Supplemental Material

Development and validation of prediction models for incident atrial fibrillation in heart failure

Nicklas Vinter, Thomas Alexander Gerds, Pia Cordsen, Jan Brink Valentin, Gregory Y.H. Lip, Emelia J. Benjamin, Søren Paaske Johnsen, and Lars Frost

Vinter et al. Prediction models for incident AF in chronic HF

Methods

Supplemental Table 1. Diagnoses.

	ICD-10	ICD-8
Atrial fibrillation and flutter	I48	42793 42794

Vinter et al. Prediction models for incident AF in chronic HF

Supplemental Table 2. Definition of candidate predictors.

Category	Predictor	Time window	Coding	Primary source	Secondary source	ICD 10	ICD 8	Procedure code	ATC
Demographic factors	Age	At HF onset	Continuous	DHFR	-	-	-	-	-
	Sex	-	Men	DHFR	-	-	-	-	-
			Women						
	Level of education	At HF onset	Group 1	DST	-	-	-	-	-
			Group 2						
			Group 3						
Health behaviors	Elevated alcohol intake	At HF onset	W: >14 drinks/week and >7* drinks/week M: >21 drinks/week and >14* drinks/week	DHFR	-	-	-	-	-
			W: ≤14 drinks/week and ≤7 drinks per week M: ≤21* drinks/week and ≤7* drinks per week,						
	Smoking status	At HF onset	Current	DHFR	-	-	-	-	-
			Former						
			Never						
Clinical data	Left ventricular ejection fraction	Between 6 months before and 7 days after HF	≥50%	DHFR	-	-	-	-	-
			>40-49%						
			25-40%						
			<25%						
	NYHA classification	At HF onset or up to 12 weeks after	I	DHFR	-	-	-	-	-
			II						
			III/IV						

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Open Heart

Vinter et al. Prediction models for incident AF in chronic HF

Category	Predictor	Time window	Coding	Primary source	Secondary source	ICD 10	ICD 8	Procedure code	ATC
Comorbidities and health factors	Treatment for hypertension	ICD: ever for missing data, since date of heart failure diagnosis for non-hypertensive patients. ATC: 6 months	Yes/no	DHFR	NPR	I10 I11 I12 I13 I15	400 401 402 403 404	-	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
	Hypercholesterolemia	Ever before HF onset	Yes/no	NPR	-	E780	27200 27900	-	-
	Diabetes mellitus	ICD: ever ATC: 6 months	Yes/no	NPR	-	E100 E101 E109 E110 E111 E119	249 250	-	A10
	Chronic kidney disease	Ever before HF onset	Yes/no	NPR	-	E102 E112 E142 I120 I131 I132 I150 I151 N03 N05 N06 N07 N08 N110 N14 N15 N16 N18 N19 N26 N27 N280 N391 Q61	-	-	-
	Obstructive sleep apnea	Ever before HF onset	Yes/no	NPR	-	G473	-	-	-
	Chronic obstructive pulmonary disease	Ever before HF onset	Yes/no	NPR	-	J44	-	-	-
	Valvular disease	Ever before HF onset	Yes/no	NPR	-	I05-I08 I34-I37 Z952	39400-39600, 4240, 4241	KFJE, KFJF, KFG, KFK, KFM	-
	Myocardial infarction	Ever before HF onset	Yes/no	NPR	-	I21 I22 I23	410	-	-
	Peripheral artery disease	Ever before HF onset	Yes/no	PNR	-	I70 I71 I73 I74	440 441 442 443 444 445	-	-

