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ORIGINAL RESEARCH

# Rate of Heart Failure Following Atrial Fibrillation According to Presence of Family History of Dilated Cardiomyopathy or Heart Failure: A Nationwide Study

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**BACKGROUND:** It is poorly understood why some patients with atrial fibrillation develop heart failure (HF) and others do not. We examined the rate of developing HF in patients with atrial fibrillation with and without first-degree family members with HF or dilated cardiomyopathy (DCM).

**METHODS AND RESULTS:** Using Danish nationwide registries, patients born after 1942 diagnosed with atrial fibrillation in the period 2005 to 2015 were identified and followed for up to 5 years. Patients with pre-existing HF, DCM, and/or ischemic heart disease diagnoses were excluded. Exposure was defined as a first-degree relative with HF or DCM. The rate of developing the composite end point of HF or death, and the components, was estimated with multivariable Cox proportional hazard regression models. We included 10 605 patients. A total of 17% had a family member with DCM/HF. Having a family member with HF/DCM was associated with an increased 5-year risk of the composite of HF/death (cumulative incidence, 9.2% [95% CI, 7.8–10.7] versus 5.6% [95% CI, 5.0–6.1]; adjusted hazard ratio [HR] 1.36 [95% CI, 1.13–1.64]). (HF 8.4% [95% CI, 7.0–9.8] versus 4.5% [95% CI, 4.1–5.0]); (adjusted HR, 1.49 [95% CI, 1.22–1.82]). However, familial HF/DCM was not significantly associated with an increased 5-year risk and rate of death (0.8% [95% CI, 0.4–1.2] versus 1.1% [95% CI, 0.8–1.3]); (adjusted HR, 0.80 [95% CI, 0.46–1.39]).

**CONCLUSIONS:** In patients with incident atrial fibrillation without prior ischemic heart disease or HF diagnoses, 1 of 6 had a first-degree relative with HF, and having such a family history of HF/DCM was associated with an 87% increase in 5-year incidence of HF compared with those without.

**Key Words:** atrial fibrillation heart failure ■ family history ■ family study

Atrial fibrillation (AF) and heart failure (HF) are global public health burdens that appear to have close linkage and increasing incidence and prevalence.[1,2] These diseases frequently coexist and together confer adverse effects on overall prognosis.[3] Despite affecting >1% of the global population, the temporal relationship between the diseases has not been fully elucidated, and it is poorly understood why some patients with AF develop HF and others do not.[1,2,4] The coexistence of AF and HF may, in part, be explained by a number of shared risk factors (eg, age, sex, obesity, diabetes, ischemic heart disease [IHD], and hypertension).[5] Shared genetic dispositions may also be of significance.[3,6,7] It is possible that patients with a first-degree relative with HF or dilated cardiomyopathy (DCM) may have a higher risk of developing

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## CLINICAL PERSPECTIVE

### What Is New?

- Our results indicate that 17% of patients who have atrial fibrillation and are younger than 73 years had a family history of heart failure (HF)/dilated cardiomyopathy.
- A family history of HF/dilated cardiomyopathy was associated with a 5-year cumulative incidence of 8% and a 49% increased relative risk of developing HF within 5 years.

### What Are the Clinical Implications?

- To prevent progression of HF, clinicians should be aware of the high prevalence of this family history and the associated increased rate of HF in younger patients presenting with incident atrial fibrillation.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **DCM** | dilated cardiomyopathy |
| **IHD** | ischemic heart disease |

HF in relation to AF than those without a family history. However, a possible association between a family history of HF/DCM and the incidence of HF in patients with AF has not been fully investigated and, to our knowledge, no studies have looked at family history as a primary factor for developing HF in patients with incident AF. Therefore, to address this gap in knowledge, we investigated whether having a family member with HF or DCM was associated with an increased rate of developing HF in patients with AF. Our hypothesis was that patients with a first-degree relative with HF/DCM had a significantly increased rate of developing HF in relation to AF.

## METHODS

Because of the sensitive nature of the data collected in this study, they are not publicly available.

### Data Sources

Denmark has a public health care system in which all individuals are provided with a unique identification number used for registration purposes.[8] Data from this study came from nationwide Danish administrative registries. Information in these registries was cross-linked using the unique and permanent personal registration numbers. Data from the following registers were used in the present study: (1) The Danish Civil Registration System, which holds information on sex, date of birth, emigration/immigration status, and all individual registration numbers of all Danish citizens since 1968. It also includes information about parents since 1930 and information about siblings from 1942 onward.[8,9] (2) The DNPR (Danish National Patient Register) holds information on dates and types of diagnoses at discharge, both inpatient and outpatient contacts, in term of *International Classification of Diseases* (*ICD*) codes since 1978.[10] (3) The Danish Register of Medicinal Products, which holds information from Danish pharmacies on all dispensed prescriptions since 1995. Danish pharmacies are mandated by law to report all prescriptions to this registry.[11] (4) The Danish Register of Causes of Death, which holds information on vital status, and date and cause of death of all Danish citizens. Physicians are required by law to complete a death certificate for any death occurring in Denmark.[12]

### Study Population

We included all Danish residents, born after January 1, 1942 (the start of the Danish Family Registry), who had been diagnosed with AF in the period 2005 to 2015. All patients had to have had a minimum age of 18 years at study start and at least 2 (parent and sibling) first-degree family members registered. Because the Danish Civil Registration System only holds information about siblings from 1942 onward, patients born before this date were excluded. Therefore, the oldest patients in this study were 73 years. Patients were excluded if they received loop diuretics at any time before AF diagnosis or had a pre-existing HF or DCM diagnosis, except if diagnosed on the same day as AF. Patients with an IHD diagnosis at study start were also excluded since IHD is a strong predictor for HF and inclusion of patients with IHD may result in bias of our result. (Ten-year follow-up data are available as supplemental material).

