

## Supplemental material

### Comparative thromboembolic risk in atrial fibrillation with and without a secondary precipitant – a Danish nationwide cohort study

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Online Table 1: Specification of diagnoses by international classification of diseases (ICD-8 and ICD-10) codes and pharmacotherapy by anatomical therapeutic chemical classification (ATC) codes.

Online Table 2: Baseline characteristics of the non-matched population, patients initiated on OAC therapy

Online Table 3: Baseline characteristics of the non-matched population, patients not initiated on OAC therapy

Online Figure 1: Adjusted Hazard ratios of long-term outcomes in patients with AF with and without a secondary precipitant. Adjustments: age groups, peripheral artery disease, heart failure, hypertension, prior thromboembolic event, ischemic heart disease, chronic kidney disease, diabetes, prior bleeding event, cancer, antiarrhythmic therapy (amiodarone, digoxin, flecainide) at the index date and OAC therapy status as a time-dependent variable.

**Online Table 1: Specification of diagnoses by international classification of diseases (ICD-8 and ICD-10) codes and pharmacotherapy by anatomical therapeutic chemical classification (ATC) codes.**

<b>Precipitants</b>	<b>ICD-10 codes and NCSP, NOMESCO Classification of Surgical Procedures</b>
Alcohol intoxication Infections	ICD-10: F100, F103, F104, R780, T51, X65 ICD-10: Certain infectious and parasitic diseases: A00-B99. Infections in the eye and adnexa: H00, H01, H10, H20, H30, H44, H60, H65-H68, H70, H73.0, H73.1 Infections in the cardiovascular organs: I30, I32, I33, I38-I41 Infections in pulmonary system: J00-J22, J32, J36, J85, J86 Infections in the gastrointestinal system: K12, K20, K35-K37, K57, K65, K67, K81, K85 Infections in the skin, subcutaneous tissue, bones, muscles, and connective tissue: L00-L08, M00, M01, M60, M63.2. M65, M86, M90.0, M90.1, M90.2 Infections in the urogenital system: N00, N01, N05, N30, N70-N77.
Myocardial infarction Pulmonary embolism Surgery	ICD-10: I21 ICD-10: I260, I269, O882D, O882E, T817D NCSP, NOMESCO Classification of Surgical Procedures: KF, KM, KN, KD, KPH, KPJ, KJ, KH, KQ, KB, KC, KL, KE, KA, KG, KK.
Thyrotoxicosis	ICD-10: E05
<b>Outcomes</b>	
Atrial fibrillation re-hospitalization Thromboembolic event	Hospital admission with primary diagnosis of atrial fibrillation: I48 Ischemic stroke: I63, I64 Death from stroke: I61-I64 Transient ischemic attack: G458, G459 Thrombosis or embolism in arteries: I74
<b>Comorbidities</b>	<b>ICD-8 and ICD-10 codes</b>

Atrial fibrillation	ICD-10: I48 ICD-8: 42793, 42794
Alcohol abuse	ICD-10: E24.4, E52, F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, L27.8A, O35.4, T51, Z71.4, Z72.1.  ATC: N07BB
Cancer	ICD-10: C
Chronic kidney disease	ICD-10: E10.2, E11.2, E13.2, E14.2, I12.0, M32.1B, N02-N08, N11, N12, N14, N15.8, N15.9, N16.0, N16.2-N16.4, N16.8, N18, N19, N26, Q61
Chronic obstructive pulmonary disease	ICD-10: J42, J43, J44
Diabetes	ATC: A10 (3 months before index)
Heart failure	ICD-10: I11.0, I42, I50, J81
Hypertension	Usage of a combination of at least two of the seven different drug classes at the same time: <ol style="list-style-type: none"> <li>1. Non-loop diuretics</li> <li>2. Loop diuretics</li> <li>3. Antiadrenergic agents</li> <li>4. Beta-blockers</li> <li>5. Vasodilators</li> <li>6. Calcium channel blockers</li> <li>7. Renin-angiotensin system inhibitors</li> </ol>
Ischemic heart disease	ICD-10: I20-I25
Peripheral artery disease	ICD-10: I70
Prior bleeding	ICD-10: D50.0, D62, G951A, H31.3, H05.2A, H35.6, H43.1, H45.0, I31.2, I60-I62, I85.0, I86.4A, J94.2, K22.8F, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.8A, K62.5, K63.8B, K63.8C, K66.1, K83.8F, K86.8G, K92.0-K92.2, N02, R04, R31, S06.4-S06.6, S36.8D
Thromboembolic event	ICD-10: G45.8, G45.9, I63, I64, I74
Valvular atrial fibrillation	Atrial fibrillation without: ICD-10: I05, I06, I080A, I081A, I082A, I083A, Z952, Z954 ICD-8: 39500-39502, 39508, 39509, 39600-39604, 39608, 39609 Procedures: FKD, FKH, FMD, FMH, FGE, FJE
<b>Pharmacotherapy</b>	<b>ACT-codes</b>

