INCIDENCE OF AND CAUSES FOR ALL-CAUSE HOSPITALIZATIONS IN PATIENTS WITH ATRIAL FIBRILLATION

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Pascal Meyre

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auf Antrag von

Prof. Dr. med. Stefan Osswald	Erstbetreuer
Prof. Dr. med. David Conen	Zweitbetreuer
Prof. Dr. med. Alexander Niessner	Externer Experte

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Prof. Dr. med. Primo Schär

Dekan der Medizinischen Fakultät, Universität Basel

TABLE OF CONTENTS

ABBREVIATIONS

AF	Atrial fibrillation
BEAT-AF	Basel Atrial Fibrillation Cohort Study
BMI	Body mass index
BNP	B-type natriuretic peptide
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
DOAC	Direct oral anticoagulant
ED	Emergency department
HR	Hazard ratio
IQR	Interquartile range
KI	Konfidenzinterval
LOS	Length-of-stay
OR	Odds ratio
PVI	Pulmonary vein isolation
SD	Standard deviation
Swiss-AF	Swiss Atrial Fibrillation Cohort Study
TIA	Transient ischemic attack
VHF	Vorhofflimmern

FIGURE LEGENDS

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SUMMARY

English summary

Background: Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice, and its prevalence is expected to further increase in the future. AF patients not only have a high number of comorbidities, but they also have an increased risk of hospital admissions compared to individuals without AF. Nevertheless, predicting hospital admission risk among patients with AF remains difficult, and possible preventive strategies unclear.

Based on these gaps in knowledge, the overall goal of this PhD thesis was to investigate the incidence of and causes for all-cause hospital admission in patients with AF. The specific aims were (1) to perform a systematic review and meta-analysis summarizing the current evidence of the incidence of and associated risk factors for hospital admissions in AF patients; (2) to identify risk factors for hospital admissions in our own cohorts and subsequently use this knowledge to develop and validate a risk score for predicting hospital admissions; (3) to identify psychosocial factors associated with hospital admissions in patients with AF.

Methods: For the meta-analysis, we performed a comprehensive literature search in PubMed, EMBASE and CENTRAL, and pooled incidence rates for hospital admissions using random-effects models. Factors associated with observed between-study heterogeneity were identified using meta-regression analysis.

For the second and third study, we used data of two ongoing, prospective observational cohort studies, the *Basel Atrial Fibrillation Cohort Study* (BEAT-AF) and the *Swiss Atrial Fibrillation Cohort Study* (Swiss-AF) in which 3,968 patients with diagnosed AF were enrolled. Unplanned hospital admissions were defined as any unpredicted admission leading to at least one overnight stay. For the second study, we used the Swiss-AF data set as the derivation cohort and performed a variable selection using the least absolute shrinkage and selection operator (LASSO) method. Multivariable adjusted Cox regression analyses were performed to assess the effect of the selected variables on all-cause hospitalization. Based on regression coefficients we constructed a risk score and subsequently validated the score in the external validation cohort (BEAT-AF).

For the third study, we used psychosocial factors, such as marital status, education, level of depression and health perception, and investigated their effects on risk of hospital admission. Cox regression analyses adjusted for conventional risk factors for hospital admission were performed to calculate hazard ratio (HR).

Results: We included 35 studies of 311'314 AF patients in the meta-analysis. The pooled incidence of all-cause hospital admissions was 43.7 per 100 person-years. AF patients were more often admitted for cardiovascular causes (26.3 per 100 person-years), but the risk of non-cardiovascular hospitalizations was substantial (15.7 per 100 person-years). Associated factors for hospital admission were older age, longer follow-up time and prevalent chronic pulmonary disease or cancer.

In the second study we found that the most important predictors for all-cause hospital admission were age (75-79 years: adjusted hazard ratio [aHR], 1.33; 95% confidence interval [95% CI], 1.00-1.77; 80-84 years: aHR, 1.51; 95% CI, 1.12-2.03; ≥85 years: aHR, 1.88; 95% CI, 1.35-2.61), prior pulmonary vein isolation (aHR, 0.74; 95% CI, 0.60-0.90), hypertension (aHR, 1.16; 95% CI, 0.99-1.36), diabetes (aHR, 1.38; 95% CI, 1.17-1.62), coronary heart disease (aHR, 1.18; 95% CI, 1.02-1.37), prior stroke/TIA (aHR, 1.28; 95% CI, 1.10-1.50), heart failure (aHR, 1.21; 95% CI, 1.04-1.41), peripheral artery disease (aHR, 1.31; 95% CI, 1.06-1.63), cancer (aHR, 1.33; 95% CI, 1.13-1.57), renal failure (aHR, 1.18, 95% CI, 1.01-1.38), and previous falls (aHR, 1.44; 95% CI, 1.16-1.78). A risk score with these variables was well calibrated, and achieved a C statistic of 0.64 (95% CI, 0.61-0.66) in the derivation and 0.59 (95% CI, 0.56-0.63) in the external validation cohort.

In the third study including patients from Swiss-AF, 1582 (67.1%) were married, 156 (6.6%) were single, 287 (12.2%) were divorced, and 333 (14.1%) were widowed. Two hundred and seventy six patients (11.7%) had at most a primary education, 1171 (49.7) had secondary education, and 911 (38.6%) had a college or university degree. Depression or depressive symptoms was present in 99 (4.2%) patients. Median health perception was 75 (interquartile range [IQR], 60-85) on a scale ranging from 0-100, with higher scores indicated better health perception. The highest risk of all-cause hospital admission was observed in single (aHR, 1.35; 95% CI, 1.05-1.75) or divorced patients (aHR, 1.26; 95% CI, 1.03-1.54), and in those who reported low health perception (aHR for <75 points, 1.40; 95% CI, 1.21-1.61).

Conclusions: The overall incidence of hospital admissions in patients with AF is high. The risk of hospital admissions is related to multiple cardiovascular and non-cardiovascular risk factors, including several psychosocial factors and subjective health perception.

Outlook: Given the high risk among AF patients of being admitted to the hospital and the high burden of associated risk factors, new multidisciplinary preventive strategies are needed with the goal to reduce hospital admissions, unfavorable patient outcomes and healthcare costs.

ZUSAMMENFASSUNG

Hintergrund: Vorhofflimmern (VHF) gilt als die häufigste Herzrhythmusstörung in der Allgemeinbevölkerung mit ansteigender Prävalenz. Es konnte gezeigt werden, dass Patienten mit VHF nicht nur eine hohe Anzahl an Komorbiditäten aufweisen, sondern im Vergleich zu Individuen ohne VHF, auch ein erhöhtes Risiko haben, in ein Spital eingeliefert zu werden. Nichtsdestotrotz, die Vorhersage von Hospitalisationen bei VHF Patienten bleibt schwierig und es gibt aktuell keine Präventionsstrategien.

Basierend auf diesen Wissenslücken, war es das Ziel dieser PhD Dissertation, das Auftreten und die Ursachen der Hospitalisationen bei Patienten mit VHF zu erforschen. Die spezifischen Ziele waren (1) einen systematischen Überblick und eine Metaanalyse zur aktuellen Literatur, bezüglich der Inzidenz und den assoziierten Risikofaktoren von Hospitalisationen bei VHF Patienten zu erstellen; (2) in unseren eigenen VHF Kohortenstudien herauszufinden, welches die Risikofaktoren für Hospitalisationen sind und anschliessend einen Risikoscore für die Prädiktion von Hospitalisationen zu erarbeiten; (3) die psychosozialen Faktoren zu finden, welche mit einem erhöhten Risiko für Hospitalisationen bei VHF Patienten einhergehen könnten.

Methoden: Für die Metaanalyse führten wir eine ausführliche Literaturrecherche in den drei bekannten Online Datenbanken PubMed, EMBASE und CENTRAL durch und fassten die Inzidenz von Hospitalisationen mit Hilfe von Random-Effects Modellen zusammen. Faktoren, welche mit der beobachteten Heterogenität assoziiert sein könnten, wurden mittels Metaregression Analysen untersucht.

Für die zweite und dritte Arbeit konnten wir die Daten zweier laufenden prospektiven Observationsstudien, die Swiss Atrial Fibrillation Cohort Study (Swiss-AF) und die Basel Atrial Fibrillation Cohort Study (BEAT-AF), mit insgesamt 3968 eingeschlossenen diagnostizierten VHF Patienten verwenden. Ungeplante Hospitalisationen wurden definiert als jede Hospitalisation, welche zu einer Übernachtung im Spital führte. Für die zweite Arbeit nutzten wir Daten der Swiss-AF Studie als Kohorte für die Entwicklung des Risikoscores und führten eine Variablenselektion mittels least absolute shrinkage and selection operator (LASSO) durch. Multivariat-adjustierte Cox Regressionsanalysen wurden durchgeführt, um den Effekt von den selektionierten Variablen auf die Hospitalisationen zu untersuchen. Mittels der Regressionskoeffizienten haben wir einen Risikoscore aufgebaut und diesen in der externen Kohorte (BEAT-AF) validiert. Für die dritte Arbeit untersuchten

wir psychosoziale Faktoren wie Zivilstand, Schulbildung, Depression und subjektive Gesundheitswahrnehmung und deren Auswirkung auf das Auftreten von Hospitalisationen. Um Hazard Ratios (HR) zu berechnen, wurden für konventionelle Risikofaktoren Cox Regressionsanalysen durchgeführt und adjustiert für Variablen, welche in der zweiten Arbeit als Prädiktoren für Hospitalisationen hervorgingen.

Resultate: Wir haben 35 Studien mit insgesamt 311'314 VHF Patienten in die Metaanalyse eingeschlossen und fanden eine zusammengeführte Inzidenz der gesamten Hospitalisationen von 43.7 pro 100 Personenjahren. VHF Patienten wurden häufiger wegen kardiovaskulärer Ursachen hospitalisiert (26.3 pro 100 Personenjahren), aber das Risiko für nicht-kardiovaskuläre Hospitalisationen war beträchtlich (15.7 pro 100 Personenjahren). Assoziierte Risikofaktoren für Hospitalisationen waren: höheres Alter, längere Beobachtungszeit, erhöhte Prävalenz von chronisch obstruktiver Lungenkrankheit (COPD) und vermehrtes Auftreten von Karzinomen.

In der zweiten Arbeit waren die wichtigsten Prädiktoren für Hospitalisationen das Alter (75-79 Jahren: adjustierte HR, 1.33; 95% Konfidenzintervall [95% KI], 1.00-1.77; 80-84 Jahren: aHR, 1.51; 95% KI, 1.12-2.03; ≥85 Jahren: aHR, 1.88; 95% KI, 1.35-2.61)), vorherige Pulmonalvenenisolation (aHR, 0.74; 95% KI, 0.60-0.90), Hypertonie (aHR, 1.16; 95% KI, 0.99-1.36), Diabetes (aHR, 1.38; 95% KI, 1.17-1.62), koronare Herzkrankheit (aHR, 1.18; 95% KI, 1.02-1.37), gehabter Schlaganfall (aHR, 1.28; 95% KI, 1.10-1.50), Herzinsuffizienz (aHR, 1.21; 95% KI, 1.04-1.41), periphere arterielle Verschlusskrankheit (aHR, 1.31; 95% KI, 1.06-1.63), Karzinom (aHR, 1.33; 95% KI, 1.13-1.57), Niereninsuffizienz (aHR, 1.18, 95% KI, 1.01-1.38) und Stürze (aHR, 1.44; 95% KI, 1.16-1.78). Einen Risikoscore mit diesen Variablen war gut kalibriert und erreichte eine C Statistik von 0.64 (95% KI, 0.61-0.66) in der Entwicklungskohorte und 0.59 (95% KI, 0.56-0.63) in der Validierungskohorte.

In der dritten Arbeit verwendeten wir ausschliesslich Patientendaten von Swiss-AF. Davon waren 1582 (67.1%) verheiratet, 156 (6.6%) alleinstehend, 287 (12.2%) geschieden, und 333 (14.1%) verwitwet. Zweihundertsechsundsiebzig Patienten (11.7%) verfügten über eine Grundschulbildung oder weniger, 1171 (49.7) über eine Sekundarschulbildung und 911 (38.6%) hatten eine Fachhochschule oder eine Universität besucht. Depressionen resp. depressive Symptome hatten 99 (4.2%) Patienten. Der Median der subjektiven Gesundheitswahrnehmung war 75

(Interquartilsabstand, 60-85) auf einer Skala von 1-100, wobei ein höherer Score eine bessere Gesundheitswahrnehmung darstellt. Das höchste Risiko für Hospitalisationen zeigten Patienten, welche alleinstehend (aHR, 1.35; 95% KI, 1.05-1.75) oder geschieden waren (aHR, 1.26; 95% KI, 1.03-1.54) und solche, welche eine subjektiv schlechtere Gesundheitswahrnehmung hatten (aHR für <75 Punkten, 1.40; 95% KI, 1.21-1.61). Für kardiovaskuläre und nicht-kardiovaskuläre Hospitalisationen war nur eine subjektiv schlechtere Gesundheitswahrnehmung ein starker Prädiktor.

Schlussfolgerungen: Die Gesamtinzidenz der Hospitalisationen von Patienten mit VHF ist hoch. Das Risiko für Hospitalisationen ist assoziiert mit multiplen kardiovaskulären und nicht-kardiovaskulären Risikofaktoren, inklusive psychosozialen Faktoren.

Ausblick: Angesichts des hohen Risikos von VHF Patienten hospitalisiert zu werden und der hohen Anzahl an assoziierten Risikofaktoren, sind neue Präventionsstrategien erforderlich mit dem Ziel die Hospitalisationsraten zu verringern, ungünstige Patientenergebnisse zu verhindern und Gesundheitskosten zu reduzieren.

1. BACKGROUND

1.1. Atrial fibrillation – risk factors and health consequences

1.1.1. Epidemiology of atrial fibrillation

Since its first ECG documentation by Willem Einthoven[1], atrial fibrillation (AF) has become the most prevalent cardiac arrhythmia, occurring in approximately 1-2% of the general population.[2,3] In the European Union and worldwide, the number of patients with AF is expected to increase substantially in the coming decades and may even double in the period from 2010 to 2060 (Figure 1).[4,5] The progressive increase of the incidence, prevalence and mortality associated with AF is expanding globally, with enormous consequences on healthcare systems and societies.

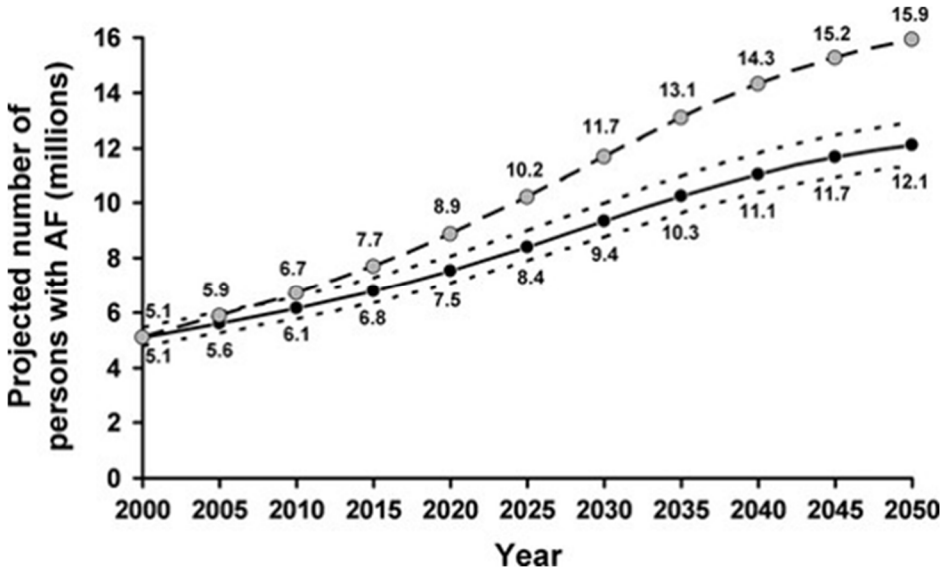

Figure 1 Projected number of persons with AF in the United States between 2000 and 2050, assuming no further increase in age-adjusted AF incidence (solid curve) and assuming a continued increase in incidence rate as evident in 1980 to 2000 (dotted curve) (Miyasaka et al., Circulation 2006).

1.1.2. Risk factors for atrial fibrillation

Several established risk factors are associated with the risk for the development of AF. The Framingham Heart Study identified various predictors for incident AF, including advanced age, hypertension, presence of heart failure or coronary heart disease, diabetes mellitus and valvular heart disease (i.e. mitral valve stenosis).[6] It has been shown that there seems to be an exponential association between advancing age and risk of new-onset AF, resulting in a lifetime risk of approximately 25%.[7] Beyond age, the most important risk factor for incident AF is heart failure. Depending on the data,

the incidence of AF among patients with diagnosed heart failure has been estimated to be 5.4 per 100 person-years.[8] In addition, the odds of developing AF in patients with preexisting heart failure has been estimated 6.1 in men and even higher in women with 8.1.[6] B-type natriuretic peptide (BNP), a vasoactive peptide predominantly secreted by cardiomyocytes, is a well-established biomarker for heart failure and has been associated with incident AF, further underscoring this important interrelationship.[9] Hypertension is one of the major risk factors for AF. Data from the Framingham Heart Study suggest that hypertension defined as a systolic blood pressure of at least 160 mmHg or a diastolic blood pressure of at least 95 mmHg is significantly associated with the risk of developing AF with odds ratio (OR) of 1.6 (95% CI, 1.2-2.2) in men and 1.7 (95% CI, 1.2-2.4) in women.[6] Consistent with these observations, data from the Atherosclerosis Risk in Communities (ARIC) Study suggest that elevated blood pressure was the largest contributor to the overall risk of AF, with an estimated population attributable fraction of 21.6%.[10] Apart from hypertension, evidence has accumulated that obesity is an independent risk factor for AF development.[11] Patients who were overweight or obese (body-mas index [BMI] ≥25-29 kg/m^2 or ≥30kg/m^2) has been estimated to account for 18% and 12% in patients with elevated BMI. It has been proposed that obesity and elevated body-fat percentage predispose left atrial enlargement and ventricular diastolic dysfunction, both are predictors of AF.[12] Heavy alcohol consumption has long been known as a risk factor for incident AF and has recently been associated to the proposed so-called “holiday heart syndrome.” Several prospective cohort studies have investigated the association of moderate to high alcohol consumption and incident AF. In the Framingham Heart Study, participants who consumed high amounts of alcohol (>36 g/day) had a significantly higher risk of incident AF.[13] Women who consumed ≥2 drinks/day also showed a higher risk of developing AF.[14] Nonetheless, a meta-analysis showed a linear dose-response relationship between alcohol consumption and the risk of developing AF, even moderate alcohol consumption, which has been proposed to be protective for other cardiovascular diseases, seems to increase the risk of AF.[15]

1.1.3. Health consequences of atrial fibrillation

The public health impact of AF is further underscored by an increased risk of stroke, congestive heart failure and death.[8,16-18] Also, AF is associated with a poor quality of life and was suggested to decrease cognitive function compared to individuals without AF.[19-21] Finally, AF also accounts for one-third of hospital admissions for cardiac

rhythm disturbances, and the rate of hospital admissions has risen in recent years.[22] Many studies have shown that AF patients have a high burden of cardiovascular co-morbidities.[23-25] For example, Caroll et al. showed that ischemic heart disease, heart failure and hypertension were the most common comorbidities associated with AF.[26] Another recent study demonstrated that a substantial number of patients with AF were also diagnosed with at least one other cardiovascular comorbidity. The investigators also found that comorbidities in AF patients extended far into other organ systems including urologic, respiratory and gastrointestinal disorders.[25] Consequently, patients with AF have a high risk of complications and adverse outcome events.[27]

Stroke

The most clinically important complication is the formation of cardiac thrombus in the atria and systemic embolization leading to strokes. A meta-analysis showed that the relative risk of stroke is 2.4 and the absolute risk is 3.6 per 1000 person-years follow-up.[27] Data from contemporary studies indicate that 20-30% of all ischemic strokes is accountable to AF and stroke risk increases by 5-fold with diagnosis of AF.[18] Oral anticoagulation has shown to be highly effective for stroke prevention, by reducing the absolute risk of stroke.[28] Also, patients with device-detected subclinical AF are at risk for stroke, whereas the absolute risk has been estimated lower compared to patients with diagnosed AF.[29] Whether these patients also benefit from oral anticoagulation is currently being investigated.[30]

Heart failure

Heart failure is not only a risk factor for developing AF, but also constitutes as an important consequence of AF. They often occur together, have similar underlying risk factors, and their combination strongly correlates with increased morbidity and mortality.[8,31,32] The pathophysiological interrelationship between AF and heart failure has been intensively investigated. It has been suggested that AF may facilitate the development and progression of heart failure thorough several different ways.[33] Through the irregular exaggerated heart rate results in a shorter diastolic filling time, which as a consequence may result in reduced cardiac output. Furthermore, the irregular contractions of the atria contributes to the development of diastolic dysfunction and subsequently heart failure. Although there seems to be a strong interrelationship between those two disorders, it remains unclear whether AF is a risk factor for heart failure or a just marker of advanced heart failure disease.

Death

Given the chronic nature of disease, AF has been independently associated with morbidity and mortality.[16] In 2 population-based cohorts, patients who had incident AF had a 2.5-fold increased risk of sudden cardiac death and a 3-fold increased risk of non-sudden cardiac death.[34] Data from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RELY) trial suggest that AF patients treated with oral anticoagulation, sudden cardiac death accounts for more than 20% of all deaths.[35] Furthermore, an analysis from the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis In Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial where AF patients were randomized to receive either edoxaban, an oral factor Xa inhibitor, or warfarin showed that over 90% of all sudden cardiac deaths occurred out of the hospital.[36] Among a population of healthy women, new-onset AF was also strongly associated with all-cause and cardiovascular death.[17] The absolute risk for non-cardiovascular death was higher than for cardiovascular deaths (6.5 vs. 4.3 per 1000 person-years of follow-up).

Cognitive dysfunction

Cognitive decline is strongly related to morbidity, leading to disability and subsequently death.[37,38] Management of dementia syndromes has been recognized as a public health priority.[39] Also, the consequences of cognitive decline and dementia are a major driver of health care costs.[40] More recent evidence suggests that patients with AF have increased risk of cognitive dysfunction and incident dementia. Clinically unrecognized (silent) cerebral infarcts may explain this association. Longitudinal data from the Rotterdam Scan Study including elderly people without AF have shown that individuals with silent brain infarcts have an increased risk of dementia and a steeper decline in cognitive function than those without such lesions.[41] This finding has recently been confirmed in a meta-analysis of patients without AF, with a pooled 1.3-fold increased risk for incident dementia.[42] Among patients with established AF, a recent study showed that these patients not only have a high burden of vascular brain lesions, such as silent infarcts, white matter lesions and microbleeds, but also that the burden of silent brain lesions was associated with cognitive dysfunction.[43] Although there is growing awareness about the relationship between AF and dementia, there is currently no screening strategy or intervention available, with most recommendations being moderate due to lack of evidence.[44]

1.2. Atrial fibrillation – risk of hospital admissions

1.2.1. Incidence rate of hospital admissions

Over the past decades evidence has accumulated suggesting that hospital admission rates in patients with AF are increasing exponentially worldwide, and recent data indicate that these rates may increase in the near future.[45-47] The clinical view has especially shifted to unplanned hospital admissions. In an emergency department setting for example, the population-adjusted rates of admission of patients with AF have been estimated to have increased from 0.6 to 1.2 per 1000 person-years of follow-up.[48] Indeed this rise in admission rates may be in part due to the aging of the general population, and also because of the increasing prevalence of conventional cardiovascular risk factors such as hypertension, diabetes and obesity. Current thinking indicates that the rates of hospital admission among AF patients will substantially rise in the near future which would pose a huge burden on our societies given the increase in health care expenditures associated with this event. Yet there remains a wide range of uncertainty on the actual risk of hospital admission and the underlying factors associated with this outcome in patients with AF.

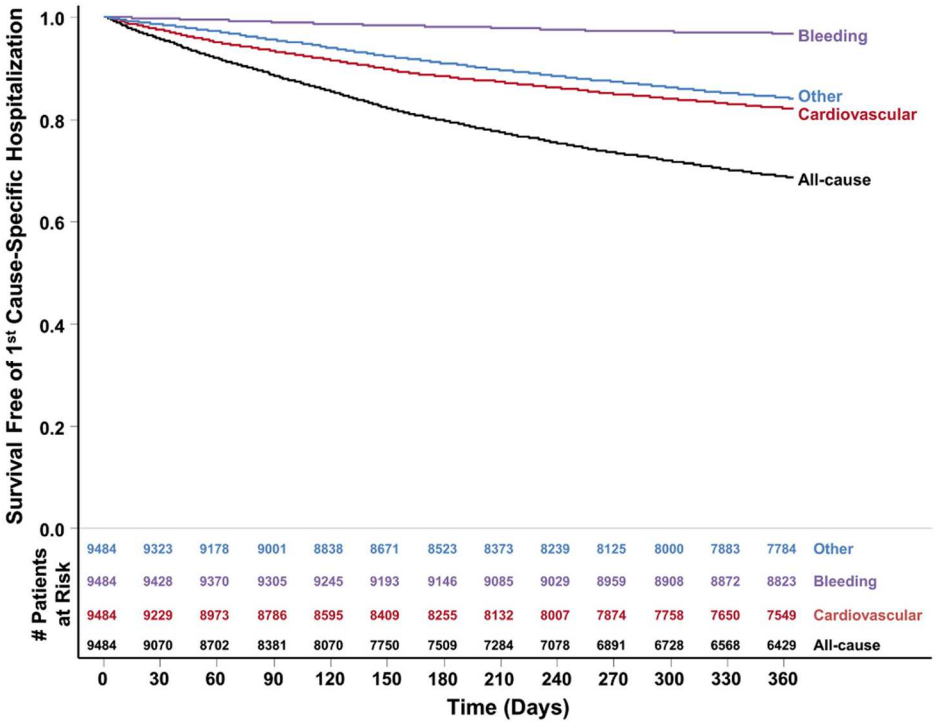

Figure 2 Kaplan-Meier rates of first hospital admission, by cause (Steinberg et al., Am Heart J 2014).

Data from the United States show that the trends of hospital admissions from 2000 to 2010 in AF patients have been continuously increasing.[47] When we look at data from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) study, a prospective multicenter outpatient registry of AF patients who were enrolled across the United States, the investigators estimated that nearly 1 in 3 patients were hospitalized within one year of follow-up (Figure 2).[49] In addition, those patients who were frequently admitted, had a higher risk of all-cause death. In this study the investigators found clinical predictors that were associated with the risk of admission such as elevated heart rate measured at baseline visit, increased AF symptom burden and coexisting heart failure. Apart from these significant predictors, AF type defined as paroxysmal, persistent or permanent was not associated with hospital admission. Nevertheless, evidence is still lacking on the long-term prognostic trend for hospital admissions in patients with AF mainly due to the short follow-up duration of 12 months in most studies. Detailed risk assessment in these patients was not established in ORBIT-AF and is therefore needed to be identified.

1.2.2. Causes for hospital admissions

Aside from the admission risk, an important aspect of frequent hospital admissions are the underlying causes. In the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation trial (ROCKET AF), the investigators sought to identify the main reasons for and associated predictors for hospital admission in AF patients.[50] They found that among this population of outpatients with diagnosed AF, almost 1 of 7 was hospitalized within 2 years and half of those admissions were due to cardiovascular causes. The primary cardiovascular reasons for admission were heart failure (14%), bleeding (12%), stroke (7%), acute coronary syndrome (5%), AF-related disorders (4%) and other cardiovascular causes (10%) (Figure 3). Although roughly 50% of all admissions were due to cardiovascular causes, both AF and bleeding were rare causes for the outcome. In a large sample of patients from the Nationwide Readmissions Database (NRD) for the year 2013, investigators evaluated 30-day readmission risk after discharge in patients with diagnosed AF.[51] They found that the most common cause behind readmission was AF (27%), heart failure (11%) and ischemic heart disease (3%). Stroke only accounted for 2.5% of all hospital admissions within 30 days after discharge. Also in short-term follow-up, stroke admissions were relatively uncommon, whereas heart failure was one of the drivers for patients being

admitted to the hospital. However, only little information is available about the non-cardiovascular causes for readmissions.

In ROCKET AF, the largest proportion of any hospital admission was due to non-cardiovascular, including diagnoses such as pneumonia, chronic obstructive pulmonary disease (COPD), and urinary tract infections. In ORBIT-AF, 43% of all admission were due to non-cardiovascular causes. However, the researchers did not provide specific reasons for these admissions. In a retrospective study using data from the United States Thomson Reuters MarketScan Medicare Supplemental and Coordination of Benefits Database showed that patients were more often hospitalized for non-cardiovascular than cardiovascular causes during the first year of follow-up. The underlying mechanism of non-cardiovascular causes for hospital admission has not been fully discussed, although gaining knowledge about these reasons are of clinical importance.

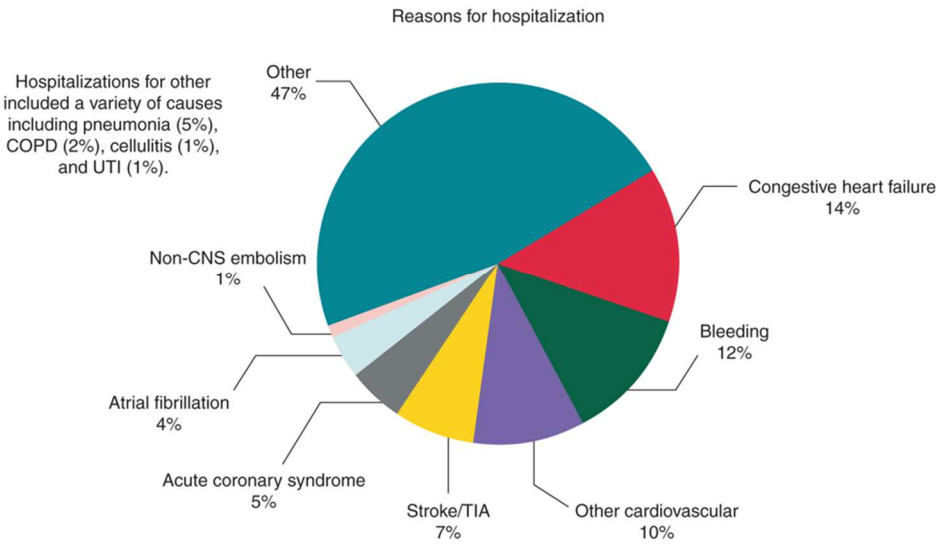

Figure 3 Reasons for hospital admission during study follow-up. This figure displays the reasons for all hospital admissions (N=2614) (DeVore et al., Europace 2016).

1.2.3. Risk factors for hospital admissions

Hospital admission is a heterogeneous outcome with many factors associated with this event. Probably the most important factors associated with the outcome are presence of multiple co-factors, such as pulmonary disorders, diabetes, hypertension and heart failure. Studies have shown that the presence of selected comorbid conditions correlates with the incidence rate of all-cause hospitalizations.[50] Especially the presence of COPD, chronic kidney disease (CKD) and heart failure were significantly associated with all-cause admission rates (Figure 3). Although a large proportion of

hospital admissions were attributable to non-cardiovascular causes, information on associated risk factors were not provided in this study. Further research is therefore needed to determine which risk factors are related to cardiovascular, but also to non-cardiovascular hospital admissions. Also for 30-day readmission, the strongest predictors for this event to occur was the presence of multiple comorbidities.[51] This suggests that multiple factors are associated with a high admission risk and therefore a multi-factorial approach might be useful in reducing those admission rates in this specific group of patients.

1.2.4. Health care costs of hospital admissions

From a socio-economic point of view, hospital admissions are one of the largest driver for health care expenditures worldwide, and costs directly correlate with the number of admissions. Data from Denmark indicate that over 50% of all costs and over 70% of AF attributable costs are due to hospital admissions.[52] A systematic review suggests that 50 to 70% of the total annual costs in patients with AF are directly attributable to hospital admissions.[53] Furthermore, a retrospective observational cohort study that used health care MarketScan data showed that direct medical costs are substantially higher in AF patients compared to medically matched non-AF controls and that the primary cause for this immense difference is due to higher inpatients cost (through more frequent hospital admissions).[54] This economic burden of AF on health care systems is likely to continue to grow in the future. Reducing the need for hospital admission is a key factors in controlling the costs. Given this, identifying preventive strategies and targets to reduce the risk of AF patients being admitted to the hospital should be public health priority.

Given the high admission rates in this patient population, suggestions for preventive strategies are particularly of interest. Implementation of preventive interventions may have the potential to assist physicians and care providers in managing acute changes in patient clinical status and may reduce unnecessary admissions. The Interventions to Reduce Acute Care Transfers (INTERACT) trail examined whether training and support for the implementation of a nursing home quality improvement program reduces hospital admissions and ED visits.[55] The recently published results from this trail were rather disappointing, showing no effects on hospitalization or ED visit rates in the overall population of residents of participating nursing homes. The Hospital Readmissions Reduction Program (HRRP) has recently been proposed as possible

intervention to reduce costly readmissions in patients who have been discharged.[56] This program reduces payments to hospitals with excess readmission, and it successfully reduced short- and long-term admissions in patients with heart failure, but there seems to be a tradeoff with an increase in 30-day and 1-year mortality.[57] Also, the performance of such interventions has not been examined in large AF populations. Thus, there is an unmet need to investigate factors that increase the risk of AF patients for being admitted to the hospital, and subsequently use this knowledge to establish and implement preventive strategies which may hopefully have an impact on admission rates in this highly vulnerable population.

2. AIMS AND OBJECTIVES

The overall, primary aim of this thesis was to investigate the incidence of and risk factors associated with hospital admissions in patients with diagnosed AF.

2.1. Incidence of and causes for hospital admissions in atrial fibrillation

The overall aim of this study was to perform a systematic review and meta-analysis assessing the incidence of and causes for hospital admissions in patients with AF.

Objectives

1. To perform a systematic review on studies reporting the incidence of hospital admission in AF patients.
2. To pool the overall incidence of all-cause hospital admission in patients with AF.
3. To compare incidence rates for cardiovascular and non-cardiovascular hospital admissions in AF patients.
4. To investigate the causes for hospital admissions in patients with AF.

Specific research questions

1. How often are patients with AF hospitalized and what is their overall risk?
2. What are the causes for hospital admissions in this population?
3. What are potential risk factors associated with increasing admission rates?

The results of this investigation are presented in the manuscript, ***Risk of Hospital Admissions in Patients with Atrial Fibrillation: A Systematic Review and Meta-analysis***, which has been published in the Canadian Journal of Cardiology (see manuscript 1, page 35). This work was also presented at the Meeting of the European Society of Cardiology in 2018 as a Poster presentation.

2.2. Risk factors and prediction of hospital admissions

The overall aim of this study was to identify independent predictors for all-cause hospital admissions in patients with established AF, and to derive and validate a prediction tool for this purpose.

Objectives

1. To identify independent risk factors associated with hospital admissions in patients with AF.
2. To derive a risk prediction rule in patients with AF.
3. To externally validate the prediction tool in another cohort of patients with AF.
4. To build a risk score identifying patients at high risk of hospital admission.

Specific research questions

1. What are risk factors associated with hospital admissions in patients with AF?
2. How can these risk factors be used to build a prediction rule for hospital admission?
3. What is the predictive performance of this new prediction tool in another cohort of patients with diagnosed AF?

The findings of this study are presented in the manuscript, ***The Admit-AF Risk Score: A Clinical Risk Score for Predicting Hospital Admissions in Patients with Atrial Fibrillation***, which has been submitted to JAMA Cardiology. The findings are presented in manuscript 2, on page 71.

2.3. Psychosocial factors and hospital admission

The overall aim of this particular study was to identify psychological and social factors and to assess their associations with the risk of hospital admission in patients with AF.

Objectives

1. To determine the prevalence of psychosocial factors and subjective health perception in a population of patients with AF.
2. To assess the association of psychosocial factors and health perception with hospital admission in AF patients.
3. To identify and evaluate the association between overall burden of psychosocial factors and admission risk in an AF population.

Specific research questions

1. What is the prevalence of psychosocial factors in AF patients?
2. What is the effect of psychosocial factors on hospital admissions and which one are the strongest predictors for hospital admission?
3. What is the cumulative effect of psychosocial factors and health perception on admission risk?

The findings of this study are presented in the manuscript, ***Psychosocial Factors Predict Hospital Admissions in Patients with Atrial Fibrillation***, which has been submitted to Annals of Internal Medicine. The manuscript 3 can be found on page 110.

3. STUDY DESIGN AND METHODS

3.1. Objective I – Systematic review and meta-analysis

For the first study, we performed a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) standards.[58,59]

3.1.1. Eligibility criteria

Studies were included if they fulfilled the following criteria:

1. Cohort studies or randomized controlled trials.
2. At least 100 patients with AF included.
3. Reported incidence rate of all-cause hospitalization or information to calculate incidence rates.
4. At least 1 year of follow-up.

Studies were excluded if they only reported cause-specific hospitalizations, such as hospitalization for heart failure.

3.1.2. Search methods

With the assistance of an experienced research librarian, we developed a comprehensive search strategy and systematically searched in MEDLINE (via PubMed), EMBASE (via Ovid) and CENTRAL (Cochrane Central Register of Controlled Trials) from database inception to December 21. 2017. We used Medical Subject Heading (MeSH) terms and keywords such as “hospital admission,” “hospitalization,” and “atrial fibrillation.” No language or geographical restrictions were applied to the search, and abstracts were included. In addition, we screened reference lists of studies fulfilling inclusion criteria for additional relevant articles. Two independent reviewers screened titles and abstracts of all articles identified in the initial search. Full-texts of all potentially eligible manuscripts were reviewed by the same authors for eligibility. Disagreements were resolved through discussion or third party arbitration. In case of incomplete data, corresponding study authors were contacted for additional information.

