Risk factors for heart failure hospitalizations among patients with atrial fibrillation

Lucien Eggimann[1,2], Steffen Blum[1,2,3], Stefanie Aeschbacher[1,2], Andreas Reusser[1,2], Peter Ammann[4], Paul Erne[5], Giorgio Moschovitis[6], Marcello Di Valentino[7], Dipen Shah[8], Jürg Schläpfer[9], Nadine Mondet[2], Michael Kühne[1,2], Christian Sticherling[1,2], Stefan Osswald[1,2], David Conen[1,2,10]*

1 Division of Cardiology, Department of Medicine, University Hospital Basel, University of Basel, Basel, Switzerland, **2** Cardiovascular Research Institute Basel, University Hospital Basel, University of Basel, Basel, Switzerland, **3** Division of Internal Medicine, Department of Medicine, University Hospital Basel, University of Basel, Basel, Switzerland, **4** Division of Cardiology, Kantonsspital St. Gallen, St. Gallen, Switzerland, **5** Laboratory for Signal Transduction, Department of Biomedicine, University Hospital Basel, Basel, Switzerland, **6** Division of Cardiology, Ospedale Regionale di Lugano, Ticino, Switzerland, **7** Division of Cardiology, Ospedale San Giovanni Bellinzona, Ticino, Switzerland, **8** Division of Cardiology, University Hospital Geneva, Geneva, Switzerland, **9** Service of Cardiology, University Hospital Lausanne, Lausanne, Switzerland, **10** Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada

* conend@mcmaster.ca

Abstract

Background

Patients with atrial fibrillation (AF) have an increased risk for the development of heart failure (HF). In this study, we aimed to detect predictors of HF hospitalizations in an unselected AF population.

Methods

The Basel Atrial Fibrillation Cohort Study is an ongoing observational multicenter cohort study in Switzerland. For this analysis, 1193 patients with documented AF underwent clinical examination, venous blood sampling and resting 12-lead ECG at baseline. Questionnaires about lifestyle and medical history were obtained in person at baseline and during yearly follow-up phone calls. HF hospitalizations were validated by two independent physicians. Cox regression analyses were performed using a forward selection strategy.

Results

Overall, 29.8% of all patients were female and mean age was 69 ±12 years. Mean follow-up time was 3.7 ±1.5 years. Hospitalization for HF occurred in 110 patients, corresponding to an incidence of 2.5 events per 100 person years of follow-up. Independent predictors for HF were body mass index (HR 1.40 [95%CI 1.17; 1.66], p = 0.0002), chronic kidney disease (2.27 [1.49; 3.45], p = 0.0001), diabetes mellitus (2.13 [1.41; 3.24], p = 0.0004), QTc interval (1.25 [1.04; 1.49], p = 0.02), brain natriuretic peptide (2.19 [1.73; 2.77], p<0.0001), diastolic blood pressure (0.79 [0.65; 0.96], p = 0.02), history of pulmonary vein isolation or electrical cardioversion (0.54 [0.36; 0.80], p = 0.003) and serum chloride (0.82 [0.70; 0.96], p = 0.02).

Data Availability Statement: The consent forms, as approved by the local ethics committee (Ethikkommission Nordwest- und Zentralschweiz), do not allow the data to be made publicly available. The participants signed a consent form, which states that data is exclusively available for professional research staff. Therefore, scientific proposals must be approved by the principal investigator (Dr. D. Conen) to assure the restrictions from the consent form and the local ethics committee. In case of any inquiries

Conclusions

In this unselected AF population, several traditional cardiovascular risk factors and arrhythmia interventions predicted HF hospitalizations, providing potential opportunities for the implementation of strategies to reduce HF among AF patients.

Introduction

Atrial Fibrillation (AF) is the most common cardiac arrhythmia [1] and its incidence is expected to further increase with the ageing of the population [2]. Lifetime risk for AF development is 1 in 4 among individuals aged 40 years or older [3], Patients with AF face an increased risk of developing stroke, heart failure (HF), cognitive dysfunction and death [4–7].

Prior studies have highlighted that HF is an important comorbidity associated with AF, and both entities frequently coexist [6]. AF occurs in more than half of individuals with HF and HF occurs in more than one third of individuals with AF [8]. While many studies have targeted the prevention of stroke in AF patients [9], little attention has been placed on the prevention of HF, despite its high prevalence and its important impact on affected patients [6, 10–12]. There is also an important economical impact, as HF predicts future hospitalizations in AF patients [13].

