Supplemental Material

Life-years lost after incident atrial fibrillation in heart failure

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1. METHODS

Supplemental Table 1. Definition of atrial fibrillation (or atrial flutter).

Characteristics	Primary source	Secondary source	ICD-8	ICD-10	ATC	Time window prior to matching date
Atrial fibrillation (or flutter)	Danish National Patient Registry	-	42793 42794	I48	-	Ever

Abbreviations: ATC = Anatomical Therapeutic Chemical classification

1. METHODS

Supplemental Table 2. Definitions of covariates and data sources.

Characteristics	Primary source	Secondary source	ICD-8	ICD-10	ATC	Time window prior to matching date
Elevated alcohol consumption	DHR	-	-	-	-	-
Smoking status	DHR	-	-	-	-	-
LVEF	DHR		-	-	-	-
NYHA class	DHR	-	-	-	-	-
Myocardial infarction	DNPR	-	410	I21 I22 I23	-	Ever
Any stroke/transient ischemic attack	DNPR	-	430 431 433 434 436 43509 43599	I60 I61 I62 I63 I64 G45	-	Ever
Diabetes mellitus*	DNPR	-	249 250	E100 E101 E109 E110 E111 E119	A10	ICD: ever ATC: 6 months
Chronic obstructive pulmonary disease	DNPR	-	-	J44	-	Ever
Hypertension**	DHR	DNPR	400 401 402 403 404	I10 I11 I12 I13 I15	Classes of antihypertensive drugs: *α adrenergic blockers:* C02A; C02B; C02C *Non-loop diuretics:* C02DA; C02L; C03A; C03B; C03D; C03E; C03X; C07B; C07C; C07D; C08G; C09BA; C09DA; C09XA52 *Vasodilators:* C02DB; C02DD; C02DG; C04; C05 *β blockers:* C07 *Calcium channel blockers:* C08; C09BB; C09DB *Renin-angiotensin system inhibitors:* C09	ICD: ever for missing data, since date of HF diagnosis for non-hypertensive patients. ATC: 6 months
Chronic kidney disease	DNPR	-	-	E102 E112 E142 I120	-	ICD: ever

			I131 I132 I150 I151 N03 N05 N06 N07 N08 N110 N14 N15 N16 N18 N19 N26 N27 N280 N391 Q61			
Overweight/obesity	DNPR	-	277	E66	-	ICD: ever
Any type of cancer except nonmelanoma skin cancer	DNPR	-	140-194 except 172, 173.09-173.49, 173.60-173.61, and 173.69-99	C00-C96, except C44	-	ICD: ever
Stroke/systemic embolism/transient ischemic attack (CHADS-VASc)	DNPR	-	43400 43309 43409 43499 43601 43690 43509 43599	I61 I64 I74 G45	-	ICD: ever
Vascular disease (CHADS-VASc)	DNPR	-	440 441 442 443 444 445	I21 I23 I702 I703 I704 I705 I706 I707 I708 I709 I739 I71 I700	-	ICD: ever
ACE inhibitors	PR	-	-	-	C09	6 months
Beta-blockers	PR	-	-	-	C07	6 months
MRAs	PR	-	-	-	C03DA	6 months
Oral anticoagulants***	PR	-	-	-	B01AA, B01AA03, B01AA04, B01AF01, B01AX06, B01AF02, B01AE07	6 months
Antiplatelet drugs***	PR	-	-	-	B01AC06, N02BA01, B01AC04, B01AC22, B01AC24,	6 months

					B01AC07, B01AC30	

Abbreviations: ATC = Anatomical Therapeutic Chemical classification; DHR = The Danish Heart Failure Registry; DNPR = The Danish National Patient Registry; The Danish National Prescription Registry = PR; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; ACE = angiotensin-converting enzyme; MRA = and mineralocorticoid receptor antagonists

*ICD code or ATC code

**Among patients without hypertension or missing in the DHR, we update the variable using DNPR, including an ICD code or at least 2 types of medication.

***Use of antithrombotic drugs after the matching day was defined as at least 1 prescription within the 6 following months.

We searched for comorbidities using diagnosis codes in the National Patient Registry since a patient's first-ever inpatient or outpatient visit up until the day before the index date. We did not account for the index date because cases, but not referents, were at a higher risk of having comorbidity diagnoses on the day of AF diagnosis due to the hospital contact. All patients had ≥5 years of exposure in the National Patient Registry.

Supplemental Figure 1. Sampling of cases and referents.
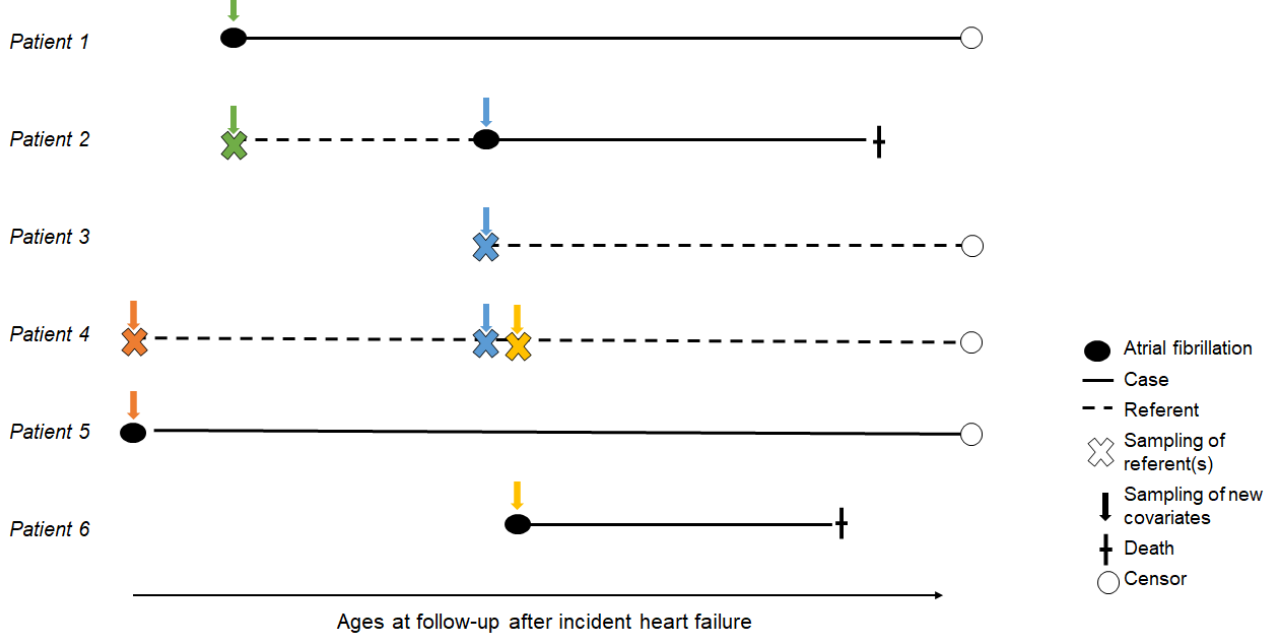
Patient 1 is AF case matched to patient 2 who is referent. Patient 2 later becomes AF case and is matched to patient 3 and 4. Patient 4 serves as a referent for patient 2, 5, and 6 at different index ages.

Supplemental Figure 2. Flowchart.

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┌─────────────────────────────┐
│ The Danish Heart Failure    │
│ Registry, 2008-2018         │
│ N=41,998                    │
└─────────────────────────────┘
           │
           │      ┌─────────────────────────────────────┐
           ├─────▶│ Missing civil registration number   │
           │      │ N=50                                │
           │      └─────────────────────────────────────┘
           │      ┌─────────────────────────────────────┐
           ├─────▶│ Registered as dead on the same day as│
           │      │ diagnosis of HF or before           │
           │      │ N=58                                │
           │      └─────────────────────────────────────┘
           │      ┌─────────────────────────────────────┐
           ├─────▶│ Danish residency for less than 5 years│
           │      │ before HF                           │
           │      │ N=484                               │
           │      └─────────────────────────────────────┘
           │      ┌─────────────────────────────────────┐
           ├─────▶│ History of AF or a diagnosis on the same│
           │      │ day as HF                           │
           │      │ N=13,451                            │
           │      └─────────────────────────────────────┘
           ▼
┌─────────────────────────────┐
│ HF cohort                   │
│ N=27,947                    │
└─────────────────────────────┘
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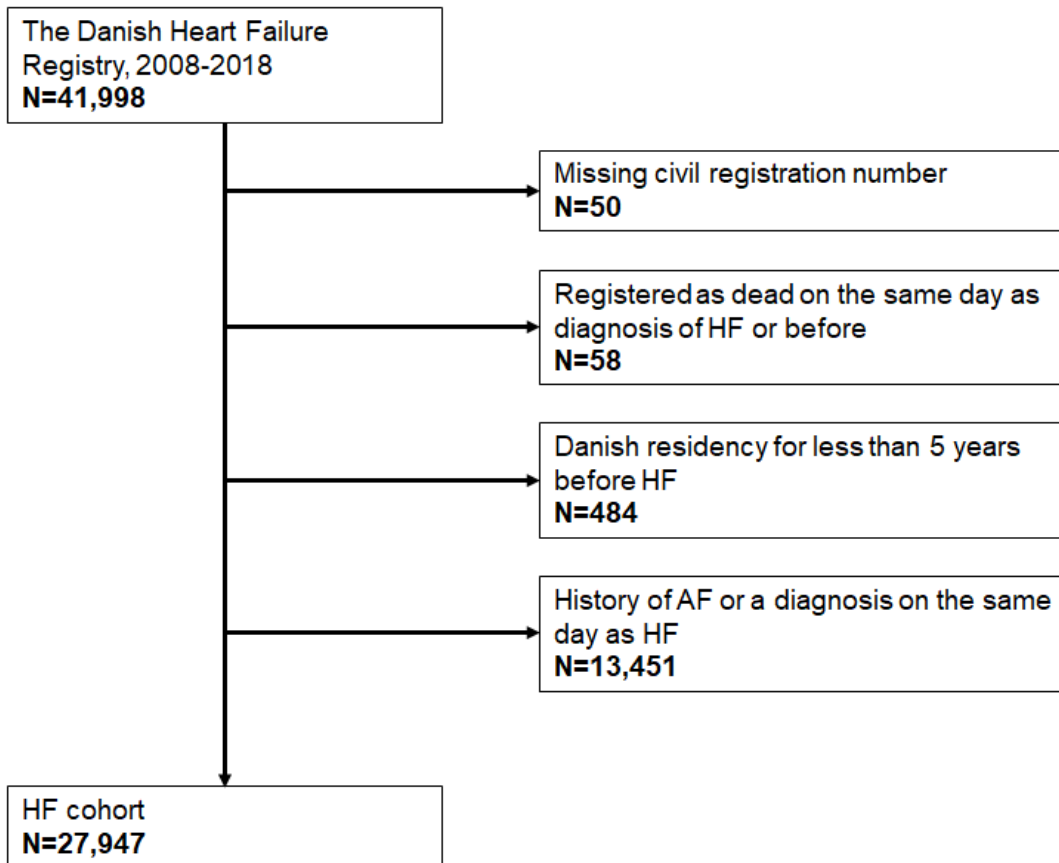
Abbreviations: HF=heart failure, AF=atrial fibrillation

We identified 27,947 HF patients with no history of AF in the DHFR from 2008 through 2018. During a median follow-up of 2.9 years, we identified 4,471 patients with an incident diagnosis of AF. The cumulative incidence of AF was 23.5% 10 years after the diagnosis of HF when accounting for the competing risk of death (Supplemental Figure 3). We excluded 8 AF cases (mean age at HF diagnosis 96.1 years; mean age at AF diagnosis 98.6 years) because no AF-free referents could be matched. The study population consisted of 4,463 AF cases and 17,792 matched referents. Of the 17,792 matched referents, 4,265 patients were selected as referent more than once and 1,455 referents later became AF case.

Supplemental Text 1. Description of data sources.

