Risk factors for atrial fibrillation incidence and progression
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Chapter 8

Discussion and future perspectives
DISCUSSION

The general aim of this thesis was to uncover associations of underlying diseases and triggers with incident AF and AF progression in contemporary AF populations. In Chapter 2 we found that the incidence of AF in a contemporary cohort in the Netherlands was 3.3 per 1000 person years which is comparable to data of older, mainly North American studies (3-19 per 1000 person years). (1) Of interest, obesity next to well-established risk factors, nowadays has become a major risk factor for incident AF. We now confirmed the association of incident AF with cardiovascular events, although overall event rates were lower than in older studies. In Chapter 3, we discussed the findings by Soliman and colleagues who found that AF was associated with a 63% increase in risk of myocardial infarction (non-ST elevation myocardial infarction). (2) These findings underscore the need for a detailed search for underlying risk factors for AF, such as vascular disease. In Chapter 4 we found that young AF patients more often were men, and had less hypertension and diastolic dysfunction than older patients. (3) However a familial component was more frequent in young patients. Lone AF was very rare, even in these young AF patients. In Chapters 5 and 6 patients with symptomatic persistent or permanent AF, respectively included in the RACE and RACE II studies were more often women and had more cardiac disease. (4,5) Symptoms were associated with worse cardiovascular outcomes.

As we demonstrated, obesity is becoming increasingly important as an AF risk factor, and may lead to atrial remodeling and hence worse outcome. In Chapter 7 we studied the association between obesity and atrial remodeling. We showed that in young patients with recent onset AF, obesity is associated with impaired left atrial function, without differences in atrial dilatation. (6) Our results suggest that left atrial dysfunction may occur before dilatation occurs, and may hence be an early prognostic marker.

PART I: RISK FACTORS FOR INCIDENT AF

AF incidence.

Prospects report that with the ageing population AF will affect 17.9 million people in Europe by the year 2016, and 6-12 million people in North-America by the year 2050. (7-10) In Chapter 2, we found that the overall incidence rate of AF in a contemporary population in the North of Netherlands was 3.3 per 1000 person years. (1,11) As reported in other cohorts AF incidence was higher in men than in women, and there was a strong increase with age. (8,9,12-16)

The incidence was lower than observed in the Rotterdam Study, also a study from the Netherlands, where the overall incidence rate of AF was 9.9 per 1000 person years.
This may relate to age differences of included individuals (in Rotterdam Study mean age 69 years, in PREVEND mean 49 years); regional lifestyle related differences between the relatively large city of Rotterdam and the smaller city of Groningen; earlier start of the Rotterdam study (inclusion 1990-1993, follow-up until 2000) than PREVEND (inclusion 1997-1998, follow-up until 2009); and the fact that the Rotterdam Study also used data from general practitioners, which may have yielded additional AF cases, especially elderly.

Likewise, populations describing AF incidence outside of the Netherlands were also of older age than the PREVEND population (mean age 55-73 years). Like the Rotterdam Study, most of these studies followed their patients to the 21st century, except for the Framingham Heart Study (inclusion 1948-1971, follow-up until 2008), and the Women's Health Initiative (inclusion 1994-1998, follow-up until 2007).

Study visits at an outpatient clinic, as performed in our study, may provide better detection of AF and comorbidities than studies that rely solely on other means of AF detection, such as hospital visits or discharge codes. Nevertheless incidence rates found in cohort studies using other means of AF detection and follow-up are often similar (2-12 per 1000 person years) to those found in studies performing study visits (3-19 per 1000 person years).

Continuously improvements are made in the treatment of cardiovascular risk factors for AF including hypertension, coronary heart disease, and heart failure. Whereas improved treatment of cardiovascular diseases may reduce the risk of incident AF, on the other hand improved life expectancy and increasing prevalence of obesity and other lifestyle changes may increase the incidence of AF. Risk factor management adapted to the changes in underlying disease may possibly improve prevention of AF.

**AF risk factors.**

Risk factors for incident AF are changing. Most data on comorbidities associated with AF in the general population have been obtained from old American cohorts starting their inclusion before the introduction of contemporary treatments for myocardial infarction, hypertension and heart failure, and increasing availability of diagnostic tests, and changing lifestyle. Recent data show that while the influence of traditional risk factors on incident AF are decreasing, obesity and, possibly as a consequence, diabetes mellitus are gaining significance over the past decades. In Chapter 2 we found similar associations of traditional risk factors with incident AF as compared with previous data.