Therefore, it is important to recognize risk factors for incident HF events among AF patients, potentially providing opportunities for preventive measures. However, comprehensive assessments on risk stratification for HF in patients with AF are scarce. To our knowledge there has no study been assessing the role of biomarkers such as brain natriuretic peptide (BNP) to predict HF in AF patients [11, 14–19]. Furthermore, prior studies enrolled either patients without history of HF or did not differentiate between known HF and no history of HF [11, 14–19].

Therefore, this study aimed to assess different predictors for HF hospitalizations including medical history-, lifestyle-, ECG- and biomarker data in an unselected cohort of patients with established AF.

Methods

Study sample

The Basel Atrial Fibrillation Cohort Study (BEAT- AF) is an ongoing prospective, observational multicenter cohort study performed in 7 centers in Switzerland. Overall, 1553 patients with documented AF were included between 2010 and 2014. The main inclusion criterion for study participation was previously documented AF. Patients with exclusively short, temporary AF episodes (e.g. AF following cardiac surgery) were excluded. Patients suffering from an acute disease were enrolled after they had recovered from their acute illness. Of 1553 patients enrolled in this study, 324 patients were excluded from this analysis because of missing laboratory values and 36 patients due to missing ECG-, medical history- or lifestyle data, resulting in a total number of 1193 patients. A total of 86 (7.2%) patients were lost to follow-up. The study protocol was approved by the local ethics committees (Ethikkommission Nordwest- und Zentralschweiz) and informed written consent was obtained from every participating patient.

Baseline assessments

All study patients were asked to complete a questionnaire about lifestyle, personal factors and comorbidities. Smoking status was categorized in current smokers and non-current smokers (past or never smokers). Exercise was graded in either doing any regular exercise or no regular exercise. Daily alcohol intake was classified as no alcohol consumption, moderate alcohol consumption (men $> 0 < 24$ g/d, women $> 0 < 12$ g/d) and high alcohol consumption (men > 24 g/d, women >12 g/d) [20]. Current medication, medical history, comorbidities and history of arrhythmia interventions (defined as previous pulmonary vein isolation or electrical cardioversion) were recorded.

At baseline, all patients underwent clinical examination, resting 12- lead ECG recording and venous blood sampling at the local study center. Standard blood and chemistry results were obtained at the local study center. Height and weight were directly measured using standardized devices. Body mass index (BMI) was calculated as weight in kg divided by height in meters squared. Blood pressure was measured twice in a resting position. Resting heart rate was obtained from the resting ECG. A 12-lead ECG was obtained with a standard ECG device in every center. QT interval was adjusted for mean heart rate (QTc) using the Bazett formula [21]. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [22]. Antiarrhythmic drug (AAD) intake was defined as treatment with rhythm control medication. AF was classified according to the guidelines of the European Society of Cardiology into paroxysmal AF (self-terminating, usually within 48 hours), persistent AF (episodes lasting longer than 7 days or requiring termination by cardioversion) or permanent AF (AF is accepted by the patient and the physician and no attempts to restore sinus rhythm are performed) [1].

Follow- up assessments

A yearly follow- up by mail and phone call was performed to update current AF type, smoking status, exercise habits and detailed medical history. The main outcome measure for this analysis was hospitalization for HF. Hospitalization for HF was defined as at least overnight admission to the hospital with clinical symptoms (e.g. leg swelling/leg edema, distension of neck veins, positive hepato-jugular reflux, rales or 3rd heart sound) and signs of HF resulting from an abnormality of cardiac structure or function. For this study we used all outcome data available until 7th of April 2017. All HF events were validated by two independent physicians in a standardized procedure, using all available information. In case of discordance, a third physician was involved.

Statistical analysis

Baseline characteristics for all patients were stratified by presence of known HF at baseline. Categorical variables were presented as counts (percentages) and compared using Chi-square tests. Distribution of continuous variables was checked using skewness, kurtosis and visual inspection of the histogram. Normally distributed continuous variables were presented as mean ± standard deviation (SD) and compared using Student's t-tests. Skewed variables were presented as median (interquartile range) and compared using Wilcoxon rank sum tests. Person-years of follow-up were calculated as the time between the date of study enrollment and the first occurrence of hospitalization for HF, death, loss to follow-up or 7th of April 2017.

