Postoperative New-Onset Atrial Fibrillation Following Cardiac Surgery with Special reference to Potential New Predictors

Gu, Jiwei

DOI (link to publication from Publisher):
10.5278/vbn.phd.med.00084

Publication date:
2016

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

POSTOPERATIVE NEW-ONSET ATRIAL FIBRILLATION FOLLOWING CARDIAC SURGERY WITH SPECIAL REFERENCE TO POTENTIAL NEW PREDICTORS

BY
JIWEI GU

DISSERTATION SUBMITTED 2016

AALBORG UNIVERSITY
DENMARK

POSTOPERATIVE NEW-ONSET ATRIAL FIBRILLATION FOLLOWING CARDIAC SURGERY WITH SPECIAL REFERENCE TO POTENTIAL NEW PREDICTORS

by

JIWEI GU

AALBORG UNIVERSITY
DENMARK

Dissertation submitted 2016

.

Dissertation submitted: December 2016

PhD supervisor: Jan Jesper Andreasen
Professor, Consultant Physician, MD, PhD
Departments of Cardiothoracic Surgery and
Clinical Medicine,
Aalborg University Hospital and University, Denmark

Assistant PhD supervisor: Christian Torp-Pedersen
Professor MD, DMSc
Institute of Health Science and Technology,
Aalborg University, Denmark

Erik Berg Schmidt
Professor MD, DMSc
Departments of Cardiology and Clinical Medicine,
Aalborg University Hospital and Aalborg University
Denmark

PhD committee: Professor Henrik Vorum (chairman)
Department of Clinical Medicine
Aalborg University, Denmark

Associate Professor Lars Peter Riber
Department of Cardiothoracic Surgery
Odense University Hospital, SDU, Denmark

Professor Egon Toft
Medical Education, College of Medicine
Qatar University, Qatar

PhD Series: Faculty of Medicine, Aalborg University

ISSN (online): 2246-1302
ISBN (online): 978-87-7112-853-6

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, 2017

CURRICULUM VITAE

Name: Jiwei Gu
Born: November 19, 1978
Civil status: Married, one child: Wenzhuo (born 2010)

Education:
Sept., 1997 – Jul., 2002 Bachelor of Medicine, Changzhi Medical College, Changzhi, Shanxi province, China

Sept., 2004 – Jul., 2007 Master of Medicine, Ningxia Medical University, Yinchuan, Ningxia province, China

Sept., 2010 – Sept., 2011 Trainee of intervention technique, General Hospital of Ningxia Medical University, Yinchuan, Ningxia province, China

Mar., 2014 – Now PhD student, Department of Cardiothoracic Surgery Aalborg University Hospital and Institute of Clinical Medicine, Aalborg University, Aalborg, Denmark

Professional Experience:

Jul., 2007 – Aug., 2011 Resident-Doctor, Department of Cardiac Surgery, Heart Centre of General Hospital, Ningxia Medical University, Yinchuan, Ningxia, China

Aug., 2011 – Now Surgeon-in-charge, Department of Cardiac Surgery, Heart Centre of General Hospital, Ningxia Medical University, Yinchuan, Ningxia, China

Apr., 2013 – Mar., 2014 Visiting doctor, Aalborg University Hospital, Aalborg, Denmark

Dec., 2015 Visiting Scholar, Wake Forest Institute of Regenerative Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina, United States

ENGLISH SUMMARY

Postoperative new onset atrial fibrillation (POAF) is a common complication following cardiac surgery and may develop in 10-65% of patients depending on the POAF definition, type of surgery and diagnostic method. Because POAF is associated with an increased risk of early and late mortality and morbidity, including stroke, POAF prevention is a focus in many centers. Medical prophylaxis is most frequently used to prevent POAF. However, medical prophylaxis for all patients may expose too many of them to potential adverse effects, and prophylactic treatment for all patients may not be cost-effective. Therefore, efforts to identify patients at an increased risk for POAF would be beneficial to take precautionary measures specifically in these high-risk patients to potentially decrease morbidity and mortality related to POAF. Therefore, a continuous awareness regarding possibilities to predict POAF is important.

The cause of POAF is multifactorial, and therefore, multidirectional efforts are needed for doctors to be able to identify more high-risk patients. The overall aim of this PhD thesis is to serve as an example of a multidirectional search for potentially new predictors of POAF by performing three individual studies.

Objectives and hypotheses:

1. To investigate whether ECG markers from routine pre-operative ECGs can be used in combination with clinical data to predict new-onset POAF following cardiac surgery. Hypothesis: Minor preoperative ECG changes can be used in combination with clinical data as predictors for the development of POAF in cardiac surgery.

2. The primary aim was to evaluate whether the storage time of transfused RBC is associated with the development of POAF in patients undergoing cardiac surgery. Furthermore, we aimed to investigate whether RBC transfusion in general is associated with an increased risk of POAF. Hypothesis: RBC transfusion in general and increased storage time of transfused RBC is associated with an increased risk of POAF.

3. To evaluate whether concentrations of n-3 PUFA in atrial tissue and in the blood (plasma phospholipids) are associated with the development of POAF and whether concentrations in the atrial wall are reflected by concentrations in the blood. Hypothesis: Specific compositions of n-3 PUFA in atrial tissue are predictors of POAF and are reflected by the fatty acid composition in the blood.

Methods:

Different study designs were used for the three individual studies included in this thesis. Study I was a retrospective case control study, while Study II was a retrospective observational cohort study based on prospectively collected data from different databases. In contrast, Study III was a prospective observational study that combined laboratory and clinical data.

In Study I, demographic and clinical data regarding 100 adult patients (50 POAF, 50 without POAF) who underwent coronary artery bypass grafting (CABG), valve surgery or combinations in Aalborg University Hospital between January 1, 2011 and December 31, 2014 were retrieved from the Western Denmark Heart Registry (WDHR) and patient records. Furthermore, paper tracings of pre-operative ECGs were collected and digitalized to perform automatic readings of specific ECG variables associated with left atrial enlargement and fibrosis. Patients with a pre-operative history of AF, left or right incomplete/complete bundle branch block and patients with permanent pacemakers were excluded.

In study II, pre-, per- and postoperative data were retrieved from the WDHR and local blood banks for patients who underwent CABG, valve surgery or combined procedures in Aalborg or Aarhus University Hospital between January 1, 2010 and December 31, 2014. Logistic regression was used to determine the risk of POAF according to the transfusion of RBCs on the day of surgery. Furthermore, we determined the trend in storage time of RBCs according to the risk of POAF using restricted cubic splines. Patients with a history of preoperative atrial fibrillation (AF), pacemakers and patients who received transfusions preoperative or beyond the day of surgery were excluded.

In study III, a total of 50 patients undergoing first-time cardiac surgery between December 1, 2014 and April 30, 2015 at Aalborg University Hospital were enrolled. Venous blood and a tissue sample from the right atrial appendage were obtained perioperative. Clinical data and demographics for the patients were retrieved from the WDHR and patient records. Patients with a known history of AF and use of a pacemaker were excluded. Using gas chromatography, we assessed the content of eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) in the atrial tissue and in plasma phospholipids, and the measurements from tissue and blood were correlated with each other as well as with the development of POAF.

Results:

Study I: A subset of four pre-specified clinical variables (age, gender, body mass index, and type of surgery) were selected together with five ECG variables (QRS duration, PR interval, P-wave duration, signs of LA enlargement, and left ventricular hypertrophy) were used in a multivariate ECG model to predict POAF. The addition of ECG variables to the specific clinical data significantly improved the area under the receiver operating characteristic curve from 0.54 to 0.67. Only 20% of patients with any one risk factors developed POAF, whereas 100% of the patients with four risk factors developed POAF.

Study II: A total of 4,766 patients underwent surgery during the study period, and 2,978 patients with a mean age of 66.4 years were included. Among these, 609 patients (21%) received ≥ 1 RBC transfusion on the day of surgery. POAF developed in 752 patients (25%), and transfused patients were at an increased risk compared with non-transfused patients (adjusted OR for patients receiving RBC: 1.37; 95% CI: 1.11-1.69, p=0.004). Although RBC transfusion was generally associated with the development of POAF, spline analyses did not reveal any systematic patterns to support an increased risk of POAF in patients receiving RBC with increasing storage time.

Study III: One patient was excluded from the study due to an insufficient amount of atrial tissue for analysis. Twenty-two, 14, 10 and three patients underwent isolated CABG, valve or combined or other cardiac surgery, respectively. The mean ± SD age was 65.98 ±10.40 years. Eighteen patients (36.7%) developed POAF. Concentrations of EPA, DPA and DHA in the atrial wall or in plasma phospholipids did not predict the development of POAF, but there were significant correlations between the levels in atrial tissue and in plasma.

Conclusion:

ECG markers obtained from routine pre-operative ECG may be helpful in combination with specific clinical data in predicting new-onset POAF in patients undergoing cardiac surgery (Study I). Furthermore, RBC transfusion is also associated with an increased risk of POAF (Study II). However, the storage time of transfused allogeneic RBCs (Study II) and the levels of EPA, DPA and DHA in the atrial wall did not predict the development of POAF (Study III). Plasma phospholipid concentrations of n-3 PUFAs correlated significantly with concentrations in the atrial wall (Study III).

The results of the individual studies included in this thesis represent a multidirectional search for potential new predictors associated with the development of POAF in patients undergoing cardiac surgery. The results from study I in particular may be helpful for the development of future predictions models regarding the risk of new-onset POAF.

DANSK RESUME

Postoperativ nyopstået atrieflimmer (POAF) er en almindelig komplikation til hjertekirurgi, og POAF ses typisk hos 10-65% af patienterne afhængig af hvordan POAF defineres, hvilken operation der gennemføres og metoden der benyttes med henblik på at stille diagnosen. Da POAF er associeret med både tidlig og sen morbiditet inklusiv apopleksi samt mortalitet, er forebyggelse med henblik på at undgå POAF i fokus i mange centre. Medicinsk profylakse kan benyttes generelt, men dette vil potentielt udsætte for mange patienter for mulige bivirkninger, og en sådan profylakse er måske ikke omkostningseffektiv. Derfor kan forsøg på at identificere patienter der er i øget risiko for at udvikle POAF være gavnlige, idet særlige tiltag kan gøres i forhold til at reducere risikoen for POAF blandt disse høj-risiko patienter. Det er vigtigt at have en vedvarende opmærksomhed på muligheden for at forudsige udvikling af POAF.

Årsagen til POAF er multifaktoriel og derfor er multidirektionale tiltag nødvendige hvis læger skal have muligheden for at identificere flere patienter der er i øget risiko for at udvikle POAF. Det overordnede formål med denne ph.d. afhandling er at give et eksempel på en multidirektional søgen efter potentielle nye prediktorer som er associeret med udvikling af POAF. Dette gøres ved at gennemføre tre individuelle undersøgelser.

Formål:

1. At undersøge om EKG markører identificeret i rutinemæssige præoperative EKG optagelser i kombination med kliniske data kan benyttes med henblik på at kunne forudsige om en patient vil udvikle POAF efter hjertekirurgi. Hypotese: Mindre præoperative EKG markører kan sammen med udvalgte data identificeres som værende prædiktorer for udvikling af POAF.

2. At undersøge om den tid erytrocytter opbevares i blodbanken før transfusion er associeret med udvikling af POAF, og at undersøge om transfusion med erytrocytter generelt er associeret med POAF. Hypotese: Transfusion med røde blodlegemer og opbevaringstiden i blodbanken er associeret med en øget risiko for at udvikle POAF efter hjertekirurgi.

3. At undersøge om koncentrationen af marine n-3 flerumættede fedtsyrer (n-3 PUFA) i atrievæv og i plasma fosfolipider er associeret med udvikling af POAF efter hjertekirurgi og om koncentrationen af n-3 PUFA i atrievævet afspejles af koncentrationen i blodet. Hypotese: Specifikke kompositioner af n-3 PUFA kan prædiktere POAF and kompositionen afspejler koncentrationen i blodet.

Metoder:

Forskellige studie design er blevet i de tre individuelle studier som indgår i denne ph.d. afhandling. Study I var et retrospektivt Case-Kontrol studie medens Study II var et retrospektivt kohorte studie baseret på prospektivt indsamlede data. I modsætning hertil var Study III et prospektivt observationsstudie hvor kliniske og laboratoriemæssige data blev kombineret.

In Studie I blev demografiske og kliniske data fra 100 voksne patienter (50 patienter med POAF og 50 uden POAF) som gennemgik koronar bypass kirurgi (CABG), klapkirurgi eller kombinationer heraf på enten Aalborg eller Aarhus universitetshospital i perioden 1. januar 2011 og 31. december 2014 indhentet fra Vestdansk Hjertedatabase (WDHR) og patientjournalerne. Endvidere blev præoperative EKG optagelser indsamlet og digitaliseret med henblik på automatisk aflæsning hvad angår specifikke EKG karakteristika som er associeret med forstørret venstre atrie eller fibrose i atrievæggen. Patienter med præoperativ AF venstre- eller højresidigt inkomplet/kompletgrenblok og patienter med permanente pacemakere blev ekskluderet.

I studie II blev præ-, per- and postoperative data indsamlet fra WDHR og lokale blodbanker hvad angår patienter der havde gennemgået CABG, klapkirurgi eller en kombineret procedure på enten Aalborg or Aarhus Universitetshospital i perioden 1. januar 2010 og 31, december 2014. Logistisk regressions analyse blev anvendt med henblik på at bestemme risikoen for udvikling af POAF i relation til transfusion med erytrocytter på operationsdagen. Vi beregnede også betydningen af opbevarelsestiden i blodbanken før transfusion hvad angår risikoen for at udvikle POAF med spline analayser Patienter hos hvem præoperativ atrieflimmer indgik i annamnesen blev ekskluderet ligesom også patienter med pacemakere og patienter der modtog transfusion senere end i operationsdøgnet blev ekskluderet.

I studie III blev 50 patients som skulle gennemgå en første-gangs CABG operation på Aalborg Universitetshospital inkluderet i perioden 1. december, 2014 og 30. april, 2015. Peroperativt blev en venøs blodprøve og en biopsi fra højre atrie indsamlet. Kliniske data blev indsamlet fra WDHR og patientjournalerne. Patienter med præoperativ AF i anamnesen og pacemaker blev ekskluderet. Ved hjælp af gas kromatografi blev indholdet af eicosapentansyre acid (EPA), docosapentansyre acid (DPA) and docosahexaensyre (DHA)bestemt i atrievæv og i plasma fosfolipider og indholdet blev korreleret til udviklingen af POAF.

Resultater:

Studie I: Fire kliniske variable (alder, køn, body mass index, og operationstype) blev sammen med fem EKG variable (QRS duration, PR interval, P-wave duration, LA enlargement, and left ventricular hypertrophy) udvalgt til at skulle indgå i en multivariat model med henblik på at forudsige risikoen for udvikling af POAF. Ved at tilføje EKG variablerne til de kliniske variabler blev arealet under en receiver operating characteristic (ROC) kurve signifikant øget fra 0.54 to 0.67. Blandt patienter med kun en risikofaktor for POAF udviklede blot 20% POAF medens 100% af patienterne med fire risikofaktorer udviklede POAF.

Studie II: I alt 4.766 patienter gennemgik hjertekirurgi af de nævnte typer i studieperioden og 2.978 patienter med en gennemsnitsalder på 66,4 år blev inkluderet i undersøgelsen. Blandt disse modtog 609 patienter (21%) ≥ 1 erytrocyttransfusion i operationsdøgnet. POAF blev diagnosticeret hos 752 patienter (25%) and patienter der modtog transfusion var i øget risiko sammenlignet med ikke-transfunderede patienter (justeret OR for patients der modtog blod: 1.37; 95% CI: 1.11-1.69, p=0.004). Selvom erytrocyttransfusion var associeret med udvikling af POAF var blodets lagringstid i blodbanken ikke systematisk associeret med en øget risiko for at udvikle POAF.

Studie III: Èn patient blev ekskluderet fra studiet idet der ikke blev udtaget en tilstrækkelig mængde atrievæv til analyse. I alt 22, 14, 10 og tre patienter gennemgik henholdsvis isoleret CABG, klapkirurgi, kombinationer heraf eller anden from for hjertekirurgi I studieperioden. Gennemsnitsalderen ± SD var 65.98 ±10.40 år. Atten patienter (36.7%) udviklede POAF. Hverken koncentrationen af EPA, DPA and DHA i atrievæggen eller i plasma kunne forudsige udvikling af POAF. Der var en significant korrellation mellem koncentrationerne i plasma og i atrievæv.

Konklusioner:

ECG variable identificeret fra rutinemæssige præoperative EKG optagelser kan sammen med udvalgte kliniske data være værdifulde ved forsøg på at forudsige hvilke patienter, der er i risko for at udvikle POAF efter hjertekirurgi (studie I). Endvidere er også transfusion med erytrocytter associeret med en øget risiko for at udvikle POAF, men blodets lagringstid i blodbanken har ikke noget særlig betydning (Studie II). Koncentrationen af EPA, DPA and DHA i atrievæggen og i plasma fosfolipider korrelerer indbyrdes med er ikke korreleret til udviklingen af POAF (Study III).

Resultaterne fra de individuelle studier inkluderet i denne ph.d. afhandling repræsenterer et forsøg på en multidirektionel søgen efter nye potentielle prædiktorer associeret med udvikling af POAF efter hjertekirurgi. Specielt resultaterne fra studie I kan viser sig værdifulde, hvis de inkluderes i fremtidige modeller der skal bruges til at forudsige patienters risiko for at udvikle POAF efter hjertekirurgi.

ACKNOWLEDGEMENTS

This dissertation is based on studies which were conducted during my time as a PhD student at the Department of Cardiothoracic Surgery at Aalborg University Hospital and Department of Clinical Medicine, Aalborg University from 2014 to 2017. There are many people who making this research project possible, which I would like to thank.

First of all, I would like to say thank you to my supervisors: Jan Jesper Andreasen, Erik Berg Schmidt, Christian Torp-Pedersen. My deepest gratitude goes first and foremost to Professor Jan Jesper Andreasen, my main supervisor, for your constant encouragement and guidance. You are always accessible, dedicated, contributing with constructive suggestion. You taught me how to do science. In fact I have learned even more from you. You has walked me through all the stages of the project. Without your consistent and illuminating instruction, this work could not have been done.

Also, I would like to thank Professor Erik Berg Schmidt for your kindness and enormous knowledge and experience in cardiology which you helped me a lot.

Professor Christian Torp-Pedersen for your great help of research with study III in the project and with your wise guidance and comments.

I would also very much like to thank Søren Lundbye-Christensen for your valuable experience of statistics.

I am thankful to all the co-authors in the three studies for your great help and make these studies better.

A special thank to Jeanett Sylvan Nielsen for your great help in a lot of practical things during the past three years.

I would like to thank all my colleagues in the Department of Cardiothoracic Surgery at Aalborg University Hospital for supporting me.

Lastly, my thanks would go to Chunlian my lovely wife for your great considerations and support in me, putting up with all the things I had to do all through these years and to my son Wenzhuo for forgive his father when he studied on abroad.

I have received financial support for the study from the Danish Council for Strategic Research (0603-00283B), S.C. Van Fonden (#1391), Region Nordjyllands Sundhedsvidenskabelige Forskningsfond and from the research fund in the

Department of Cardiothoracic Surgery, Aalborg University Hospital, Denmark and Department of Cardiovascular Surgery, Heart Centre of General Hospital, Ningxia Medical University, Yinchuan, Ningxia, China.