ADP-receptor blockers	B01AC04, B01AC22, B01AC24
Amiodarone	C01BD01
Antiadrenergic agents	C02A, C02B, C02C
Oral anticoagulation therapy	Vitamin K antagonists: B01AA03, B01AA04 Non-vitamin K antagonist oral anticoagulants: B01AF01, B01AF02, B01AE07
Beta-blockers	C07A, C07B, C07C, C07D, C07F
Calcium channel blockers	C08, C09BB, C09DB
Digoxin	C01AA
Flecainide	C01BC
Loop diuretics	C03C, C03EB
Non-loop diuretics	C02DA, C03EA, C03EB, C02L, C03A, C03B, C03D, C03E, C03X, C07B, C07C, C07D, C08G, C09BA, C09DA, C09XA52
Renin-angiotensin system inhibitors	C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C09XA02, C09XA52
Vasodilators	C02DB, C02DD, C02DG

Online Table 2: Baseline characteristics of the non-matched population, patients initiated on OAC therapy

	AF with a secondary precipitant N=10,673						AF without a secondary precipitant N=37,827
	Alcohol intoxication N=33	Thyro- toxicosis N=1103	Myocardial infarction N=1312	Surgery N=1151	Infection N=5987	>1 precipitant N=1087	
<b>Demographics</b>							
Age, median (IQR*)	64 (55-68)	72 (64-79)	75 (68-81)	74 (67-81)	77 (69-83)	75 (68-81)	72 (64-79)
Male, n (%)	28 (84.8)	259 (23.5)	842 (64.2)	667 (57.9)	3189 (53.3)	634 (58.3)	21,386 (56.5)
<b>Comorbidities, n (%)</b>							
Cancer	≤3	114 (10.3)	146 (11.1)	239 (20.8)	927 (15.5)	171 (15.1)	4617 (12.2)
Chronic kidney disease	4 (12.1)	23 (2.1)	62 (4.7)	65 (5.6)	372 (6.2)	59 (5.4)	1011 (2.7)
COPD <sup>†</sup>	≤3	106 (9.6)	133 (10.1)	128 (11.1)	1251 (20.9)	157 (14.4)	3426 (9.1)
Diabetes	≤3	84 (7.6)	159 (12.1)	111 (9.6)	712 (11.9)	112 (10.3)	3384 (8.9)
Heart failure	6 (18.2)	236 (21.4)	464 (35.4)	228 (19.8)	1440 (24.1)	359 (33.0)	6791 (18.0)
Hypertension	11 (33.3)	658 (59.7)	982 (74.8)	687 (59.7)	3652 (61.0)	723 (66.5)	23,057 (61.0)
IHD <sup>‡</sup>	5 (15.2)	129 (11.7)	1312 (100)	434 (37.7)	1202 (20.1)	744 (68.4)	7360 (19.5)
PAD <sup>§</sup>	≤3	29 (2.6)	83 (6.3)	101 (8.8)	353 (5.9)	77 (7.1)	1258 (3.3)
Prior bleeding event	7 (21.2)	86 (7.8)	150 (11.4)	213 (18.5)	966 (16.1)	182 (16.7)	4564 (12.1)
Prior thromboembolic event	≤3	60 (5.4)	142 (10.8)	153 (13.3)	672 (11.2)	133 (12.2)	3313 (8.8)
<b>Risk scores</b>							
CHA <sub>2</sub> DS <sub>2</sub> -VASc <sup>  </sup>							
Median (IQR*)	1 (0-2)	3 (2-4)	4 (3-5)	3 (2-4)	3 (2-4)	4 (3-5)	3 (2-4)
0	11 (33.3)	134 (12.2)	0	74 (6.4)	269 (4.5)	28 (2.6)	3592 (9.5)
1-2	16 (48.5)	263 (23.8)	181 (13.8)	289 (25.1)	1493 (24.9)	181 (16.6)	12,341 (32.6)
≥3	6 (18.2)	706 (64.0)	1131 (86.2)	788 (68.5)	4225 (70.6)	878 (80.8)	21,894 (57.9)
HAS-BLED <sup>#</sup>							
Median (IQR*)	2 (1-3)	2 (1-2)	3 (2-3)	2 (1-3)	2 (1-3)	2 (2-3)	2 (1-3)
0	0	128 (11.6)	32 (2.4)	60 (5.2)	259 (4.3)	33 (3.0)	3361 (8.9)
1-2	21 (63.6)	706 (64.0)	571 (43.5)	611 (53.1)	3433 (57.3)	515 (47.4)	22,792 (60.3)
≥3	12 (36.4)	269 (24.4)	709 (54.0)	480 (41.7)	2295 (38.3)	539 (49.6)	11,674 (30.9)
<b>Pharmacotherapy, n (%)</b>							