3.1.3. Data extraction and outcome assessment

From each eligible study the following information were extracted in duplicate using a standardized case report form: Study design, country, year of publication, sample size,

AF type, follow-up duration, age of patients, sex, cardiovascular risk factors (i.e. hypertension, diabetes), cardiovascular comorbidities including coronary artery disease, heart failure, prior stroke or transient ischemic attack (TIA) and peripheral vascular disease; and non-cardiovascular comorbidities including chronic pulmonary disease, chronic kidney disease and cancer. The primary outcome of this study was incidence of all-cause hospital admission. We extracted the reported incidence of all-cause hospital admissions and, if available, we also extracted incidences on admissions for cardiovascular versus non-cardiovascular causes. Data were entered into a Microsoft Access database (Microsoft Corp., Redmond, WA, USA).

3.1.4. Study quality assessment

We evaluated the methodological quality of included studies using a modified version of the Newcastle-Ottawa Scale.[60] We specifically assessed the following criteria: Representativeness of the study population, methods used for outcome assessment, and adequacy of follow-up assessment. Studies were categorized as having a high (3 points), moderate (2 points) or low study quality (≤1 point).

3.1.5. Statistical analysis

If not available in the original publication, we calculated the incidence of all-cause, cardiovascular and non-cardiovascular hospital admissions by dividing the number of admissions by the mean follow-up time in years multiplied with the total number of AF patients. We calculated 95% confidence intervals (95% CI) approximating the Poisson distribution. Incidence rates were pooled using random-effect models according to the method described by DerSimonian and Liard.[61] We performed a sensitivity analysis to test the influence of each individual study on the overall incidence estimate by sequentially excluding each study and subsequently repeating meta-analysis. Between-study heterogeneity was computed using the Cochran's Q statistic and quantified by the I^2 statistic. We considered I^2 values ≥50% to indicate substantial heterogeneity and values ≥75% considerable heterogeneity.[62]

To explore between-study heterogeneity, we divided study results into subgroups according to predefined study-level characteristics (including geographical region, sample size, study design [retrospective, prospective or randomized controlled trial], publication status [peer-reviewed article versus abstract] and study quality) and compared them using random-effects meta-regression.[63] Differences in incidence across predefined characteristics (age, sex, follow-up duration, hypertension, diabetes,

coronary artery disease, prior stroke or transient ischemic attack, heart failure, peripheral vascular disease, chronic pulmonary disease, chronic kidney disease and cancer) were explored using meta-regression analysis. The R^2 value was used to indicate the proportion of between-study variability explained by the model. Multivariable meta-regression analyses were not performed due to the limited number of available studies.

Causes for hospital admissions were extracted if available, and classified into the following categories: AF related, heart failure, bleeding, stroke, myocardial infarction, systemic embolism, bacterial and viral infections, gastrointestinal, respiratory, renal, neurological, cancer, endocrine and metabolic, hematological, skin and soft tissue, and psychiatric. Proportions of each cause category and corresponding 95% CIs were calculated and subsequently pooled using random-effects meta-analysis.

Publication bias was assessed by visual inspection of funnel plots and by Egger's tests.[64,65] All analyses were performed using Stata, version 13.0 (StataCorp. 2013). Statistical tests were 2-tailed and a $P<0.05$ was considered to indicate statistical significance.

3.2. Objective II – Prediction tool for hospital admission

The second study is based on data of the *Swiss Atrial Fibrillation Study* (Swiss-AF) and *Basel Atrial Fibrillation Study* (BEAT-AF). This work followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement for developing and validating multivariable prediction models.[66]

3.2.1. Derivation and validation cohorts

The Swiss-AF study, an ongoing prospective, observational multicenter cohort study that enrolled from 2014 to 2017, 2,415 patients with established and previously documented AF across 14 centers in Switzerland. More methodological details have been published previously.[43,67] Swiss-AF was used as the derivation cohort for this analysis. For the external validation cohort we used the BEAT-AF cohort study, an ongoing prospective, observational multicenter cohort study of 1,553 patients with previously documented AF. Patients were enrolled from 2010 to 2014 across 7 centers in Switzerland. In BEAT-AF, yearly information on new hospital admissions were collected only after the second year of follow-up. Therefore, the second year of follow-up was used as the baseline visit in BEAT-AF.

Inclusion criteria

In both cohorts, similar eligibility criteria were applied.

- AF diagnosed from a surface electrocardiogram.
- Aged 65 years or older.

Exclusion criteria

- Secondary reversible forms of AF (i.e. episodes after cardiac surgery).
- Acute illness within the last 4 weeks.
- Inability to give informed consent.

Patients enrolled in BEAT-AF were not eligible to participate in Swiss-AF, and vice versa.

3.2.2. Study population

From each patient, data on baseline characteristics were collected using standardized case report forms. These characteristics included age, sex, marital status, education, health perception, lifestyle factors, AF type, history of rhythm control interventions, history of device implantation, cardiovascular and non-cardiovascular comorbidities,

information on oral anticoagulation and family history of cardiovascular diseases. Characteristics were updated at yearly follow-up visits through on site patient visit or phone calls. AF type was classified according to the guidelines of the European Society of Cardiology into paroxysmal AF (self-terminating, usually within 48 hours), persistent AF (episodes either lasting longer than 7 days or requiring termination by electrical/pharmacologic cardioversion) or permanent AF (AF is accepted by patient and physician).[68]

3.2.3. Outcomes

The outcome of this study was the occurrence of unplanned all-cause hospital admissions after 1 year. We assessed 1-year admission risk on the basis of previous observational data reporting a 1-year incidence rate of hospital admission of 30%.[49] All-cause hospital admissions were defined as non-elective admissions with at least one overnight stay. Secondary outcomes were cardiovascular admissions (due to myocardial infarction, heart failure, stroke or TIA, bleeding, or deep vein thrombosis) and non-cardiovascular hospital admission. Information on each admission was obtained from patients or by review of medical files of the patients corresponding to the hospital admission. Planned hospital admissions for complementary investigations or treatment (i.e. elective pulmonary vein isolation) were excluded from this analysis.

3.2.4. Statistical analysis

Candidate variables were selected based on literature review, clinical plausibility and availability in both cohorts. Baseline characteristics of the derivation and validation cohorts are presented for comparison purposes. Using the derivation cohort, candidate variable for the prediction model were selected based on the method of least absolute shrinkage and selection operator (LASSO).[69] LASSO is a regularized regression method, which penalizes the absolute size of coefficient estimates. It shrinks the β coefficients which allows to select the strongest variables associated with the outcome. As a result, variables with regression coefficients that shrink to zero are eliminated. The variables most strongly associated with the outcome are kept for the final model. Of the selected variables, time to first hospital admission was estimated by the Kaplan–Meier method, and differences between groups were assessed by the log-rank test. A combined Cox proportional hazard model was used to determine the association of the selected variables with the cumulative incidence of hospital admissions.

We used a point-based risk scoring system to create a score that estimates the risk of hospital admissions based on the β coefficients from the model in the derivation cohort (rounded to the nearest integer). For each patient we calculated the total point score by adding together the points corresponding to risk factors. The risk score was categorized into three risk classes based on admission risks from the derivation, defined as low (<10%/year), intermediate (10-20%/year) and high risk (>20%/year). Discrimination of the models was evaluated using Harrell's C statistic for survival models.[70] Calibration was assessed graphically by comparing the observed versus the predicted risk at 1 and 3 years stratified by deciles.[71] Kaplan-Meier curves for patients stratified by the 3 risk groups were generated to illustrate the risk of hospital admission and log-rank test was used to assess differences between groups.

To evaluate the clinical usefulness of the prediction model, the derivation and validation cohorts were combined into one data set (N=3687) and the net benefit of using the model as a prediction tool was evaluated using decision curve analysis.[72] The net benefit is defined as the difference of the proportion of patients who are true-positive from the proportion who are false-positive, weighted by the specific threshold probability. A decision curve is then created by calculating the net benefits for all possible thresholds. A model with a high net benefit (all positive at any threshold) is preferred. The curve is graphically illustrated by displaying potential thresholds for hospital admission risk (x axis) and the net benefit (y axis) assuming that no patient will have an admission.

All analyses were performed using Stata, version 13.0 (StataCorp. 2013); variable selection with LASSO was performed using the lassopack.[73] A 2-sided P value of <0.05 was considered to indicate statistical significance.

3.3. Objective III – Psychosocial factors and hospital admission

The third study is based on data of the Swiss-AF study.

3.3.1. Procedures and psychosocial factors

From each patient, we collected information on demographic and medical characteristics using standardized case report forms and validated questionnaires. Yearly follow-up visits were performed either by face-to-face contact or by telephone calls, to update patient characteristics, clinical measures and to collect information on outcome events. Follow-up visits were performed through local study personnel at each study center.

Psychosocial factors consisted of marital status (married, single, divorced or widowed), education, and presence of depression or depressive symptoms. Information on marital status was ascertained at baseline. Education level was assessed using the sum of completed years in school, high school or college, and defined as primary or less (less than compulsory education curriculum, <6 years), secondary (high school or similar, 6-12 years) and college or university (college or university degree, >12 years). Depression and depressive symptoms were assessed using the Geriatric Depression Scale (GDS), and a total score of >5 points indicates depression.[74,75] Health perception was self-assessed by patients indicating their current state of health using a visual analogue scale (VAS) ranging from 0 (worst) to 100 (best). The VAS used in this study is very similar to the EuroQol VAS, and has been validated for AF patients.[76,77]

3.3.2. Outcomes

The primary end point of this study was time to first all-cause hospital admission defined as any unplanned admission leading to at least 1 overnight stay. Secondary outcomes were time to first cardiovascular (due to myocardial infarction, heart failure, stroke/TIA, bleeding, deep vein thrombosis) and non-cardiovascular hospital admission. Information on the occurrence of an event was obtained from patients or their family doctor, who were contacted at regular yearly follow-up visits. The occurrence and type of the events was assessed at a yearly follow-up investigation (i.e., on-site visit, phone call, or information gathered from the family doctor).

3.3.3. Statistical analysis

Baseline characteristics are presented as mean ± standard deviation (SD) for continuous variables or as counts (percentages) for categorical variables. Incidence

rates and 95% confidence intervals (CI) for primary and secondary outcomes were calculated per 100 person years of follow-up. Time to first hospital admission was estimated and plotted using the Kaplan-Meier method. We constructed Cox proportional hazard models to test the associations of psychosocial factors and health perception with the risk of hospital admission, adjusting for cardiovascular and non-cardiovascular covariates. These covariates included age, sex, body-mass index (BMI), history of hypertension, diabetes, coronary heart disease, prior stroke/TIA, heart failure, peripheral vascular disease, renal failure, cancer, previous falls. We constructed a combined multivariable model including all psychosocial factors in a single model to determine the strongest predictors for hospital admission. Multivariable and combined models included 2349 patients because of missing data in 9 patients (0.4 %). The appropriateness of the proportional hazards assumption was investigated by calculating Schoenfeld residuals.

To evaluate overall burden of psychosocial factors and its effect on hospital admission risk, we used the variables that remained associated in the combined model, with a P value threshold of <0.05. Patients were categorized into groups according to the presence of the factors. We performed multivariable Cox models, adjusted for the same covariates as listed above, and tested for trend of the survivor function across groups.

All analyses were performed using Stata, version 13 (StataCorp). All test were 2-sided and a $p<0.05$ was considered statistical significance.

4. MANUSCRIPT 1 – Risk of hospital admissions atrial fibrillation

Risk of Hospital Admissions in Patients with Atrial Fibrillation: A Systematic Review and Meta-analysis

Pascal Meyre[1,2], Steffen Blum[1,2], Sebastian Berger[1,2], Stefanie Aeschbacher[1,2], Hadrien Schoepfer[2], Matthias Briel[3,4], Stefan Osswald[1,2], David Conen[1,2,5]

1 Division of Cardiology, Department of Medicine, University Hospital Basel, Switzerland
2 Cardiovascular Research Institute Basel, University Hospital Basel, Switzerland
3 Basel Institute for Clinical Epidemiology and Biostatistics, Department of Clinical Research, University Hospital Basel, Switzerland
4 Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada
5 Population Health Research Institute, McMaster University, Hamilton, ON, Canada

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Systematic Review/Meta-analysis

Risk of Hospital Admissions in Patients With Atrial Fibrillation: A Systematic Review and Meta-analysis

Pascal Meyre, MD,[a,b] Steffen Blum, MD,[a,b] Sebastian Berger, MD,[a,b] Stefanie Aeschbacher, PhD,[a,b] Hadrien Schoepfer, BSc,[b] Matthias Briel, MD, MSc,[c,d] Stefan Osswald, MD,[a,b] and David Conen, MD, MPH[a,b,e]

[a] *Division of Cardiology, Department of Medicine, University Hospital Basel, Switzerland*

[b] *Cardiovascular Research Institute Basel, University Hospital Basel, Switzerland*

[c] *Basel Institute for Clinical Epidemiology and Biostatistics, Department of Clinical Research, University Hospital Basel, Switzerland*

[d] *Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada*

[e] *Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada*

See editorial by Samuel and Brophy, pages 1291–1293 of this issue.

ABSTRACT

Background: Atrial fibrillation (AF) is associated with multiple comorbidities and various adverse outcome events, suggesting a high risk of hospital admissions in this patient population. However, its exact incidence and potential underlying causes are not well defined. The objective of this systematic review was to investigate the incidence and risk factors for hospital admissions in patients with AF.

Methods: We systematically searched MEDLINE, EMBASE, and CENTRAL for studies providing information on all-cause hospital admissions. Studies were included if they provided information on the incidence of all-cause hospital admissions in ≥ 100 patients with AF, and had ≥ 1 year of follow-up. Incidence estimates were pooled using random-effects models. Meta-regression analysis was performed to identify characteristics associated with between-study heterogeneity.

Results: Thirty-five studies (n = 311,314 patients) were included. The pooled incidence of all-cause hospital admissions was 43.7 (95% confidence interval [CI], 38.5-48.9; I^2 = 99.9%) per 100 person-years. In 24 studies (n = 234,028 patients) that provided information on admission causes, cardiovascular hospitalizations were more

RÉSUMÉ

Contexte : La fibrillation auriculaire (FA) est associée à de multiples maladies concomitantes et à diverses issues défavorables, ce qui donne à penser qu'un risque élevé d'hospitalisation existe au sein de la population de patients qu'elle touche. Cependant, son incidence exacte et ses causes sous-jacentes potentielles ne sont pas bien définies. Le présent article propose une revue systématique des données sur l'incidence et les facteurs de risque d'hospitalisation chez les patients atteints de FA.

Méthodologie : Nous avons effectué dans MEDLINE, EMBASE et CENTRAL une recherche systématique d'études fournissant des renseignements sur les hospitalisations toutes causes confondues. Les études retenues pour les besoins de notre revue de données devaient fournir des renseignements sur l'incidence des hospitalisations toutes causes confondues chez ≥ 100 patients atteints de FA et comporter une période de suivi d'au moins un an. Les estimations de l'incidence ont été regroupées à l'aide de modèles à effets aléatoires. Une analyse de métarégression a été effectuée afin de cerner les caractéristiques associées à l'hétérogénéité interétude.

Atrial fibrillation (AF) affects more than 3% of the general adult population, and its prevalence is expected to further increase over the next decades.[1-3] Patients with AF have an increased risk of death, stroke, and heart failure, and they also seem to have a higher risk of non-cardiovascular diseases.[4-8] Accordingly, patients with AF have a higher risk of being admitted to the hospital compared with individuals without AF.[9] Hospital admissions seem to account for the highest proportion of direct health care expenditure.[10-12] A recent systematic review estimated that in patients with AF, 50% to 70% of the annual direct costs were directly attributable to hospitalizations and inpatient care.[13]

Unfortunately, precise data on the incidence and underlying causes of hospital admissions in AF patients are not readily available. Such information would be of major interest, as they may help to plan resource use, develop prevention

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Corresponding author: Dr David Conen, McMaster University, Population Health Research Institute, 237 Barton Street East, Hamilton, Ontario L8L 2X2, Canada. Tel.: +1-905-522-1155; fax: +1-905-521-6068.
E-mail: conend@mcmaster.ca

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common than noncardiovascular hospitalizations (pooled incidence 26.3 [95% CI, 22.7-29.9; I^2 = 99.9%] vs 15.7 [95% CI, 12.5-18.9; I^2 = 99.8%] per 100 person-years). In meta-regression analyses, older age (β = 1.4 [95% CI, 0.33-2.53], P = 0.01, R^2 = 15.7%) and prevalence of chronic pulmonary disease (β = 1.5 [95% CI, 0.57-2.45], P = 0.005, R^2 = 49.8%) were associated with an increased rate of all-cause hospital admissions.

Conclusions: Patients with AF have a very high risk of being admitted to the hospital, both for cardiovascular and noncardiovascular causes. The development and implementation of preventive strategies should be a public health priority.

Résultats : Trente-cinq études (n = 311 314 patients) ont été retenues. L'incidence des hospitalisations toutes causes confondues chez ces patients après regroupement des données s'est établie à 43,7 (intervalle de confiance [IC] à 95 % de 38,5 à 48,9; I^2 = 99,9 %) par 100 années-personnes. Dans 24 études (n = 234 028 patients) qui comportaient des renseignements sur les causes d'admission, les hospitalisations attribuables à des causes cardiovasculaires étaient plus fréquentes que les hospitalisations attribuables à des causes autres que cardiovasculaires (incidence après regroupement des données de 26,3 [IC à 95 % de 22,7 à 29,9; I^2 = 99,9 %] vs 15,7 [IC à 95 % de 12,5 à 18,9; I^2 = 99,8 %] par 100 années-personnes). Dans les analyses de métarégression, l'âge avancé (β = 1,4 [IC à 95 % de 0,33 à 2,53], P = 0,01, R^2 = 15,7 %) et la prévalence de maladies pulmonaires chroniques (β = 1,5 [IC à 95 % de 0,57 à 2,45], P = 0,005, R^2 = 49,8 %) étaient associés à une augmentation du taux d'hospitalisation toutes causes confondues.

Conclusions : Les patients atteints de FA courent un risque très élevé d'hospitalisation tant pour des causes cardiovasculaires que non cardiovasculaires. L'élaboration et la mise en œuvre de stratégies de prévention devraient être une priorité de santé publique.

strategies to minimize the risk of costly hospital admissions, and improve outcomes among AF patients.[14]

We therefore conducted a comprehensive systematic review and meta-analysis to summarize the available information on the risk of hospital admissions and underlying causes among patients with AF.

Methods

This systematic review and meta-analysis was not registered but complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) standards.[15,16]

Eligibility criteria

Studies were included if they fulfilled all of the following criteria: (1) They were cohort studies or randomized controlled trials, (2) reported data on at least 100 patients with AF, (3) reported the incidence of all-cause hospital admissions in patients with AF or sufficient information to calculate it, and (4) had at least 1 year of follow-up. To minimize the risk of reporting bias, we excluded studies that reported only on cause-specific hospital admissions, such as hospitalizations for heart failure.

Search methods

We developed a search strategy in collaboration with an experienced research librarian and systematically searched MEDLINE (via PubMed), CENTRAL (Cochrane Central Register of Controlled Trials), and EMBASE (via Ovid) from database inception to December 21, 2017. In addition, we screened reference lists of studies fulfilling inclusion criteria for additional relevant articles. In case of incomplete data, we contacted the corresponding study authors to provide us with additional information. For our search, we used Medical Subject Heading (MeSH) terms and keywords such as "hospital admission," "hospitalization," and "atrial fibrillation." No language or geographical restrictions were applied to the search, and abstracts were included. The complete search strategy is outlined in Supplemental Figure S1.

Two independent reviewers (P.M. and Se.B.) screened titles and abstracts of all articles identified in the initial search. Full texts of all potentially eligible manuscripts were reviewed by the same authors for eligibility. Disagreements were resolved through discussion or third-party arbitration (St.B.).

Data extraction and outcome assessment

From each eligible study, we extracted in duplicate the following information using a standardized case report form: study design, participating country, year of publication, total number of patients, AF type, follow-up time, average age of patients, number and percentages of male patients, cardiovascular risk factors (hypertension, diabetes), cardiovascular comorbidities including coronary artery disease, heart failure, previous stroke or transient ischemic attack (TIA), and peripheral vascular disease and noncardiovascular comorbidities including chronic pulmonary disease, chronic kidney disease, and cancer.

As the main outcome, we extracted the reported incidence of all-cause hospital admissions. If available, we also extracted incidences on admissions for cardiovascular vs noncardiovascular causes. Extracted data were entered into a Microsoft Access database (Microsoft Corp, Redmond, Washington).

Assessment of study quality

The methodological quality of included studies was evaluated using a modified version of the Newcastle-Ottawa Scale.[17] We focused on the individual components of the Newcastle-Ottawa Scale and excluded the comparability component from the scale because it did not apply to this meta-analysis. The following quality components were evaluated: representativeness of the study population, methods of the outcome assessment, and adequacy of follow-up assessment. Studies were categorized as having a high study quality

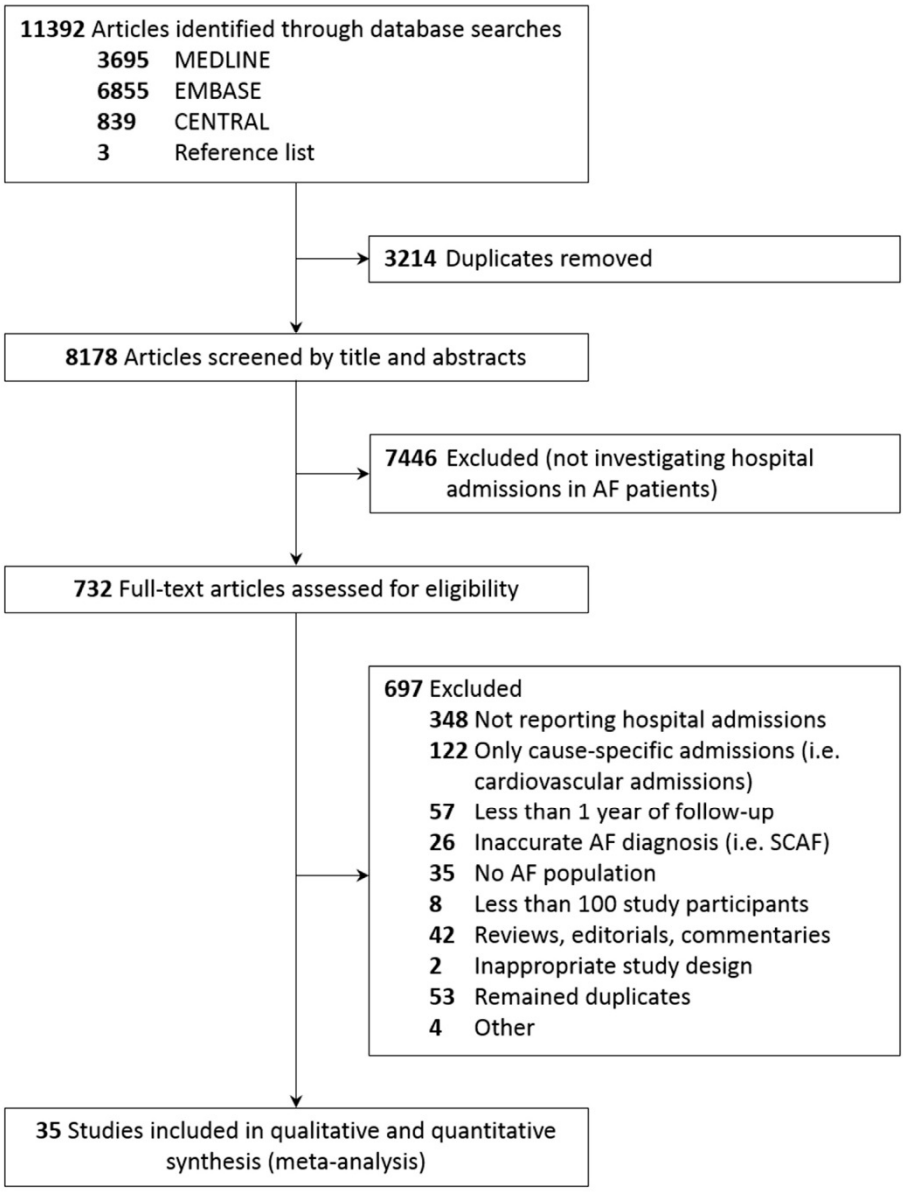

Figure 1. Flow diagram of literature search strategy. SCAF, subclinical atrial fibrillation.

(3 points), moderate study quality (2 points), or low study quality ($\leq$ 1 point).

Statistical analyses

If not available in the original publication, we calculated the incidence of all-cause, cardiovascular and noncardiovascular hospital admissions by dividing the number of admissions by the mean follow-up time in years multiplied with the total number of patients with AF. We calculated 95% confidence intervals (95% CI) approximating the Poisson distribution. Incidence rates were pooled using random-effect models according to the method described by DerSimonian and Liard.[18]

The influence of each individual study on the overall incidence estimate was tested in a sensitivity analysis by sequentially excluding each study and subsequently repeating the meta-analysis. The between-study heterogeneity was assessed using the Cochran's Q statistic and quantified by the I^2 statistic. We considered I^2 values $\geq$ 50% to indicate substantial heterogeneity and values $\geq$ 75% considerable heterogeneity.[19]

To explore the between-study heterogeneity, we divided study results into subgroups according to predefined study-level characteristics (geographical region, sample size, study design, publication status [peer-reviewed article versus abstract], and study quality) and compared them using random-effects meta-regression.[20] Differences in incidence across

Table 1. Characteristics of included studies

Author, year	Study design	Country	No. of patients	Age, years	Male sex, no. (%)	Hypertension, no. (%)	Heart failure, no. (%)	Prior stroke/TIA, no. (%)	Follow-up, years	NOS*
Hohnloser et al.[23] 2000	Randomized controlled trial	Germany	252	Mean (SD), 60.5 (9.5)	184 (73)	123 (49)	0 (0)	N/R	Mean: 1	1
Inglis et al.[24] 2004	Randomized controlled trial	Australia	152	Mean (SD), 73.3 (8.8)	81 (53)	85 (56)	87 (57)	N/R	Mean: 5	3
Nieuwlaat et al.[25] 2008	Prospective cohort	Europe	3890	Mean (SD), 66.4 (12.1)	2199 (57)	N/R	N/R	N/R	Median (IQR), 1 (1-1.1)	2
Ahmed et al.[26] 2009	Randomized controlled trial	United States, Canada	487	Mean (SD), 63.2 (11.2)	417 (86)	286 (59)	487 (100)	N/R	Median (range), 1.8 (1-50)	2
Connolly et al.[27] 2009	Randomized controlled trial	International	18113	Mean (SD), 72 (8.7)	11514 (64)	14283 (79)	5793 (32)	3623 (20)	Median: 2.0	3
Reynolds et al.[28] 2010	Prospective cohort	United States, Canada	933	Mean (SD), 66 (14)	559 (60)	452 (48)	423 (45)	N/R	Mean (SD), 2.0 (0.8)	2
Yusuf et al.[29] 2011	Randomized controlled trial	International	9016	Mean (SD), 69.5 (9.7)	5475 (61)	7929 (88)	2881 (32)	1212 (13)	4.1	3
Linssen et al.[30] 2011	Randomized controlled trial	Netherlands	336	Mean (SD), 73 (9.5)	218 (65)	154 (46)	336 (100)	57 (17)	1.5	2
Torp-Pedersen et al.[31] 2011	Randomized controlled trial	International	4628	Mean (SD), 71.6 (9)	2459 (53)	3995 (86)	979 (21)	N/R	Mean (SD), 1.8 (0.4)	3
Amin et al.[32] 2012	Retrospective cohort	United States	3498	Mean (SD), 80 (7.6)	1484 (42)	3119 (89)	0 (0)	546 (16)	1	2
Naccarelli et al.[33] 2012	Retrospective cohort	United States	55774	Mean (SD), 77.7 (6.8)	29129 (52.2)	44877 (80)	0 (0)	4186 (8)	Mean (SD), 2.0 (0.7)	1
Piccini et al.[34] 2012	Retrospective cohort	United States	15423	Mean (SD), 72 (5.3)	9158 (59)	12072 (78)	3980 (26)	992 (6)	1	2
Vidal-Perez et al.[35] 2013	Prospective cohort	Spain	778	Mean (SD), 74.8 (9.2)	413 (53)	595 (76)	96 (12)	64 (8)	Mean (SD), 2.8 (0.7)	3
Hohnloser et al.[36] 2013	Randomized controlled trial	International	5599	Mean (SD), 70 (9.5)	3277 (59)	4837 (86)	2171 (39)	764 (14)	Mean: 1.1	2
Mohanty et al.[55] 2013	Randomized controlled trial†	Italy	360	Mean (SD), 61.5 (9.5)	273 (76)	N/R	N/R	N/R	Mean (SD), 1.7 (0.8)	0
LaPointe et al.[57] 2014	Retrospective cohort	United States	79232	Median (IQR), 57 (51-61)	50708 (64)	40408 (51)	9508 (12)	3962 (5)	Median (IQR), 1.1 (0.5-2.0)	2
Bengtson et al.[38] 2014	Prospective cohort	United States	932	Mean (SD), 73.5 (4.8)	519 (56)	559 (60)	98 (11)	N/R	Mean (SD), 4.1 (3.6)	2
Gallagher et al.[39] 2014	Retrospective cohort	United Kingdom	16513	Mean (SD), 74 (12)	8592 (52)	8113 (49)	1357 (8)	1844 (11)	Mean (SD), 1.9 (1.4)	2
Lip et al.[40] 2014	Prospective cohort	International	2589	Mean (SD), 68.7 (11.6)	1568 (61)	N/R	N/R	N/R	Mean (SD), 1 (0.1)	2
Ozin et al.[56] 2014	Prospective cohort†	Turkey	213	N/R	N/R	N/R	N/R	N/R	1	1
Steinberg et al.[9] 2014	Prospective cohort	United States	9484	Median (IQR), 75 (67-82)	5406 (57)	7872 (83)	3073 (32)	1423 (15)	1	3
Whitbeck et al.[41] 2014	Prospective cohort	United States, Canada	3804	Mean (SD), 69.7 (9)	61‡	N/R	N/R	N/R	Mean: 3.5	2
Khazanie et al.[42] 2014	Retrospective cohort	United States	11535	Mean (range), 81 (75-87)	54444 (47)	8406 (73)	11535 (100)	1911 (17)	3	2
Freeman et al.[43] 2015	Retrospective cohort	United States	14787	Mean (SD), 71.7 (11.3)	7714 (52)	11573 (78)	0 (0)	877 (6)	Median (IQR), 1.2 (0.5-2.0)	3
Wu et al.[44] 2015	Retrospective cohort	Canada	25284	Mean (SD), 70.4 (13.8)	14122 (56)	13270 (52)	4945 (20)	1631 (6)	1	1
DeVore et al.[45] 2016	Prospective cohort	International	14171	Median (IQR), 73 (65-78)	8566 (60)	12824 (90)	8851 (6)	7767 (55)	Median (IQR), 1.8 (1.3-2.3)	3

Continued

Table 1. Continued.

Author, year	Study design	Country	No. of patients	Age, years	Male sex, no. (%)	Hypertension, no. (%)	Heart failure, no. (%)	Prior stroke/TIA, no. (%)	Follow-up, years	NOS*
Kuck et al.[46] 2016	Randomized controlled trial	Europe	750	Mean (SD), 60 (9.5)	457 (61)	436 (58)	209 (28)	30 (4)	Mean (SD), 1.5 (0.8)	2
Steinberg et al.[47] 2016	Prospective cohort	United States	5738	Median (IQR), 71 (64-79)	3339 (58)	N/R	1187 (21)	683 (12)	Median: 1	2
Wen et al.[57] 2016	Retrospective cohort†	China	992	Mean (SD), 73.8 (11.7)	N/R	387 (39)	99 (10)	992 (100)	Mean (SD), 1.3 (0.4)	1
Cadrin-Tourigny et al.[48] 2017	Randomized controlled trial	International	655	Mean (SD), 69.8 (10.4)	530 (81)	N/R	655 (100)	49 (7)	Mean (SD), 3.1 (1.6)	2
Chamberlain et al.[49] 2017	Prospective cohort	United States	1430	Mean (SD), 73.6 (13.8)	695 (49)	1016 (71)	260 (18)	208 (15)	Mean (SD), 6.3 (3.9)	2
Ferguson et al.[50] 2017	Prospective cohort	Australia	133	Mean (SD), 72 (16)	87 (65)	85 (64)	133 (100)	29 (22)	1	2
Gibson et al.[51] 2017	Randomized controlled trial	International	2124	Mean (SD), 70.1 (8.9)	1581 (74)	1571 (74)	542 (26)	N/R	1	3
Vora et al.[52] 2017	Prospective cohort	India	1537	Mean (SD), 54.7 (15.9)	746 (49)	482 (31)	288 (19)	141 (9)	1	2
Zweiker et al.[53] 2017	Retrospective cohort	Austria	172	Median (IQR), 82 (78-85)	107 (62)	143 (83)	25 (15)	N/R	1	1

IQR, interquartile range; NOS, Newcastle Ottawa Scale; N/R, not reported; Ref., reference; SD, standard deviation TIA, transient ischemic attack.
* 3 points indicate high quality, 2 points moderate, and ≤ 1 point low quality.
† Abstract from conferences.
‡ This information was extracted from the baseline characteristics reported in the main study.

predefined characteristics (age, sex, duration of follow-up, hypertension, diabetes, coronary artery disease, previous stroke or TIA, heart failure, peripheral vascular disease, chronic pulmonary disease, chronic kidney disease, and cancer) were explored using meta-regression analysis. The R^2 value was used to indicate the proportion of between-study variability explained by the model. As most characteristics were available only in a minority of studies, we did not perform multivariable analyses.

Specific causes for hospital admissions were extracted if available and classified into the following categories: AF-related, heart failure, bleeding, stroke, myocardial infarction, systemic embolism, bacterial and viral infections, gastrointestinal, respiratory, renal, neurological, cancer, endocrine and metabolic, hematological, skin and soft tissue, and psychiatric. Proportions for each cause category and corresponding 95% CIs were calculated and subsequently pooled using random-effects meta-analysis.

Publication bias was examined by visual inspection of funnel plots and using Egger's tests.[21,22] All analyses were performed using Stata, version 13.0 (StataCorp LLC, College Station, Texas). Statistical tests were 2-tailed, and a $P < 0.05$ was considered to indicate statistical significance.

Results

Characteristics of included studies

A total of 35 studies including 311,314 patients with AF were included, 32 full-text articles,[9,23-54] and 3 abstracts (Fig. 1, Table 1).[55-57] Twenty-five articles were prospective studies (13 prospective cohorts and 12 randomized controlled trials) (n = 88,104), and 10 were retrospective cohort studies (n = 223,210). Fourteen studies were conducted in North America, 10 in Europe, 2 in Australia, 1 in China, 1 in India, and 7 were international studies. The median number of participants per study was 3498 (interquartile range [IQR], 750-9,484). The average age in each study ranged from 55 to 82 years, and 42% to 86% of the participants were men. The average duration of follow-up was 1.5 (range: 1 to 6.3) years. From the assessment of study quality using the Newcastle-Ottawa Scale, 9 studies received 3 points, 19 studies received 2 points, 6 studies received 1 point, and 1 abstract received 0 points (Table 1) (see full study quality assessment in the Supplemental Table S1).

Incidence of all-cause hospital admissions

The pooled incidence of all-cause hospital admissions was 43.7 (95% CI, 38.5-48.9) per 100 person-years. The individual incidence rates ranged from 8.9 to 88.0 per 100 person-years, indicating considerable between-study heterogeneity ($I^2 = 99.9\%$, $P < 0.001$) (Fig. 2). None of the individual studies strongly influenced the pooled estimate, as shown in Supplemental Table S2. There was no statistically significant difference in the incidence of hospital admission across different geographic regions, sample size, study design, publication status, or total Newcastle Ottawa Scale (all P for difference > 0.05), as shown in Figure 3.