Next to these well-established risk factors, obesity was an important contributor to AF risk. Obesity often co-exists with other cardiovascular risk factors and diseases (e.g. diabetes, metabolic syndrome), and the sleep apnea syndrome. However, obesity by itself
Discussion and future perspectives

may also induce AF (Figure 1). It has been shown that epicardial fat may directly induce atrial fibrosis, and may even infiltrate the atrial myocardium. Importantly, obesity is a modifiable risk factor, and recently it was shown that strict weight reduction significantly decreased the AF burden and atrial remodeling. In Chapter 2 the population attributable risk of obesity provided an indication that 9% reduction of incident AF could be achieved if the risk factor obesity could be completely removed from the population.

Bidirectional relation of atrial fibrillation and myocardial infarction.

It is well known that myocardial infarction increases the risk of incident AF. Conversely, recent studies suggest that AF is also associated with incident myocardial infarction, as was discussed in Chapter 3. The most recent of these studies described the association of AF with myocardial infarction in the Atherosclerosis Risk in Communities (ARIC) Study. AF was associated with a 63% increase in risk of myocardial infarction (predominantly NSTEMI) after multivariable adjustments. The analyses in other cohorts by the same authors did not elaborate on the type of myocardial infarction (i.e. NSTEMI vs. STEMI). As was observed in the analyses in other AF cohorts, women had higher risks of developing myocardial infarction, than men. As discussed in Chapter 3 there may be multiple explanations for these findings. These include use of high-sensitive troponin assays in recent years, which have improved detection of minimal myocardial damage. Myocardial infarction, especially NSTEMI, is therefore diagnosed more often than before, and may even represent small myocardial damage as result of AF itself rather than result of atherosclerosis and significant coronary artery disease. Myocardial infarction may also be caused by AF through increased heart rate and increased oxygen demand, sympathetic activation, endothelial dysfunction, and pro-inflammatory and pro-thrombotic effects. Although AF and myocardial infarction share many risk factors, the association of AF and myocardial infarction may reflect on a final common pathway of underlying vascular disease.

Mechanistic ideas on the relation of AF and stroke may also be used to support this notion. A recent study among 187 patients with ischemic stroke during continuous monitoring by implanted devices showed that longer episodes of AF (≥5 hours) were temporally linked to the occurrence of stroke. This fits Virchow’s triad with low flow, increased plasma clotting factors and atrial wall abnormalities as a cause of thromboembolism. On the other hand data from 51 patients from the ASymptomatic atrial fibrillation and Stroke Evaluation in pacemaker patients and the atrial fibrillation Reduction atrial pacing Trial (ASSERT) showed, in contrast, a temporal disconnect between stroke and continuously monitored occurrence of AF episodes >6 minutes. Only 4 patients had longer lasting episodes (hours to days) within a 30 day period before the stroke, which may have caused the results to be statistically underpowered. Of note, atrial high rate
episodes >6 minutes were associated with stroke in the ASSERT study.\(^{(40)}\) Results from these small studies should be viewed as hypothesis generating. Possibly, a temporal link between AF and stroke is only established after a threshold of arrhythmia duration, while a non-temporal association is caused by underlying vascular disease. This suggests that stroke, and probably also myocardial infarction, and AF have pathophysiological mechanisms in common. This is also reflected by the CHA\(_2\)DS\(_2\)-VASc score, the risk of

![Figure 1](image_url)

Figure 1. Conceptual figure of the association of typical AF related symptoms (often palpitations) and comorbidity related symptoms (often dyspnea or fatigue) with increasing AF chronicity, atrial remodeling, numbers of AF risk factors and age. No association exists between AF related symptoms and outcome. However comorbidity related symptoms are associated with adverse outcomes. Since AF-related symptoms and comorbidity related symptoms may overlap, clinicians should be aware of changes or increases of symptoms in individual patients. In general, women have more symptoms and, at older age, are at increased risk of adverse outcomes than men.
stroke depends on the number of cardiovascular conditions, and is higher in women at age >65 years.\(^{(41)}\)