To identify predictors for HF hospitalizations, we constructed Cox regression models to assess hazard ratios (HR) and 95% confidence intervals (95%CI) and to adjust for potential confounders. In a first step, continuous variables were used as quartiles in order to check for linearity of the association. If the shape of the association was linear, these variables were used

in the continuous form. For continuous variables, HR were calculated per one SD increase. We then used a forward selection process to obtain a set of independent predictors. A p-value of 0.05 was used as cut-off to enter the model. Variables used for the forward selection were: Sex, age, BMI, resting heart frequency, systolic blood pressure, diastolic blood pressure, QRS interval, QTc interval, alcohol consumption (moderate and high alcohol consumption), known history of HF at baseline as well as the laboratory parameters albumin, brain natriuretic peptide (BNP), C-reactive protein, chloride, potassium, serum lactate dehydrogenase, sodium and eGFR. History of stroke, AF type (paroxysmal/ non paroxysmal), diabetes mellitus, device implantation, atrial flutter, chronic kidney disease, obstructive sleep apnea, cardiac valve surgery, coronary artery disease (CAD), hypertension, exercise, smoking habits, beta blocker intake, AAD intake, and history of arrhythmia intervention were included as time updated variables in the Cox regression model.

Given the strong impact of a previous history of HF on future HF hospitalizations [23, 24], we performed a sensitivity analysis among those patients without a history of HF (n = 951). The proportional hazard assumption was checked by including a logarithm of time x predictor variable into the models, and no violations were detected [25]. As a sensitivity analysis we recalculated the main models using competing risk subdistribution hazard models as described by Fine and Gray [26]. A two-sided p value <0.05 was considered to indicate statistical significance. All statistical analyses were performed using SAS 9.4 (SAS Corporation, Cary, North Carolina, USA).

Results

We included 1193 patients in this study, 951 (79.7%) of them without a previous history of HF at baseline. Baseline characteristics stratified by history of HF at baseline are presented in Table 1. Mean age of all patients was 69 ±12 years. Overall, 29.8% were females and mean BMI was 27 ±4.6 kg/m^2, both without significant difference in patients with and without HF at baseline. Paroxysmal AF was present in 32.6% and 60.4% of the patients with and without HF (p<0.0001). Individuals with HF at baseline had more often diabetes mellitus (p = 0.0008). Median BNP levels were 243 (128; 458) ng/L and 109 (52; 209) ng/L for patients with and without a baseline history of HF (p<0.0001).

Over a mean follow-up of 3.7±1.5 years, 110 patients were hospitalized for HF. The incidence for HF hospitalizations was 2.5 events per 100 person years of follow-up. Multivariable adjusted predictors for incident HF are presented in Table 2, and include BMI (HR 1.40 [95% CI 1.17; 1.66], p = 0.0002), chronic kidney disease (2.27 [1.49; 3.45], p = 0.0001), diabetes mellitus (2.13 [1.41; 3.24], p = 0.0004), QTc interval (1.25 [1.04; 1.49], p = 0.018), BNP (2.19 [1.73; 2.77], p<0.0001), diastolic blood pressure (0.79 [0.65; 0.96], p = 0.016), history of arrhythmia intervention (0.54 [0.36; 0.80], p = 0.003) and serum chloride (0.82 [0.70; 0.96], p = 0.015).

Among patients without known HF at baseline, mean follow-up was 3.9 (±1.4) years. Hospitalization for HF occurred in 60 patients. The incidence rate was 1.6 per 100 person years of follow-up. Multivariable adjusted predictors associated with HF hospitalizations were age (HR 1.51 [95%CI 1.002; 2.29], p = 0.049), BMI (1.46 [1.14; 1.87], p = 0.003), diabetes mellitus (2.72 [1.57; 4.71], p = 0.0004), history of valve surgery (3.10 [1.58; 6.10], p = 0.001), QTc interval on the ECG (1.44 [1.14; 1.83], p = 0.002), BNP (1.92 [1.30; 2.83], p = 0.001) and history of arrhythmia intervention (0.41 [0.23; 0.76], p = 0.004), as shown in Table 2.

Results of the sensitivity analyses are presented in S1 Table. By taking death as a competing risk into account, diastolic blood pressure and QTc interval were no longer significant predictors of HF hospitalizations in the whole population. The HR for all other predictors remained similar compared to the main model.

Table 1. Baseline characteristics.