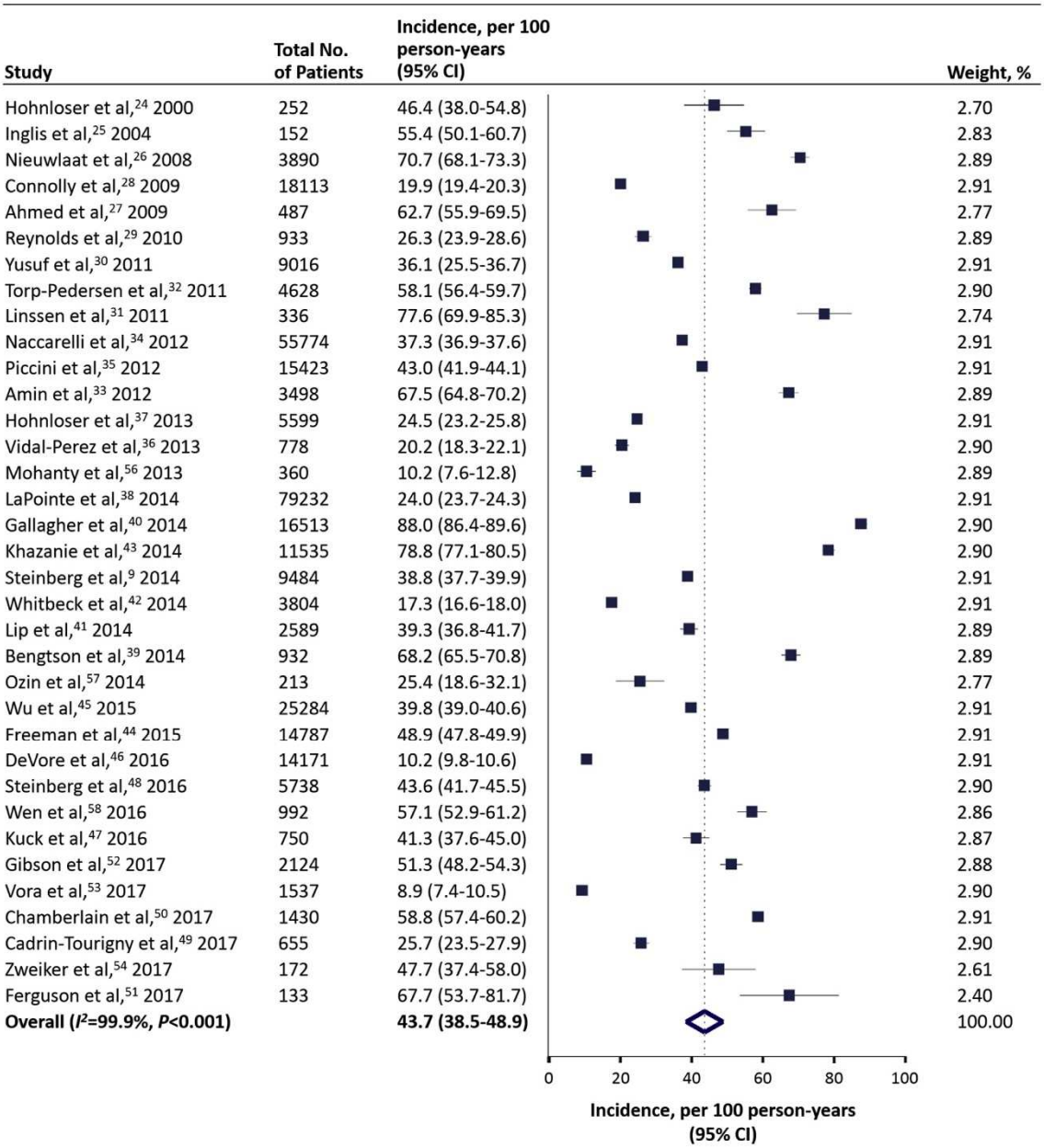

Figure 2. Cumulative incidence of all-cause hospital admissions. **Small black squares** represent the individual study incidence estimates with corresponding 95% confidence interval denoted by **black lines**. The **blue diamond** represents the pooled incidence estimate. Meta-anaylsis is done with random-effects model.

Cardiovascular vs noncardiovascular hospital admissions

Twenty-four studies including 234,028 patients provided separate data on the rates of cardiovascular and noncardiovascular admissions. In these studies, the pooled incidence of cardiovascular and noncardiovascular hospital admissions was 26.3 (95% CI, 22.7-29.9; I^2 = 99.9%, P < 0.001) and 15.7 (95% CI, 12.5-18.9; I^2 = 99.8%, P < 0.001) per 100 person-years, respectively (Figs. 4 and 5). None of the individual studies significantly affected the summary estimates of either cardiovascular or noncardiovascular admissions (Supplemental Tables S3 and S4). No statistically significant variations in cardiovascular hospital admission rates were observed by geographic region, sample size, study design, and total Newcastle-Ottawa Scale (all P for difference > 0.05) (Supplemental Fig. S2). There were significant differences in incidence estimates of

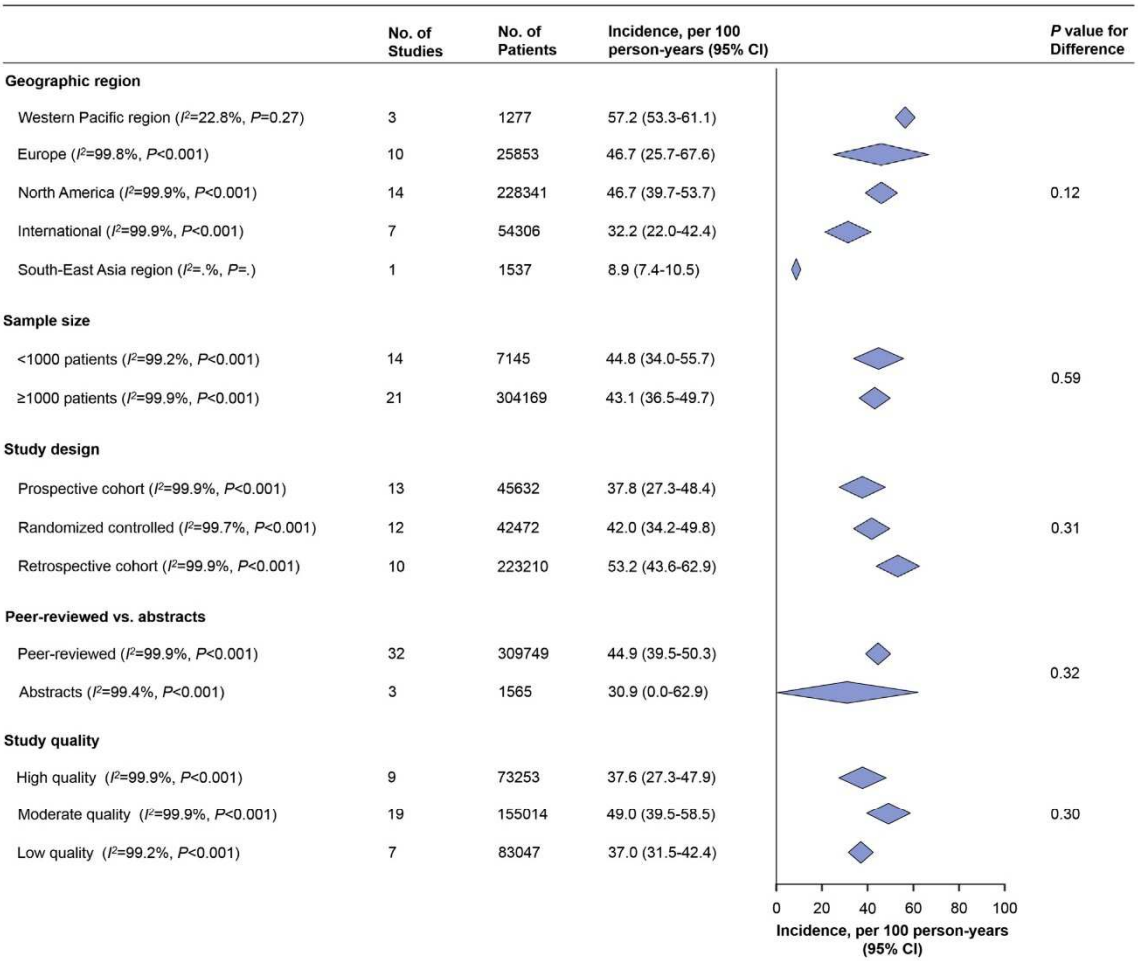

Figure 3. Cumulative incidence of all-cause hospital admissions stratified by study-level characteristics. **Blue diamonds** represent the pooled incidence estimate for each subgroup computed by random-effects models. Pooled estimates are weighted according to number of studies within the subgroups. *P* for difference between subgroups was calculated using random-effects meta-regression.

noncardiovascular admissions across different geographic regions (P for difference = 0.04). Further significant differences in incidence estimates of noncardiovascular admissions by sample size, study design and total Newcastle-Ottawa Scale were not observed, as presented in the Supplemental Fig. S3 (all P for difference > 0.05).

Specific causes for cardiovascular hospital admissions were reported in all 24 studies. AF-related admissions (22.0% [95% CI, 16.7%-27.2%]; $I^2 = 99.8\%$, $P < 0.001$) and admissions due to heart failure (16.6% [95% CI, 13.1%-20.2%]; $I^2 = 99.8\%$, $P < 0.001$) were the most common causes for cardiovascular admissions, followed by bleedings (5.9% [95% CI, 4.4%-7.5%]; $I^2 = 98.8\%$, $P < 0.001$), stroke (4.5% [95% CI, 4.4%-7.5%]; $I^2 = 97.9\%$, $P < 0.001$), and myocardial infarction (4.4% [95% CI, 3.4%-5.3%]; $I^2 = 97.2\%$, $P < 0.001$) (Supplemental Fig. S4). Four studies [24,36,45,51] including 22,046 patients provided specific causes for noncardiovascular hospital admissions, with the most common being bacterial infections (6.9% [95% CI, 0.0%-15.4%]; $I^2 = 99.2\%$, $P < 0.001$), gastrointestinal disorders (6.5% [95% CI, 4.3%-8.6%]; $I^2 = 88.5\%$, $P < 0.001$), and respiratory diseases (6.1% [95% CI, 3.2%-8.9%]; $I^2 = 94.5\%$, $P < 0.001$) (Supplemental Fig. S5).

Characteristics associated with hospital admissions

In meta-regression analyses, average age (R^2 across 34 studies 15.7%) and prevalence of chronic pulmonary disease (R^2 across 13 studies 49.8%) were significantly associated with the incidence of all-cause hospital admissions (Table 2). No significant associations were observed for sex; duration of follow-up; prevalence of hypertension, diabetes, coronary artery disease, history of stroke/TIA, heart failure, or chronic kidney disease (meta-regression plots of statistically significant associations are presented in Supplemental Fig. S6). No significant predictor for cardiovascular hospital admissions was identified (Table 2). Mean duration of follow-up, prevalence of chronic pulmonary disease, and prevalence of cancer were associated with a higher incidence of noncardiovascular

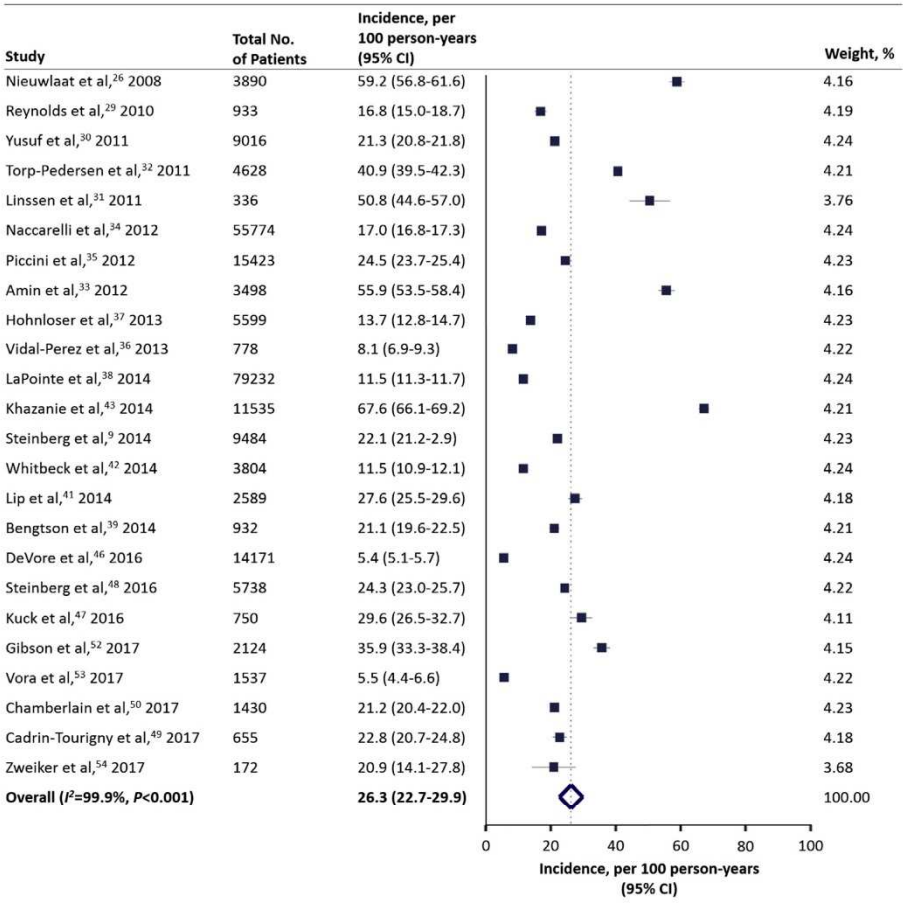

Figure 4. Cumulative incidence of cardiovascular hospital admissions. **Small black squares** represent the individual study incidence estimates with corresponding 95% confidence interval denoted by **black lines**. The **blue diamond** represents the pooled incidence estimate. Meta-anaylsis is done with random-effects model.

hospital admissions. Prevalence of chronic pulmonary disease explained 52.4% of the observed between-study heterogeneity across 9 studies, longer duration of follow-up explained 15.2% of the observed heterogeneity across 24 studies, and prevalence of cancer explained 99.9% of the observed heterogeneity across 3 studies.

Publication bias

Visual inspection of the funnel plot of studies reporting on cardiovascular hospitalizations showed some asymmetry (Supplemental Fig. S7) and the Egger's test indicated some evidence for publication bias suggesting that smaller studies present more extreme incidence rates ($P = 0.05$). No evidence of publication bias was observed for studies reporting on all-cause hospitalizations ($P = 0.06$), and noncardiovascular hospitalizations ($P = 0.87$), as shown in Supplemental Figs. S8 and S9.

Discussion

In this systematic review and meta-analysis of 35 studies including 311,314 patients with AF, we found a very high risk of hospital admissions, with a pooled incidence of 43.7 per 100 person-years. Patients with AF were more often admitted for cardiovascular causes (26.3 per 100 person-years) but also had substantial risk of admissions for noncardiovascular causes (15.7 per 100 person-years). Main risk factors for hospital admissions were older age, duration of follow-up, and major comorbidities such as chronic pulmonary disease and cancer.

In 2013, the estimated AF-related health care spending in the United States reached $27.7 billion, of which 41% was directly attributable to inpatient care.[58] Annual hospital admission rates in the general United States population were 10.4 per 100 person-years in 45 to 64 year old individuals, and 26.4 per 100 person-years in 65 to 84 year olds.[59] Our meta-analysis suggests that this risk is 1.6 times higher among patients with AF, underscoring the enormous burden these hospitalizations represent, both from a health and an economical perspective.

Most admissions for patients with AF are due to cardiovascular causes, with a pooled incidence of 26.3 per 100 person-years. Not surprisingly, the most common individual causes were due to AF-related conditions, heart failure, and stroke. Although lower, the risk of admissions for noncardiovascular causes was also considerable, with a pooled incidence of 15.7 per

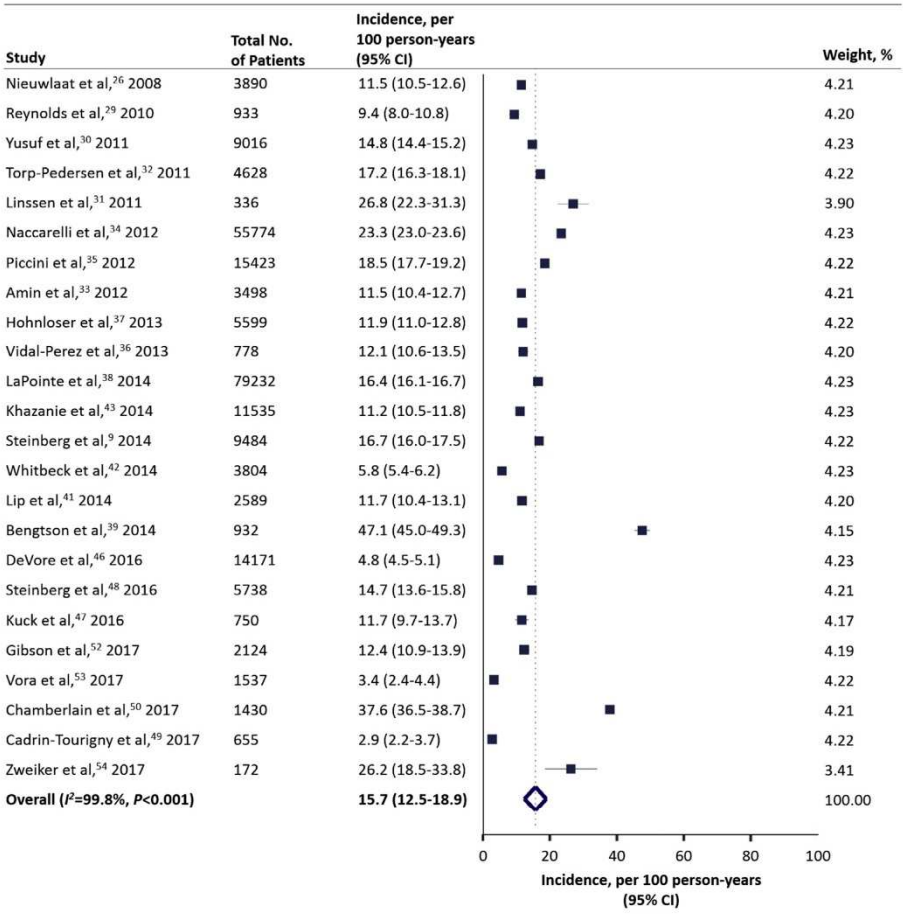

Figure 5. Cumulative incidence of noncardiovascular hospital admissions. **Small black squares** represent the individual study incidence estimates with corresponding 95% confidence intervals denoted by **black lines**. The blue diamond represents the pooled incidence estimate. Meta-anaylsis is done with random-effects model.

100 person-years. Unfortunately, information on specific admission causes was unavailable in most studies. Getting a better understanding on causes for noncardiovascular admissions will be crucial to develop effective prevention strategies.

Several patient characteristics significantly contributed to the observed between-study heterogeneity. Studies including older patients or patients who had a higher prevalence of chronic pulmonary disease or cancer had a higher incidence for all-cause or noncardiovascular admissions. None of the assessed characteristics explained the heterogeneity for cardiovascular admissions. Studies with longer follow-up duration resulted in higher incidence rates for noncardiovascular admissions, and there was some evidence of publication bias for all-cause and cardiovascular admissions. Regional differences in hospital admission did not significantly explain the observed heterogeneity in our study. Given the small number of studies in the subgroups and the potential associated decrease in statistical power, we cannot exclude the possibility that significant variations in admission rates exist across different subgroups. These data indicate that large long-term studies with more complete reporting of comorbidities are needed to get a better understanding in this area.

Reducing hospital admissions should be a major public health priority, not only from an economic perspective. Hospitalized patients with AF have a substantially higher risk of stroke and all-cause death compared with outpatients.[60,61] For example, an analysis of the **A**pixaban **Ver**sus Acetylsalicylic Acid (ASA) to P**r**event Str**oke**s in Atrial Fibrillation Patient**s** Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial showed that, compared with patients who did not need hospital admission, those admitted had an almost 4-fold higher risk of death after discharge.[36] This observation may also account for some of the variability in reported outcome rates in the literature. However, it is important to note that hospital admissions should be seen as a marker for patients who may have a worse prognosis because it is patient illness severity rather than hospital admission that increases the risk of death and other complications among admitted patients. Consequently, preventive interventions to reduce unplanned hospital admissions may also reduce other adverse events in this patient population.

Given the multiple cardiovascular and noncardiovascular causes associated with admissions for patients with AF,

Table 2. Meta-regression analyses

Characteristic	All-cause hospital admission				Cardiovascular hospital admission				Noncardiovascular hospital admission			
	No. of studies	β coefficient (95% CI)	*P* value	R^2, %*	No. of studies	β coefficient (95% CI)	*P* value	R^2, %*	No. of studies	β coefficient (95% CI)	*P* value	R^2, %*
Mean age, years	34/35	1.43 (0.33-2.53)	0.012	15.73	24/24	0.87 (−0.19 to 1.92)	0.10	-	24/24	0.51 (−0.13 to 1.16)	0.11	-
Male sex, %	33/35	−0.47 (−1.27 to 0.34)	0.25	-	24/24	−0.39 (−1.29 to 0.50)	0.37	-	24/24	−0.25 (−0.80 to 0.29)	0.34	-
Follow-up duration, years	35/35	1.48 (−4.24 to 7.21)	0.60	-	24/24	−1.62 (−7.06 to 3.81)	0.54	-	24/24	3.20 (0.20-6.21)	0.038	15.23
History of hypertension, %	29/35	−0.10 (−0.59 to 0.39)	0.69	-	20/24	0.16 (−0.32 to 0.64)	0.50	-	20/24	0.02 (−0.29 to 0.33)	0.90	-
History of diabetes mellitus, %	26/35	0.59 (−0.51 to 1.70)	0.28	-	18/24	0.42 (−0.69 to 1.52)	0.44	-	18/24	0.14 (−0.58 to 0.86)	0.68	-
History of coronary artery disease, %	28/35	0.23 (−0.13 to 0.59)	0.20	-	19/24	0.28 (−0.07 to 0.63)	0.11	-	19/24	−0.01 (−0.26 to 0.24)	0.93	-
Prior stroke/TIA, %	22/35	0.06 (−0.43 to 0.56)	0.79	-	16/24	−0.11 (−0.99 to 0.77)	0.79	-	16/24	−0.14 (−0.56 to 0.28)	0.48	-
History of heart failure, %	31/35	0.11 (−0.13 to 0.35)	0.36	-	22/24	0.20 (−0.03 to 0.43)	0.09	-	22/24	−0.10 (−0.26 to 0.06)	0.22	-
History of peripheral vascular disease, %	14/35	1.25 (−0.65 to 3.15)	0.18	-	12/24	0.83 (−1.27 to 2.92)	0.40	-	12/24	0.57 (−0.06 to 1.21)	0.07	-
History of chronic pulmonary disease, %	13/35	1.51 (0.57-2.45)	0.005	49.76	9/24	1.36 (−0.27 to 3.00)	0.09	-	9/24	0.91 (0.19-1.64)	0.021	52.40
History of chronic kidney disease, %	10/35	0.35 (−1.15 to 1.86)	0.60	-	7/24	−0.11 (−1.85 to 1.63)	0.88	-	7/24	0.14 (−0.73 to 1.01)	0.70	-
History of cancer, %	5/35	0.64 (−0.68 to 1.96)	0.22	-	3/24	0.14 (−4.73 to 5.00)	0.78	-	3/24	0.71 (0.47-0.95)	0.017	99.99

* R^2 value is only displayed if *P* value was < 0.05.

multidisciplinary approaches are needed to have a significant effect.[62] Previous studies suggested that providing access to health care to patients with chronic conditions reduces their need for future hospital readmissions.[63] As for the high burden of comorbidities, specific treatment should be optimized to reduce admission risk.[64] Self-management programs for patients with heart failure have shown to substantially reduce all-cause readmissions and readmissions due to heart failure; however, these effects remain to be determined in patients with AF.[65,66]

Limitations

There are some limitations that should be considered when interpreting the findings of this meta-analysis. First, this current study is based on aggregated published data from studies with different methodologies and patient characteristics and not from individual patient-level data. The lack of standardized definitions for variables could have led to misclassification, particularly in retrospective studies that used administrative databases to collect data. However, there was no significant difference in incidence rates for admission across subgroups. Accordingly, the risk of misclassification bias seems low. Second, a substantial amount of the observed between-study heterogeneity remained largely unexplained by the variables examined. Third, some of the included studies did not report the incidence rate or person-years of follow-up. Both variables had to be calculated from the information available and might therefore slightly differ from the true results. Finally, data on cause specific hospital admissions were incomplete, particularly for studies related to noncardiovascular admissions.

Conclusions

Patients with AF have a very high risk of being admitted to the hospital, both for cardiovascular and noncardiovascular causes. Further research is needed to determine interdisciplinary strategies for reducing unplanned hospital admissions and subsequently preventing adverse events in this population. Successful strategies to prevent hospital admissions may have a large impact not only on individual patients but also on the overall health care system, as hospital admissions constitute more than 50% of the estimated health care spending in AF patients.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.05.024.

Supplement

Risk of Hospital Admissions in Patients with Atrial Fibrillation: A Systematic Review and Meta-analysis

Pascal Meyre, Steffen Blum, Sebastian Berger, Stefanie Aeschbacher, Hadrien Schoepfer, Matthias Briel, Stefan Osswald, David Conen

Figure S9 Funnel Plot Assessing Small Study Effects in 24 Studies Reporting on the Incidence of Non-cardiovascular Hospital Admissions

Figure legends

Figure S2 Cumulative Incidence of Cardiovascular Hospital Admissions Stratified by Study-Level Characteristics

Blue diamonds represent the pooled incidence estimate for each subgroup computed by random-effects models. Pooled estimates are weighted according to number of studies within the subgroups. P for difference between subgroups was calculated using random-effects meta-regression.

Figure S3 Cumulative Incidence of Non-cardiovascular Hospital Admissions Stratified by Study-Level Characteristics

Blue diamonds represent the pooled incidence estimate for each subgroup computed by random-effects models. Pooled estimates are weighted according to number of studies within the subgroups. P for difference between subgroups was calculated using random-effects meta-regression.

Figure S4 Meta-analysis of the Proportions of Specific Causes for Cardiovascular Hospital Admissions

Proportions from each study were pooled using random-effects meta-analysis. Gray diamonds represent the pooled proportion of each specific cause for cardiovascular hospitalization.

Figure S5 Meta-analysis of the Proportions of Specific Causes for Non-cardiovascular Hospital Admissions

Proportions from each study were pooled using random-effects meta-analysis. Gray diamonds represent the pooled proportion of each specific cause for non-cardiovascular hospitalization.

Figure S6 Meta-regression Plots of the Associations Between Incidence of Hospital Admissions and Study and Patient Characteristics

Each study is depicted by a circle, the size of the circle represents the weight of the study in the random-effects meta-analysis. The regression line is the best fit for the meta-regression model with the estimated 95% CI denoted as dashed lines.

A) Association between incidence of all-cause hospital admissions and mean age.

B) Association between incidence of all-cause hospital admissions and prevalence of chronic pulmonary disease.

C) Association between incidence of non-cardiovascular admissions and mean follow-up duration.

D) Association between incidence of non-cardiovascular admissions and prevalence of chronic pulmonary disease.

E) Association between incidence of non-cardiovascular admissions and prevalence of cancer.

Figure S7 Funnel Plot Assessing Small Study Effects in 35 Studies Reporting on the Incidence of All-cause Hospital Admissions

Each dot represents a single study. On the x-axis are the log transformed incidence estimates and the corresponding standard errors are on the y-axis. Larger studies are placed towards the top and smaller studies are placed towards the bottom. Visually inspected smaller studies show larger standard errors and larger incidence rates. Results from the Egger's test indicate marginally no evidence of publication bias (p=0.06).

Figure S8 Funnel Plot Assessing Small Study Effects in 24 Studies Reporting on the Incidence of Cardiovascular Hospital Admissions

Each dot represents a single study. On the x-axis are the log transformed incidence estimates and the corresponding standard errors are on the y-axis. Larger studies are placed towards the top and smaller studies are placed towards the bottom. Visually inspected smaller studies show larger standard errors and larger incidence rates. Results from the Egger's test indicate statistically significant evidence of publication bias (p=0.05).

Figure S9 Funnel Plot Assessing Small Study Effects in 24 Studies Reporting on the Incidence of Non-cardiovascular Hospital Admissions

Each dot represents a single study. On the x-axis are the log transformed incidence estimates and the corresponding standard errors are on the y-axis. Larger studies are placed towards the top and smaller studies are placed towards the bottom. Visually only few studies show larger standard errors and larger incidence rates. Results from the Egger's test indicate no statistically significant evidence of publication bias (p=0.87).

Figure S1 Literature Search Strategy

Search documentation from 12/21/2017.

Literature search in MEDLINE (via PubMed):

Concept 1 **Atrial Fibrillation**	MeSH "Atrial Fibrillation"[Mesh] OR Keywords atrial fibrillation*[Title/Abstract] OR AF[Title/Abstract] OR AFib[Title/Abstract] OR auricular fibrillation[Title/Abstract]

AND

Concept 2 **Hospitalization**	MeSH "Hospitalization"[Mesh] OR "Patient Admission"[Mesh] OR "Patient Readmission"[Mesh] OR Keywords hospitalization*[Title/Abstract] OR hospitalisation*[Title/Abstract] OR hospitalized[Title/Abstract] OR hospitalised[Title/Abstract] OR rehospitalization*[Title/Abstract] OR rehospitalisation*[Title/Abstract] OR rehospitalized[Title/Abstract] OR rehospitalised[Title/Abstract] OR hospital admission*[Title/Abstract] OR hospital readmission*[Title/Abstract]

Literature search in EMBASE:

Concept 1 **Atrial Fibrillation**	Emtree 'atrial fibrillation'/exp OR Title, abstract, keywords 'atrial fibrillation*':ti,ab,kw OR 'AF':ti,ab,kw OR 'AFib':ti,ab,kw OR 'auricular fibrillation':ti,ab,kw

AND

Concept 2 **Hospitalization**	Emtree 'hospitalization'/exp OR Title, abstract, keywords

	'hospitalization*':ti,ab,kw OR 'hospitalisation*':ti,ab,kw OR 'hospitalized':ti,ab,kw OR 'hospitalised':ti,ab,kw OR 'rehospitalization*':ti,ab,kw OR 'rehospitalisation*':ti,ab,kw OR 'rehospitalized':ti,ab,kw OR 'rehospitalised':ti,ab,kw OR 'hospital admission*':ti,ab,kw OR 'hospital readmission*':ti,ab,kw

Literature search in the CENTRAL:

Concept 1 **Atrial Fibrillation**	MeSH "Atrial Fibrillation"[Mesh] OR Keywords atrial fibrillation*[Title/Abstract] OR AF[Title/Abstract] OR AFib[Title/Abstract] OR auricular fibrillation[Title/Abstract]

AND

Concept 2 **Hospitalization**	MeSH "Hospitalization"[Mesh] OR "Patient Admission"[Mesh] OR "Patient Readmission"[Mesh] OR Keywords hospitalization*[Title/Abstract] OR hospitalisation*[Title/Abstract] OR hospitalized[Title/Abstract] OR hospitalised[Title/Abstract] OR rehospitalization*[Title/Abstract] OR rehospitalisation*[Title/Abstract] OR rehospitalized[Title/Abstract] OR rehospitalised[Title/Abstract] OR hospital admission*[Title/Abstract] OR hospital readmission*[Title/Abstract]

Table S1 Sensitivity Analysis of the Incidence of All-cause Hospital Admissions

Study excluded, Year	Pooled incidence, per 100 person-years	95% confidence interval	I^2
Excluding Hohnloser et al, 2000	43.6	38.3-48.9	99.9%
Excluding Inglis et al, 2004	43.3	38.1-48.6	99.9%
Excluding Nieuwlaat et al, 2008	42.9	37.7-48.1	99.9%
Excluding Ahmed et al, 2009	43.1	37.9-48.4	99.9%
Excluding Connolly et al, 2009	44.4	38.9-49.9	99.9%
Excluding Reynolds et al, 2010	44.2	38.9-49.5	99.9%
Excluding Yusuf et al, 2011	43.9	38.5-49.4	99.9%
Excluding Linssen et al, 2011	42.7	37.5-48.0	99.9%
Excluding Torp-Pedersen et al, 2011	43.2	38.0-48.4	99.9%
Excluding Amin et al, 2012	43.0	37.7-48.2	99.9%
Excluding Naccarelli et al, 2012	43.9	38.3-49.5	99.9%
Excluding Piccini et al, 2012	43.7	38.4-49.0	99.9%
Excluding Vidal-Perez et al, 2013	44.4	39.1-49.7	99.9%
Excluding Hohnloser et al, 2013	44.3	38.9-49.6	99.9%
Excluding Mohanty et al, 2013	44.7	39.4-49.9	99.9%
Excluding LaPointe et al, 2014	44.3	38.4-50.3	99.9%
Excluding Bengtson et al, 2014	42.9	37.7-48.2	99.9%
Excluding Gallagher et al, 2014	42.3	37.4-47.2	99.9%
Excluding Lip et al, 2014	43.8	38.5-49.1	99.9%
Excluding Ozin et al, 2014	44.2	38.9-49.5	99.9%
Excluding Steinberg et al, 2014	43.8	38.5-49.1	99.9%
Excluding Whitbeck et al, 2014	43.7	38.5-48.9	99.9%
Excluding Khazanie et al, 2014	42.6	37.6-47.6	99.9%
Excluding Freeman et al, 2015	43.5	38.3-48.7	99.9%
Excluding Wu et al, 2015	43.8	38.5-49.1	99.9%
Excluding DeVore et al, 2016	44.7	39.8-49.5	99.9%
Excluding Kuck et al, 2016	43.7	38.5-49.0	99.9%
Excluding Steinberg et al, 2016	43.7	38.4-49.0	99.9%
Excluding Wen et al, 2016	43.3	38.0-48.5	99.9%
Excluding Cadrin-Tourigny et al, 2017	44.2	38.9-49.5	99.9%
Excluding Chamberlain et al, 2017	43.2	38.1-48.4	99.9%
Excluding Gibson et al, 2017	43.5	38.2-48.7	99.9%
Excluding Ferguson et al, 2017	43.1	37.8-48.3	99.9%
Excluding Vora et al, 2017	44.7	39.5-50.0	99.9%
Excluding Zweiker et al, 2017	43.6	38.3-48.8	99.9%
Pooled estimate	43.7	38.5-48.9	99.9%

Table S2 Sensitivity Analysis of the Incidence of Cardiovascular Hospital Admissions

Study excluded, Year	Pooled incidence, per 100 person-years	95% confidence interval	I^2
Excluding Nieuwlaat et al, 2008	24.9	21.4-28.4	99.9%
Excluding Reynolds et al, 2010	26.7	23.1-30.4	99.9%
Excluding Yusuf et al, 2011	26.6	22.8-30.3	99.9%
Excluding Linssen et al, 2011	25.4	21.7-29.0	99.9%
Excluding Torp-Pedersen et al, 2011	25.7	22.1-29.2	99.9%
Excluding Amin et al, 2012	25.0	21.5-28.6	99.9%
Excluding Naccarelli et al, 2012	26.8	22.5-31.0	99.9%
Excluding Piccini et al, 2012	26.4	22.7-30.1	99.9%
Excluding Vidal-Perez et al, 2013	27.1	23.4-30.8	99.9%
Excluding Hohnloser et al, 2013	26.9	23.2-30.6	99.9%
Excluding Mohanty et al, 2013	26.3	22.7-29.9	99.9%
Excluding LaPointe et al, 2014	27.0	22.7-31.4	99.9%
Excluding Bengtson et al, 2014	26.6	22.9-30.2	99.9%
Excluding Gallagher et al, 2014	26.3	22.7-29.9	99.9%
Excluding Lip et al, 2014	26.3	22.6-29.9	99.9%
Excluding Steinberg et al, 2014	26.5	22.8-30.2	99.9%
Excluding Whitbeck et al, 2014	26.3	22.7-29.9	99.9%
Excluding Khazanie et al, 2014	24.5	21.3-27.6	99.9%
Excluding DeVore et al, 2016	27.2	23.7-30.8	99.9%
Excluding Kuck et al, 2016	26.2	22.5-29.8	99.9%
Excluding Steinberg et al, 2016	26.4	22.7-30.1	99.9%
Excluding Cadrin-Tourigny et al, 2017	26.5	22.8-30.2	99.9%
Excluding Chamberlain et al, 2017	26.6	22.9-30.2	99.9%
Excluding Gibson et al, 2017	25.9	22.3-29.6	99.9%
Excluding Vora et al, 2017	27.2	23.6-30.9	99.9%
Excluding Zweiker et al, 2017	26.5	22.9-30.2	99.9%
Pooled estimate	26.3	22.7-29.9	99.9%

Table S3 Sensitivity Analysis of the Incidence of Non-cardiovascular Hospital Admissions

Study excluded, Year	Pooled incidence, per 100 person-years	95% confidence interval	I^2
Excluding Nieuwlaat et al, 2008	15.9	12.5-19.3	99.9%
Excluding Reynolds et al, 2010	16.0	12.6-19.4	99.9%
Excluding Yusuf et al, 2011	15.7	12.3-19.2	99.9%
Excluding Linssen et al, 2011	15.2	12.0-18.5	99.9%
Excluding Torp-Pedersen et al, 2011	15.6	12.3-18.9	99.9%
Excluding Amin et al, 2012	15.9	12.6-19.2	99.9%
Excluding Naccarelli et al, 2012	15.3	12.4-18.2	99.8%
Excluding Piccini et al, 2012	15.6	12.3-19.9	99.9%
Excluding Vidal-Perez et al, 2013	15.9	12.5-19.3	99.9%
Excluding Hohnloser et al, 2013	15.9	12.5-19.2	99.9%
Excluding Mohanty et al, 2013	15.7	12.5-18.9	99.8%
Excluding LaPointe et al, 2014	15.7	12.0-19.3	99.8%
Excluding Bengtson et al, 2014	14.3	11.1-17.5	99.8%
Excluding Gallagher et al, 2014	15.7	12.5-18.9	99.8%
Excluding Lip et al, 2014	15.9	12.6-19.1	99.9%
Excluding Steinberg et al, 2014	15.6	12.3-19.0	99.9%
Excluding Whitbeck et al, 2014	16.1	12.8-19.4	99.8%
Excluding Khazanie et al, 2014	15.9	12.5-19.2	99.9%
Excluding DeVore et al, 2016	16.1	13.2-19.1	99.8%
Excluding Kuck et al, 2016	15.9	12.6-19.1	99.9%
Excluding Steinberg et al, 2016	15.7	12.4-19.0	99.9%
Excluding Cadrin-Tourigny et al, 2017	16.2	13.0-19.5	99.8%
Excluding Chamberlain et al, 2017	14.7	11.6-17.8	99.8%
Excluding Gibson et al, 2017	15.8	12.5-19.1	99.9%
Excluding Vora et al, 2017	16.2	13.0-19.5	99.8%
Excluding Zweiker et al, 2017	15.3	12.1-18.6	99.9%
Pooled estimate	15.7	12.5-18.9	99.8%

