Towards improved risk prediction of incident atrial fibrillation and progression of atrial fibrillation

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DOI:
10.33612/diss.136550017

Chapter 8

Discussion and future perspectives.

DISCUSSION AND FUTURE PERSPECTIVES

This general aim of the present thesis was to improve risk prediction of incident AF and progression of atrial fibrillation (AF). First we investigated markers to predict incident AF. In **chapter 2** we showed the relation of renal dysfunction with incident AF and the association with cardiovascular morbidity and mortality by using the Prevention of Renal and Vascular End-stage Disease (PREVEND) study. Our analyses showed that increased albumin excretion and not estimated glomerular filtration rate, as is most often used in clinical practice, was associated with incident AF. In **chapter 3** we evaluated metabolic profiling in the relation to incident AF in the Framingham Heart Study. In contrast to previous studies, we observed no relation between small-molecule metabolites in diverse biological systems and incident AF. For prediction of incident AF but even more for progression of AF assessment of the actual severity of structural remodelling is essential. In **chapter 4** we aimed to improve assessment of the severity of atrial structural remodelling using body surface ECG mapping to measure P wave complexity. We showed that a higher number of peaks in the P-wave and larger P-wave terminal force in lead V1 can differentiate between patients with and without a history of AF, i.e. help to assess severity of atrial remodelling. In the last part of this thesis we assessed the prevalence and predictors of AF progression in different patient populations. In **Chapter 5** (Young AF cohort) we investigated young onset AF patients (mean age 49 years). Interestingly, even in this young population risk factors and comorbidities were present in 89% of the patients. AF progression to permanent AF and cardiovascular events occurred in 2% and 2.4% per year, respectively. Cardiovascular events increased after AF progression had occurred. Predictors in this population included PR interval and left ventricular hypertrophy. In **Chapter 6** (AF-Risk cohort) we included patients (mean age 60 years) with short-lasting AF. AF progression occurred in 13% of patients in this group during 1-year follow-up. An increased left atrial volume, elevated NT-proBNP and lower PAI-1, possibly as sign of inflammation, were associated with AF progression. Also in this study patients with AF progression had a higher event rate during follow-up. Finally, since nowadays there is an increasing awareness that sex is a major determinant of the incidence, etiology, and clinical presentation of AF, one chapter was about sex differences. Until now, women are not only underrepresented in major AF trials, in addition, data on clinical profile and outcome in young AF patients is limited. Therefore we aimed to investigate the clinical profile, AF progression rate and cardiovascular outcome between sexes in patients with young-onset AF in **Chapter 7** (Young AF cohort).

The atrial fibrillation epidemic

AF is the most frequent arrhythmia in men and women and its incidence is continuously rising reflected by a population with increasing comorbidities and risk factors, a seden-

tary lifestyle, and longer life expectancy.[1] The prevalence of AF increases with age and is doubled for every decade after the age of 50, reaching approximately 10% in persons ≥ 80 years.[2] AF itself is associated with an increased risk for stroke, heart failure, cognitive dysfunction, dementia and for mortality,[3-9] which is further increased in the presence of more comorbidities and risk factors.[1] AF is a complex disease associated with electrical, mechanical, and structural abnormalities of the atria due to AF but also due to its risk factors and comorbidities.[10] In the last few decades knowledge on the pathophysiological substrate of AF and the role of comorbidities, risk factors, biomarkers and genetics has increased substantially.