It has been speculated that older women with AF are at increased risk of stroke, through increased pulse pressure and worse blood pressure regulation compared to men, which is associated with endothelial dysfunction.\(^{(42,43)}\) Pro-thrombotic factors have also been shown to be higher in women with AF than men.\(^{(42,44)}\) Given the higher incidence of myocardial infarction in women with AF in the studies of Soliman et al.\(^{(34,35)}\) it may be possible that mechanisms increasing the risk of stroke in women, may also increase the risk of myocardial infarction.\(^{(42,44)}\)

**Age differences in prevalence of AF risk factors.**

In *Chapter 4* we demonstrated that compared to older patients, young AF patients were more often men, being taller, with less often hypertension, lower NT-proBNP and less signs of left atrial and ventricular remodeling and diastolic dysfunction.\(^{(3)}\) Young patients had a higher prevalence of familial AF and cardiomyopathies. Compared to controls, young AF patients more often had hypertension and young AF men were taller. Obesity was highly prevalent in both age groups.

Male sex is a well established risk factor for incident AF, independent of associated comorbidities such as coronary heart disease.\(^{(22)}\) The higher prevalence of men found in the young AF group of *Chapter 4* is consistent with data from population based studies, where younger AF patients were predominantly men.\(^{(3,8,17,45)}\) This difference has been described to diminish with increasing age of the population.\(^{(8,17,45)}\) Possibly, taller stature in men may contribute to the observed differences in sex distributions.\(^{(22)}\) Anatomically larger atria are suggested as the main reason for an increased risk of AF in tall people. Reported risk increases for each 10 cm increase in height range from 1.3 to 1.6 fold.\(^{(13,14,46-50)}\) This may relate to the fact that larger atria can host more reentry circuits.\(^{(51)}\) One study evaluated lean body mass using dual-energy X-ray absorptiometry, which was found to increase AF risk in post-menopausal women, independent of fat mass.\(^{(52)}\) Data on left atrial size was not available in that study. The authors speculate that high body size (which is related to tall stature) may increase AF risk through effects other than adiposity, like larger atria, genetic predisposition or hormonal effects related to skeletal muscle.\(^{(52)}\)

Differences in cardiac gene expression or influences of sex hormones between men and women could make men prone to AF at younger age, or alternatively protect young women from AF at younger age.\(^{(53,54)}\) It has been described that electrophysiological differences exist between premenopausal women, post-menopausal women and age-matched men, that may possibly protect young women against AF through influence of sex hormones.\(^{(54)}\)
Hypertension is one of the most prevalent risk factors for AF, both in men and in women, and its prevalence increases with age. (8,16,17,22) In Chapter 4 the prevalence of hypertension in young AF patients was 41%, which was higher than in controls, but lower than in older patients, suggesting that even in young patients hypertension plays a major role in AF development. (3) Hypertension may lead to left ventricular hypertrophy and diastolic dysfunction, both of which have also been identified as AF risk factors. (22,55) LV hypertrophy and LV remodeling were present in 20% of young patients versus 40% in older patients, in conjunction with the prevalence of hypertension in both age groups.

Young patients also had better diastolic function, lower indexed atrial volumes, better atrial function and lower NTproBNP. The younger age itself and the lower prevalence of hypertension in young patients are the most likely contributors to these findings. (55) Still, atrial reservoir function was significantly impaired compared to controls in the literature suggesting the presence of atrial remodeling. (56,57) Both diastolic dysfunction and atrial remodeling are well known risk factors for AF. (22)

We also described that young onset AF is more often accompanied with a family history of AF and cardiomyopathies, than AF at older age. Previous studies have shown that family history of AF is associated with increased risk of developing AF, but also with younger age of AF onset. (58,59) Several genetic variants or mutations associated with AF have been identified. (60) These may directly lead to AF, but may also modulate the risk of developing AF through AF risk factors or cardiovascular disease. (61) Overlap exists between genetic variants and mutations associated with AF, and those found in cardiomyopathies or electrical cardiac diseases. (60,62,63) Young onset AF may be determined by genetic factors in greater part than in older AF patients, which is related to a higher prevalence of cardiomyopathies.