Table S4 Assessment of Study Quality Using a Modified Version of the Newcastle Ottawa Scale (NOS)

Author (study)	Representativeness of the population	Standardization of outcome assessment	Losses to follow-up	Total
Hohnloser et al, 2000	**0** (Only persistent AF, patients with HF excluded)	**0** (not reported)	**1** (2.3%)	**1**
Inglis et al, 2004	**1** (Recurrent paroxysmal or sustained AF patients)	**1** (Computerized medical records system and individual case records.)	**1** (Minimal loss, but no description)	**3**
Nieuwlaat et al, 2008	**1** (18 years or older and had AF on ECG or Holter recording)	**1** (medical records and patient interview)	**0** (20%)	**2**
Ahmed et al, 2009	**1** (Patients with history of AF)	**1** (Investigators were blinded to the outcome ascertained)	**0** (not reported)	**2**
Connolly et al, 2009	**1** (AF documented on ECG)	**1** (Two blinded independent investigators performed outcome assessment)	**1** (0.1%)	**3**
Reynolds et al, 2010	**1** (AF/AFL documented on ECG)	**1** (Standardized case report forms)	**0** (not reported)	**2**
Yusuf et al, 2011	**1** (Permanent AF or at least two episodes of intermittent AF in the previous 6 months)	**1** (Independent blind assessment)	**1** (2.5%)	**3**

Linssen et al, 2011	**1** (Heart failure population with and without diagnosed AF on ECG)	**1** (chart reviews, databases and interviews)	**0** (not reported)	**2**
Torp-Pedersen et al, 2011	**1** (Patients with paroxysmal or persistent AF, or AFL)	**1** (Categorized by the investigator)	**1** (0.04%)	**3**
Amin et al, 2012	**1** (Patients hospitalized with AF/AFL as the primary diagnosis [ICD])	**1** (Recordings for outcome assessment: PharMetrics Patient-Centric database)	**0** (not reported)	**2**
Naccarelli et al, 2012	**0** (AF patients aged <65 years and with histories of heart failure were excluded)	**1** (Classified using the primary ICD-9-CM diagnosis code)	**0** (not reported)	**1**
Piccini et al, 2012	**1** (AF patients aged <65 years were excluded)	**1** (Categorized hospitalizations using ICD-9-CM codes)	**0** (not reported)	**2**
Vidal-Perez et al, 2013	**1** (GP enrolled all his/her patients aged >18 years with AF)	**1** (Assessment from patients' clinical interview and hospital records)	**1** (2.5%)	**3**
Hohnloser et al, 2013	**1** (Patients aged ≥50 years and ECG documented AF)	**1** (From local investigator through hospitalization case report forms)	**1** (not reported)	**2**
Mohanty et al, 2013	**0** (Only patients with paroxysmal AF and right-AFL)	**0** (not reported)	**0** (not reported)	**0**

LaPointe et al, 2014	**1** (AF patients aged <65 years)	**1** (ICD-9-CM codes were used for assessment)	**0** (not reported)	**2**
Bengtson et al, 2014	**1** (AF patients aged >65 years)	**1** (Medicare claims were classified based on the primary discharge diagnosis code [ICD-9-CM codes])	**0** (not reported)	**2**
Gallagher et al, 2014	**1** (AF documented in data bases)	**1** (From databases using primary ICD-10 codes)	**0** (not reported)	**2**
Lip et al, 2014	**1** (ECG-confirmed diagnosis of AF)	**1** (by local cardiologist investigator)	**0** (15%)	**2**
Ozin et al, 2014	**1** (Patients aged >18 years with AF)	**0** (not reported)	**0** (not reported)	**1**
Steinberg et al, 2014	**1** (Patients aged >18 years and had ECG-confirmed diagnosis of AF.)	**1** (Web-based case report form using patients' medical record and information from physicians)	**1** (0%)	**3**
Whitbeck et al, 2014	**1** (AF patients aged ≥65 years and a least one comorbidity)	**1** (Investigators were blinded to the outcome ascertained)	**0** (not reported)	**2**
Khazanie et al, 2014	**1** (Patients aged ≥65 years with AF diagnosis based on the ICD-9-CM code)	**1** (Identified on the basis of inpatient claims)	**0** (not reported)	**2**

Freeman et al, 2015	**1** (Patients aged ≥21 years and diagnosed AF or AFL based on the ICD-9-CM code)	**1** (Using comprehensive hospital discharge and billing claims databases)	**1** (0%)	**3**
Wu et al, 2015	**1** (Albertans aged ≥20 years with diagnosed AF in any healthcare encounter using the ICD-9-CM code)	**0** (not reported)	**0** (not reported)	**1**
DeVore et al, 2016	**1** (Patients with paroxysmal or persistent AF.)	**1** (Standardized questionnaire was used to query patients for all-cause hospitalizations)	**1** (0.23%)	**3**
Kuck et al, 2016	**0** (Only patients with paroxysmal AF)	**1** (Personal study visits and phone interviews)	**1** (1%)	**2**
Steinberg et al, 2016	**1** (Patients ≥21 years of age with ECG-confirmed diagnosis of AF)	**1** (Web-based case report form was used)	**0** (not reported)	**2**
Wen et al, 2016	**0** (All patients had history of ischemic stroke)	**1** (Outpatient and inpatient medical records were followed)	**0** (not reported)	**1**
Cadrin-Tourigny et al, 2017	**0** (All AF patients had concomitant heart failure)	**1** (Outcomes were reviewed and classified by an independent blinded adjudicating committee)	**1** (9.7%)	**2**
Chamberlain et al, 2017	**1** (Patients ≥18 years of age and AF diagnosis using the ICD-9-CM code)	**1** (Data were obtained from a medical records-linkage system [REP])	**0** (not reported)	**2**

Ferguson et al, 2017	**1** (Patients aged ≥18 years and with heart failure and concomitant AF of any type)	**1** (Data were obtained using a standardized case report form)	**0** (not reported)	**2**
Gibson et al, 2017	**1** (Patients >18 years of age with ECG-confirmed diagnosis of paroxysmal, persistent, or permanent AF)	**1** (Two physicians blinded to study drug assignment were classified with a list of adverse events associated with rehospitalization)	**1** (0%)	**3**
Vora et al, 2017	**1** (All AF types considered)	**1** (Inperson visit at the recruitment site)	**0** (10.55%)	**2**
Zweiker et al, 2017	**0** (Only patients undergoing TAVI)	**1** (Inpatient records and physical archives were reviewed)	**0** (not reported)	**1**

Figure S2 Cumulative Incidence of Cardiovascular Hospital Admissions Stratified by Study-Level Characteristics

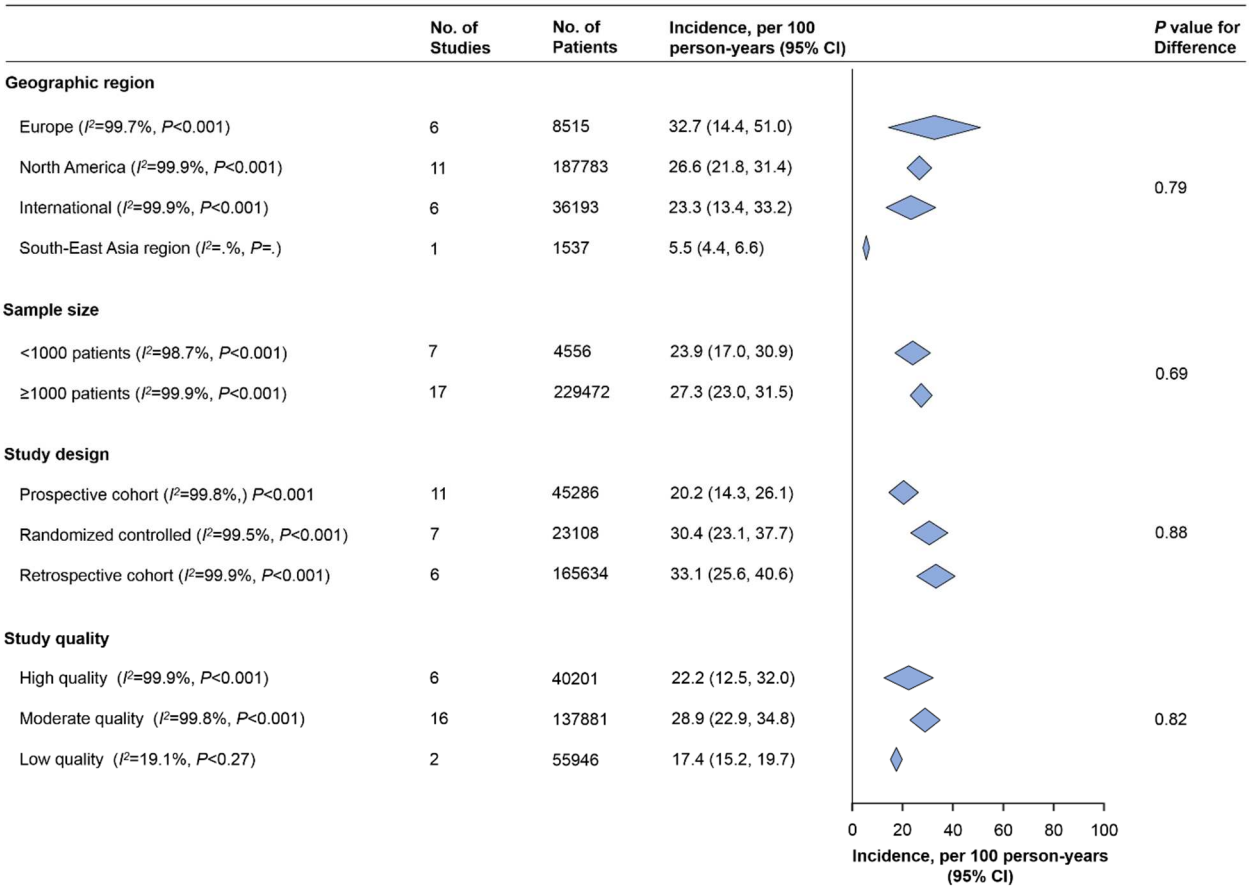


Figure S3 Cumulative Incidence of Non-cardiovascular Hospital Admissions Stratified by Study-Level Characteristics

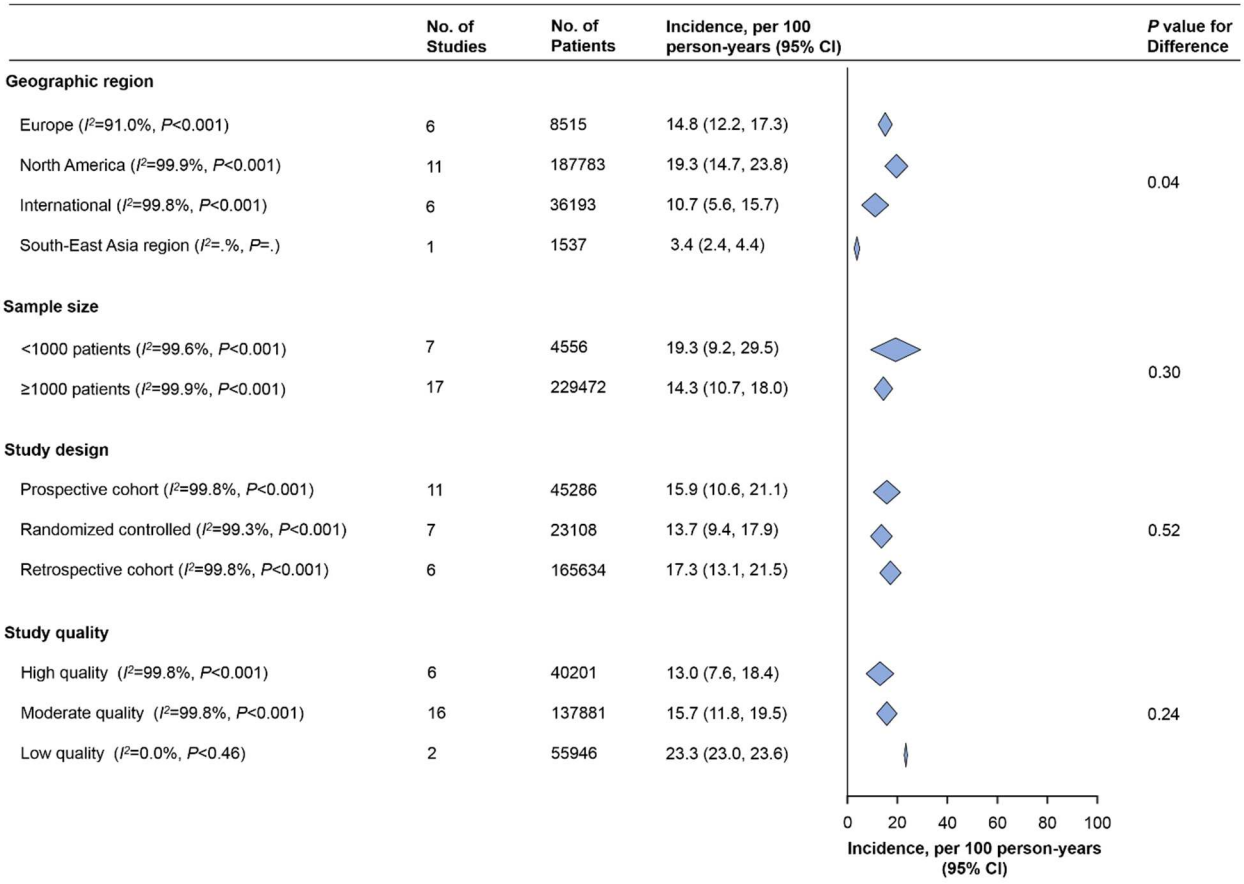


Figure S4 Meta-analysis of the Proportions of Specific Causes for Cardiovascular Hospital Admissions

	No. of studies	No. of hospital admissions	No. of patients	Proportion, % (95% CI)
Cardiovascular causes				
AF related (I^2=99.8%, P<0.001)	17	22475	217110	22.0 (16.7, 27.2)
Heart failure (I^2=99.8%, P<0.001)	20	13689	209513	16.6 (13.1, 20.2)
Bleeding (I^2=98.8%, P<0.001)	12	1719	106547	5.9 (4.4, 7.5)
Stroke (I^2=97.9%, P<0.001)	15	4258	113739	4.5 (3.4, 5.5)
Myocardial infarction (I^2=97.2%, P<0.001)	15	3004	103136	4.4 (3.4, 5.3)
Systemic embolism (I=91.0%, P<0.001)	5	155	33499	0.6 (0.2, 1.0)

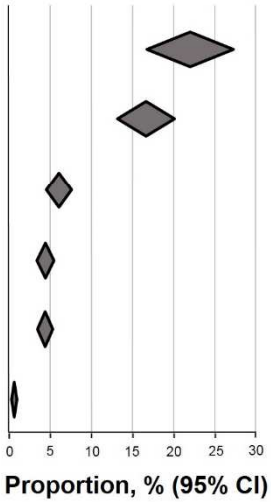


Figure S5 Meta-analysis of the Proportions of Specific Causes for Non-cardiovascular Hospital Admissions

	No. of studies	No. of hospital admissions	No. of patients	Proportion, % (95% CI)
Non-cardiovascular causes				
Bacterial infections (I^2=99.2%, P<0.001)	2	320	16295	6.9 (0.0, 15.4)
Gastrointestinal (I^2=88.5%, P<0.001)	3	311	21894	6.5 (4.3, 8.6)
Respiratory (I^2=94.5%, P<0.001)	4	321	22046	6.1 (3.2, 8.9)
Renal (I^2=93.4%, P<0.001)	3	127	21894	2.8 (0.9, 4.7)
Neurological (I^2=95.8%, P<0.001)	3	125	21894	2.5 (0.6, 4.3)
Cancer (I^2=83.9%, P=0.002)	3	110	21894	2.3 (1.2, 3.4)
Endrocrine & metabolic (I^2=63.5%, P=0.065)	3	81	21894	1.5 (0.9, 2.1)
Viral infections (I^2=87.8%, P<0.001)	3	74	21894	1.5 (0.5, 2.4)
Hematological (I^2=79.7%, P=0.026)	2	28	16295	0.9 (0.0, 1.7)
Skin & soft tissue (I^2=0.0%, P=0.603)	2	20	16295	0.5 (0.3, 0.8)
Psychiatric (I^2=0.0%, P=0.787)	2	19	16295	0.5 (0.3, 0.7)

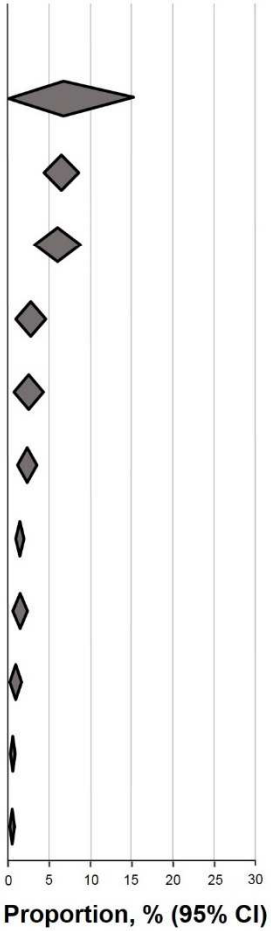


Figure S6 Meta-regression Plots of the Associations Between Incidence of Hospital Admissions and Study and Patient Characteristics

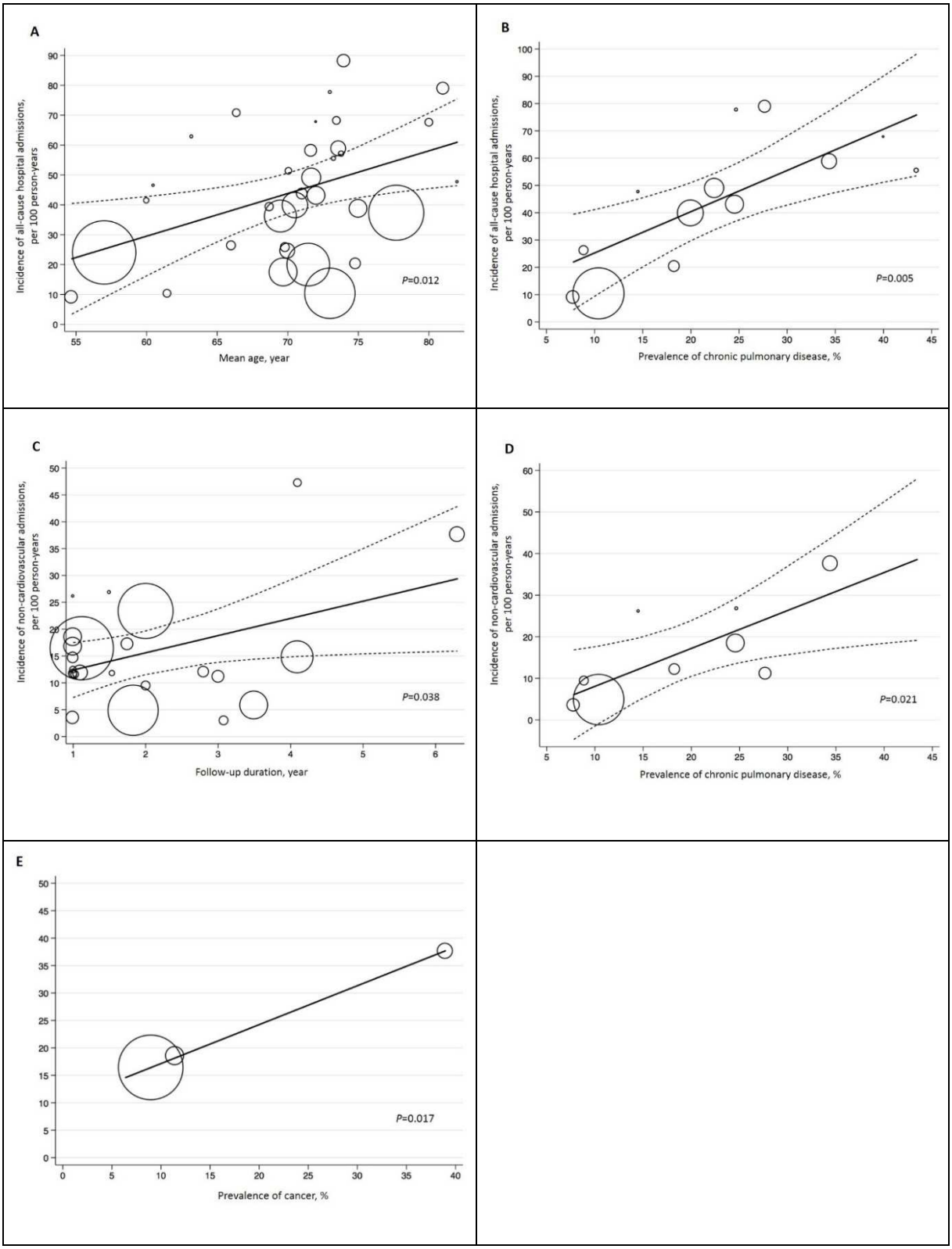


Figure S7 Funnel Plot Assessing Small Study Effects in 35 Studies Reporting on the Incidence of All-cause Hospital Admissions

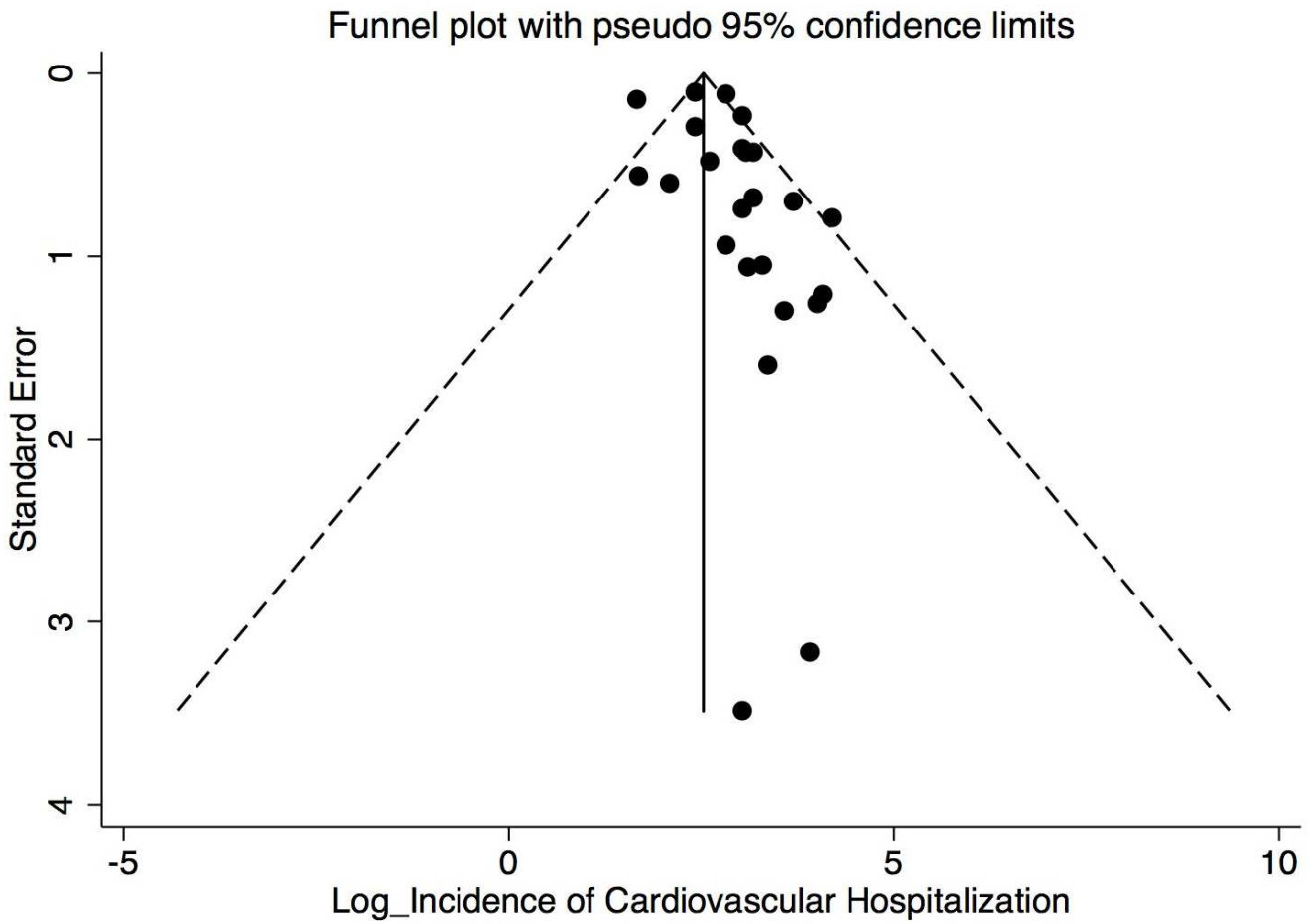


Figure S8 Funnel Plot Assessing Small Study Effects in 24 Studies Reporting on the Incidence of Cardiovascular Hospital Admissions

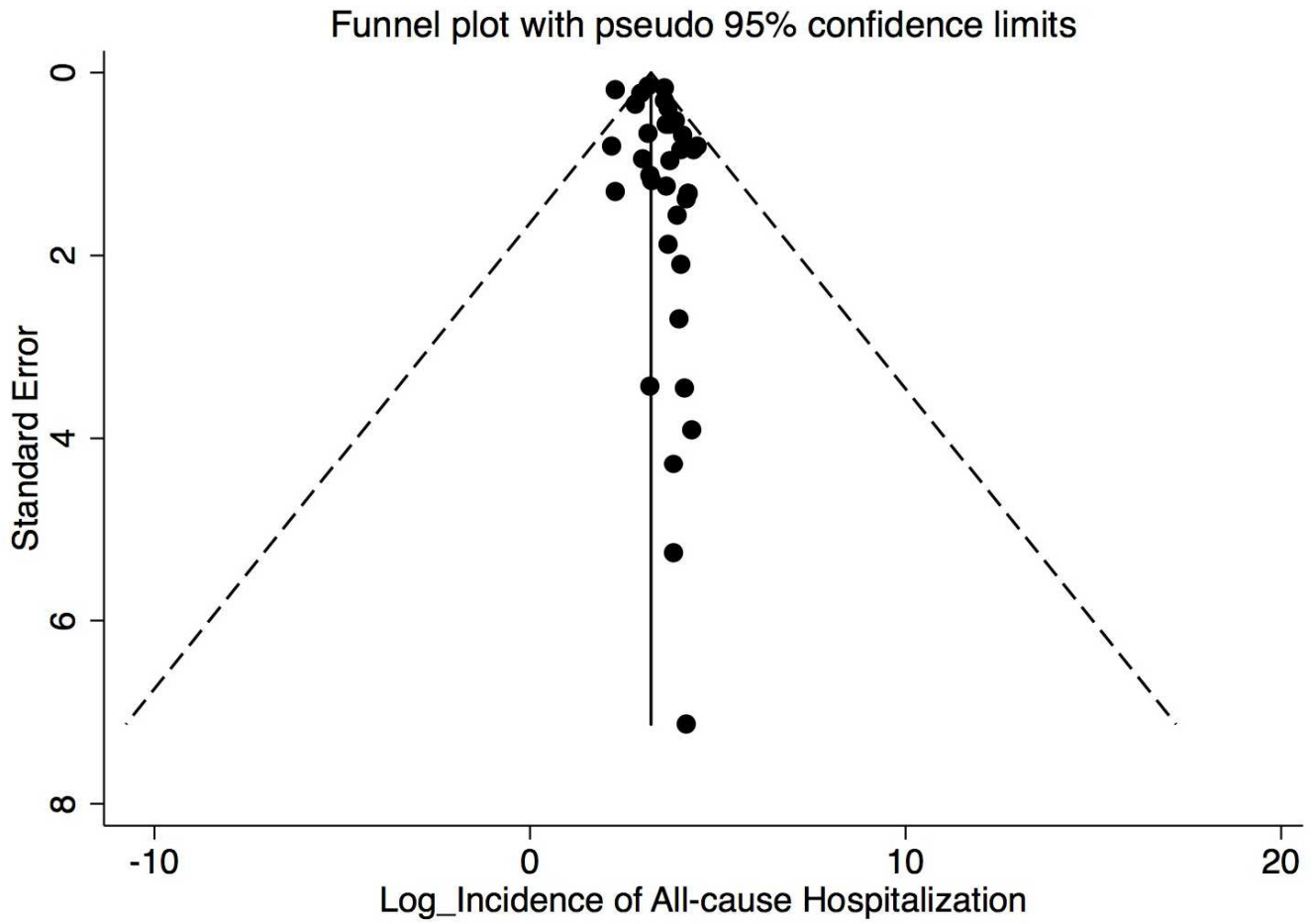
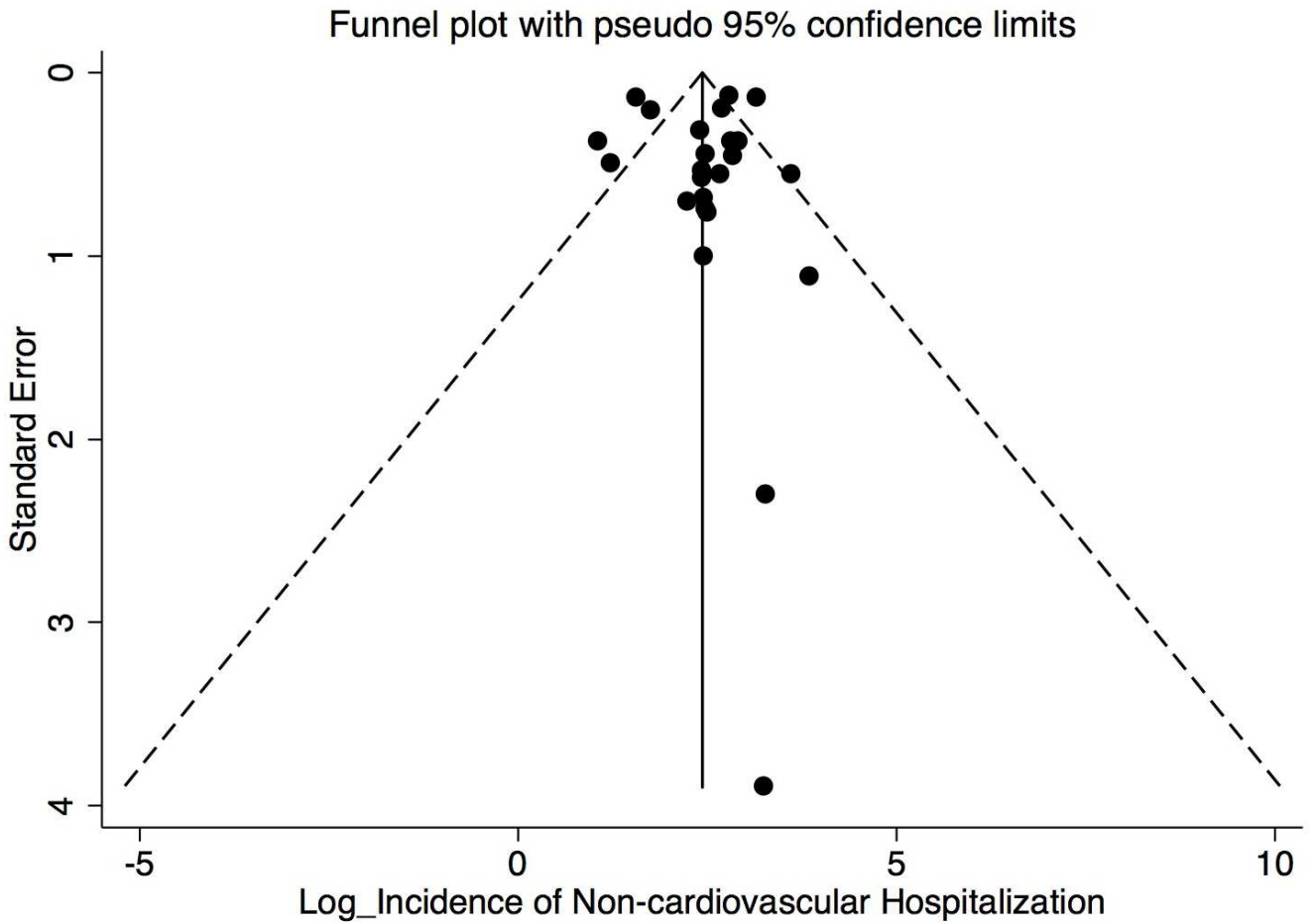


Figure S9 Funnel Plot Assessing Small Study Effects in 24 Studies Reporting on the Incidence of Non-cardiovascular Hospital Admissions



5. MANUSCRIPT 2 – Risk score predicting hospital admission in atrial fibrillation

The Admit-AF Risk Score: A Clinical Risk Score for Predicting Hospital Admissions in Patients with Atrial Fibrillation

Pascal Meyre, Stefanie Aeschbacher, Steffen Blum, Michael Coslovsky, Jürg H. Beer, Giorgio Moschovitis, Nicolas Rodondi, Oliver Baretella, Richard Kobza, Christian Sticherling, Leo H. Bonati, Matthias Schwenkglenks, Michael Kühne, Stefan Osswald, David Conen

CURRENT STANDING: SUBMITTED

The Admit-AF Risk Score: A Clinical Risk Score for Predicting Hospital Admissions in Patients with Atrial Fibrillation

Pascal Meyre, MD[1,2]; Stefanie Aeschbacher, PhD[1,2]; Steffen Blum, MD, PhD[1,2]; Michael Coslovsky, PhD[2]; Jürg H. Beer, MD[3]; Giorgio Moschovitis, MD[4]; Nicolas Rodondi, MD, MAS[5,6]; Oliver Baretella, MD[5,6]; Richard Kobza, MD[7]; Christian Sticherling, MD[1,2]; Leo H. Bonati, MD[8]; Matthias Schwenkglenks, PhD, MPH[9]; Michael Kühne, MD[1,2]; Stefan Osswald, MD[1,2]; and David Conen, MD, MPH[2,10]; on behalf of the Swiss-AF and BEAT-AF Investigators

[1] Division of Cardiology, Department of Medicine, University Hospital Basel, Switzerland
[2] Cardiovascular Research Institute Basel, University Hospital Basel, Switzerland
[3] Department of Medicine, Cantonal Hospital of Baden and Molecular Cardiology, University Hospital of Zürich, Switzerland
[4] Division of Cardiology, EOC, Ospedale Regionale di Lugano, Switzerland
[5] Institute of Primary Health Care (BIHAM), University of Bern, Switzerland
[6] Department of General Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland
[7] Department of Cardiology, Luzerner Kantonsspital, Switzerland
[8] Department of Neurology and Stroke Center, University Hospital Basel, University of Basel, Switzerland
[9] Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Switzerland
[10] Population Health Research Institute, McMaster University, Hamilton, ON, Canada

Brief Title:

Risk score for hospital admissions in AF patients

Word Count: 2474

Address for Correspondence:

David Conen, MD, MPH

Population Health Research Institute

237 Barton Street East

Hamilton Ontario L8L 2X2

Phone: +1 905-521-2100 Ext. 40690

Fax: +1 905-521-6068

Email: conend@mcmaster.ca

Key Points

Question: Can a risk score accurately predict future hospital admissions in unselected patients with atrial fibrillation (AF)?

Findings: A risk score was developed in 2387 patients, and externally validated in 1300 patients. Variables selected for the score were age, prior pulmonary vein isolation, hypertension, diabetes, coronary heart disease, prior stroke/TIA, heart failure, peripheral artery disease, cancer, renal failure, and previous falls. The score was well calibrated, and successfully validated in an independent cohort.

Meaning: Multiple risk factors were associated with hospital admissions in AF patients. Our prediction tool selects high-risk patients who may benefit from preventive interventions.

Abstract

Importance: Patients with atrial fibrillation (AF) have a high risk of hospital admissions, but there is no validated prediction tool to identify those at highest risk.

Objective: To develop and externally validate a risk score for all-cause hospital admissions in patients with AF.

Design, Setting, and Participants: Derivation cohort of 2387 patients with established AF in Switzerland; Validation cohort in a separate prospective, multicenter cohort of 1300 AF patients. Data were analyzed from March 26 to August 23, 2019.

Exposures: Independent risk factors were selected from a broad range of variables using the least absolute shrinkage and selection operator (LASSO) method fit to a Cox regression model.

Main Outcomes and Measures: Time to first unplanned hospital admission.

Results: In the derivation cohort (mean age: 73 years, 27% women), 891 patients (37.3%) were admitted to the hospital during a median follow-up of 2.0 years. In the validation cohort (mean age: 70 years, 30% women), hospital admission occurred in 719 patients (55.3%) during a median follow-up of 1.9 years. The most important predictors for admission were age (75-79 years: adjusted hazard ratio [aHR], 1.33; 95% confidence interval [95% CI], 1.00-1.77; 80-84 years: aHR, 1.51; 95% CI, 1.12-2.03; ≥85 years: aHR, 1.88; 95% CI, 1.35-2.61), prior pulmonary vein isolation (aHR, 0.74; 95% CI, 0.60-0.90), hypertension (aHR, 1.16; 95% CI, 0.99-1.36), diabetes (aHR, 1.38; 95% CI, 1.17-1.62), coronary heart disease (aHR, 1.18; 95% CI, 1.02-1.37), prior stroke/TIA (aHR, 1.28; 95% CI, 1.10-1.50), heart failure (aHR, 1.21; 95% CI, 1.04-1.41), peripheral artery disease (aHR, 1.31; 95% CI, 1.06-1.63), cancer (aHR, 1.33; 95% CI, 1.13-1.57), renal failure (aHR, 1.18, 95% CI, 1.01-1.38), and previous falls (aHR, 1.44; 95% CI, 1.16-1.78). A risk score with these variables was well calibrated, and achieved a C-index of 0.64 (95% CI, 0.61-0.66) in the derivation and 0.59 (95% CI, 0.56-0.63) in the validation cohort.