	All patients (n = 1193)	Patients without known HF at baseline (n = 951)	Patients with known HF at baseline (n = 242)	p-value*
Age (years)	68.9 (±11.7)	68.1 (±11.8)	72 (±10.5)	<0.0001
Female sex	356 (29.8%)	290 (30.5%)	66 (27.3%)	0.33
BMI (kg/m²)	27 (±4.6)	26.9 (±4.4)	27.4 (±5.1)	0.15
SBP (mmHg)	134.9 (±18.8)	136.7 (±18.4)	127.8 (±19)	<0.0001
DBP (mmHg)	78.4 (±12.3)	79.3 (± 11.9)	74.7 (±13.2)	<0.0001
Heart frequency (bpm)	67 (58; 80)	66 (57; 79)	70 (60; 83)	0.003
Paroxysmal AF	653 (54.7%)	574 (60.4%)	79 (32.6%)	<0.0001
Diabetes mellitus	171 (14.3%)	120 (12.6%)	51 (21.1%)	0.0008
Hypertension	825 (69.2%)	630 (66.3%)	195 (80.6%)	<0.0001
History of stroke	155 (13%)	121 (12.7%)	34 (14.1%)	0.58
Obstructive sleep apnea	135 (11.3%)	96 (10.1%)	39 (16.1%)	0.008
CAD	247 (20.7%)	162 (17%)	85 (35.1%)	<0.0001
History of valve surgery	91 (7.6%)	51 (5.4%)	40 (16.5%)	<0.0001
Chronic kidney disease	193 (16.2%)	96 (10.1%)	97 (40.1%)	<0.0001
History of arrhythmia intervention	544 (45.6%)	423 (44.5%)	121 (50%)	0.12
Current smoker	107 (9%)	82 (8.6%)	25 (10.3%)	0.41
Regular exercise	636 (53.3%)	539 (56.7%)	97 (40.1%)	<0.0001
Beta blocker intake	832 (69.7%)	636 (66.9%)	196 (81%)	<0.0001
AAD intake	340 (28.5%)	266 (28%)	74 (30.6%)	0.42
QTc interval (ms)	438.1 (±43.6)	433.4 (± 42.5)	456.4 (±43.1)	<0.0001
BNP (ng/L)	128 (58; 252)	109 (52; 209)	243 (128; 458)	<0.0001
Chloride (mmol/l)	102.5 (±3.15)	102.8 (±3)	101.5 (±3.6)	<0.0001

Data are presented as number (percentages) or mean (± standard deviation) or median (interquartile range), as appropriate. BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; CAD = coronary heart disease; AAD = antiarrhythmic drug; BNP = brain natriuretic peptide; History of arrhythmia intervention = previous pulmonary vein ablation or/and electrical cardioversion. Heart frequency and BNP were log-transformed.

* P-values compare patients with and patients without known HF at baseline and are based on chi-square tests or t-tests/Wilcoxon rank sum tests, as appropriate.

https://doi.org/10.1371/journal.pone.0191736.t001

Discussion

In this prospective cohort study of patients with AF, several independent risk factors for HF hospitalizations were identified. Higher BMI, elevated BNP, diabetes mellitus, chronic kidney disease and longer QTc interval were associated with an increased risk of HF, whereas patients with higher diastolic blood pressure, higher serum chloride and history of arrhythmia-related interventions were significantly less likely to develop HF. Finally, most risk factors identified in this study were similar whether patients had known HF at baseline or not. Thus, although the absolute risk for HF development is higher among patients with known HF [16, 18], preventive strategies are probably the same.

Several of these predictors are established cardiovascular risk factors and amenable to prevention, providing a great potential opportunity to reduce the HF burden among patients with AF. Both obesity and type 2 diabetes mellitus have been firmly related to the occurrence of cardiovascular events [27–29], and both were related to AF and HF incidence [29–32]. Moreover, prior studies have shown that they were associated with incident HF in patients with AF [11, 15, 17], a finding that is confirmed by our results. On the other hand, some studies suggested that a higher BMI is associated with a lower all-cause mortality among AF patients [33, 34]. Additionally, in a cohort of patients suffering from AF and HF together, overweight and

Table 2. Predictors of hospitalization for heart failure (HF) in patients with and without known HF at baseline.

	HR (95% CI)	p-value
Predictor in patients with and without known HF at baseline	**n = 1193**	
BMI (kg/m^2)	1.40 (1.17; 1.66)	0.0002
Diastolic blood pressure (mmHg)	0.79 (0.65; 0.96)	0.016
Chronic kidney disease	2.27 (1.49; 3.45)	0.0001
Diabetes mellitus	2.13 (1.41; 3.24)	0.0004
History of arrhythmia intervention	0.54 (0.36; 0.80)	0.003
QTc interval (ms)	1.25 (1.04; 1.49)	0.018
BNP (ng/L)	2.19 (1.73; 2.77)	< 0.0001
Chloride (mmol/l)	0.82 (0.70; 0.96)	0.015
Predictor in patients without known HF at baseline	**n = 951**	
Age (years)	1.51 (1.002; 2.29)	0.049
BMI (kg/m^2)	1.46 (1.14; 1.87)	0.003
Diabetes mellitus	2.72 (1.57; 4.71)	0.0004
History of valve surgery	3.10 (1.58; 6.10)	0.001
History of arrhythmia intervention	0.41 (0.23; 0.76)	0.004
QTc interval (ms)	1.44 (1.14; 1.83)	0.002
BNP (ng/L)	1.92 (1.30; 2.83)	0.001