The Danish National Patient Registry was established in 1977 and contains prospectively registered information on all inpatients and after 1995 also all outpatients. Data include individual-level information on dates of admission and discharge, surgical procedures performed, and one primary and multiple secondary diagnoses per discharge. Coding of diagnoses followed the Danish version of the International Classification of Diseases 8th Revision (ICD-8) before 1994 and the 10th revision (ICD-10) from 1994 and onwards. The physician who discharged a patient coded all diagnoses for that patient. The registry provided information on comorbidities.

The Danish National Prescription Registry contains individual-level data on all dispensed prescriptions since 1994 and was used to retrieve all information on pharmacological treatments.[1] The coding of medications followed the Anatomical Therapeutic Chemical (ATC) Classification System.

The Danish Civil Registration System contains daily updated individual-level information on sex, date of birth, migration status and dates, and vital status and date of death.[2] All Danish citizens are assigned a unique 10-digit Civil Registration number that enabled linkage of data between registries.

1.   Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health*. 2011;**39**:38-41.
2.   Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull*. 2006;**53**:441-449.

Supplemental Text 2. Missing data
Variables with missing values included LVEF, NYHA class, alcohol use, and smoking status. We used multiple imputation to account for missing values in all analyses except the LVEF subgroup analysis in which patients with missing LVEF were excluded. The imputation model included case/referent status, age at HF, sex, age at matching, time since diagnosis of HF, history of acute myocardial infarction, stroke, diabetes, chronic obstructive pulmonary disease, hypertension, chronic kidney disease, cancer, use of ACE inhibitor/ARB treatment, beta-blocker, MRA, and an outcome indicator. We created 10 imputed datasets and combined the estimates with Rubin's rules. We used the mi command in Stata to perform multiple imputation.

2. CUMULATIVE INCIDENCE OF AF

Supplemental Figure 3. Cumulative incidence of AF accounting for the competing risk of death.
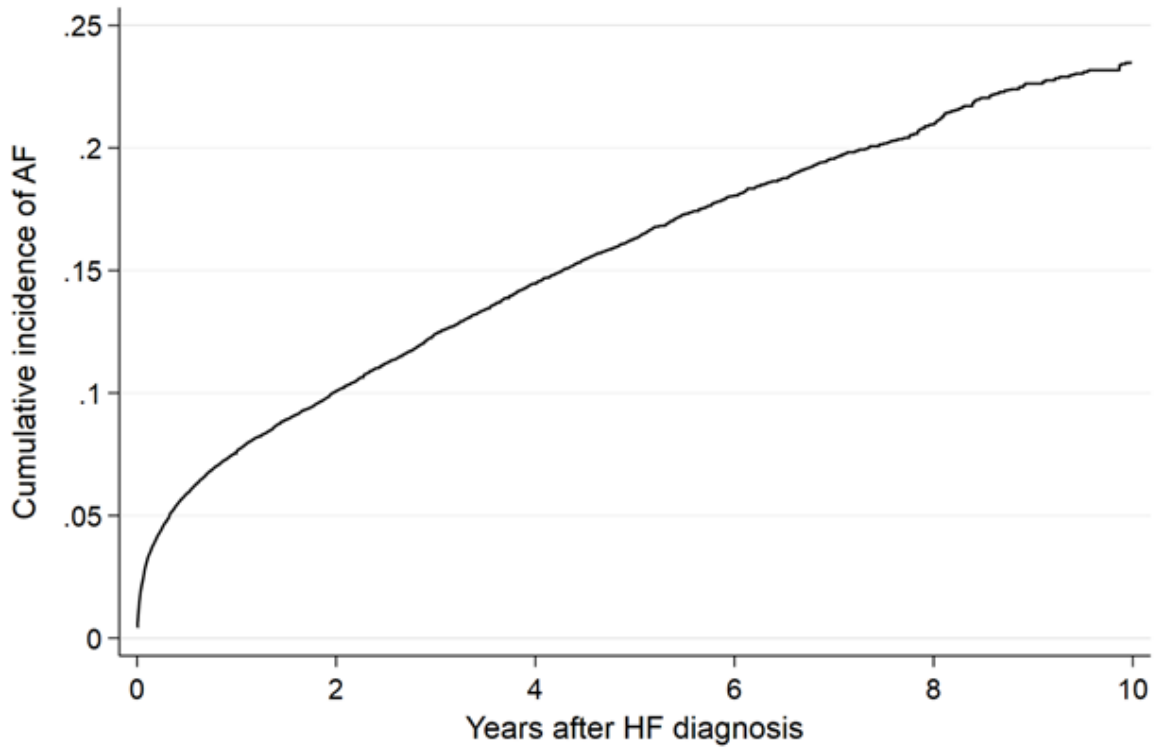
Number at risk

27947	16919	10576	5973	2671	657

3. USE OF ANTITHROMBOTIC TREATMENT AMONG CASES

Supplemental Table 3. Use of Oral anticoagulants and antithrombotic treatment among AF cases.

	AF cases N=4,463
Oral anticoagulants, N (%)	49.4 (47.9-50.8)
Antiplatelet medication, N (%)	29.1 (27.8-30.5)

Use defined as cumulative incidence of redeeming at least 1 prescription within 3 months after the diagnosis of AF. The estimates account for the competing risk of death.

3. USE OF ANTITHROMBOTIC TREATMENT AMONG CASES

4. HAZARD RATIO

Supplemental Figure 4. Hazard ratio with 95% confidence interval and time index date.
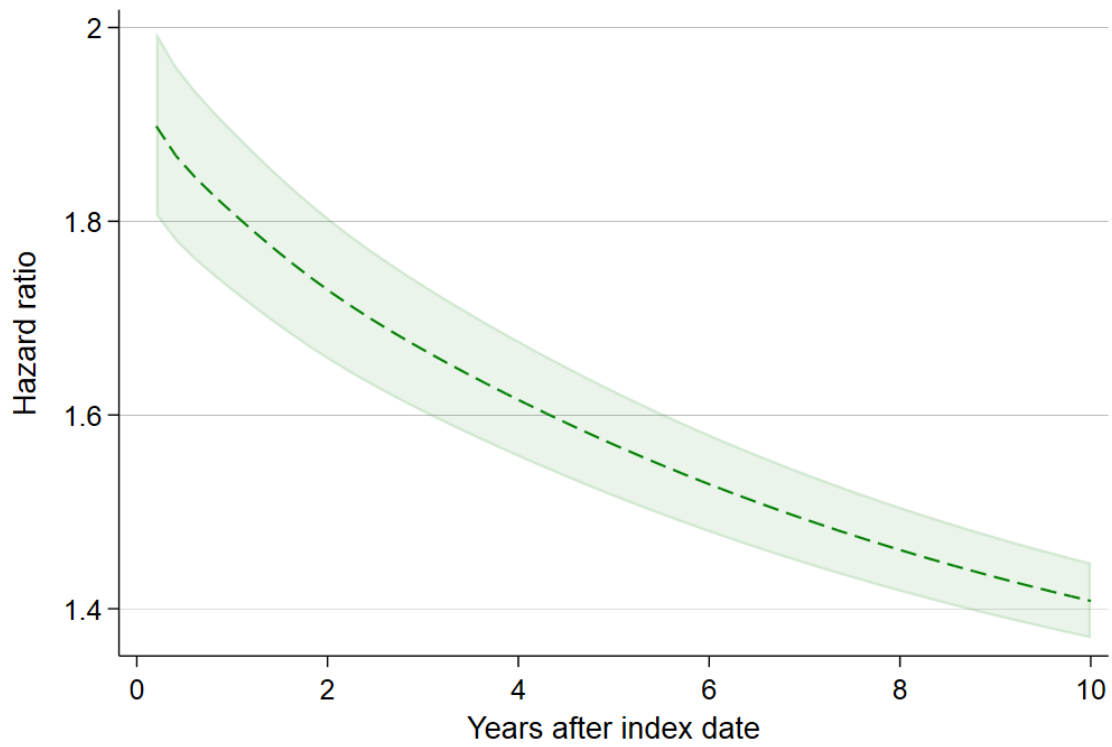
5. SUBGROUP ANALYSIS BY TIME WITH HF

Supplemental Table 4. Characteristics of HF patients with incident AF and matched referents at the index day, by time with HF.

	Time > 1 year		Time ≤ 1 year	
	AF cases N=2,384	Referents N=9,712	AF cases N=2,079	Referents N=8,080
Demographics				
Age, years, mean (SD)	74.6 (11.3)	74.6 (11.2)	72.5 (11.4)	72.5 (11.5)
Female sex	706 (29.6)	2,884 (29.7)	589 (28.3)	2,264 (28.0)
Lifestyle factors				
Elevated alcohol consumption	189 (9.4)	663 (8.0)	173 (9.7)	602 (8.7)
Smoking status				
Never	560 (26.5)	2,293 (26.0)	505 (27.0)	1,882 (25.4)
Former	991 (46.8)	4,044 (45.8)	866 (46.3)	3,486 (47.1)
Current	566 (26.7)	2,489 (28.2)	498 (26.7)	2,029 (27.4)
Clinical data				
LVEF				
<25%	478 (20.7)	1,886 (19.9)	598 (29.3)	1,768 (22.4)
25-40%	1,465 (63.3)	6,107 (64.4)	1,206 (59.1)	5,033 (63.6)
>40-49%	183 (7.9)	756 (8.0)	113 (5.5)	537 (6.8)
≥50%	188 (8.1)	736 (7.8)	123 (6.0)	573 (7.2)
NYHA class				
I	283 (13.5)	1,549 (17.5)	216 (11.7)	1,143 (15.4)
II	1,299 (62.0)	5,466 (61.9)	1,062 (57.5)	4,493 (60.7)
III/IV	513 (24.5)	1,822 (20.6)	569 (30.8)	1,770 (23.9)
Time since HF, years, median (Q1-Q3)	3.8 (2.6-5.6)	3.7 (2.5-5.5)	0.8 (0.4-1.0)	0.8 (0.4-1.0)
Age at HF diagnosis, years, mean (SD)	70.9 (11.4)	70.9 (11.3)	72.3 (11.4)	72.1 (11.4)
History of comorbidity				
Myocardial infarction	814 (34.1)	3,340 (34.4)	593 (28.5)	2,673 (33.1)
Any stroke/TIA	385 (16.2)	1,034 (10.7)	305 (14.7)	856 (10.6)
Diabetes mellitus	561 (23.5)	1,738 (17.9)	412 (19.8)	1,463 (18.1)
COPD	393 (16.5)	1,180 (12.2)	288 (13.9)	939 (11.6)
Hypertension	1,138 (47.7)	3,923 (40.4)	959 (46.1)	3,507 (43.4)
CKD	294 (12.3)	691 (7.1)	168 (8.1)	536 (6.6)
Overweight/obesity*	244 (10.2)	567 (5.8)	146 (7.0)	451 (5.6)
Cancer	363 (15.2)	1,172 (12.1)	297 (14.3)	936 (11.6)
Current HF medication**				
ACE inhibitors/ARBs	1,394 (58.5)	4,716 (48.6)	1,458 (70.1)	4,801 (59.4)
Beta-blockers	1,369 (57.4)	4,578 (47.1)	1,333 (64.1)	4,296 (53.2)
MRAs	549 (23.0)	1,611 (16.6)	510 (23.5)	1,691 (20.9)

We matched each HF patient with incident AF to up to 4 referents on age at diagnosis of HF, sex, and time since diagnosis of HF. Characteristics were collected at the time of AF diagnosis or corresponding age for referents, except alcohol consumption, smoking status, LVEF, and NYHA, which were collected at the time of HF diagnosis.

Abbreviations: AF= atrial fibrillation, LVEF= left ventricular ejection fraction, NYHA= New York Heart Association, HF= heart failure, TIA=transient ischemic attack, COPD=chronic obstructive pulmonary disease, CKD=chronic kidney disease, ACE-angiotensin converting enzyme; ARB=angiotensin receptor blocker; MRA= mineralocorticoid receptor antagonist.

Missing, N (%): alcohol consumption: 3,250 (14.6), smoking: 2,046 (9.2), LVEF: 505 (2.3), NYHA: 2,070 (9.3).
*Defined by ICD codes. **Defined as fulfilling at least 1 prescription within 6 months prior to the index date.

