J Cardiol. 2016 Mar;32(3):344–8.

73. Almeida ED, Guimarães RB, Stephan LS, Medeiros AK, Foltz K, Santanna RT, et al. Clinical Differences between Subtypes of Atrial Fibrillation and Flutter: Cross-Sectional Registry of 407 Patients. Arq Bras Cardiol. 2015 Jul;105(1):3–10.

74. Jannou V, Timsit S, Nowak E, Rouhart F, Goas P, Merrien F-M, et al. Stroke with atrial fibrillation or atrial flutter: a descriptive population-based study from the Brest stroke registry. BMC Geriatr. 2015;15:63.

75. Clementy N, Desprets L, Pierre B, Lallemand B, Simeon E, Brunet-Bernard A, et al. Outcomes After Ablation for Typical Atrial Flutter (from the Loire Valley Atrial Fibrillation Project). Am J Cardiol. Elsevier Inc.; 2014 Nov 1;114(9):1361–7.

76. Carandang R, Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Kannel WB, et al. Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. JAMA. 2006 Dec 27;296(24):2939–46.

77. Tomson TT, Kapa S, Bala R, Riley MP, Lin D, Epstein AE, et al. Risk of stroke and atrial fibrillation after radiofrequency catheter ablation of typical atrial flutter. Heart Rhythm. 2012 Nov;9(11):1779–84.

78. Vidaillet H, Granada JF, Chyou P o-H, Maassen K, Ortiz M, Pulido JN, et al. A population-based study of mortality among patients with atrial fibrillation or flutter. Am J Med. 2002 Oct 1;113(5):365–70.

79. Scheuermeyer FX, Grafstein E, Heilbron B, Innes G. Emergency department management and 1-year outcomes of patients with atrial flutter. Ann Emerg Med. 2011 Jun;57(6):564–71.e2.

80. Seara JG, Roubin SR, Gude Sampedro F, Barreiro VB, Sande JM, Mañero MR, et al. Risk of atrial fibrillation, stroke, and death after radiofrequency catheter ablation of typical atrial flutter. Clin Res Cardiol. 2014 Jul;103(7):543–52.

81. Wood KA, Eisenberg SJ, Kalman JM, Drew BJ, Saxon LA, Lee RJ, et al. Risk of thromboembolism in chronic atrial flutter. Am J Cardiol. 1997 Apr 15;79(8):1043–7.

82. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, et al. Subclinical atrial fibrillation and the risk of stroke. N Engl J Med. 2012 Jan 12;366(2):120–9.

83. Vadmann H, Nielsen PB, Hjortshøj SP, Riahi S, Rasmussen LH, Lip GYH, et al. Atrial flutter and thromboembolic risk: a systematic review. Heart. 2015;1446–55.

84. Kircher S, Hindricks G, Sommer P. Long-term success and follow-up after atrial fibrillation ablation. Curr Cardiol Rev. 2012 Nov;8(4):354–61.

APPENDIX A. TABLES PAPER II:

Supplementary table 1: Event counts, rates, and Cox hazard ratios after 5 years of follow-up

	Ablation procedure	
	Atrial fibrillation	Atrial flutter
Death		
Events (n)	36	38
Rate, per 100 person-years (95% CI)	0.56 (0.41-0.78)	1.08 (0.78-1.48)
HR (95% CI)		
Crude	1.00 (reference)	1.92 (1.22-3.03)
Adjusted[1]	1.00 (reference)	1.68 (1.05-2.69)
Adjusted[2]	1.00 (reference)	1.50 (0.92-2.45)
Thrombo-embolic events		
Events (n)	22	16
Rate, per 100 person-years (95% CI)	0.35 (0.23-0.53)	0.46 (0.28-0.75)
HR (95% CI)		
Crude	1.00 (reference)	1.34 (0.71-2.56)
Adjusted[*]	1.00 (reference)	1.32 (0.69-2.55)
Adjusted[**]	1.00 (reference)	1.22 (0.62-2.41)

[*]Adjusted for: age (restricted cubic spline), sex, hypertension, and diabetes mellitus,

[**]Adjusted for: age (restricted cubic spline), sex, hypertension, diabetes mellitus, time with diagnosis (restricted cubic spline) and anticoagulant therapy (time-varying: less than 90 days since last warfarin prescription redemption).

HR: hazard ratio; CI: confidence interval, TE: Stroke, transient ischemic attack and pulmonary embolisms.