Data are Hazard Ratios (HR) and 95% confidence intervals (95%CI). HR for continuous variables are per one standard deviation increase. BMI = body mass index; BNP = brain natriuretic peptide; history of arrhythmia intervention = previous pulmonary vein ablation or/and electrical cardioversion. BNP was log-transformed.

obesity were also associated with a lower risk of all-cause mortality [35]. Whether these differential findings suggests different associations between BMI and outcomes or whether they are at least in part due to residual confounding should be assessed in future studies.

A prolonged QTc interval has been associated with a higher rate of cardiovascular events including HF and death in a population based cohort [36]. However, in patients with AF there is only little information available about this association. The results of our study presenting prolonged QTc interval as an independent predictor for HF should be further investigated. QTc interval can be easily assessed in clinical daily routine and therefore, it may be a simple tool for risk stratification.

BNP levels are of major importance for the management of patients with acute or chronic HF [37, 38]. To our knowledge, there is no prospective study assessing the relationship between BNP levels and incident HF in patients with AF. The findings of our study indicate that BNP is a strong predictor of HF also in patients with AF, who usually have a higher burden of comorbidities and higher BNP levels compared to the general population [39, 40]. As BNP levels were also predictive of incident HF among patients without a history of HF, BNP may help to identify AF patients at increased risk of HF in the future. Previous history of known HF, which was associated with increased risk of recurring HF generally [23, 24] and in AF patients [16, 18], was not a predictor for future HF hospitalizations in our study, which might be a result of the correlation between BNP and previous history of HF.

Several studies showed the prognostic implications of renal function in patients with heart failure [41] and the relationship between renal function and cardiovascular morbidity and mortality [42]. Additionally, renal dysfunction was also reported to promote HF in patients with AF [14, 17], which is in line with our results. Low serum chloride was a predictor for HF in our study, similar to a previously published population based cohort [43] and among

patients with hypertension [44]. Moreover, there are some prognostic data available in patients with acute decompensated [45] and chronic heart failure [46].

Higher DBP was associated with a better outcome in the current study. Previous studies showed that low DBP was an independent predictor of re-hospitalization for HF in a cohort of patients with acute decompensated HF [47]. Another study also related low DBP to higher mortality in patients with systolic HF [48]. Low DBP might impair coronary blood flow during diastole, which might result in a decreased coronary perfusion that affects the myocardium and promotes the development of HF. Additionally, with increasing aortic stiffness, diastolic BP is decreasing and the prognosis for adverse outcomes is increasing. Finally, arrhythmia-related interventions but not AAD intake was associated with a reduced risk of incident HF in our study. Prior studies on rhythm versus rate control did not show an advantage of rhythm control [49]. Whether the current findings are due to selection bias or whether more modern rhythm control interventions such as pulmonary vein isolation do have a prognostic benefit is a question of ongoing trials.

Several risk scores to predict HF among AF patients have been evaluated. Imai et al. included age, heart rate, hypertension und history of HF in their score [18]. In Suzuki et al., HF, anemia, renal dysfunction, diabetes mellitus and the use of diuretics were included [17]. More studies are needed to assess whether these differences across studies are due to differences in the patient populations, ethnicity, methodology used or other factors.

The strengths of this study are the large unselected cohort of extensively phenotyped patients who were followed-up for a relatively long period of time. Limitations which need to be considered when interpreting the results of this study are the following: First, due to observational study design, we are not able to prove causality. Second, despite the liberal inclusion criteria, there is always a possibility of selection bias, or residual confounding. Third, the patient population consists mainly of white individuals and the generalizability of our results is unclear. Moreover, echocardiographic data was not systematically available. These data would have been useful to improve the characterization of the study population. Fourth, updating covariates such as AF type on a yearly basis may have induced some imprecision in the variable classification.

Conclusion

In this large cohort of patients with AF, we found several potentially modifiable predictors of HF, providing potential opportunities for the implementation of preventive strategies. Risk factors were similar whether patients had known HF at baseline or not. Future studies should assess whether modifying these risk factors can decrease the risk for HF in AF patients.