### Definitions of AF, Exposure, and Outcomes

The presence of AF was defined by a primary diagnosis of AF for a given hospital contact, both inpatient and outpatient, as defined by the *ICD, Tenth Revision* classification (DI-48). This definition has been validated with a positive predictive value of 92.6% (95% CI, 88.8–95.2) using the DNPR.[13] The primary outcome of the study was the composite end point of incident HF or death. Secondary outcomes were the components of the primary outcome. The diagnosis HF was combined with DCM to increase sensitivity. Both HF and DCM were identified using the DNPR. Both diseases had to be either primary or secondary diagnoses. Both inpatient and outpatient diagnoses

were included. HF and DCM were defined via *ICD-10* codes: DI-50 and DI-420, respectively. The positive predictive value of HF using these criteria has been estimated to be between 81% and 100%.[10,14,15] Date of death was obtained from the Danish Register of Causes of Death. Exposure was defined as having a family member (biological mother, father, or sibling) diagnosed with HF/DCM any time before reaching outcome during the 5-year follow-up period. Adopted persons were excluded, and individuals who had migrated before or during follow-up were excluded and censored, respectively. The patients were followed for up to 5 years upon entering the study.

## Comorbidities and Concomitant Pharmacotherapy

Comorbidities at baseline were selected based on relevance to mortality rate and the development of AF and HF. These comorbidities were included as diagnoses up to 5 years before study start as defined by the *ICD-10* classification (Table S1). Pharmacotherapy was selected with relevance to outcome and comorbidities and was included up to 6 months before study start, including the day of study start (Table S2).

## Statistical Analysis

Baseline characteristics are presented as numbers with percentages for categorical data and median with interquartile range for continuous data. The absolute risks of outcome not including all-cause mortality (ie, HF) were estimated using the Aalen-Johansen estimator, taking the competing risk of death into account, and differences between groups were assessed using Gray's test. Absolute risks of outcomes including all-cause mortality were estimated using the Kaplan–Meier estimator, and differences between groups were assessed using the log-rank test. Cause-specific Cox regression models were used to compare the outcomes between groups. The models were adjusted for age (modeled as a restricted cubic spline with 3 knots [10th, 50th, and 90th percentile]), sex, year of diagnosis, type 2 diabetes, chronic obstructive pulmonary disease, hypertension, chronic kidney disease, cancer, stroke, and peripheral artery disease as well as the listed medications in the Table. The models showed no interaction for the adjusted parameters, and fulfilled the proportional hazards assumption. Proportional hazard assumptions were assessed using graphical diagnostics and Schoenfeld residuals and could be assumed for the categorical variables included in the models. Statistical significance was defined as 2-sided *P* value <0.05. Parameter estimates were made with 95% CI and medians with interquartile range. Statistical analyses were performed using R (R Core Team 2018)[16] and SAS (SAS Institute, Inc., Cary, NC).[17]

**Table. Baseline Characteristics of the Study Population**

| Characteristics | No family member with HF or DCM (n=8809) | Family member with HF or DCM (n=1796) | *P* value |
|---|---|---|---|
| Demographics | | | |
| Male sex, n (%) | 6436 (73.1) | 1,328 (74.8) | 0.46 |
| Age, y, median [IQR] | 49 [40–54] | 52 [47–56] | <0.0001 |
| Parents with HF, n (%) | NA | 1.669 (92.9) | NA |
| Siblings with HF, n (%) | NA | 127 (7.1) | NA |
| Comorbidities, n (%) | | | |
| Type 2 diabetes | 386 (4.4) | 101 (5.6) | 0.026 |
| Hypertension | 769 (8.7) | 193 (10.7) | 0.008 |
| Atherosclerosis | 206 (2.3) | 43 (2.4) | 0.955 |
| Chronic kidney disease | 45 (0.5) | 9 (0.5) | 1 |
| Chronic obstructive pulmonary disease | 95 (1.1) | 20 (1.1) | 0.995 |
| Cancer | 215 (2.4) | 44 (2.4) | 1 |
| Concomitant pharmacotherapy, n (%) | | | |
| Calcium channel blockers | 916 (10.4) | 231 (12.9) | 0.003 |
| Non-loop diuretics | 871 (9.9) | 250 (13.9) | <0.0001 |
| RAAS | 1437 (16.3) | 398 (22.2) | <0.0001 |
| Vit. K antagonist | 1390 (15.8) | 345 (19.2) | <0.0001 |
| Aspirin | 886 (10.1) | 220 (12.2) | 0.006 |
| Statins | 901 (10.2) | 252 (14.0) | <0.0001 |

DCM indicates dilated cardiomyopathy; HF, heart failure; IQR, interquartile range; NA, not applicable; and RAAS, renin-angiotensin-aldosterone system.

## Approvals and Ethics

In Denmark, studies that use retrospective anonymized register-based data are not required to apply for approval from the Research Ethics Committee System. The study was registered and approved by the data-responsible institute (Region Hovedstaden; Approval number: P-2019-382) in accordance with the General Data Protection Regulation. Institutional Review Board approval was obtained according to the guidelines pertaining to human studies. No informed consent was required.

# RESULTS

## Study Population

We identified a final total cohort of 10 605 patients diagnosed with AF in the period 2005 to 2015 in Denmark. Of those patients, 1796 (17%) had at least 1 family member with HF/DCM. See the flowchart for an overview of the study population selection (Figure 1). Baseline characteristics of patients with and without a family history of HF/DCM are shown in the Table. Of the patients with and without family members with HF/DCM, 75% and 73% were men, respectively. The median ages at AF diagnosis were 52 years (interquartile range, 47–56) and 49 years