Supplemental Table 5. Marginal cumulative mortality and marginal restricted mean survival times, with 95% confidence intervals, by time with HF.

	Time >1 year			Time ≤ 1 year		
	1 year	5 years	10 years	1 year	5 years	10 years
Marginal cumulative mortality (%)						
HF patients with AF	21.7 (20.5-22.9)	61.8 (60.0-63.6)	83.4 (81.4-85.3)	15.4 (14.3-16.4)	46.3 (44.4-48.2)	69.0 (66.9-71.1)
HF patients without AF	9.6 (9.1-10.1)	36.4 (35.3-37.6)	61.1 (58.6-63.7)	10.9 (10.4-11.5)	36.4 (35.3-37.4)	58.7 (57.0-60.5)
Risk difference	12.1 (11.0-13.2)	25.4 (23.4-27.3)	22.2 (20.5-24.0)	4.4 (3.5-5.4)	9.9 (7.9-12.0)	10.3 (8.2-12.3)
Marginal restricted mean survival time (months)						
HF patients with AF	10.4 (10.3-10.5)	37.1 (36.3-37.9)	52.5 (50.7-54.3)	10.9 (10.8-11.0)	43.5 (42.7-44.3)	68.2 (66.3-70.0)
HF patients without AF	11.3 (11.3-11.4)	48.1 (47.7-48.5)	78.2 (76.8-79.5)	11.2 (11.2-11.3)	47.6 (47.2-.48.0)	78.5 (77.4-79.6)
Difference in RMST	-0.9 (- 0.8- -1.0)	-11.0 (-10.1- -11.9)	-25.7(-23.7- -27.7)	-0.3 (-0.3- -0.4)	-4.1 (-3.2- -5.0)	-10.4 (-8.2- -12.5)

Adjusted for characteristics in Table 1.

Supplemental Figure 5. Marginal survival curves by time with HF.
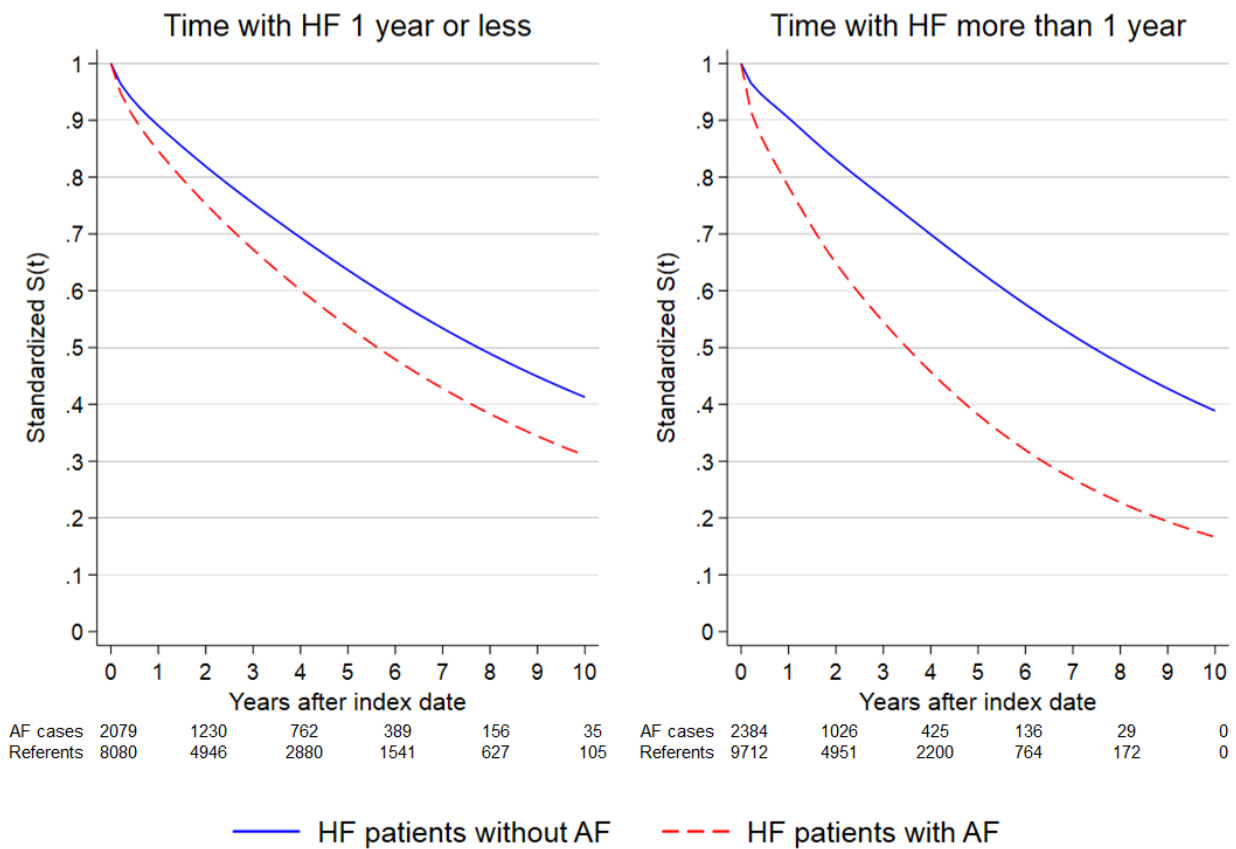
Marginal curves accounting for characteristics in Table 1.

Supplemental Figure 6. Marginal restricted mean survival times and difference between marginal restricted mean survival times, with 95% confidence interval, by time with HF

Time with HF 1 year or less

Time with HF more than 1 year
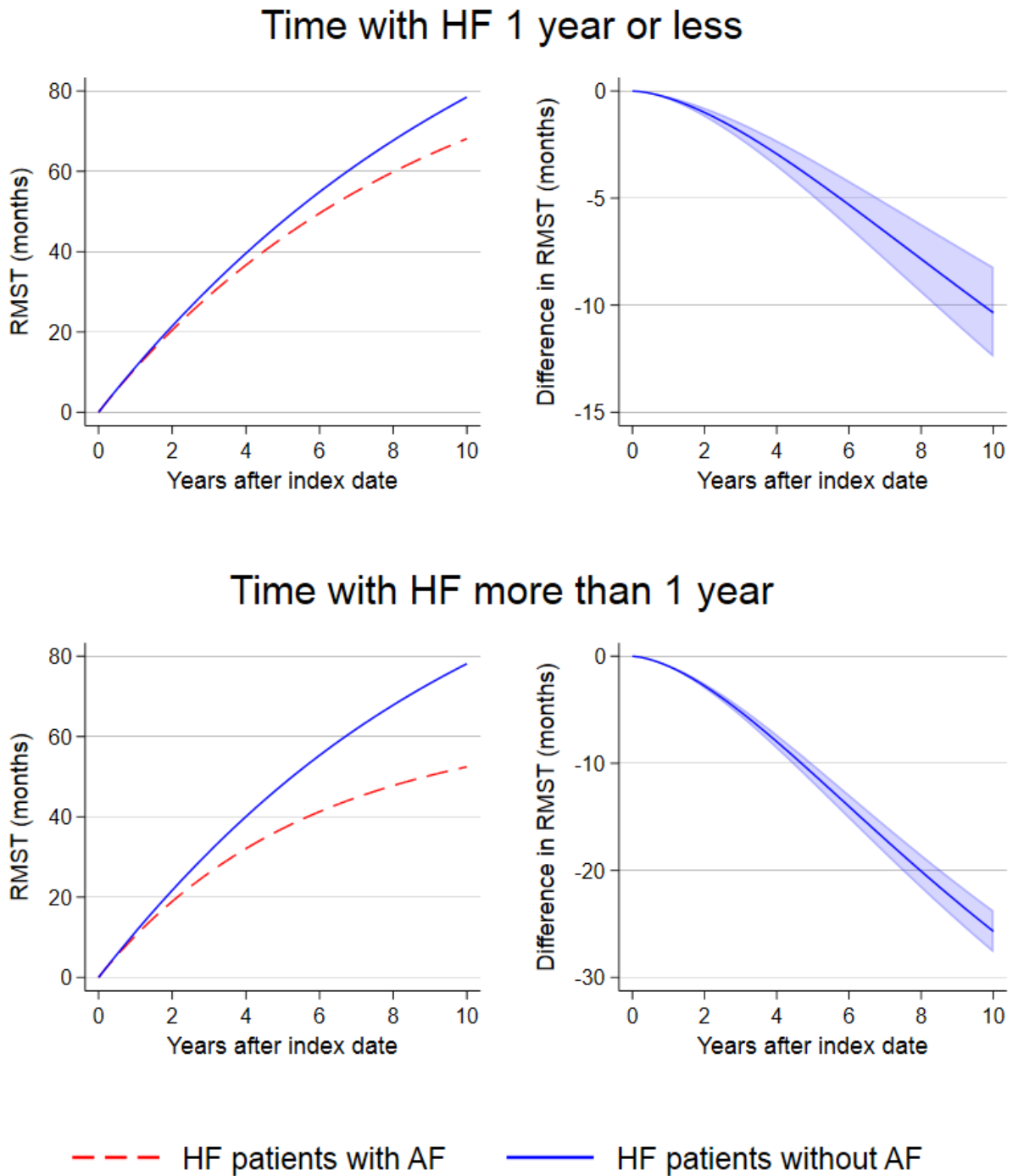
Marginal curves accounting for characteristics in Table 1.

6. SUBGROUP ANALYSIS BY SEX

Supplemental Table 6. Characteristics of HF patients with incident AF and matched referents at the index day, by sex.

	Women		Men	
	AF cases N=1,295	Referents N=5,148	AF cases N=3,168	Referents N=12,644
Demographics				
Age, years, mean (SD)	77.2 (11.3)	77.2 (11.1)	72.2 (11.1)	72.2 (11.1)
Lifestyle factors				
Elevated alcohol consumption	44 (4.1)	142 (3.3)	318 (11.6)	1,123 (10.3)
Smoking status				
Never	397 (36.2)	1,729 (37.8)	668 (23.1)	2,446 (21.0)
Former	436 (39.8)	1,715 (37.5)	1,421 (49.2)	5,815 (49.9)
Current	263 (24.0)	1,128 (24.7)	801 (27.7)	3,390 (29.1)
Clinical data				
LVEF				
<25%	258 (20.7)	1,054 (21.3)	818 (26.3)	2,600 (20.9)
25-40%	758 (60.9)	3,099 (62.7)	1,913 (61.5)	8,041 (64.6)
>40-49%	102 (8.2)	428 (8.7)	194 (6.2)	865 (7.0)
≥50%	126 (10.1)	361 (7.3)	185 (6.0)	948 (7.6)
NYHA class				
I	120 (10.9)	568 (12.5)	379 (13.3)	2,124 (18.2)
II	646 (58.8)	2,803 (61.7)	1,715 (60.3)	7,156 (61.2)
III/IV	333 (30.3)	1,170 (25.8)	749 (26.4)	2,422 (20.7)
Time since HF, years, median (Q1-Q3)	1.84 (0.84-4.04)	1.83 (0.85-4.02)	1.72 (0.81-3.91)	1.72 (0.81-3.90)
Age at HF diagnosis, years, mean (SD)	75.0 (11.3)	75.0 (11.1)	70.1 (11.2)	70.0 (11.2)
History of comorbidity				
Myocardial infarction	344 (26.6)	1,525 (29.6)	1,053 (33.2)	4,515 (35.7)
Any stroke/TIA	209 (15.8)	505 (9.9)	490 (15.5)	1,381 (10.9)
Diabetes mellitus	260 (20.1)	809 (15.7)	709 (22.4)	2,368 (18.7)
COPD	239 (18.5)	738 (14.3)	474 (15.0)	1,365 (10.8)
Hypertension	671 (51.8)	2,323 (45.1)	1,427 (45.0)	5,107 (40.4)
CKD	137 (10.6)	341 (6.6)	331 (10.5)	941 (7.2)
Overweight/obesity*	145 (11.2)	369 (7.2)	245 (7.7)	649 (5.1)
Cancer	208 (15.8)	728 (14.1)	461 (14.6)	1,371 (10.8)
Current HF medication**				
ACE inhibitors/ARBs	791 (61.1)	2,826 (54.9)	2,050 (64.7)	6,744 (53.3)
Beta-blockers	774 (57.5)	2,586 (50.2)	1,935 (61.1)	6,342 (50.2)
MRAs	282 (21.8)	968 (18.8)	754 (23.8)	2,365 (18.7)

We matched each HF patient with incident AF to up to 4 referents on age at diagnosis of HF, sex, and time since diagnosis of HF. Characteristics were collected at the time of AF diagnosis or corresponding age for referents, except alcohol consumption, smoking status, LVEF, and NYHA, which were collected at the time of HF diagnosis.