Supporting information

S1 Table. Predictors of hospitalization for heart failure (HF) in patients with and without known HF at baseline by using subdistribution hazard models.
(DOCX)

S1 File. Questionnaire.
(PDF)

Author Contributions

Conceptualization: Peter Ammann, Paul Erne, Giorgio Moschovitis, Marcello Di Valentino, Dipen Shah, Jürg Schläpfer, Michael Kühne, Christian Sticherling, Stefan Osswald, David Conen.

References

1. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace. 2010; 12(10):1360–420. https://doi.org/10.1093/europace/euq350 PMID: 20876603.

2. Krijthe BP, Kunst A, Benjamin EJ, Lip GY, Franco OH, Hofman A, 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):2746–51. https://doi.org/10.1093/eurheartj/eht280 PMID: 23900699; PubMed Central PMCID: PMCPmc3858024.

3. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation. 2004; 110(9):1042–6. https://doi.org/10.1161/01.CIR.0000140263.20897.42 PMID: 15313941.

4. Bunch TJ, Weiss JP, Crandall BG, May HT, Bair TL, Osborn JS, et al. Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. Heart Rhythm. 2010; 7(4):433–7. https://doi.org/10.1016/j.hrthm.2009.12.004 PMID: 20122875.

5. Conen D, Chae CU, Glynn RJ, Tedrow UB, Everett BM, Buring JE, et al. Risk of death and cardiovascular events in initially healthy women with new-onset atrial fibrillation. JAMA. 2011; 305(20):2080–7. https://doi.org/10.1001/jama.2011.659 PMID: 21610240; PubMed Central PMCID: PMCPmc3105776.

6. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation. 2003; 107(23):2920–5. https://doi.org/10.1161/01.CIR.0000072767.89944.6E PMID: 12771006.

7. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991; 22(8):983–8. PMID: 1866765.

8. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, et al. Atrial Fibrillation Begets Heart Failure and Vice Versa: Temporal Associations and Differences in Preserved Versus Reduced Ejection Fraction. Circulation. 2016; 133(5):484–92. https://doi.org/10.1161/CIRCULATIONAHA.115.018614 PMID: 26746177; PubMed Central PMCID: PMCPMC4738087.

9. Nieuwlaat R, Olsson SB, Lip GY, Camm AJ, Breithardt G, Capucci A, et al. Guideline-adherent antithrombotic treatment is associated with improved outcomes compared with undertreatment in high-risk

patients with atrial fibrillation. The Euro Heart Survey on Atrial Fibrillation. Am Heart J. 2007; 153 (6):1006–12. https://doi.org/10.1016/j.ahj.2007.03.008 PMID: 17540203.

10. Heo S, Moser DK, Lennie TA, Zambroski CH, Chung ML. A comparison of health-related quality of life between older adults with heart failure and healthy older adults. Heart Lung. 2007; 36(1):16–24. https://doi.org/10.1016/j.hrtlng.2006.06.003 PMID: 17234473.

11. Potpara TS, Polovina MM, Licina MM, Marinkovic JM, Lip GY. Predictors and prognostic implications of incident heart failure following the first diagnosis of atrial fibrillation in patients with structurally normal hearts: the Belgrade Atrial Fibrillation Study. Eur J Heart Fail. 2013; 15(4):415–24. https://doi.org/10.1093/eurjhf/hft004 PMID: 23302606.

12. Thihalolipavan S, Morin DP. Atrial fibrillation and heart failure: update 2015. Prog Cardiovasc Dis. 2015; 58(2):126–35. https://doi.org/10.1016/j.pcad.2015.07.004 PMID: 26192885.

13. Steinberg BA, Kim S, Fonarow GC, Thomas L, Ansell J, Kowey PR, et al. Drivers of hospitalization for patients with atrial fibrillation: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). Am Heart J. 2014; 167(5):735–42 e2. https://doi.org/10.1016/j.ahj.2014.02.003 PMID: 24766985; PubMed Central PMCID: PMCPMC4006943.

14. Pandey A, Kim S, Moore C, Thomas L, Gersh B, Allen LA, et al. Predictors and Prognostic Implications of Incident Heart Failure in Patients With Prevalent Atrial Fibrillation. JACC Heart Fail. 2017; 5(1):44–52. https://doi.org/10.1016/j.jchf.2016.09.016 PMID: 28034376

15. Schnabel RB, Rienstra M, Sullivan LM, Sun JX, Moser CB, Levy D, et al. Risk assessment for incident heart failure in individuals with atrial fibrillation. Eur J Heart Fail. 2013; 15(8):843–9. https://doi.org/10.1093/eurjhf/hft041 PMID: 23594831; PubMed Central PMCID: PMCPMC3858114.