Page **17** of **21**

Vinter et al. Prediction models for incident AF in chronic HF

Category	Predictor	Time window	Coding	Primary source	Secondary source	ICD 10	ICD 8	Procedure code	ATC
	Hyperthyroidism	ICD: At HF onset and 6 months before. ATC: AT HF onset and 6 months before.	Yes/no	NPR or DPR	-	E05 E06	24200 24208 24209 24219 24220 24228 24229	-	H03B
	Ischemic stroke	Ever before HF onset	Yes/no	NPR	-	I63 I64	433 434	-	-
	Systemic embolism	Ever before HF onset	Yes/no	NPR	-	I74	444	-	-
	Sepsis	Up 1 months before HF		NPR	-	A021 A282B A267 A327 A392 A394 A400 A401 A402 A403 A408 A409 A41 A427 A499A B377 R572	-	-	-
	Pneumonia	Up 1 months before HF	Yes/no	NPR	-	J12 J13 J14 J15 J16 J17 J18	-	-	-
	Pulmonary embolism	Up 1 months before HF	Yes/no	NPR	-	I26	-	-	-
	Acute respiratory distress syndrome	Up 1 months before HF	Yes/no	NPR	-	J809	-	-	-
	Admitted to intensive care unit	Up 1 months before HF	Yes/no	NPR	-	-	-	NABE or NABB	-
	Surgery	Up 1 months before HF	Yes/no	NPR	-	-	-	Bypass: KFNA, KFNB, KFNC, KFND, KFNE, KFNF, KFNH, KFNJ, KFNK, KFNW Valve: KFJE, KFJF, KFG, KFK, KFM Lung resection: KGDC, KGDD Esophagogastrostomy: KJCB, KJCD, KJDC40	-

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance
placed on this supplemental material which has been supplied by the author(s)

Open Heart

Vinter et al. Prediction models for incident AF in chronic HF

Category	Predictor	Time window	Coding	Primary source	Secondary source	ICD 10	ICD 8	Procedure code	ATC
	Cancer	6 months prior to diagnosis of HF	Yes/no	NPR	-	C00-C96, except C44	-	-	-
Medication**	ACE-inhibitors/ARBs	6 months prior to diagnosis of HF	Yes/no	DPR	-	-	-	-	C09
	Beta-blockers	6 months prior to diagnosis of HF	Yes/no	DPR	-	-	-	-	C07
	MRAs	6 months prior to diagnosis of HF	Yes/no	DPR	-	-	-	-	C03DA
	Statins	6 months prior to diagnosis of HF	Yes/no	DPR	-	-	-	-	C10
	Aspirin or clopidogrel	6 months prior to diagnosis of HF	Yes/no	DPR					B01AC06 B01AC04
	NSAID	6 months prior to diagnosis of HF	Yes/no	DPR					M01A