Jiwei Gu

Aalborg, December 2016

ACRONYMS AND ABBREVIATIONS

AF:	Atrial fibrillation
ACC:	Aortic cross clamp
ACE:	Angiotensin-converting enzyme
AUC:	Areas under the curve
BMI:	Body mass index
CABG:	Coronary artery bypass grafting
CI:	Confidence interval
COPD:	Chronic obstructive pulmonary disease
CPB:	Cardiopulmonary bypass
DHA:	Docosahexaenoic acid
DPA:	Docosapentaenoic acid
ECG:	Electrocardiogram
EPA:	Eicosapentaenoic acid
FPR:	False positive rate
IABP:	Intra-aortic balloon pump
LAE:	Left atrial enlargement
LVH:	Left ventricular hypertrophy
NOPOAF:	No postoperative atrial fibrillation
n-3 PUFA:	n-3 polyunsaturated fatty acids
POAF:	Postoperative atrial fibrillation

RBC:	Red blood cell
ROC:	Receiver operating characteristic
TPR:	True positive rate
WDHR:	Western Denmark Heart Registry

LIST OF PAPERS

Paper 1: Gu J, Andreasen JJ, Melgaard J, Lundbye-Christensen S, Hansen J, Schmidt EB, Thorsteinsson K, Graff C. Preoperative electrocardiogram score for predicting new-onset postoperative atrial fibrillation in patients undergoing cardiac surgery. J Cardiothorac Vasc Anesth 2016 [Epub ahead of print]. DOI: 10.1053/j.jvca.2016.05.036

Paper 2: Gu J, Skals RK, Torp-Pedersen C, Lundbye-Christensen S, Jakobsen C-J, Bæch J, Petersen MS, Andreasen JJ. Storage time of transfused allogeneic red blood cells is not associated with new-onset postoperative atrial fibrillation in cardiac surgery. Submitted to PLOS ONE. December 2016.

Paper 3: Gu J, Lundbye-Christensen S, Eschen RB, Andreasen A, Andreasen JJ. Marine n-3 fatty acids are incorporated into atrial tissue but do not correlate with postoperative atrial fibrillation in cardiac surgery. Vascular Pharmacology 2016; 87: 70–75.

TABLE OF CONTENTS

TABLE OF FIGURES AND TABLES

Tables: 3

Figures: 10

CHAPTER 1. INTRODUCTION

1.1 Cardiac surgery and postoperative complications

Cardiac surgery is still experiencing developments. Surgery is offered to patients with increasing age and an increasing number of comorbidities. In this chapter, I will provide a brief review of cardiac surgery in general, including common postoperative complications.

After the first successful heart surgery was performed by Dr. Ludwig Rehn of Frankfurt, Germany, who repaired a stab wound to the right ventricle on September 7, 1896, a new age of cardiac surgery started (1). Due to the rapid development of the heart-lung machine and anesthesia, cardiac surgery became safe and widely available. However, patients undergoing cardiac surgery are still at risk of morbidity and mortality. Potential postoperative complications include, e.g., complications related to the cardiovascular and respiratory systems, the kidneys and the central nervous system such as congestive heart and respiratory failure, myocardial infarction, renal failure and thromboembolic complications including stroke (2–4). The use of cardiopulmonary bypass equipment also introduces a distinguished set of potential postoperative complications involving vasospasm, altered platelet-endothelial cell interactions and a generalized inflammatory response initiated by blood contacting the synthetic surfaces of the extracorporeal circulation. All these complications play a role in relation to postoperative morbidity and mortality following cardiac surgery (5,6).

One of the most common complications following cardiac surgery is new-onset postoperative atrial fibrillation (7,8). In the rest of this thesis, the abbreviation of POAF will refer to new-onset postoperative atrial fibrillation.

The mechanisms by which POAF develops following cardiac surgery are not fully understood, but they seem to be multifactorial (9). Because POAF is associated with early and long-term negative outcomes following cardiac surgery (5,10–13), more information is needed regarding the predictors and risk factors for POAF to be able to direct increased attention toward the prevention of POAF in high-risk patients. Multidirectional efforts should be conducted to identify potentially new predictors and risk factors for POAF to be able to identify a greater number of high-risk patients.

This PhD thesis will focus on identifying potentially new risk factors and predictors of POAF following cardiac surgery, thus serving as an example of a multidirectional approach to this research field in cardiac surgery.

The studies included in this thesis may increase the possibility of identifying more patients at high risk of POAF following cardiac surgery. Furthermore, an increased focus on identifying patients at high risk may contribute to a reduction in postoperative morbidity and mortality in cardiac surgery if prophylactic treatment is initiated among these patients.

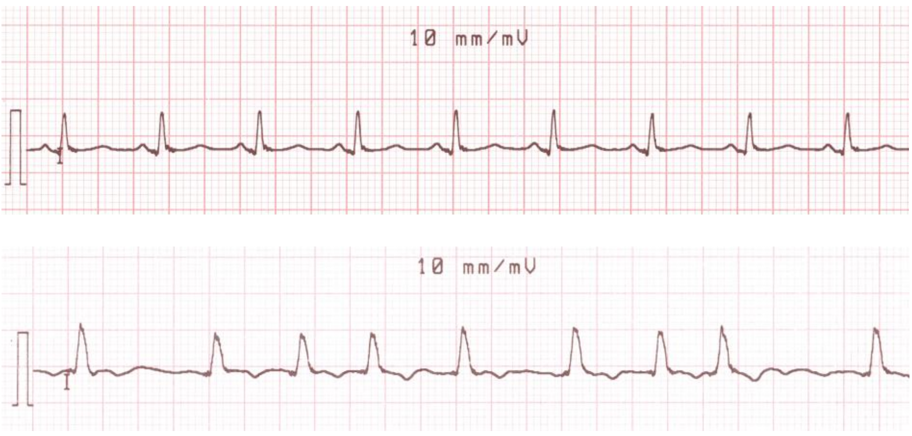
In the next chapter, I will provide a review of the definition, incidence, pathophysiology, risk factors, prognosis and preventive strategies related to POAF.

1.2 Postoperative new-onset atrial fibrillation following cardiac surgery

1.2.1 Definition and incidence of POAF

Atrial fibrillation (AF) is a cardiac arrhythmia with irregular atrial activity that restricts the function of effective atrial contraction and causes a disordered rhythm that often occurs rapidly, with or without symptoms (14). Figure 1 shows electrocardiogram (ECG) recordings from patients with sinus rhythm and AF, respectively.

Figure 1. Sinus rhythm (above) and atrial fibrillation (below) in the electrocardiogram.



AF is a common adverse outcome following cardiac surgery, and if this arrhythmia develops in patients who never experienced this arrhythmia prior to surgery, this arrhythmia is called POAF.

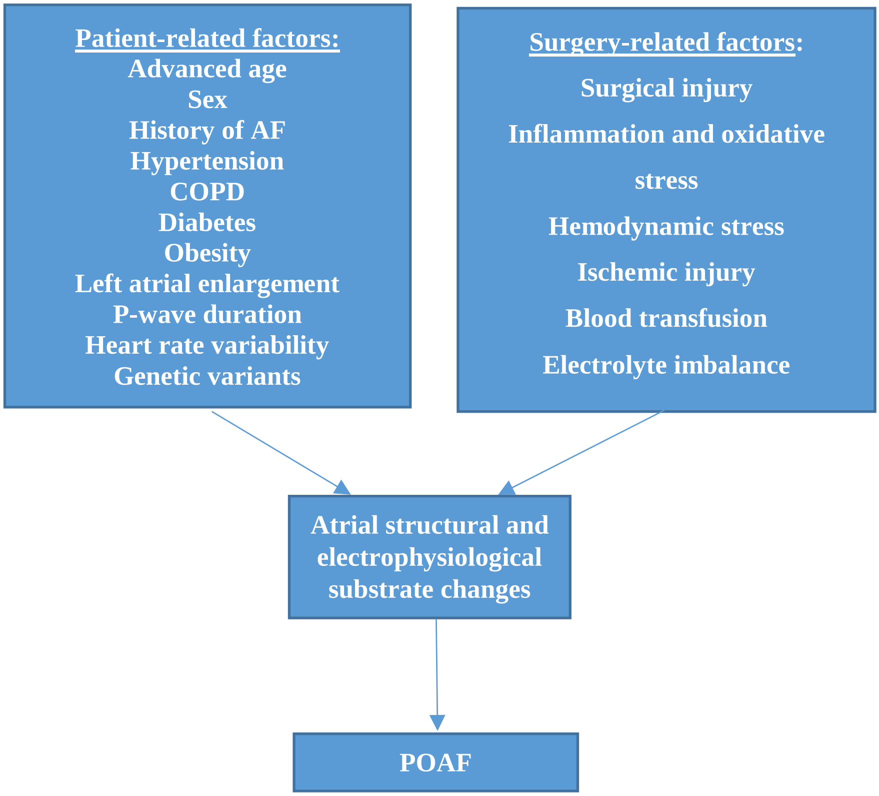
POAF develops in 10-65% of patients undergoing cardiac surgery, depending on the definition, type of surgery and diagnostic criteria (15–18). In a multicenter study, the incidence of POAF following coronary artery bypass grafting (CABG) was similar among patients in South America (17.4%) and Asia (15.7%), but the incidence was higher in the United States (33.7%), Canada (36.6%), Europe (34.0%), the United Kingdom (31.6%), and the Middle East (41.6%) ($p<0.001$) (19). POAF develops most frequently between the second and fourth days after cardiac surgery, but it can start at any point during the recovery period (20).The development of POAF prolongs the hospital stay and is associated with an increased risk of early and late stroke as well as mortality (21–23).

1.2.2 Pathophysiology and risk factors/predictors of POAF

To date, the precise electrophysiological mechanisms underlying the development of POAF remain incompletely understood, and the cause is likely multifactorial. Several predictors and risk factors (patient-related, surgical and postoperative factors) have been associated with the development of POAF in cardiac surgery. Pre-operative patient-related factors that have been identified are, e.g., advanced age, gender, pulmonary hypertension, diabetes, body mass index (BMI), left atrial enlargement (LAE), left ventricular hypertrophy (LVH), antiarrhythmic drug use, and gene expression. Perioperative factors are, e.g., type of surgery, surgical atrial incisions, atrial ischemia, pulmonary vein vent, venous cannulation, cardiopulmonary bypass time, and aortic cross-clamp time; post-operative factors are, e.g., volume overload, oxidative stress, pericardial inflammation, excessive production of catecholamines, enhanced sympathetic nervous system activity, and interstitial mobilization of fluid after surgery, respiratory compromise, and chronic obstructive pulmonary disease (COPD) (17,19,24–34). Figure 2 shows most of the common risk factors/predictors for POAF.

Many of the abovementioned factors are probably triggers and associated with the development of POAF due to atrial incisions, the development of atrial ischemia and myocardial fibrosis, which might distinguish atrial effective refractory periods and slow atrial conduction (17,19,24–34). This phenomenon may explain the increased range of the P-wave duration in a signal-averaged electrocardiogram related to the increased risk of POAF in cardiac patients in a observational study (31) (Figure 2). Furthermore, the surgical procedure itself physically alters the cardiac structure and likely creates the electrophysiologic substrate, which may be vulnerable to rhythm disturbances and contribute to both abnormal atrial conduction and refractoriness and the growing rate of the occurrence of triggering events (17). Occasionally the occurrence of AF is accompanied by electrophysiological remodeling and atrial structural remodeling. The former appears within a shorter time of the onset of arrhythmia in comparison to the latter, which more likely occurs over a longer timescale (14). Electrical remodeling in atrial tissue is delayed after depolarization and decreases the action potential, depending on the ion channel, which may be prone to AF (14,35). Three electrophysiological models have been proposed that include the "multiple-wavelets" hypothesis (36), the single- or multiple-driver model of the genesis of AF (37) and the focal activity in the pulmonary veins near the left atrium (38). Furthermore, atrial structural remodeling with atrial dilation also supports induced AF (39). According to multiple plausible models, the underlying mechanisms of POAF development may be multifactorial and not understood completely for cardiac surgical patients. The initiation of POAF depends on the presence of an electrophysiological substrate that triggers multiple re-entry wavelets resulting from the dispersion of atrial refractoriness (40). These risk factors may alter normal atrial conduction and refractoriness. It is still attractive to explore the possible mechanism linking cardiac surgery and new-onset POAF.

Figure 2. Risk factors/predictors and potential mechanisms of postoperative atrial fibrillation.



Note: AF: atrial fibrillation; COPD: chronic obstructive pulmonary disease; POAF: postoperative atrial fibrillation.

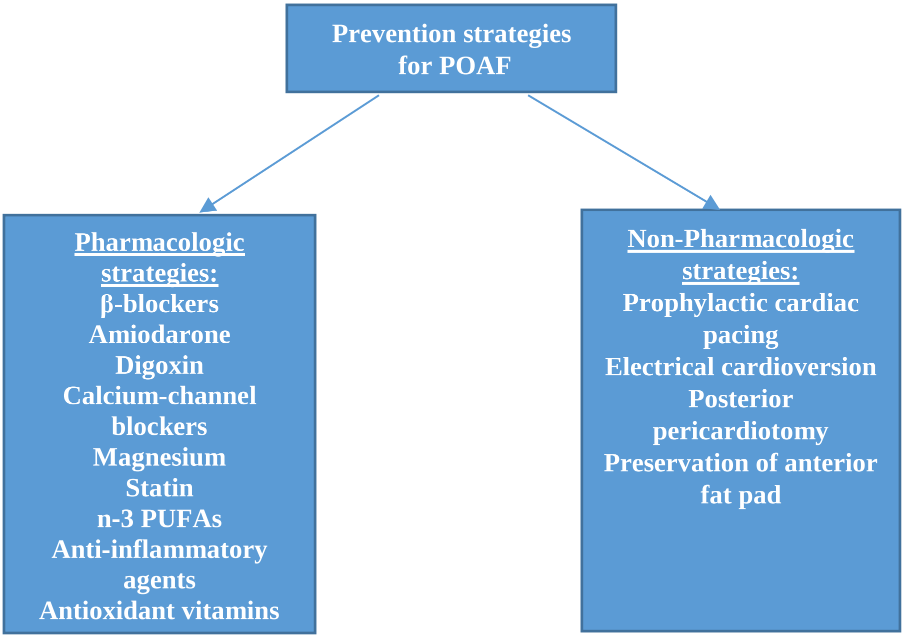
1.2.3 Prognosis of POAF

For many years, POAF in patients undergoing cardiac surgery was considered to be an unimportant, self-limiting arrhythmia that self-resolved to a normal sinus rhythm in a short time. Furthermore, POAF does not always lead to discomfort, cerebrovascular accident and in-hospital mortality (41). However, several postoperative negative outcomes have been associated with POAF. Some research has identified an association between POAF and a two- to four-fold increased risk of stroke (8,42). In a study among 6,477 patients who underwent isolated first-time CABG, the prolonged hospital stay after surgery was 14 days for patients with POAF compared with 10 days for patients without POAF ($p<0.0001$) (8). In another study, a similar result was described regarding the length of hospital stay (15.3±28.6 vs. 9.3±19.6; mean number of days± standard deviation, $p=0.001$), corresponding to an additional cost of more than $10,055 for each patient in hospital stay (43). Other negative postoperative outcomes that have been associated with POAF are acute kidney injury, perioperative myocardial infarction, cardiac failure, ventricular arrhythmias, need of intra-aortic balloon pump use, encephalopathy and infections, prolonged ventilation, hypotension, pulmonary edema, and increased need for pacing and readmission to the intensive care unit (8,15,41,44–46). Whether there is a cause-effect relationship between POAF and the outcome mentioned remains to be elucidated.

1.2.4 Preventive strategies for POAF

As described previously, the incidence of POAF is associated with increased morbidity and mortality as well as increased costs after cardiac surgery. Therefore, several preventive strategies have been evaluated to prevent development of POAF. Some of these strategies will be discussed below. Figure 3 shows commonly used strategies for POAF.

Figure 3. Preventive strategies for postoperative atrial fibrillation.



Note: n-3 PUFA: n-3 polyunsaturated fatty acids; POAF: postoperative atrial fibrillation

The prevention of POAF may involve medical prevention. Medical prevention to reduce the risk of POAF includes the use of β-blockers (e.g., metoprolol and sotalol), amiodarone, steroids and antioxidant vitamins. The benefit of these therapies in relation to POAF after cardiac surgery have been demonstrated in a number of previous studies (47–49) (Figure 3). In the 2016 European Society of Cardiology (ESC) Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS), perioperative oral β-blocker therapy had been recommended for the prevention of POAF after cardiac surgery (Class I, Level B) (50). Amiodarone is also recommended as a prophylactic therapy to prevent the development of POAF after cardiac surgery (Class IIa, Level A) (50). In a randomized, controlled, double-blind trial including 250 consecutive CABG patients, postoperative prophylaxis with amiodarone reduced the risk of POAF. The occurrence of AF after operation in the amiodarone prophylaxis group was lower compared with the placebo group (11% versus 26%, $p < 0.01$); however, the number of hospital stay days was not significantly different between the two groups (9.0 (95% confidence interval (CI): 8.0–10) vs.9.4 (95% CI: 7.6–11.2), p=0.69) (51) (Figure 3).

Decreased levels of serum electrolytes such as potassium and magnesium may increase the risk of POAF in patients after surgery, and perioperative repletion of empiric potassium and magnesium therapy in adult cardiac surgical patients may decrease the risk of POAF (52,53) (Figure 3).

Some others possibly effective therapies may also prevent the development of POAF, including digoxin, antiarrhythmic drugs, calcium channel blockers, angiotensin inhibition, statins, N-acetylcysteine, colchicine, fish oil, glucocorticoids, posterior pericardiotomy and anterior fat pad preservation (19,34,48,54–60) (Figure 3), but these modes of preventions have not been well validated.

Results from studies regarding the benefit of prophylactic epicardial atrial pacing are controversial. Some studies have demonstrated a benefit of pacing for the prevention of POAF (61–64) (Figure 3), whereas other studies have not (65,66). With regard to the atrial pacing strategy, which may include left atrial, right atrial and bilateral atrial pacing protocols, controversial results have been obtained (61–66). In a randomized study including a total of 132 patients who underwent CABG, the prevalence of POAF was significantly decreased in the biatrial pacing group compared with the no pacing group (12.5% vs. 41.9%; p<0.05) (62). This result was consistent with previous findings (64). However, in two randomized studies with 61 CABG patients and 154 cardiac surgery patients, respectively, there were no significant differences regarding the occurrence of POAF (37% vs. 33%, p>0.7 and 26% vs. 37.5%, p=0.4, respectively), or between the right atrial pacing group and the no pacing group (29% vs. 33%, p>0.7) as well as left atrial pacing group and no pacing group (20% vs. 37.5%, p=0.14), respectively (61,65). In a randomized, double-blind cohort study with 118 cardiac surgery patients, there was a significant reduction in the occurrence of POAF among 41 patients with biatrial pacing compared with 38 patients with right atrial pacing (10% vs. 32%; p=0.01) (63). Similar results have been described in another randomized study among 132 CABG patients (62). Interestingly, a randomized study including 100 patients undergoing CABG showed that the incidence of POAF was comparable with patients without pacing by postoperative day 4 (25.5% vs. 28.6%; p=0.90), even though atrial ectopy significantly differed between the two groups (2,106 ± 428 vs. 866 ± 385 per 24 hours, p=0.0001) (66).

The cause of POAF is multifactorial and still not fully understood, and more knowledge about risk factors and predictors would facilitate the development of more efficient methods to prevent this common postoperative complication. One strategy would be to look for potential new risk factors and predictors.

1.3 Potential new predictors and risk factors of POAF in cardiac surgery

Efforts to reduce the negative outcomes following POAF should include efforts to identify new predictors and risk factors of POAF, thus increasing the possibility of identifying more patients with a high risk of POAF for whom prophylactic measurements can be taken.