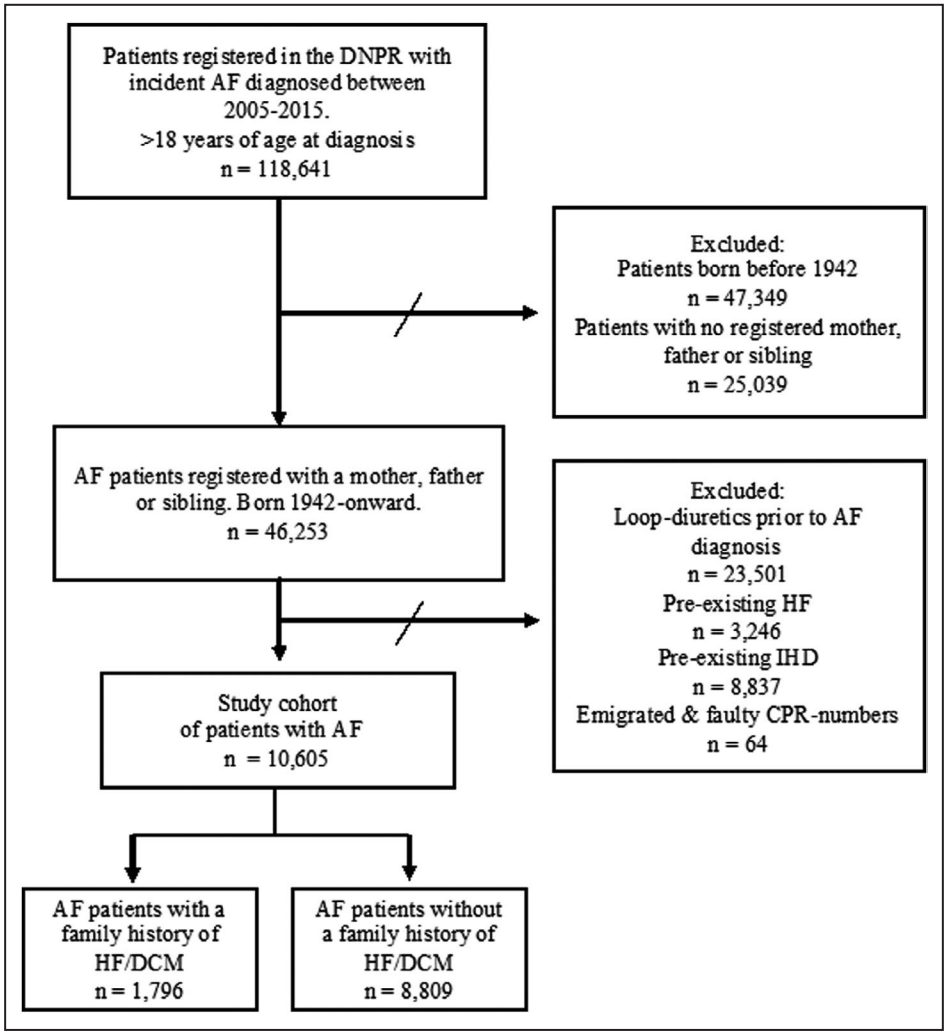


**Figure 1. Flowchart of study population selection.**
Selection of the study population and the distribution of patients with and without a family member with HF or DCM. AF indicates atrial fibrillation; CPR, civil registration system; DCM, dilated cardiomyopathy; DNPR, Danish National Patient Registry; HF, heart failure; and IHD, ischemic heart disease.

(interquartile range, 40–54) with and without a family history of HF/DCM, respectively. The majority of family members with HF/DCM were parents (93%), with only 7% being siblings. One hundred eighteen patients were diagnosed with HF on the same day as study start, and 347 patients were diagnosed with HF 6 months after study start. Patients with AF with a family history of HF/DCM had a higher prevalence of type 2 diabetes and hypertension. For other comorbidities, the 2 groups were comparable and showed no statistically significant differences. Patients with AF with a family history had significantly higher frequencies of pharmacotherapy use at baseline.

## Rate of HF and Death

During the 5-year follow-up, 626 (6%) patients reached the primary composite outcome of HF development or all-cause mortality. Of these patients, 537 (5%) developed HF. Median follow-up time for the overall study cohort was 3.5 years (25th–75th percentile, 2.8–4.4 years). Figure 2A shows that the 5-year cumulative incidence of the primary composite outcome of HF or death was 9.2% (95% CI, 7.8%–10.7%) and 5.6% (95% CI, 5.0%–6.1%) in patients with and without a family history of HF or DCM, respectively (Gray's test, $P<0.0001$). Figure 2B shows that the cumulative incidence of the secondary outcome of HF was 8.4% (95% CI, 7.0%–9.8%) and 4.5% (95% CI, 4.1%–5.0%) with and without a family history of HF or DCM (log-rank test, $P<0.0001$). Finally, Figure 2C shows that the cumulative incidence of all-cause mortality was 0.8% (95% CI, 0.4%–1.2% and 1.1% [95% CI, 0.8%–1.3%] with and without a family member with HF/DCM [log-rank test, $P=0.38$]). In multivariable Cox regression models, the primary composite outcome of HF

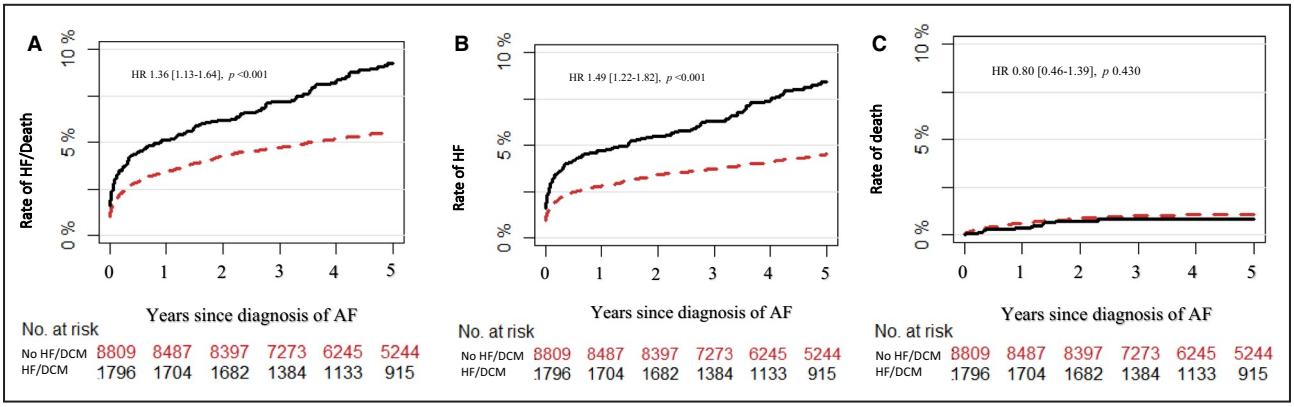


**Figure 2. Five-year cumulative incidence with HR of composite outcome of HF and all-cause mortality (A), HF (B), and all-cause mortality (C) in patients with and without a family member with HF/DCM, respectively.**
Solid lines represent patients with a family member with HF or DCM and dashed lines represent patients without a family member with HF or DCM. AF indicates atrial fibrillation; DCM, dilated cardiomyopathy; HF, heart failure; HR, hazard ratio; and IHD, ischemic heart disease.

or death was higher in patients with a family history of HF or DCM compared with those without (adjusted hazard ratio [HR], 1.36 [95% CI, 1.13–1.64]). Likewise, HF was more common in patients with a family history of HF or DCM compared with those without (adjusted HR, 1.49 [95% CI, 1.22–1.82]). However, all-cause mortality was not significantly different in patients with and without a family history of HF or DCM (adjusted HR, 0.80 [95% CI, 0.46–1.39]).