Abbreviations: DHFR= Danish Heart Failure Registry; DST= Statistics Denmark; NPR = Danish National Patient Registry; DPR=Danish Prescription Registry
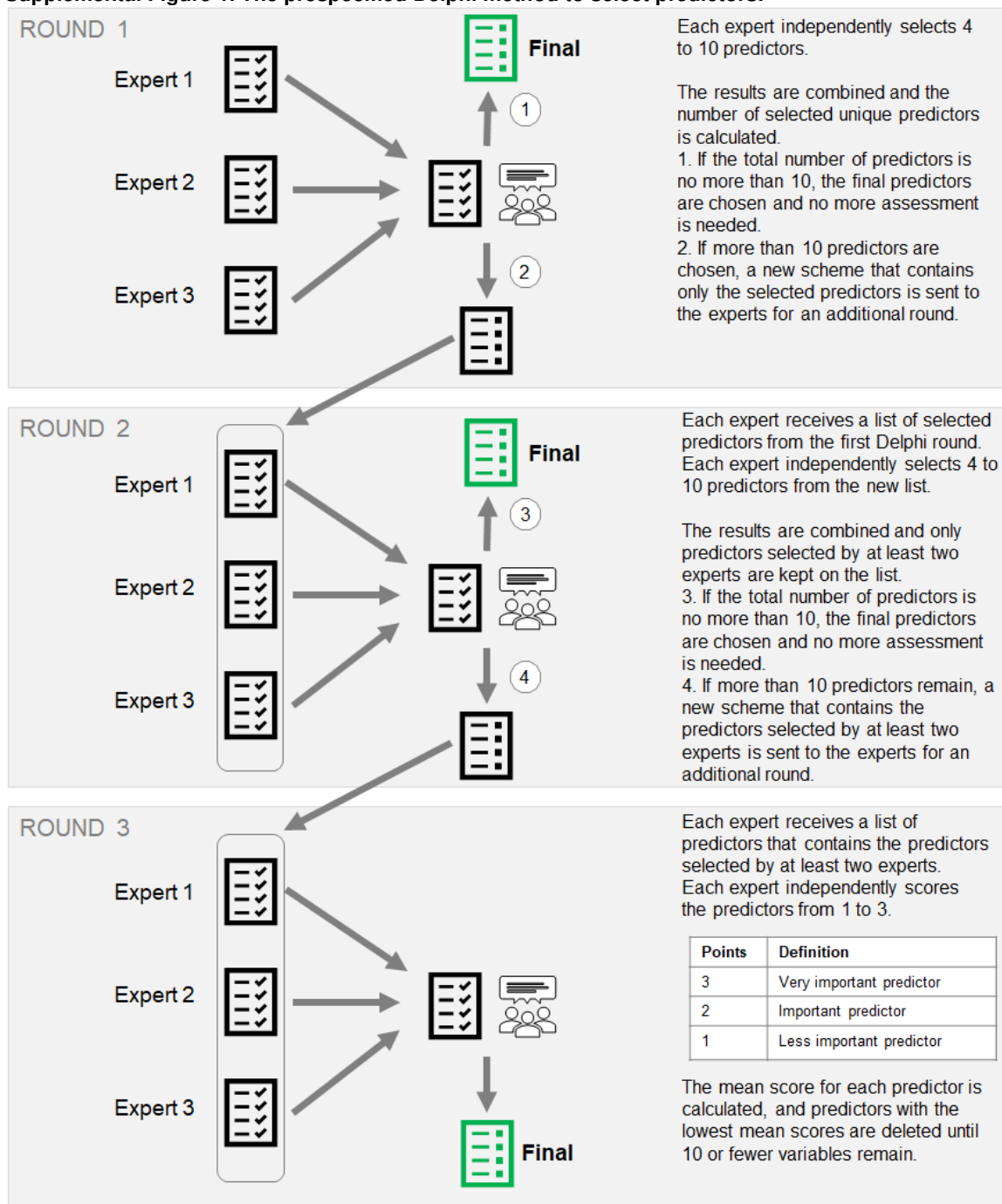
*After July 1, 2015.

**Defined as at least 1 prescription within 3 months prior to the diagnosis of HF.

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

Hyperthyroidism: A diagnosis within 6 months or a prescription within 6 months.

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Open Heart

Vinter et al. Prediction models for incident AF in HF

Supplemental Figure 1. The prespecified Delphi method to select predictors.

ROUND 1

Expert 1
Expert 2
Expert 3

Final
1
2

Each expert independently selects 4 to 10 predictors.

The results are combined and the number of selected unique predictors is calculated.
1. If the total number of predictors is no more than 10, the final predictors are chosen and no more assessment is needed.
2. If more than 10 predictors are chosen, a new scheme that contains only the selected predictors is sent to the experts for an additional round.

ROUND 2

Expert 1
Expert 2
Expert 3

Final
3
4

Each expert receives a list of selected predictors from the first Delphi round. Each expert independently selects 4 to 10 predictors from the new list.

The results are combined and only predictors selected by at least two experts are kept on the list.
3. If the total number of predictors is no more than 10, the final predictors are chosen and no more assessment is needed.
4. If more than 10 predictors remain, a new scheme that contains the predictors selected by at least two experts is sent to the experts for an additional round.

ROUND 3

Expert 1
Expert 2
Expert 3

Final

Each expert receives a list of predictors that contains the predictors selected by at least two experts. Each expert independently scores the predictors from 1 to 3.

Points	Definition
3	Very important predictor
2	Important predictor
1	Less important predictor

The mean score for each predictor is calculated, and predictors with the lowest mean scores are deleted until 10 or fewer variables remain.