Abbreviations: AF= atrial fibrillation, LVEF= left ventricular ejection fraction, NYHA= New York Heart Association, HF= heart failure, TIA=transient ischemic attack, COPD=chronic obstructive pulmonary disease, CKD=chronic kidney disease, ACE-angiotensin converting enzyme; ARB=angiotensin receptor blocker; MRA= mineralocorticoid receptor antagonist.

Missing, N (%): alcohol consumption: 3,250 (14.6), smoking: 2,046 (9.2), LVEF: 505 (2.3), NYHA: 2,070 (9.3).
*Defined by ICD codes. **Defined as fulfilling at least 1 prescription within 6 months prior to the index date.

Supplemental Table 7. Marginal cumulative mortality and marginal restricted mean survival times, with 95% confidence intervals, by sex.

	Women			Men		
	1 year	5 years	10 years	1 year	5 years	10 years
Marginal cumulative mortality (%)						
HF patients with AF	21.5 (19.9-23.1)	60.3 (57.9-62.6)	83.2 (81.0-85.4)	17.2 (16.2-18.1)	51.5 (50.0-53.1)	73.6 (71.7-75.4)
HF patients without AF	11.5 (10.8-12.3)	40.1 (38.6-41.6)	66.5 (63.9-69.1)	9.8 (9.3-10.2)	34.9 (34.0-35.8)	56.8 (55.0-58.6)
Risk difference	9.9 (8.4-11.4)	20.2 (17.6-22.8)	16.7 (14.6-18.9)	7.4 (6.5-8.2)	16.6 (14.9-18.3)	16.8 (15.2-18.4)
Marginal restricted mean survival time (months)						
HF patients with AF	10.4 (10.3-10.5)	37.6 (36.5-38.7)	53.4 (51.2-55.7)	10.8 (10.7-10.8)	41.4 (40.8-42.1)	63.1 (61.5-64.6)
HF patients without AF	11.2 (11.1-11.2)	46.4 (45.9-47.0)	73.7 (72.2-75.3)	11.3 (11.3-11.4)	48.3 (48.0-48.7)	80.3 (79.3-81.3)
Difference in RMST	-0.8 (-0.7- -0.9)	-8.8 (-7.6- -10.0)	-20.3 (-17.7- -21.9)	-0.6 (-0.5- -0.6)	-6.9 (-6.2- -7.6)	-17.2 (-15.5- -19.0)

Adjusted for characteristics in Table 1.

Supplemental Figure 7. Marginal survival curves by sex.

	Women					
AF cases	1295	603	315	134	50	11
Referents	5148	2817	1437	652	245	30

	Men					
AF cases	3168	1653	872	391	135	24
Referents	12644	7080	3643	1653	554	75

——— HF patients without AF   - - - HF patients with AF
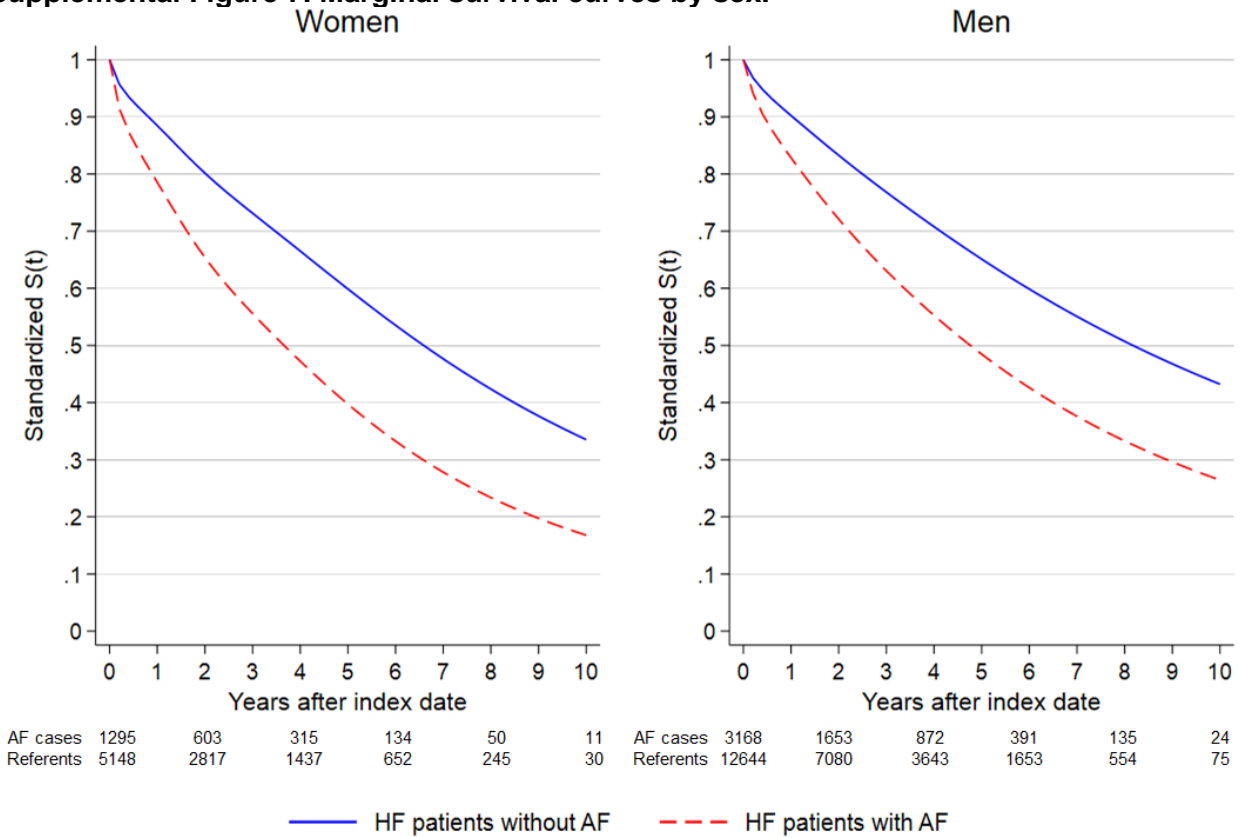
Marginal curves accounting for characteristics in Table 1.

Supplemental Figure 8. Marginal restricted mean survival times and difference between marginal restricted mean survival times, with 95% confidence interval, by sex

Women

Men
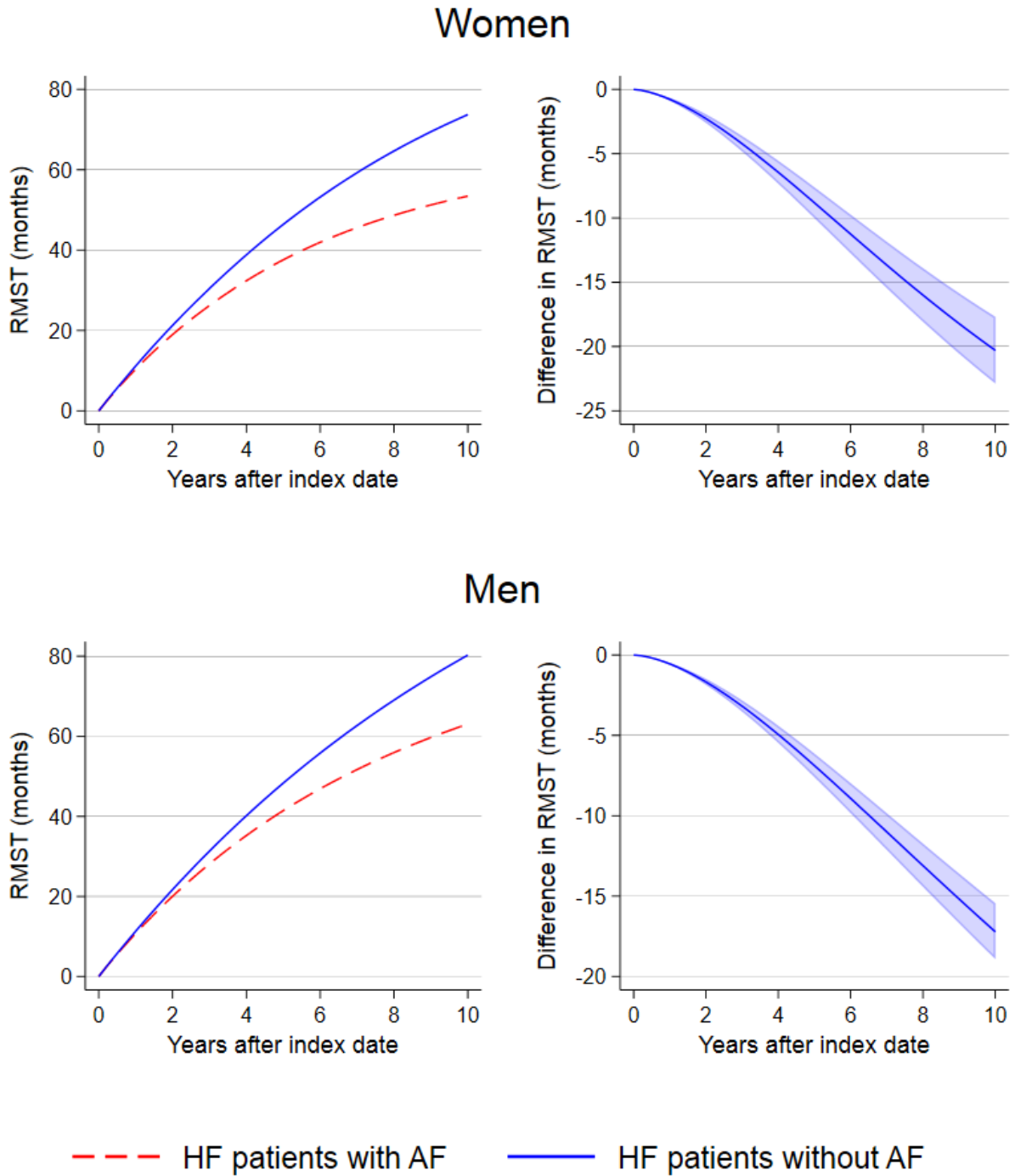
Marginal curves accounting for characteristics in Table 1.

7. SUBGROUP ANALYSIS BY AGE (≥/< 75 YEARS)

Supplemental Table 8. Characteristics of HF patients with incident AF and matched referents at the index day, by age group.