Many studies have been conducted to elucidate risk factors and predictors related to the development of POAF in patients undergoing cardiac surgery. Several predictors of POAF are well known, such as age, race, hypertension, BMI, myocardial infarction (MI), COPD, prior stroke, low left ventricular ejection fraction (LVEF), and type of surgery (23,67–70) (Figure 2). However, more information about potential new predictors is needed to identify more patients with a higher risk.

1.3.1 ECG markers as predictors for AF and POAF

POAF does not differ from other types of AF in ECG. Some characteristics of ECG have demonstrated great potential for predicting POAF in patients who might be at a high risk prior to cardiac surgery in several studies (31,71–75). Steinberg et al. enrolled a total of 130 patients undergoing cardiac surgery in a prospective observational study, in which 33 patients (25%) developed POAF at 2.6 ± 2.0 (days ± SD), and the signal-averaged P-wave duration was significantly ($p<0.001$) longer in the POAF group (71). A case-control study with 105 consecutive patients undergoing elective CABG showed that a combination of a P-wave duration >155 ms and serum magnesium on the first postoperative day of <0.7 mmol/L had a sensitivity of 75%, a specificity of 80% and a positive predictive accuracy of 62% for predicting POAF (72). In a large study with more than 280,000 individuals, both short and long P-wave durations (76) and PR intervals (77) in the ECG were associated with an increased risk of AF during a median follow-up of 6.7 years. In the National Registry to Advance Heart Health study of 25,268 patients from 106 centers with left ventricular dysfunction, the QRS duration was a strong independent predictor of AF (odds ratio (OR): 1.20; 95% CI: 1.14–1.25) (78). In a large ECG study, a J-shaped association was found between the heart rate-corrected (QTc) interval duration and the risk of AF(79). In another study, POAF was independently related to the presence and number of fragmented QRS complexes (fQRS) in patients undergoing CABG surgery. In addition, fQRS on pre-op surface ECG had high predictive value for new-onset POAF (80). Nevertheless, the predictive ability of all of the studies with their final prediction model was moderate. In contrast, in a study with a total of 13,356 patients undergoing cardiac surgery, there was no relationship between the P-wave duration, PR interval, QRS duration and semi-quantitative ECG diagnosis of atrial enlargement and an increased risk of POAF (74). This result is likely due to the complex and multifactorial nature of this arrhythmia. The effect of electrophysiological measurements aimed at predicting the risk of POAF in routine clinical settings necessitates further investigation. Therefore, more studies of ECG markers from routine pre-operative ECGs should be performed that combine, e.g., clinical data with ECG findings to enhance the possibility of predicting the risk of POAF following cardiac surgery.

1.3.2 Allogeneic red blood cell transfusion and POAF

Perioperative blood transfusion in patients undergoing cardiac surgery, whether of allogeneic red blood cells (RBC), platelets or plasma, is an important technology, and transfusion rates ranging between 30% and 90% are often described (81,82). Perioperative allogeneic blood transfusion is associated with the risk of transfusion reactions, transmission of infections and increased morbidity and mortality (83). Furthermore, RBC transfusion seems to be associated with an increased risk of the development of POAF (84,85). A plausible reason for such an association may be the relationship between intraoperative blood transfusion and a postoperative systemic inflammatory response syndrome (SIRS) (86). In this observational study among 553,288 patients with a broad spectrum of surgeries (general surgical, vascular, thoracic, ear-nose-throat, and orthopedic procedures), RBC transfusion was associated an increased risk of SIRS compared with non-transfused patients ($p<0.001$) (86). The concept that inflammation is a causative pathophysiologic factor in relation to the development of POAF is sustained by accumulating evidence (87). In several studies, a number of inflammatory changes, including raised CRP levels, interleukin-6, and leukocyte counts, are associated with the development POAF in patients undergoing cardiac surgery (88–92). In a study of 5,841 patients undergoing cardiac surgery, intensive care unit transfusion was associated with an increased risk of POAF (OR per unit transfused: 1.18; 95% CI: 1.14-1.23; $p<0.0001$). Among 1,360 propensity-matched patients undergoing cardiac surgery, similar results were obtained (85). Another retrospective cohort study in a single center involving 4,028 patients undergoing cardiac surgery showed that blood transfusion in patients was directly related to an increased risk of POAF during the postoperative period in comparison to non-transfused patients (27% vs. 20.4%, $p<0.001$) (93). Furthermore, the risk of POAF in CABG patients increased significantly with an increasing number of transfused RBC units in two retrospectively studies including 98 and 879 participants, respectively (both $p<0.001$) (94,95). However, in a more recent prospective randomized trial involving 446 patients undergoing on-pump CABG, there was no association between the number of transfused RBC units during surgery and the increased risk of POAF ($p=0.7$) (96). However, the abovementioned studies investigating the association between blood transfusions and POAF did not consider the age of the transfused blood. A number of studies have focused on whether an increased storage time of RBCs in the blood bank prior to transfusion is related to an increased risk of adverse outcomes in patients undergoing cardiac surgery. The results from these studies are controversial (97–101). Several observational studies have shown that storage of RBC for >2 weeks is related to adverse events, e.g., infections, renal and respiratory disorders, in-hospital mortality and one-year mortality (97,100).

However, other studies have failed to provide results consistent with these findings focusing on early or late mortality and multiple organ dysfunction (98,99,101). A plausible explanation for adverse outcomes correlated to older blood are the well described "storage lesions," which are structural and functional changes that occur in stored RBCs over time (102,103). The storage time of RBCs prior to transfusion may play a role as RBCs undergo significant changes during storage, which may potentially increase the risk of SIRS and other negative outcomes (104,105) including POAF. Indeed, only a few studies have focused on the development of POAF in patients undergoing cardiac surgery in relation to the transfusion of "older" versus "younger" blood (106), and therefore additional investigations regarding this issue are needed.

1.3.3 Marine n-3 fatty acids in relation to POAF

Marine long-chain n-3 polyunsaturated fatty acids (n-3 PUFA) are fatty acids with the first double bond located at the third carbon atom from the methyl terminus of the carbon chain (107). Alpha-linolenic acid (ALA, 18:3w3), eicosapentaenoic acid (EPA, 20:5w3), docosapentaenoic acid (DPA, 22:5w3) and docosahexaenoic acid (DHA, 22:6w3) are members of the n-3 PUFA family. EPA and DHA are believed to have more important biological functions (108,109). Humans must obtain marine n-3 PUFA from external sources such as seafood. In general, fish oils, with their three major n-3 PUFAs (EPA,DPA and DHA), may have beneficial anti-inflammatory and anti-fibrotic as well as direct electrophysiological effects in cardiac myocytes (110–112). These observed properties of n-3 PUFAs make them attractive potential agents to decrease the occurrence of POAF in cardiac surgery patients. Moreover, treatment with n-3 PUFAs in animal studies has revealed a significant reduction of the atrial effective refractory period and inducibility associated with AF (113). Therefore, intake of marine n-3 PUFAs might facilitate the prevention of POAF (59,113). Such beneficial effects are supported by results from several randomized studies (113). In two recent meta-analyses including 2,687 patients from 8 randomized controlled trials and 4,335 patients from 19 randomized controlled trials, respectively, it was concluded that n-3 PUFA supplementation reduced the incidence of POAF in patients undergoing cardiac surgery (114,115). However, other studies concluded that there was no convincing evidence for the reduction of POAF following the use of n-3 PUFAs (116–122). In a double-blind, randomized, controlled trial involving 194 subjects undergoing cardiac surgery, all of the participants received either high monounsaturated sunflower oil or 4.6 g/day of n-3 PUFAs three weeks before surgery, and the incidences of POAF were 48% in the control group (high monounsaturated sunflower oil) and 37% in the fish oil group (4.6 g/day of n-3 PUFAs), respectively, (OR: 0.70; 95% CI: 0.39-1.28; p=0.25) (123). In another randomized, double-blind, multicenter, clinical trial involving 1,516 patients undergoing cardiac surgery, the occurrence of POAF was 30.0% in the fish oil group and 30.7% in the control group (olive oil) (OR: 0.96; 95% CI: 0.77-1.20; p=0.74) (124). Because of the different conclusions, additional studies are needed to evaluate the therapeutic potential of n-3 PUFAs and the efficacy for the prevention of POAF in patients after cardiac surgery. Furthermore, laboratory studies investigating the degree of marine fatty acid incorporation into tissues, including the atrial wall, are needed. To date, no studies have investigated the relationship between the content of marine n-3 PUFAs in atrial tissue and the risk of POAF after cardiac surgery.

The literature review described above supports a multifactorial cause of POAF. Several predictors and risk factors have been associated with development of POAF in patients undergoing cardiac surgery, but further multidirectional efforts are needed for doctors to be able to identify more patients at an increased risk of developing POAF. The results from studies investigating potentially new risk factors and predictors of POAF will improve knowledge to facilitate strategies to identify patients who may benefit the most from initiatives to prevent the risk of POAF.

CHAPTER 2. AIMS AND HYPOTHESES

The overall aim of this PhD thesis is to serve as an example of a multidirectional search for potential new predictors of POAF by performing the three individual studies outlined below.

1. The aim of study I was to investigate whether ECG markers from routine pre-operative ECGs can be used in combination with clinical data to predict new-onset POAF following cardiac surgery using an electronic algorithm capable of reading minor ECG changes. We hypothesized that minor preoperative ECG markers in combination with clinical data can be identified as predictors for development of POAF in cardiac surgery.

2. The aim of study II was to evaluate whether RBC transfusion in general and the storage time of allogeneic RBCs in the blood bank (i.e., age of transfused allogeneic RBCs) is associated with the development of POAF following cardiac surgery. We hypothesized that RBC transfusion in general and a prolonged storage time of transfused RBC in the blood bank is associated with an increased risk of POAF in cardiac surgery.

3. The aim of study III was to evaluate whether n-3 PUFA concentrations in the atrial tissue and in the blood (plasma phospholipids) could predict the development of POAF and whether concentrations in the atrial wall reflected concentrations in the blood. We hypothesized that specific compositions of n-3 PUFAs in the atrial tissue are associated with a decreased risk of POAF and the composition of fatty acids in the atrial tissue reflects fatty acids in the blood.

CHAPTER 3. METHODOLOGY, MATERIALS AND METHODS

3.1 Study designs

Different study designs were used in the three studies included in this thesis.

Study I and II were retrospective studies based on clinical and laboratory data available from different existing databases, registers and patient records, while study III was a prospective study in which both clinical and laboratory data were collected.

Study I was a retrospective case-control study, while Study II was a retrospective observational cohort study based on prospectively collected data from different databases. In contrast, Study III was a prospective observational study combining laboratory and clinical data.

3.2 Data from clinical databases and registers

The studies were based on data collected from the patient records (Study I&III), the Western Denmark Heart Registry (WDHR) (Study I, II, III), local databases in the blood banks (Study II), and blood and tissue samples (Study III).

As the primary data for Study II in particular were retrieved from existing clinical databases and registers, it is important to be aware that the Danish National Health Service provides tax-funded medical care for all Danish residents. Due to the unique Central Personal Registry number assigned to each Danish citizen at birth and to immigrated residents, the linkage between hospital administrative systems and several clinical and laboratory databases can be performed at an individual level.

The Danish Civil Registration System was built in 1968 and contains information recorded electronically regarding sex, date of birth and other continuously updated information including place of residence, citizenship, emigration, immigration, spouse, parents and children, and siblings (125).

The WDHR is a population-based clinical database containing health care information. The WDHR was launched on January 1, 1999, and it contains detailed information on all patients with validated data (detailed patient and procedural data) (126). The purpose of maintaining the database is to monitor and improve the quality of cardiac intervention in the Central and Western Denmark Regions comprising approximately three million inhabitants, which is equivalent to 55% of the Danish population.

Information related to all blood transfusions (RBCs, platelet or plasma) delivered to the patients were retrieved from local databases in the blood banks located at Aalborg and Aarhus University Hospital (components, number of units, date of delivery and storage time in days prior to transfusion).

3.3 Study populations and methods

In the following sections, materials and methods, including the description of study populations, are provided in individual papers. A brief description of the studies is given below.

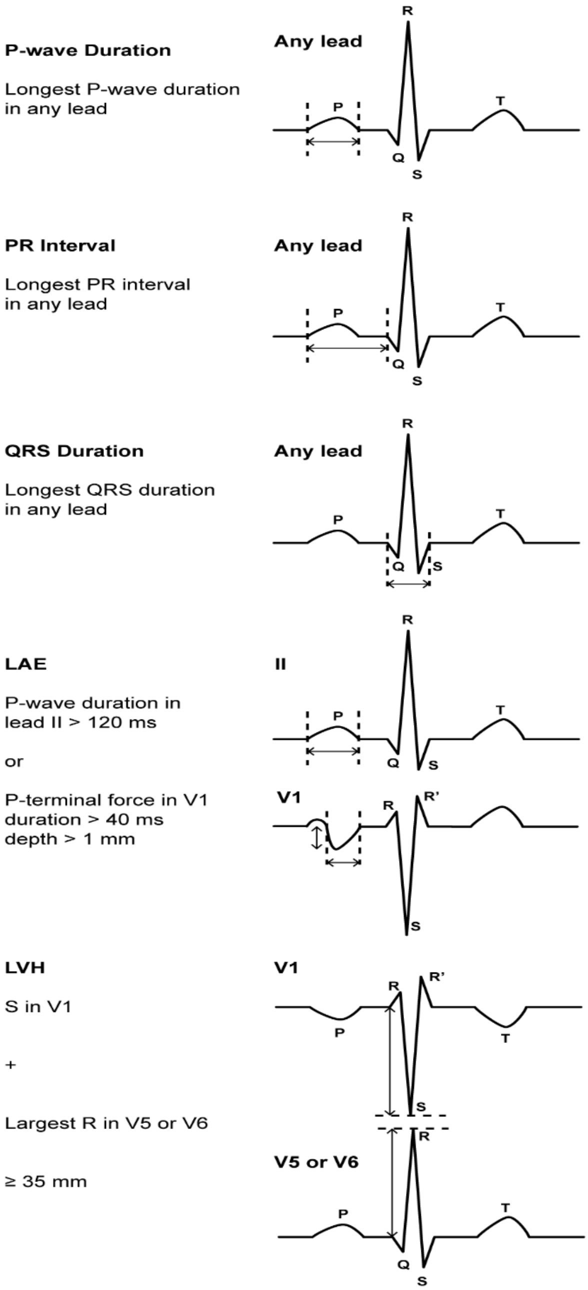
Study I:

A total of 100 patients who underwent elective first-time cardiac surgery between January 1, 2011 and December 31, 2014, including CABG, aortic or mitral valve surgery or a combination of these procedures, were included in the study. Using the patient records, we identified 50 patients who developed POAF and 50 control patients who did not develop POAF (NOPOAF). No specific matching was performed, and the total number of 100 patients was chosen arbitrarily because this was a hypothesis-generating study that could not be based on information from previous studies. Most of the patients included in the analysis underwent surgery consecutively, but a few additional patients were included due to missing data in the patient records, thus extending the time period. Patients with a pre-operative history of AF, left and right incomplete or complete bundle branch block, and patients with permanent pacemakers were excluded.

POAF was defined as new-onset AF prior to hospital discharge, documented by paper ECG and the requirement for medical attention and treatment. Clinical data and patient demographics were retrieved from the WDHR or from the patient records they were not available in the registry.

Paper ECGs within a month prior to operation were retrieved from the patient records and converted to a digital version for analysis. Five ECG parameters (QRS duration, PR interval, P-wave duration, LAE, and LVH correlating with LAE and fibrosis) were measured by two independent reviewers (Figure 4) (127), and four multivariate models to predict POAF were assessed using logistic regression. They consisted of a clinical model (Model C), an ECG model (Model E), a combined clinical/ECG model using all nine variables (Model CE-9) and a combined clinical/ECG model using univariate pre-specified variables (Model CE-4) (127).

Figure 4. ECG interval and amplitude measurements (127).



Study II:

A total of 4,766 consecutive adult patients (>18 years old) who underwent either on or off pump CABG, conventional valve and combined surgeries at Aalborg or Aarhus University Hospitals between January 1, 2010 to December 31, 2014 were identified from the hospital administrative systems and the WDHR (126). The two hospitals serve a population of approximately 2.5 million people, corresponding to approximately 33% of the total population in Denmark. Patients with a history of atrial fibrillation or flutter prior to surgery and patients with an invalid personal registration number were excluded. Patients who died or did not receive RBC transfusions on the day of surgery were excluded because those who died did not have the opportunity to develop POAF and to ensure that a blood transfusion was administered prior to development of the primary outcome of interest, i.e., POAF. Information about all blood transfusions (RBC, platelet or plasma) delivered to the patients was retrieved from local databases in the blood banks (components, number of units, date of delivery and storage time in days prior to transfusion). Patients were classified as having received either no or an actual number of RBC units.

POAF was defined as new-onset AF or atrial flutter occurring postoperatively during hospitalization regardless of the duration and whether the patient required treatment due to POAF.

Study III:

A total of 50 patients who underwent first-time elective cardiac surgery were enrolled between December 1, 2014 and April 30, 2015 at Aalborg University Hospital, Denmark. Twenty-two, 14, 10 and three patients underwent isolated CABG, isolated valve surgery, combinations or other cardiac surgery, respectively. The main exclusion criteria were a history of any type of preoperative atrial fibrillation or atrial flutter, use of a pacemaker and non-elective surgery. Clinical demographic data and perioperative data were retrieved from the WDHR and electronic patient records. A 10-ml blood sample and a right atrial tissue sample were obtained from each patient during surgery. Extraction of total lipids from plasma and atrial tissue (128,129) and separation of the phospholipid fatty acid fraction (130) were performed by a modified version of a previously described method. The fatty acid composition both in plasma and atrial tissue were identified and analyzed by gas chromatography and expressed as a percentage of the total fatty acid content after methylation.

Any episode of POAF prior to hospital discharge was documented by paper ECG using the same definition applied in study I.

3.4 Statistical analysis

The statistical method varied among the three studies. Baseline and surgery characteristics for continuous variables are expressed as the mean ± standard deviation (SD), and an absolute number or percentage is reported for categorical variables. Chi-squared tests for categorical variables and analysis of variance for continuous variables were used (Study II). A $p<0.05$ (two-tailed) was defined as statistically significant, and confidence intervals (CIs) were determined at the 95% level. Stata 13 (StataCorp LP, Tx, USA) (Study I&III) and R version 3.2.2 (Study II) were employed to analyze the data.

3.4.1 Study I

The univariate independent t-test and combined multivariate logistic regression were performed to assess the association between predictors and POAF. The area under a receiver operating characteristic (ROC) curve was used to evaluate the predictive abilities of all four prediction models. Cross-validated areas under the curve (AUC) were computed by eliminating each patient once from the sample to accommodate for over-fitting (131). The Youden index was used to measure the maximized sensitivity + specificity from ROC curves to optimize thresholds of POAF prediction from univariate clinical and ECG variables (132). Any clinical or ECG variable value exceeding the ROC was considered the optimal threshold and considered a risk factor for POAF. Furthermore, in the prediction models, the cut-off value for high risk was modified from 0 to 100%, and any patient with a predicted POAF probability who exceeded the cut-off value was stratified as high risk.

3.4.2 Study II

The association between RBC transfusion on the day of surgery, RBC storage time and dose-dependence for the subpopulation of patients who received RBCs and had a risk of developing POAF was evaluated by multiple logistic regression. The OR was adjusted by the following potential confounders: patient age, gender, COPD, presence of peripheral arteriosclerosis, preoperative treatment with a β-blocker, ACEI and calcium antagonists and type of surgery including on and off pump regarding the CABG patients. A restricted cubic spline was applied to evaluate the association between the specific storage time of the RBCs and the risk of POAF in the transfused patients.