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance
placed on this supplemental material which has been supplied by the author(s)

Open Heart

Vinter et al. Prediction models for incident AF in HF

Results
Supplemental Table 3. Risk of atrial fibrillation (AF) and mortality at 1 year after heart failure (HF) by year of HF diagnosis.

Year of HF diagnosis	One-year risk of AF, %	One-year mortality, %
2008	6.8	9.2
2009	6.5	9.9
2010	6.4	9.5
2011	7.4	9.1
2012	8.5	9.2
2013	7.1	9.6
2014	8.8	9.0
2015	8.3	7.7
2016	8.6	8.3
2017	8.7	9.4

Vinter et al. Prediction models for incident AF in HF

Supplemental Table 4. Characteristics of complete cases based on selected variables by experts.

	Total N=25,289	Development data N=13,009	Validation data N=12,280
Demography			
Female sex, N (%)	8,243 (32.6)	4,248 (32.7)	3,995 (32.5)
Age, years, mean (SD)	67.9 (12.9)	68.0 (13.0)	67.9 (12.8)
Highest completed education, N (%)			
Group 1	10,478 (42.9)	5,664 (45.5)	4,814 (40.2)
Group 2	10,167 (41.6)	4,993 (40.1)	5,174 (43.2)
Group 3	3,799 (15.5)	1,802 (14.5)	1,997 (16.7)
Lifestyle factors, N (%)			
Elevated alcohol consumption	2,010 (9.0)	992 (8.8)	1,018 (9.2)
Smoking status			
Never	6,075 (25.8)	2,928 (24.5)	3,147 (27.1)
Former	10,191 (43.3)	5,099 (42.7)	5,092 (43.9)
Current	7,284 (30.9)	3,925 (32.8)	3,359 (29.0)
Clinical Data, N (%)			
Left ventricular ejection fraction			
<25%	5,993 (23.9)	2,914 (22.8)	3,079 (25.2)
25-40%	15,930 (63.6)	0,049 (62.9)	7,881 (64.4)
>40-49%	1,549 (6.2)	957 (7.5)	592 (4.8)
≥50%	1,571 (6.3)	880 (6.9)	691 (5.6)
NYHA class			
I	4,061 (16.1)	2,028 (15.6)	2,033 (16.6)
II	15,264 (60.4)	7,645 (58.8(	7,619 (62.0)
III/IV	5,964 (23.6)	3,336 (25.6)	2,628 (21.4)
Comorbidities and health factors, N (%)			
Hypertension	10,593 (41.9)	5,119 (60.7)	6,806 (55.4)
Hypercholesterolemia	5,225 (20.7)	2,750 (21.1)	2,475 (79.9)
Diabetes mellitus	5,112 (20.2)	2,639 (20.3)	2,473 (20.1)
Chronic kidney disease	1,789 (7.1)	878 (7.8)	911 (7.4)
Obstructive sleep apnea	590 (2.3)	222 (1.7)	368 (3.0)
Chronic obstructive pulmonary disease	3,138 (12.4)	1,623 (12.5)	1,515 (12.3)
Valvular heart disease	2,239 (8.9)	1,173 (9.0)	1,066 (8.7)
Myocardial infarction	9,801 (38.8)	5,311 (40.8)	4,490 (36.6)
Peripheral artery disease	3,010 (11.9)	1,544 (11.9)	1,466 (11.9)
Hyperthyroidism within 6 months	269 (1.1)	149 (1.2)	120 (1.0)
Sepsis*	-		
Pneumonia*	1,135 (4.5)	609 (4.7)	526 (4.3)
Pulmonary embolism*	247 (1.0)	98 (0.8)	149 (1.2)
Acute respiratory distress syndrome*	-		
Cardiac and non-cardiac thoracic surgery*	408 (1.6)	198 (1.5)	210 (1.7)
Admission to intensive care unit*	347 (1.4)	176 (1.4)	171 (1.4)
Cancer within 6 months	1,034 (4.1)	459 (3.5)	575 (4.7)
Medication, N (%)**			
ACE inhibitor or ARB	15,189 (60.1)	7,945 (61.1)	7,244 (59.0)
Beta-blocker	11,564 (45.7)	6,200 (47.7)	5,364 (43.7)
MRA	2,750 (10.9)	1,469 (11.3)	1,281 (10.4)
Statin	12,621 (49.9)	6,655 (51.2)	5,966 (48.6)
Aspirin and/or clopidogrel	13,876 (54.9)	7,498 (57.6)	6,378 (51.9)
NSAID	4,171 (16.5)	2,368 (18.2)	1,803 (14.7)