Genetic predisposition also seems to be involved in differences in AF risk across different ethnicities. Black individuals have more cardiovascular risk factors than white persons. (64) Nevertheless, white persons are at increased risk of AF after correction for other cardiovascular risk factors, in several populations worldwide. (13,14,50,64-66) In the ASSERT study even the unadjusted AF incidence rates were lower in blacks. (67) Interestingly, in African Americans, every 10% increase in European ancestry was associated with a 17% increase in the risk of incident AF. (64) Outcomes for African Americans with AF, however, are worse, possibly because of differences in lifestyle, higher prevalence of cardiovascular risk factors and disparities in AF treatment. (20) These differences between black and white Americans may also underlie the higher incidence of myocardial infarction after the diagnosis of atrial fibrillation in black individuals. African Americans were also shown to have the highest risk of in-hospital mortality during AF hospitalizations among all ethnic groups. (68) More research is needed to enable specific AF prediction in different ethnicities.
The prevalence of lone AF was very low in Chapter 4, even among young AF patients (2%). It is still often believed that AF in young patients is accompanied with few, if any concomitant cardiovascular disease. As knowledge about new risk factors for AF increases, the question is raised whether lone AF may exist at all. Systematic and thorough evaluation of young, seemingly ‘lone’, AF patients is therefore essential.

PART II: RISK FACTORS FOR AF PROGRESSION

Prediction models.

AF progression is a continuum of atrial remodeling, increased AF chronicity and occurrence of cardiovascular events. Underlying disease and comorbidities including age, sex, hypertension, heart failure previous stroke and vascular disease are the most important determinants of AF progression and AF related outcomes. Risk prediction models that use these risk factors to estimate an individual's risk of morbidity and mortality are important to guide AF therapy. The most important adverse cardiovascular outcome of atrial fibrillation is stroke. Several risk scores have been developed, most widely used are the CHADS2 and CHA2DS2-VASc scores. Although these scores are developed specifically for stroke, C-statistics are <0.70, meaning that a large proportion of the risk remains unexplained. Efforts are continuously being made to improve AF risk prediction, which has lead to a great variety of risk prediction schemes.

The CHA2DS2-VASc score was shown to have comparable prediction of high stroke risk as other stroke risk schemes, including the CHA2DS2, 8th American College of Chest Physician Guidelines and National Institute for Health and Clinical Excellence. The strength of the CHA2DS2-VASc score, however, lies in better identification of patients at low risk for stroke, as compared to the CHADS2 and other risk scores, enabling improved selection of patients requiring oral anticoagulation. Other risk scores that have not yet reached daily clinical practice due to limited validation or less practical applicability are the R2CHADS2, QStroke and Atria Stroke Risk scores. Still, adequate identification of patients requiring oral anticoagulation remains challenging, since patients treated with oral anticoagulation may be at risk of bleeding.

Apart from stroke prediction schemes, scores assessing the risk of AF progression may further improve risk stratification. Progression from paroxysmal AF to permanent AF may occur with ageing and increasing numbers of concomitant conditions (and hence increasing CHADS2 and CHA2DS2-VASc scores) and is therefore associated with cardiovascular outcomes. The HATCH scoring system, calculates 1 point for hypertension, age ≥75 years, chronic obstructive pulmonary disease, and 2 points for transient ischemic attack or stroke, and heart failure, allowing instant classifica-
tion of the risk of progression to persistent or permanent AF in patients with paroxysmal AF.\(^{(71)}\) The studies that defined AF progression using clinical definitions (i.e. AF progression as assessed by the treating cardiologist) found reasonable predictive capabilities of the HATCH score.\((\text{Table 1})\) Interestingly, a recent study among 321 patients with dual-chamber pacemakers found that only a minority of patients showed progression of AF burden during a mean of 3 years of follow-up with continuous monitoring.\((88)\) Only a diagnosis of heart failure, not the HATCH score, was predictive of AF progression.\((88)\) Of course, results from a population with indication for dual-chamber pacemaker may not be generalized to the overall AF population. Possibly increased availability of continuous monitoring tools may soon help to improve prediction of AF progression in general AF populations.