	Age <75 years		Age ≥75 years	
	AF cases N=2,588	Referents N=10,328	AF cases N=1,875	Referents N=7,464
Demographics				
Female sex	573 (22.1)	2,280 (22.1)	722 (38.5)	2,868 (38.4)
Lifestyle factors				
Elevated alcohol consumption	292 (13.1)	983 (11.0)	70 (4.5)	282 (4.5)
Smoking status				
Never	590 (24.9)	2,204 (23.0)	475 (29.4)	1,971 (29.6)
Former	995 (42.0)	4,064 (42.5)	862 (53.3)	3,466 (52.1)
Current	784 (33.1)	3,305 (34.5)	280 (17.3)	1,213 (18.2)
Clinical data				
LVEF				
<25%	719 (28.2)	2,247 (22.0)	357 (19.8)	1,407 (19.6)
25-40%	1,513 (59.2)	6,415 (62.8)	1,158 (64.3)	4,725 (65.8)
>40-49%	169 (6.6)	796 (7.8)	127 (7.1)	497 (6.9)
≥50%	153 (6.0)	760 (7.4)	158 (8.8)	549 (7.7)
NYHA class				
I	333 (14.3)	1,891 (19.7)	166 (10.3)	801 (12.3)
II	1,429 (61.2)	5,921 (61.6)	932 (58.0)	4,038 (60.8)
III/IV	573 (24.5)	1,794 (18.7)	509 (31.7)	1,798 (27.1)
Time since HF, years, median (Q1-Q3)	1.95 (0.84-4.47)	1.95 (0.84-4.46)	1.56 (0.78-3.34)	1.55 (0.78-3.31)
Age at HF, years, mean (SD)	64.0 (8.6)	64.0 (8.6)	81.9 (4.8)	81.8 (4.8)
History of comorbidity				
Myocardial infarction	632 (33.7)	2,412 (32.3)	632 (33.7)	2,412 (32.3)
Any stroke/TIA	364 (14.1)	963 (9.3)	330 (17.6)	926 (12.4)
Diabetes mellitus	632 (24.4)	2,044 (19.8)	337 (18.0)	1,133 (15.2)
COPD	388 (15.0)	1,129 (10.9)	325 (17.3)	974 (13.1)
Hypertension	1,140 (44.1)	3,995 (38.7)	958 (51.1)	3,435 (46.0)
CKD	264 (10.2)	637 (6.2)	204 (10.9)	618 (8.3)

Overweight/obesity*	293 (11.3)	768 (7.4)	97 (5.2)	250 (3.4)
Cancer	346 (13.4)	1,040 (10.1)	319 (17.0)	1,059 (14.2)
Current HF medication				
ACE inhibitors/ARBs	1,749 (67.6)	6,060 (58.7)	1,092 (58.2)	3,510 (47.0)
Beta-blockers	1,637 (63.3)	5,675 (55.0)	1,042 (55.6)	3,253 (43.6)
MRAs	681 (26.3)	2,240 (21.7)	355 (18.9)	1,093 (14.6)

We matched each HF patient with incident AF to up to 4 referents on age at diagnosis of HF, sex, and time since diagnosis of HF. Characteristics were collected at the time of AF diagnosis or corresponding age for referents, except alcohol consumption, smoking status, LVEF, and NYHA, which were collected at the time of HF diagnosis.

Abbreviations: AF= atrial fibrillation, LVEF= left ventricular ejection fraction, NYHA= New York Heart Association, HF= heart failure, TIA=transient ischemic attack, COPD=chronic obstructive pulmonary disease, CKD=chronic kidney disease, ACE-angiotensin converting enzyme; ARB=angiotensin receptor blocker; MRA= mineralocorticoid receptor antagonist.

Missing, N (%): alcohol consumption: 3,250 (14.6), smoking: 2,046 (9.2), LVEF: 505 (2.3), NYHA: 2,070 (9.3).

*Defined by ICD codes.

**Defined as fulfilling at least 1 prescription within 6 months prior to the index date.

Supplemental Table 9. Marginal cumulative mortality and restricted mean survival times, with 95% confidence interval, by age.

	Age <75 years			Age ≥75 years		
	1 year	5 years	10 years	1 year	5 years	10 years
Marginal cumulative mortality (%)						
HF patients with AF	11.5 (10.6-12.4)	39.0 (37.0-41.0)	62.5 (59.6-65.4)	27.9 (26.4-29.5)	75.2 (73.3-77.1)	94.7 (93.5-95.8)
HF patients without AF	5.9 (5.5-6.3)	22.6 (21.6-23.6)	40.7 (38.5-42.9)	16.4 (15.7-17.2)	54.6 (53.2-55.9)	81.7 (79-8-83.7)
Risk difference	5.6 (4.8-6.4)	16.4 (14.3-18.5)	21.8 (19.3-24.4)	11.5 (10.0-12.9)	20.6 (18.4-22.8)	12.9 (11.4-14.5)
Marginal restricted mean survival time (months)						
HF patients with AF	11.2 (11.1-11.2)	46.7 (46.0-47.5)	75.7 (73.7-77.7)	10.0 (9.8-10.1)	31.3 (30.3-32.4)	39.0 (37.2-40.8)
HF patients without AF	11.6 (11.5-11.6)	52.7 (52.4-53.0)	93.5 (92.4-94.6)	10.8 (10.8-10.9)	41.0 (41.5-41.6)	59.1 (57.8-60.4)
Difference in RMST	-0.4 (-0.4- -0.5)	-6.0 (-5.2- -6.8)	-17.8 (-15.6- -20.0)	-0.9 (-0.8- -1.0)	-0.7 (-8.6- -10.8)	-20.1 (-17.9- -22.2)

Adjusted for characteristics in Table 1.

Supplemental Figure 9. Marginal survival curves by age group at matching.
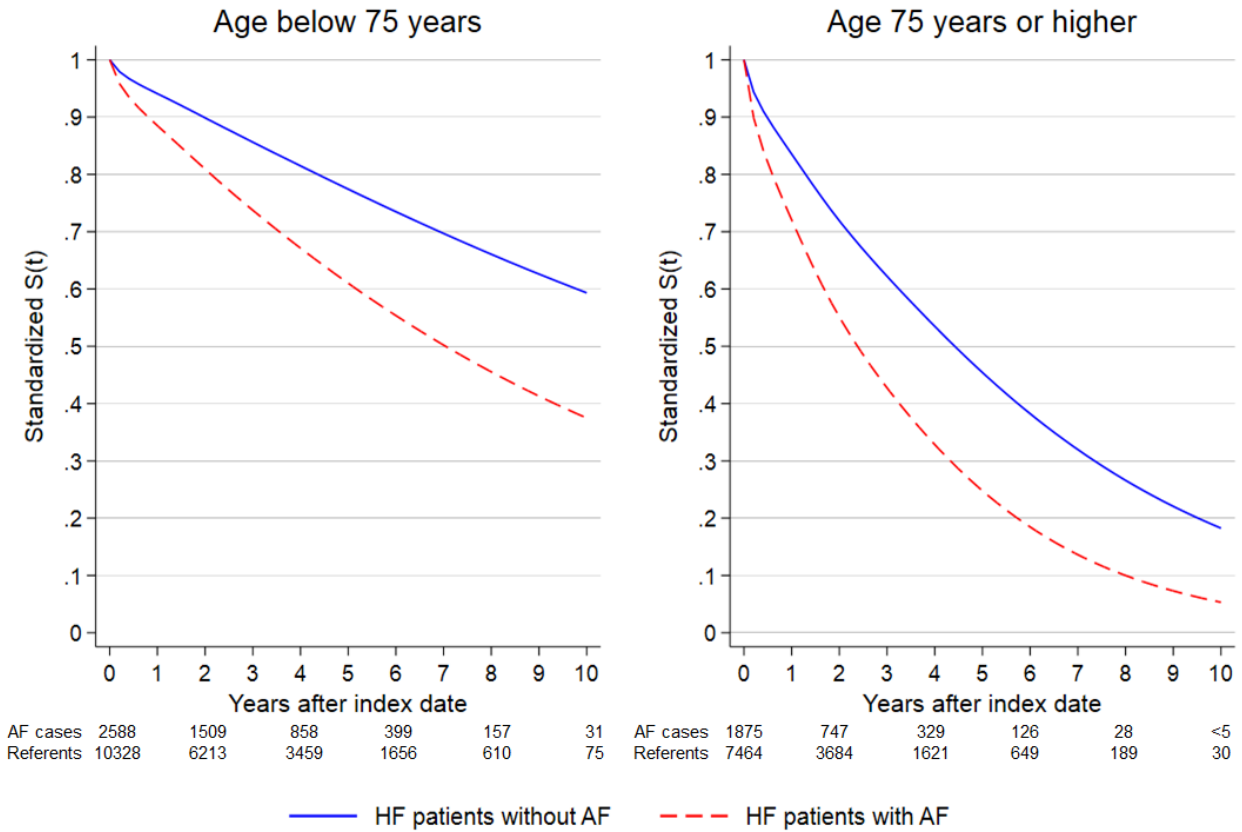
Marginal curves accounting for characteristics in Table 1.

Supplemental Figure 10. Marginal restricted mean survival times and difference between marginal restricted mean survival times, with 95% confidence interval, by age group at matching.

Age below 75 years

Age 75 years or higher

– – – HF patients with AF ——— HF patients without AF
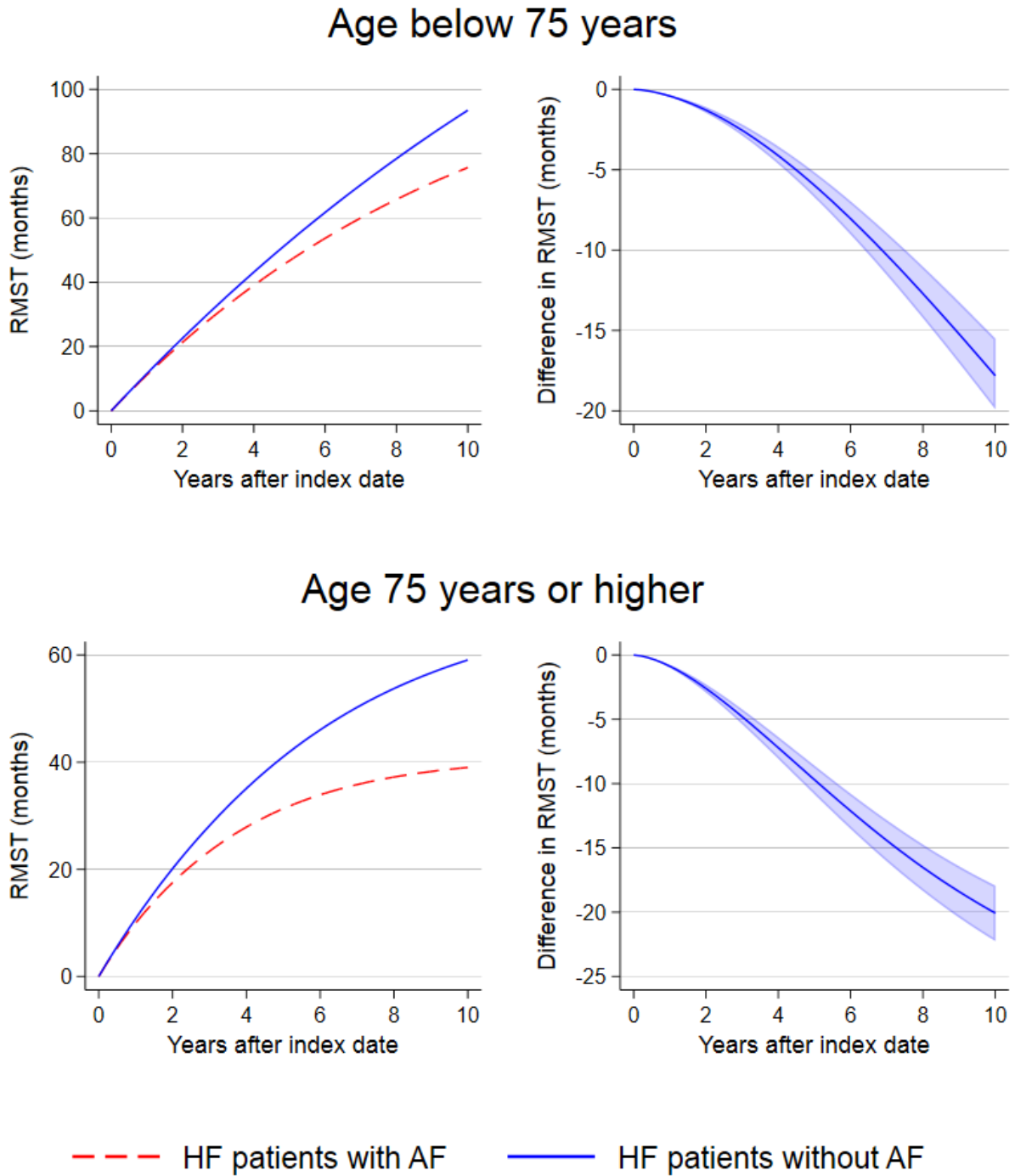
Adjusted for characteristics in Table 1.