Vinter et al. Prediction models for incident AF in HF

Abbreviations: NYHA=New York Heart Association; ACE=angiotensin-converting enzyme; ARB= angiotensin receptor blockers; MRA=mineralocorticoid receptor antagonist; NSAID=non-steroidal anti-inflammatory drugs
Missing in development dataset, N (%): alcohol: 1,788 (13.7); smoking: 1,057 (8.1); LVEF: 209 (1.6); education: 550 (4.2). Missing in validation dataset, N (%): alcohol: 1,164 (9.5); smoking: 682 (5.6); LVEF: 37 (0.3); education: 295 (2.4).

*At least 1 prescription within 6 months before HF
**Within 1 month before HF

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Open Heart

Vinter et al. Prediction models for incident AF in HF

Supplemental Table 5. Characteristics of complete cases based on selected variables by experts and patients diagnosed in 2008-2017.

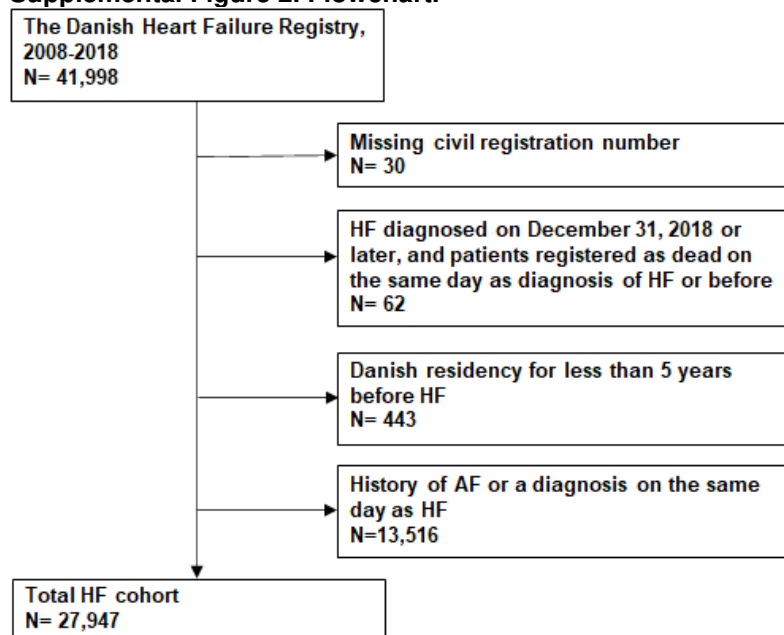|	Total N=22,810
Demography	
Female sex, N (%)	7,449 (32.7)
Age, years, mean (SD)	67.9 (12.9)
Highest completed education, N (%)	
Group 1	9,527 (32.3)
Group 2	9,116 (31.4)
Group 3	3,383 (15.4)
Lifestyle factors, N (%)	
Elevated alcohol consumption	1,783 (8.9)
Smoking status	
Never	5,403 (25.5)
Former	9,178 (32.3)
Current	6,631 (31.3)
Clinical Data, N (%)	
Left ventricular ejection fraction	
<25%	5,371 (23.8)
25-40%	14,307 (63.4)
>40-49%	1,446 (6.4)
≥50%	1,452 (6.4)
NYHA class	
I	3,649 (16.0)
II	13,677 (60.0)
III/IV	5,484 (24.0)
Comorbidities and health factors, N (%)	
Hypertension	9,482 (41.6)
Hypercholesterolemia	4,769 (20.9)
Diabetes mellitus	4,626 (20.3)
Chronic kidney disease	1,590 (7.0)
Obstructive sleep apnea	489 (2.1)
Chronic obstructive pulmonary disease	2,848 (12.5)
Valvular heart disease	2,018 (8.9)
Myocardial infarction	8,929 (39.2)
Peripheral artery disease	2,741 (12.0)
Hyperthyroidism within 6 months	254 (1.1)
Sepsis*	-
Pneumonia*	1,037 (4.6)
Pulmonary embolism*	212 (0.9)
Acute respiratory distress syndrome*	-
Cardiac and non-cardiac thoracic surgery*	374 (1.6)
Admission to intensive care unit*	321 (1.4)
Cancer within 6 months	903 (4.0)
Medication, N (%)**	
ACE inhibitor or ARB	13,688 (60.0)
Beta-blocker	10,516 (46.1)
MRA	2,504 (11.0)
Statin	11,413 (50.0)
Aspirin and/or clopidogrel	12,607 (55.3)
NSAID	3,831 (16.8)