I. Risk markers for incident atrial fibrillation

Population-based studies have identified numerous cardiovascular and non-cardiovascular comorbidities and risk factors that individually, as well as in combination with each other, increase AF susceptibility.[11,12] As there are so many conditions link to AF, the historical term 'lone AF' should rarely be used.[13] The best known classical risk factors for AF include age, male sex, hypertension, left ventricular hypertrophy, coronary artery disease, heart failure (HF), and valve disease.[6,14-19] Elevated blood pressure is the single most important contributor to AF and the population-attributable risk has been estimated at 14-20%, reaching almost 25% if borderline hypertension is also included.[16,20] HF is an outcome associated with AF, as well as a risk factor. AF and HF are closely intertwined, share common risk factors, influence each other, and together carry a poorer prognosis than either condition alone.[18,21-23] Other demographic and lifestyle factors include age, male sex, alcohol consumption, and body mass index (BMI).[6,14,16,24] BMI is linearly related to the incidence of AF. Obesity accounted for 9% of incident AF in the contemporary Prevention of Renal and Vascular End-Stage Disease (PREVEND) study population and per every 5 kg/m^2 increase in BMI the hazard ratio increased with 1.45.[24] In the ARIC study having overweight was the second-most important risk for AF, contributing to 17.9% of the population-attributable risk of AF.[16] Other conditions include diabetes mellitus, obstructive sleep apnea syndrome (OSAS), chronic obstructive pulmonary disease (COPD), metabolic syndrome, chronic kidney disease (CKD) based on the different established CKD stadia, hyperthyroidism, and genetic factors.[14,25-30] Again, lone AF seems not to exists.[13] Diabetes is present in up to 19% of patients with AF. OSAS and COPD are general cardiovascular risk factors associated with HF, hypertension and AF. The clustering of risk factors included in the metabolic syndrome may exponentially increase the risk of developing AF.[31,32] Patients with reduced renal function are at risk of developing AF, independently from other risk factors.[33,34] AF and CKD share cardiovascular risk factors suggesting a common pathophysiologic substrate.[35] Nevertheless, in the absence of these risk factors and hemodynamic factors there are CKD-associated non-hemodynamic factors that may contribute to the greater burden of AF in those with renal dysfunction.

These include activation of the renin-angiotensin system, stimulant iron-dependent oxidative stress, increased sympathetic activation, chronic inflammation, and stimulation of pro-hypertrophic and pro-fibrogenic factors.[36,37] Different studies used different methods to assess renal function. We assessed in different populations (Framingham, PREVEND, AF-Risk) risk factors for incident AF. In **chapter 2** the association of several renal function measures and incident AF, cardiovascular morbidity and mortality was studied in 8265 participant included in in a community-based prospective cohort included in the PREVEND study.[38] We showed that in this cohort increased albumin excretion, and not estimated glomerular filtration rate (eGFR), was associated with incident AF, even after adjustments for established cardiovascular risk factors. While eGFR is a measurement of kidney function, albumin excretion reflects kidney damage which may be an early sign of kidney disease before kidney function deteriorates. In PREVEND only 5.7% had an estimated GRF <60 ml/min/1.73m^2 while 21.3% had albuminuria. Additionally, besides being associated with incident AF, albumin excretion confers an increased risk of death or cardiovascular events at any level or stage of eGFR.[39] Despite these well-known associations the exact pathophysiological mechanisms linking renal dysfunction to AF risk is unknown and it remains unclear whether CKD precedes AF or is AF induced. More likely, both could be a marker of underlying vascular disease.[40] CKD is now not part of risk schemes in the treatment of AF but may potentially be useful for assessment of the risk for incident AF and AF progression.

Another pathway to assess the risk for incident AF is by means of metabolomics. Metabolomics serve as a reflection of genes' and proteins' functional activity. By this mechanism, it is possible to collect information before the start of a disease phenotype. This happens while straddling the field from genetic sequence to cellular physiology.[41] Previous metabolomics investigations have focused on identifying metabolic pathways responsible for the initiation and maintenance of the arrhythmia in patients with known AF or postoperative AF.[32] Studies have examined circulating biomarkers representing distinct pathophysiological pathways including inflammation (CRP, IL-6), neurohumoral activation (ANP, BNP), oxidative stress and endothelial dysfunction (homocysteine), renin-angiotensin-aldosterone dysfunction (renin and aldosterone), thrombosis (D-dimer, vWF, plasminogen activator inhibitor type 1), and endothelial/vascular dysfunction ([micro]albuminuria), as potential new way to enhance AF risk prediction and to provide new insights into the pathophysiology of AF which may help identify novel therapy targets.[42,43] We assessed metabolomics in **chapter 3,** in which a targeted liquid chromatography-tandem mass spectrometry method was used to identify novel metabolic markers and confirm previously reported metabolites in relation to new-onset AF by investigating metabolite profiles of 2458 ancestry participants from a prospective cohort the Framingham Heart Study.[42,44] We assessed in total 217 metabolomic markers:

several amino acids, organic acids, lipids, and other plasma metabolites to assess the risk for AF. Only fructose, glucose, and/or galactose met our a priori specified Bonferroni corrected level of significance when adjusted for age and gender.[44] None of the metabolites met our corrected level of significance with additional adjustments. This in direct contradiction with the results of the ARIC study which identified bile acids glycolithocolate sulphate and glycocholenate sulphate as markers of increased risk of new-onset AF. The mechanism responsible for the association of these higher levels of bile acids with the risk of AF is unknown. While increased levels of liver enzymes have been associated with AF the identified bile acids in the ARIC study were increased independent from other markers of liver function.[42] The latter stresses the significant role of heterogeneity that often seems to play a role in participant profiles, tissue specific biomarker profiles, and study designs.

The focus has traditionally been to identify biomarkers that can predict AF outcome remote from the 'scene of calamity', i.e. the atria themselves. Blood collected in the atria may be a stronger predictor for AF than blood collected peripherally. When sampled locally in the atria biomarkers – including novel ones with short half-lives or low levels - may be found which are not detectable anymore more peripheral. Lim et al. previously described differences in coagulation markers in patients undergoing pulmonary vein isolation.[45] Prothrombotic activation occurred to a greater extent in the human left atrium compared with systemic circulation.[45] In the Reappraisal of Atrial Fibrillation: Interaction between hypercoagulability, Electrical remodeling, and Vascular Destabilization in the Progression of AF (RACE V) Study (Clinicialtrials.gov Identifier: NCT02726698) acute (time of calamity) and situational (scene of calamity) phenotyping will be performed. Higher risk patients for AF progression and cardiovascular morbidity and mortality may be distinguished from true low-risk patients by applying these different diagnostic approaches. Additionally, it may further elucidate the relationship between local biomarker release triggered by AF versus biomarker assessment obtained from a peripheral vene and differences in biomarker profiles during AF versus during sinus rhythm.

Despite knowledge on all these risk factors it remains difficult to predict the risk of developing AF for individual subjects. There have been many risk prediction models for incident AF with only moderate discriminatory ability and still a substantial proportion of AF risk remains unexplained.[15,46] Vice versa, it remains unclear why some patients never develop AF. It may be that certain genes or other mechanisms could help the body to maintain the normal rhythm and/ or repair itself. Therefore, even if some individuals are exposed to high levels of stressors, their bodies may help them to cope with it , thereby preventing the development of AF.[47]

II. Assessment of remodeling of the atrium

The severity of structural remodeling and subsequent substrate for initiation and progression of AF is time dependent and is influenced by the normal aging process as well as comorbidities and risk factors.[48] Assessing the severity of atrial remodeling is difficult and challenging.[49] This can be done by electrocardiographic parameter or by assessing severity of atrial remodeling by means of echocardiography.[50] The abnormal propagation of atrial impulses may become reflected in electrocardiographic findings, such as PR interval and P wave duration.[51-53] AF also induces ultrastructural changes that modify cardiomyocyte electrophysiology and conduction disturbances.[54] Over the years several electrocardiographic (ECG) parameters have been used to predict incident AF, with P-wave duration and PR-interval being the most studied parameters.[55,56] The risk score for atrial fibrillation from the Framingham Heart Study, as well as long-term follow up in the Framingham study showed that P wave duration was associated with the risk of developing AF making it a possible valuable long-term risk indicator.[15,57] **In chapter 4,** we compared a wide variety of P-wave parameters in patients with and without a history of AF to identify subtle (regional) P-wave conduction disturbances associated with prevalent AF using body surface mapping. We demonstrated that a higher number of peaks in the P-wave, especially in leads located on the back cranial to leads V7-V8, are associated with a history of AF. These P-waves with complex activation patterns might reflect a higher degree of (regional) atrial conduction disturbances and activation delays due to atrial fibrosis and epicardial fat.[58-60]