Expanding the follow-up to 10 years yielded results similar to the main analyses. Figure S1 shows the distribution of age of relatives. Figure S2 shows the cumulative incidence and HRs with a 10-year follow-up. Table S3 shows the comorbidities of relatives at index date and Table S4 shows the HRs for adjusted and unadjusted outcomes. Table S5 shows the HRs for each adjustment factor based on outcome.

# DISCUSSION

## Main Findings

In this nationwide cohort study, we examined the long-term rate of developing HF in patients <73 years of age with newly diagnosed AF based on their familial history of HF or DCM. The study yielded 2 main findings. First, having a family member with HF or DCM was associated with a >50% increase in the rate of incident HF during the following 5 years after AF. However, after 5 years only 5% of the cohort developed HF. Second, around one sixth (17%) of patients with AF in the study had a family member with pre-existing HF or DCM.

## Previous Studies

As shown by other studies, the epidemiological profiles of HF and AF have shared characteristics. This includes but is not limited to age-dependent incidence rates of HF and AF, dependence on both comorbidities and genetics, as well as conditions being greater among men than women.[9,18–22] Data have shown that close to two thirds of people living with AF from any cause will develop HF during the course of their disease, whereas AF develops in only one third of people with pre-existing HF.[3,23] Our study showed a significantly lower incidence of HF development in patients with AF, which may be because of the relatively short follow-up period, as well as the young median age of the cohort. Furthermore, our research found 17% of the study population to have 1 or more family members with HF or DCM. Whether this is specific to patients with AF or merely representative of the general population requires further research looking at an otherwise heart-healthy cohort and their respective family members' HF prevalence and rate of reaching outcome. As mentioned, it is poorly understood why some patients with AF develop HF and others do not. Our findings may support the idea of a genetic component in HF/DCM because there is a significantly increased rate of developing HF in situations where patients have AF and a family member has HF/DCM. However, the combined interplay of physiological processes underlying each condition makes the true temporal relationship between AF and HF challenging to fully uncover. Because no other studies appear to have looked specifically at family history as primary indication for developing HF in patients with incident AF, data on the area for comparison are scarce.

Similar to our study, however, other data point to AF incidence being greater among men than women on a global scale, and the incidence doubles with every advancing decade of life.[21,22,24]

## Clinical Implications

Based on our results, it may be suggested that clinical patients with AF and a family history of HF/DCM

should be followed closely because AF may be a clinical precursor of cardiomyopathy. Risk factors for HF/DCM such as hypertension, asymptomatic left ventricular systolic dysfunction, or increased left ventricular mass should be modified with appropriate afterload reduction (especially angiotensin-converting enzyme inhibitors should be considered) and serial echocardiograms may be helpful.[14,25] The safety and efficacy of early radiofrequency ablation of AF on HF in this patient group remain to be determined. Genetic testing and counseling of families with different members presenting with either sporadic DCM or AF need to be further explored. In the present study, we found a higher rate of HF in patients with AF and a family history of HF/DCM. Since we do not have a nationwide biobank of genetics, myocardial biopsies, or data on magnetic resonance imaging, the exact cause of the cardiomyopathy underlying the clinical diagnosis of HF cannot be diagnosed.[26] In that context, it should also be noted that patients with AF with a family history of DCM/HF were older with a higher burden of treated risk factors (eg, more often in treatment with statins and aspirin) than patients with AF without a family history.

## Strengths and Limitations

The main strength of this study was the extensiveness of available data in a relatively large cohort of patients with AF. Despite this, and the fact that a minimal number of patients were lost to follow-up, the study did have some limitations. First, and arguably the most important limitation, was the fact that the results were derived from administrative registries and, as with all such studies, there is a risk of unmeasured and residual confounding. Misclassification may also occur, but in the Danish registries, there are high positive predictive values of the AF, HF, and IHD diagnoses.[13,14,26] Also, since this study was performed using Danish registries only, it did not allow us to generalize beyond and reflect on a more diverse setting. However, it is worth noting that Denmark represents a country of mainly White people of European ancestry with a high standard of living. It is therefore reasonable to expect comparable results in similar settings around the world. Second, we did not know whether rate versus rhythm controlling strategies were attempted for the study population and whether this had affected outcome. Third, the young age of the study population could have had a limiting effect on the number of patients included and may also represent a different type of patient than those who are older at age of onset of AF. The fact that the cohort consisted of young patients also made it difficult to extrapolate results to an older population. Fourth, since this study was observational, it limited our capabilities to determine causations, but rather only associations between the diseases and thus impeded a cause–effect assessment. We excluded patients with use of loop diuretics to avoid inclusion of patients potentially treated for HF without having it diagnosed at a hospital. Fifth, a significant part of the cohort was excluded based on previous IHD diagnoses. This limited the number of patients that otherwise could had been included. Without the exclusion of IHD patients, however, the specificity of the cause of HF would had been negatively affected, because IHD is known to cause HF frequently and to be the strongest known exposure.[25] Also, worth noting is the fact that certain baseline characteristics differed between the groups of patients with and without a family history of HF, albeit their absolute differences were minimal and likely not clinically relevant. We used administrative registries and therefore cannot distinguish HF with preserved from reduced ejection fraction. It also is not possible to present data on remission of left ventricular systolic dysfunction ("Tachy-arrhythmia induced cardiomyopathy"[27]). Our data provide new information on the rate of clinical HF.[8,10,13–15,26–28] A family history of AF may reflect either an increased risk of HF, or early stages of HF caused by, for example, diastolic dysfunction and increased left atrial volume and thus secondary AF. Based on our administrative data, the 2 clinical scenarios cannot be separated, and we can solely conclude that the rate of HF is higher in patients with AF with a family history of DCM/HF than in those without. Cardiologists should be aware of this increased rate during the clinical examination and plan follow-up accordingly. Despite these limitations, the present study was the first to investigate the long-term rate of developing HF in patients with existing AF and family history of HF using large-scale data from nationwide registries. Nevertheless, more studies are needed to confirm our results.