8. SUBGROUP ANALYSIS BY LVEF (HFREF, HFMREF, AND HFPEF)

Supplemental Table 10. Characteristics of HF patients with incident AF and matched referents at the index day, by LVEF.

	LVEF ≤40%		LVEF >40-49%		LVEF ≥50%	
	AF cases N= 3,747	Referents N=14,930	AF cases N=286	Referents N=1,082	AF cases N= 305	Referents N=1,123
Demographics						
Age, years, mean (SD)	73.1 (11.4)	73.1 (11.3)	74.7 (10.4)	74.2 (10.1)	76.0 (11.1)	75.8 (10.3)
Female sex	1,016 (27.1)	4,031 (27.0)	95 (33.2)	347 (32.1)	123 (40.3)	426 (37.9)
Lifestyle factors						
Elevated alcohol consumption	324 (10.0)	1,087 (8.4)	22 (9.1)	68 (7.5)	12 (4.9)	64 (6.9)
Smoking status						
Never	894 (26.4)	3,466 (25.2)	66 (26.5)	263 (26.7)	79 (30.2)	248 (25.2)
Former	1,556 (46.0)	6,209 (45.1)	130 (52.2)	452 (45.9)	127 (48.5)	490 (49.9)
Current	937 (27.7)	4,090 (29.7)	53 (21.3)	269 (27.3)	56 (21.4)	245 (24.9)
Clinical data						
NYHA class						
I	410 (12.0)	2,160 (15.5)	38 (16.9)	230 (25.1)	79 (30.2)	234 (24.0)
II	2,065 (60.2)	8,714 (62.4)	151 (67.1)	565 (61.6)	127 (48.5)	499 (51.2)
III/IV	957 (27.9)	3,103 (22.2)	36 (16.0)	122 (13.3)	56 (21.4)	242 (24.8)
Time since HF, years, median (Q1-Q3)	1.66 (0.80-3.83)	1.66 (0.80-3.82)	2.28 (0.96-4.41)	2.23 (0.96-4.17)	2.06 (0.92-4.34)	1.91 (0.93-4.14)
Age at HF diagnosis, years, mean (SD)	71.0 (11.4)	71.0 (11.3)	72.2 (10.6)	71.8 (10.2)	73.7 (11.2)	73.6 (10.4)
History of comorbidity						
Myocardial infarction	1,148 (30.6)	5,001 (33.5)	112 (39.2)	417 (38.5)	81 (26.6)	391 (34.8)
Any stroke/TIA	589 (15.7)	1,575 (10.6)	54 (18.9)	127 (11.7)	40 (13.1)	129 (11.5)
Diabetes mellitus	800 (21.4)	2,712 (18.2)	82 (28.7)	230 (21.3)	69 (22.6)	225 (20.0)
COPD	581 (15.5)	1,646 (11.0)	48 (16.8)	135 (12.5)	51 (16.7)	135 (12.0)
Hypertension	1,687 (45.0)	6,321 (42.3)	178 (62.2)	528 (48.8)	178 (58.4)	544 (48.4)
CKD	368 (9.8)	1,048 (7.0)	42 (14.7)	94 (8.7)	37 (12.1)	90 (8.0)
Overweight/obesity*	312 (8.3)	778 (5.2)	38 (13.3)	82 (7.6)	29 (9.5)	59 (5.3)
Cancer	554 (14.8)	1,783 (11.9)	51 (17.8)	116 (10.7)	51 (16.7)	157 (14.0)

Current HF medication**						
ACE inhibitors/ARBs	2,438 (65.1)	8,154 (54.6)	183 (64.0)	560 (51.8)	181 (59.3)	559 (49.8)
Beta-blockers	2,333 (62.3)	7,756 (52.0)	176 (61.5)	510 (47.1)	169 (55.4)	508 (45.2)
MRAs	916 (24.5)	3,092 (20.7)	52 (18.2)	120 (11.1)	55 (18.0)	128 (11.4)

We matched each HF patient with incident AF to up to 4 referents on age at diagnosis of HF, sex, time since diagnosis of HF, LVEF group. Characteristics were collected at the time of AF diagnosis or corresponding age for referents, except alcohol consumption, smoking status, LVEF, and NYHA, which were collected at the time of HF diagnosis.

Abbreviations: AF= atrial fibrillation, LVEF= left ventricular ejection fraction, NYHA= New York Heart Association, HF= heart failure, TIA=transient ischemic attack, COPD=chronic obstructive pulmonary disease, CKD=chronic kidney disease, ACE-angiotensin converting enzyme; ARB=angiotensin receptor blocker; MRA= mineralocorticoid receptor antagonist.
Missing, N (%): alcohol consumption: 2,989 (13.9), smoking: 1,851 (8.6), NYHA: 1,737 (8.1).
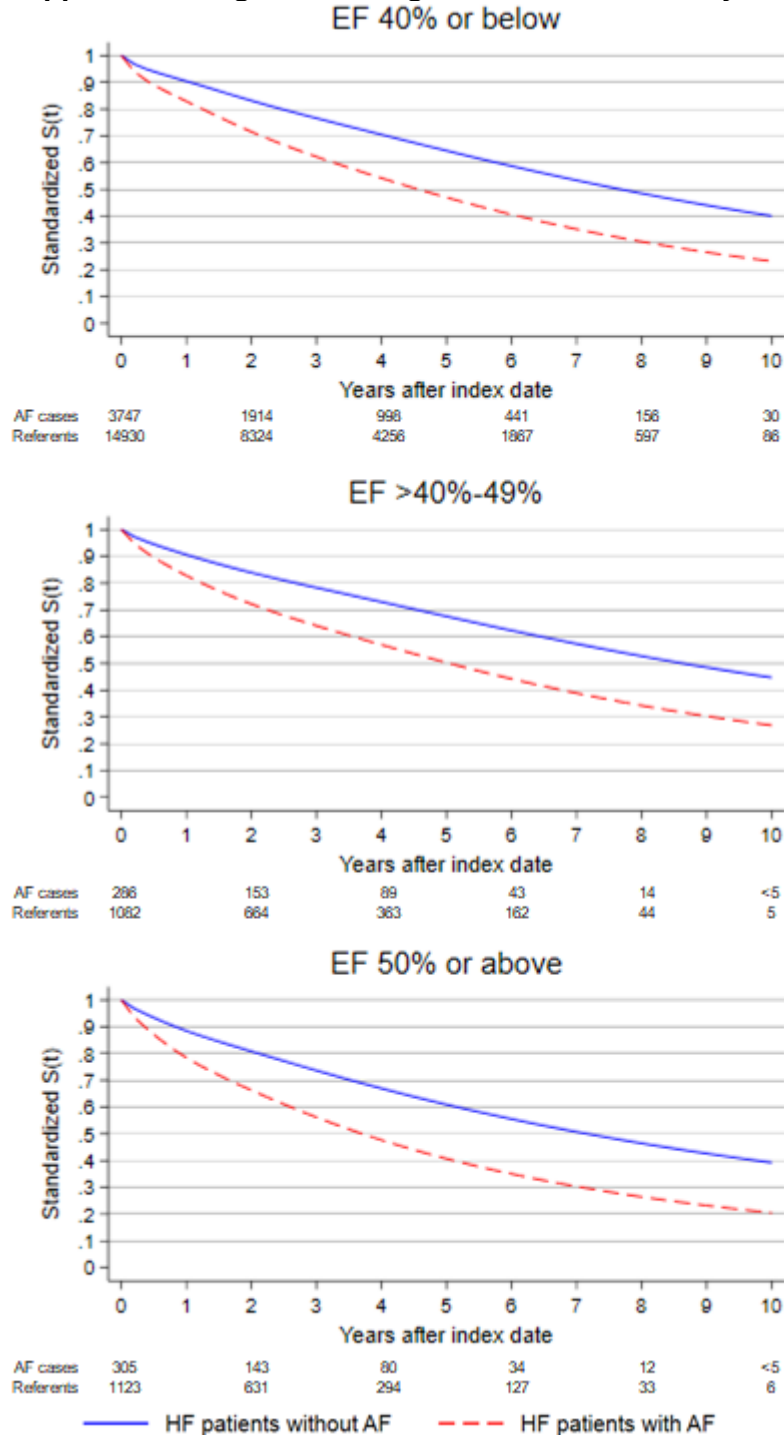*Defined by ICD codes.
**Defined as fulfilling at least 1 prescription within 6 months prior to the index date.

Supplemental Table 11. Marginal cumulative mortality and restricted mean survival times, with 95% confidence interval, by LVEF.

	LVEF ≤40%			LVEF >40-49%			LVEF ≥50%		
	1 year	5 years	10 years	1 year	5 years	10 years	1 year	5 years	10 years
Marginal cumulative mortality (%)									
HF patients with AF	17.1 (16.2-17.9)	53.0 (51.5-54.4)	76.8 (75.1-78.4)	17.2 (14.2-20.3)	49.7 (44.6-54.8)	73.1 (66.8-79.3)	48.7 (-4.7-102.1)	59.3 (54.4-64.1)	79.5 (74.2-84.7)
HF patients without AF	9.6 (9.2-10.0)	35.5 (34.6-36.4)	59.9 (58.2-61.5)	9.4 (7.9-10.9)	32.4 (29.4-35.4)	55.2 (49.2-61.3)	34.5 (-10.8-79.9)	39.1 (35.9-42.2)	60.7 (55.0-66.5)
Risk difference	7.5 (6.7-8.3)	17.5 (15.9-19.0)	16.9 (15.5-18.4)	7.8 (5.0-10.7)	17.3 (11.7-22.9)	17.8 (12.3-23.4)	14.2 (5.0-23.4)	20.2-14.8-25.6)	18.7 (13.9-23.6)
Marginal restricted mean survival time (months)									
HF patients with AF	10.8 (10.7-10.8)	31.1 (40.4-41.7)	61.2 (59.8-62.6)	10.8 (10.6-11.0)	41.9 (39.7-44.1)	64.3 (59.1-69.4)	38.8 (-16.8-94.4)	38.0 (35.8-40.2)	55.5 (50.6-60.3)
HF patients without AF	11.3 (11.3-11.4)	48.2 (47.9-48.6)	79.1 (78.2-80.0)	11.4 (11.3-11.5)	49.1 (48.0-50.2)	82.3 (79.1-85.6)	48.6 (-24.7-122.0)	46.7 (45.6-47.9)	76.2 (72.9-79.5)
Difference in RMST	-0.6 (-0.5- -0.6)	-7.2 (-6.5- -7.9)	-17.9 (1-6.3- -19.5)	-0.6 (-0.4- -0.8)	-7.1 (-4.7- -9.6)	-10.1 (-12.3- -23.9)	-9.8 (8.5- -28.2)	-8.8 (-6.3- -11.2)	-20.7 (-15.2- -26.3)

Adjusted for characteristics in Table 1.

Supplemental Figure 11. Marginal survival curves by LVEF group.

EF 40% or below

AF cases	3747	1914	998	441	156	30
Referents	14930	8324	4256	1867	597	86

EF >40%-49%

AF cases	286	153	89	43	14	<5
Referents	1082	664	363	162	44	5

EF 50% or above

AF cases	305	143	80	34	12	<5
Referents	1123	631	294	127	33	6

——— HF patients without AF   – – – HF patients with AF

Marginal curves accounting for characteristics in Table 1.