3.4.3 Study III

The proportions of marine n-3 PUFAs (EPA, DPA, DHA, EPA+DHA and EPA+DPA+DHA) both in plasma and atrial tissue contents were calculated for the Pearson product-moment correlation and supplemented with confidence intervals. Scatter plots with a regression line and superimposed confidence bands were drawn to display the correlations. Logistic regression was performed to evaluate the association between the marine n-3 PUFA levels and the risk of POAF, which was adjusted by the following variables (age, CABG and COPD). ORs with 95% CIs were reported. The area under the receiver operating characteristics curve was used to assess the predictive value from marine n-3 PUFAs for POAF. Cross-validation was applied to accommodate for potential overfitting.

3.5 Ethics considerations

Study I and II were approved by the Danish Data Protection Agency (record numbers: 2008-58-0028 and 2014-41-3419). Informed consent was obtained from each patient before participation in Study III, which was approved by the Research Ethical Committee of the Northern Denmark Region (N-20140070). All three studies were conducted in accordance with The Code of Ethics of the Helsinki Declaration. For register-based studies, there is no requirement for either ethical approval or informed consent from the participants in Denmark.

CHAPTER 4. RESULTS

Detailed results from the individual studies are described in the individual papers. A summary is provided below.

4.1. Study I

Demographic and operative details of the patients in the two study groups are shown on Table 1 (127).

Table 1. Patient demographics and operative information (127).

Variables	NOPOAF (n=50)	POAF (n=50)	p value
Age, years	65.5 ± 10.4	69.6 ± 9.6	0.044
Male, %	66	72	0.666
Body mass index, kg/m^2	27.4 ± 5.3	27.6 ± 4.6	0.825
Prior myocardial infarction, %	26	28	1.000
LVEF, %	56.1 ± 9.5	55.3 ± 10.6	0.692
Logistic EuroSCORE II	4.6 ± 3.0	5.2 ± 2.2	0.271
Peripheral vascular disease, %	2	2	1.000
Comorbidities			
Diabetes Mellitus, %	30	22	0.225
COPD, %	2	12	0.112
Pre-operative medications			
β-blockers, %	44	44	1.000
Calcium antagonists, %	22	32	0.368
ACE inhibitors-captopril, %	30	38	0.527
Operative data			
CABG, %	58	64	0.666
Valve surgery, %	34	28	0.208
Combination, %	8	8	1.000
CPB time, min	108.8 ± 34.0	104.9 ± 32.3	0.620
ACC time, min	72.6 ± 32.0	70.7 ± 28.3	0.785

NOTE: Data are presented as the mean ± standard deviation or as a percentage. Abbreviations: POAF, postoperative atrial fibrillation; NOPOAF, no postoperative atrial fibrillation; LVEF, left ventricular ejection fraction; COPD, Chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; ACC, aortic cross clamp; IABP, intra-aortic balloon pump

Males made up 72% and 66% of each group consisting of a total of 100 patients. As might be expected, age differed significantly (p=0.044) between the groups; the mean age ± SD was 69.6 ± 9.6 years and 65.5 ± 10.4 years in the POAF and NOPOAF group, respectively. Four ECG variables, including a longer P-wave duration (7 ms, p=0.006; 95% CI: 2-12), PR interval (19 ms, p=0.014; 95% CI: 3-21), QRS duration (12 ms, p=0.003; 95% CI: 5-20) and signs of LAE (38%, p=0.0001; 95% CI: 21%-55%) could be used to distinguish between patients who developed and who did not develop POAF.

AUCs with and without cross-validation of the four models (Model C, Model E, Model CE-9 and Model CE-4) are shown in Table 2.

The predictability of the development of POAF in Model E (AUC=0.713; 95% CI: 0.610-0.815, with cross-validation) was significantly powerful compared with Model C (AUC=0.536; 95% CI: 0.421-0.650, with cross-validation) and is shown in Figure 5.

The optimal univariate thresholds (OT) of the ROC curve determined using Youden indices for the predictability of the development of POAF from clinical characteristics, which include age (>65 years), gender (male), BMI (>25 kg/m^2) and valve surgery or combined surgery, and ECG characteristics including QRS duration (>118 ms), PR interval (>192 ms), LAE and LVH.

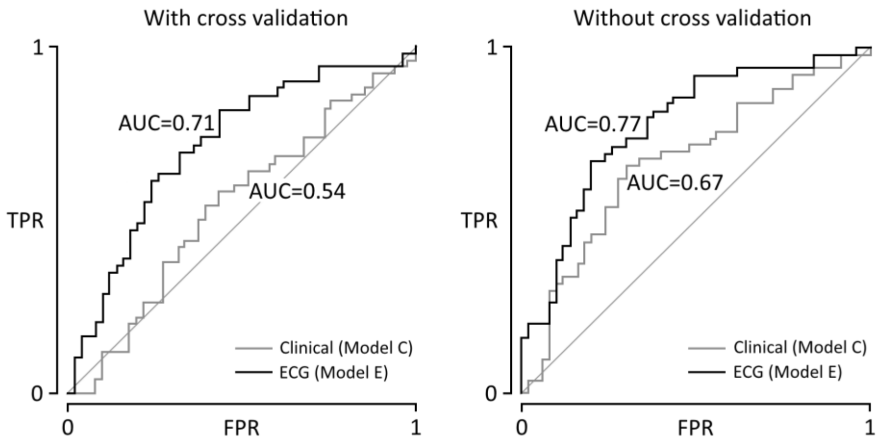
For patients having any combination of one to four of the risk factors in Model CE-4 exceeding OT, the likelihoods of POAF were 20% (one variable >OT), 50% (two variables >OT), 80% (three variables >OT), and 100% (four variables >OT), as shown in Fig 6.

Table 2. Area under the ROC curve (127).

	AUC	[95% CI]	
Clinical (Model C)			
(Age, gender, BMI, type of surgery)			
w/o cross validation	0.671	[0.561	0.781]
with cross validation	0.536	[0.421	0.650]
ECG (Model E)			
(PR, P-dur, QRS-dur, LAE, LVH)			
w/o cross validation	0.774	[0.682	0.867]
with cross validation	0.713	[0.610	0.815]
Clinical & ECG (Model CE-9)			
(Age, gender, BMI, type of surgery, PR, P-dur, QRS-dur, LAE, LVH)			
w/o cross validation	0.792	[0.705	0.879]
with cross validation	0.665	[0.557	0.774]
Clinical & ECG (Model CE-4)			
(Age, PR, QRS-dur, LAE)			
w/o cross validation	0.780	[0.696	0.865]
with cross validation	0.736	[0.643	0.830]

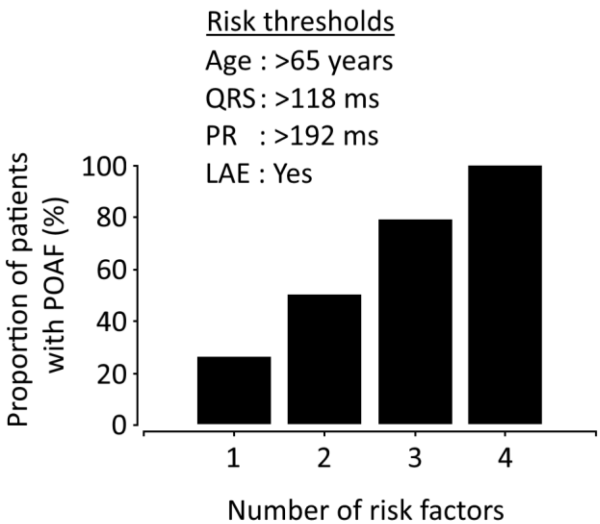
NOTE: CI, confidence interval; AUC, area under the curve; BMI, body mass index; LAE, left atrial enlargement; LVH, left ventricular hypertrophy; dur, duration.

Figure 5. ROC curves for the clinical model and the ECG model (127).



NOTE: FPR: false positive rate; TPR: true positive rate.

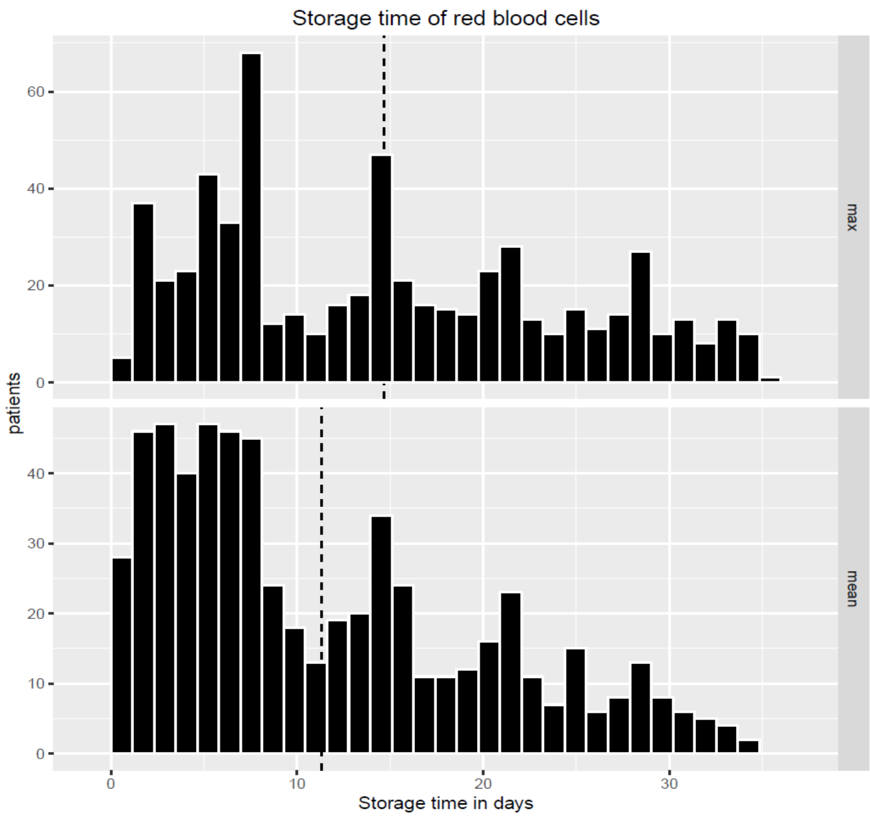
Figure 6. Proportion of patients with POAF as a function of risk factors in the POAF prediction model (127).



4.2 Study II

A total of 4,766 patients underwent cardiac surgery during the study period in the two hospitals. We included 2,978 patients with a mean age ± SD of 66.4 ± 10.7 years, among whom 752 patients (25%) developed POAF. Patients with POAF were more likely to be older (70.0 ± 9.4 vs. 65.2 ± 10.8 years, $p<0.0001$) and to suffer from comorbidities such as diabetes mellitus, COPD and previous stroke in comparison to patients without POAF. Furthermore, valve or combined surgery were more common among patients who developed POAF. Overall, 609 patients (20.4%) received ≥1 transfusion of RBC on the day of surgery. Transfused patients were more likely to be older compared with non-transfused patients (70.5 ± 10.5 vs. 65.4 ± 10.5 years, $p<0.0001$). The distribution of the maximal and mean storage time of RBC units transfused into patients is shown in Figure 7.

Figure 7. Distribution of the maximum (on top) and mean (below) storage time of transfused red blood cells.



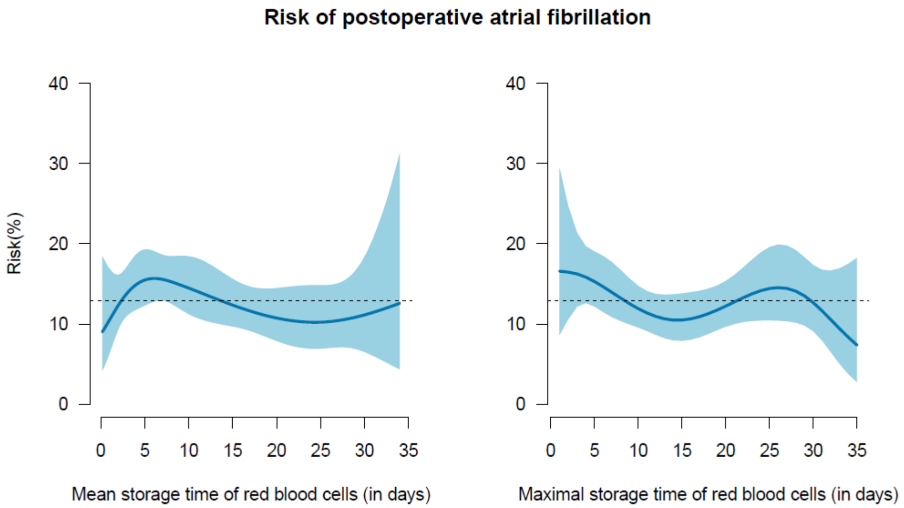
Note: Dashed lines represent the average storage time.

Transfused patients had a higher risk of developing POAF compared with non-transfused patients (OR: 1.79; 95% CI: 1.48-2.17; p<0.001; OR: 1.37; 95% CI: 1.11-1.69; p=0.004, after adjustment). There was a dose-dependent risk for the development of POAF in transfused patients receiving 4-6 units of RBCs compared with patients receiving 1-3 units of RBCs (OR: 1.62; 95% CI: 1.08-2.42; p=0.019).

The ORs for developing POAF among patients who were transfused with RBCs stored either <14 days or ≥14 days according to the maximal storage time of the RBCs and non-transfused patients were 2.01 (95% CI: 1.56-2.59; p<0.001) and 1.59 (95% CI: 1.23-2.06; p<0.001), and 1.50 (95% CI: 1.15-1.97; p=0.003) and 1.24 (95% CI: 0.94-1.64; p=0.120), after adjustment, respectively. The same pattern was observed for transfused patients divided according to the mean storage time of the transfused RBCs.

The association between the RBC storage time and the risk of developing POAF are shown in Figure 8. The baseline risk (dotted line) was computed as the risk when receiving 1-3 units of RBC, male gender, age <60 years, receiving no medication (β-blocker, ACE-inhibitor, calcium antagonist), not having COPD or peripheral arteriosclerosis and undergoing a combined surgery type.

Figure 8. Risk of developing postoperative atrial fibrillation according to the storage time of transfused red blood cells.



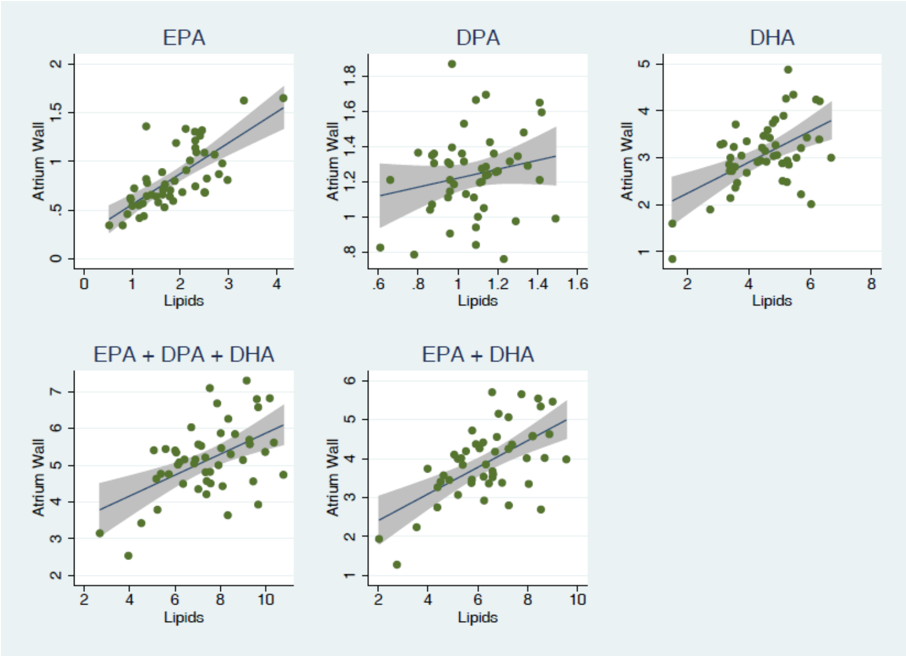
4.3 Study III

Blood and tissue samples were obtained from 50 patients, but the tissue sample from one patient was insufficient for analysis. Therefore, we only included 49 of the patients in the analyses. The mean age ± SD of these participants was 66.0 ± 10.4 years. A total of 22 patients underwent isolated CABG, 14 patients underwent a valve procedure, and ten or three patients underwent combined or other cardiac surgery. Overall, 18 patients (36.7%) developed POAF. The patients who developed POAF tended to be older (68.0 ± 9.3 vs. 64.9 ± 11.0 years), were more commonly females and diabetics, and had a longer ECC time (121.2±65.6 vs. 104.5 ± 32.1 minutes), aortic cross-clamp time (85.0±47.8 vs. 60.6±32.2 minutes) and postoperative ventilation time (35.5±72.8 vs. 13.8±12.7 hours) compared with the patients in the NOPOAF group.

There were no correlations between the development of POAF and the concentrations of n-3 PUFAs in atrial tissue and blood, and the concentrations of n-3 PUFAs in the atrial wall and blood did not predict the development of POAF. However, significant correlations were observed between n-3 PUFAs in tissue and blood. There were significant correlations of EPA, DHA, EPA+DHA and total marine n-3 PUFA (but not DPA) content between plasma and right atrial wall tissue.

Thus, the concentrations of n-3 PUFAs in the atrial tissue and plasma phospholipids failed to predict the development of POAF. Therefore, we did find significant correlations of the EPA (0.72), DHA (0.52), EPA+DHA (0.60) and total marine n-3 PUFA (0.51) (but not DPA (0.21) composition between plasma phospholipids and atrial tissue (Figure 9). There was no association between the concentration of marine n-3 PUFAs in atrial tissue and the risk of POAF with or without adjustment (Table 3 and Figure 10).

Figure 9. Correlations of marine n-3 PUFA concentrations in plasma phospholipids and in atrial tissue.



Note: PUFA, polyunsaturated fatty acids; EPA, eicosapentaenoic acid; DPA, docosapentaenoic acid; DHA, docosahexaenoic acids.

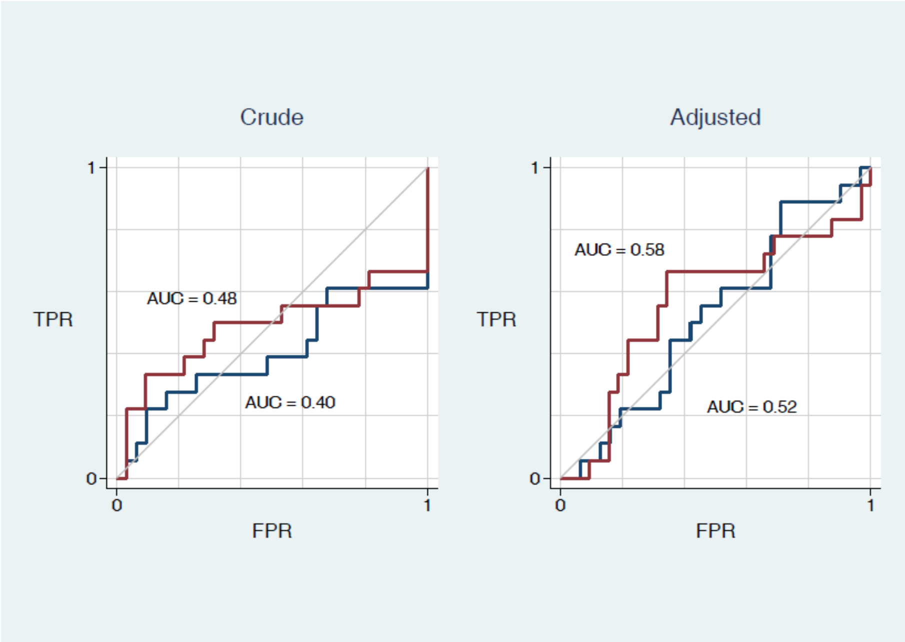
Table 3. Association between concentrations of marine n-3 PUFAs in atrial tissue and the risk of POAF.