Conclusions and Relevance: Multiple risk factors were associated with hospital admissions in AF patients. Our prediction tool selects high-risk patients who may benefit from preventive interventions.

Keywords: Atrial fibrillation, comorbidities, hospital admission, prediction model, risk score

Introduction

Atrial fibrillation (AF) is increasing in prevalence and an important risk factor for hospital admissions.[1,2] The overall risk of being admitted to the hospital among patients with AF is approximately 44% per year, which is 1.6 times higher than non-AF populations.[3,4]

It is well-established that AF patients have a high prevalence of cardiovascular risk factors and comorbidities,[5] which is one reason why they face an increased risk of cardiovascular and non-cardiovascular adverse events.[6-9] However, it is currently unclear which of the many potential comorbidities independently contribute to the high risk of hospital admissions and whether at least some of them are preventable.

A recent systematic review suggested that 50 to 70% of the total annual costs in AF are directly attributable to hospital admissions, making it the highest proportion of direct healthcare spending in this population.[10] But this is an important issue not only from a monetary perspective, because AF patients with a previous hospital admission have a significantly higher risk of adverse outcome events and death after discharge.[11] Therefore, we need major efforts to prevent hospital admissions in this growing patient population. An accurate and practical risk predication tool may help to identify high risk AF patients who may then be targeted with specific interventions.[12]

In this context, the objective of this study was to identify factors associated with hospital admissions in a large group of AF patients, and to derive and validate a risk prediction tool in this patient population.

Methods

This study followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement for developing and validating multivariable prediction models.[13]

Cohorts

Between 2014 and 2017, the Swiss Atrial Fibrillation (Swiss-AF) observational multicenter cohort study enrolled 2,415 patients with previously documented AF across 14 centers in Switzerland. Methodological details have been published previously.[14,15] Swiss-AF was used as the derivation cohort for this analysis.

For external validation, we used data from the Basel Atrial Fibrillation (BEAT-AF) cohort, an ongoing prospective, observational multicenter cohort study of 1,553 patients with previously documented AF. Patients were enrolled from 2010 to 2014 across 7 centers in Switzerland. In BEAT-AF, we started collecting yearly information on hospital admissions the second year of follow-up. For the purpose of this analysis we therefore used the second year visit as baseline in BEAT-AF.

In both cohorts, eligible patients had AF previously diagnosed by surface electrocardiogram. Patients were excluded if they had secondary forms of AF or were unable to sign informed consent. Patients enrolled in BEAT-AF could not participate in Swiss-AF. Both study protocols were approved by the local ethics committees, and written informed consent was obtained from all participants.

Study Population

Data on a large number of baseline characteristics and comorbidities were collected using standardized case report forms that were very similar between the two cohorts. These characteristics included age, sex, marital status, education, health perception, lifestyle habits, AF type, history of rhythm control interventions, history of device implantation, cardiovascular and non-cardiovascular comorbidities, information on oral anticoagulation and family history of cardiovascular diseases. AF type was classified according to the guidelines of the European Society of Cardiology into paroxysmal AF (self-terminating, usually within 48 hours), persistent AF (episodes either lasting longer than 7 days or requiring termination by electrical/pharmacologic cardioversion) or permanent AF (AF is accepted by patient and physician).[16]

Study Outcome Assessment

The main outcome for this analysis was any unplanned overnight hospital admission. In both cohorts, information on admissions was obtained from patients and by medical record review during yearly follow-up visits. In this analysis we only looked at time to first hospital admission. Elective hospital admissions were not considered an event.

Statistical Analysis

Candidate variables for our analyses were selected based on literature review, clinical plausibility and availability in both cohorts, with the aim of being inclusive given the large number of endpoints available. Using the derivation cohort, independent predictors for the model were selected based on the least absolute shrinkage and selection operator (LASSO) method.[17] LASSO is a linear regression analysis that simultaneously performs variable selection and regularization using machine learning algorithms. The method takes all candidate variables into one model, and shrinks the absolute size of the regression coefficients towards zero. This shrinkage is achieved by placing a penalty to the summation of estimated regression coefficients. As a result, variables with regression coefficients that shrink to zero are eliminated. The variables most strongly associated with the outcome are kept in the model. These independent variables were entered in a multivariable-adjusted Cox proportional hazards model to assess their associations with time to first hospital admission.

We established a point-based risk scoring system for unplanned hospital admissions, based on the regression coefficients from the derivation cohort model (rounded to the nearest integer).[18] We calculated the total point score for each patient. The risk score was categorized into three risk classes based on admission risks from the derivation, defined as low (<10%/year), intermediate (10-20%/year) and high risk (>20%/year). Kaplan-Meier curves were used to compare the incidence of hospital admissions across risk score categories. Its predictive ability was validated in the external validation cohort. Model discrimination was assessed using Harrell's C statistic for survival models.[19] Calibration was assessed graphically by comparing the observed versus the predicted risk at 1 and 3 years stratified by deciles.[20]

In order to evaluate the clinical usefulness of the prediction model, the derivation and validation cohorts were combined into one data set (N=3687) and the net benefit of using the model as a prediction tool was evaluated using decision curve analysis.[21] The net benefit is defined as the difference of the proportion of patients who are true-

positive from the proportion who are false-positive, weighted by the specific threshold probability. A decision curve is then created by calculating the net benefits for all possible thresholds. A model with a high net benefit (all positive at any threshold) is preferred. The curve is graphically illustrated by displaying potential thresholds for hospital admission risk (x axis) and the net benefit (y axis) assuming that no patient will have an admission.

All analyses were performed using Stata, version 13 (StataCorp. 2013. College Station, TX: StataCorp LP.); variable selection with LASSO was performed using the lassopack.22 A 2-sided P value of <0.05 was considered to indicate statistical significance.

Results

A total of 2,387 AF patients were included in the derivation cohort and 1,300 patients in the external validation cohort (Figure S1 in the Supplement). Baseline characteristics stratified by cohort are presented in Table 1. The mean (±SD) age was 73 (8) years in the derivation cohort and 70 (12) years in the validation cohort; 27% and 30% were women, respectively. Over 90% of patients in the derivation cohort and 67% in the validation cohort were on oral anticoagulation.

In the derivation cohort, 891 patients (37.3%) were admitted to the hospital after a median follow-up of 2.0 years (4664 person-years of follow-up), with an incidence rate of 19.1 (95% confidence interval [CI], 17.9-20.4) per 100 person-years. Cardiovascular admissions occurred in 377 (15.8%) and non-cardiovascular in 629 (26.4%) (Table S1 in the Supplement). From the 41 initially tested variables (Table S2 in the Supplement), LASSO identified 11 variables independently associated with the risk of hospital admission: age, previous pulmonary vein isolation (PVI), hypertension, diabetes, coronary heart disease, prior stroke or transient ischemic attack (TIA), heart failure, peripheral vascular disease, cancer, renal failure and previous falls (Figures S2 and S3 in the Supplement). Table 2 lists the adjusted regression coefficients and hazard ratios from the derivation cohort of the 11 variables. The hospital admission risk was higher in older patients (75-79 year: adjusted hazard ratio [aHR], 1.33; 95% confidence interval [95% CI], 1.00-1.77; 80-84 years: aHR, 1.51; 95% CI, 1.12-2.03; □85 years: aHR, 1.88; 95% CI, 1.35-2.61), and in those with diabetes (aHR, 1.38; 95% CI, 1.17-1.62), coronary heart disease (aHR, 1.18; 95% CI, 1.02-1.37), prior stroke/TIA (aHR, 1.28; 95% CI, 1.10-1.50), heart failure (aHR, 1.21; 95% CI, 1.04-1.41), peripheral artery disease (aHR, 1.31; 95% CI, 1.06-1.63), renal failure (aHR, 1.18, 95% CI, 1.01-1.38), cancer (aHR, 1.33; 95% CI, 1.13-1.57) and previous falls (aHR, 1.44; 95% CI, 1.16-1.78). Previous PVI was inversely associated with the risk of hospital admission (aHR, 0.74; 95% CI, 0.60-0.90).

The multivariable adjusted regression coefficients from the derivation cohort were used to construct the Hospital Admission in Atrial Fibrillation (Admit-AF) risk score for hospital admissions (Figure 2). The number of points assigned to each risk factor is presented in Table S3 in the Supplement. The Admit-AF score achieved a c-index of 0.64 (95% CI, 0.61-0.66) for 1-year predicted risk and 0.63 (95% CI, 0.61-0.65) for 3-year hospital admission risk (Figures S4A and S4C in the Supplement). The cumulative

incidence of hospital admission up to 4 years in the derivation cohort is shown in Figure 1A. Hazard ratios for 1-year risk across predefined risk classes were 2.2 for intermediate versus low risk, and 4.1 for high versus low risk for Admit-AF score (Table 3). Hazard ratios for the 3-year admission risk were similar (Table 3).

In the validation cohort, the incidence rate for incident hospital admissions was 26.1 (95% CI, 24.2-28.1) per 100 person-years. Cardiovascular and non-cardiovascular admissions occurred in 357 (27.5%) and 514 (39.5%), respectively (incidence rates, see Table S1 in the Supplement). The risk score yielded a c-index of 0.59 (95% CI, 0.56-0.63) for the 1-year risk and 0.59 (95% CI, 0.57-0.61) for 3-year hospital admission risk (Figures S5B and S5D in the Supplement).

The models were well calibrated for 1-year and 3-year risk prediction in both the derivation and the validation cohort (Figures S4A-S4D in the Supplement). The probability of hospital admission up to 4 years in the validation cohort is presented in Figure 2B. Hazard ratios for 1-year risk were 1.3 for intermediate versus low risk, and 1.7 for high versus low risk. Hazard ratios for 3-year risk of hospital admission were 1.4 and 2.0, respectively (Table 3). Decision curve analysis indicated a consistent positive net benefit of using the risk score for decision of 1-year and 3-year hospital admission risk, as shown in Figure S5 in the Supplement.

Discussion

This comprehensive analysis investigated risk factors for hospital admissions in patients with AF. Several important findings were identified. First, the cumulative incidence of hospital admission was very high in both the derivation and the validation cohort. Second, many independent risk factors predicted hospital admissions. Third, the Admit-AF score for 1-year and 3-year risk prediction was established and validated. The use of this score provided a significant net clinical benefit in decision curve analysis.

The Admit-AF score is easy to calculate, consisting of variables that are readily available during regular patient visits. Calculation of the score is straightforward and it can be widely implemented. In contrast to other hospital admission scores, using retrospective administrative data and short-term follow-up,[23] our score uses prospective real time data predicting longer-term admission risks. The score was built using appropriate statistical methods, and the model development process adhered to the TRIPOD statement.[13] The use of machine learning algorithms from LASSO for variable selection is a well-established method that has been previously utilized in non-AF populations.[24-26] The advantage of this method is that is produces a stable model, which is particularly important when it is applied to other external cohorts. Indeed, our model was robust and well calibrated in both the derivation and in the validation cohorts.

A recent meta-analysis demonstrated that the average admission rate in AF patients across several studies was 44% per year.[3] While most of these admissions were due to cardiovascular causes, over one-third were attributable to non-cardiovascular causes. The current study confirmed the high admission rate, but demonstrated that admissions for non-cardiovascular causes were more common than those for cardiovascular reasons. This can be explained by two factors. First, in contrast to randomized trials, AF patients in cohort studies may have more medical comorbidities and exhibit a lower health status, which may result in higher admission rates for non-cardiovascular causes. Second, prior studies mainly focused on specific types of admissions, such as cardiovascular or short-term readmissions after hospital discharge. Our study was more inclusive with evaluating any unplanned hospital admissions.

Hospital admission is a highly heterogeneous outcome without a single underlying cause. Many clinical variables therefore impact only a part of the overall endpoint. The Admit-AF risk score consists of variables from both the cardiovascular (i.e. hypertension, diabetes, heart failure) and non-cardiovascular domain (i.e. cancer, renal failure, previous falls). Large observational studies found similar associations of these variables with hospital admissions in AF patients.[11,27] In addition, we found that cancer and previous falls were both strongly related to admission risk. This is an important finding as several studies have shown an association of AF with both cancer and recurrent falls.[9,28] Given this heterogeneity, it seems likely that only a multidisciplinary integrated approach will help to improve patient outcomes by reducing hospital admissions in AF patients.

Prediction tools such as the Admit-AF score can be used to identify patients at high risk for hospital admissions who may benefit most from preventive interventions. A recent work demonstrated that a multidisciplinary AF treatment pathway resulted in a 3.7-fold reduction in hospital admissions and a 1.6-fold reduction in average length-of-stay for admitted AF patients.[29] The Hospital Readmissions Reduction Program (HRRP) has recently been proposed as possible intervention to reduce costly readmissions.[30] This program reduces payments to hospitals with excess readmission, and it successfully reduced short- and long-term admissions in patients with heart failure, but there seems to be a tradeoff with an increase in 30-day and 1-year mortality.[31] Nonetheless, these interventions are mainly hospital-based and it is unclear whether they are applicable in outpatient setting. Primary care and home-based interventions need to be developed, to reduce the likelihood of hospital admission in AF patients. Such interventions have shown favorable results in heart failure patients.[32]

Strengths and Limitations

Deriving our model in a large multicenter population-based cohort of well-characterized patients with a very low rate of missing values and being able to validate the model using a similar, high quality, external source lends much strength to our results. Nevertheless, this study has some potential limitations that need to be acknowledged. The model predicts only time to first hospital admissions, ignoring repetitive admissions which usually occurs more often in high-risk patients. Also, the score does not include elective admissions, which suggests that the overall admission problem may even be underestimated. Finally, both the derivation and the validation cohort have been

established in Switzerland, and the generalizability of the model to other populations or health care systems remains to be determined.

In conclusion, we identified a multitude of risk factors for hospital admissions in patients with established AF, suggesting that a multi-factorial approach is essential to reduce the admission rate in this high risk patient population. The Admit-AF score contains 11 readily available variables, and will help to identify high-risk AF patients who may benefit from preventive strategies.

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Conflict of interest disclosures

Dr. Kühne has served on the speakers' bureau for Boston Scientific, St. Jude Medical and Biotronik. He has received lecture/consulting fees from Sorin, Boehringer Ingelheim, Bayer, Sanofi Aventis, Novartis and MSD and has received unrestricted grants from Sanofi Aventis, Bayer and Boehringer Ingelheim. He is a proctor for Medtronic (Cryoballoon); Dr. Conen has received consultant/speaker fees from Servier Canada. Dr. Sticherling has received speaker honoraria from Biosense Webster and Medtronic and research grants from Biosense Webster, Daiichi-Sankyo, and Medtronic. The remaining authors have no relationships with industry to disclose.

Abbreviations

AF	Atrial fibrillation
CHD	Coronary heart disease
LASSO	Least absolute shrinkage and selection operator
PAD	Peripheral artery disease
PVI	Pulmonary vein isolation
SD	Standard deviation
TIA	Transient ischemic attack

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Figure legends

Figure 1 Kaplan–Meier Curves for Incident Hospital Admissions According to Risk Score Categories

The risk classes were categorized based on admission risks from the derivation, defined as low (<10%/year), intermediate (10-20%/year) and high risk (>20%/year).

Figure 2 Admit-AF Score for Hospital Admissions in AF Patients

Abbreviations: PVI, pulmonary vein isolation; CHD, coronary heart disease, TIA, transient ischemic attack; PAD, peripheral artery disease.

Data are presented for all patients (N=3687) and predicted hospital admission risk was estimated over the entire follow-up duration. Points can be assigned for each variable and summed to obtain a total risk score, which can be used to determine the patient's corresponding predicted risk of hospital admission.

Table 1 Baseline Characteristics of the Derivation and External Validation Cohort

Characteristics	Swiss-AF Derivation Cohort (N=2387)	BEAT-AF Validation Cohort (N=1300)
Demographics		
Age, mean (SD), y	73.2 (8.4)	69.8 (11.5)
Female sex, n (%)	652 (27.3)	386 (29.7)
Smoking status, n (%)		
Current	174 (7.3)	90 (6.9)
Past	1162 (48.7)	604 (46.5)
Never	1049 (44.0)	605 (46.6)
Atrial fibrillation type, n (%)		
Paroxysmal	1070 (44.8)	777 (59.9)
Persistent	702 (29.4)	251 (19.3)
Permanent	615 (25.8)	270 (20.8)
Coexistent atrial flutter, n (%)	508 (21.3)	327 (25.2)
Comorbidities, n (%)		
Hypertension	1658 (69.5)	876 (67.4)
Diabetes	406 (17.0)	173 (13.3)
Coronary artery disease	727 (30.5)	287 (22.1)
Stroke/TIA	475 (19.9)	183 (14.1)
Heart failure	617 (25.9)	263 (20.3)
Peripheral artery disease	192 (8.0)	82 (6.3)
Obstructive sleep apnea	358 (15.0)	149 (11.5)
Pulmonary embolism/DVT	216 (9.1)	101 (7.8)
Renal failure	500 (21.0)	205 (15.8)
Cancer	380 (15.9)	238 (18.3)
Bleeding	371 (15.5)	163 (12.5)
Peptic ulcer	106 (4.4)	71 (5.5)
Recurrent falls	200 (8.4)	100 (7.7)
CHA_2DS_2-VASc score, mean (SD)	3.5 (1.7)	2.9 (1.7)
Oral anticoagulation, n (%)	2157 (90.4)	890 (68.5)
Warfarin	940 (39.4)	670 (51.5)
Direct oral anticoagulants	1216 (51.0)	220 (16.9)
Antiplatelet therapy, n (%)	471 (19.7)	240 (18.5)
Family history, n (%)		
Hypertension	859 (36.0)	618 (47.5)
Diabetes	528 (22.1)	299 (23.0)
Obesity	772 (32.3)	422 (32.5)
Coronary heart disease	921 (38.6)	518 (39.9)

Abbreviations: DVT, deep vein thrombosis.
Bleeding was defined as major or minor bleeding.

Table 2 Adjusted Predictors for Incident Hospital Admission in the Derivation Cohort

	Model		
Predictors	**β Coefficient (SE)**	**Adjusted HR (95% CI)**	**P Value**
Age, year			
<65	1 [Reference]	NA	NA
65-69	0.12 (0.15)	1.13 (0.84-1.51)	0.42
70-74	0.14 (0.14)	1.15 (0.87-1.53)	0.32
75-79	0.29 (0.15)	1.33 (1.00-1.77)	0.049
80-84	0.41 (0.15)	1.51 (1.12-2.03)	0.007
≥85	0.63 (0.17)	1.88 (1.35-2.61)	<0.001
Previous PVI	-0.31 (0.10)	0.74 (0.60-0.90)	0.003
Hypertension	0.15 (0.08)	1.16 (0.99-1.36)	0.06
Diabetes	0.32 (0.08)	1.38 (1.17-1.62)	<0.001
Coronary artery disease	0.17 (0.07)	1.18 (1.02-1.37)	0.023
Prior stroke/TIA	0.25 (0.08)	1.28 (1.10-1.50)	0.002
Heart failure	0.20 (0.08)	1.21 (1.04-1.41)	0.012
Peripheral artery disease	0.27 (0.11)	1.31 (1.06-1.63)	0.014
Renal failure	0.16 (0.08)	1.18 (1.01-1.38)	0.043
Cancer	0.29 (0.08)	1.33 (1.13-1.57)	0.001
Previous falls	0.36 (0.11)	1.44 (1.16-1.78)	0.001

Abbreviations: SE, standard error; HR, hazard ratio; NA, not applicable.
The model includes all variables listed (age, previous PVI, hypertension, diabetes, coronary heart disease, prior stroke/TIA, heart failure, peripheral artery disease, renal failure, cancer, previous falls).

Table 3 Risk of Hospital Admission According to Risk Score Categories

Risk Category	No. of Patients (%)	1-Year Risk			3-Year Risk		
		Events	Incidence*	HR (95% CI)	Events	Incidence*	HR (95% CI)
Derivation Cohort (N=2387)							
Low risk (-3-1 points)	400 (16.8)	33	8.58 (6.10-12.07)	1 [Reference]	71	8.05 (6.38-10.16)	1 [Reference]
Intermediate risk (2-7 points)	974 (40.8)	165	18.71 (16.07-21.80)	2.18 (1.50-3.17)	294	15.83 (14.12-17.75)	1.94 (1.50-2.52)
High risk (≥8 points)	1013 (42.4)	299	34.94 (31.20-39.14)	4.07 (2.84-5.84)	485	29.81 (27.27-32.59)	3.59 (2.80-4.61)
Validation Cohort (N=1300)							
Low risk (-3-1 points)	386 (29.7)	72	20.55 (16.31-25.89)	1 [Reference]	159	19.14 (16.38-22.36)	1 [Reference]
Intermediate risk (2-7 points)	479 (36.9)	110	25.84 (21.44-31.15)	1.26 (0.94-1.70)	244	27.04 (23.85-30.66)	1.42 (1.16-1.74)
High risk (≥8 points)	435 (33.5)	124	33.75 (28.30-40.24)	1.66 (1.24-2.21)	254	36.71 (32.46-41.51)	1.95 (1.60-2.38)

Abbreviations: HR, hazard ratio.
* per 100 person-years of follow-up.

Figure 1 Kaplan–Meier Curves for Incident Hospital Admissions According to Risk Score Categories

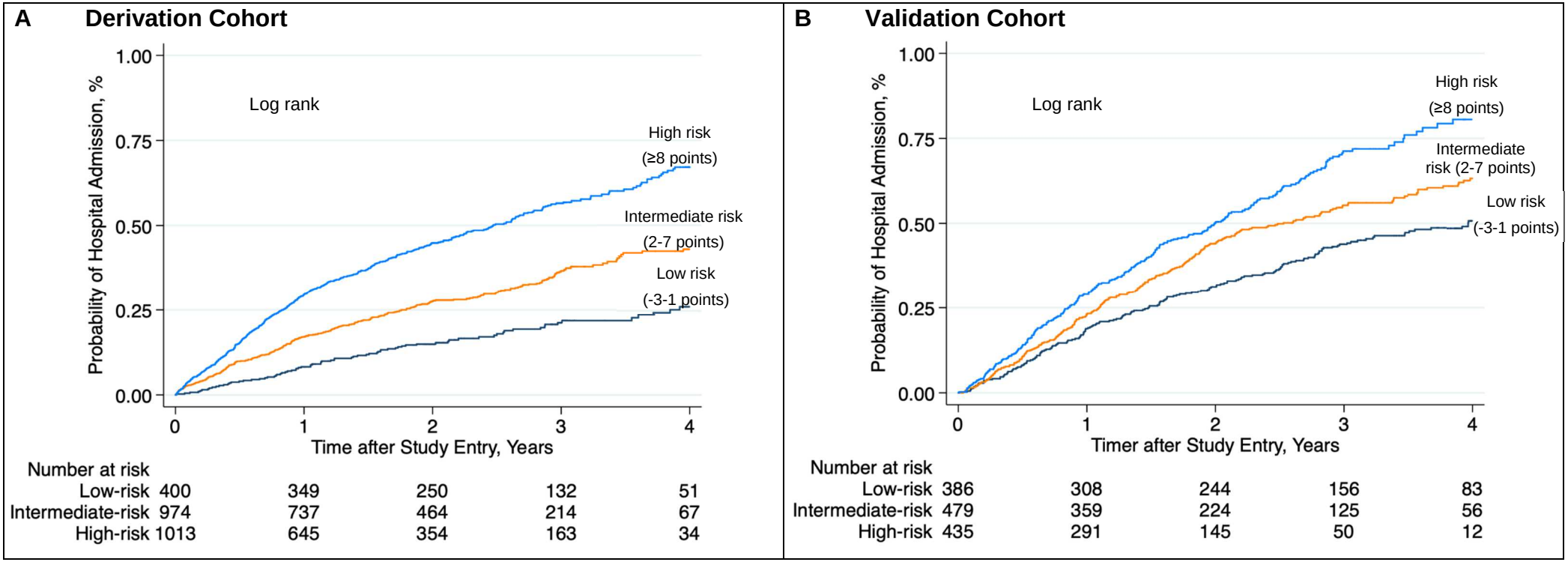


Figure 2 Admit-AF Score for Hospital Admissions in AF Patients

Age, y	Points
<65	0
65-69	1
70-74	1
75-79	3
80-84	4
≥85	6

Previous PVI	Points
No	0
Yes	3

History of hypertension	Points
No	0
Yes	2

History of diabetes	Points
No	0
Yes	3

History of CHD	Points
No	0
Yes	2

Prior stroke/TIA	Points
No	0
Yes	3

History of heart failure	Points
No	0
Yes	2

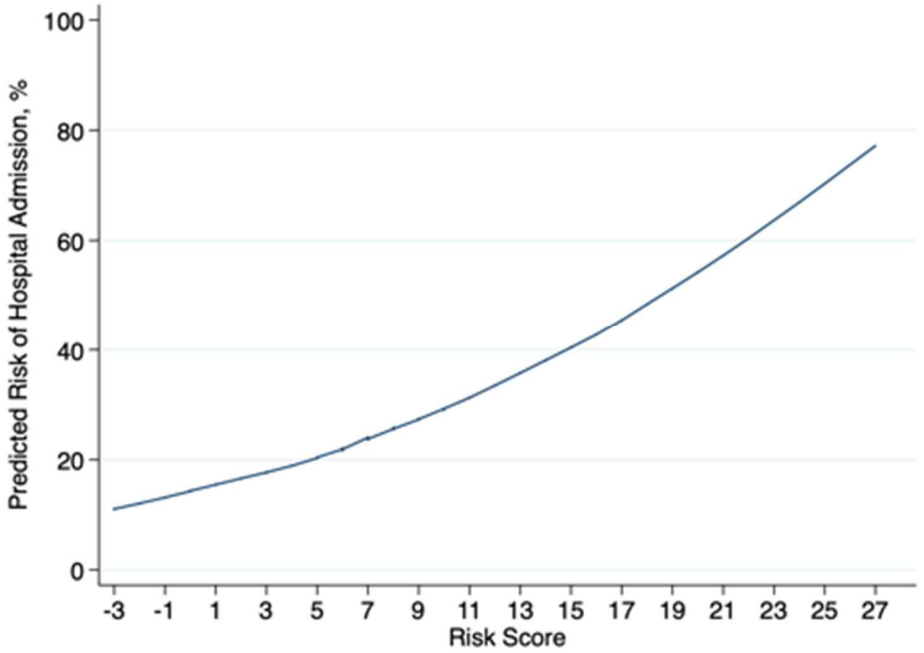
History of PAD	Points
No	0
Yes	3

History of cancer	Points
No	0
Yes	3

History of renal failure	Points
No	0
Yes	2

Previous falls	Points
No	0
Yes	4

Sum of points	
Age	+
Previous PVI	-
History of hypertension	+
History of diabetes	+
History of CHD	+
Prior stroke/TIA	+
History of heart failure	+
History of PAD	+
History of cancer	+
History of renal failure	+
Previous falls	+
Total Risk Score=	



Risk Score Quintile	Predicted Risk of Hospital Admission, %	Patients in Risk Quintile, No. (%)	
		Derivation Cohort	Validation Cohort
-3-2	12-18	485 (20)	462 (36)
3-5	>18-20	549 (23)	272 (21)
6-8	>20-25	558 (23)	214 (16)
9-11	>25-37	367 (15)	172 (13)
≥12	>37	428 (18)	180 (14)

Supplement

The Admit-AF Risk Score: A Clinical Risk Score for Predicting Hospital Admissions in Patients with Atrial Fibrillation

Pascal Meyre, Stefanie Aeschbacher, Steffen Blum, Michael Coslovsky, Jürg H. Beer, Giorgio Moschovitis, Nicolas Rodondi, Oliver Baretella, Richard Kobza, Leo H. Bonati, Christian Sticherling, Matthias Schwenkglenks, Michael Kühne, Stefan Osswald, David Conen, on behalf of the Swiss-AF and BEAT-AF Investigators

Swiss-AF Investigators

University Hospital Basel/Basel University: Stefanie Aeschbacher, Steffen Blum, Leo Bonati, Peter Hämmerle, Philipp Krisai, Christine Meyer-Zürn, Pascal Meyre, Andreas U. Monsch, Christian Müller, Christiane Pudenz, Philipp Reddiess, Javier Ruperti Repilado, Aleksandra Schweizer, Anne Springer, Fabienne Steiner, Christian Sticherling, Thomas Szucs, Gian Voellmin, Leon Zwimpfer. Local Principal Investigator: Michael Kühne; Principal Investigators; Stefan Osswald, David Conen.

University Hospital Bern: Faculty: Drahomir Aujesky, Urs Fischer, Juerg Fuhrer, Laurent Roten, Simon Jung, Heinrich Mattle; Research fellows: Luise Adam, Carole Elodie Aubert, Martin Feller, Claudio Schneider, Axel Loewe, Elisavet Moutzouri; Study nurses: Tanja Flückiger, Cindy Groen, Nathalie Schwab. Local Principal Investigator: Nicolas Rodondi.

Stadtspital Triemli Zurich: Christopher Beynon, Roger Dillier, Franz Eberli, Christine Franzini, Isabel Juchli, Claudia Liedtke, Jacqueline Nadler, Thayze Obst, Noreen Tynan, Xiaoye Schneider, Katrin Studerus, Dominik Weishaupt. Local Principal Investigator: Andreas Müller.

Kantonspital Baden: Simone Fontana, Silke Kuest, Karin Scheuch, Denise Hischier, Nicole Bonetti, Corina Bello, Henriette Isberg, Alexandra Grau, Jonas Villinger, Mary-Monica Papaux, Eva Laube, Philipp Baumgartner, Mark Filipovic, Marcel Frick, Stefanie Leuenberger. Local Principal Investigator: Jürg H. Beer.

Cardiocentro Lugano: Angelo Auricchio, Adriana Anesini, Cristina Camporini, Giulio Conte, Maria Luce Caputo, Francois Regoli, Tiziano Moccetti. Local Principal Investigator: Tiziano Moccetti.

Kantonsspital St. Gallen: Roman Brenner, David Altmann, Manuela Forrer, Michaela Gemperle. Local Principal Investigator: Peter Ammann.

Hôpital Cantonal Fribourg: Mathieu Firmann, Sandrine Foucras. Local Principal Investigator: Daniel Hayoz.

Luzerner Kantonsspital: Benjamin Berte, Andrea Kaeppeli, Myriam Roth, Brigitta Mehmann, Markus Pfeiffer, Ian Russi, Kai Schmidt, Vanessa Weberndoerfer, Mabelle Young, Melanie Zbinden; Local Principal Investigator: Richard Kobza.

Ente Ospedaliero Cantonale Lugano: Luisa Vicari, Jane Frangi-Kultalahti, Tatiana Terrot. Local Principal Investigator: Giorgio Moschovitis.

University Hospital Geneva: Georg Ehret, Hervé Gallet, Elise Guillermet, Francois Lazeyras, Karl-Olof Lovblad, Patrick Perret, Cheryl Teres. Local Principal Investigator: Dipen Shah.

University Hospital Lausanne: Nathalie Lauriers, Marie Méan, Sandrine Salzmann. Local Principal Investigator: Jürg Schläpfer.

Bürgerspital Solothurn: Nisha Arenja, Andrea Grêt, Sandra Vitelli. Local Principal Investigator: Frank-Peter Stephan.

Ente Ospedaliero Cantonale Bellinzona: Jane Frangi, Augusto Gallino. Local Principal Investigator: Marcello Di Valentino.

St. Anna Spital Luzern: Renate Schoenenberger-Berzins.

University of Zurich/University Hospital Zurich: Fabienne Witassek, Matthias Schwenkglenks, Christoph Stippich.

Medical Image Analysis Center AG Basel: Ernst-Wilhelm Radue, Tim Sinnecker, Jens Würfel.

Clinical Trial Unit Basel: Pascal Benkert, Thomas Fabbro, Patrick Simon, Michael Coslovsky.

Schiller AG Baar: Ramun Schmid.

Table S1. Incidence of All-cause, Cardiovascular and Non-cardiovascular Hospital Admissions in the Derivation and Validation Cohort

	Cohort			
	Swiss-AF Derivation Cohort		BEAT-AF Validation Cohort	
Outcome	**Events/No. at risk**	**Incidence***	**Events/No. at risk**	**Incidence***
All-cause hospital admission	891/2387	19.1 (17.9-20.4)	719/1300	26.1 (24.2-28.1)
Cardiovascular hospital admission	377/2387	7.0 (6.3-7.7)	357/1300	10.3 (9.3-11.4)
Non-cardiovascular hospital admission	629/2387	12.4 (11.5-13.4)	514/1300	16.2 (14.9-17.7)

* per 100 person-years of follow-up.

Table S2. Variables included in the LASSO Variable Selection Method

Variable	Data Source	Comment
Age	CRF	Age in years
Sex	CRF	Female, male
Marital status	CRF	Married, single, divorced, widowed
Education level	CRF	Basic (<6 years), middle (6-12 years), advanced (>12 years)
Visual analogue scale	CRF	0-100
Smoking status	CRF	Never, past, active
Alcohol consumption	CRF	Non, <1 drink/day, 1-2 drinks/day, >2 drinks/day
Caffeine intake	CRF	Non, <1 cup/day, 1-2 cup/day, >2 cup/day
Physical activity	CRF	Rarely/never, 1-2/week, 3-4/week, >4/week
Atrial fibrillation type	CRF	Paroxysmal, persistent, permanent
Coexistent atrial flutter	CRF	Yes, no
Prior electrical cardioversion	CRF	Yes, no
Prior AF ablation	CRF	Yes, no
Device	CRF	No, pacemaker, CRT/CRT-ICD, ICD
Coronary artery disease	CRF	Yes, no
Stroke/TIA	CRF	Yes, no
Systemic embolism	CRF	Yes, no
Heart failure	CRF	Yes, no
Obstructive sleep apnea	CRF	Yes, no
Hypertension	CRF	Yes, no
Diabetes	CRF	Yes, no
Peripheral artery disease	CRF	Yes, no
Renal failure	CRF	Yes, no
Hyperthyroidism	CRF	Yes, no
Hypothyroidism	CRF	Yes, no
Pulmonary embolism/DVT	CRF	Yes, no
Cancer	CRF	Yes, no; any malignoma.
History of any bleed	CRF	Yes, no
History of peptic ulcer	CRF	Yes, no
Recurrent falls	CRF	Yes, no
Oral anticoagulation	CRF	Yes, no
Vitamin K antagonist	CRF	Marcoumar, Sintrom
DOAC	CRF	Apixaban, Dabigatran, Edoxaban, Rivaroxaban
Family history of hypertension	CRF	Yes, no/unknown
Family history of diabetes	CRF	Yes, no/unknown
Family history of obesity	CRF	Yes, no/unknown

Family history of coronary artery disease	CRF	Yes, no/unknown
EHRA score	CRF	I, II, III, IV
CRF, standardized case report form; CRT, cardiac resynchronization therapy; intracardial defibrillator; TIA, transient ischemic attack; DVT, deep vein thrombosis; DOAC, direct oral anticoagulants.		

Table S3. Components of the Admit-AF Score

Variable	Points
Age, y	
<65	0
65-69	1
70-74	1
75-79	3
80-84	4
≥85	6
Previous PVI	-3
Hypertension	2
Diabetes	3
Coronary heart disease	2
Prior stroke/TIA	3
Heart failure	2
Peripheral artery disease	3
Renal failure	2
Cancer	3
Previous falls	4

Abbreviations: PVI, pulmonary vein isolation; TIA, transient ischemic attack.

Table S4. Predictors of Hospital Admissions from Multivariable Models in the Validation Cohort (BEAT-AF, n=1300)

	Model		
Predictors	**β Coefficient (SE)**	**Adjusted HR (95% CI)**	**P Value**
Age, year			
<65	1 [Reference]	NA	NA
65-70	0.48 (0.11)	1.62 (1.30-2.02)	<0.001
71-75	0.45 (0.13)	1.55 (1.21-1.98)	0.001
76-80	0.54 (0.13)	1.71 (1.33-2.19)	<0.001
81-85	0.42 (0.16)	1.52 (1.12-2.08)	0.008
>85	0.48 (0.19)	1.61 (1.11-2.35)	0.013
Previous PVI	-0.05 (0.09)	0.95 (0.80-1.14)	0.60
Hypertension	-0.01 (0.09)	0.99 (0.84-1.17)	0.90
Diabetes	0.29 (0.11)	1.34 (1.09-1.64)	0.006
Coronary heart disease	0.01 (0.10)	1.01 (0.83-1.22)	0.95
Prior stroke/TIA	-0.19 (0.11)	0.82 (0.66-1.03)	0.09
Heart failure	0.26 (0.10)	1.30 (1.08-1.57)	0.006
Peripheral vascular disease	0.42 (0.14)	1.52 (1.15-2.01)	0.003
Cancer	0.18 (0.10)	1.20 (0.99-1.44)	0.058
Renal failure	0.08 (0.11)	1.08 (0.87-1.34)	0.48
Previous falls	0.15 (0.14)	1.16 (0.88-1.54)	0.29

Abbreviations: SE, standard error; HR, hazard ratio; NA, not applicable.
The model includes all variables listed (age, previous PVI, hypertension, diabetes, coronary heart disease, prior stroke/TIA, heart failure, peripheral artery disease, renal failure, cancer, previous falls).