III. Risk markers for progression of atrial fibrillation.

Progression of AF is in general considered as AF being transformed from paroxysmal episodes to more sustained episodes of AF. This progression is associated with an increased cardiovascular morbidity and mortality.[61,62] The 2016 European Society of Cardiology guidelines for the management of atrial fibrillation distinguish 4 different phases of AF: first diagnosed, paroxysmal, persistent, long-standing persistent and permanent AF.[11] Generally, AF acts as a disease that advances over time to more complex phases of AF **(figure 1)**. This transition is referred to as AF progression. Electrical and structural atrial remodelling create a substrate for AF to initiate and maintain supported by the underlying comorbidities and risk factors. In many patients atrial remodelling starts years before the first clinical manifestation of AF **(figure 1)**. One main driving risk factors of AF progression is atrial size, developed due to underlying comorbidities and risk factors. Larger atria likely reflect more atrial stretch, a known pro-fibrosis phenomenon.[63-65] Progression rates range roughly from 3 to over 30% a year.[12,66,67] Data from the Euro Heart Survey assessed AF progression from paroxysmal, self-terminating to non-self-terminating, persistent AF, and observed a progression rate of 15% in 1-year of follow up.[62,68] In patients without detected comorbidities, the AF progression numbers are in

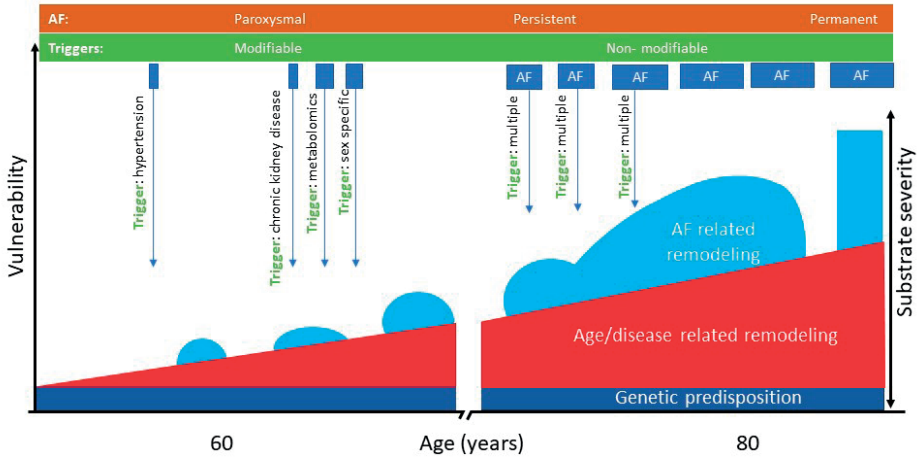

Figure 1. Conceptual framework of atrial fibrillation initiation, maintenance, and progression. Modified with permission of [76].

general lower. A 30-year progression rate of 29% (which implies a very low progression percentage per year) has been described in a young population without demonstrable associated conditions.[69] A recent meta-analysis showed a progression rate of 8.1% per 100 patients years.[67] Clearly more data are needed as type of patients, definition of AF progression, and follow-up duration differed among those trial included in that meta-analysis. **Chapter 6** describes preliminary results of the identification of a risk profile to guide atrial fibrillation (AF-Risk) study (Clinicaltrials.gov identifier NCT01510210). An AF progression rate of 13% was found during 1 year of follow up in patients with paroxysmal AF. Left atrial volume, NT-proBNP and PAI-1 were associated with AF progression in this study and patients who had AF progression had a higher event rate. **Table** 1 shows the differences between patients included in **chapter 5 and 6.** Predicting patients at risk for AF progression is difficult. Patients with limited clinical cardiovascular disease may progress quickly, while others may remain in paroxysmal AF for decades even with more advanced cardiovascular comorbidities.[70] The RACE V trial is currently enrolling patients to study clinical factors and (blood) biomarkers related to progression of AF in patients diagnosed with self-terminating AF with special reference to hypercoagulability. Several coagulation factors, including thrombin, stimulate protease activated receptors that promote pro-fibrotic, pro-inflammatory and vascular alterations which causes structural atrial changes that enhances susceptibility for AF.[71] It subsequently enables the arrhythmia to progress. Gaining insight in the role of hypercoagulability in the progression of AF and incorporating this into AF-progression risk models, might improve risk-stratification.

Table 1. Differences between patients included in chapter 5 (Young AF) and chapter 6 (AF-Risk).