16. Lip GY, Laroche C, Popescu MI, Rasmussen LH, Vitali-Serdoz L, Dan GA, et al. Heart failure in patients with atrial fibrillation in Europe: a report from the EURObservational Research Programme Pilot survey on Atrial Fibrillation. Eur J Heart Fail. 2015; 17(6):570–82. https://doi.org/10.1002/ejhf.254 PMID: 25727992.

17. Suzuki S, Sagara K, Otsuka T, Matsuno S, Funada R, Uejima T, et al. A new scoring system for evaluating the risk of heart failure events in Japanese patients with atrial fibrillation. Am J Cardiol. 2012; 110 (5):678–82. https://doi.org/10.1016/j.amjcard.2012.04.049 PMID: 22621797.

18. Imai K, Okura H, Tamada T, Fukuhara K, Koyama T, Kume T, et al. Prediction of congestive heart failure in patients with non valvular atrial fibrillation. Intern Med. 2014; 53(1):7–12. PMID: 24390521.

19. Fukuda T, Yamashita T, Sagara K, Kato T, Sawada H, Aizawa T. Development of congestive heart failure in Japanese patients with atrial fibrillation. Circ J. 2007; 71(3):308–12. PMID: 17322626.

20. Burger M, Bronstrup A, Pietrzik K. Derivation of tolerable upper alcohol intake levels in Germany: a systematic review of risks and benefits of moderate alcohol consumption. Prev Med. 2004; 39(1):111–27. https://doi.org/10.1016/j.ypmed.2003.11.011 PMID: 15207992.

21. Bazett H. An analysis of the time-relations of electrocardiograms. Heart. 1920;(7):353–67.

22. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150(9):604–12. PMID: 19414839; PubMed Central PMCID: PMC2763564.

23. Dunlay SM, Redfield MM, Weston SA, Therneau TM, Hall Long K, Shah ND, et al. Hospitalizations after heart failure diagnosis a community perspective. J Am Coll Cardiol. 2009; 54(18):1695–702. https://doi.org/10.1016/j.jacc.2009.08.019 PMID: 19850209; PubMed Central PMCID: PMCPMC2803107.

24. Bueno H, Ross JS, Wang Y, Chen J, Vidan MT, Normand SL, et al. Trends in length of stay and short-term outcomes among Medicare patients hospitalized for heart failure, 1993–2006. JAMA. 2010; 303 (21):2141–7. https://doi.org/10.1001/jama.2010.748 PMID: 20516414; PubMed Central PMCID: PMCPMC3020983.

25. Cox DR. Regression models and life tables. J Roy Stat Soc B 1972.

26. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. J Am Stat Assoc. 1999; 94(446):469–509.

27. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation. 1983; 67(5):968–77. PMID: 6219830.

28. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA. 1979; 241(19):2035–8. PMID: 430798.

29. Cavender MA, Steg PG, Smith SC Jr., Eagle K, Ohman EM, Goto S, et al. Impact of Diabetes Mellitus on Hospitalization for Heart Failure, Cardiovascular Events, and Death: Outcomes at 4 Years From the Reduction of Atherothrombosis for Continued Health (REACH) Registry. Circulation. 2015; 132 (10):923–31. https://doi.org/10.1161/CIRCULATIONAHA.114.014796 PMID: 26152709.

30. Lee DS, Massaro JM, Wang TJ, Kannel WB, Benjamin EJ, Kenchaiah S, et al. Antecedent blood pressure, body mass index, and the risk of incident heart failure in later life. Hypertension. 2007; 50(5):869–76. https://doi.org/10.1161/HYPERTENSIONAHA.107.095380 PMID: 17893376.

31. Tedrow UB, Conen D, Ridker PM, Cook NR, Koplan BA, Manson JE, et al. The long- and short-term impact of elevated body mass index on the risk of new atrial fibrillation the WHS (women's health study). J Am Coll Cardiol. 2010; 55(21):2319–27. https://doi.org/10.1016/j.jacc.2010.02.029 PMID: 20488302; PubMed Central PMCID: PMCPMC2880879.

32. Schoen T, Pradhan AD, Albert CM, Conen D. Type 2 diabetes mellitus and risk of incident atrial fibrillation in women. J Am Coll Cardiol. 2012; 60(15):1421–8. https://doi.org/10.1016/j.jacc.2012.06.030 PMID: 22981550; PubMed Central PMCID: PMCPMC4277997.