# CONCLUSIONS

In this nationwide cohort study of patients <73 years of age with incident AF and without prior HF or IHD, we observed that having a family member with HF/DCM substantially increased the rate of developing HF. Also, we found patients with AF to have a significant prevalence (17%) of family history of HF/DCM.

## ARTICLE INFORMATION

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None.

## Disclosures

None.

## Supplementary Material

Tables S1–S5
Figures S1–S2

## REFERENCES

1. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH, Zheng ZJ, et al. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. *Circulation*. 2014;129:837–847. doi: 10.1161/CIRCULATIONAHA.113.005119
2. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. *Nat Rev Cardiol*. 2016;13:368–378. doi: 10.1038/nrcardio.2016.25
3. Santhanakrishnan R, Wang NA, Larson MG, Magnani JW, McManus DD, Lubitz SA, Ellinor PT, Cheng S, Vasan RS, Lee DS, et al. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation*. 2016;133:484–492. doi: 10.1161/CIRCULATIONAHA.115.018614
4. Khan MA, Satchithananda DK, Mamas MA. The importance of interactions between atrial fibrillation and heart failure. *Clin Med (Lond)*. 2016;16:272–276. doi: 10.7861/clinmedicine.16-3-272
5. Prabhu S, Voskoboinik A, Kaye DM, Kistler PM. Atrial fibrillation and heart failure — cause or effect? *Heart Lung Circ*. 2017;26:967–974. doi: 10.1016/j.hlc.2017.05.117
6. Fox CS, Parise H, D'Agostino RB, Lloyd-Jones DM, Vasan RS, Wang TJ, Levy D, Wolf PA, Benjamin EJ. Parental atrial fibrillation as a risk factor for atrial fibrillation in offspring. *J Am Med Assoc*. 2004;291:2851–2855. doi: 10.1001/jama.291.23.2851
7. Burke MA, Cook SA, Seidman JG, Seidman CE. Clinical and mechanistic insights into the genetics of cardiomyopathy. *J Am Coll Cardiol*. 2016;68:2871–2886. doi: 10.1016/j.jacc.2016.08.079
8. Pedersen CB. The Danish civil registration system. *Scand J Public Health*. 2011;39:22–25. doi: 10.1177/1403494810387965
9. Gundlund A, Olesen JB, Staerk L, Lee C, Piccini JP, Peterson ED, Kober L, Torp-Pedersen C, Gislason GH, Fosbol EL. Outcomes associated with familial versus nonfamilial atrial fibrillation: a matched nationwide cohort study. *J Am Heart Assoc*. 2016;5:e003836. doi: 10.1161/JAHA.116.003836
10. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish national patient registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449–490. doi: 10.2147/CLEP.S91125
11. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data resource profile: the Danish national prescription registry. *Int J Epidemiol*. 2017;46:798–798f. doi: 10.1093/ije/dyw213
12. Helweg-Larsen K. The Danish register of causes of death. *Scand J Public Health*. 2011;39:26–29. doi: 10.1177/1403494811399958
13. Rix TA, Riahi S, Overvad K, Lundbye-Christensen S, Schmidt EB, Joensen AM. Validity of the diagnoses atrial fibrillation and atrial flutter in a Danish patient registry. *Scand Cardiovasc J*. 2012;46:149–153. doi: 10.3109/14017431.2012.673728
14. Kümler T, Gislason GH, Kirk V, Bay M, Nielsen OW, Køber L, Torp-Pedersen C. Accuracy of a heart failure diagnosis in administrative registers. *Eur J Heart Fail*. 2008;10:658–660. doi: 10.1016/j.ejheart.2008.05.006
15. Mard S, Nielsen FE. Positive predictive value and impact of misdiagnosis of a heart failure diagnosis in administrative registers among patients admitted to a university hospital cardiac care unit. *Clin Epidemiol*. 2010;2:235–239. doi: 10.2147/CLEP.S12457
16. core Team R. R: A. Language and Environment for Statistical Computing. *R Found Stat Comput Vienna, Austria*. 2018.
17. SAS Institute Inc., Cary, NC U. Sas® 9.4. *SAS Inst Inc, Cary, NC, USA*. 2017. doi: 10.1016/0370-2693(82)91293-X
18. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, Jacobsen SJ. Trends in heart failure incidence and survival in a community-based population. *J Am Med Assoc*. 2004;292:344–350. doi: 10.1001/jama.292.3.344
19. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KKL, Murabito JM, Vasan RS. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med*. 2002;347:1397–1402. doi: 10.1056/NEJMoa020265
20. Ling LH, Kistler PM, Kalman JM, Schilling RJ, Hunter RJ. Comorbidity of atrial fibrillation and heart failure. *Nat Rev Cardiol*. 2016;13:131–147. doi: 10.1038/nrcardio.2015.191
21. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg CD, Rautaharju PM. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation*. 1997;96:2455–2461. doi: 10.1161/01.CIR.96.7.2455
22. 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. *J Am Med Assoc*. 1994;271:840–844. doi: 10.1001/jama.1994.03510350050036
23. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation*. 2003;107:2920–2925. doi: 10.1161/01.CIR.0000072767.89944.6E
24. Heeringa J, Van Der Kuip DAM, Hofman A, Kors JA, Van Herpen G, Stricker BHC, Stijnen T, Lip GYH, Witteman JCM. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J*. 2006;27:949–953. doi: 10.1093/eurheartj/ehi825
25. Schmidt M, Pedersen L, Sørensen HT. The Danish civil registration system as a tool in epidemiology. *Eur J Epidemiol*. 2014;29:541–549. doi: 10.1007/s10654-014-9930-3
26. Steenbergen C, Frangogiannis NG. Ischemic heart disease, Chapter 36. In: Hill JA, Olson EN, eds. *Muscle*. Academic Press; 2012:495–521.
27. Lynge E, Sandegaard JL, Rebolj M. The Danish national patient register. *Scand J Public Health*. 2011;39:30–33. doi: 10.1177/1403494811401482
28. Sundbøll J, Adelborg K, Munch T, Frøslev T, Sørensen HT, Bøtker HE, Schmidt M. Positive predictive value of cardiovascular diagnoses in the Danish national patient registry: a validation study. *BMJ Open*. 2016;6:e012832. doi: 10.1136/bmjopen-2016-012832