Supplemental Figure 12. Marginal restricted mean survival times and difference between marginal restricted mean survival times, with 95% confidence interval, by LVEF group.
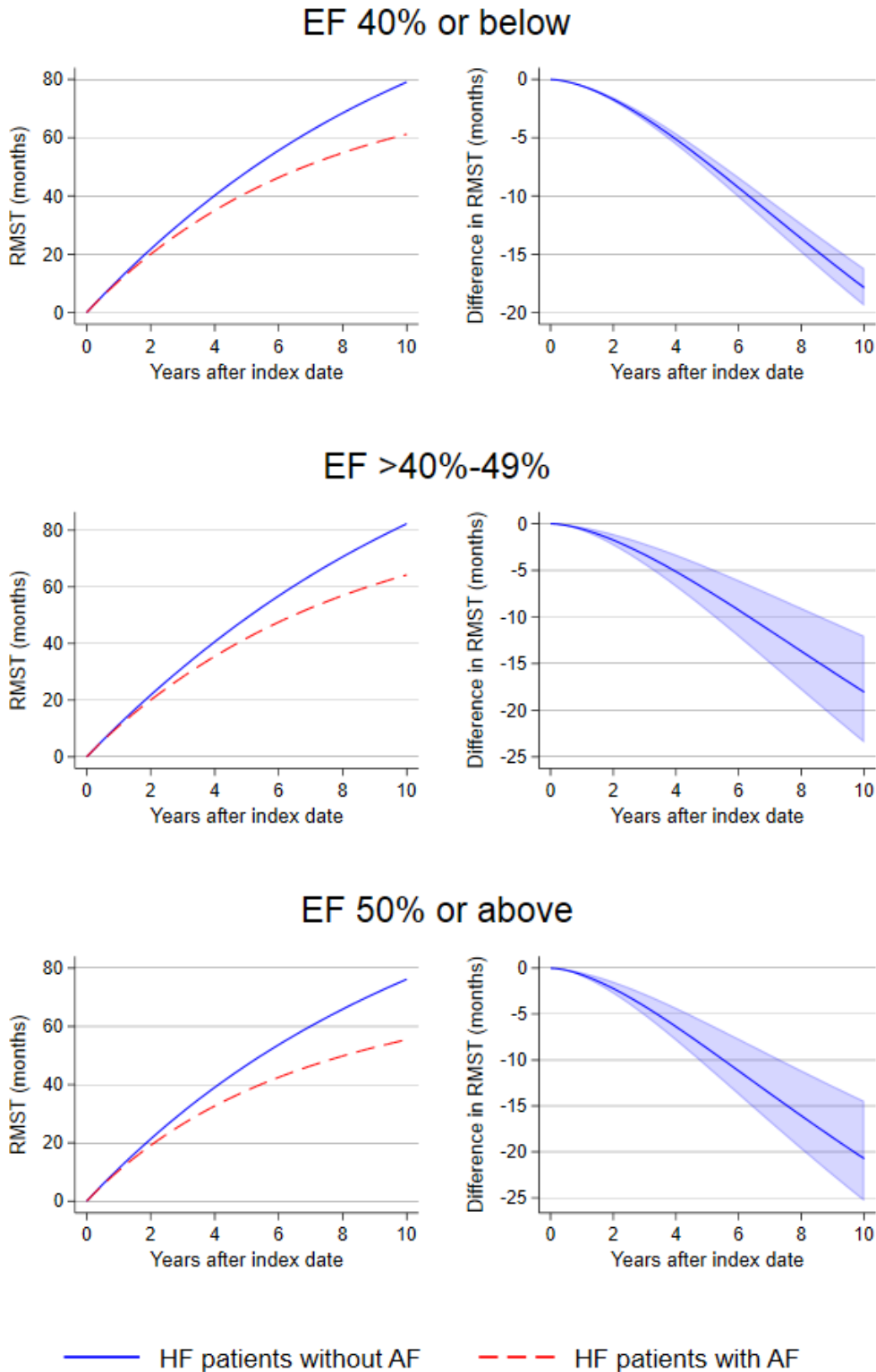
Marginal curves accounting for characteristics in Table 1.

Supplemental Table 12. Characteristics of HF patients with and without missing values of LVEF, at diagnosis of HF.

	Missing LVEF N=617	Not missing LVEF N=27,330
Demographics		
Age, years, mean (SD)	79.7 (11.6)	68.3 (13.1)
Female sex	325 (52.7)	9,072 (33.2)
Lifestyle factors		
Elevated alcohol consumption	18 (4.4)	2,169 (9.2)
Smoking status		
Never	112 (27.3)	6,404 (25.6)
Former	196 (47.8)	10,787 (43.1)
Current	102 (24.9)	7,839 (31.3)
Clinical data		
LVEF		
<25%	-	6,559 (24.0)
25-40%	-	17,047 (62.4)
>40-49%	-	1,841 (6.7)
≥50%	-	1,883 (6.9)
NYHA class		
I	37 (15.0)	4,024 (16.1)
II	102 (41.5)	15,162 (60.5)
III/IV	107 (43.5)	5,857 (23.4)
History of comorbidity		
Myocardial infarction	178 (28.9)	9,725 (35.6)
Any stroke/TIA	117 (19.0)	3,433 (12.6)
Diabetes mellitus	143 (23.2)	5,477 (20.0)
COPD	110 (17.8)	3,125 (11.4)
Hypertension	244 (39.6)	11,468 (42.0)
CKD	62 (10.1)	1,857 (6.8)
Overweight/obesity*	58 (9.4)	2,102 (7.7)
Cancer	81 (13.1)	3,704 (13.6)
Current HF medication**		
ACE inhibitors/ARBs	335 (54.3)	14,422 (52.8)

Beta-blockers	268 (32.4)	11,003 (40.3)
MRAs	91 (14.8)	2,468 (9.0)

Abbreviations: AF= atrial fibrillation, LVEF= left ventricular ejection fraction, NYHA= New York Heart Association, HF= heart failure, TIA=transient ischemic attack, COPD=chronic obstructive pulmonary disease, CKD=chronic kidney disease, ACE-angiotensin converting enzyme; ARB=angiotensin receptor blocker; MRA= mineralocorticoid receptor antagonist.

Missing, N (%): alcohol consumption: 3,864 (13.8), smoking: 2,507 (8.9), NYHA: 2,568 (9.5).

*Defined by ICD codes.

**Defined as fulfilling at least 1 prescription within 6 months prior to the HF diagnosis.

9. SUBGROUP ANALYSIS BY CHA$_2$DS$_2$-VASC

Supplemental Table 13. Characteristics of HF patients with incident AF and matched referents at the index day, by CHA$_2$DS$_2$-VASc among cases.

	Low		Medium		High	
	AF cases N=382	**Referents** N=1,520	**AF cases** N=2,959	**Referents** N=11,801	**AF cases** N= 1,122	**Referents** N=4,471
Demographics						
Age, years, mean (SD)	55.4 (7.7)	55.5 (7.7)	73.8 (10.6)	73.8 (10.5)	79.4 (7.5)	79.3 (7.5)
Female sex	84 (22.0)	328 (21.6)	838 (28.3)	3,337 (28.3)	749 (66.8)	2,988 (66.8)
Lifestyle factors						
Elevated alcohol consumption	63 (18.0)	161 (12.1)	236 (9.4)	881 (8.7)	63 (6.6)	223 (5.9)
Smoking status						
Never	127 (35.6)	354 (24.9)	704 (26.7)	2,739 (25.4)	234 (23.5)	1,082 (27.0)
Former	105 (29.4)	458 (32.2)	1,216 (46.2)	5,030 (46.2)	536 (53.9)	2,042 (50.9)
Current	125 (35.0)	609 (42.9)	715 (27.1)	3,021 (28.0)	223 (22.5)	888 (22.1)
Clinical data						
LVEF						
<25%	146 (38.3)	384 (25.5)	730 (25.4)	2,421 (21.0)	200 (18.2)	849 (19.5)
25-40%	196 (51.4)	901 (59.7)	1,750 (60.9)	7,416 (64.3)	725 (66.1)	2,823 (65.0)
>40-49%	16 (4.2)	121 (8.0)	184 (6.4)	844 (7.3)	96 (8.8)	328 (7.6)
≥50%	23 (6.0)	103 (6.8)	212 (7.4)	860 (7.5)	76 (6.9)	346 (8.0)
NYHA class						
I	61 (18.1)	300 (21.0)	352 (13.4)	1,840 (17.1)	86 (8.8)	552 (13.7)
II	201 (59.5)	880 (61.7)	1,596 (60.7)	6,595 (61.2)	564 (57.8)	2,484 (61.6)
III/IV	76 (22.5)	247 (17.3)	680 (25.9)	2,345 (21.8)	326 (33.4)	1,000 (24.8)
Time since HF, years, median (Q1-Q3)	1.16 (0.64-3.34)	1.16 (0.64-3.34)	1.79 (0.82-4.04)	1.79 (0.83-4.04)	1.91 (0.87-3.85)	1.89 (0.86-3.84)
Age at HF diagnosis, years, mean (SD)	53.7 (7.7)	53.7 (7.6)	71.7 (10.6)	71.6 (10.6)	77.2 (7.9)	77.1 (7.8)
History of comorbidity						
Myocardial infarction	0 (0)	505 (33.2)	749 (74.7)	7,880 (66.8)	654 (58.3)	1,531 (23.2)
Any stroke/TIA	15 (3.9)	111 (7.3)	199 (6.7)	1,232 (10.4)	460 (41.0)	547 (12.2)
Diabetes mellitus	0 (0)	256 (16.8)	499 (15.2)	2,087 (17.7)	514 (45.8)	797 (17.8)
COPD	31 (8.1)	113 (7.4)	411 (13.9)	1,384 (11.7)	232 (20.7)	606 (13.6)

Hypertension	0 (0)	496 (32.6)	1,226 (41.4)	4,971 (42.1)	870 (77.5)	1964 (43.9)
CKD	9 (2.4)	83 (5.5)	261 (8.8)	811 (6.9)	185 (16.5)	355 (7.9)
Overweight/obesity*	32 (8.4)	141 (9.3)	236 (8.0)	670 (5.7)	122 (10.9)	209 (4.7)
Cancer	36 (9.4)	101 (6.6)	413 (14.0)	1,408 (11.9)	202 (18.0)	577 (12.9)
Current HF medication**						
ACE inhibitors/ARBs	239 (62.6)	1,002 (65.9)	1,840 (62.2)	6,244 (52.9)	774 (69.0)	2,253 (50.4)
Beta-blockers	223 (58.4)	933 (61.4)	1,750 (59.1)	5,805 (49.2)	736 (65.6)	2,092 (46.8)
MRAs	102 (26.7)	373 (24.5)	703 (23.8)	2,174 (18.4)	256 (22.8)	773 (17.3)

We matched each HF patient with incident AF to up to 4 referents on age at diagnosis of HF, sex, time since diagnosis of HF, LVEF group. Characteristics were collected at the time of AF diagnosis or corresponding age for referents, except alcohol consumption, smoking status, LVEF, and NYHA, which were collected at the time of HF diagnosis.