**Table 1.** Studies describing prediction of AF progression by HATCH score.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Setting</th>
<th>AF progression assessment</th>
<th>% AF progression</th>
<th>Mean HATCH</th>
<th>HATCH predictive ability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugihara et al. (2015)(88)</td>
<td>323</td>
<td>Dual-chamber pacemaker</td>
<td>Continuous monitoring</td>
<td>0.34% per year AF burden increase (3y FU)</td>
<td>1.7</td>
<td>NS</td>
</tr>
<tr>
<td>Chen et al. (2015)(149)</td>
<td>216</td>
<td>Succesfull atrial flutter ablation</td>
<td>24h Holter 3 and 6 mo, every 6 mo therafter</td>
<td>39% new onset AF after AFL ablation (2.5y FU)</td>
<td>2 in patients with AF 1 without AF</td>
<td>AUC 0.743</td>
</tr>
<tr>
<td>Potpara et al. (2012) (150)</td>
<td>242</td>
<td>Hospital based registry</td>
<td>Clinician</td>
<td>27% progression to permanent AF (assessed by clinician, 12y FU)</td>
<td>0.78</td>
<td>C-statistic 0.6</td>
</tr>
<tr>
<td>De Vos et al. (2010)(71)</td>
<td>1219</td>
<td>Hospital-based registry</td>
<td>Clinician</td>
<td>15% paroxysmal to persistent / permanent (assessed by clinician, 1y FU)</td>
<td>NA</td>
<td>AUC 0.675</td>
</tr>
</tbody>
</table>

Abbreviations: AF=atrial fibrillation; AUC=area under the curve; FU=follow-up; HATCH: risk score for AF progression, calculates 1 point for hypertension, age \(\geq\) 75 years, chronic obstructive pulmonary disease, and 2 points for transient ischemic attack or stroke, and heart failure; N=number of patients; NA=not available; NS not significant; P=population; y=year.

**Cardiovascular outcomes in the contemporary population.**

In Chapter 2 we found that incident AF was associated with a 2-fold increase of cardiovascular events including stroke, a 5-fold increased heart failure risk, and a 2-fold increased risk of all cause mortality, confirming the association of AF with cardiovascular events in a contemporary population.\((1)\) Although the risks of events associated with AF were comparable to those found in other studies, overall event rates in the present study were lower than in older studies.\((89,90)\) Compared to the Framingham Heart
Study, incidence of heart failure following incident AF was relatively low (18 vs. 33-43 per 1000 person years) (89), as well as mortality (30 vs. 51-74 per 1000 person years).(91) There are several reasons why morbidity and mortality associated with AF was lower in our population. First, treatment of AF has significantly changed during the last decades. The most important change has been use of oral anticoagulation in individuals at risk for stroke, independent of preservation of sinus rhythm.(21) In addition improvements in oral anticoagulation have been made, further reducing the risk of stroke.(92-94) Second, beside anticoagulation use, treatment of other cardiovascular disease has also improved, which may have caused the further decline of event rates. For example fewer cardiovascular events occurred during follow-up of the RACE II study (95) (2005-2009) than in the RACE study (96) (1998-2001; Figure 3).

Although stroke prevention still is the cornerstone for improving AF related outcomes, the risk of heart failure and all cause mortality associated with AF should also be emphasized.(90)

AF and heart failure are strongly interrelated and have multiple risk factors in common. (22,72) In Chapter 2 incident AF was associated with both heart failure with reduced ejection fraction (HFrEF) and with preserved ejection fraction (HFpEF).(1) Limited data exists on the association of AF with the both subtypes of heart failure. Recent data suggest that men are at highest risk of developing HFrEF, while women are more likely to develop HFpEF, at older age than men.(97-99) This is most likely caused by differences in underlying disease such as more coronary heart disease in men and more hypertensive heart disease in older women.(97-99) A recent analysis in the PRVEND population showed that AF prevalent at baseline increased risk of HFpEF in women, but not in men. (98) On the other hand, the prevalence of HFrEF seems to decline, in part due to the excellent treatment of acute myocardial infarction.(100) The diagnosis of HFpEF in patients with AF, however, remains cumbersome,(101) possibly leading to underestimation of its incidence and prevalence. Overlap between (yet undiagnosed) HFpEF and AF symptoms may exist, predominantly in women, possibly leading to adverse outcomes because of undertreatment.

Although anticoagulation until now is the only AF treatment that has proven to reduce mortality (through reduction of thromboembolism), efforts are being made to find additional means of improving AF related survival. Although effects on mortality have not yet been published, strategies aiming on weight loss and improvement of cardiorespiratory fitness have shown promising results through reduction of AF burden and reverse atrial and ventricular remodeling (Figure 4).(27,30,32,102) Trials applying early contemporary rhythm control strategies that may improve cardiovascular outcomes are underway, and the results are eagerly awaited.(103,104) Next to stroke prevention and lifestyle changes, focus on prevention of heart failure and mortality in individuals with AF is important in the years to come, to further improve prognosis of those with AF.
Figure 2. Prevalence of comorbidities according to different clinical AF types in the AF-NET registry (A), Euro Heart Survey (B), EORP-AF registry (C), and RealiseAF registry (D). The prevalence of comorbidities is greater in patients with persistent and permanent AF forms than in paroxysmal AF. *P<0.05
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Symptoms as a marker of cardiovascular outcome in AF.