Table S5. Predictors of Hospital Admissions from Multivariable Model of Combined Cohorts (n=3687)

	Model		
Predictors	**β Coefficient (SE)**	**Adjusted HR (95% CI)**	**P Value**
Age, year			
<65	1 [Reference]	NA	NA
65-70	0.20 (0.09)	1.22 (1.03-1.45)	0.023
71-75	0.13 (0.09)	1.14 (0.95-1.36)	0.15
76-80	0.30 (0.19)	1.35 (1.13-1.62)	0.001
81-85	0.32 (0.10)	1.38 (1.12-1.69)	0.002
>85	0.54 (0.12)	1.72 (1.35-2.19)	<0.001
Previous PVI	-0.10 (0.07)	0.91 (0.80-1.03)	0.14
Hypertension	0.09 (0.06)	1.09 (0.97-1.23)	0.13
Diabetes	0.31 (0.07)	1.36 (1.20-1.55)	<0.001
Coronary artery disease	0.07 (0.06)	1.08 (0.96-1.21)	0.21
Prior stroke/TIA	0.08 (0.06)	1.08 (0.95-1.22)	0.24
Heart failure	0.21 (0.06)	1.23 (1.09-1.38)	0.001
Peripheral artery disease	0.31 (0.09)	1.36 (1.15-1.62)	<0.001
Cancer	0.27 (0.06)	1.31 (1.16-1.49)	<0.001
Renal failure	0.12 (0.06)	1.13 (0.99-1.28)	0.058
Previous falls	0.28 (0.09)	1.32 (1.11-1.57)	0.001

Abbreviations: SE, standard error; HR, hazard ratio; NA, not applicable.
The model includes all variables listed (age, previous PVI, hypertension, diabetes, coronary heart disease, prior stroke/TIA, heart failure, peripheral artery disease, renal failure, cancer, previous falls).

Figure S1

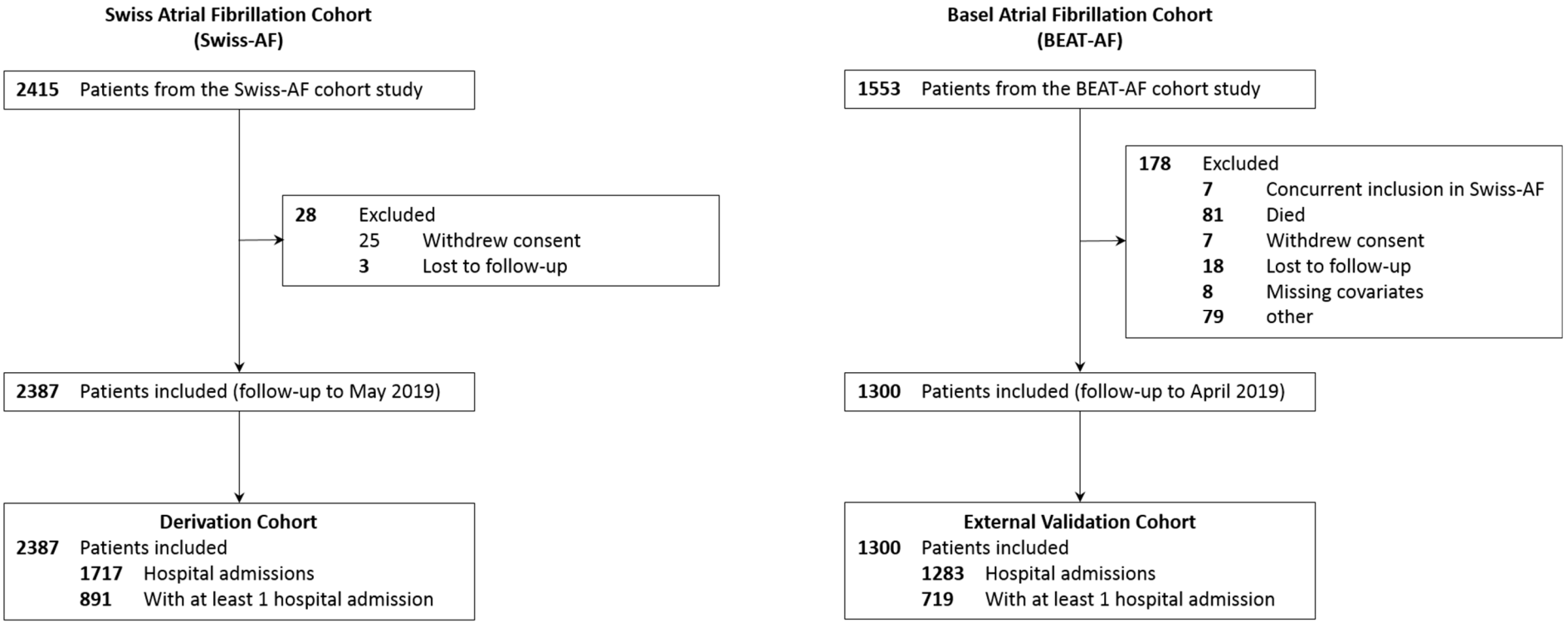
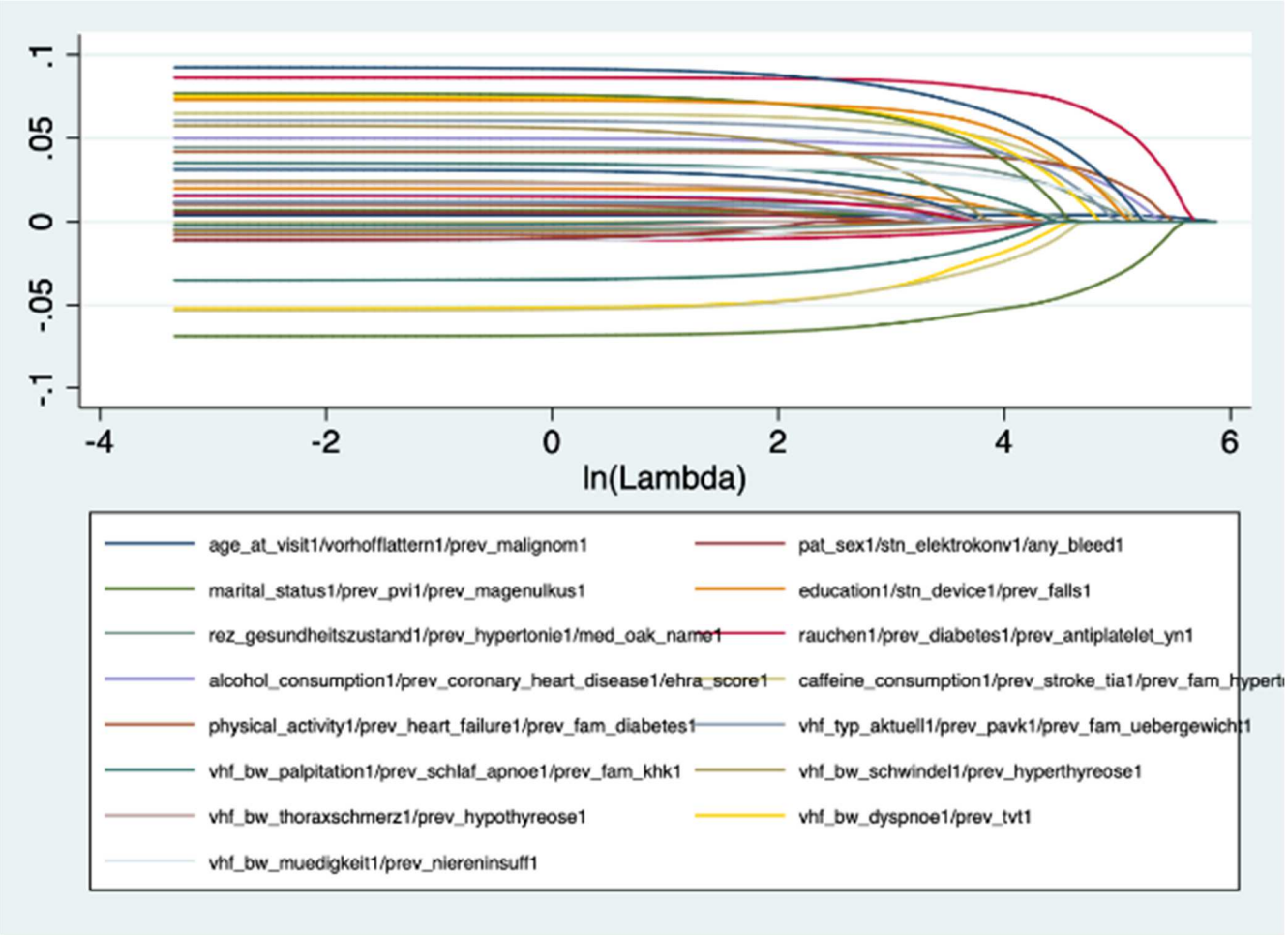

Swiss Atrial Fibrillation Cohort
(Swiss-AF)
2415 Patients from the Swiss-AF cohort study
28 Excluded
25 Withdrew consent
3 Lost to follow-up
2387 Patients included (follow-up to May 2019)
Derivation Cohort
2387 Patients included
1717 Hospital admissions
891 With at least 1 hospital admission
Basel Atrial Fibrillation Cohort
(BEAT-AF)
1553 Patients from the BEAT-AF cohort study
178 Excluded
7 Concurrent inclusion in Swiss-AF
81 Died
7 Withdrew consent
18 Lost to follow-up
8 Missing covariates
79 other
1300 Patients included (follow-up to April 2019)
External Validation Cohort
1300 Patients included
1283 Hospital admissions
719 With at least 1 hospital admission

Figure S2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education1/stn_device1/prev_falls1
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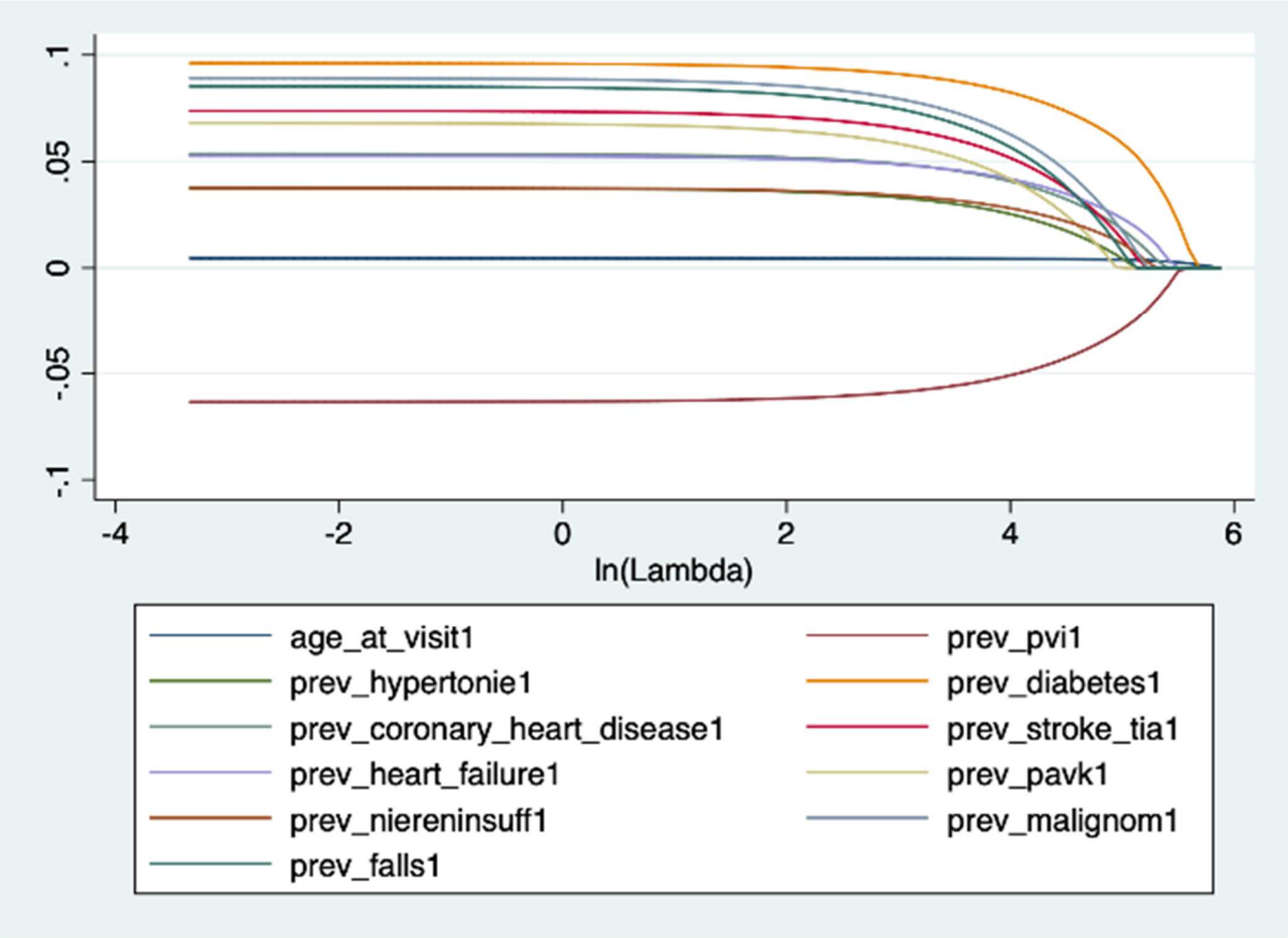
Figure S3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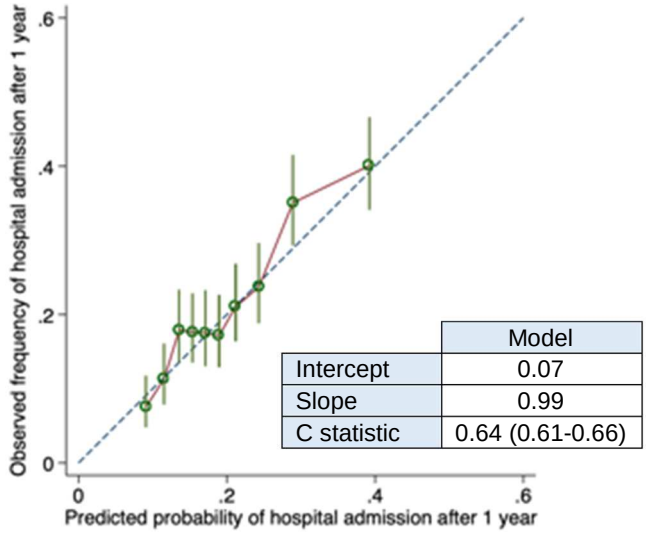
prev_hypertonie1
prev_coronary_heart_disease1
prev_heart_failure1
prev_niereninsuff1
prev_falls1
prev_pvi1
prev_diabetes1
prev_stroke_tia1
prev_pavk1
prev_malignom1

Figure S4

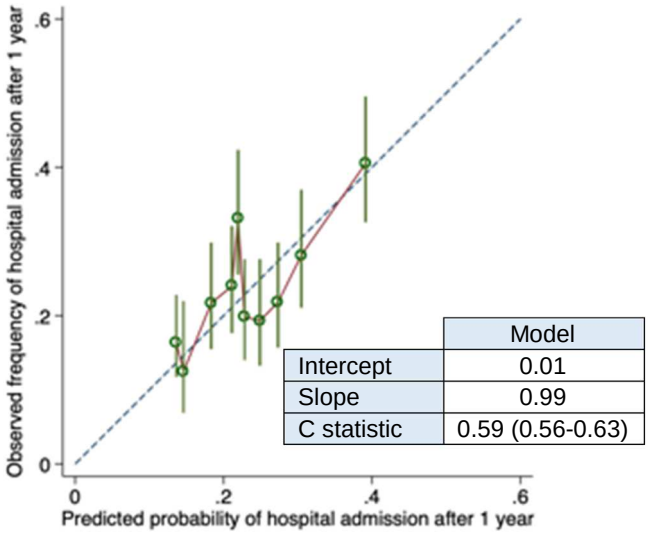
1-Year Risk

A Derivation Cohort



	Model
Intercept	0.07
Slope	0.99
C statistic	0.64 (0.61-0.66)

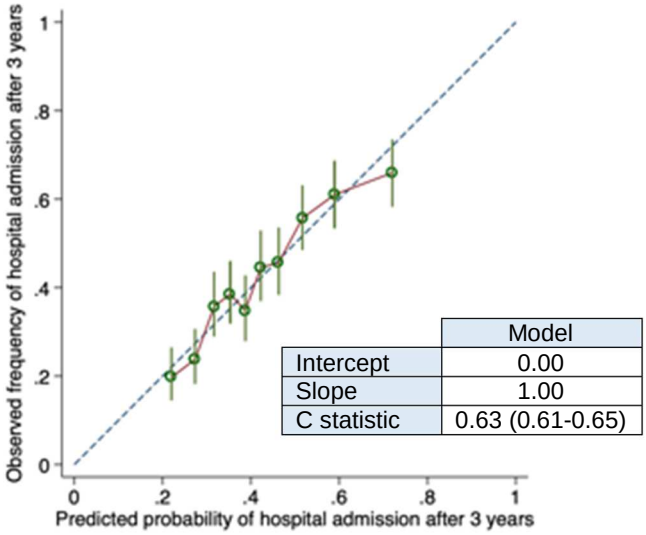
B Validation Cohort



	Model
Intercept	0.01
Slope	0.99
C statistic	0.59 (0.56-0.63)

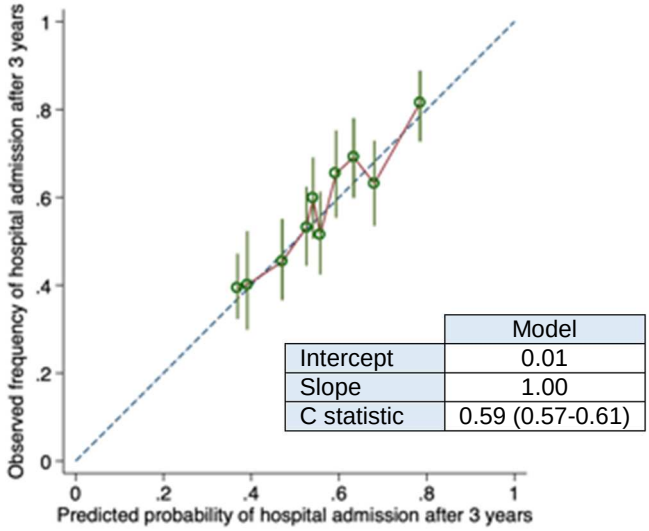
3-Year Risk

C Derivation Cohort



	Model
Intercept	0.00
Slope	1.00
C statistic	0.63 (0.61-0.65)

D Validation Cohort



	Model
Intercept	0.01
Slope	1.00
C statistic	0.59 (0.57-0.61)

Figure S5

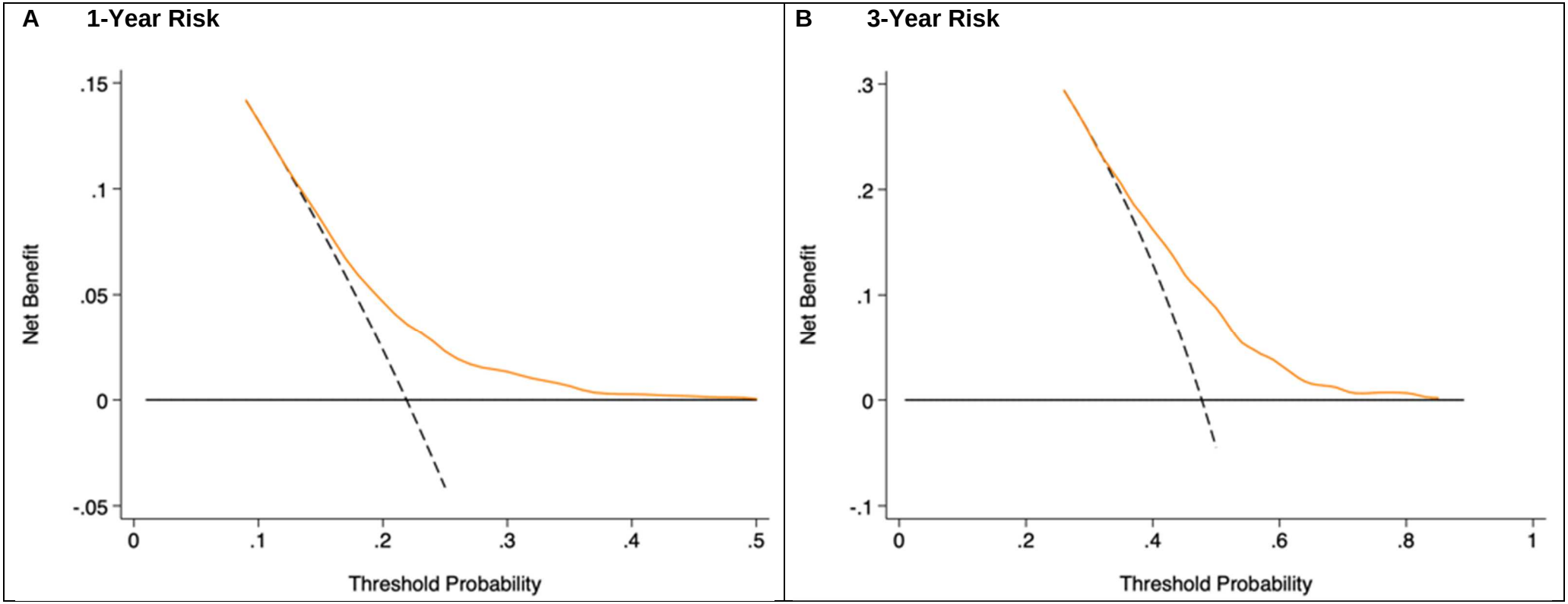

A
1-Year Risk
Net Benefit
.15
.1
.05
0
-.05
0
.1
.2
.3
.4
.5
Threshold Probability
B
3-Year Risk
Net Benefit
.3
.2
.1
0
-.1
0
.2
.4
.6
.8
1
Threshold Probability

Figure legends

Figure S1 Formation of the Derivation and Validation Cohorts

Figure S2 Visual Inspection of the Path of Variable Selection Using LASSO

Figure S3 Variables selected by LASSO (N=11)

Figure S4 Calibration Plots with C Statistics for the Predicted Versus Observed 1-year and 3-year Hospital Admission Risk of the Prediction Model

Derivation cohort (n=2387) and validation cohort (n=1300). Error bars indicate 95% confidence intervals. Red line connects the estimates of each decile.

Figure S5 Decision Curve Analysis for the Admit-AF Score

The net clinical benefit using the risk prediction models to guide clinical decision in relation to assuming that no one is at risk (x axis) or that all are at risk (y axis) for hospital admission. The x axis of different decision thresholds is plotted against the y axis (N=3687).

6. MANUSCRIPT 3 – Psychosocial factors for hospital admissions

Psychosocial Factors Predict Hospital Admissions in Patients with Atrial Fibrillation

Pascal Meyre, Anne Springer, Stefanie Aeschbacher, Steffen Blum, Nicolas Rodondi, Jürg H. Beer, Peter Ammann, Marcello Di Valentino, Manuel Blum, Rebecca Mathys, Christine Meyer-Zürn, Matthias Schwenkglenks, Leo H. Bonati, Michael Kühne, David Conen, Stefan Osswald

CURRENT STANDING: SUBMITTED

Psychosocial Factors Predict Hospital Admissions in Patients with Atrial Fibrillation: Evidence from the Swiss Atrial Fibrillation Study

Pascal Meyre[1,2], Anne Springer[1,2], Stefanie Aeschbacher[1,2], Steffen Blum[1,2], Nicolas Rodondi[3,4], Jürg H. Beer[5], Peter Ammann[6], Marcello Di Valentino[7], Manuel Blum[3,4], Rebecca Mathys[2], Christine Meyer-Zürn[1,2], Matthias Schwenkglenks[8], Leo H. Bonati[9], Michael Kühne[1,2], David Conen[2,10], Stefan Osswald[1,2], on behalf of the Swiss-AF Investigators

[1] Division of Cardiology, Department of Medicine, University Hospital Basel, Switzerland
[2] Cardiovascular Research Institute Basel, University Hospital Basel, Switzerland
[3] Institute of Primary Health Care (BIHAM), University of Bern, Switzerland
[4] Department of General Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland
[5] Department of Medicine, Cantonal Hospital of Baden and Molecular Cardiology, University Hospital of Zürich, Switzerland
[6] Department of Cardiology, Kantonsspital St. Gallen, Switzerland
[7] Department of Cardiology, Ospedale San Giovanni, Bellinzona, Switzerland
[8] Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Switzerland
[9] Department of Neurology and Stroke Center, University Hospital Basel, University of Basel, Switzerland
[10] Population Health Research Institute, McMaster University, Hamilton, ON, Canada

Brief title:

Psychosocial factors predict hospitalizations in AF

Word count: 2276

Address for correspondence:

Stefan Osswald MD

University Hospital Basel

Petersgraben 4

4031 Basel, Switzerland

Phone: +41 61 265 5226

Email: stefan.osswald@usb.ch

Abstract

Background: A high burden of cardiovascular comorbidities puts patients with atrial fibrillation (AF) at increased risk for being admitted to the hospital. However, whether psychosocial factors may contribute to the high rate of unplanned hospital admissions remains unclear.

Objectives: To assess the relationships of psychosocial factors with the incidence of hospital admissions in patients with AF.

Methods: We prospectively evaluated associations of psychosocial factors (i.e., marital status, education, depression and health perception) with the incidence of hospital admission in 2358 patients with AF from the Swiss Atrial Fibrillation Cohort (Swiss-AF). The primary outcome was defined as time to first unplanned all-cause hospital admission, while secondary outcomes were time to first cardiovascular and non-cardiovascular admissions. Associations of psychosocial factors with the incidence of hospital admission were tested by multivariable Cox regression models. Patients were categorized into three groups according to their overall burden of psychosocial conditions, and compared using multivariable Cox models.

Results: During a median follow-up of 2.0 years, 877 (37%) patients had at least one all-cause hospital admission, while 367 (16%) patients were hospitalized for cardiovascular and 618 (26%) for non-cardiovascular causes. The highest risk of all-cause hospital admission was observed in single patients (adjusted hazard ratio [aHR], 1.35; 95% confidence interval [CI], 1.05-1.75) and divorced patients (aHR, 1.26; 95% CI, 1.03-1.54) and in those who reported low health perception (aHR, 1.40; 95% CI, 1.21-1.62). For cardiovascular and non-cardiovascular admissions, only low health perception was a strong predictor. When patients were categorized according to their burden of psychosocial conditions, adjusted hazard ratios for all-cause hospital admission were 1.83 (95% CI, 1.47-2.29) for single or divorced patients with low health perception relative to patients without. Adjusted hazard ratio for patients who were single or divorced, or had low health perception compared to patients who had none was 1.35 (95% CI, 1.16-1.56). Similar associations were indicated for cardiovascular and non-cardiovascular admissions.

Conclusions: Psychosocial factors, namely marital status and health perception, are predictive of hospital admissions in AF patients. Hence, treatment strategies may profit from complementary psychosocial interventions in this patient population.

Keywords: Atrial fibrillation, psychosocial factors, health perception, unplanned hospitalization

Introduction

The prevalence of atrial fibrillation (AF) is increasing and expected to affect nearly 18 million Europeans in the future.[1] Patients with AF have multiple comorbidities and a high risk of stroke and death,[2-4] which puts them at increased risk of being admitted to the hospital.[5] Although most hospital admissions are essentially triggered by medical disorders, non-medical factors may be crucial as well.

It is well-established that factors that promote health are not only lifestyle modifications and medical treatments, but also a patient's social and psychological conditions (i.e., marital status, education, mental health).[6] These psychosocial factors were shown to affect the risk of cardiovascular disease,[7,8] and evidence suggests that the effects are comparable in strength to those associated with physical activity, smoking, or alcohol use.[9,10] Prior studies addressed the relationships of psychosocial risk factors with incident AF and heart failure admissions.[11-13] It showed that among AF patients, those who had low social status, low education, or low household income levels demonstrated a higher risk of mortality as compared to individuals without such psychosocial constrains.14

However, only very little is known about how psychosocial factors may affect the risk of unplanned hospital admissions in AF populations. For instance, patients with low social support may be less able to cope with health conditions and life crises, which may increase their tendency to seek medical hospital care. If there is evidence in support of this notion, it may sensitize physicians to advise psychosocial interventions. Given that hospital admissions are strong drivers of healthcare expenditures, such evidence may imply new strategies to reduce costs related to hospital admission rates.

We therefore aimed to investigate the prevalence of psychosocial factors and their effects on hospital admissions in a comprehensive cohort of clinically well-characterized patients with AF.

Methods

Study population

The Swiss Atrial Fibrillation Cohort (Swiss-AF) is a large prospective cohort study of 2415 patients with diagnosed AF, recruited between 2014 and 2017 across 14 centers in Switzerland. Details of the study design and first results have been published previously.[15,16] Patients were enrolled if they had documented AF (at least 1 electrocardiogram recording showing AF) and were ≥65 years of age. Patients were excluded if they had only short, reversible AF episodes (i.e., AF occurring after cardiac surgery) or if they were unable to give informed consent. Of the 2415 patients included, 57 (2.4%) were excluded from the present analysis due to drop-out or consent withdrawal (n=28, 1.2%) or missing values regarding psychosocial factors (n=29, 1.2%). Thus, the analyses included a total of 2358 patients. The study protocol was approved by the local ethics committees, and written informed consent was obtained from all participants.

Procedures

Demographic and clinical information were collected using standardized case report forms and validated questionnaires. Yearly follow-up visits were performed by local study personnel, either face-to-face or by phone calls, to collect patient characteristics, clinical measures and outcome events.

Marital status and education level were defined as social factors, and presence of depression and health perception were considered as the psychological component. Marital status was requested in terms of married, single, divorced or widowed. Education level was evaluated using the sum of completed years at school, high school or college, and defined as primary or less (less than compulsory education curriculum: ≤6 years), secondary (high school or similar: 6 to ≤12 years) and college or university (college or university degree: >12 years of education). Depression and depressive symptoms were measured using the Geriatric Depression Scale (GDS),[17,18] with a total point score ranging from 0 to 15, and a total score of >5 points was taken to indicate depression. Health perception was self-assessed by patients indicating their current state of health using a visual analogue scale (VAS) ranging from 0 (worst) to 100 (best). The VAS used in this study was based on the EuroQol VAS and has been validated for AF patients.[19,20] For the purpose of the present analyses, the median was set for the threshold of low (<75%) versus high (≥75) health perception.

Outcomes

The primary outcome of this study was time to first all-cause hospital admission, defined as any unplanned admission leading to at least 1 overnight stay. Secondary outcomes were time to first cardiovascular and non-cardiovascular hospital admissions, with cardiovascular admissions being defined as admission due to heart failure, stroke or transient ischemic attack (TIA), myocardial infarction, bleeding, or deep vein thrombosis. Repeated admissions were not counted. The occurrence and type of events were assessed at yearly follow-up examinations (i.e., on-site visit, phone call, or information gathered from the family doctor).

Statistical analysis

Baseline characteristics are presented as means with standard deviation (SD) for continuous variables and as counts (percentages) for categorical variables. Incidence rates and 95% confidence intervals (CI) for primary and secondary outcomes were calculated per 100 patients-years of follow-up. Kaplan-Meier plots were used to describe the cumulative incidence of hospital admissions. We constructed Cox proportional hazards models to test the associations of psychosocial factors with the risk of hospital admission, adjusting for cardiovascular and non-cardiovascular covariates. These covariates included age, sex, body mass index (BMI), history of hypertension, diabetes, coronary heart disease, prior stroke or transient ischemic attack (TIA), heart failure, peripheral vascular disease, renal failure, cancer, and previous falls.

We then constructed a combined multivariable model including all psychosocial factors to determine the strongest predictors for all-cause hospital admissions. Multivariable and combined models included 2349 patients due to missing data of 9 patients (0.4 %). To investigate the proportional hazards assumption, we calculated Schoenfeld residuals.[21]

To evaluate the overall burden of psychosocial factors and their impact on hospital admissions, we used the variables that were associated with all-cause hospital admission from the combined model, and categorized patients according to the presence of these factors into three groups. The groups were compared using multivariable Cox models, adjusted for the same covariates as listed above, and tested for trend of the survivor function across groups.

All analyses were performed using Stata, version 13 (StataCorp. 2013. College Station, TX: StataCorp LP).

Results

Baseline characteristics are shown in Table 1. Of the 2358 patients included in this analysis, mean age was 73.2 (SD, 8.5) years, and 639 (27.1%) were women. Regarding the marital status, 1582 (67.1%) were married, 156 (6.6%) were single, 287 (12.2%) were divorced, and 333 (14.1%) were widowed. Two hundred and seventy six patients (11.7%) had primary or less education, 1171 (49.7) had secondary education, and 911 (38.6%) had college or university degree. Depression was present in 99 (4.2%) patients and median health perception was 75% (interquartile range [IQR], 60%-85%).

During a median of 2.0 (IQR, 1.0-3.0) years of follow-up, 877 (37%) patients had at least one hospital admission, with an incidence of 19.0 per 100 patient-years (95% confidence interval [CI], 17.8-20.3). Over the same follow-up time, 367 (16%) patients were hospitalized for cardiovascular and 618 (26%) for non-cardiovascular causes, with incidence rates of 6.9 and 13.4 per 100 person-years, respectively. Tables S1 in the Supplement shows the number of events and incidence rates for all-cause, cardiovascular and non-cardiovascular hospital admissions stratified by psychosocial factors and health perception.

Patients who were not married, had secondary education, symptoms of depression, or exhibited low health perception a higher risk of all-cause hospital admission (Table 2). In multivariable analyses, patients who were single (adjusted hazard ratio [aHR], 1.38; 95% CI, 1.07-1.78) or divorced (aHR, 1.26; 95% CI, 1.03-1.55) and those who had a low health perception (aHR, 1.43; 95% CI, 1.24-1.62) showed an increased risk of all-cause hospital admission (Table 2). These findings persisted in the combined model (all $P<0.05$) (Table 2).

For cardiovascular hospital admissions, only low health perception remained strongly associated with the outcome in the combined multivariable model (aHR, 1.47; 95% CI, 1.18-1.83) (Table S2 in the Supplement). Similar for non-cardiovascular admissions, only low health perception remained associated with the outcome in the combined model (aHR, 1.39; 95% CI, 1.17-1.64) (Table S3 in the Supplement).

From the combined model, being single or divorced and having low health perception were identified as predictors for all-cause hospital admissions and patients were categorized accordingly. Cumulative incidences of all-cause hospital admission across categories are presented in Figure 1. Hazard ratios for the risk of all-cause hospital

admission were 1.83 (95% CI, 1.47-2.29) for patients who were single or divorced and had low health perception versus patients who had none of these factors. Patients who were either single or divorced, or had low health perception had a higher risk of admission as compared to those without any of these factors (aHR, 1.36; 95% CI, 1.14-1.61) (Table 4).

Kaplan-Meier curves for cardiovascular and non-cardiovascular hospital admissions were plotted according to marital status and health perception (Figures S1A and S1B in the Supplement). Patients who were single or divorced and had low health perception had a higher risk of cardiovascular admission as compared to patients without any of these factors (aHR, 1.90; 95% CI, 1.36-2.65). Patients who were either single or divorced, or showed low health perception exhibited a higher risk cardiovascular admission than patients without these factors (aHR, 1.38; 95% CI, 1.09-1.74). Similar for non-cardiovascular admissions, hazard ratios were 1.66 (95% CI, 1.27-2.18) for patients who were single or divorced and had low health perception relative to those exhibiting none of these factors. Patients who were either single or divorced, or showed low health perception indicated a higher risk of non-cardiovascular admission as compared to patients without such psychosocial conditions (aHR, 1.26; 95% CI, 1.03-1.53) (Table 3).

Discussion

The present study investigated the relationships between psychosocial factors and the risk of unplanned hospital admissions in patients with AF. Several important findings emerged. First, the incidence of hospital admission was high in this patient population, with nearly two-thirds of admissions being due to non-cardiovascular causes. Second, patients who were single or divorced, or indicated a low health perception had a significantly higher risk of hospital admission. This risk was even higher among patients to whom both of these psychosocial conditions applied, suggesting that the overall burden of psychosocial conditions matters.

Our study showed that patients who were single or divorced revealed a higher risk of all-cause hospital admission relative to those who were married. Consistently, previous studies showed higher admission rates for unmarried relative to married individuals from non-AF population.[22,23] These findings are in line with the notion that relative to those living alone (single, divorced), patients who have close relationships to others can rely on better social support, acting to decrease psychological distress,[24] and may therefore show increased needs for institutionalized hospital care.[25]

Our results indicated that the risk of all-cause hospital admission was associated with subjective evaluations of health, which was also indicated for cardiovascular and non-cardiovascular admissions. Specifically, patients who felt in relatively good health conditions were generally less prone to seek for hospital care relative to those who felt less healthy. Evidence from studies of non-AF populations showed that patients who reported poor or fair health conditions exhibited an up to five time higher risk of hospital admission or death as compared to those reporting excellent or good health.[26,27] Previous studies suggested that self-efficacy is a key predictor of heart failure hospital admission and all-cause death.[28] One may assume that social support and help of close others strengthen self-efficacy beliefs, acting as a buffer of distress due to medical illness, which prevents patients with high social support from striving for hospital admission. This account corresponds to the high admission rates of unmarried patients observed in the present study. Moreover, low evaluations of health have often been reported for AF population.[29]

In an attempt to identify patients at high risk of hospital admissions, we stratified patients into three groups according to their burden of psychosocial conditions. Results showed that the risk of all-cause hospital admission increased with increasing burden

of psychosocial factors (see Table 3, Figure 1). Similar effects were observed for cardiovascular and non-cardiovascular admissions (Table 3, Figure S1A and S1B in the Supplement). Further studies are required to highlight the impact of social support and self-efficacy on admission risk, and to better understand how the overall burden of distinct psychosocial factors may influence this adverse outcomes in AF patients.