	Chapter 5 (Young AF)	Chapter 6 (AF-Risk)
Mean age (years)	49	60
Men	76%	62%
Predictors for AF progression	Diastolic blood pressure	NT-proBNP
	Left atrial size	Left atrial volume
		Plasminogen activator inhibitor-1
AF progression rate	2.0% per year	13% at 1 year

AF progression is relevant as it has prognostic value. Vanassche et al. reported a higher stroke rate in patients with permanent AF (4.2%), compared to persistent (3.0%) and paroxysmal AF (2.1%).[72] Also in a post-hoc analysis of The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) it was shown that in 11548 patients, paroxysmal AF was associated with lower rates of stroke, thromboembolic events and mortality, compared to patients with persistent AF.[73] This is in accordance with the findings in **chapter 5**. In patients with young-onset AF (patients age 49 years, age of onset 46 years), the incidence of cardiovascular events was higher after AF progressed to permanent AF compared to patients without AF progression. The other way around, is that incident AF in older patients is associated with a high risk of mortality in the first 5 years after the diagnosis, especially due to bleeding events and stroke.[74] Also heart failure was common, however, not being associated with mortality.[74] In Young AF **(Chapter 5)** Overall progression rate was low (2.0%/year) and with only a median of 7.2 years of follow up, prognosis was relatively mild with an incidence rate of cardiovascular events of 2.4%/year. In the AF-risk study **(chapter 6)** we found a 13% progression rate during 1-year follow up in patients with paroxysmal AF. Important predictors in **chapter 5** (where we studied Young AF patients) for AF progression were increased PR interval (an electrical phenomenon reflecting an increased atrial size) and left ventricular hypertrophy. **Chapter 6** furthermore showed that left atrial volume, increased level of NT-proBNP and PAI-1 were associated with AF progression (all reflections of more severe underlying comorbidities).The patients who had progression of AF had a significant higher event rate as compared to those without progression of AF. To what extent these biomarkers will be useful in clinical practice remains uncertain, nevertheless left atrial volume is easily obtained and interpreted for the individual patient. In **chapter 7** a sex specific analysis was performed as women with AF may have worse cardiovascular outcome, but also tend to be older and have more comorbidities.[75] In this chapter we found no sex differences in cardiovascular outcome in our young-onset AF cohort, which can be partially accounted to the relatively low number of events in general due to the young age. Yet, a trend was observed towards a higher event rate in women, especially

after 3 years of follow-up, which could be related to differences in underlying disease in men and women. Future research should therefore be tailored towards individual and sex specific drivers of progression.[75]

FUTURE PERSPECTIVES

The causes of AF are very diverse.[13] AF should be considered as the final product of a wide range of clinical conditions.[65] The exact combination of individual pathophysiological processes contributing to the onset of incident AF and AF progression is likely distinct for the individual patient and also depends on race and sex.[65,75-77] Further understanding of the connection between risk factors and comorbidities for incident and AF progression is required to provide enhanced patient tailored therapy is the different patient categories.[65,76] Many data are available that optimal risk factor management in patients with increased CV risk, like our AF patients, results in better prognosis.[78-80] This was also tested in RACE 3 and it showed that by addressing the underlying conditions and risk factors it is possible to maintain a higher percentage of sinus rhythm at one year.[81] This concept of focused therapy on underlying conditions should be extended in future studies.

In conclusion, early identification of patients who are at risk for incident AF and associated complications is still not perfect. However, early identification of AF and underlying comorbidities with therapy focused not only on the ECG but also on the comorbidities could eventually lead to slower progression of AF and improvement of cardiovascular outcomes.

FIGURE LEGENDS:

Figure 1. A. In patients with a sufficiently large genetic predisposition, AF onset may occur at a relatively young age. AF-induced remodeling helps to maintain the arrhythmia, as well as promoting AF progression. B. In most patients, the genetic substrate alone does not provide sufficient susceptibility for AF. Additional disease-related remodeling may increase vulnerability and allow the initiation of paroxysmal AF episodes. Over time, some patients with paroxysmal AF may progress to longer-lasting persistent AF forms. C. Because of the composition of substrate and trigger, some patients have a first AF episode lasting >7 d and may progress to permanent AF due either to progression of underlying disease or to a medical decision to leave the patient in AF. (Note that for convenience the time scale for AF episodes, in grey, is expanded compared with the lower axis providing a sense of lifetime time course.) Adapted with permission from Heijman et al.[76]

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NEDERLANDSE SAMENVATTING (POPULAR DUTCH SUMMARY)