In Chapter 5 we analyzed the clinical profile and outcome related to symptomatic persistent AF in the RACE study (Figure 1).(4) In Chapter 6, we investigated the clinical profile and outcome related to tertiles of the AF Severity Scale,(5) a validated AF symptom score in patients with permanent AF included in RACE II.(105) We showed that symptomatic persistent AF patients in the RACE study, and patients with permanent AF with higher AF symptom severity in RACE II, were more often women and had more severe cardiovascular disease, predominantly heart failure. Symptomatic AF or higher AF severity was associated with worse cardiovascular outcomes (Figure 1). This was driven by more heart failure hospitalizations in both studies, and adverse effects of antiarrhythmic and rate control drugs in the RACE study. No difference in the occurrence of thromboembolic complications was observed.

Symptoms and AF temporal patterns.

In general, patients with longer AF episodes (persistent and permanent AF) experience the least (overt) symptoms, while short-lasting paroxysmal AF episodes are most symptomatic (Figure 1; Figure 3 of Chapter 1).(86,106-110) Also, while dyspnea and fatigue are reported more by patients with longer more persistent AF episodes, palpitations are most common in patients with short, paroxysmal episodes (Figure 1; Figure 3 of Chapter 1). In Chapters 5 and 6 we found that presence of symptoms in persistent AF, and increased symptom severity in permanent AF may be related to more severe underlying heart disease, predominantly heart failure, and worse cardiovascular outcomes.(4,5) A similar study was performed in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) population.(111,112) In AFFIRM, 60% of patients had paroxysmal AF, the thers had persistent or permanent AF. It was shown that symptomatic AF was associated with more severe cardiac disease, but relations with outcome were not significant.(111) Given the distinct relation of symptoms with different AF temporal patterns, the relation of symptoms with underlying disease, and therefore outcome may vary in different populations. Paroxysmal AF patients in general are highly symptomatic but often have less severe underlying disease.(86,106,113,114)(Figures 1 and 2) Since 60% of the AFFIRM population consists of paroxysmal AF patients, associations of symptoms with outcome may have been diluted.(4,111)

Several analyses investigating the association of AF symptoms with underlying disease and outcome were published from hospital-based AF registries.(108-110) Similar to AFFIRM, the majority of patients included in these studies had paroxysmal AF.(108-110) Symptomatic patients had more paroxysmal AF, younger age, were more often women, less often had underlying heart disease, and hence no relation of symptoms with worse outcome was found.(108-110) A recent meta-analysis found similar results.(115) However differences in AF temporal patterns between populations were
not adjusted for.(115) In paroxysmal AF, symptoms may be driven by the arrhythmia itself rather than by the underlying heart disease (AF related symptoms, Figure 1).(86) Patients with persistent or permanent AF in general have less symptoms. However, a high symptom burden within persistent or permanent AF patients may point to more severe and possibly undertreated comorbidities (comorbidity related symptoms, Figure 1) and hence worse outcome.(4,5) Since AF-related symptoms and comorbidity related symptoms may overlap, clinicians should be aware of changes or increases of symptoms in individual patients and look for undertreated or new comorbidities.

### AF symptom assessment.

Assessment of symptoms by the treating physician may, in part, be responsible for different relations of symptoms with underlying disease and outcome among populations.(40,106,111,116-121) Most studies report AF symptoms as assessed by the treating physician in a binary manner (yes / no), as was used in Chapter 5.(4,23,122) The 2010 European Society of Cardiology guidelines recommend classification using the European Heart Rhythm Association (EHRA) AF-related symptom score,(72,73) which has recently been validated and improved.(123) This score enables the physician to categorize symptoms according to severity. Still, assessment of symptoms by the treating physician may be less accurate than direct reporting by the patient. Therefore several scoring systems have been developed and validated specifically for AF-related symptoms, which enables the patient to accurately report symptoms.(23,122) These include the University of Toronto AF Symptom Severity Scale, the Symptom Checklist, and the Canadian Society Severity of Atrial Fibrillation Scale and the Atrial Fibrillation 6 Scale.(105,124-127) In Chapter 6, increasing severity of AF symptoms in permanent AF, assessed using the Toronto AF severity scale, was associated with more severe underlying disease and worse outcomes, similar to physician-assessed symptoms in Chapter 5.(4,5) Interestingly, when symptoms were assessed by the physician a large proportion of patients (70%) in the lowest tertile of the AFSS, who reported mild symptoms on the
questionnaire, were classified as asymptomatic by the physician (Figure 5). In addition, the most symptomatic patients according to the AFSS had relatively few individual symptoms as assessed by the physician. Similar findings were recently reported from the ORBIT-AF registry, where 11% of patients that were assessed as asymptomatic by the treating physician, reported mild symptoms on the Atrial Fibrillation Effect on Quality-of-Life questionnaire (AFEQT). It seems that self-reported standardized symptom severity scores are more sensitive than history taking by the treating physician.