Abbreviations: NYHA=New York Heart Association; ACE=angiotensin-converting enzyme; ARB= angiotensin receptor blockers; MRA=mineralocorticoid receptor antagonist; NSAID=non-steroidal anti-inflammatory drugs

Vinter et al. Prediction models for incident AF in HF

Missing in development dataset, N (%): alcohol: 2,7190 (11.9); smoking: 1,598 (7.0); LVEF: 234 (1.0); education: 784 (3.4).

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

Open Heart

Vinter et al. Prediction models for incident AF in HF

Supplemental Figure 2. Flowchart.

Abbreviations: HF=heart failure; AF=atrial fibrillation.

Vinter et al. Prediction models for incident AF in HF

Supplemental Figure 3. Results of first Delphi Round.
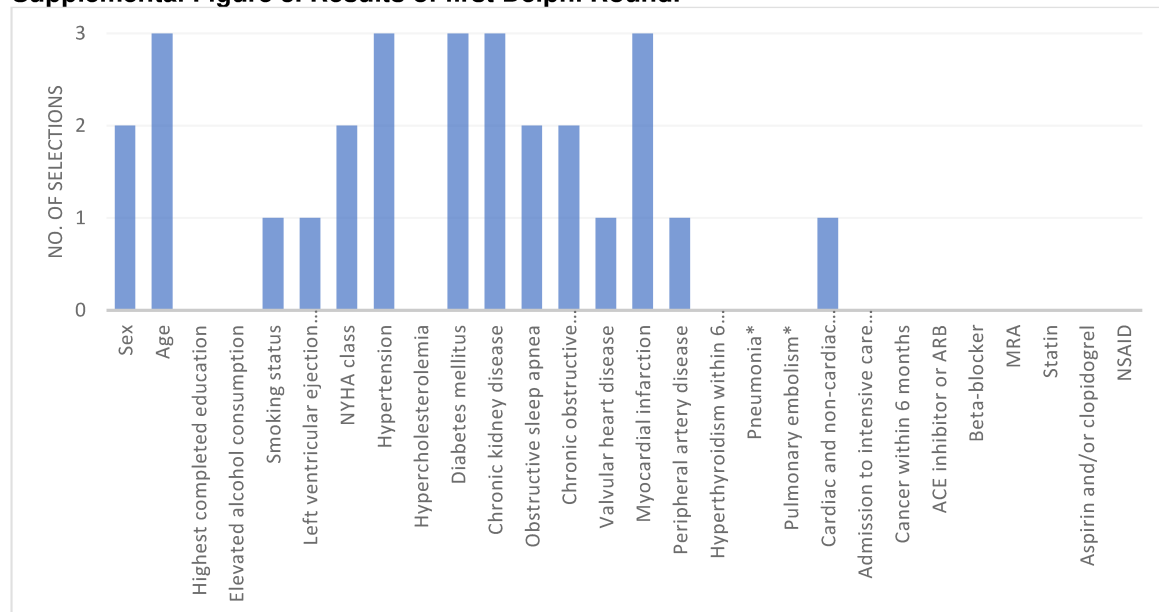
Abbreviations: NYHA=New York Heart Association; ACE=angiotensin-converting enzyme; ARB= angiotensin receptor blockers; MRA=mineralocorticoid receptor antagonist; NSAID=non-steroidal anti-inflammatory drugs