Atrial Tissue	wt% of the total fatty acids(mean± SD)		Crude Odds Ratio (95% CI)	p	Adjusted* Odds Ratio (95% CI)	p
	POAF n=18	NOPOAF n=31				
EPA	0.81±0.28	0.85±0.34	0.67(0.10-4.36)	0.67	0.26(0.03-2.39)	0.23
DPA	1.24±0.33	1.24±0.17	0.93(0.08-10.99)	0.96	1.17(0.08-17.45)	0.91
DHA	3.08±0.49	3.06±0.85	1.05(0.47-2.35)	0.90	0.84(0.34-2.08)	0.70
EPA+DHA	3.89±0.65	3.91±1.08	0.98(0.53-1.84)	0.96	0.76(0.37-1.58)	0.47
EPA+DPA+DHA	5.13±0.70	5.15±1.13	0.98(0.54-1.78)	0.95	0.80(0.41-1.57)	0.52

Note: *Adjusted by age, chronic obstructive pulmonary disease and coronary artery bypass grafting.

PUFA, polyunsaturated fatty acids; SD, standard deviation; POAF, postoperative new-onset atrial fibrillation; NOPOAF, no postoperative new-onset atrial fibrillation; CI: confidence interval; EPA, eicosapentaenoic acid; DPA, docosapentaenoic acid; DHA, docosahexaenoic acids.

Figure 10. ROC curves regarding the risk of POAF following cardiac surgery based on marine n-3 PUFA concentrations in plasma phospholipids (red line) and atrial tissue (blue line).



Note: Adjustments by age, chronic obstructive pulmonary disease and coronary artery bypass grafting were performed.

ROC, receiver operating characteristic; POAF, postoperative new-onset atrial fibrillation; PUFA, polyunsaturated fatty acids; AUC, area under the curve; FPR: false positive rate; TPR: true positive rate.

CHAPTER 5. DISCUSSION

5.1 General discussion in relation to the literature

The overall aim of this thesis was to serve as an example of a multidirectional search for potential new risk factors and predictors of POAF following cardiac surgery by performing the three above-described individual studies. The three studies were performed with a focus on a potential association between POAF and preoperative ECG diagnostics in combination with clinical patient characteristics, storage time of the transfused RBCs, and the n-3 fatty acid composition in the atrial wall, respectively. Of these potential predictors of POAF, only ECG diagnostics combined with clinical data provided any value for predicting the development of POAF.

However, no single risk factor or prognostic factor for the development of POAF in cardiac surgery is effective alone, and combinations of different risk factors and predictors should be included in prediction models in relation to the development of this condition.

In a multicenter risk model with multivariable factors including, e.g., age and type of surgery, treatment with medicine to predict the development of POAF in 4,657 patients undergoing CABG surgery revealed an area under the ROC curve showing that the power of the predictive probability of POAF was 0.77 (19). In another predictive model with 1,851 CABG patients, only four variables (age, prior history of AF, P–wave duration and low cardiac output) were involved, and the area under the ROC curve was 0.69 (133). A POAF scoring system was derived and validated by Giovanni et al. in a study of 17,262 patients following cardiac surgery and included preoperative factors. This system indicated that the incidence of POAF was 42.5% in patients with a POAF score ≥3 (134). More recently, a number of studies have reported that the CHADS2 and CHA2DS2-VASc scoring systems, which is normally used to predict stroke in AF, are useful for predicting the development of POAF in patients undergoing cardiac surgery (135–138). However, the prediction of POAF using these scoring systems is moderate, and no single predictive model regarding POAF following cardiac surgery has ever shown adequate power to be superior to the others. Multidirectional studies of risk factors and predictors of POAF in cardiac surgery patients are required to enhance these prediction models.

5.2 ECG diagnostics for the prediction of POAF

Study I indicated that a multivariate ECG model for the prediction of POAF using the PR interval, P-duration, QRS-duration, LAE, and LVH should be combined with clinical characteristics such as age, gender, BMI and type of surgery to significantly increase the possibility of predicting POAF in patients undergoing cardiac surgery.

A predominant patient characteristic in our prediction model was patient age, as the association between age and POAF has been consistently described in several studies (139) and the incidence of POAF has been reported to increase with increasing age (19,41,50). In a retrospective cohort study including 6,475 patients who underwent CABG, POAF was diagnosed in 994 patients, and an age >65 years was an independent predictor for development of POAF (OR: 2.4; 95% CI: 2.06-2.74; p<0.0001) (8). In another recent retrospective analysis among 999 patients undergoing cardiac surgery, age ≥65 years was also a risk factor for the development of POAF (24). In a population-based prospective cohort study among non-surgical patients regarding the prevalence, incidence and lifetime risk of AF included 6,432 persons with a mean follow-up time of 6.9 years, the AF incidence rate increased from 0.7% at the age of 55-59 years to 17.8% among those aged 85 years and above (140). An increasing incidence of AF with increasing age was also observed in two other studies, including 9511 non-surgical patients (age >50 years) and 5201 non-surgical patients (age >65 years), respectively (141,142). In the 2016 ESC Guidelines, opportunistic screening using ECG for AF is also recommended among all patients aged >65 years (Class I, Level B) (50).

In previous studies, male gender (142), BMI (143), and type of surgery (19) have been shown to be risk factors for POAF in addition to advanced age both in a prospective observational study including 5,201 non-surgical patients, among 4,657 cardiac surgery patients and in a meta-analysis including 36,147 patients undergoing cardiac surgery (19,142,143). This finding is in accordance with the results presented in Study I of the present thesis. However, the results reported in the literature are inconsistent. In a cohort study of 5,201 non-surgical people aged ≥65 years, the incidences of AF per 1000 person years by age were 26.4% for men and 14.1% for women, with or without cardiovascular disease (142). However, another recent observational study conducted in 144 patients following adult aortic arch repair requiring deep hypothermic circulatory arrest evaluated gender in relation to POAF using univariate analysis (29). In concordance with Study I in the present thesis, this study did not identify gender as a risk factor for POAF (OR: 1.32; 95% CI: 0.68-2.58; p=0.41).

In a meta-analysis of 18 observational studies with 36,147 patients evaluating whether obesity (defined as a BMI > 30 kg/m^2) was associated with POAF in patients undergoing cardiac operations, obese patients had a modestly higher risk of POAF compared with non-obese patients (OR: 1.12; 95% CI: 1.04-1.21; p<0.002) (143). In contrast, obesity did not show an increased risk of POAF in another meta-analysis including 44,647 patients undergoing cardiac surgery (144). In study I of the present thesis, we initially attempted to include BMI in our Clinical Model, but it was excluded in the final prediction model. The above meta-analyses supported our opinion that BMI was not a major risk factor for POAF.

In one of the meta-analyses mentioned above (143), the association between obesity and POAF did not vary significantly according to the type of cardiac surgery. In contrast, in a large multicenter prospective observational cohort study of 4,657 patients undergoing cardiac surgery in 17 countries, 32.3% of the patients developed POAF, and patients who underwent valve surgery were at a higher risk of POAF (OR: 1.74; 95% CI: 1.31-2.32; p<0.001) (19). In Study I, we did not find any significant association between POAF and BMI and the type of surgery. These contradictory results may be explained by differences, e.g., in patient cohorts, surgical and anesthesiological techniques, local diet, genetics and the relatively small number of patients included in our study.

In model E of Study I, four ECG parameters (P-wave duration, PR intervals, QRS duration and signs of LAE) showed significant differences between the two groups, but not LVH. For Model CE-4, the P-wave duration was included in the definition of LAE. The significance of the three variables in model E and the one variable in model C was therefore selected for the final model called Model CE-4. Several previous studies have shown a strong correlation between the LA size and the risk of new onset AF (142,145). In the Framingham Heart Study (145), M-mode echocardiography was routinely performed in 1,924 subjects aged >59 years. This study showed that for every five mm increase in LA diameter, the risk of AF increased by 39% (p=0.001). In the Cardiovascular Health Study consisting of 5,201 adults aged ≥65 years (142), the risk of new onset AF was more than four times higher in patients with a LA diameter exceeding 50 mm (assessed by echocardiography) compared with <30 mm.

In another study of 265 patients with isolated mitral valve disease, aortic valve disease or asymmetric septal hypertrophy, AF was rare when the LA diameter was <40 mm but common when the diameter was >40 mm (146). A prospective study with a total of 205 patients undergoing cardiac surgery showed that the left atrial volume (LAV) measured by transthoracic echo was significantly larger in patients with AF and was a strong independent predictor of the occurrence of POAF, with a 26% increased risk of AF for every 10 ml/m^2 increase in LAV (147).

The study also showed that patients with LAV >32 ml/m^2 had an almost five-fold incremental risk of POAF, even after adjusting for age and clinical risk factors. The LA dimension and volume assessed by echocardiography have also been used in different research as strong predictors of POAF combined with other risk factors in patients who had undergone cardiac surgery (24,74,148).

In a recent two-dimensional speckle tracking echocardiography study of 48 consecutive CABG patients, the left atrial volume index (LAVI) and fibrosis were significantly higher in patients who developed POAF, and a LAVI >36 ml/m^2 predicted POAF with a sensitivity of 84.6% and a specificity of 68.6% (149).

The prediction of AF based on ECG parameters has been carried out in several studies (71,72,74–78,80,150–152). We found that the combination of the P-terminal force on the ECG and P-wave duration in lead II were significantly associated with POAF, in accordance with previous findings (74,76,151). The Framingham Heart Study (151), with 1,550 participants aged ≥60 years, showed that the upper 5% of the P-wave maximum duration had a HR of 2.19 (95% CI: 1.46-3.30; p<0.001) and a HR of 2.51 (95% CI: 1.13-5.57; p=0.024) in a gender- and age-adjusted analysis and a multivariable-adjusted analysis for AF, respectively. In the Copenhagen ECG Study (76), the long P-wave duration also showed a strong association with an increased risk of AF. A study conducted in 13,356 cardiac surgery patients revealed a more negative deflection of the P-wave in V1, even after adjustment associated with an increased risk of POAF (74). This result can likely be explained by a delayed depolarization wave front in LAE through the enlarged LA wall, resulting in a delay of the terminal portion of the P-wave and thus extending the P-wave duration. Furthermore, LA could also rotate the P-wave vector to the left in ECG, causing a negative terminal component of the P-wave in lead V1.

Prolongation of the electrocardiographic PR interval and QRS duration was shown to be associated with POAF in Study I. These findings are supported by various studies in cardiac surgery and in other conditions (73–75,77,78,80,152–154). An association between an electrocardiographic PR interval and incident AF was observed in the Framingham Heart Study and was included as a risk score for AF (154). A PR interval above the 95th percentile (≥196 ms for women, ≥ 204 ms for men) has also been shown to be associated with AF when evaluated using a multivariable-adjusted hazard ratio (HR) (77). There was an 18% increased risk in women and an 30% increased risk in men in this large population during an average follow-up of 5.7 years in the Copenhagen ECG Study (77). This is also in accordance with a recent prospective cohort study of a total of 1,227 CABG patients, in which a significantly longer PR interval was found in 377 (31%) of the POAF cohort (152).

In another study of cardiac surgical patients, the OR for POAF was 1.01 using a univariate analysis of the PR interval (75). This study showed that the inclusion of different ECG variables in a prediction model with only clinical predictors significantly improved the area under the ROC from 0.71 to 0.78 (p<0.01). Myocardial fibrosis, changes in sympathetic and parasympathetic tone, medications, ischemia, and degenerative conduction diseases may all alter the PR interval, which is the period reflecting the time required for conduction from the atrial myocardium surrounding the sinus node through the AV node to the Purkinje fibers (42,51,155,156).

In a multicenter ADVANCET study of 25,268 patients with LVEF <40%, the OR for AF was 1.20 if the QRS duration was prolonged after adjusting for potential AF risk factors. The QRS duration was independently associated with AF (78). In another study, a prolonged QRS time (p=0.004) was also significantly related to POAF in patients undergoing isolated CABG (80). In a study investigating patients with cardiomyopathy, the QRS complex duration correlated with the extent of ventricular fibrosis (153), and the characteristics of the QRS complex duration in these participants was also probably related to a generalized myocardial fibrosis including atrial fibrosis, which may function as a substrate for POAF.

The results obtained for Study I may, in part, be explained by local fibrosis in dilated atria because these pathological changes may alter the normal atrial electrical refractoriness and conduction (157–159). Such abnormalities may be detected by routine ECG due to the change in P-wave morphology and conduction (75,160,161), PR-interval (77) and QRS-duration (78) in patients, providing the substrate for POAF.

5.3 "Fresh" vs. "old" blood transfusion in cardiac surgery

Study II showed that transfused patients were older and had an increased risk for the development of POAF compared with non-transfused patients with or without adjustment. An increased risk of POAF showed a dose-dependent relationship in transfused patients receiving 4-6 units of RBCs compared with those receiving 1-3 units of RBCs in Study II. However, there was no association between the RBC storage time and risk of POAF in patients receiving RBCs who had undergone cardiac surgery. Other observational studies (85,94,95), but not all (96), also found a dose-dependent association between RBC transfusion and the risk of POAF. In a retrospective study of 5,841 on-pump open heart surgery patients and 451 off-pump CABG patients, the risk of POAF increased with an increasing number of transfused RBC units in ICU patients following isolated off-pump and on-pump CABG (OR: 1.22; 95% CI: 1.05-1.41; $p=0.0075$; OR: 1.25; 95% CI: 1.16-1.34; $p<0.0001$; respectively) (85). Interestingly, in the same study, a reduced risk of POAF was observed when on-pump cardiac surgery populations received RBCs in the operating room (OR: 0.954; 95% CI: 0.912-0.998; $p=0.039$) (85). This finding is difficult to explain. In another study including only 98 patients undergoing on or off-pump CABG surgery, the patients who developed POAF received more units of transfused RBCs compared with those who did not develop POAF(9.29 ± 3.34 vs. 6.00 ± 2.15, $p<0.001$) (94). RBC transfusion was associated with an increased risk of POAF compared with non-transfused patients (OR: 1.586; 95% CI: 1.252-2.008; $p<0.001$) (94). However, the authors did not evaluate the relationship between the storage time of transfused RBCs and POAF.

A more recent observational study with a total of 879 CABG patients showed that the risk of POAF increased with the amount of transfused RBCs. Using logistic regression analysis, patients receiving 1-3 units, 4-6 units and 7+ units of RBCs had an OR of 1.35 (95% CI: 0.89-2.07), 2.28 (95% CI: 1.35-3.87) and 2.21 (95% CI: 1.14-4.28) for the risk of POAF, respectively. However, there was no linear relationship between the number of transfused RBC units and POAF (95). In contrast, there was no statistical association between the development of POAF and intraoperative as well as total RBC unit transfusions among 446 patients undergoing on-pump CABG in terms of the risk of POAF (p=0.7, p=0.2, respectively) (96). Regarding intraoperative transfusions, this result is consistent with those presented in Study II.

The development of storage techniques for RBCs has led to increased storage times and better quality of the stored RBCs. During storage, RBCs and their supernatant undergo progressive structural and functional changes that result in biochemical and biomechanical alternations, including cellular membrane changes, reductions of 2,3-diphosphoglycerate and adenosine triphosphate, and accumulations of bioactive substances in the RBC storage medium, leading to a diminished RBC deformability, decreased oxygen delivery, increased immunologic activation or suppression and the release of proinflammatory cytokines (162,163). These “storage lesions”, which cannot be avoided completely, may reduce RBC function and viability and initiate an inflammatory response (164) in the recipient, potentially leading to adverse clinical events in patients receiving “older” RBCs. In study II, we divided transfused patients arbitrarily into two groups according to the storage time of a single transfused RBC unit (RBCs stored for either <14 days or ≥14 days), or to either the mean and maximum storage age of transfused blood if patients received >1 unit of RBCs. This strategy was based on the knowledge that “storage lesions” reflect the deterioration of RBCs by biochemical and morphologic changes that most commonly begin to occur following two weeks of storage in the blood bank (165). These storage lesions have been associated with several postoperative complications, including increased mortality. In a large retrospective cohort study among 1,813 trauma patients, RBCs stored for more than two weeks appeared to be related to an increase in mortality among the patients (166). In another study of 6,002 cardiac surgical patients, patients who were transfused with RBCs that had been stored >2 weeks had a higher risk of postoperative complications compared with those who were transfused with RBCs stored <2 weeks (97). Both short-term and long-term survival were significantly decreased (97). These investigations implied that the shelf life time of stored RBCs is approximately 2 weeks. Several studies have also divided transfused blood into “fresh” or “old” blood” using a cut-off of approximately 14 days (167).

Only very few studies have investigated the association between the storage time of transfused RBCs and the development of POAF (106). In an observational study of 819 isolated CABG patients, POAF developed significantly more often in transfused patients who received blood units stored for >14 days compared with those who received blood units stored for <14 days (OR: 1.67; 95% CI: 1.19-2.34; p=0.007) (106). However, in Study II, we found no association between an increased storage time of allogeneic RBCs and development of POAF in transfused patients following cardiac surgery. These distinct findings may be explained by, e.g., differences in patient cohorts, different definitions of POAF and different methods for obtaining the diagnosis.

The storage time of RBCs in relation to postoperative outcomes has been investigated in other studies focusing on mortality and morbidity other than POAF (101,168,169).

In a single-center study of 1,153 adult patients undergoing cardiac surgery, there were no significant differences between patients who received RBCs stored for ≤14 days compared with those who received RBCs stored for >14 days, regarding the development of postoperative renal failure, or infectious or pulmonary complications (168). Another retrospective cohort study including 2,715 patients undergoing CABG, valve or combined cardiac surgery showed no association between the 1-year survival of patients who had received “old” RBCs and “young” RBCs (hazard ratios: 0.97; 95% CI: 0.69-1.35; p=0.98). However, the risk of 1-year survival significantly decreased with an increased number of transfused RBC units (169). In a recent multi-center randomized, controlled study including 9,285 cardiovascular surgical patients, there was no significant difference in in-hospital mortality (12.3% and 11.2%, respectively; OR: 1.13; 95% CI: 0.99–1.29; p=0.08) between the short-term storage group (mean storage time=13.0 days) and the long-term storage group (mean storage time=23.6 days) (101). In contrast, in a retrospective study of 819 consecutive isolated CABG patients, the authors found that patients who were transfused with > 14 days old RBC units had a significantly higher risk of POAF compared with patients who were transfused with < 14-day-old RBC units (OR: 1.67; 95% CI: 1.19-2.34; p=0.007) (106).

Theoretically, storage lesions in transfused blood may be a possible causal explanation for the development of POAF due to the inflammatory response initiated by the transfused blood (86). Thus, storage lesions in transfused blood might be an explanation for the positive correlation shown by some researchers between RBC transfusion and an increased risk of POAF. However, contradictory results from different studies may relate to differences in patient populations, different study designs, residual confounding and differences regarding the type of blood stored in the blood bank, i.e., leukocyte reduced or non-leucocyte reduced RBC units. Prospective randomized trials are required to confirm the relationship between the storage effects of transfused RBCs and the development of POAF in cardiac surgery patients.