Van alle hartritmestoornissen is boezemfibrilleren de meest voorkomende hartritmestoornis. De verwachting is dat boezemfibrilleren alleen maar zal toenemen in de komende jaren. Dit komt deels omdat de bevolking ouder wordt en dat de leefstijl aan het veranderen is. Boezemfibrilleren gaat gepaard met verschillende complicaties zoals herseninfarcten, hartfalen, dementie, mortaliteit, verminderde kwaliteit van leven en hogere ziektekosten. In de afgelopen jaren is het duidelijk geworden dat de behandeling van risicofactoren zoals hypertensie, ischemie en hartfalen zeer belangrijk is in de behandeling van boezemfibrilleren. Bij sommige patiënten is het na het starten van de behandeling het lastig om sinusritme, het normale hartritme, voor lange tijd te behouden. Daarnaast zien we bij een behoorlijk aantal patiënten progressie (verergering) van het boezemfibrilleren. Er is meer inzicht nodig in het remodeleringsproces van de boezems om de behandeling van boezemfibrilleren te kunnen verbeteren. De afgelopen jaren zijn er steeds meer aanwijzingen dat de remodelering in de boezems vaker te maken heeft met onderliggende vaatziekten. Het is daarom van essentieel belang om de pathofysiologische factoren die een rol spelen bij de vaatproblemen om die goed in kaart te brengen met als doel om de behandeling bij boezemfibrilleren beter te kunnen sturen. Daarbij is het ook belangrijk om de factoren bij progressie van boezemfibrilleren beter te begrijpen om de behandeling hierop aan te kunnen passen.

Het doel van dit proefschrift is om te zoeken naar risicofactoren bij nieuw ontstaan boezemfibrilleren en naar factoren die bijdragen aan progressie van boezemfibrilleren. Tevens beoordelen we met nieuwe niet-invasieve technieken de ernst van het boezemfibrilleren.

In **hoofdstuk 1** werd gestart met een algemene introductie op het thema van dit proefschrift.

In **hoofdstuk 2** hebben we uit een groot cohortstudie, de PREVEND-studie, gekeken naar de relatie tussen renale dysfunctie met boezemfibrilleren en cardiovasculaire morbiditeit en mortaliteit. Bij dit onderzoek was duidelijk dat vasculaire schade gemeten door albumine excretie in de urine geassocieerd is met nieuw ontstaan boezemfibrilleren. Dit was onafhankelijk van bestaande cardiovasculaire risicofactoren. Veder was de cardiovasculaire mortaliteit onafhankelijk van het incident boezemfibrilleren. Dit laat zien dat onderliggend vaatprobleem een belangrijke rol speelt bij het ontstaan van boezemfibrilleren.

In **hoofdstuk 3** hebben we uitgebreid gekeken naar verschillende metabolieten (biomarkers) in het bloed en of ze het ontstaan van boezemfibrilleren kunnen voorspellen. Hiervoor is een populatie gebruikt van 2458 gezonde mensen. In totaal hebben we 217 metabolieten die in het bloed voorkomen onderzocht. Van geen enkele metaboliet kon een relatie worden aangetoond met nieuw boezemfibrilleren.

In **hoofdstuk 4** hebben we gekeken naar verschillende karakteristieken van de p-golf bij patiënten die kort bekend zijn met boezemfibrilleren. We hebben dit vergeleken met een groep patiënten die geen boezemfibrilleren hebben, maar wel risicofactoren voor het ontwikkelen van boezemfibrilleren hebben (bijvoorbeeld diabetes). We zien geen verschil in de PR-tijd, iets wat gemakkelijk met een ECG gemeten kan worden. Als je met meerdere electroden (door middel van body surface mapping) gaat kijken naar de P-golf dan zie je dat de groep die bekend is met boezemfibrilleren meer pieken heeft in de p-golf en een hogere P-wave terminal force heeft dan de groep zonder boezemfibrilleren.

In **hoofdstuk 5** hebben wij gekeken naar de progressie van boezemfibrilleren. Hiervoor hebben we een populatie van jonge patiënten met nieuw boezemfibrilleren gevolgd. Gedurende 7 jaar heeft 11% van de populatie progressie laten zien. Er was geen verschil in progressie van boezemfibrilleren te zien tussen patiënten die medicatie kregen of ablatie ondergingen. Diastolisch bloeddruk en linker atrium grootte waren de bepalende factoren voor progressie van boezemfibrilleren. Patiënten met progressie van boezemfibrilleren hadden per jaar een hogere kans op cardiovasculair events.