Whether the relationship of symptomatic AF and higher symptom severity with worse outcomes is caused by a direct effect on cardiovascular outcome, or whether symptoms are a marker of severity of disease (and predominantly [diastolic] heart failure) in persistent and permanent AF is uncertain. Clearly, what precisely causes symptoms and symptom severity in the individual patient warrants further investigation.

Figure 4. Data from the LEGACY study. Effects of weight loss and cardiovascular risk factor management on body mass index (A), systolic blood pressure (B), diabetes mellitus with HbA1c ≥7 (C), echocardiographic left atrial volume (D) and E/’ (E), Symptom severity on the Toronto AF Severity Scale (105) (F), AF free survival during 5 years of follow-up, without anti-arrhythmic drugs or pulmonary vein isolation (G).
In Chapters 5 and 6 (4,5) symptomatic AF was more common in women, at older age (Chapter 5), (4) was associated with more comorbidities and especially heart failure. Whether this is caused by differences in age and comorbidities between men and women, (120,128) differences in disease coping and disease burden, (129) or differences in the incentive to seek medical attention, (130) is not completely understood. (131)

The relation of symptoms with underlying disease and predominantly heart failure in Chapters 5 and 6 suggest that heart failure is an important determinant of symptomatic AF in persistent and permanent AF. (4,5) HFpEF and HFrEF were not separately defined in both studies. However, in Chapter 5 symptomatic patients had more coronary heart
disease and more signs of systolic dysfunction on echocardiography, suggesting a higher presence of HFrEF in these patients. (4) Importantly, since the RACE study period (1998-2001) important improvements have been made in the treatment of myocardial infarction, reducing the overall prevalence of HFrEF. (100) In the more contemporary RACE II study (Chapter 6; 2005-2009) symptomatic patients more often had a previous heart failure hospitalization and had higher NT-proBNP, although no differences in systolic dysfunction were found, suggesting a high presence of HFpEF. (5,132)

Symptomatic patients in Chapters 5 and 6 were more often women, and were older (Chapter 5) than asymptomatic patients. (4,5) Recent data shows that women develop heart failure at an older age than men, and more often have HFpEF rather than HFrEF. (97,120,128,133,134) AF and HFpEF frequently coincide, but HFpEF may be hard to diagnose, especially in patients with AF. (101) Possibly, the association symptoms, female sex, older age and adverse outcomes may be mediated through yet undiagnosed HFpEF. Indeed, our analyses in Chapters 5 and 6 were adjusted for (among others) heart failure, coronary heart disease, systolic dysfunction on echocardiography and (in Chapter 6) NTproBNP, which did not attenuate the observed associations with outcome. (4,5) However no echocardiographic data on diastolic function was available. Clinicians should be aware of possible underlying HFpEF in symptomatic patients with persistent or permanent atrial fibrillation, especially in older women.

**Effect of randomized treatment strategies on symptoms.**

Theoretically, symptoms may be affected by differences in treatment strategy. The RACE study randomized patients with persistent AF to rhythm or rate control. (96) In RACE II, permanent AF patients were randomized to either strict or lenient rate control. (95) In Chapters 5 and 6 no differences were found in AF treatment strategies between symptomatic and asymptomatic patients in the RACE and RACE II studies. (4,5)