In our study, the mean storage time of transfused RBC was approximately 11 days, and the patients who were transfused with more than one unit of RBCs would potentially receive a combination of “fresh” and “old” blood if a cut-off value of a storage time of < 14 days was used to define “fresh” blood. Therefore, interpretations of associations between outcomes and the age of the transfused blood may be very difficult.

There was inadequate evidence in Study II to conclude that the storage time of transfused allogeneic RBCs was associated with the development of POAF in patients undergoing cardiac surgery, but the association between RBC transfusion and an increased risk of POAF has been confirmed in most studies (85,93,95). As allogeneic RBC transfusions are associated with increased mortality and morbidity, inclusion of the risk of POAF multimodal efforts to decrease rates of allogeneic blood transfusion in patients undergoing cardiac surgery are still important and continuously carried out in many centers (170).

5.4 Marine n-3 fatty acids and POAF in cardiac surgery

Study III demonstrated that there was no association between the concentrations of marine n-3 PUFAs (EPA, DPA, DHA, EPA+DHA and EPA+DPA+DHA), both in plasma phospholipids and atrial tissue, and the risk of developing of POAF following cardiac surgery. Another finding in Study III was the significant correlations between the content of EPA (r=0.72), DHA (r=0.52), EPA+DHA (r=0.60) and EPA+DPA+DHA (r=0.51), but not DPA(r=0.21), between the atrium and in plasma phospholipids.

We did not find that the content of marine n-3 PUFAs, EPA, DPA and DHA in atrial tissue or in plasma phospholipids could forecast an enhanced risk of POAF in patients undergoing cardiac surgery. Our study therefore lends no support to an effect of n-3 PUFAs in relation to prevention of the development of POAF. This finding is supported by a randomized, double-blind, placebo-controlled clinical trial including 108 patients undergoing on-pump CABG. This study did not show any beneficial effect of n-3 PUFAs on the occurrence of POAF either in univariate or in multivariate Cox regression models, even though levels of EPA and DHA in serum and atrial tissue increased in response to n-3 PUFAs over a short-term therapy duration (171). In another randomized, double-blinded, placebo-controlled study with 200 patients undergoing valve and CABG surgery, the incidence of POAF in the fish oil group (intake 4.6 g/day of n-3 PUFAs, 3 weeks prior to surgery) was not statistically significant compared with a control group with or without adjustment (OR: 0.70; 95% CI: 0.39 -1.28; p=0.25; and OR: 0.63; 95% CI: 0.35-1.11; p=0.11; respectively) (123). More recently, n-3 PUFA reduction of inflammatory and oxidative stress was confirmed in patients undergoing on-pump cardiac surgery, but the risk of POAF was not diminished in patients treated with n-3 PUFAs (2 g⁄day, one week prior to surgery) plus vitamin C (1 g⁄day, two days prior to surgery) and E (400 IU⁄day, two days prior to surgery) until discharge compared with the placebo group (RR: 0.32; 95% CI: 0.72–2.71; p=0.325) (172). In a meta-analysis including 11 randomized controlled trials with 3,137 patients undergoing cardiac surgery, oral n-3 PUFAs alone (average of 2 g⁄day) before or after surgery were not effective for the prevention of POAF, whereas combination treatment with n-3 PUFAs and vitamins C and E provided beneficial results (173). Some other studies have provided consistent results (119,122). The results from Study III did not support the association of n-3 PUFAs with the risk of POAF. However, interest in n-3 PUFAs has grown in recent years, and their intake, which leads to their incorporation into plasma and cardiac myocytes, is believed to have anti-inflammatory, anti-oxidative, antifibrotic and antiarrhythmic effects (110,112,174,175). An antiarrhythmic effect is supported by several studies that reported significant decreases in POAF with n-3 PUFA supplementation (115). N-3 PUFAs have been shown to prevent the occurrence of POAF in isolated CABG patients who experienced a MI within 3 months (176). A randomized controlled trial combining data (n=355) from Australia and Iceland indicated that there may be a U-shape relationship between DHA levels in RBCs and POAF (121). In a meta-analysis including eight randomized controlled studies with 2,687 patients who underwent open cardiac surgery, n-3 PUFAs reduced the incidence of POAF both in a fixed-effects model (OR: 0.84; 95% CI: 0.71-0.99; p=0.04) and a random-effects model (OR: 0.75; 95% CI: 0.57-1.00; p=0.05), in particular in patients undergoing isolated CABG (OR: 0.66; 95% CI: 0.50-0.87; p=0.003) (59). More recently, another two meta-analyses reported identical results, and moreover, n-3 PUFAs decreased the hospital stay (114,115). The mechanisms underlying the potential antiarrhythmic effect of n-3 PUFAs remain unclear. One potential mechanism may be that n-3 PUFAs in cardiac membrane phospholipids increase the membrane fluidity (177) and thereby shift the state of cytokines (178), further altering the threshold level for the induction of arrhythmia (179), reducing the beating rate and inhibiting the inward sodium current and L-type inward calcium current, which inhibits the induction of tachyarrhythmia (180). Other potential mechanisms may be responsible for the role of n-3 PUFAs in preventing AF, such as a beneficial effect on ion channel conductance through incorporation into cardiac membrane phospholipids (181). We failed to show any correlation between n-3 PUFA concentrations in the atrial wall and blood and the risk of POAF, which indicated that the concentrations in the atrial wall were not directly related to the risk of POAF development.

Further studies with a larger number of patients undergoing cardiac surgery are warranted to further examine the role of n-3 PUFA concentrations in the atrial tissue, including the effects of a seafood diet as well as of oral and intravenous administration of n-PUFAs on these concentrations.

Although there were no associations between the levels of marine n-3 PUFAs in atrial tissue or plasma phospholipids and the risk of POAF development in the patients in study III, there were significant correlations between the content of total marine n-3 PUFAs in the atrium and in plasma phospholipids. In a previous study of 61 on-pump CABG patients, samples from both the right atrial appendages and blood were collected during surgery. Correlations between the content of marine n-3 PUFAs in the atrium and in plasma were identified in accordance with the results from study III (182). In a randomized study including a total of 84 subjects undergoing cardiac surgery, the EPA and DHA contents in erythrocytes and in myocardial phospholipids were correlated in humans (183), providing results that were very similar to ours. This observation might also suggest that the fatty acid composition of atrial tissue can be readily changed because plasma phospholipids reflect the last few weeks of dietary fatty acid intake. However, we cannot exclude the possibility that the diets of the participants were constant on a long-term basis. The content of plasma marine n-3 PUFAs in plasma phospholipids were significantly associated with the atrial tissue levels, indicating that plasma, which is much easier to obtain than atrial tissue - might be a useful surrogate marker for the n-3 PUFA status in atrial tissues in humans.

In the following chapter, I will discuss the strengths and limitations in relation to the three studies included in this thesis.

CHAPTER 6. STRENGTHS AND LIMITATIONS

The studies included in this thesis have several important limitations. Study I and II were limited by their retrospective nature, which can only detect associations in contrast to causality between the outcome of interest and the exposures. A multivariate logistic regression was applied to minimize confounding due to well-known predictors of POAF in all three studies. However, residual confounding may also exist. A relatively small cohort size was included in Study I and III, increasing the risk of type II error and the single-institution data limit generalizability. The findings from these hypothesis-generating studies should therefore preferably be evaluated in prospective studies that include a larger number of patients.

Only patients who develop POAF during the hospital stay in the primary cardiac center are registered in the WDHR, and thus there is a risk that we did not register all POAF cases for each patient. POAF may occur after discharge from the hospital, which may result in misclassification regarding the outcome in all three studies and weaken the predictive model of POAF development in Study I. However, we have no reason to believe that any potential misclassification was related indications of RBC transfusion or intake of n-3 PUFAs prior to surgery. Another weakness of the studies is that we did not continuously monitor ECGs during the total stay of the patients in the hospital after surgery, and thus we might have missed clinically silent episodes of POAF. Again, we have no reason to believe that our POAF monitoring differed within transfused and non-transfused patients or according to n-3 PUFA intake.

An inflammatory response may be one of several potential mechanisms whereby RBC transfusion contributes to POAF (86). We did not collect information about levels of inflammatory markers such as IL-6, TNF-α and CRP in our dataset. These markers of inflammation have all been related to the development of POAF in previous studies (184–186), and missing information for these markers may considered a limitation in studies examining risk factors for POAF.

It is a strength of Study II that we included a relatively large number of consecutive patients from two university hospitals, which was rather homogenous and used a validated database.

One of the strengths of Study III is that we obtained tissue from atrial appendages, giving us the opportunity to examine atrial tissue levels of total and individual marine n-3 PUFAs and their relationship to POAF, which theoretically may develop in the atrial wall and/or in tissue closely related to the atrial wall.

CHAPTER 7. MAIN CONCLUSIONS

The studies included in this dissertation represent an example of a multimodal approach to contribute new knowledge regarding the prediction of POAF in patients undergoing cardiac surgery. The positive results from study I in particular may improve future clinical decision-making regarding prophylactic treatment to prevent POAF development following cardiac surgery.

The main findings in the individual studies included in this thesis are described below.

Study I: ECG markers obtained from a routine preoperative ECG may be helpful in predicting new-onset POAF in patients undergoing cardiac surgery, especially if combined with specific clinical data.

Study II: In contrast to allogeneic RBC transfusion in general, an increased storage time of RBCs is not associated with the development of POAF in cardiac surgery.

Study III: Levels of marine n-3 PUFAs in the atrial wall are not associated with the risk of POAF following cardiac surgery, despite significant correlations of marine n-3 PUFAs in the atrium and in plasma phospholipids.

There are still many unanswered questions regarding the possibility of predicting POAF in patients undergoing cardiac surgery.

CHAPTER 8. CLINICAL IMPLICATIONS AND FUTURE RESEARCH

New-onset POAF in patients undergoing cardiac surgery is common, and the cause of POAF seems to be multifactorial. Numerous risk factors and predictors of POAF have been identified and used to guide decision-making regarding prophylactic measurements to avoid POAF in patients undergoing cardiac surgery. However, we are still not able to identify all patients at risk, and risk models must be improved due to the lack of convincing tools.

Results from this PhD study indicate that accurate prediction models may be developed based on various perioperative ECG characteristics and clinical data. The result from Study I should be evaluated in larger patient cohorts potentially with echocardiographic variables related to electrical conduction abnormalities, which may be associated with the development of POAF. Clinical data including dietary habits, such as biomarkers related to the intake of marine fatty acids, may also be included in future prediction models.

Future studies should focus on acquiring a better understanding of the mechanisms underlying the development of POAF.

POAF is associated with increased morbidity and mortality that develops several years following discharge (8,187). However, it is hard to explain a cause-effect relationship between POAF for a few hours in the hospital and an ischemic stroke that occurs several years later, unless POAF is just a marker of an increased risk of stroke several years after surgery potentially due to the development of AF later in life. Future research should be directed towards assessing whether the prevention of POAF in the early postoperative period decreases the risk of a future stroke. Furthermore, it would be interesting to determine whether predictive models for POAF in the early postoperative period would also be able to predict the risk of AF and stroke later in life among patients who have undergone cardiac surgery several years prior to these situations.

REFERENCES

1. First successful cardiac operation in a human, 1896 : a documentation : the life, the times and the work of Ludwig Rehn (1849-1930) - NLM Catalog - NCBI [Internet]. [cited 2016 Aug 29]. Available from: http://www.ncbi.nlm.nih.gov/nlmcatalog/?term=Absolon%20KB,%20Naficy%20MA%20(2002).%20First%20successful%20cardiac%20operation%20in%20a%20human,%201896:%20a%20documentation:%20the%20life,%20the%20times,%20and%20the%20work%20of%20Ludwig%20Rehn%20(1849%E2%80%931930).%20Rockville,%20MD%20:%20Kabel,%202002

2. Bharucha DB, Kowey PR. Management and prevention of atrial fibrillation after cardiovascular surgery. Am J Cardiol. 2000 May 25;85(10A):20D–24D.

3. Fuller JA, Adams GG, Buxton B. Atrial fibrillation after coronary artery bypass grafting. Is it a disorder of the elderly? J Thorac Cardiovasc Surg. 1989 Jun;97(6):821–5.

4. Kalman JM, Munawar M, Howes LG, Louis WJ, Buxton BF, Gutteridge G, et al. Atrial fibrillation after coronary artery bypass grafting is associated with sympathetic activation. Ann Thorac Surg. 1995 Dec;60(6):1709–15.

5. El-Chami MF, Kilgo P, Thourani V, Lattouf OM, Delurgio DB, Guyton RA, et al. New-Onset Atrial Fibrillation Predicts Long-Term Mortality After Coronary Artery Bypass Graft. J Am Coll Cardiol. 2010 Mar 30;55(13):1370–6.

6. Philip F, Becker M, Galla J, Blackstone E, Kapadia SR. Transient post-operative atrial fibrillation predicts short and long term adverse events following CABG. Cardiovasc Diagn Ther. 2014 Oct;4(5):365–72.

7. Shen J, Lall S, Zheng V, Buckley P, Damiano Jr. RJ, Schuessler RB. The persistent problem of new-onset postoperative atrial fibrillation: A single-institution experience over two decades. J Thorac Cardiovasc Surg. 2011 Feb;141(2):559–70.

8. Villareal RP, Hariharan R, Liu BC, Kar B, Lee V-V, Elayda M, et al. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. J Am Coll Cardiol. 2004 Mar 3;43(5):742–8.

9. Raiten JM, Ghadimi K, Augoustides JGT, Ramakrishna H, Patel PA, Weiss SJ, et al. Atrial fibrillation after cardiac surgery: clinical update on mechanisms and prophylactic strategies. J Cardiothorac Vasc Anesth. 2015;29(3):806–16.

10. Filardo G, Hamilton C, Hebeler RF, Hamman B, Grayburn P. New-onset postoperative atrial fibrillation after isolated coronary artery bypass graft surgery and long-term survival. Circ Cardiovasc Qual Outcomes. 2009 May;2(3):164–9.

11. Filardo G, Hamilton C, Hamman B, Hebeler RF, Adams J, Grayburn P. New-onset postoperative atrial fibrillation and long-term survival after aortic valve replacement surgery. Ann Thorac Surg. 2010 Aug;90(2):474–9.

12. Horwich P, Buth KJ, Légaré J-F. New Onset Postoperative Atrial Fibrillation is Associated with a Long-Term Risk for Stroke and Death Following Cardiac Surgery. J Card Surg. 2013 Jan 1;28(1):8–13.

13. Lee S-H, Kang DR, Uhm J-S, Shim J, Sung J-H, Kim J-Y, et al. New-onset atrial fibrillation predicts long-term newly developed atrial fibrillation after coronary artery bypass graft. Am Heart J. 2014 Apr;167(4):593–600.e1.

14. Ferrari R, Bertini M, Blomstrom-Lundqvist C, Dobrev D, Kirchhof P, Pappone C, et al. An update on atrial fibrillation in 2014: From pathophysiology to treatment. Int J Cardiol. 2016 Jan 15;203:22–9.

15. Creswell LL, Schuessler RB, Rosenbloom M, Cox JL. Hazards of postoperative atrial arrhythmias. Ann Thorac Surg. 1993 Sep;56(3):539–49.

16. Andrews TC, Reimold SC, Berlin JA, Antman EM. Prevention of supraventricular arrhythmias after coronary artery bypass surgery. A meta-analysis of randomized control trials. Circulation. 1991 Nov;84(5 Suppl):III236-244.

17. Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. Ann Intern Med. 2001 Dec 18;135(12):1061–73.

18. Banach M, Kourliouros A, Reinhart KM, Benussi S, Mikhailidis DP, Jahangiri M, et al. Postoperative atrial fibrillation - what do we really know? Curr Vasc Pharmacol. 2010 Jul;8(4):553–72.

19. Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazer CD, et al. A multicenter risk index for atrial fibrillation after cardiac surgery. JAMA. 2004 Apr 14;291(14):1720–9.

20. Shrivastava R, Smith B, Caskey D, Reddy P. Atrial fibrillation after cardiac surgery: does prophylactic therapy decrease adverse outcomes associated with atrial fibrillation. J Intensive Care Med. 2009 Feb;24(1):18–25.

21. Kalavrouziotis D, Buth KJ, Ali IS. The impact of new-onset atrial fibrillation on in-hospital mortality following cardiac surgery. Chest. 2007 Mar;131(3):833–9.

22. Bramer S, van Straten AHM, Soliman Hamad MA, Berreklouw E, Martens EJ, Maessen JG. The Impact of New-Onset Postoperative Atrial Fibrillation on Mortality After Coronary Artery Bypass Grafting. Ann Thorac Surg. 2010 Aug;90(2):443–9.

23. Almassi GH, Pecsi SA, Collins JF, Shroyer AL, Zenati MA, Grover FL. Predictors and impact of postoperative atrial fibrillation on patients' outcomes: A report from the Randomized On Versus Off Bypass trial. J Thorac Cardiovasc Surg. 2012 Jan;143(1):93–102.

24. Tran DTT, Perry JJ, Dupuis J-Y, Elmestekawy E, Wells GA. Predicting New-Onset Postoperative Atrial Fibrillation in Cardiac Surgery Patients. J Cardiothorac Vasc Anesth. 2015 Oct;29(5):1117–26.

25. Weidinger F, Schachner T, Bonaros N, Hofauer B, Lehr EJ, Vesely M, et al. Predictors and consequences of postoperative atrial fibrillation following robotic totally endoscopic coronary bypass surgery. Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg. 2014 Feb;45(2):318–22.

26. Amat-Santos IJ, Rodés-Cabau J, Urena M, DeLarochellière R, Doyle D, Bagur R, et al. Incidence, predictive factors, and prognostic value of new-onset atrial fibrillation following transcatheter aortic valve implantation. J Am Coll Cardiol. 2012 Jan 10;59(2):178–88.

27. Motloch LJ, Reda S, Rottlaender D, Khatib R, Müller-Ehmsen J, Seck C, et al. Postprocedural atrial fibrillation after transcatheter aortic valve implantation versus surgical aortic valve replacement. Ann Thorac Surg. 2012 Jan;93(1):124–31.

28. Arakawa M, Miyata H, Uchida N, Motomura N, Katayama A, Tamura K, et al. Postoperative atrial fibrillation after thoracic aortic surgery. Ann Thorac Surg. 2015 Jan;99(1):103–8.

29. Augoustides JGT, Szeto W, Ochroch EA, Cowie D, Weiner J, Gambone AJ, et al. Atrial fibrillation after aortic arch repair requiring deep hypothermic circulatory arrest: incidence, clinical outcome, and clinical predictors. J Cardiothorac Vasc Anesth. 2007 Jun;21(3):388–92.

30. Hashimoto K, Ilstrup DM, Schaff HV. Influence of clinical and hemodynamic variables on risk of supraventricular tachycardia after coronary artery bypass. J Thorac Cardiovasc Surg. 1991 Jan;101(1):56–65.

31. Zaman AG, Archbold RA, Helft G, Paul EA, Curzen NP, Mills PG. Atrial fibrillation after coronary artery bypass surgery: a model for preoperative risk stratification. Circulation. 2000 Mar 28;101(12):1403–8.

32. Melby SJ, George JF, Picone DJ, Wallace JP, Davies JE, George DJ, et al. A time-related parametric risk factor analysis for postoperative atrial fibrillation after heart surgery. J Thorac Cardiovasc Surg. 2015 Mar;149(3):886–92.

33. Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, Kronmal RA, et al. Inflammation as a risk factor for atrial fibrillation. Circulation. 2003 Dec 16;108(24):3006–10.