# SUPPLEMENTAL MATERIAL

**Table S1. Specification of comorbidities by International Classification of Diseases (ICD), ICD-10 codes.**

| Comorbidity | ICD-10 code |
|---|---|
| **Cancer** | DC00-DC97 |
| **Chronic obstructive pulmonary disease** | DJ42, DJ43, DJ44 |
| **Diabetes mellitus** | DE10-14. ATC: A10 (6 months before AF diagnosis) |
| **Chronic kidney disease** | DN03-08, DN11-12, DN14, DN18-19, DN26, DQ61, N158-160, N162-164, N168, E102, E112, E132, E142, I120, M321B, DN19, DR34, DT858, DT859, DZ992 |
| **Hypertension** | DI10-15 |
| **Peripheral artery disease** | DI70 |
| **Stroke** | DI63-64 |
| **Liver disease** | DB15-19, DC22, DK70-77, Z9422, I982, D684C, Q618A |
| **Ischemic heart disease** | DI20-21, DI23-25 |

**Table S2. Specification of concomitant pharmacotherapy by Anatomical Therapeutic Chemical Classification (ATC), ATC-codes.**

| Pharmacotherapy | ATC-code |
|---|---|
| **Calcium channel blockers** | C08, C09BB, C09DB |
| **Non-loop diuretics** | C02L, C03A, C03B, C03D, C03E, C03X, C07B, C07C, C07D, C08G, C02DA, C09BA, C09DA, C09XA52 |
| **RAAS** | C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C09XA02, C09XA52 |
| **Vit. K antagonists** | B01AA03, B01AA04 |
| **Aspirin** | B01AC06, N02BA01 |
| **Statins** | C10AA |

**Table S3. Comorbidities of relatives at index date.**

| **Comorbidities, N (%)** | **No HF or DCM** | **HF or DCM** | ***P* value** |
|---|---|---|---|
| Type 2 Diabetes | 1948 (6.7) | 610 (22.9) | <0.0001 |
| Hypertension | 5760 (19.8) | 1298 (48.8) | <0.0001 |
| Stroke or peripheral artery disease | 2611 (9.0) | 741 (27.8) | <0.0001 |
| Chronic kidney disease | 823 (2.8) | 392 (14.7) | <0.0001 |
| Chronic obstructive pulmonary disease | 1882 (6.5) | 771 (29.0) | <0.0001 |
| Cancer | 5012 (17.2) | 732 (27.5) | <0.0001 |

**Table S4. Hazard ratios for adjusted and unadjusted outcomes.**

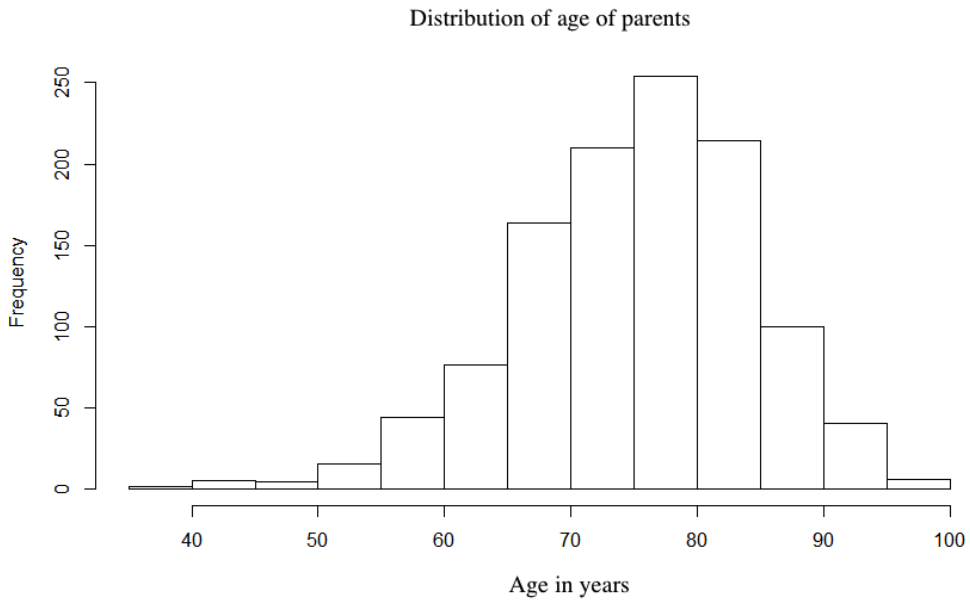
| | Composite outcome | HF | All-cause mortality |
|---|---|---|---|
| Adjusted HR [95% CI] | 1.36 [1.13;1.64] | 1.49 [1.22;1.82] | 0.80 [0.46;1.39] |
| Unadjusted HR [95% CI] | 1.56 [1.30;1.88] | 1.75 [1.44;2.14] | 0.80 [0.46;1.38] |

**Table S5. Hazard ratios for each adjustment factor based on outcome.**

| | Composite outcome [95% CI] | HF [95% CI] | All-cause mortality [95% CI] |
|---|---|---|---|
| Family history of HF/DCM | 1.36 [1.13;1.64] | 1.49 [1.22;1.82] | 0.81 [0.47;1.41] |
| Age | 1.04 [1.03;1.05] | 1.04 [1.03;1.05] | 1.01 [0.99;1.03] |
| Sex (male) | 2.40 [1.82;2.90] | 2.78 [2.11;3.67] | 1.21 [0.77;1.89] |
| Diabetes type 2 | 1.22 [0.88;1.70] | 1.12 [0.78;1.62] | 1.76 [0.82;3.78] |
| COPD | 1.29 [0.71;2.35] | 0.86 [0.38;1.92] | 2.86 [1.13;7.26] |
| Hypertension | 0.74 [0.56;0.99] | 0.75 [0.55;1.03] | 0.67 [0.30;1.50] |
| Atherosclerosis | 1.35 [0.85;2.15] | 1.04 [0.60;1.80] | 3.57 [1.39;9.19] |
| CKD | 1.78 [0.83;3.80] | 0.73 [0.18;2.95] | 5.08 [1.84;13.98] |
| Cancer | 2.42 [1.76;3.34] | 0.89 [0.51;1.56] | 12.93 [8.16;20.50] |
| Digoxin | 2.03 [1.54;2.68] | 1.91 [1.40;2.60] | 2.43 [1.31;4.54] |
| CCB | 0.79 [0.61;1.03] | 0.82 [0.62;1.09] | 0.66 [0.32;1.36] |
| Non-loop diuretics | 0.79 [0.60;1.04] | 0.73 [0.52;1.00] | 1.11 [0.53;2.30] |
| RAAS | 1.78 [1.42;2.24] | 1.92 [1.50;2.46] | 1.24 [0.67;2.30] |
| Vitamin K. antagonists | 0.98 [0.80;1.20] | 1.02 [0.81;1.27] | 0.83 [0.49;1.43] |
| ASA | 0.93 [0.72;1.18] | 0.84 [0.63;1.10] | 1.40 [0.82;2.40] |
| NOAC | 0.73 [0.54;0.99] | 0.85 [0.62;1.17] | 0.83 [0.65;1.05] |
| Statins | 0.73 [0.55;0.96] | 0.87 [0.65;1.16] | 0.16 [0.05;0.47] |