Symptoms are an important determinant of quality of life, (119,121) Previous analyses from the RACE study showed that quality of life was similar between AF patients with long-term sinus rhythm (effectively treated with rhythm control), and AF patients with permanent AF (treated with rate control). (135) More recently, the RACE II investigators demonstrated that in patients with permanent AF, stringency of heart rate control did not influence quality of life, but that among others the severity of the underlying disease influenced quality of life. (121) In addition, no differences in quality of life were found when comparing permanent AF patients treated with successful strict rate control, unsuccessful strict rate control or lenient rate control. (136) In contrast to our studies, symptomatic patients in AFFIRM in the rate control arm more often underwent electrical cardioversion (although randomized to rate control) because of intractable symptoms. (111) It is likely that these patients were severely symptomatic paroxysmal AF patients,
although this was not further specified by the authors.(111) Nevertheless, in AFFIRM no differences in quality of life were seen between rate or rhythm control.(137)

New markers of AF progression
Development of underlying disease, increasing duration of AF episodes and development of cardiovascular events often go hand in hand with atrial remodeling in AF patients.(22) LA volume was associated with cardiovascular events and mortality in AF patients who otherwise had no overt cardiovascular disease.(138,139). However left atrial function may be impaired in the presence of comorbidities before atrial dilatation occurs, as an earlier marker of atrial remodeling.(140-147) A previous study in AF patients undergoing pulmonary vein isolation (mean AF duration 5 years) showed that left atrial function was reduced in obese patients compared to patients with normal weight. (146) However baseline differences in comorbidities were not adjusted for. In Chapter 7 we reported that in young patients with recent onset AF, obesity was independently associated with impaired left atrial reservoir function, as evaluated with echocardiographic strain analysis.(6) Of interest, there were no differences in atrial size or atrial dilatation yet. Reservoir strain was also lower in both AF groups than in a previous report in healthy controls.(56) The mechanistic link between obesity and atrial remodeling is multifactorial, and includes shared cardiovascular risk factors, but also direct pro-fibrotic effects of epicardial adipose tissue and fatty infiltration of atrial myocardium.(27) Recent studies showed that weight loss did not only reduce AF burden, but also reduced cardiac remodeling and pericardial adipose tissue on magnetic resonance imaging.(31,32) As an early sign of atrial remodeling, atrial function may be associated with AF progression and cardiovascular events.(138) The prognostic relevance of impaired atrial function needs to be further established.

FUTURE PERSPECTIVES

With the changing epidemiology of AF, better prediction of incident AF and AF progression are needed. Obesity has gained importance as an AF risk factor in recent years, in both young and older patients (Chapters 2 and 4).(1,3) Aggressive strategies aiming on weight loss, cardiovascular risk reduction and improvement of physical fitness showed promising results in reductions of AF burden and improvements of atrial and ventricular remodeling, which offers huge opportunities for treatment of AF patients, when these strategies are incorporated in daily AF care.(30-32,102) However, inspiring patients to lose weight and to sustain lifestyle modifications is challenging, and requires highly motivated patients.(30-32,102) Relations of AF with (sub)clinical vascular disease are currently under investigation, which may provide additional risk stratification
Discussion and future perspectives

Tools. (Chapter 3) (2,148) Symptoms in persistent and permanent AF may also provide additional indications of the presence underlying disease and risk for cardiovascular outcomes (Chapters 5 and 6). (4,5)

Novel echocardiographic methods including echocardiographic strain analysis may provide additional mechanistic insights into atrial remodeling, which may enable early detection of patients at risk for AF progression and adverse outcomes (Chapter 7). (6) This may also apply to other cardiovascular imaging modalities including computed tomography and magnetic resonance imaging, which may provide important information on pericardial fat, atrial fibrosis, and possibly atrial function as well. (25)

Currently, inclusion in the Routine versus Aggressive upstream rhythm Control for prevention of Early AF in heart failure (RACE 3) study is being finalized. (103) This study combines lifestyle management with an aggressive contemporary rhythm control approach, aiming to improve rhythm control and prognosis in patients with early AF and heart failure. (21,103) Other studies investigating whether contemporary AF treatment may improve cardiovascular outcomes are the Early treatment of Atrial fibrillation for Stroke prevention Trial (EAST) (104) and the Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial (CABANA; ClinicalTrials.gov Identifier NCT00911508) Currently application of anticoagulants is the only treatment that has proven to improve prognosis. (77,92-94) Possibly state of the art rhythm control, including contemporary ablation strategies but also embracing lifestyle changes may be the next AF therapeutic strategy that improves AF prognosis.
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Chapter 8