33. Sandhu RK, Ezekowitz J, Andersson U, Alexander JH, Granger CB, Halvorsen S, et al. The 'obesity paradox' in atrial fibrillation: observations from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial. Eur Heart J. 2016; 37(38):2869–78. https://doi.org/10.1093/eurheartj/ehw124 PMID: 27071819

34. Ardestani A, Hoffman HJ, Cooper HA. Obesity and outcomes among patients with established atrial fibrillation. Am J Cardiol. 2010; 106(3):369–73. https://doi.org/10.1016/j.amjcard.2010.03.036 PMID: 20643247; PubMed Central PMCID: PMCPMC2962431.

35. Wang J, Yang YM, Zhu J, Zhang H, Shao XH. Obesity paradox in patients with atrial fibrillation and heart failure. Int J Cardiol. 2014; 176(3):1356–8. https://doi.org/10.1016/j.ijcard.2014.07.264 PMID: 25129300.

36. Beinart R, Zhang Y, Lima JA, Bluemke DA, Soliman EZ, Heckbert SR, et al. The QT interval is associated with incident cardiovascular events: the MESA study. J Am Coll Cardiol. 2014; 64(20):2111–9. https://doi.org/10.1016/j.jacc.2014.08.039 PMID: 25457400; PubMed Central PMCID: PMCPMC4254697.

37. Berger R, Huelsman M, Strecker K, Bojic A, Moser P, Stanek B, et al. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. Circulation. 2002; 105(20):2392–7. PMID: 12021226.

38. Levin ER, Gardner DG, Samson WK. Natriuretic peptides. N Engl J Med. 1998; 339(5):321–8. https://doi.org/10.1056/NEJM199807303390507 PMID: 9682046.

39. Wozakowska-Kaplon B. Effect of sinus rhythm restoration on plasma brain natriuretic peptide in patients with atrial fibrillation. Am J Cardiol. 2004; 93(12):1555–8. https://doi.org/10.1016/j.amjcard.2004.03.013 PMID: 15194036.

40. Ellinor PT, Low AF, Patton KK, Shea MA, Macrae CA. Discordant atrial natriuretic peptide and brain natriuretic peptide levels in lone atrial fibrillation. J Am Coll Cardiol. 2005; 45(1):82–6. https://doi.org/10.1016/j.jacc.2004.09.045 PMID: 15629379.

41. Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ, Yusuf S, et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation. 2006; 113(5):671–8. https://doi.org/10.1161/CIRCULATIONAHA.105.580506 PMID: 16461840.

42. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation. 2003; 108(17):2154–69. https://doi.org/10.1161/01.CIR.0000095676.90936.80 PMID: 14581387.

43. De Bacquer D, De Backer G, De Buyzere M, Kornitzer M. Is low serum chloride level a risk factor for cardiovascular mortality? J Cardiovasc Risk. 1998; 5(3):177–84. PMID: 10201555.

44. McCallum L, Jeemon P, Hastie CE, Patel RK, Williamson C, Redzuan AM, et al. Serum chloride is an independent predictor of mortality in hypertensive patients. Hypertension. 2013; 62(5):836–43. https://doi.org/10.1161/HYPERTENSIONAHA.113.01793 PMID: 23980073.

45. Grodin JL, Simon J, Hachamovitch R, Wu Y, Jackson G, Halkar M, et al. Prognostic Role of Serum Chloride Levels in Acute Decompensated Heart Failure. J Am Coll Cardiol. 2015; 66(6):659–66. https://doi.org/10.1016/j.jacc.2015.06.007 PMID: 26248993.

46. Testani JM, Hanberg JS, Arroyo JP, Brisco MA, Ter Maaten JM, Wilson FP, et al. Hypochloraemia is strongly and independently associated with mortality in patients with chronic heart failure. Eur J Heart Fail. 2016; 18(6):660–8. https://doi.org/10.1002/ejhf.477 PMID: 26763893.

47. Chen CY, Yoshida A, Asakura M, Hasegawa T, Takahama H, Amaki M, et al. Serum blood urea nitrogen and plasma brain natriuretic Peptide and low diastolic blood pressure predict cardiovascular morbidity and mortality following discharge in acute decompensated heart failure patients. Circ J. 2012; 76(10):2372–9. PMID: 22785557.

48. Javaheri S, Shukla R, Zeigler H, Wexler L. Central sleep apnea, right ventricular dysfunction, and low diastolic blood pressure are predictors of mortality in systolic heart failure. J Am Coll Cardiol. 2007; 49 (20):2028–34. https://doi.org/10.1016/j.jacc.2007.01.084 PMID: 17512359.

49. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002; 347(23):1825–33. https://doi.org/10.1056/NEJMoa021328 PMID: 12466506.