Overall, the present results may also be informative for clinical purposes. Greater awareness of the patients' psychosocial conditions may help clinicians to intervene more sensitively and to be more responsive to the specific support needs that are activated by illness. Interventions may thus include to improve the patient's social relations and to strengthen their self-efficacy in face of illness, which may imply psychosocial counselling, self-help group assignment, or psychotherapy. To highlight this issue, future studies should include direct measures of social support. Also, effects of psychosocial treatment as complementary strategy of AF-related medical treatment should be addressed.

Strengths and Limitations

This study is, to our best knowledge, the first to highlight associations of psychosocial factors and hospital admissions in patients with AF, based on a comprehensive multicenter population-based cohort of clinically well-characterized patients. However, some limitations emerge. First, the variables representing psychosocial factors were collected based on availability in the cohort data set. However, additional factors, such as income or measures of social deprivation, may matter. Second, we assessed time to first hospital admission, and ignored any repeated admissions. Lastly, our results stem from a national cohort of AF patients in Switzerland, implying limited generalizability.

In conclusion, our findings suggest that low social support and low health evaluations are associated with an increased risk of hospital admission in AF patients. These findings may sensitize clinicians to identify AF patients who may benefit from complementary intervention strategies aiming to improving psychosocial conditions. Enhancing psychosocial conditions may even contribute to reduced health care costs due to decreased needs for hospital medical care in this patient population.

Funding

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Disclosures

Dr. Kuehne received consulting fees from Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Pfizer and Bristol-Myers Squibb; Dr. Sticherling has received speaker honoraria from Biosense Webster and Medtronic and research grants from Biosense Webster, Daiichi-Sankyo, and Medtronic; Dr. Conen received consulting fees from Servier, Canada.

Abbreviations

AF	Atrial fibrillation
BMI	Body mass index
IQR	Interquartile range
SD	Standard deviation
TIA	Transient ischemic attack
VAS	Visual analogue scale

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Figure legends

Figure 1 Cumulative incidence of all-cause hospital admission according to the burden of marital status and health perception

Abbreviations: HP, health perception

Table 1 Baseline characteristics

Characteristic	Overall (N=2358)
Age, mean (SD), y	73.2 ± 8.5
Female sex	639 (27.1)
Marital status	
Married	1582 (67.1)
Single	156 (6.6)
Divorced	287 (12.2)
Widowed	333 (14.1)
Education	
Primary or less	276 (11.7)
Secondary	1171 (49.7)
College, or university	911 (38.6)
Depression or depressive symptoms	99 (4.2)
Health perception, median (IQR), %	75 (60-85)
Atrial fibrillation type	
Paroxysmal	1059 (44.9)
Persistent	694 (29.4)
Permanent	605 (25.7)
Body mass index, median (IQR), kg/m^2	27.0 (24.4-30.4)
Comorbidities	
Hypertension	1640 (69.6)
Diabetes	399 (16.9)
Coronary artery disease	721 (30.6)
Stroke/TIA	467 (19.8)
Heart failure[b]	608 (25.8)
Peripheral vascular disease	186 (7.9)
Bleeding	370 (15.7)
CHA_2DS_2-VASc score, median (IQR)[c]	3.0 (2.0-5.0)
Oral anticoagulation	2157 (90.4)
Vitamin K antagonist	932 (39.5)
Direct oral anticoagulants	1197 (50.8)
Antiplatelet therapy[d]	468 (19.9)

Abbreviations: IQR= interquartile range; CHA_2DS_2-VASc=congestive heart failure, hypertension, age 75≥ years (2 points), diabetes, prior stroke or TIA or thromboembolism (2 points), vascular disease, age 65 to 74 years, female sex. Bleeding= major bleeding or clinically relevant non-major bleeding;
[a] N=16 missing values; [b] N=2 missing values; [c] N=3 missing values; [d] N=4 missing values.

Table 2 Association of psychosocial factors and health perception with all-cause hospital admission

	All-cause hospital admission						
Variables	**Events/ No. at risk**	**Unadjusted HR (95% CI)**	**P value**	**Adjusted HR (95% CI)***	**P value**	**Combined adjusted HR (95% CI)†**	**P value**
Marital status							
Married	560/1582	1 [Reference]		1 [Reference]		1 [Reference]	
Single	69/156	1.32 (1.03-1.70)	0.03	1.38 (1.07-1.78)	0.01	1.35 (1.05-1.75)	0.02
Divorced	118/287	1.24 (1.01-1.51)	0.04	1.26 (1.03-1.55)	0.02	1.26 (1.03-1.54)	0.03
Widowed	130/333	1.24 (1.02-1.50)	0.03	1.05 (0.85-1.29)	0.65	1.04 (0.85-1.28)	0.71
Education							
College, or university	308/911	1 [Reference]		1 [Reference]		1 [Reference]	
Secondary	463/1171	1.20 (1.04-1.39)	0.01	1.14 (0.98-1.32)	0.08	1.15 (1.00-1.34)	0.05
Primary or less	106/276	1.18 (0.94-1.47)	0.14	1.09 (0.86-1.38)	0.48	1.04 (0.85-1.28)	0.50
Depression							
No	828/2259	1 [Reference]		1 [Reference]		1 [Reference]	
Yes	49/99	1.53 (1.14-2.04)	0.004	1.23 (0.91-1.65)	0.17	1.12 (0.83-1.51)	0.46
Health perception							
High: ≥75%	403/1334	1 [Reference]		1 [Reference]		1 [Reference]	
Low: <75%	474/1024	1.81 (1.58-2.07)	<0.001	1.43 (1.24-1.65)	<0.001	1.41 (1.22-1.62)	<0.001

Data are presented as hazard ratio (HR) with 95% confidence intervals (CI).

*Models were adjusted for age, sex, body mass index, hypertension, diabetes, coronary heart disease, prior stroke/TIA, heart failure, peripheral vascular disease, renal failure, cancer, and previous falls.

† Model was combined and adjusted for age, sex, body mass index, hypertension, diabetes, coronary heart disease, prior stroke/TIA, heart failure, peripheral vascular disease, renal failure, cancer, and previous falls.

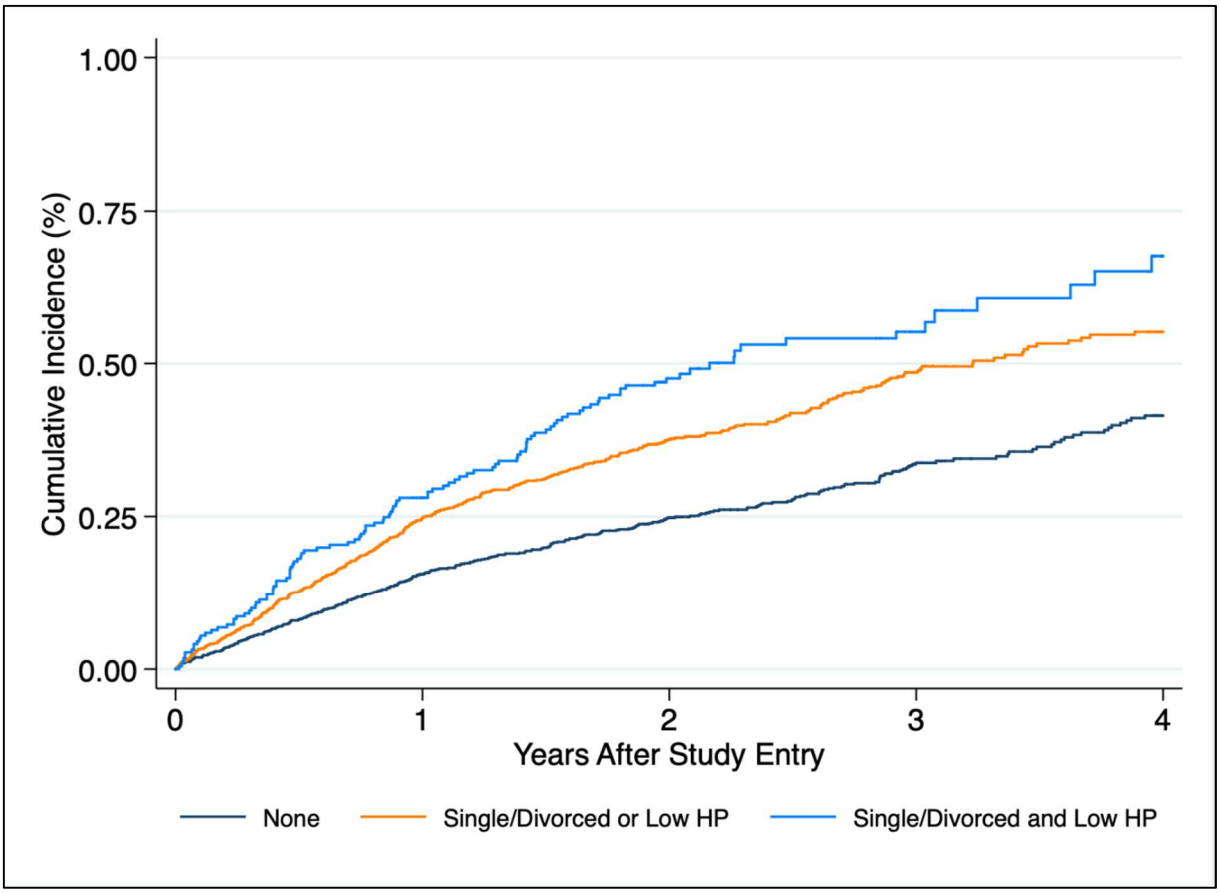
Table 3 Risk of all-cause hospital admission according to marital status and health perception

Outcome	No. of Events/ Patients	Incidence[a]	Adjusted HR (95% CI)*	P value	P trend
All-cause hospital admission					
None	330/1112	14.0 (12.6-15.6)	1 [Reference]		<0.001
Single/divorced or low health perception	433/1025	23.0 (20.9-25.3)	1.35 (1.16-1.56)	<0.001	
Single/divorced and low health perception	114/221	30.6 (25.5-36.8)	1.83 (1.47-2.29)	<0.001	
Cardiovascular hospital admission					
None	125/1112	4.7 (4.0-5.6)	1 [Reference]		<0.001
Single/divorced or low health perception	188/1025	8.4 (7.3-9.7)	1.38 (1.09-1.74)	0.007	
Single/divorced and low health perception	54/221	11.7 (8.9-15.2)	1.90 (1.36-2.65)	<0.001	
Non-cardiovascular hospital admission					
None	234/1112	9.3 (8.2-10.6)	1 [Reference]		<0.001
Single/divorced or low health perception	310/1025	14.9 (13.4-16.7)	1.37 (1.15-1.64)	<0.001	
Single/divorced and low health perception	74/221	17.2 (13.7-21.5)	1.66 (1.27-2.18)	<0.001	

[a] Incidence per 100 patient-years of follow-up (95% CI)

*****Adjusted for age, sex, body mass index, hypertension, diabetes, coronary heart disease, prior stroke/TIA, heart failure, peripheral vascular disease, renal failure, cancer, and previous falls.

Figure 1 Cumulative incidence of all-cause hospital admission according to the burden of marital status and health perception



Supplement

Psychosocial Factors Predict Hospital Admissions in Patients with Atrial Fibrillation: Evidence from the Swiss Atrial Fibrillation Study

Pascal Meyre, Anne Springer, Stefanie Aeschbacher, Steffen Blum, Nicolas Rodondi, Jürg H. Beer, Peter Ammann, Marcello Di Valentino, Manuel Blum, Rebecca Mathys, Christine Meyer-Zürn, Matthias Schwenkglenks, Leo H. Bonati, Michael Kühne, David Conen, Stefan Osswald, on behalf of the Swiss-AF Investigators

Swiss-AF Investigators

University Hospital Basel/Basel University: Stefanie Aeschbacher, Steffen Blum, Leo Bonati, Peter Hämmerle, Philipp Krisai, Christine Meyer-Zürn, Pascal Meyre, Andreas U. Monsch, Christian Müller, Christiane Pudenz, Philipp Reddiess, Javier Ruperti Repilado, Aleksandra Schweizer, Anne Springer, Fabienne Steiner, Christian Sticherling, Thomas Szucs, Gian Voellmin, Leon Zwimpfer. Local Principal Investigator: Michael Kühne; Principal Investigators; Stefan Osswald, David Conen.

University Hospital Bern: Faculty: Drahomir Aujesky, Urs Fischer, Juerg Fuhrer, Laurent Roten, Simon Jung, Heinrich Mattle; Research fellows: Luise Adam, Carole Elodie Aubert, Martin Feller, Claudio Schneider, Axel Loewe, Elisavet Moutzouri; Study nurses: Tanja Flückiger, Cindy Groen, Nathalie Schwab. Local Principal Investigator: Nicolas Rodondi.

Stadtspital Triemli Zurich: Christopher Beynon, Roger Dillier, Franz Eberli, Christine Franzini, Isabel Juchli, Claudia Liedtke, Jacqueline Nadler, Thayze Obst, Noreen Tynan, Xiaoye Schneider, Katrin Studerus, Dominik Weishaupt. Local Principal Investigator: Andreas Müller.

Kantonspital Baden: Simone Fontana, Silke Kuest, Karin Scheuch, Denise Hischier, Nicole Bonetti, Corina Bello, Henriette Isberg, Alexandra Grau, Jonas Villinger, Mary-Monica Papaux, Eva Laube, Philipp Baumgartner, Mark Filipovic, Marcel Frick, Stefanie Leuenberger. Local Principal Investigator: Jürg H. Beer.

Cardiocentro Lugano: Angelo Auricchio, Adriana Anesini, Cristina Camporini, Giulio Conte, Maria Luce Caputo, Francois Regoli, Tiziano Moccetti. Local Principal Investigator: Tiziano Moccetti.

Kantonsspital St. Gallen: Roman Brenner, David Altmann, Manuela Forrer, Michaela Gemperle. Local Principal Investigator: Peter Ammann.

Hôpital Cantonal Fribourg: Mathieu Firmann, Sandrine Foucras. Local Principal Investigator: Daniel Hayoz.

Luzerner Kantonsspital: Benjamin Berte, Andrea Kaeppeli, Myriam Roth, Brigitta Mehmann, Markus Pfeiffer, Ian Russi, Kai Schmidt, Vanessa Weberndoerfer, Mabelle Young, Melanie Zbinden; Local Principal Investigator: Richard Kobza.

Ente Ospedaliero Cantonale Lugano: Luisa Vicari, Jane Frangi-Kultalahti, Tatiana Terrot. Local Principal Investigator: Giorgio Moschovitis.

University Hospital Geneva: Georg Ehret, Hervé Gallet, Elise Guillermet, Francois Lazeyras, Karl-Olof Lovblad, Patrick Perret, Cheryl Teres. Local Principal Investigator: Dipen Shah.

University Hospital Lausanne: Nathalie Lauriers, Marie Méan, Sandrine Salzmann. Local Principal Investigator: Jürg Schläpfer.

Bürgerspital Solothurn: Nisha Arenja, Andrea Grêt, Sandra Vitelli. Local Principal Investigator: Frank-Peter Stephan.

Ente Ospedaliero Cantonale Bellinzona: Jane Frangi, Augusto Gallino. Local Principal Investigator: Marcello Di Valentino.

St. Anna Spital Luzern: Renate Schoenenberger-Berzins.

University of Zurich/University Hospital Zurich: Fabienne Witassek, Matthias Schwenkglenks, Christoph Stippich.

Medical Image Analysis Center AG Basel: Ernst-Wilhelm Radue, Tim Sinnecker, Jens Würfel.

Clinical Trial Unit Basel: Pascal Benkert, Thomas Fabbro, Patrick Simon, Michael Coslovsky.

Schiller AG Baar: Ramun Schmid.

Table S1 Incidence of hospital admissions according to psychosocial factors

Psychosocial risk factors	All-cause hospital admission		Cardiovascular hospital admission		Non-cardiovascular hospital admission	
	Events/ No. of patients	Incidence[a]	Events/ No. of patients	Incidence[a]	Events/ No. of patients	Incidence[a]
Marital status						
Married	560/1582	17.5 (16.2-19.1)	233/1582	6.3 (5.6-7.2)	391/1582	11.3 (10.2-12.5)
Single	69/156	23.5 (18.6-29.8)	29/156	8.4 (5.9-12.1)	48/156	14.7 (11.1-19.5)
Divorced	118/287	21.9 (18.3-26.2)	53/287	8.3 (6.3-10.8)	80/287	13.5 (10.9-16.8)
Widowed	130/333	22.2 (18.7-26.4)	52/333	7.5 (5.7-9.9)	99/333	15.5 (12.8-18.9)
Education						
College, or university	308/911	16.9 (15.1-18.9)	133/911	6.3 (5.4-7.6)	217/911	11.0 (9.6-12.6)
Secondary	463/1171	20.4 (18.7-22.4)	194/1171	7.3 (6.3-8.4)	326/1171	13.2 (11.9-14.7)
Primary or less	106/276	20.2 (16.7-24.4)	41/276	6.5 (4.8-8.9)	75/276	13.0 (10.4-16.3)
Depression						
No	828/2259	18.6 (17.4-20.0)	345/2259	6.7 (6.0-7.5)	585/2259	12.1 (11.2-13.1)
Yes	49/99	30.0 (17.4-38.3)	22/99	10.1 (6.7-15.4)	33/99	17.5 (12.4-24.6)
Health perception						
High: ≥75%	403/1334	14.3 (13.0-15.8)	153/1334	4.8 (4.1-5.6)	288/1334	9.6 (8.6-10.8)
Low: <75%	474/1024	26.4 (24.2-28.9)	214/1024	9.8 (8.6-11.2)	330/1024	16.3 (14.7-18.2)

[a] Incidence per 100 patient-years of follow-up (95% CI)

Table S2 Association of psychosocial factors with cardiovascular hospital admission

	Cardiovascular hospital admission						
Variables	**Events/ No. at risk**	**Unadjusted HR (95% CI)**	**P value**	**Adjusted HR (95% CI)***	**P value**	**Combined adjusted HR (95% CI)†**	**P value**
Marital status							
Married	233/1582	1 [Reference]		1 [Reference]		1 [Reference]	
Single	29/156	1.30 (0.89-1.92)	0.18	1.36 (0.92-2.01)	0.12	1.31 (0.89-1.95)	0.17
Divorced	53/287	1.28 (0.95-1.73)	0.10	1.31 (0.97-1.78)	0.08	1.29 (0.95-1.75)	0.10
Widowed	52/333	1.14 (0.84-1.54)	0.85	1.03 (0.74-1.42)	0.17	1.03 (0.75-1.42)	0.19
Education							
College, or university	133/911	1 [Reference]		1 [Reference]		1 [Reference]	
Secondary	194/1171	1.14 (0.91-1.42)	0.25	1.05 (0.84-1.32)	0.67	1.06 (0.85-1.34)	0.59
Primary or less	41/276	1.02 (0.72-1.45)	0.89	0.95 (0.65-1.38)	0.77	0.94 (0.65-1.37)	0.76
Depression							
No	345/2259	1 [Reference]		1 [Reference]		1 [Reference]	
Yes	22/99	1.51 (0.98-2.31)	0.06	1.23 (0.79-1.91)	0.36	1.12 (0.72-1.74)	0.63
Health perception							
High: ≥75%	153/1334	1 [Reference]		1 [Reference]		1 [Reference]	
Low: <75%	214/1024	1.97 (1.60-2.43)	<0.001	1.47 (1.18-1.83)	<0.001	1.44 (1.16-1.80)	0.001

Data are presented as hazard ratio (HR) with 95% confidence intervals (CI).

*Models were adjusted for age, sex, body mass index, hypertension, diabetes, coronary heart disease, prior stroke/TIA, heart failure, peripheral vascular disease, renal failure, cancer, and previous falls.

† Model was combined and adjusted for age, sex, body mass index, hypertension, diabetes, coronary heart disease, prior stroke/TIA, heart failure, peripheral vascular disease, renal failure, cancer, and previous falls.

Table S3 Association of psychosocial factors and health perception with non-cardiovascular hospital admission

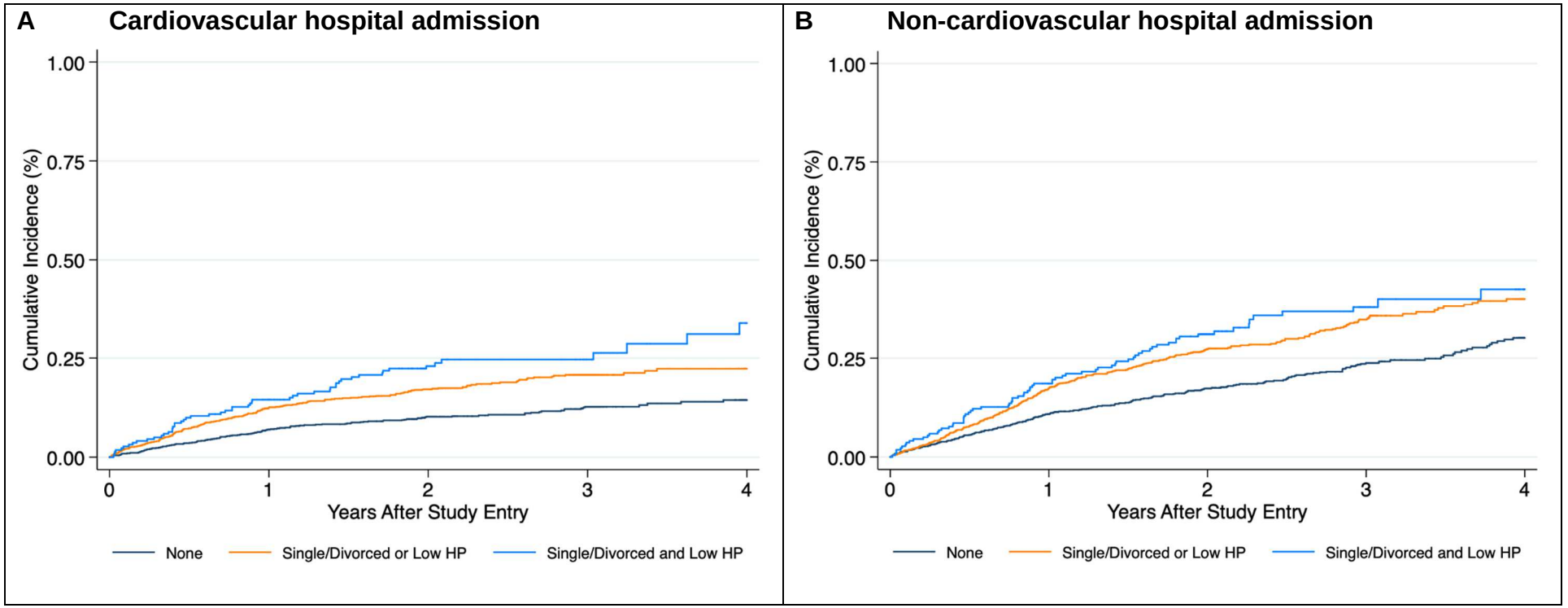
	Non-cardiovascular hospital admission						
Variables	**Events/ No. at risk**	**Unadjusted HR (95% CI)**	**P value**	**Adjusted HR (95% CI)***	**P value**	**Combined adjusted HR (95% CI)†**	**P value**
Marital status							
Married	391/1582	1 [Reference]		1 [Reference]		1 [Reference]	
Single	48/156	1.28 (0.95-1.73)	0.10	1.31 (0.97-1.78)	0.08	1.29 (0.95-1.75)	0.11
Divorced	80/287	1.19 (0.93-1.51)	0.16	1.23 (0.96-1.57)	0.10	1.21 (0.95-1.55)	0.12
Widowed	99/333	1.34 (1.07-1.67)	0.01	1.10 (0.87-1.40)	0.41	1.09 (0.86-1.39)	0.47
Education							
College, or university	217/911	1 [Reference]		1 [Reference]		1 [Reference]	
Secondary	326/1171	1.19 (1.01-1.42)	0.04	1.14 (0.95-1.36)	0.15	1.15 (0.96-1.37)	0.12
Primary or less	75/276	1.18 (0.90-1.53)	0.23	1.07 (0.81-1.41)	0.66	1.05 (0.79-1.39)	0.72
Depression							
No	585/2259	1 [Reference]		1 [Reference]		1 [Reference]	
Yes	33/99	1.42 (0.99-2.01)	0.051	1.19 (0.83-1.71)	0.33	1.09 (0.76-1.56)	0.66
Health perception							
High: ≥75%	288/1334	1 [Reference]		1 [Reference]		1 [Reference]	
Low: <75%	330/1024	1.67 (1.43-1.96)	<0.001	1.40 (1.19-1.66)	<0.001	1.39 (1.17-1.64)	<0.001

Data are presented as hazard ratio (HR) with 95% confidence intervals (CI).

*Models were adjusted for age, sex, body mass index, hypertension, diabetes, coronary heart disease, prior stroke/TIA, heart failure, peripheral vascular disease, renal failure, cancer, and previous falls.

† Model was combined and adjusted for age, sex, body mass index, hypertension, diabetes, coronary heart disease, prior stroke/TIA, heart failure, peripheral vascular disease, renal failure, cancer, and previous falls.

Figure S1 Probability of cardiovascular and non-cardiovascular hospital admissions stratified by psychosocial burden groups



7. SUMMARY OF MAIN FINDINGS

7.1. Incidence and causes of hospital admission in atrial fibrillation

The pooled incidence of all-cause hospital admission was estimated to be 43.2 per 100 person-years. Cardiovascular admission were more common than non-cardiovascular (pooled incidence 26.3 vs 15.7 per 100 person-years). In meta-regression analyses including several variables, older age and prevalence of COPD were associated with an increased rate of all-cause hospital admissions. Patients with AF have a high risk of being admitted to the hospital, both for cardiovascular and non-cardiovascular causes.

7.2. Risk score for predicting hospital admissions in atrial fibrillation

In the derivation cohort (Swiss-AF), 891 patients (37.3%) were admitted to the hospital over a median follow-up of 2.0 years (incidence 19.1 per 100 person-years). Cardiovascular admissions occurred in 377 (15.8%) and non-cardiovascular in 629 (26.4%). Overall, 11 variables were selected by LASSO that were independently associated with the risk of hospital admission: age, previous PVI, hypertension, diabetes, coronary heart disease, prior stroke or TIA, heart failure, peripheral vascular disease, cancer, renal failure and previous falls. The Admit-AF score achieved a c-index of 0.64 for 1-year predicted risk and 0.63 for 3-year hospital admission risk in the derivation cohort. In the validation cohort (BEAT-AF), 719 patients (55.3%) were admitted to the hospital after a median follow-up of 1.9 years (cumulative incidence 26.1 per 100 person-years). Cardiovascular and non-cardiovascular admissions occurred in 357 (27.5%) and 514 (39.5%), respectively. The Admit-AF score yielded a c-index of 0.59 for the 1-year risk and 0.59 for 3-year hospital admission risk. Model calibration for 1-year and 3-year risk was accurate in the derivation cohort and remained well calibrated in the validation cohort.

7.3. Psychosocial factors for hospital admissions in atrial fibrillation

Of the 2,358 patients included in this analysis, 877 (37%) had at least one all-cause hospital admission, 367 (16%) patients were hospitalized for cardiovascular and 618

(26%) for non-cardiovascular causes after a median follow-up of 2.0 years. Patients who were single or divorced, and those who had a low health perception had the highest risk of all-cause hospital admission. For cardiovascular and non-cardiovascular admissions, only low health perception remained strongly associated with the secondary outcomes. When patients were categorized according to their burden of psychosocial conditions, adjusted hazard ratios for all-cause hospital admission were 1.83 (95% CI, 1.47-2.29) for single or divorced patients with low health perception compared to patients without. Adjusted hazard ratio for patients who were single or divorced, or had low health perception compared to patients who had none of these psychosocial conditions was 1.35 (95% CI, 1.16-1.56). Similar associations were identified for cardiovascular and non-cardiovascular admissions.

The main findings are summarized in Figure 4:

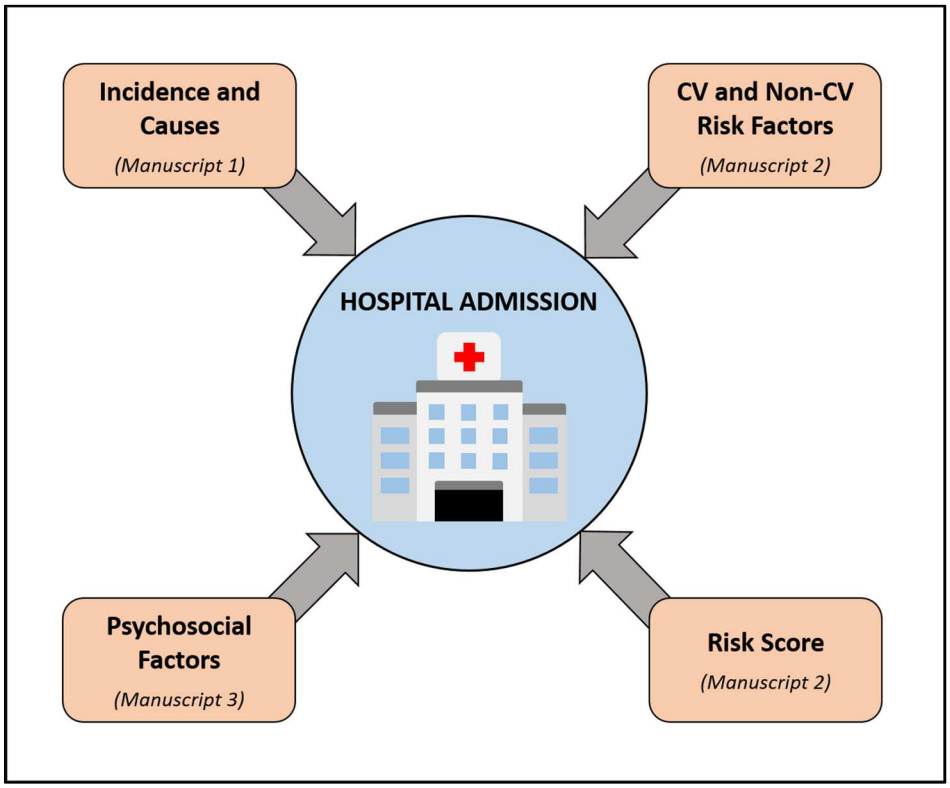


Figure 4 Illustration of the main investigations of the project.

8. DISCUSSION

In the following sections the findings of the three works of this PhD project will be discussed in light of the current literature and important potential implications will be emphasized. In addition, the discussion will critically evaluated the methodological aspects of the three works, including the strengths and limitations of this project. The potential implications of this project for future research will be outlined to further increase the knowledge in this important research field. Lastly, the specific contributions of the PhD student will be presented at the end of the discussion.

8.1. Specific discussion on the topic

8.1.1. Hospital admission and its consequence

There is a large body of evidence indicating that hospital admissions are increasing and that they are an important risk factor for adverse events. Extensive research has been conducted to examine the causes for readmissions in patients without AF who were discharged from the hospital. The researchers found that approximately 25% of all readmissions occurring within 30 days after discharge are preventable.[78] Also, patients who have recently been hospitalized have an increased risk for adverse events, such as heart failure, acute myocardial infarction, pneumonia and death.[79] These observations underscore that hospital admissions may be seen as a marker for patients who may have worse prognosis because of the underlying severity of illness. Consequently, preventing unnecessary admissions could have a positive impact on the overall risk of adverse outcomes in these patients.

Several published studies that assessed factors associated with hospital admission focused only on specific patient populations, such as patients with specific diagnosis such as HIV, heart failure, dementia or psychiatric disease.[80-82] This complicates the ability to compare admission rates and associated risk factors, and further limits the possibility for policy makers to establish and implement preventive interventions amongst a general population of patients.

From an economic point of view, hospital admissions represents the largest driver of health care costs, regardless of the examined patient populations. This is also true for AF populations. Overall, the estimated care costs of hospitalized AF patients are 9 to 23-fold greater than for those without AF.[83] In the Cardiovascular Health Study and the

Framingham Heart Study, investigators matched patients with newly diagnosed AF to controls free from AF.[84] They found that AF was associated with large incremental hospital and clinical care costs. The authors further suggested that the expected increase in AF prevalence worldwide may bring an increase in health care expenses which will pose a substantial burden on our health care systems.

There are also individual economic consequences for the patients who are admitted to the hospital. Reports from the United States indicate that individuals face considerable economic consequences of hospital admissions mainly through the impact on labor earnings.[85] It has been estimated that earnings decline associated with hospital admissions are similar to the existing estimates of the earnings consequences of job displacement. However, such data have not been investigated in AF populations, but it can be speculated that AF patients may also face similar earning consequences.

Taken together, hospital admissions have a substantial impact on the patient's prognosis and are associated with complications and economic consequences for the individual patient, but also for the health care system and our societies.

8.1.2. Incidence of hospital admissions

Patients with AF have multiple cardiovascular and non-cardiovascular comorbidities and therefore have an increased risk of various adverse outcome events, such as stroke and heart failure. Given this, these patients are particularly at high risk of being admitted to the hospital. Based on the results of our meta-analysis which included 35 studies with 311314 AF patients, the pooled incidence of all-cause hospital admission was very high, with 43.7 (95% CI, 38.5-48.9) per 100 person-years. In our two cohorts we observed an incidence of all-cause hospital admission of 19.1 (95% CI, 17.9-20.4) per 100 person-years in Swiss-AF and an incidence of 26.1 (95% CI, 24.2-28.1) per 100 person-years in BEAT-AF. The lower incidence rates in Swiss- and BEAT-AF explained by the stable condition of our patients compared to those in other studies and may reflect that most patients are well treated medically. Another reason could be that hospital admissions have not been evaluated similarly. Indeed, we observed in our meta-analysis that there was substantial between-study heterogeneity. It is possible that studies reported hospital admissions differently, which could have contributed to the different reported admission incidences. Also, although all studies included patients with AF, information about comorbidities is not fully available and it could be that differences in burden of comorbidities may have led to the observed

differences in incidence rates. This difference was further examined in our meta-analysis by performing subgroup and meta-regression analyses. Interestingly, it seems that among AF populations that had a high prevalence of COPD, patients had a significant higher overall incidence for all-cause hospital admission. The impact of AF in patients with COPD has been investigated in several publications.[86] The results showed that the incidence of hospital admission for AF was twice as high in COPD patients compared to those without AF. Also, they found that COPD patients with concomitant AF have a significantly higher prevalence of comorbidities as compared to patients who had COPD alone. Also, increasing age was associated with an overall higher incidence rate for all-cause hospital admission, which is not unexpected.

In our meta-analysis, 24 studies provided information on the rates of cardiovascular and non-cardiovascular admissions. The pooled incidence of cardiovascular and non-cardiovascular admissions was 26.3 (95% CI, 22.7-29.9) and 15.7 (95% CI, 12.5-18.9) per 100 person-years, respectively. In Swiss-AF the observed incidence of cardiovascular admission was 7.0 (95% CI, 6.3-7.7) per 100 person-years and it was 10.3 (95% CI, 9.3-11.4) per 100 person-years in BEAT-AF. The incidence of non-cardiovascular admission in Swiss-AF was 12.4 (11.5-13.4) per 100 person-years and 16.2 (14.9-17.7) per 100 person-years in BEAT-AF. Interestingly, we found that rates of non-cardiovascular admissions reported in our meta-analysis were very similar to the ones shown in our two cohorts. However, in our cohorts there were lower incidence rates for cardiovascular admission compared to the ones reported in the meta-analysis. This observation may be explained by two reasons. First, studies used different definitions of cardiovascular hospital admission. For example, events such as major or minor bleedings were inconstantly categorized as either cardiovascular or non-cardiovascular admission.[87] In AF populations, bleedings are events of relative frequent occurrence, such that a different categorization of the event may at least partly explain the differing incidence rates. Second, in contrast to randomized controlled trials, patients who are enrolled in cohort studies may have more medical comorbidities and exhibit a lower health status, which may result in higher admission rates.

Data from large databases in the United States indicate that in individuals aged between 45 to 64 years without AF the incidence of any hospital admission is about 10% per year.[88] When looking at the 65 to 84 year olds, the incidence is higher with 26% per year. Compared to these estimates, in the meta-analysis we showed that AF

patients have a 1.6 times higher risk than individuals without the arrhythmia, further underscoring the importance admissions in this groups of patients.

8.1.3. Risk factors for hospital admissions

Getting knowledge in clinical predictors for hospital admission in AF patients may help to identify those who are at highest risk. Increasing age is one of the major risk factors associated with hospital admission that is non-modifiable. Several published reports have shown that age strongly correlates with the individual admission risk in AF patients.[49,89] We found similar results, where increasing age was strongly associated with higher admission rates, in the meta-regression and also in our cohorts. However, age is a strong risk factor for many diseases and adverse outcomes,[90] which certainly contributes to the increased admission rates. In our meta-analysis we found that increasing average age was associated with a higher hospital admission incidence and explained some proportion of the observed heterogeneity in meta-regression analysis (R^2 across 34 studies 15.7%).[91] This suggests that age at least in part promotes admission risk in this population.