**Figure S1. Distribution of age of relatives.**

**a) Distribution of age of parents**




**b) Distribution of age of siblings**

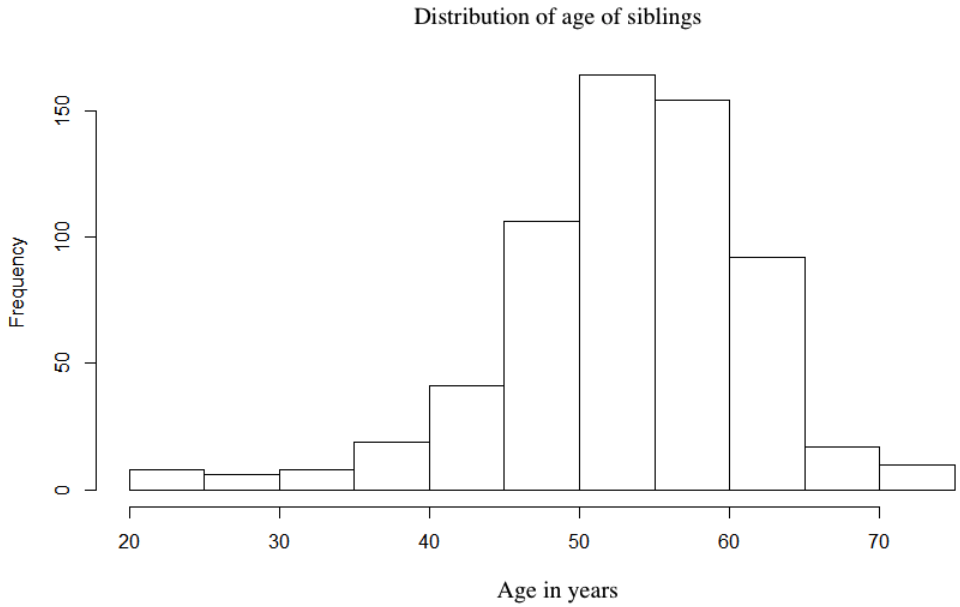
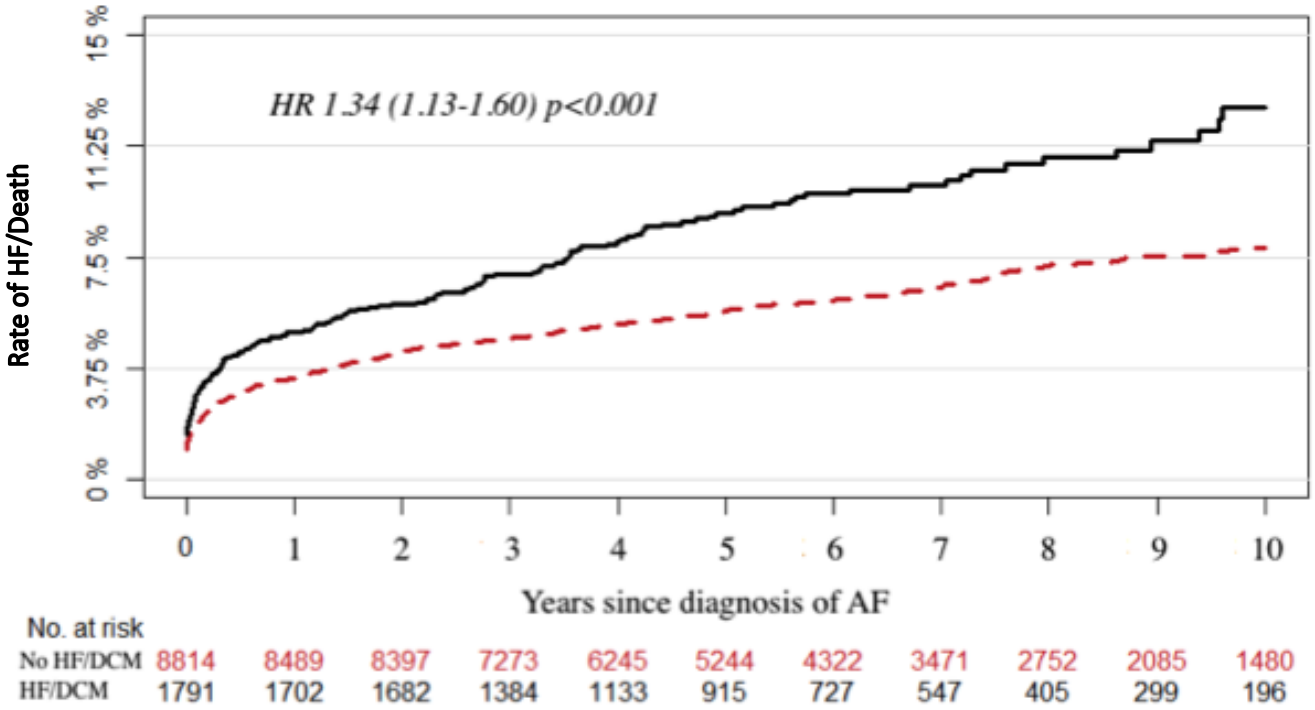
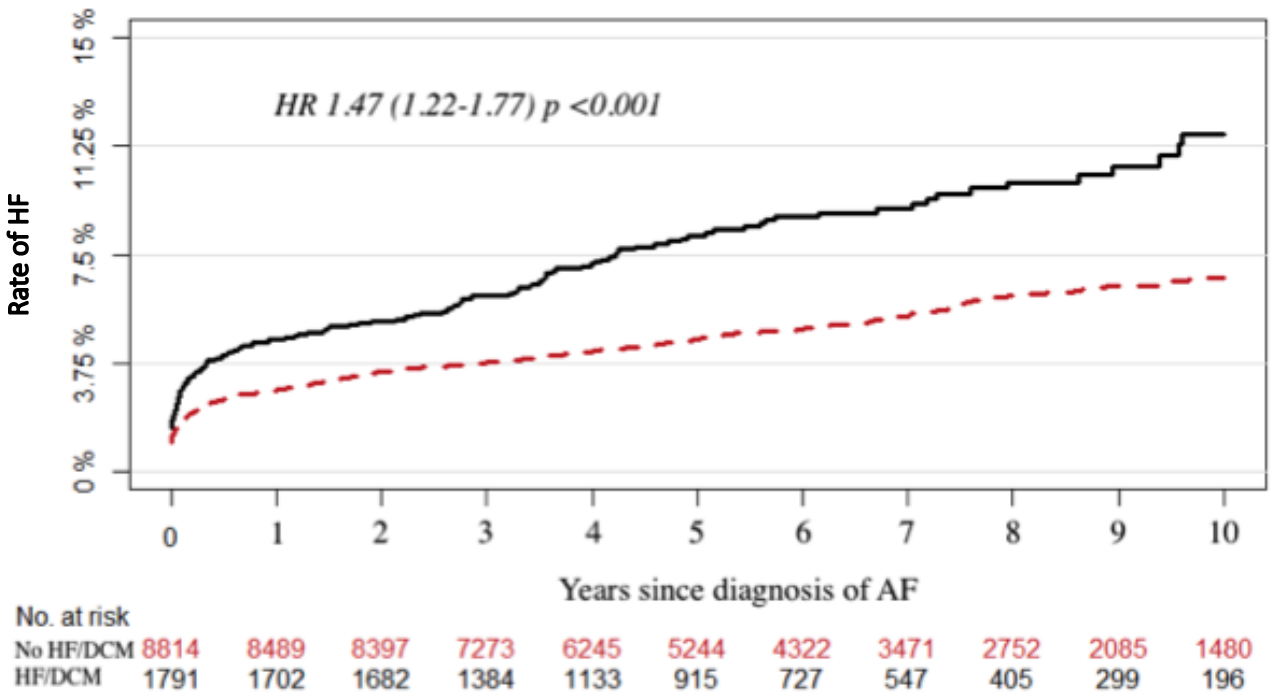