Vinter et al. Prediction models for incident AF in HF

Supplemental Figure 4. Risk prediction of death.
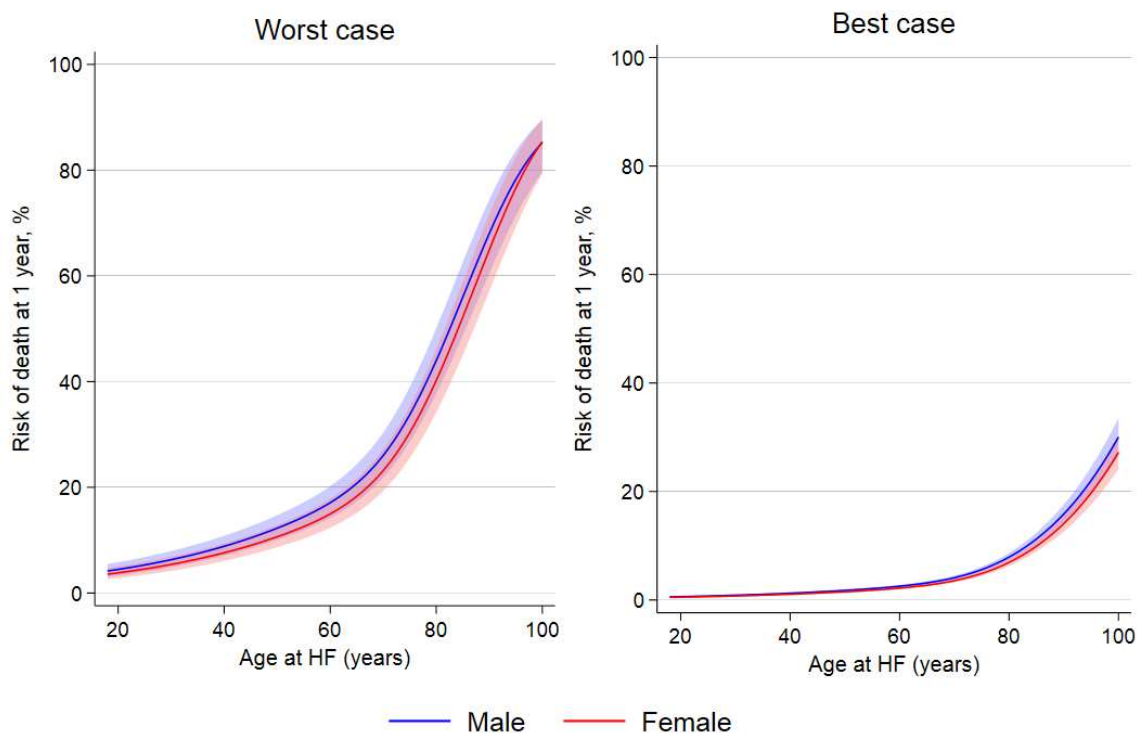
Worst case scenario: Patient has NYHA class III/IV, hypertension, diabetes mellitus, chronic kidney disease, obstructive sleep apnea, chronic obstructive pulmonary disease, and myocardial infarction. Best case scenario: Patient has NYHA class I, no hypertension, no diabetes mellitus, no chronic kidney disease, no obstructive sleep apnea, no chronic obstructive pulmonary disease, and no history of myocardial infarction.