34. Patti G, Chello M, Candura D, Pasceri V, D'Ambrosio A, Covino E, et al. Randomized trial of atorvastatin for reduction of postoperative atrial fibrillation in patients undergoing cardiac surgery: results of the ARMYDA-3 (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery) study. Circulation. 2006 Oct 3;114(14):1455–61.

35. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation. 1995 Oct 1;92(7):1954–68.

36. Moe GK, Rheinboldt WC, Abildskov JA. A COMPUTER MODEL OF ATRIAL FIBRILLATION. Am Heart J. 1964 Feb;67:200–20.

37. Sahadevan J, Ryu K, Peltz L, Khrestian CM, Stewart RW, Markowitz AH, et al. Epicardial mapping of chronic atrial fibrillation in patients: preliminary observations. Circulation. 2004 Nov 23;110(21):3293–9.

38. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998 Sep 3;339(10):659–66.

39. Sanfilippo AJ, Abascal VM, Sheehan M, Oertel LB, Harrigan P, Hughes RA, et al. Atrial enlargement as a consequence of atrial fibrillation. A prospective echocardiographic study. Circulation. 1990 Sep;82(3):792–7.

40. Echahidi N, Pibarot P, O'Hara G, Mathieu P. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. J Am Coll Cardiol. 2008 Feb 26;51(8):793–801.

41. Auer J, Weber T, Berent R, Ng C-K, Lamm G, Eber B. Risk factors of postoperative atrial fibrillation after cardiac surgery. J Card Surg. 2005 Oct;20(5):425–31.

42. Mathew JP, Parks R, Savino JS, Friedman AS, Koch C, Mangano DT, et al. Atrial fibrillation following coronary artery bypass graft surgery: predictors, outcomes, and resource utilization. MultiCenter Study of Perioperative Ischemia Research Group. JAMA. 1996 Jul 24;276(4):300–6.

43. Aranki SF, Shaw DP, Adams DH, Rizzo RJ, Couper GS, VanderVliet M, et al. Predictors of atrial fibrillation after coronary artery surgery. Current trends and impact on hospital resources. Circulation. 1996 Aug 1;94(3):390–7.

44. Almassi GH, Schowalter T, Nicolosi AC, Aggarwal A, Moritz TE, Henderson WG, et al. Atrial fibrillation after cardiac surgery: a major morbid event? Ann Surg. 1997 Oct;226(4):501-511-513.

45. Ducceschi V, D’Andrea A, Liccardo B, Alfieri A, Sarubbi B, De Feo M, et al. Perioperative clinical predictors of atrial fibrillation occurrence following coronary artery surgery. Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg. 1999 Oct;16(4):435–9.

46. Maisel WH, Kuntz KM, Reimold SC, Lee TH, Antman EM, Friedman PL, et al. Risk of initiating antiarrhythmic drug therapy for atrial fibrillation in patients admitted to a university hospital. Ann Intern Med. 1997 Aug 15;127(4):281–4.

47. Arsenault KA, Yusuf AM, Crystal E, Healey JS, Morillo CA, Nair GM, et al. Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. Cochrane Database Syst Rev. 2013;(1):CD003611.

48. Ho KM, Tan JA. Benefits and risks of corticosteroid prophylaxis in adult cardiac surgery: a dose-response meta-analysis. Circulation. 2009 Apr 14;119(14):1853–66.

49. Halonen J, Loponen P, Järvinen O, Karjalainen J, Parviainen I, Halonen P, et al. Metoprolol versus amiodarone in the prevention of atrial fibrillation after cardiac surgery: a randomized trial. Ann Intern Med. 2010 Dec 7;153(11):703–9.

50. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESCEndorsed by the European Stroke Organisation (ESO). Eur Heart J. 2016 Aug 27;

51. Zebis LR, Christensen TD, Kristiansen IS, Hjortdal VE. Amiodarone cost effectiveness in preventing atrial fibrillation after coronary artery bypass graft surgery. Ann Thorac Surg. 2008 Jan;85(1):28–32.

52. Wahr JA, Parks R, Boisvert D, Comunale M, Fabian J, Ramsay J, et al. Preoperative serum potassium levels and perioperative outcomes in cardiac surgery patients. Multicenter Study of Perioperative Ischemia Research Group. JAMA. 1999 Jun 16;281(23):2203–10.

53. Cagli K, Ozeke O, Ergun K, Budak B, Demirtas E, Birincioglu CL, et al. Effect of low-dose amiodarone and magnesium combination on atrial fibrillation after coronary artery surgery. J Card Surg. 2006 Oct;21(5):458–64.

54. Weiner B, Rheinlander HF, Decker EL, Cleveland RJ. Digoxin prophylaxis following coronary artery bypass surgery. Clin Pharm. 1986 Jan;5(1):55–8.

55. Gold MR, O'Gara PT, Buckley MJ, DeSanctis RW. Efficacy and safety of procainamide in preventing arrhythmias after coronary artery bypass surgery. Am J Cardiol. 1996 Nov 1;78(9):975–9.

56. Davison R, Hartz R, Kaplan K, Parker M, Feiereisel P, Michaelis L. Prophylaxis of supraventricular tachyarrhythmia after coronary bypass surgery with oral verapamil: a randomized, double-blind trial. Ann Thorac Surg. 1985 Apr;39(4):336–9.

57. Ozaydin M, Icli A, Yucel H, Akcay S, Peker O, Erdogan D, et al. Metoprolol vs. carvedilol or carvedilol plus N-acetyl cysteine on post-operative atrial fibrillation: a randomized, double-blind, placebo-controlled study. Eur Heart J. 2013 Feb;34(8):597–604.

58. Imazio M, Brucato A, Ferrazzi P, Rovere ME, Gandino A, Cemin R, et al. Colchicine reduces postoperative atrial fibrillation: results of the Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) atrial fibrillation substudy. Circulation. 2011 Nov 22;124(21):2290–5.

59. Costanzo S, di Niro V, Di Castelnuovo A, Gianfagna F, Donati MB, de Gaetano G, et al. Prevention of postoperative atrial fibrillation in open heart surgery patients by preoperative supplementation of n-3 polyunsaturated fatty acids: An updated meta-analysis. J Thorac Cardiovasc Surg. 2013 Oktober;146(4):906–11.

60. Cummings JE, Gill I, Akhrass R, Dery M, Biblo LA, Quan KJ. Preservation of the anterior fat pad paradoxically decreases the incidence of postoperative atrial fibrillation in humans. J Am Coll Cardiol. 2004 Mar 17;43(6):994–1000.

61. Greenberg MD, Katz NM, Iuliano S, Tempesta BJ, Solomon AJ. Atrial pacing for the prevention of atrial fibrillation after cardiovascular surgery. J Am Coll Cardiol. 2000 May;35(6):1416–22.

62. Fan K, Lee KL, Chiu CS, Lee JW, He GW, Cheung D, et al. Effects of biatrial pacing in prevention of postoperative atrial fibrillation after coronary artery bypass surgery. Circulation. 2000 Aug 15;102(7):755–60.

63. Daoud EG, Dabir R, Archambeau M, Morady F, Strickberger SA. Randomized, double-blind trial of simultaneous right and left atrial epicardial pacing for prevention of post-open heart surgery atrial fibrillation. Circulation. 2000 Aug 15;102(7):761–5.

64. Levy T, Fotopoulos G, Walker S, Rex S, Octave M, Paul V, et al. Randomized controlled study investigating the effect of biatrial pacing in prevention of atrial fibrillation after coronary artery bypass grafting. Circulation. 2000 Sep 19;102(12):1382–7.

65. Gerstenfeld EP, Hill MR, French SN, Mehra R, Rofino K, Vander Salm TJ, et al. Evaluation of right atrial and biatrial temporary pacing for the prevention of atrial fibrillation after coronary artery bypass surgery. J Am Coll Cardiol. 1999 Jun;33(7):1981–8.

66. Chung MK, Augostini RS, Asher CR, Pool DP, Grady TA, Zikri M, et al. Ineffectiveness and potential proarrhythmia of atrial pacing for atrial fibrillation prevention after coronary artery bypass grafting. Ann Thorac Surg. 2000 Apr;69(4):1057–63.

67. Kaw R, Hernandez AV, Masood I, Gillinov AM, Saliba W, Blackstone EH. Short- and long-term mortality associated with new-onset atrial fibrillation after coronary artery bypass grafting: A systematic review and meta-analysis. J Thorac Cardiovasc Surg. 2011 Maj;141(5):1305–12.

68. Rostagno C, La Meir M, Gelsomino S, Ghilli L, Rossi A, Carone E, et al. Atrial Fibrillation After Cardiac Surgery: Incidence, Risk Factors, and Economic Burden. J Cardiothorac Vasc Anesth. 2010 Dec;24(6):952–8.

69. Jayam VKS, Flaker GC, Jones JW. Atrial fibrillation after coronary bypass: etiology and pharmacologic prevention. Cardiovasc Surg. 2002 Aug;10(4):351–8.

70. Sun X, Boyce SW, Hill PC, Bafi AS, Xue Z, Lindsay J, et al. Association of Body Mass Index With New-Onset Atrial Fibrillation After Coronary Artery Bypass Grafting Operations. Ann Thorac Surg. 2011 Jun;91(6):1852–8.

71. Steinberg JS, Zelenkofske S, Wong SC, Gelernt M, Sciacca R, Menchavez E. Value of the P-wave signal-averaged ECG for predicting atrial fibrillation after cardiac surgery. Circulation. 1993 Dec;88(6):2618–22.

72. Zaman AG, Alamgir F, Richens T, Williams R, Rothman MT, Mills PG. The role of signal averaged P wave duration and serum magnesium as a combined predictor of atrial fibrillation after elective coronary artery bypass surgery. Heart Br Card Soc. 1997 Jun;77(6):527–31.

73. Passman R, Beshai J, Pavri B, Kimmel S. Predicting post-coronary bypass surgery atrial arrhythmias from the preoperative electrocardiogram. Am Heart J. 2001 Nov;142(5):806–10.

74. Rader F, Costantini O, Jarrett C, Gorodeski EZ, Lauer MS, Blackstone EH. Quantitative electrocardiography for predicting postoperative atrial fibrillation after cardiac surgery. J Electrocardiol. 2011 Dec;44(6):761–7.

75. Wong JK, Lobato RL, Pinesett A, Maxwell BG, Mora-Mangano CT, Perez MV. P-wave characteristics on routine preoperative electrocardiogram improve prediction of new-onset postoperative atrial fibrillation in cardiac surgery. J Cardiothorac Vasc Anesth. 2014 Dec;28(6):1497–504.

76. Nielsen JB, Kühl JT, Pietersen A, Graff C, Lind B, Struijk JJ, et al. P-wave duration and the risk of atrial fibrillation: Results from the Copenhagen ECG Study. Heart Rhythm Off J Heart Rhythm Soc. 2015 Apr 23;

77. Nielsen JB, Pietersen A, Graff C, Lind B, Struijk JJ, Olesen MS, et al. Risk of atrial fibrillation as a function of the electrocardiographic PR interval: Results from the Copenhagen ECG Study. Heart Rhythm. 2013 Sep;10(9):1249–56.

78. El-Chami MF, Brancato C, Langberg J, Delurgio DB, Bush H, Brosius L, et al. QRS duration is associated with atrial fibrillation in patients with left ventricular dysfunction. Clin Cardiol. 2010 Mar;33(3):132–8.

79. Nielsen JB, Graff C, Pietersen A, Lind B, Struijk JJ, Olesen MS, et al. J-Shaped Association Between QTc Interval Duration and the Risk of Atrial Fibrillation: Results From the Copenhagen ECG Study. J Am Coll Cardiol. 2013 Jun 25;61(25):2557–64.

80. Çetin M, Kocaman SA, Erdoğan T, Durakoğlugil ME, Çiçek Y, Bozok Ş, et al. Fragmented QRS may predict postoperative atrial fibrillation in patients undergoing isolated coronary artery bypass graft surgery. Anadolu Kardiyol Derg AKD Anatol J Cardiol. 2012 Nov;12(7):576–83.

81. Stover EP, Siegel LC, Parks R, Levin J, Body SC, Maddi R, et al. Variability in transfusion practice for coronary artery bypass surgery persists despite national consensus guidelines: a 24-institution study. Institutions of the Multicenter Study of Perioperative Ischemia Research Group. Anesthesiology. 1998 Feb;88(2):327–33.

82. Rogers MAM, Blumberg N, Saint S, Langa KM, Nallamothu BK. Hospital variation in transfusion and infection after cardiac surgery: a cohort study. BMC Med. 2009 Jul 31;7:37.

83. Lelubre C, Vincent J-L. Red blood cell transfusion in the critically ill patient. Ann Intensive Care. 2011 Oct 4;1:43.

84. Alghamdi AA, Davis A, Brister S, Corey P, Logan A. Development and validation of Transfusion Risk Understanding Scoring Tool (TRUST) to stratify cardiac surgery patients according to their blood transfusion needs. Transfusion (Paris). 2006 Jul;46(7):1120–9.

85. Koch CG, Li L, Van Wagoner DR, Duncan AI, Gillinov AM, Blackstone EH. Red Cell Transfusion is Associated With an Increased Risk for Postoperative Atrial Fibrillation. Ann Thorac Surg. 2006 Nov;82(5):1747–56.

86. Ferraris VA, Ballert EQ, Mahan A. The relationship between intraoperative blood transfusion and postoperative systemic inflammatory response syndrome. Am J Surg. 2013 Apr;205(4):457–65.

87. Anselmi A, Possati G, Gaudino M. Postoperative Inflammatory Reaction and Atrial Fibrillation: Simple Correlation or Causation? Ann Thorac Surg. 2009 Jul;88(1):326–33.

88. Lo B, Fijnheer R, Nierich AP, Bruins P, Kalkman CJ. C-reactive protein is a risk indicator for atrial fibrillation after myocardial revascularization. Ann Thorac Surg. 2005 May;79(5):1530–5.

89. Gaudino M, Andreotti F, Zamparelli R, Di Castelnuovo A, Nasso G, Burzotta F, et al. The -174G/C interleukin-6 polymorphism influences postoperative interleukin-6 levels and postoperative atrial fibrillation. Is atrial fibrillation an inflammatory complication? Circulation. 2003 Sep 9;108 Suppl 1:II195-199.

90. Ishida K, Kimura F, Imamaki M, Ishida A, Shimura H, Kohno H, et al. Relation of inflammatory cytokines to atrial fibrillation after off-pump coronary artery bypass grafting. Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg. 2006 Apr;29(4):501–5.

91. Abdelhadi RH, Gurm HS, Van Wagoner DR, Chung MK. Relation of an exaggerated rise in white blood cells after coronary bypass or cardiac valve surgery to development of atrial fibrillation postoperatively. Am J Cardiol. 2004 May 1;93(9):1176–8.

92. Lamm G, Auer J, Weber T, Berent R, Ng C, Eber B. Postoperative white blood cell count predicts atrial fibrillation after cardiac surgery. J Cardiothorac Vasc Anesth. 2006 Feb;20(1):51–6.

93. Dorneles C de C, Bodanese LC, Guaragna JCV da C, Macagnan FE, Coelho JC, Borges AP, et al. The impact of blood transfusion on morbidity and mortality after cardiac surgery. Rev Bras Cir Cardiovasc Órgão Of Soc Bras Cir Cardiovasc. 2011 Jun;26(2):222–9.

94. Topal AE, Eren MN. Predictors of atrial fibrillation occurrence after coronary artery bypass graft surgery. Gen Thorac Cardiovasc Surg. 2011 Apr;59(4):254–60.

95. Alameddine AK, Visintainer P, Alimov VK, Rousou JA. Blood transfusion and the risk of atrial fibrillation after cardiac surgery. J Card Surg. 2014 Sep;29(5):593–9.

96. Vlahou A, Diplaris K, Ampatzidou F, Karagounnis L, Drossos G. The Role of Blood Transfusion in the Development of Atrial Fibrillation after Coronary Artery Bypass Grafting. Thorac Cardiovasc Surg. 2016 Aug 30;

97. Koch CG, Li L, Sessler DI, Figueroa P, Hoeltge GA, Mihaljevic T, et al. Duration of red-cell storage and complications after cardiac surgery. N Engl J Med. 2008 Mar 20;358(12):1229–39.

98. van Straten AHM, Soliman Hamad MA, van Zundert AAJ, Martens EJ, ter Woorst JF, de Wolf AM, et al. Effect of duration of red blood cell storage on early and late mortality after coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2011 Jan;141(1):231–7.

99. Steiner ME, Ness PM, Assmann SF, Triulzi DJ, Sloan SR, Delaney M, et al. Effects of red-cell storage duration on patients undergoing cardiac surgery. N Engl J Med. 2015 Apr 9;372(15):1419–29.

100. Ng MSY, Ng ASY, Chan J, Tung J-P, Fraser JF. Effects of packed red blood cell storage duration on post-transfusion clinical outcomes: a meta-analysis and systematic review. Intensive Care Med. 2015 Dec;41(12):2087–97.

101. Heddle NM, Cook RJ, Arnold DM, Liu Y, Barty R, Crowther MA, et al. Effect of Short-Term vs. Long-Term Blood Storage on Mortality after Transfusion. N Engl J Med. 2016 Nov 17;375(20):1937–45.

102. Berezina TL, Zaets SB, Morgan C, Spillert CR, Kamiyama M, Spolarics Z, et al. Influence of storage on red blood cell rheological properties. J Surg Res. 2002 Jan;102(1):6–12.

103. Almac E, Ince C. The impact of storage on red cell function in blood transfusion. Best Pract Res Clin Anaesthesiol. 2007 Jun;21(2):195–208.

104. Andreasen JJ, Dethlefsen C, Modrau IS, Baech J, Schonheyder HC, Moeller JK, et al. Storage time of allogeneic red blood cells is associated with risk of severe postoperative infection after coronary artery bypass grafting. Eur J Cardiothorac Surg. 2011 Jan 3;39(3):329–34.

105. Koch CG, Figueroa PI, Li L, Sabik III JF, Mihaljevic T, Blackstone EH. Red Blood Cell Storage: How Long Is Too Long? Ann Thorac Surg. 2013 Nov;96(5):1894–9.

106. Kinnunen E-M, Sabatelli L, Juvonen T, Biancari F. Red blood cell storage time and the outcome after coronary surgery. J Surg Res. 2015 Jul;197(1):58–64.

107. Scorletti E, Byrne CD. Omega-3 fatty acids, hepatic lipid metabolism, and nonalcoholic fatty liver disease. Annu Rev Nutr. 2013;33:231–48.

108. Hallaq H, Smith TW, Leaf A. Modulation of dihydropyridine-sensitive calcium channels in heart cells by fish oil fatty acids. Proc Natl Acad Sci U S A. 1992 Mar 1;89(5):1760–4.

109. Kang JX, Leaf A. Prevention and termination of beta-adrenergic agonist-induced arrhythmias by free polyunsaturated fatty acids in neonatal rat cardiac myocytes. Biochem Biophys Res Commun. 1995 Mar 17;208(2):629–36.

110. Li G-R, Sun H-Y, Zhang X-H, Cheng L-C, Chiu S-W, Tse H-F, et al. Omega-3 polyunsaturated fatty acids inhibit transient outward and ultra-rapid delayed rectifier K+currents and Na+current in human atrial myocytes. Cardiovasc Res. 2009 Feb 1;81(2):286–93.

111. Chapkin RS, Kim W, Lupton JR, McMurray DN. Dietary docosahexaenoic and eicosapentaenoic acid: emerging mediators of inflammation. Prostaglandins Leukot Essent Fatty Acids. 2009 Sep;81(2–3):187–91.

112. Kumar S, Sutherland F, Rosso R, Teh AW, Lee G, Heck PM, et al. Effects of chronic omega-3 polyunsaturated fatty acid supplementation on human atrial electrophysiology. Heart Rhythm Off J Heart Rhythm Soc. 2011 Apr;8(4):562–8.