Among the cardiovascular factors we found that history of diabetes (HR, 1.38) and peripheral artery disease (HR, 1.31) were strongly associated with the risk of being admitted to the hospital for any cause. Other studies also found similar associations of those risk factors with hospital admissions.[49,50,89] It has been shown that diabetes and prediabetes are strong drivers of hospital admissions, and the risk is proportional to higher levels of glycated hemoglobin (HbA1c).[92,93] Also, diabetes is an independent risk factor of incident AF, further highlighting this interrelationship.[6] We found that presence of peripheral artery disease strongly correlates with the risk of hospital admission. A community-based case-control study showed that 85% of patients with peripheral artery disease were hospitalized at least once over e median follow-up of 5.6 years.[94] Also, peripheral artery disease has been known to be associated with the risk of AF.[95,96] Other than peripheral artery disease, additional important cardiovascular risk factors were coronary heart disease, prior stroke/TIA, and heart failure. These factors have been strongly linked to AF, and represent important components of the CHA_2DS_2-VASc score, which predicts the risk of stroke in AF patients.[97] Patients who have a history of coronary heart disease or myocardial infarction are especially prone to be admitted to the hospital, mostly for cardiovascular causes, due to heart failure and recurrent acute coronary syndrome. Heart failure admission are one of the most

important adverse events of patients with AF because they occur frequently and is strongly associated with worse prognosis.[98] All these factors taken together clearly illustrate the high cardiovascular burden that AF patients are exposed to, and each of these factors itself adds to the risk of hospital admissions in these patients. These risk factors may either be key factors for hospital admissions, or they may also just represent the overall frailty level of patients. However, each of these factors is a strong predictor for hospital admission in AF patients. Given this, optimal treatment of those factors may help to improve patient's outcomes and subsequently reduce admission rates.

From the non-cardiovascular domain, we found that renal failure, history of cancer and previous falls were independently associated with hospital admissions, and the effects were even stronger compared to cardiovascular predictors. In Swiss-AF we found that the risk of all-cause hospital admission in patients with renal failure was 1.2 times higher as compared to patients without renal failure. In ROCKET AF the investigators also found a similar association of renal dysfunction with increased hospital admission risk.[50] In this study impaired renal function, measured by creatinine clearance resulted in a hazard ratio of 1.07 (95% CI 1.04–1.10) per 5 unit decrease in creatinine clearance below 65 mL/min. Renal function, measured by estimated glomerular filtration rate (eGFR), has shown an independent and graded association with hospital admission risk, and this risk even increases when patients have concomitant AF.[99-101] Renal function is particularly important in AF populations given that most AF patients are taking an oral anticoagulant, and the risk of bleeding increases with lower renal function, particularly when patients are on a direct oral anticoagulant (DOAC). We further recognized that history of cancer was among the major non-cardiovascular predictors. However, this association is not surprising given that patients who have cancer are particularly at great risk of being admitted to the hospital, which has been illustrated in several studies.[102,103] It can he hypothesized that cancer may be the driver for these admission, but there is also evidence that cancer-related treatment such as chemotherapy could contribute to the high risk.[104] Prior reports have suggested the potential interrelationship between cancer and AF.[105,106] AF patients with concomitant cancer are more likely to be in reduced health status due to cancer but also because of coexisting AF. Given the relationship between AF and cancer, those patients are particularly at high risk to be admitted in the future. Lastly, we found that previous falls strongly predict the risk of future hospital admissions. This is important from two

aspects. First, given that a large proportions of AF patients is taking an oral anticoagulant, falls can potentially lead to traumatic intracranial bleedings, which is one reason why some physicians tend to remove those patients from oral anticoagulation. Second, previous falls are a frequent clinical presentation of frailty, which itself is an independent predictor for hospital admission.

Prior history of pulmonary vein isolation (PVI) was inversely associated with hospital admissions in the derivation cohort. The HR of patients with previous PVI was 0.7, suggesting that those patients who had PVI procedures in the past might have a 30% lower risk of future hospital admissions. Several studies have shown the potential effect of PVI on readmission and hospital admission rates.[107,108] In the Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial where AF patients were randomized to receive either PVI procedure or conventional antiarrhythmic medical therapy, the researchers found that PVI reduces the risk of the composite of death and cardiovascular hospital admission.[109] However, PVI was not associated with a reduction in all-cause mortality, suggesting that the reduction in hospital admissions was the strong contributor of this difference in the composite endpoint. The Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) trial also showed a favorable effect of PVI on hospital admission rates in AF patients with concomitant heart failure.[110] However, in this study there was no effect for all-cause hospital admission, which stands in contrast to our findings. In BEAT-AF, however, the association between catheter ablation and reduction in admission risk could not be confirmed. In both cohorts Swiss-AF and BEAT-AF, information on when the procedure was performed and whether it was a single procedure or redo ablation was not available. Therefore, it remains speculative whether PVI procedures significantly reduce admission rates, mainly because there are currently no studies available that sufficiently investigated this outcome.

8.1.4. Risk score for predicting hospital admissions

We developed the Admit-AF risk score to predict all-cause hospital admission in patients with AF. The risk score consists of the predictors that were identified from the variable selection method LASSO. These risk predictors were age, prior PVI, hypertension, diabetes, coronary heart disease, prior stroke/TIA, heart failure, peripheral artery disease, cancer, renal failure, and previous falls. In the derivation

cohort (Swiss-AF), the Admit-AF score showed moderate discriminative ability for 1-year and 3-year admission risk with C statistic of 0.64 and 0.63, respectively. In the validation cohort (BEAT-AF), it showed overall lower C statistics of 0.59 for 1- and 3-years risk prediction of hospital admission. The Admit-AF score was well calibrated in Swiss-AF and in BEAT-AF. Although we have been very inclusive and used a broad range of variables to build this risk score, the predictive ability was moderate and it was even lower in BEAT-AF. There several explanations for this observation. First, the outcome all-cause hospital admission is very heterogeneous, including a wide range of potential causes for admission. Therefore, to find specific variables that are associated with the outcome is complex. Prior studies have also attempted to develop risk prediction models for hospital admission, showing somewhat similar discriminative ability. For instance, the HOSPITAL score was derived in consecutive patients who were discharged from a hospital in the United States.[111] In this retrospective cohort, 17.7% had diagnosed AF based on administrative data. The primary outcome was 30-day readmission and the HOSPITAL score was developed using multivariable logistic regression analysis. The investigators found a high 30-day readmission rate of 22.3%. The derived HOSPITAL score consisted of administrative (i.e. length of stay, prior oncology service visit, or index type of admission) and laboratory variables (i.e. hemoglobin and sodium level at discharge). This score showed a better discriminatory performance compared to our Admit-AF score, with a C statistic of 0.71 and it was also well calibrated. The HOSPITAL score was then validated in 9 hospitals across 4 different countries, including one hospital from Switzerland.[112] Again, similar predictive ability was achieved, with a C statistic of 0.72. However, the C statistic from the hospital in Switzerland was lower with 0.68. Although the model was accurately developed in this study, the overall discriminatory power was modest with 0.72, and 0.68 for Switzerland. Our study showed nearly similar C statistic of 0.64 in AF patients. Taken together, these observations underscore the difficulty and challenge to assess this heterogenetic outcome of hospital admission. Further, the results indicate that although a broad range of variables was used to build the 30-day readmission risk HOSPITAL model including laboratory data, it somehow did not achieve enough power to predict short-term future admissions. In addition, the outcome in the study where the HOSPITAL score was developed, was defined as any readmission within 30 days after hospital discharge. Patients how were discharged may have a high risk of being readmitted within the next weeks. In contrast, our prediction tool was developed in an

outpatient setting, suggesting that the score may be more applicable in patients who are seen by their family doctor or general practitioner. Also, it can be speculated that the prediction of short-term outcomes may be simpler and easier as compared to long-term (≥1 year) outcomes, which may reflect the slightly better discriminative ability of the HOSPITAL score.

8.1.5. Psychosocial factors and hospital admissions

We found that patients who were single or divorced had an increased risk of all-cause hospital admission compared to patients who were married. Similar effects of marital status on the risk of hospital admission have been observed in non-AF populations, suggesting lower admission rates among patients who were married.[113,114] This confirms the hypothesis that being married may provide a low level of stress and great social support. Contrarily, being single or widowed increases emotional stress which could result in a higher risk of seeking medical support. Poor health perception is common in AF populations, and seems to be poorer in women.[115] We showed that subjective health evaluations on a VAS scale has an impact on hospital admission risk, which was also indicated for cardiovascular and non-cardiovascular admissions. Patients who felt in relatively good health conditions were less prone to seek for hospital care, indicated by lower admission rates compared to those with lower evaluations of health. In other populations such as heart failure patients, patients who reported poor or fair health perception had an up to five time higher risk of hospital admission or death compared to patients who reported excellent or good health perception.[116,117] Based on evidence showing that self-efficacy is a key predictor of heart failure hospital admission and all-cause death,[118] it can be speculated that social support and marriage partners may strengthen the patient's self-efficacy and health-evaluations, preventing them from hospital admissions. Almost two-third of all hospital admissions were for non-cardiovascular reasons. This appears counterintuitive given that AF patients are known to have a high burden of cardiovascular comorbidities.[25] AF patients may feel well positioned with regard to their cardiovascular treatment strategy and may therefore be more sensitive to non-cardiovascular symptoms and disorders. Also, given that most admissions were triggered by non-cardiovascular reasons may also point to the involvement of psychosocial factors in this population. We also found that when patients single or divorced and showed low heath perception, they exhibit a substantial higher risk of hospital admission. This risk gradually increased with a higher burden of psychosocial factors. Social support may have a

protective impact by keeping patients from the hospital, which suggests that considering psychosocial conditions in AF care strategies may be beneficial. Improving psychosocial conditions, such as thorough psychotherapy, psychosocial counselling, or self-help group assignment, may improve the individual psychosocial situation and may foster patient's resilience and self-efficacy in face of health-related conditions. In future studies it would be promising to include direct measures of social support and to systematically compare AF treatment with versus without consideration of psychosocial support factors. Improvements of psychosocial conditions in AF patients may have the potential to contribute to reduced health-care costs arising from hospital admissions.

8.2. Methodological aspects

In order to conduct a prospective multicenter study of a specific patient population is challenging and requires not only substantial financial sponsoring, but also a lot of technical support and personal efforts. A recent published report indicated that nearly 25% of all randomized trials in Switzerland had to discontinue prematurely, mainly because of recruitment problems and financial difficulties.[119] Investigators are constantly facing issues and difficulties within the long course of a study. It is not enough to have an interesting research question, but feasibility and technical aspects are just as important. Therefore, it is not unusual that adjustments of the study protocol need to be performed and processes need to be updated in order to continue the study. With regard to Swiss-AF we tried to use the most accurate methods currently available to address and investigate the research questions that have been raised. Swiss-AF is a prospective multicenter cohort study including AF patients that are well-characterized and using highly standardized measurements. Also, for each procedure there is extensive written standard operating procedure available (SOP), which incorporates all important steps in the conduct of a patient visit and examination. These factors were implemented with the aim to minimize potential systemic errors, and to enhance the quality of the data obtained. However, there remain several aspects that need to be discussed in the light of potential limitations. In the following sections, important features and potential limitations of the three works will be discussed with regard to methodological aspects.

8.2.1. Study design and assessment of study variables

Study design

Swiss-AF and BEAT-AF are observational cohort studies. Although both studies have a prospective design and patients were enrolled based on predefined inclusion criteria, causality of the observed associations cannot be proven. In cohort studies, residual confounding has always to be taken into account when interpreting presented results. However, there are several possibilities to address the issue of confounding. First, recruitment strategy of the population of interest should be established appropriately to avoid selection bias. This can be done by being inclusive, and avoid a high number of exclusion criteria. Also, as for being a community-based cohort study, recruitment of patients should focus on different sources, such as hospital, outpatient clinics etc. In both cohorts we tried to activate several channels to recruit patients with AF, with the intention of having a representative study population from Switzerland. Randomized controlled trials usually have strict inclusion and exclusion criteria of patients which questions the generalizability of the presented results. Second, although the recruitment strategy was chosen appropriately, there are still other potential sources of confounding. Patients in Swiss-AF and BEAT-AF were very well geno-and phenotyped, which allows us to perform statistical adjustments for the relationships being assessed. In the second work we first performed a variable selection and subsequently combined the 11 variables found to be associated with hospital admission into one multivariable Cox model. In the third work we used univariable and multivariable models to test associations of those psychosocial factors with hospital admission risk. Covariates used in the multivariable models were the ones that were found to be strongly associated with hospital admission from the second work. Although we performed several adjustments, residual confounding may still persist. Such confounders may be factors the investigators were not aware of or they may be factors which simply haven't been measured in the study. Through technical improvements in genetic engineering methods, additional opportunities for accounting residual confounding have opened up. Mendelian randomization has been proposed as a method to overcome some of the residual confounding.[120,121] This method uses measured variations in genes of known function to investigate the potential causal effect of an exposure on the development of a disease or outcome. Social or behavioral confounding factors are particularly difficult to measure accurately and difficult to control for in analyses. Mendelian randomization allows to test for a causal effect from

observational data in the presence of confounding factors by using common genetic polymorphism with known effects. Nonetheless, whether the use of genetic information will add to population-based research needs to be evaluated and confirmed in the future. Also, how these results can be transferred into clinical practice has to be investigated.

Assessment of clinical variables and hospital admissions

In the Swiss-AF study, several demographic and clinical characteristics were obtained from all patients included in the study. Information in demographic parameters was collected using standardized case report forms (CRF). Several large cohort studies have used a similar approach to perform broad data collection of enrolled patients. For instance, in the Framingham Heart Study, the investigators use a 44-page CRF to collect information about all important variables that can be directly obtained during a patient visit. The design and formatting of the CRF allows the examiner to choose and tick prespecified answers, which enhances overall data quality and reduces free text options. During yearly follow-up visits, patients enrolled in Swiss-AF were reassessed for medical information, comorbidities and blood sampling. This enables us to capture temporal fluctuations of important variables, which helps us to better understand associations between certain exposures and the outcome in the population.

In the second and third work the primary outcome was all-cause hospital admission. In Swiss-AF, we used a section in the CRF where patients were asked whether they had an unplanned hospital admission within the last year. However, this outcome was not centrally adjudicated or validated. As this is an outcome that usually occurs often in a population of the elderly individuals, a central adjudicated event assessment would have increased the quality of the admission events. Furthermore, although the CRF allows the investigator to distinguish whether the patient had experienced a cardiovascular or a non-cardiovascular admission, further information in the admission event was not systematically collected. Therefore, information on cause-specific admissions were not available. This additive information would certainly allow to better understand the underlying causes for admissions and may point to additional risk factors for hospital admissions. Also, information on the length-of-stay of in the hospital was not collected in both studies. Several reports have been published indicating that the individual length-of-stay (LOS) of a patient in the hospital strongly correlates with outcomes in the future. For instance, an analysis using administrative data from the Global Comparators Project from 26 hospitals on patients discharged from the hospital

between 2007 and 2012 including showed that patients who were in the upper quartile of LOS had a higher odds of death compared to those who were in the lowest quartile of LOS.[122] Reports from heart failure populations indicated similar results, whereas 30-day mortality risk was highest after long LOS.[123] Interestingly, this study demonstrated a U-shaped relationship between LOS and cardiovascular and non-cardiovascular readmissions, with higher rates in patients who had a short LOS or a long LOS. It is unclear how LOS affects admission rates in AF patients, and so far no study has addressed this question.

8.2.2. Statistical analysis

Meta-analysis

In the first study we performed a meta-analysis of studies that reported the incidence of hospital admissions. After extensive literature reviewing, we pooled the collected data using random effects meta-analysis. The advantage of this type of review is that it can be completed relatively quickly, it is low-cost and most of the data is relatively easy to access. However, several statistical aspects need to be discussed. From the studies that were deemed eligible for quantitative synthesis in our meta-analysis, we recognized that incidence rates were not always reported appropriately. To allow us to pool the data we had to calculate the incidence rates from the information available using Poisson distribution. We checked for the validity of our models by comparing the calculated incidences with the ones reported in studies with this information available. We found that the calculated incidence rates were similar to those reported in the studies. Prior meta-analyses have used a similar approach,[124] indicating that this approach is valid to use. Nevertheless, the calculated estimates reported in our meta-analysis may differ from the true incidence rates and this should be taking into account when interpreting the results.

Another important limitation of the meta-analysis is that the results of the study are based on aggregated published data and does not include individual patient-level data. This method is susceptible to publication bias, researchers usually have limited control over the data and the interpretation of the summary estimates has to be done in the context of between-study heterogeneity. This heterogeneity often arises as a result from different study designs, study populations, model selections and analyses, and categorization of variables in the original studies. In order to address this issue we

used random effects models which accounts for the anticipated high level of between-study heterogeneity.

Variable selection

In the second manuscript we used predictors associated with hospital admissions to establish a new risk prediction model. We used a variable selection method that accurately selected the appropriate variables, which then could be entered on the prediction model. The variable selection method called least absolute shrinkage and selection operator (LASSO) is a linear regression analysis that simultaneously performs variable selection and regularization by using machine learning algorithms.[69] All candidate variables available in Swiss-AF and BEAT-AF were included in one model, LASSO performed regression analyses, and shrinked the absolute size of the regression coefficients towards zero. This shrinkage is achieved by placing a penalty to the summation of the regression coefficients of the variables included. Therefore, variables with regression coefficients that shrink to zero are eliminated. The variables most strongly associated with the outcome remain in the final model. This method has been introduced many years ago, and it has been used in several publications where variable selection and model development was performed.[125,126] The advantage is that it operates completely independent and is not influenced by the investigator's preferences in choosing the optimal set of variables for the model. LASSO has total control over the selection process and does not add any subjective modifications. There is another advantage which LASSO has over conventional model development strategies, such as backward or forward variable selection. Because LASSO shrinks the regression coefficients of the variables towards zero, it not only keeps the most powerful predictors, but it also builds a highly robust and simple model. Also, conventional regression analysis usually produces models that tend to be overfitted. By adding a penalization to the regression coefficients, LASSO produces a robust model, which can be applied in other populations. Potential limitation of this method is that it only works with those variables that are entered into the program. Therefore, in order to find the most strongly associated predictors for the outcome of interest, it is important to include a broad range of different variables. Also, it is possible that LASSO produces a model including variables which may be difficult to obtain in clinical practice, which limits its practicability. This is why the model selection process should always incorporate variables which are simple to collect in order to maximize the usability of the prediction tool.

Risk scoring system

We build a point-based risk scoring system for unplanned hospital admissions by using the regression coefficients from the model. This method has been proposed because it adds weights coefficients of the predictors, which enhances the model performance substantially.[127] This technique has been used extensively, and several reports have shown that the risk score can be implemented appropriately.[128,129] The risk score achieved a C statistic of 0.64 in the derivation and a C statistic of 0.59 in the validation cohort. Although the model was well calibrated in the derivation and also in the validation cohort, it showed moderate discriminative ability to predict future hospital admissions. Although this technique adds weights to points based on regression coefficients, it may not be completely represent the overall weight of each predictor. In example, hypertension did not fully reach statistical significance in the multivariable model. When applying the point-based scoring system, this variable received the same amount of points as the variable coronary heart disease, which was statistical significant in the multivariable model. Thus, both variables were similarly weighted, although only history of coronary heart disease was significantly associated. Nevertheless, it is reasonable to include non-significant variables into the model, as non-significance may not necessary mean that there is no evidence for an effect of the predictor, which is indicated by the regression coefficient.[130] This issue should be a matter of debate and biological plausibility.

8.3. Relevance and future implications

8.3.1. Relevance of the study

We showed based on data from our meta-analysis that the incidence of hospital admission in AF patients is high. Results from out cohorts suggested that several cardiovascular and non-cardiovascular factors are associated with an increased risk of admission, also including psychosocial factors. These findings underscore the importance that detailed risk assessment and implementation of focused treatment strategies in AF patients should be a key priority for physicians and health care providers. Based on our data available we established a new risk score for accurately predicting long-term admission risk. We suggest that this score is a first step towards preventive approaches to reduce rates of unnecessary hospital admissions in AF populations. The score was successfully validated in another external AF cohort, but further analyses are needed to further assess the practicability of this score in

identifying high risk patients. Public health organizations and policy makers should give efforts to establish preventive programs to reduce unnecessary admissions in this vulnerable population. Together such strategies will not only have an impact on the patients outcome, but they may also help reducing health care expenditures.

8.3.2. Future implications and outlook

The three presented works show that hospital admissions is a problem in AF patients, and there are no strategies available to reduce these admission rates appropriately. Swiss-AF and BEAT-AF are both ongoing cohort studies. In the future we will be able to assess the long-term consequences of hospital admissions in AF, and investigate whether risk factors for admission change over time. In the second work we found that several cardiovascular and non-cardiovascular factors were associated with a higher admission risk. Given this information, new research questions and projects should focus on optimizing treatment in AF patients in a broader way. This could mean that a complementary treatment strategy, which includes risk factors assessment, individualized patient-specific therapy and psychosocial counselling and advisory. As mentioned, we also found that psychosocial factors predict hospital admissions. This finding highlights that apart from conventional risk factors, there are other mechanisms that may influence the overall risk of patients for being admitted to the hospital. Being single or divorced, or having low health perception are important factors for hospital admissions. Given these findings, additional factors may also contribute to this high admission risk in AF population. Future studies should address the question whether factors such as social support may provide insights in the overall wellbeing of a patient. In addition, studies are needed that investigate if cultural differences and household income discrepancies may add to the risk of admission. Also, it could be assessed whether there are significant differences in admission rates between patients depending on their living environment (rural versus urban).

In the future, we are planning to conduct a randomized trail within our cohort Swiss-AF to assess the effect of an integrated AF-care system on hospital admissions and other adverse outcomes in those patients.[131,132] The hypothesis is that a comprehensive integrated AF-care system within the heath care facility incorporating trained AF specialists and nurses who can intervene in those situations where AF patients might seek health care. This AF care system could consist of cardiovascular risk factor and lifestyle counseling, nurse-guided patient training, guideline-based optimization of

medical treatment and tele medical patient assistance via a 24/7 AF helpline in addition to routine standard care has the potential to develop favorable effects on outcome and ambulatory contacts and hospital admissions. AF patients could receive a booklet on the management of AF and related risk factors and additional group training session, which covers general behavioral, AF-specific and self-management trainings. Furthermore, patients may visit a trained nurse, who performs a detailed review of the cardiovascular risk factors, lifestyle habits (blood pressure, weight, smoking, physical activity) and the completion of questionnaires on drug adherence and anxiety, followed by a detailed discussion about the personal goals and possible strategies for a change in habits. This may help to optimize the patient's individual treatment strategy, and subsequently reduce adverse outcomes.[133] Also, 24/7 AF helpline could be offered to inform and help AF patients who are feel in health distress. All these potential interventions could result in substantial reduction of unplanned hospital admissions.

8.4. Conclusions

Patients with AF are highly vulnerable populations for adverse outcomes. We assessed the overall incidence of hospital admissions, identified risk factors associated with admissions patients with AF and developed a prediction tool to predict the risk of future hospital admissions. Based on the high incidence and the strong associations of several risk factors with hospital admissions, we suggest an interrelationship between the burden of risk factors and hospital admissions. Because there are many different factors associated with hospital admissions, including cardiovascular but also non-cardiovascular factors, this risk can only be tackled when taking into account the overall comorbidity burden of the individual patient. Therefore it is assumable that new preventive strategies that aim to reduce admission should incorporate a multi-factorial approach. The results presented in this research work can be taken to develop new research questions to further explore in depth the underlying causes for hospital admissions and to establish preventive strategies that may help to reduce these rising admission rates and improve outcomes in patients with diagnosed AF.

8.5. Specific contributions by the PhD student

After the successful application for the PhD program in clinical research, I have been introduced to the Swiss-AF and BEAT-AF cohort and the study team. The study team consisting of study coordinators and MD students provided me a detailed introduction in the conduct and processes of the two cohort studies. By then, I was fully engaged with daily routines of Swiss-AF by spending a lot of time in actively recruiting new patients for the study and performed many study visits, which mostly consisted of taking a medical history, performing physical examinations, neurocognitive tests and performing electrocardiogram recording. Also, I took over the planning follow up visits within the cohort and started to work on my research proposal. During this intensive writing period, I've gained valuable knowledge from the development of the research hypothesis to the structuring and writing of a full research proposal. During that important time, I regularly reviewed current scientific literature on AF in general and especially on hospital admissions in AF to further specify my research question and to prepare my systematic review. During the second and third PhD years I learned a lot about how to compute and perform statistical analyses using Stata. For the meta-analysis I performed the data collection, data management and performed the statistical analysis. For the second and third paper I performed the LASSO variable selection process and computed all the statistical models using the same statistical software.

During my PhD time, I actively participated in weekly Journal Clubs at the Cardiovascular Research Institute Basel (CRIB), where residents and research fellows of the Department of Cardiology presented the newest research data or their our own work. Also, I participated in the weekly study meetings. After gaining some knowledge in the conduct of meta-analysis, I got the opportunity to assist research fellow in the conduct of meta-analyses outside of my PhD project.

Furthermore, I got the opportunity to present my research work on several national (Joint Annual Meeting of the Swiss Society of Cardiology) and international (European Society of Cardiology) scientific conferences. Also, I got the opportunity to be part of the Swiss-AF sub-study called Swiss-AF Burden by contributing in the design and implementation of the study. Together with the team, I wrote a standard operating procedure for the scientific evaluation of the 7-day Holter electrocardiogram recordings. During the course of my PhD, I was more and more involved in the

supervision of doctoral students and Masters students. I provided methodological and statistical assistance to the doctoral students and supervised Masters students in their daily work in our research group.

Overall, I can say that I have learned many important aspects during my time as a PhD student. I was able to gain a lot of knowledge in health research methodology, data analysis and scientific writing by direct teaching from my supervisors as well as through close collaboration with other excellent researchers and epidemiologists outside from our research group and from international experts.

9. CURRICULUM VITAE

Personal information

Name:	Pascal Meyre
Date of birth:	March 31, 1987
Place of birth:	Cham, Zug, Switzerland
Citizenship:	Basel, Switzerland
Marital status:	Single
Languages:	German, English, French
Private address:	Schweizeraustrasse 15, 4132 Muttenz, Switzerland
Work address:	Cardiovascular Research Institute Basel Spitalstrasse 2, 4056 Basel, Switzerland
Email:	pascal.meyre@gmail.ch
Phone:	+41 76 527 25 32

Professional curriculum

2020 – 2022	Residency in Internal Medicine, Kantonsspital Olten, Switzerland
Nov 2016 – Dec 2019	MD PhD Program in Clinical Research
2010 – 2016	Medical school, University of Basel, Switzerland
2008 – 2009	Law school, University of Basel, Switzerland

Work experience

Dec 2015	Internship in Acute Geriatric Care, Felix Platter Hospital, Basel, Switzerland
Nov 2015	Internship in Internal Medicine, Hospital in Rheinfelden, Aargau, Switzerland
Jul – Oct 2015	Internship in General Surgery and Internal Medicine, St. Claraspital, Basel, Switzerland
Jun 2015	Internship in Pediatric Surgery, University Children Hospital Basel, Switzerland
Apr – May 2015	Internship in Internal Medicine, University Hospital Basel, Switzerland

Examinations and certifications

2019	Doctoral Thesis (Dissertation) on „Risk of Hospital Admission in Patients with Atrial Fibrillation: A Systematic Review and Meta-analysis". Department of Cardiology, University Hospital Basel (Prof. Dr. S. Osswald)
2019	Unites States Medical Licensing Examination (USMLE) Step 2

2018	Unites States Medical Licensing Examination (USMLE) Step 1
2017	Principles and Practice in Clinical Research, Harvard T.H. Chan School of Public Health, Boston, USA
2017	Basic Good Clinical Practice (GCP) and clinical research training course (CTU Basel)
2017	Basic Course in Emergency Ultrasound (SGUM), University Hospital of Basel, Switzerland
2016	Swiss Federal Medical Examination (Staatsexamen)
2016	Basic Course in Abdominal Ultrasound (SGUM), University Hospital of Basel, Switzerland

Teaching activities

Present	Electrocardiogram course for medical students, Cardiovascular Research Institute Basel (CRIB), Basel, Switzerland
2016	Tutor in Clinical Examination (Dr. S. Trüstedt), University of Basel, Switzerland
2016	Tutor at Institute of Physiology (Prof. Dr. D. Kunz), University of Basel, Switzerland
2012 – 2014	Tutor at Institute of Anatomy (Prof. Dr. M. Müller-Gerbl), University of Basel, Switzerland

Scientific output

Peer-reviewed publications

1. Froehlich L, **Meyre P**, Aeschbacher S, Blum S, Djokic D, Kühne M, Osswald S, Kaufmann BA, Conen D. Left atrial dimension and cardiovascular outcomes in patients with and without atrial fibrillation: a systematic review and meta-analysis. *Heart*. **2019** Aug 17. pii: heartjnl-2019-315174. doi: 10.1136/heartjnl-2019-315174. [Epub ahead of print]
2. **Meyre P**, Blum S, Berger S, Aeschbacher S, Schoepfer H, Briel M, Osswald S, Conen D. Risk of Hospital Admissions in Patients with Atrial Fibrillation: A Systematic Review and Meta-analysis. *Can J Cardiol.* **2019** May 24. pii: S0828-282X(19)30361-7. doi: 10.1016/j.cjca.2019.05.024. [Epub ahead of print] Review.
3. Bum S, **Meyre P**, Aeschbacher S, Berger S, Auberson C, Briel M, Osswald S, Conen D. Incidence and predictors of atrial fibrillation progression: A systematic review and meta-analysis. *Heart Rhythm.* **2019**;16(4):502-510.
4. Conen D, Rodondi N, Müller A, Beer JH, Ammann P, Moschovitis G, Auricchio A, Hayoz D, Kobza R, Shah D, Novak J, Schläpfer J, Di Valentino M, Aeschbacher S, Blum S, **Meyre P**, Sticherling C, Bonati LH, Ehret G, Moutzouri E, Fischer U, Monsch AU, Stippich C, Wuerfel J, Sinnecker T, Coslovsky M, Schwenklglenks M, Kühne M, Osswald S. Relationships of Overt and Silent

Brain Lesions With Cognitive Function in Patients With Atrial Fibrillation. *J Am Coll Cardiol.* **2019**;73(9):989-999.

5. Berger S, **Meyre P**, Blum S, Aeschbacher S, Ruegg M, Briel M, Conen D. Bariatric surgery among patients with heart failure: a systematic review and meta-analysis. *Open Heart.* **2018**;5(2):e000910
6. Egli P, Aeschbacher S, Bossard M, Eggimann L, Blum S, **Meyre P**, Bargetzi L, Estis J, Todd J, Risch M, Risch L, Conen D. Relationships of kidney injury molecule-1 with renal function and cardiovascular risk factors in the general population. *Clin Chim Acta*. **2017** Dec 14;478:13-17.
7. van der Stouwe JG, Aeschbacher S, Krisai P, Schoen T, **Meyre P**, Todd J, Risch M, Risch L, Conen D. Plasma levels of glucagon-like peptide 1 and markers of obesity among young and healthy adults. *Clinical endocrinology*. **2015**;83(5):636-42.

Peer-reviewed conference contributions

1. **Meyre P**, Fröhlich L, Aeschbacher S, Blum S, Djokic D, Kühne M, Osswald S, Kaufmann B, Conen D. Left atrial dimension and risk of cardiovascular outcomes in patients with and without atrial fibrillation: a systematic review and meta-analysis. Accepted for presentation at the European Society of Cardiology meeting, August 30-September 03 **2019**. Paris, France.
2. **Meyre P**, Gugganig R, Aeschbacher1 S, Leong DP, Blum S, Coslovsky M, Beer JH, Moschovitis G, Müller D, Rodondi N, Stempfel S, Müller C, Kühne M, Conen D, Osswald S, for the Swiss-AF Investigators. Frailty to predict unplanned hospitalizations, stroke, bleeding and death in atrial fibrillation. Accepted for presentation at the European Society of Cardiology meeting, August 30-September 03 **2019**. Paris, France.
3. Aeschbacher s, Blum S, Meyer-Zürn C, Vischer AS, **Meyre P**, Rodondi N, Beer JH, Moschovitis G, Moutzouri E, Sticherling C, Wuerfel J, Bonati LH, Osswald S, Conen D, Kuehne M. Blood pressure and white matter lesions in patients with atrial fibrillation. Accepted for presentation at the European Society of Cardiology meeting, August 30-September 03 **2019**. Paris, France.
4. Aeschbacher S, Mongiat M, Bernasconi R, Blum S, **Meyre P,** Krisai P, Ceylan S, Risch M, Risch L, Conen D. Relationship between aldosterone-to-renin ratio and blood pressure in young adults from the general population. Accepted for presentation at the European Society of Cardiology meeting, August 25-29 **2018**. Munich, Germany.
5. **Meyre P**, Blum S, Berger S, Aeschbacher S, Schöpfer H, Briel M, Osswald S, Conen D. Incidence and risk factors for hospitalization in patients with atrial fibrillation: A systematic review and meta-analysis. Accepted for presentation at the European Society of Cardiology meeting, August 25-29 **2018**. Munich, Germany.
6. Brenner R, Aeschbacher S, Blum S, **Meyre P**, Ammann P, Erne P, Moschovitis G, Di Valentino M, Shah D, Schlaepfer J, Kühne M, Sticherling C, Osswald S, Conen D. Physical activity and outcome in patients with atrial fibrillation. Accepted for presentation at the European Society of Cardiology meeting, August 25-29 **2018**. Munich, Germany.

7. Blum S, Aeschbacher S, **Meyre P**, Ammann P, Erne P, Moschovitis G, Di Valentino M, Shah D, Schläpfer J, Schnabel RB, Kühne M, Sticherling C, Osswald S, Conen D. Long-term incidence and predictors for progression of atrial fibrillation. Accepted for presentation at the American Heart Association meeting, November 11-15 **2017**. Anaheim, California, USA.
8. Blum S, Aeschbacher S, **Meyre P**, Ammann P, Erne P, Moschovitis G, di Valentino M, Shah S, Schläpfer J, Kühne M, Sticherling C, Osswald S, Conen D. Risk for adverse outcome events according to paroxysmal vs. non-paroxysmal atrial fibrillation. Accepted for presentation at the European Society of Cardiology meeting, August 26-30 **2017**. Barcelona, Spain.
9. **Meyre P**, Eggimann L, Beer JH, Bonati LH, Di Valentino M, Kühne M, Monsch A, Moschovitis G, Aubert C, Shah D, Sticherling C, Stippich C, Wuerfel J, Mueller A, Osswald S. Cognitive function correlates with CHA2DS2-VASc score in patients with atrial fibrillation: The Swiss atrial fibrillation cohort study. Accepted for presentation at the European Society of Cardiology meeting, August 26-30 **2017**. Barcelona, Spain.
10. Blum S, Aeschbacher S, **Meyre P**, Ammann P, Erne P, Moschovitis G, di Valentino M, Shah D, Schläpfer J, Kühne M, Sticherling C, Osswald S, Conen D. Risk for adverse outcome events according to paroxysmal vs. non-paroxysmal atrial fibrillation. Accepted for presentation at the Swiss Society of Cardiology meeting 2017, June 7-9 **2017**. Baden, Switzerland.

Peer-reviewed conference contributions (oral presentation)

1. **Meyre P**, Fröhlich L, Aeschbacher S, Blum S, Djokic D, Kühne M, Osswald S, Kaufmann B, Conen D. Left atrial dimension and risk of cardiovascular outcomes in patients with and without atrial fibrillation: a systematic review and meta-analysis. Accepted for presentation at the Swiss Society of Cardiology meeting 2017, June 19-21 **2019**. Interlaken, Switzerland.
2. **Meyre P**, Gugganig R, Aeschbacher1 S, Leong DP, Blum S, Coslovsky M, Beer JH, Moschovitis G, Müller D, Rodondi N, Stempfel S, Müller C, Kühne M, Conen D, Osswald S, for the Swiss-AF Investigators. Frailty to predict unplanned hospitalizations, stroke, bleeding and death in atrial fibrillation. Accepted for presentation at the Swiss Society of Cardiology meeting 2017, June 19-21 **2019**. Interlaken, Switzerland.
3. Blum S, Kühne M, Rodondi N, Mueller A, Ammann P, Moschovitis G, Kobza R, Schlaepfer J, **Meyre P**, Bonati LH, Ehret G, Sticherling C, Schwenkglenks M, Osswald S, Conen D. Prevalence of silent vascular brain lesions among patients with atrial fibrillation and no known history of stroke. Accepted for presentation at the European Society of Cardiology meeting, August 25-29 **2018**. Munich, Germany.
4. **Meyre P**, Eggimann L, Kühne M, Osswald S, Conen D. Cognitive function in patients with atrial fibrillation. The Swiss atrial fibrillation cohort study (Swiss-AF). Accepted for presentation at the Swiss Society of Cardiology meeting 2017, June 7-9 **2017**. Baden, Switzerland.

Further publications (not peer-reviewed) and case reports

1. **Meyre P**, Eggimann L, Beer JH, Bonati LH, Di Valentino M, Kühne M, Monsch A, Moschovitis G, Aubert C, Shah D, Sticherling C, Stippich C, Wuerfel J, Mueller A, Osswald S. Vorhofflimmern: Mikroblutungen im Gehirn erhöhen Demenz-Risiko. Pressetext DGK 08/**2017**.

Peer review activities for scientific journals

- Journal of the American College of Cardiology
- European Heart Journal
- European Journal of Preventive Cardiology
- BMJ Open

Memberships

European Society of Cardiology

Languages

German mother tongue, English fluent, French basic

Data processing

Microsoft Word, Microsoft Excel, Microsoft PowerPoint, Microsoft Access, Stata, R studio, RevMan

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1. Einthoven W. Le telecardiogramme. *Arch Int de Physiol.* 1906:132–164.
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4. Krijthe BP, Kunst A, Benjamin EJ, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J.* 2013;34(35):2746-2751.
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6. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA.* 1994;271(11):840-844.
7. Staerk L, Wang B, Preis SR, et al. Lifetime risk of atrial fibrillation according to optimal, borderline, or elevated levels of risk factors: cohort study based on longitudinal data from the Framingham Heart Study. *BMJ.* 2018;361:k1453.
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Intervention For End Point Reduction in Hypertension (LIFE) study. *J Am Coll Cardiol.* 2005;45(5):705-711.

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