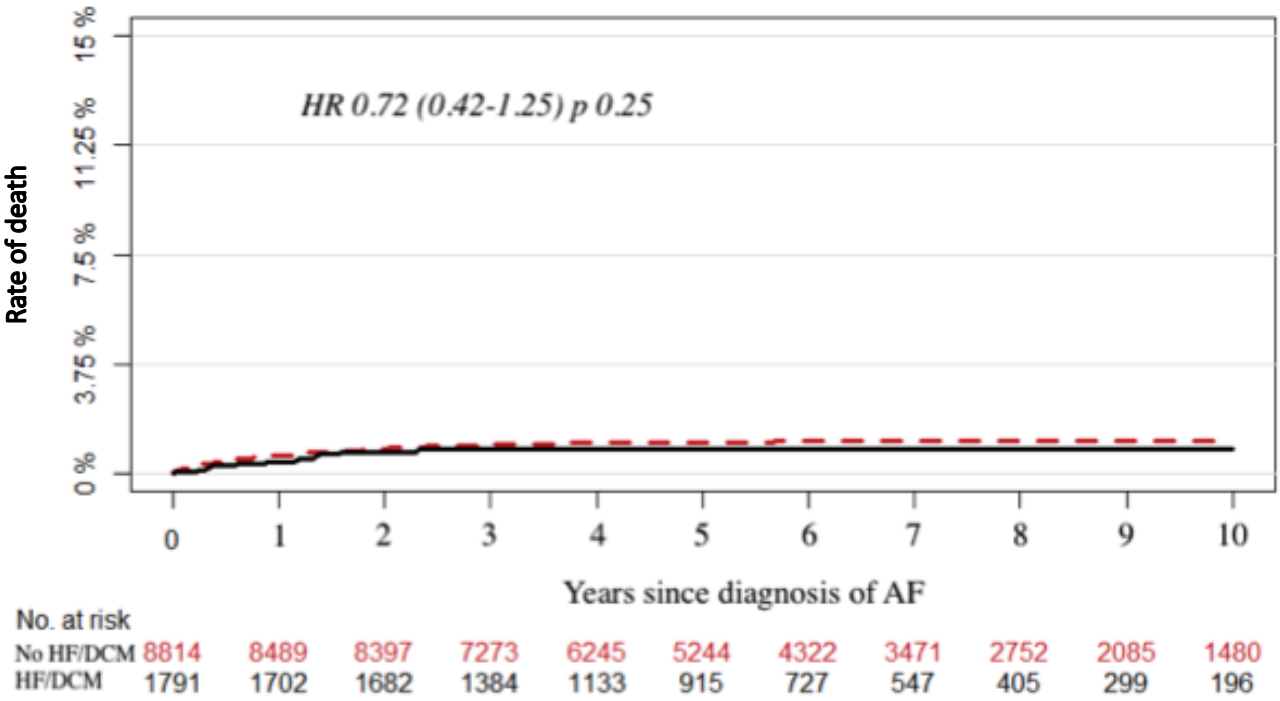
**Figure S2. Cumulative incidence and hazard ratios with a 10-year follow-up.**



**a)**


HR 1.47 (1.22-1.77) p <0.001
Rate of HF
0 %
3.75 %
7.5 %
11.25 %
15 %
0
1
2
3
4
5
6
7
8
9
10
Years since diagnosis of AF
No. at risk
No HF/DCM 8814 8489 8397 7273 6245 5244 4322 3471 2752 2085 1480
HF/DCM 1791 1702 1682 1384 1133 915 727 547 405 299 196

**b)**




| No. at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| No HF/DCM | 8814 | 8489 | 8397 | 7273 | 6245 | 5244 | 4322 | 3471 | 2752 | 2085 | 1480 |
| HF/DCM | 1791 | 1702 | 1682 | 1384 | 1133 | 915 | 727 | 547 | 405 | 299 | 196 |