Supplementary table 2: Univariate mortality hazard ratio by baseline characteristics

Hazard ratio (95% CI)

	Atrial Flutter	Atrial fibrillation
Male sex	1.42 (0.85-2.39)	1.50 (0.85-2.64)
Age	1.08 (1.05-1.11)	1.06 (1.02-1.09)
Time with diagnosis	0.96 (0.88-1.04)	0.97 (0.89-1.06)
Hypertension	1.49 (0.93-2.38)	1.48 (0.85-2.58)
Diabetes mellitus	1.60 (0.69-3.68)	2.32 (0.92-5.84)
Chronic obstructive pulmonary disease	1.16 (0.28-4.74)	3.13 (0.98-10.03)

CI= Confidence interval

APPENDIX B. TABLES PAPER III

Supplementary table 1: Transition rates for each ablation group and adjusted hazard ratios (95% confidence intervals) with atrial fibrillation ablation as reference group.

Transition	**Rate per 100 person-years (number of events)**		**Hazard ratio (95 % CI)[1,2]**
	Atrial flutter	**Atrial fibrillation**	
All-cause mortality	1.34 (78)	0.56 (54)	1.85 (1.29-2.66)
Initial ablation to	***(n=1,096)***	***(n=2,266)***	
T1: Death	1.10 (43)	0.41 (24)	1.85 (1.09-3.13)
T2: Arrhythmia management	9.23 (360)	16.0 (923)	0.72 (0.63-0.81)
- Atrial flutter ablation	3.69 (144)	1.76 (102)	2.80 (2.16-3.62)
- Atrial fibrillation ablation	3.97 (155)	13.20 (763)	0.38 (0.31-0.45)
- Pacemaker implantation	1.56 (61)	1.00 (58)	1.66 (1.14-2.41)
T3: Heart failure	1.13 (44)	1.00 (58)	1.14 (0.76-1.71)
Arrhythmia management to	***(n=360)***	***(n=923)***	
T4: Death	1.16 (20)	0.62 (23)	1.70 (0.91-3.17)
T5: Heart failure	1.27 (22)	0.92 (34)	1.36 (0.78-2.35)
Heart failure to	***(n=66)***	***(n=92)***	
T6: Death	7.29 (15)	2.87 (7)	2.97 (1.11-7.91)

[1]Atrial fibrillation as reference

[2]Adjusted for age, sex, hypertension and diabetes.

Supplementary table 3: Table 2 and sensitivity analysis removing patients with pacemaker implantation within 30 days after initial ablation and prior heart operation.

Transition	Rate per 100 person-years (number of events)		Hazard ratio (95 % CI)[1,2]	Hazard ratio (95 % CI)[1,2,3]
	Atrial flutter	Atrial fibrillation		
All-cause mortality	1.34 (78)	0.56 (54)	1.85 (1.29-2.66)	
Initial ablation to	***(n=1,096)***	***(n=2,266)***		
T1: Death	1.10 (43)	0.41 (24)	1.85 (1.09-3.13)	1.83 (1.08-3.11)
T2: Arrhythmia management	9.23 (360)	16.0 (923)	0.72 (0.63-0.81)	0.73 (0.64-0.83)
- Atrial flutter ablation	3.69 (144)	1.76 (102)	2.80 (2.16-3.62)	
- Atrial fibrillation ablation	3.97 (155)	13.20 (763)	0.38 (0.31-0.45)	
- Pacemaker implantation	1.56 (61)	1.00 (58)	1.66 (1.14-2.41)	
T3: Heart failure	1.13 (44)	1.00 (58)	1.14 (0.76-1.71)	1.77 (1.23-2.56)
Arrhythmia management to	***(n=360)***	***(n=923)***		
T4: Death	1.16 (20)	0.62 (23)	1.70 (0.91-3.17)	
T5: Heart failure	1.27 (22)	0.92 (34)	1.36 (0.78-2.35)	
Heart failure to	***(n=66)***	***(n=92)***		
T6: Death	7.29 (15)	2.87 (7)	2.97 (1.11-7.91)	2.86 (1.06-7.68)

[1]Atrial fibrillation as reference

[2]Adjusted for age, sex, hypertension and diabetes

[3]Removed prior heart arrhythmia operation and heart valve surgery

APPENDIX C. PAPERS

Atrial flutter and thromboembolic risk: a systematic review

Vadmann H, Nielsen PB, Hjortshøj SP, Riahi S,RasmussenLH, Lip GY, Larsen TB. Heart. 2015Sep;101(18):1446-55

Death and thromboembolic risk after ablation of atrial flutter compared to atrial fibrillation: A nationwide cohort study

Vadmann H, Gorst-Rasmussen A, Hjortshøj S, Riahi S, LipGY, Larsen TB. Europace 2006(doi:10.1093/europace/euw107)

ISSN (online): 2246-1302
ISBN (online): 978-87-7112-555-9

AALBORG UNIVERSITY PRESS