In **hoofdstuk 6** hebben we in de AF-RISK-studie (cohortstudie) gekeken naar de klinische, echocardiografisch en biomarkers voor de progressie van boezemfibrilleren. Patiënten met nieuw boezemfibrilleren werden in de studie gevolgd. Progressie van boezemfibrilleren binnen 1 jaar gebeurd in 13% van de populatie. Een grotere linker atrium volume, verhoogde cardiale stressmakers (NT-proBNP) en een lager fibrinolyse biomarker (PAI-1) waarde waren geassocieerd met voor progressie van boezemfibrilleren. Tot slot, in **hoofdstuk 7** onderzochten we of er verschil zit tussen mannen en vrouwen bij de progressie van boezemfibrilleren. We hebben hiervoor een populatie onderzoek gedaan en de patiënten vervolgd in de tijd. Wij observeerden wel een verschil in klinisch profiel tussen de geslachten, maar er is geen verschil in de mate van progressie van boezemfibrilleren.

Concluderend beschrijven wij in dit proefschrift nieuwe risicofactoren bij nieuw ontstaan boezemfibrilleren. Tevens beoordeelden we met nieuwe niet-invasieve technieken afwijkingen aan de p-golf van patiënten met boezemfibrilleren. Daarnaast hebben we

verschillen in factoren die bijdragen aan de progressie van boezemfibrilleren in zowel mannen als vrouwen onderzocht.

DANKWOORD

Het is zo ver en het promotietraject wordt afgesloten. Gedurende dit promotietraject werd ik als promovendus altijd met raad en daad door een aantal mensen bijgestaan. Een aantal mensen wil ik daarom graag persoonlijk bedanken.

Allereerst wil ik mijn promotor prof. dr. I.C. van Gelder bedanken: beste Isabelle, ik wil je bedanken dat ik de mogelijkheid heb gehad om een mooi onderzoek te mogen verrichten bij jou en je team. Daarnaast voor je begeleiding, je kritische blik op de artikelen en alle onderwijsmomenten. Verder wil ik je ook hartelijk bedanken voor de mogelijkheid die ik heb gehad om bij mijn ouders te kunnen zijn in de moeilijke periode rond de ziekte van mijn vader. Je begrip en medegevoel hiervoor waarderen ik en mijn familie heel erg van je.

Mijn tweede promotor, prof. dr. M. Rienstra. Beste Michiel, bedankt voor je steun, je commentaren, je begeleiding, je kritische blik en je adviezen gedurende mijn promotietraject. Je kwaliteiten als promotor hebben mij de laatste jaren zeker gevormd.

Mijn co-promoter, dr. B.A. Mulder. Beste Bart, jij bent er vanaf het begin bij geweest en nu ook weer aan het einde. Samen eerst in het triade en nu in de Academiezaal. Ik wil je bedanken voor het begeleiden bij de laatste hoofdstukken en je blijvende motivatie om er iets moois van te maken.

Ik wil de leden van de beoordelingscommissie hartelijk bedanken voor het lezen van dit proefschrift: prof. dr. A. A. Voors, prof. dr. L.V.A. Boersma, prof. dr. S.J.L. Bakker.

Mijn paranimfen, Bastiaan en Meelad. Bedankt dat jullie mijn paranimfen willen zijn. Een promovendus heeft altijd reflectie nodig en wij hebben vaak goede gesprekken over vele onderwerpen gehad. Ik waardeer het dan ook heel erg om jullie als collega te hebben.

Voor de AF-Risk studie wil ik een aantal mensen in het bijzonder bedanken, want zonder hun hulp was het zeker niet mogelijk om deze studie te realiseren en dit proefschrift te schrijven. Ik wil graag mijn collega's in Groningen: Marcelle, Hessel, Rob, Ismael, Rosanne, Marjolein, Anne, Ruben, Jenny en Meelad bedanken voor hun medewerking aan deze studie. Het screenen, includeren en vervolgen van de patiënten is erg belangrijk geweest voor het succes van de studie. De collega's promovendi in Maastricht (Theo, Ionne en Elton) wil ik hierbij ook graag bedanken voor de hulp bij de studie. .