113. Savelieva I, Camm AJ. Polyunsaturated fatty acids for prevention of atrial fibrillation: a ‘fishy’ story. Eur Eur Pacing Arrhythm Card Electrophysiol J Work Groups Card Pacing Arrhythm Card Cell Electrophysiol Eur Soc Cardiol. 2011 Feb;13(2):149–52.

114. Ali-Hassan-Sayegh S, Mirhosseini SJ, Rezaeisadrabadi M, Dehghan HR, Sedaghat-Hamedani F, Kayvanpour E, et al. Antioxidant supplementations for prevention of atrial fibrillation after cardiac surgery: an updated comprehensive systematic review and meta-analysis of 23 randomized controlled trials. Interact Cardiovasc Thorac Surg. 2014 May;18(5):646–54.

115. Langlois PL, Hardy G, Manzanares W. Omega-3 polyunsaturated fatty acids in cardiac surgery patients: An updated systematic review and meta-analysis. Clin Nutr Edinb Scotl. 2016 May 27;

116. Armaganijan L, Lopes RD, Healey JS, Piccini JP, Nair GM, Morillo CA. Do omega-3 fatty acids prevent atrial fibrillation after open heart surgery? A meta-analysis of randomized controlled trials. Clin São Paulo Braz. 2011;66(11):1923–8.

117. Mozaffarian D, Wu JHY, de Oliveira Otto MC, Sandesara CM, Metcalf RG, Latini R, et al. Fish oil and post-operative atrial fibrillation: a meta-analysis of randomized controlled trials. J Am Coll Cardiol. 2013 May 28;61(21):2194–6.

118. Benedetto U, Angeloni E, Melina G, Danesi TH, Di Bartolomeo R, Lechiancole A, et al. n-3 Polyunsaturated fatty acids for the prevention of postoperative atrial fibrillation: a meta-analysis of randomized controlled trials. J Cardiovasc Med Hagerstown Md. 2013 Feb;14(2):104–9.

119. Wu JHY, Marchioli R, Silletta MG, Macchia A, Song X, Siscovick DS, et al. Plasma phospholipid omega-3 fatty acids and incidence of postoperative atrial fibrillation in the OPERA trial. J Am Heart Assoc. 2013 Oct;2(5):e000397.

120. Zhang B, Zhen Y, Tao A, Bao Z, Zhang G. Polyunsaturated fatty acids for the prevention of atrial fibrillation after cardiac surgery: an updated meta-analysis of randomized controlled trials. J Cardiol. 2014 Jan;63(1):53–9.

121. Metcalf RG, Skuladottir GV, Indridason OS, Sullivan TR, Bjorgvinsdottir L, Sanders P, et al. U-shaped relationship between tissue docosahexaenoic acid and

atrial fibrillation following cardiac surgery. Eur J Clin Nutr. 2014 Jan;68(1):114–8.

122. Lomivorotov VV, Efremov SM, Pokushalov EA, Romanov AB, Ponomarev DN, Cherniavsky AM, et al. Randomized trial of fish oil infusion to prevent atrial fibrillation after cardiac surgery: data from an implantable continuous cardiac monitor. J Cardiothorac Vasc Anesth. 2014 Oct;28(5):1278–84.

123. Farquharson AL, Metcalf RG, Sanders P, Stuklis R, Edwards JRM, Gibson RA, et al. Effect of dietary fish oil on atrial fibrillation after cardiac surgery. Am J Cardiol. 2011 Sep 15;108(6):851–6.

124. Mozaffarian D, Marchioli R, Macchia A, Silletta MG, Ferrazzi P, Gardner TJ, et al. Fish oil and postoperative atrial fibrillation: the Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation (OPERA) randomized trial. JAMA. 2012 Nov 21;308(19):2001–11.

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

126. Schmidt M, Maeng M, Jakobsen C-J, Madsen M, Thuesen L, Nielsen PH, et al. Existing data sources for clinical epidemiology: The Western Denmark Heart Registry. Clin Epidemiol. 2010;2:137–44.

127. Gu J, Andreasen JJ, Melgaard J, Lundbye-Christensen S, Hansen J, Schmidt EB, et al. Preoperative Electrocardiogram Score for Predicting New-Onset Postoperative Atrial Fibrillation in Patients Undergoing Cardiac Surgery. J Cardiothorac Vasc Anesth. 2016 May 24;

128. Folch J, Lees M, Sloane Stanley GH. A simple method for the isolation and purification of total lipides from animal tissues. J Biol Chem. 1957 May;226(1):497–509.

129. Andreasen JJ, Aardestrup IV, Eschen RB, Obel T, Lundbye-Christensen S, Schmidt EB. Fatty acid composition of the internal mammary artery in relation to dietary intake of marine n-3 polyunsaturated fatty acids and association with flow-mediated vasodilation. Cell Mol Biol Noisy--Gd Fr. 2010;56(1):10–7.

130. Burdge GC, Wright P, Jones AE, Wootton SA. A method for separation of phosphatidylcholine, triacylglycerol, non-esterified fatty acids and cholesterol esters from plasma by solid-phase extraction. Br J Nutr. 2000 Nov;84(5):781–7.

131. Clinical prediction models : a practical approach to development, validation, and updating - NLM Catalog - NCBI [Internet]. [cited 2016 Sep 16]. Available from:

https://www.ncbi.nlm.nih.gov/nlmcatalog/?term=Clinical%20Prediction%20Models:%20A%20Practical%20Approach%20to%20Development,%20Validation,%20and%20Updating

132. Youden WJ. Index for rating diagnostic tests. Cancer. 1950 Jan;3(1):32–5.

133. Amar D, Shi W, Hogue CW, Zhang H, Passman RS, Thomas B, et al. Clinical prediction rule for atrial fibrillation after coronary artery bypass grafting. J Am Coll Cardiol. 2004 Sep 15;44(6):1248–53.

134. Mariscalco G, Biancari F, Zanobini M, Cottini M, Piffaretti G, Saccocci M, et al. Bedside Tool for Predicting the Risk of Postoperative Atrial Fibrillation After Cardiac Surgery: The POAF Score. J Am Heart Assoc. 2014 Apr 25;3(2):e000752.

135. Chua S-K, Shyu K-G, Lu M-J, Lien L-M, Lin C-H, Chao H-H, et al. Clinical utility of CHADS2 and CHA2DS2-VASc scoring systems for predicting postoperative atrial fibrillation after cardiac surgery. J Thorac Cardiovasc Surg. 2013 Oct;146(4):919–926.e1.

136. Borde D, Gandhe U, Hargave N, Pandey K, Mathew M, Joshi S. Prediction of postoperative atrial fibrillation after coronary artery bypass grafting surgery: is CHA 2 DS 2 -VASc score useful? Ann Card Anaesth. 2014 Sep;17(3):182–7.

137. Yin L, Ling X, Zhang Y, Shen H, Min J, Xi W, et al. CHADS2 and CHA2DS2-VASc scoring systems for predicting atrial fibrillation following cardiac valve surgery. PloS One. 2015;10(4):e0123858.

138. Erdem K. Usefulness of CHA2DS2-VASc scoring system in predicting atrial fibrillation after coronary artery bypass grafting. ResearchGate. 2016 Jan 4;24(1):27–33.

139. Yadava M, Hughey AB, Crawford TC. Postoperative atrial fibrillation: incidence, mechanisms, and clinical correlates. Cardiol Clin. 2014 Nov;32(4):627–36.

140. Heeringa J, van der Kuip DAM, Hofman A, Kors JA, van Herpen G, Stricker BHC, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J. 2006 Apr;27(8):949–53.

141. Schnabel RB, Yin X, PhilimonGona, Larson MG, Beiser AS, McManus DD, et al. Fifty-Year Trends in Atrial Fibrillation Prevalence, Incidence, Risk Factors, and Mortality in the Community. Lancet Lond Engl. 2015 Jul 11;386(9989):154–62.

142. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, et al. Incidence of and risk factors for atrial fibrillation in older adults. Circulation. 1997 Oct 7;96(7):2455–61.

143. Hernandez AV, Kaw R, Pasupuleti V, Bina P, Ioannidis JPA, Bueno H, et al. Association between obesity and postoperative atrial fibrillation in patients undergoing cardiac operations: a systematic review and meta-analysis. Ann Thorac Surg. 2013 Sep;96(3):1104–16.

144. Wanahita N, Messerli FH, Bangalore S, Gami AS, Somers VK, Steinberg JS. Atrial fibrillation and obesity--results of a meta-analysis. Am Heart J. 2008 Feb;155(2):310–5.

145. Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. Circulation. 1994 Feb;89(2):724–30.

146. Henry WL, Morganroth J, Pearlman AS, Clark CE, Redwood DR, Itscoitz SB, et al. Relation between echocardiographically determined left atrial size and atrial fibrillation. Circulation. 1976 Feb;53(2):273–9.

147. Osranek M, Fatema K, Qaddoura F, Al-Saileek A, Barnes ME, Bailey KR, et al. Left atrial volume predicts the risk of atrial fibrillation after cardiac surgery: a prospective study. J Am Coll Cardiol. 2006 Aug 15;48(4):779–86.

148. Özlü MF, Erdem K, Kırış G, Parlar Aİ, Demirhan A, Ayhan SS, et al. Predictive value of total atrial conduction time measured with tissue Doppler imaging for postoperative atrial fibrillation after coronary artery bypass surgery. J Interv Card Electrophysiol Int J Arrhythm Pacing. 2013 Jun;37(1):27–33.

149. Ozben B, Akaslan D, Sunbul M, Filinte D, Ak K, Sari İ, et al. Postoperative Atrial Fibrillation after Coronary Artery Bypass Grafting Surgery: A Two-dimensional Speckle Tracking Echocardiography Study. Heart Lung Circ. 2016 Oct;25(10):993–9.

150. Soliman EZ, Prineas RJ, Case LD, Zhang Z, Goff DC. Ethnic distribution of ECG predictors of atrial fibrillation and its impact on understanding the ethnic distribution of ischemic stroke in the Atherosclerosis Risk in Communities (ARIC) study. Stroke J Cereb Circ. 2009 Apr;40(4):1204–11.

151. Magnani JW, Johnson VM, Sullivan LM, Gorodeski EZ, Schnabel RB, Lubitz SA, et al. P wave duration and risk of longitudinal atrial fibrillation in persons ≥ 60 years old (from the Framingham Heart Study). Am J Cardiol. 2011 Mar 15;107(6):917–921.e1.

152. Sigurdsson MI, Muehlschlegel JD, Fox AA, Heydarpour M, Lichtner P, Meitinger T, et al. Genetic Variants Associated With Atrial Fibrillation and PR Interval Following Cardiac Surgery. J Cardiothorac Vasc Anesth. 2015 Jun;29(3):605–10.

153. Mazzoleni A, Curtin ME, Wolff R, Reiner L, Somes G. On the relationship between heart weights, fibrosis, and QRS duration. J Electrocardiol. 1975 Jul;8(3):233–6.

154. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. Lancet Lond Engl. 2009 Feb 28;373(9665):739–45.

155. Allessie MA, Boyden PA, Camm AJ, Kléber AG, Lab MJ, Legato MJ, et al. Pathophysiology and prevention of atrial fibrillation. Circulation. 2001 Feb 6;103(5):769–77.

156. Levy MN. Sympathetic-parasympathetic interactions in the heart. Circ Res. 1971 Nov;29(5):437–45.

157. Spach MS, Dolber PC. Relating extracellular potentials and their derivatives to anisotropic propagation at a microscopic level in human cardiac muscle. Evidence for electrical uncoupling of side-to-side fiber connections with increasing age. Circ Res. 1986 Mar;58(3):356–71.

158. Lie JT, Hammond PI. Pathology of the senescent heart: anatomic observations on 237 autopsy studies of patients 90 to 105 years old. Mayo Clin Proc. 1988 Jun;63(6):552–64.

159. Kitzman DW, Edwards WD. Age-related changes in the anatomy of the normal human heart. J Gerontol. 1990 Mar;45(2):M33-39.

160. Aytemir K, Aksoyek S, Ozer N, Aslamaci S, Oto A. Atrial fibrillation after coronary artery bypass surgery: P wave signal averaged ECG, clinical and angiographic variables in risk assessment. Int J Cardiol. 1999 Apr 30;69(1):49–56.

161. Zhang B-C, Che W-L, Li W-M, Xu Y-W. Meta-analysis of P wave character as predictor of atrial fibrillation after coronary artery bypass grafting. Int J Cardiol. 2011 Oct 20;152(2):260–2.

162. Spinella PC, Sparrow RL, Hess JR, Norris PJ. Properties of stored red blood cells: understanding immune and vascular reactivity. Transfusion (Paris). 2011 Apr;51(4):894–900.

163. Aubron C, Nichol A, Cooper DJ, Bellomo R. Age of red blood cells and transfusion in critically ill patients. Ann Intensive Care. 2013 Jan 15;3(1):2.

164. van Straten AHM, Bekker MWA, Soliman Hamad MA, van Zundert AAJ, Martens EJ, Schönberger JPAM, et al. Transfusion of red blood cells: the impact on short-term and long-term survival after coronary artery bypass grafting, a ten-year follow-up. Interact Cardiovasc Thorac Surg. 2010 Jan;10(1):37–42.

165. Relevy H, Koshkaryev A, Manny N, Yedgar S, Barshtein G. Blood banking-induced alteration of red blood cell flow properties. Transfusion (Paris). 2008 Jan;48(1):136–46.

166. Weinberg JA, McGwin G, Griffin RL, Huynh VQ, Cherry SA, Marques MB, et al. Age of transfused blood: an independent predictor of mortality despite universal leukoreduction. J Trauma. 2008 Aug;65(2):279-282-284.

167. Lelubre C, Vincent J-L. Relationship between red cell storage duration and outcomes in adults receiving red cell transfusions: a systematic review. Crit Care Lond Engl. 2013;17(2):R66.

168. McKenny M, Ryan T, Tate H, Graham B, Young VK, Dowd N. Age of transfused blood is not associated with increased postoperative adverse outcome after cardiac surgery. Br J Anaesth. 2011 May;106(5):643–9.

169. Desmarets M, Bardiaux L, Benzenine E, Dussaucy A, Binda D, Tiberghien P, et al. Effect of storage time and donor sex of transfused red blood cells on 1-year survival in patients undergoing cardiac surgery: an observational study. Transfusion (Paris). 2016 May;56(5):1213–22.

170. Andreasen JJ, Sindby JE, Brocki BC, Rasmussen BS, Dethlefsen C. Efforts to change transfusion practice and reduce transfusion rates are effective in coronary artery bypass surgery. J Cardiothorac Vasc Anesth. 2012 Aug;26(4):545–9.

171. Saravanan P, Bridgewater B, West AL, O'Neill SC, Calder PC, Davidson NC. Omega-3 fatty acid supplementation does not reduce risk of atrial fibrillation after coronary artery bypass surgery: a randomized, double-blind, placebo-controlled clinical trial. Circ Arrhythm Electrophysiol. 2010 Feb;3(1):46–53.

172. Castillo R, Rodrigo R, Perez F, Cereceda M, Asenjo R, Zamorano J, et al. Antioxidant therapy reduces oxidative and inflammatory tissue damage in

patients subjected to cardiac surgery with extracorporeal circulation. Basic Clin Pharmacol Toxicol. 2011 Apr;108(4):256–62.

173. Guo X-Y, Yan X-L, Chen Y-W, Tang R-B, Du X, Dong J-Z, et al. Omega-3 fatty acids for postoperative atrial fibrillation: alone or in combination with antioxidant vitamins? Heart Lung Circ. 2014 Aug;23(8):743–50.

174. Korantzopoulos P, Kolettis TM, Goudevenos JA. The anti-inflammatory and antioxidant effects of long-chain n-3 fatty acids or oil-rich fish may favorably affect atrial remodeling in atrial fibrillation. Med Hypotheses. 2005;64(6):1245–6.

175. Reiffel JA, McDonald A. Antiarrhythmic effects of omega-3 fatty acids. Am J Cardiol. 2006 Aug 21;98(4A):50i–60i.

176. Wilbring M, Ploetze K, Bormann S, Waldow T, Matschke K. Omega-3 polyunsaturated Fatty acids reduce the incidence of postoperative atrial fibrillation in patients with history of prior myocardial infarction undergoing isolated coronary artery bypass grafting. Thorac Cardiovasc Surg. 2014 Oct;62(7):569–74.

177. Leifert WR, Jahangiri A, McMurchie EJ. Membrane fluidity changes are associated with the antiarrhythmic effects of docosahexaenoic acid in adult rat cardiomyocytes. J Nutr Biochem. 2000 Jan;11(1):38–44.

178. Grynberg A, Fournier A, Sergiel JP, Athias P. Membrane docosahexaenoic acid vs. eicosapentaenoic acid and the beating function of the cardiomyocyte and its regulation through the adrenergic receptors. Lipids. 1996 Mar;31 Suppl:S205-210.

179. Charnock JS. Omega-3 polyunsaturated fatty acids and ventricular fibrillation: the possible involvement of eicosanoids. Prostaglandins Leukot Essent Fatty Acids. 1999 Oct;61(4):243–7.

180. Leaf A, Kang JX, Xiao Y-F, Billman GE. Clinical prevention of sudden cardiac death by n-3 polyunsaturated fatty acids and mechanism of prevention of arrhythmias by n-3 fish oils. Circulation. 2003 Jun 3;107(21):2646–52.

181. Leaf A, Xiao Y-F, Kang JX, Billman GE. Membrane effects of the n-3 fish oil fatty acids, which prevent fatal ventricular arrhythmias. J Membr Biol. 2005 Jul;206(2):129–39.

182. Metcalf RG, Cleland LG, Gibson RA, Roberts-Thomson KC, Edwards JR, Sanders P, et al. Relation between blood and atrial fatty acids in patients undergoing cardiac bypass surgery. Am J Clin Nutr. 2010 Mar;91(3):528–34.

183. Metcalf RG, James MJ, Gibson RA, Edwards JR, Stubberfield J, Stuklis R, et al. Effects of fish-oil supplementation on myocardial fatty acids in humans. Am J Clin Nutr. 2007 May;85(5):1222–8.

184. Ucar HI, Tok M, Atalar E, Dogan OF, Oc M, Farsak B, et al. Predictive significance of plasma levels of interleukin-6 and high-sensitivity C-reactive protein in atrial fibrillation after coronary artery bypass surgery. Heart Surg Forum. 2007;10(2):E131-135.

185. Elahi MM, Flatman S, Matata BM. Tracing the origins of postoperative atrial fibrillation: the concept of oxidative stress-mediated myocardial injury phenomenon. Eur J Cardiovasc Prev Rehabil Off J Eur Soc Cardiol Work Groups Epidemiol Prev Card Rehabil Exerc Physiol. 2008 Dec;15(6):735–41.

186. Wu N, Xu B, Xiang Y, Wu L, Zhang Y, Ma X, et al. Association of inflammatory factors with occurrence and recurrence of atrial fibrillation: a meta-analysis. Int J Cardiol. 2013 Oct 25;169(1):62–72.

187. Ahlsson A, Fengsrud E, Bodin L, Englund A. Postoperative atrial fibrillation in patients undergoing aortocoronary bypass surgery carries an eightfold risk of future atrial fibrillation and a doubled cardiovascular mortality. Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg. 2010 Jun;37(6):1353–9.

APPENDICES

Appendix A. Paper I

Appendix B. Paper II

Appendix C. Paper III

ISSN (online): 2246-1302
ISBN (online): 978-87-7112-853-6

AALBORG **UNIVERSITY PRESS**