Amiodarone	0	19 (1.7)	104 (7.9)	181 (15.7)	261 (4.4)	141 (13.0)	1493 (3.9)
Digoxin	11 (33.3)	605 (54.9)	437 (33.3)	312 (27.1)	2847 (47.6)	368 (33.9)	14,803 (39.1)
Flecainide	0	5 (0.5)	≤3	≤3	10 (0.2)	≤3	248 (0.7)

\*IQR: interquartile range. †COPD: chronic obstructive pulmonary disease. ‡IHD: ischemic heart disease. §PAD: peripheral artery disease. ||CHA<sub>2</sub>DS<sub>2</sub>-VASc: Risk score for stroke: congestive heart failure/LV function, hypertension, age 65-74 years, age>74 years (2 points), diabetes, stroke/TIA/systemic embolism (2 points), vascular disease, sex category (female); #HAS-BLED: Risk score for bleeding: hypertension, abnormal renal/liver function, history of stroke, history of bleeding, INR (left out due to missing data), age>65 years, drug consumption with antiplatelet agents/non-steroidal inflammatory drugs, alcohol abuse.

Online Table 3: Baseline characteristics of the non-matched population, patients not initiated on OAC therapy

	AF with a secondary precipitant N=29,403						AF without a secondary precipitant N=60,361
	Alcohol intoxication N=302	Thyro- toxicosis N=1408	Myocardial infarction N=3508	Surgery N=4101	Infection N=16,079	>1 precipitant N=4005	
<b>Demographics</b>							
Age, median (IQR*)	58 (48-66)	74 (62-82)	78 (69-84)	76 (67-82)	80 (72-87)	76 (68-83)	69 (58-80)
Male, n (%)	248 (82.1)	263 (18.7)	1907 (54.4)	2069 (50.5)	7352 (45.7)	2073 (51.8)	31,074 (51.5)
<b>Comorbidities, n (%)</b>							
Cancer	15 (5.0)	174 (12.4)	454 (12.9)	1115 (27.2)	3474 (21.6)	795 (19.9)	7915 (13.1)
Chronic kidney disease	7 (2.3)	38 (2.7)	236 (6.7)	289 (7.0)	1223 (7.6)	375 (9.4)	1733 (2.9)
COPD <sup>†</sup>	26 (8.6)	128 (9.1)	495 (14.1)	539 (13.1)	3493 (21.7)	765 (19.1)	4544 (7.5)
Diabetes	24 (7.9)	105 (7.5)	417 (11.9)	396 (9.7)	1473 (9.2)	387 (9.7)	3566 (5.9)
Heart failure	18 (6.0)	209 (14.8)	1218 (34.7)	744 (18.1)	3752 (23.3)	1231 (30.7)	6328 (10.5)
Hypertension	53 (17.5)	653 (46.4)	2348 (66.9)	1808 (44.1)	6942 (43.2)	1991 (49.7)	22,309 (37.0)
IHD <sup>‡</sup>	38 (12.6)	207 (14.7)	3508 (100)	1326 (32.3)	3558 (22.1)	2354 (58.8)	11,528 (19.1)
PAD <sup>§</sup>	6 (2.0)	49 (3.5)	298 (8.5)	371 (9.0)	1057 (6.6)	374 (9.3)	1913 (3.2)
Prior bleeding event	74 (24.5)	157 (11.2)	585 (16.7)	1062 (25.9)	3420 (21.3)	998 (24.9)	7616 (12.6)