CHA$_2$DS$_2$VASc groups: Low: women 1-2; men 1. Medium: women 3-5; men 2-4. High: women >5; men >4

Abbreviations: AF= atrial fibrillation, LVEF= left ventricular ejection fraction, NYHA= New York Heart Association, HF= heart failure, TIA=transient ischemic attack, COPD=chronic obstructive pulmonary disease, CKD=chronic kidney disease, ACE-angiotensin converting enzyme; ARB=angiotensin receptor blocker; MRA= mineralocorticoid receptor antagonist.
Missing, N (%): alcohol consumption: 3,250 (14.6), smoking: 2,046 (9.2), LVEF: 505 (2.3), NYHA: 2,070 (9.3).
*Defined by ICD codes.
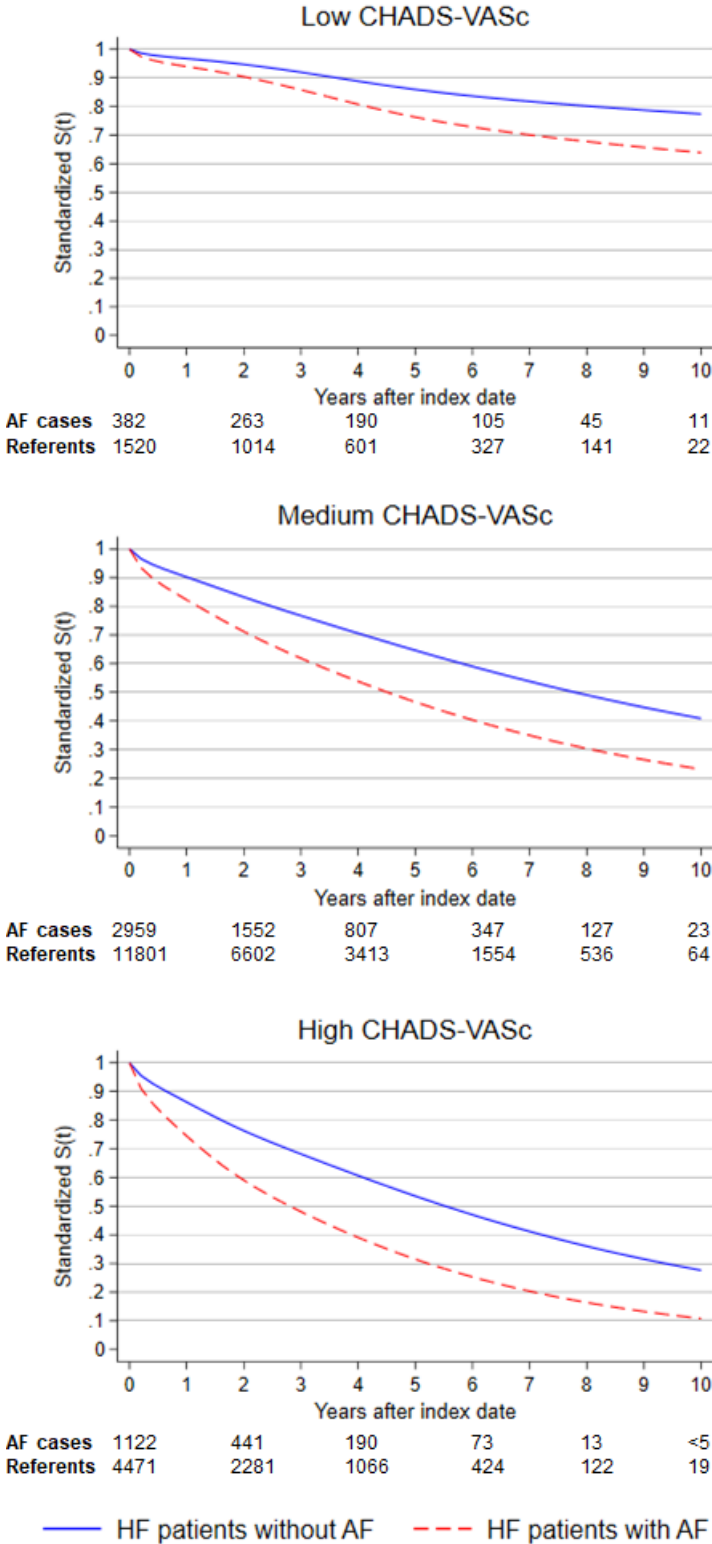**Defined as fulfilling at least 1 prescription within 6 months prior to the index date.

Supplemental Table 14. Marginal cumulative mortality and restricted mean survival times, with 95% confidence interval, by CHA$_2$DS$_2$-VASc.

|	Low			Medium			High		
	1 year	5 years	10 years	1 year	5 years	10 years	1 year	5 years	10 years
Marginal cumulative mortality (%)									
HF patients with AF	6.0 (4.2-7.9)	23.7 (18.6-28.8)	36.1 (28.6-43.6)	17.7 (16.8-18.7)	53.4 (51.7-55.0)	76.8 (75.0-78.7)	25.5 (23.5-27.5)	68.5 (65.7-71.3)	89.2 (86.9-91.4)
HF patients without AF	3.3 (2.5-4.0)	14.0 (11.9-16.2)	22.6 (18.6-26.5)	9.8 (9.3-10.3)	35.4 (34.4-36.4)	59.1 (57.3-61.0)	13.7 (12.8-14.6)	46.5 (44.8-48.2)	72.4 (69.5-75.2)
Risk difference	2.8 (1.1-4.5)	9.7 (4.3-15.1)	13.5 (6.1-20.9)	8.0 (7.0-8.9)	18.0 (16.2-19.8)	17.7 (16.0-19.4)	11.8 (9.8-13.8)	22.0 (18.8-25.2)	16.8 (14.4-19.3)
Marginal restricted mean survival time (months)									
HF patients with AF	11.5 (11.4-11.7)	52.6 (50.9-43.3)	94.2 (88.9-99.5)	10.7 (10.6-10.8)	40.8 (40.1-41.5)	60.8 (59.2-62.5)	10.2 (10.0-10.3)	34.0 (32.6-35.3)	45.5 (42.8-48.2)
HF patients without AF	11.8 (11.7-11.8)	55.8 (55.1-56.4)	104.5 (102.3-106.7)	11.3 (11.3-11.3)	48.2 (47.9-48.6)	79.3 (78.3-80.4)	11.0 (11.0-11.1)	44.0 (43.4-44.7)	67.5 (65.8-69.3)
Difference in RMST	-0.2 (-0.1- -0.4)	-3.2 (-1.4- -5.0)	-10.3 (-4.6- -16.1)	-0.6 (-0.5- -0.7)	-7.4 (-6.7- -8.2)	-18.5 (-16.7- -20.4)	-0.9 (-0.7- -1.0)	-10.1 (-8.5- -11.6)	-22.1 (-18.8- -22.3)

Adjusted for characteristics in Table 1.
CHA$_2$DS$_2$VASc groups: Low: women 1-2; men 1. Medium: women 3-5; men 2-4. High: women >5; men >4

Supplemental Figure 13. Marginal survival curves by CHA$_2$DS$_2$-VASc.

Marginal curves accounting for characteristics in Table 1. CHA$_2$DS$_2$VASc groups: Low: women 1-2; men 1. Medium: women 3-5; men 2-4. High: women >5; men >4

Supplemental Figure 14. Marginal restricted mean survival times and difference between marginal restricted mean survival times, with 95% confidence interval, by CHA$_2$DS$_2$-VASc group.
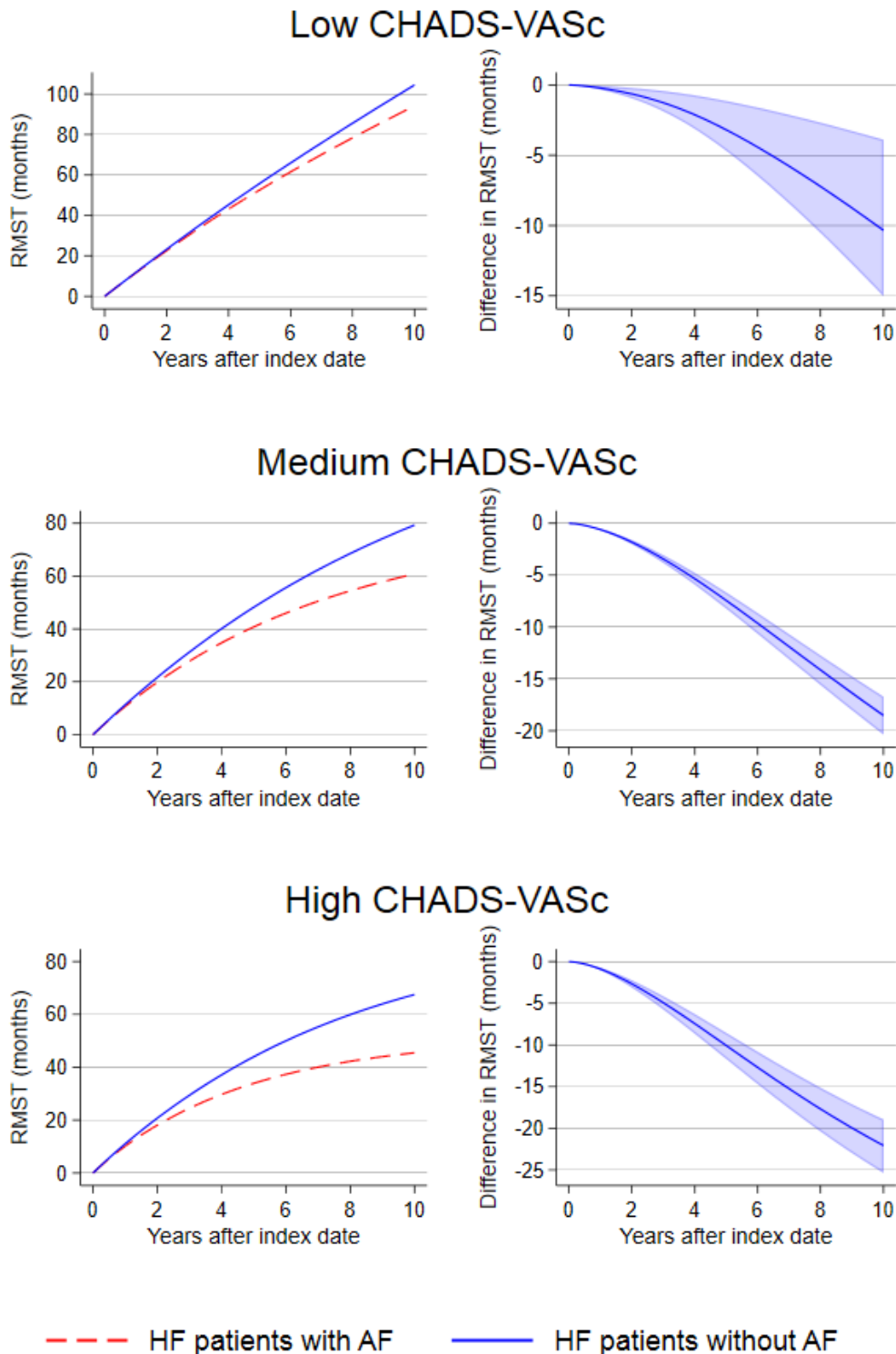
Marginal curves accounting for characteristics in Table 1. CHA$_2$DS$_2$VASc groups: Low: women 1-2; men 1. Medium: women 3-5; men 2-4. High: women >5; men >4

10. SENSITIVITY ANALYSES

Supplemental Table 15. Marginal cumulative mortality and restricted mean survival times with 95% confidence intervals, after excluding HF patients who died within 30 days after the diagnosis of HF.

	Time after index date		
	1 year	**5 years**	**10 years**
Marginal cumulative mortality (%)			
HF patients with AF	17.6 (16.8-18.4)	53.6 (52.3-54.9)	76.0 (74.5-77.5)
HF patients without AF	10.1 (9.7-10.4)	36.6 (35.8-37.4)	59.7 (58.2-61.2)
Risk difference	7.5 (6.8-8.3)	17.0 (15.5-18.4)	16.3 (15.0-17.7)
Marginal restricted mean survival time (months)			
HF patients with AF	10.7 (10.7-10.8)	40.7 (40.1-31.3)	60.9 (59.6-62.2)
HF patients without AF	11.3 (11.3-11.3)	47.8 (47.5-48.1)	78.3 (77.5-79.1)
Difference in RMST	-0.6 (-0.5- -0.6)	-7.1 (-6.5- -7.7)	-17.4 (-15.9- -18.9)

Adjusted for characteristics in Table 1.

Supplemental Table 16. Marginal cumulative mortality and restricted mean survival times with 95% confidence intervals, after excluding HF patients who died within 30 days after the diagnosis of AF.

	Time after matching day		
	1 year	**5 years**	**10 years**
Marginal cumulative mortality (%)			
HF patients with AF	14.7 (14.0-15.4)	48.1 (46.7-49.5)	71.9 (70.2-73.6)
HF patients without AF	9.5 (9.1-9.9)	35.5 (34.7-36.3)	59.1 (57.6-60.7)
Risk difference	5.2 (4.5-5.9)	12.6 (11.1-14.1)	12.8 (11.3-14.2)
Marginal restricted mean survival time (months)			
HF patients with AF	11.1 (11.0-11.1)	43.2 (42.7-43.8)	66.4 (65.1-67.8)
HF patients without AF	11.4 (11.4-11.4)	48.3 (48.9-48.6)	79.4 (78.5-80.2)
Difference in RMST	-0.3 (-0.3- -0.4)	-5.1 (-4.4- -5.7)	-12.9 (-11.4- -14.4)

Adjusted for characteristics in Table 1.