Ik wil enkele collega's speciaal bedanken voor hun geweldige werk en steun aan dit project en dat zijn: Anne, Ruben, Mariëlle en Michiel. Ruben en Mariëlle wil ik ook graag bedanken voor de hulp bij het schrijven van de artikelen. Dankzij jullie steun hebben we mooie artikelen kunnen schrijven van de AF-risk data. Verder wil ik de verpleegkundigen van cardioresearch bedanken voor de fijne samenwerking. Met name ook voor alle praktische zaken rond het verrichten van onderzoek, en dan met name Carlien, Maaike, Greetje, Tialda. Verder ook Bernard, Anja, Carla, Carolien, Geert, Karin, Margriet, Peter, Saphirah en Trienke. Op de poli cardiologie wil ik alle secretaresse bedanken die zich druk bezighielden met het inplannen van alle studie patiënten op de poli, evenals alle medewerkers van de Holterkamer (alle eventrecorder!) en Jaap Haaksma.

Daarnaast wil ik natuurlijk Audrey en Alma bedanken voor hun hulp tijdens mijn promotietraject en alle vragen die hiermee gepaard gaan.

Voor de PREVEND-studie wil ik graag Michiel bedanken voor de mogelijkheid die ik heb gekregen om mee te werken aan dit succesvolle project. Verder wil ik Rob bedanken voor het verzamelen van alle ECG's (een enorme klus!). Mijn dank gaat ook aan Bastiaan Geelhoed voor zijn statistische expertise die van onschatbare waarde is.

De collega's van Framingham Heart Study wil ik graag bedanken voor hun zeer fijne samenwerking de afgelopen periode wat in een mooi artikel is geresulteerd. Hierbij wil ik met name Darae Ko en Emelia Benjamin hartelijk bedanken.

Verder wil ik alle mede promovendi van de afgelopen jaren bedanken voor hun collegialiteit en gezelligheid de afgelopen jaren, en dat zijn: Rob, Ismael, Hessel, Marjolein, Rosanne, Anne, Ruben, Meelad, Bastiaan, Thomas, Ali,Frank, Nicolas, Vincent, Chris, Wouter, Ijsbrand, Marlies, Ymkje, Karim, Renee, Suzan, Imke, Arjen, Licette, Matia, Sven, Hanna, Eline, Binjam en alle studenten die afgelopen jaren hun wetenschappelijke stage bij ons hebben gedaan.

Mijn familie, mijn moeder en 2 zussen, wil ik ook hartelijk bedanken voor hun interesse en steun in deze periode. Pap, ik mis je nog elke dag. Bedankt voor je motiverende woorden toen je nog bij ons was.

Mijn lieve vrouw Joana, bedankt voor je steun, begrip en je onvoorwaardelijke liefde. Het was soms wat zwaar voor je de afgelopen periode. Ik hoop nog veel mooie dingen met je in de toekomst te beleven en dat we samen onze plannen kunnen realiseren.

Lieve Ariana en Elyshah, mijn prinsesjes. Wat fijn om jullie als dochter te hebben. Het is vaak een uitdaging geweest in de avond om wat werk te verrichten, want jullie willen Papi altijd in de buurt hebben als jullie in bed liggen. Die momenten heb ik vaak gebruikt om rustig over nieuwe ideeën na te denken. Jullie aanwezigheid vullen mijn hart met heel veel vreugde en jullie geven mij heel veel energie.

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BIOGRAPHY

Ernaldo Gonsalvis Marcos was born the 25th of March 1983 on a beautiful Caribbean island with one of the best beaches on the world, Curacao. (*http://www.caribbean360.com/travel/two-caribbean-beaches-named-among-25-best-world*).

After finishing his pre-university secondary school (Maria Immaculata Lyceum) at Curacao, he started the Medical school at University of Groningen. As a medical doctor he became involved in professor van Gelder's research group in Groningen and he became a PhD fellow under supervision of Prof.dr Isabelle van Gelder and dr.Michiel Rienstra focusing on the AF-risk study. The results of his PhD are presented in this thesis.

Despite his interest in cardiology, he found that he would like to practice medicine in a more generalistic field. Therefore, he is now doing his specialism in gerontology.