Prior thromboembolic event	22 (7.3)	78 (5.5)	350 (10.0)	422 (10.3)	2029 (12.6)	478 (11.9)	4301 (7.1)
<b>Risk scores</b>							
CHA <sub>2</sub> DS <sub>2</sub> -VASc <sup>  </sup>							
Median (IQR*)	1 (0-2)	3 (2-4)	4 (3-5)	3 (2-4)	3 (2-4)	4 (2-5)	2 (0-4)
0	147 (48.7)	271 (19.2)	0	317 (7.7)	1059 (6.6)	241 (6.0)	15,957 (26.4)
1-2	102 (33.8)	270 (19.2)	489 (13.9)	1119 (27.3)	3671 (22.8)	824 (20.6)	17,513 (29.0)
≥3	53 (17.5)	867 (61.6)	3019 (86.1)	2665 (65.0)	11,349 (70.6)	2940 (73.4)	26,891 (44.6)
HAS-BLED <sup>#</sup>							
Median (IQR*)	2 (1-3)	2 (1-3)	3 (2-3)	2 (1-3)	2 (1-3)	2 (2-3)	2 (1-3)
0	0	228 (16.2)	102 (2.9)	229 (5.6)	745 (4.6)	175 (4.4)	12,875 (21.3)
1-2	211 (69.9)	756 (53.7)	1424 (40.6)	2265 (55.2)	8795 (54.7)	1924 (48.0)	31,914 (52.9)
≥3	91 (30.1)	424 (30.1)	1982 (56.5)	1607 (39.2)	6539 (40.7)	1906 (47.6)	15,572 (25.8)

<b>Pharmacotherapy, n (%)</b>							
Amiodarone	≤3	14 (1.0)	259 (7.4)	262 (6.4)	361 (2.2)	278 (6.9)	1133 (1.9)
Digoxin	38 (12.6)	398 (28.3)	784 (22.3)	782 (19.1)	5210 (32.4)	828 (20.7)	10,336 (17.1)
Flecainide	0	8 (0.6)	8 (0.2)	10 (0.2)	30 (0.2)	5 (0.1)	786 (1.3)

\*IQR: interquartile range. †COPD: chronic obstructive pulmonary disease. ‡IHD: ischemic heart disease. §PAD: peripheral artery disease. ||CHA<sub>2</sub>DS<sub>2</sub>-VASc: Risk score for stroke: congestive heart failure/LV function, hypertension, age 65-74 years, age>74 years (2 points), diabetes, stroke/TIA/systemic embolism (2 points), vascular disease, sex category (female); #HAS-BLED: Risk score for bleeding: hypertension, abnormal renal/liver function, history of stroke, history of bleeding, INR (left out due to missing data), age>65 years, drug consumption with antiplatelet agents/non-steroidal inflammatory drugs, alcohol abuse.



**Online Figure 1: Adjusted Hazard ratios of long-term outcomes in patients with AF with and without a secondary precipitant.**

**Adjustments: age groups, peripheral artery disease, heart failure, hypertension, prior thromboembolic event, ischemic heart disease, chronic kidney disease, diabetes, prior bleeding event, cancer, antiarrhythmic therapy (amiodarone, digoxin, flecainide) at the index date and OAC therapy status as a time-dependent variable.**

