

## Supplementary Material S3

Socioeconomic inequality in oral anticoagulation therapy initiation in atrial fibrillation patients with high risk of stroke: a register-based observational study  
by

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### S3a. ICD- and ATC-codes used in this study

If not specified below, we registered the surgical procedures and diagnoses occurring within 10 years prior to baseline (AF diagnosis), and drug prescriptions should be claimed within one year prior to baseline (1).

Diagnosis	Classification system	Codes
Atrial fibrillation <sup>1</sup>	ICD-10	I48 (we did not include emergency department diagnoses)
Hypertension <sup>2</sup>	ICD-8	400-404
	ICD-10	I10-15
One ICD-code and/or at least two different classes of antihypertensive drugs and/or minimum one antihypertensive combination drug.	ATC	<p>α adrenergic blocker: C02A; C02B and C02C</p> <p>Non-loop diuretics: C07C; C07D; C08G; C09BA; C09DA; C09XA52; C02DA; C02L; C03A; C03B; C03D C03E</p> <p>Vasodilators: C04; C02DB; C02DD; C02DG</p> <p>β blocker: C07</p> <p>Calcium channel blockers: C07F; C08; C09BB and C09DB</p> <p>Renin-angiotensin system inhibitors: C09</p> <p>Antihypertensive combination drug: C09BB04; C09DA; C09DB; C09DX01; C07B; C09BA02; C09BA03; C09BA04 and C09BA05</p>
Moderate to severe liver disease <sup>3</sup>	ICD-8	4560; 57300; 07000; 07002; 07004; 07006; 07008
	ICD-10	B15.0; B16.0; B16.2; B19.0; I85; K70.4; K72; K76.6
Moderate to severe renal disease <sup>3</sup>	ICD-8	7531; 792; 403-404; 580-584; 59009; 59319
	ICD-10	N00-N05; N07; N11; N14; N17; N18; N19; Q61, I12; I13;
Ischemic stroke <sup>4</sup>	ICD-8	43690; 43601; 43309; 43399; 43409; 43499
	ICD-10	I63 (not I63.6), I64
Transient ischemic attack <sup>5</sup>	ICD-8	435
	ICD-10	G45
	ICD-8	444

Systemic arterial embolism <sup>6</sup>	ICD-10	I74
Ischemic heart disease <sup>7</sup>	ICD-8	410-414
	ICD-10	I20-I25
Myocardial infarction <sup>7</sup>	ICD-8	410
	ICD-10	I21; I22; I23
Peripheral artery diseases and aortic plaque <sup>8</sup>	ICD-8	44009; 44020; 44030; 44500; 44509; 44590; 44599
	ICD-10	I700; I702; I739
Bleeding <sup>9</sup>	ICD-8	430; 431; 45601; 53098; 53190; 53192; 53195; 53290; 53390; 53490; 53501; 56915; 28001; N852-N853
	ICD-10	I60; I61; I62; K250; K252; K254; K256; K260; K262; K264; K266; K270; K272; K274; K276; K280; K282; K284; K286; K290; K625; K921; K922; I850; D62; J942; N02; R04; R31; R58; S064-S066
Congestive heart failure <sup>10</sup>	ICD-8	78249; 42719; 42709; 42710; 42711; 42899;
	ICD-10	I110; I130; I132; I420; I50
	ATC	C03C
Diabetes mellitus <sup>11</sup>	ICD-8	249; 250
	ICD-10	E10; E11
	ATC	A10
Alcoholism <sup>12</sup>	ICD-8	291; 303; 57110; 57710
	ICD-10	G621; G721; F10; G312; K860; K292; K70; Z714, Z502; Z721; K852; I426; E244; O354; Z502; K852; Z721
Thyrotoxicosis <sup>13</sup>	ICD-8	242
	ICD-10	E05
	ATC	H03B
Venous thromboembolism (VTE) (deep venous thrombosis (DVT) and/or lung embolism (LE)) <sup>14</sup>	ICD-8	45099; 45100; 45108; 45109; 45190; 45192; 45199; 45302; 45304; 67101-67109; 67309; 67399
	ICD-10	I801; I802; I803; I808; I809; I828; I822; I829; I823; I26; O223; O229; O871; O882; O879  Within six months prior to baseline.
Hip or knee arthroplastic surgery <sup>15</sup>	NCSP	KNFB, KNFC, KNGB, KNGC  Within two months prior to baseline.
Valvular heart diseases (in relation to AF) - Exclusion criteria) <sup>16</sup>	ICD-8	39400; 39401; 39402; 39408; 39409; 39490; 39492; 39600; 39601; 39602; 39604; 39608, 39609; 39690; 39691; 42400
	ICD-10	Z952; I05; I342
	NCSP	FCA60; FGE00; FJF00; FKD00; FMD00; FKA
	DCSP	31130; 31269; 30358; 31100; 31101

VKA -Warfarin -Phenprocoumon	ATC	B01AA03 B01AA04 Outcome: -30 days to + 90 days of baseline.
Aspirin		B01AC06
NOAC -Rivaroxaban  -Apixaban -Edoxaban -Dabigatran		B01AF01 (from 2013), B01AX06 before 2013) B01AF02 B01AF03 B01AE07 Outcome: -30 days to + 90 days of baseline.
Antiplatelet therapy - Aspirin - Clopidogrel, - Prasugrel - Ticagrelor - Dipyridamol	ATC	B01AC06, N02BA01 B01AC04 B01AC22 B01AC24 B01AC07, B01AC30
NSAID	ATC	M01A

Link to the codes used in this study (Accessed: August 5 2019)

ICD-8	<a href="https://sundhedsdatastyrelsen.dk/-/media/sds/filer/rammer-og-retningslinjer/klassifikationer/sks-download/lukkede-klassifikationer/icd-8-klassifikation.txt?la=da">https://sundhedsdatastyrelsen.dk/-/media/sds/filer/rammer-og-retningslinjer/klassifikationer/sks-download/lukkede-klassifikationer/icd-8-klassifikation.txt?la=da</a>
ICD-10	<a href="https://icd.who.int/browse10/2016/en">https://icd.who.int/browse10/2016/en</a>
NOMESCO	<a href="https://norden.diva-portal.org/smash/get/diva2:970547/FULLTEXT01.pdf">https://norden.diva-portal.org/smash/get/diva2:970547/FULLTEXT01.pdf</a>
DCSP	<a href="ftp://filer.sst.dk/filer/sks/data/skscomplete/OPRklass_1995.txt">ftp://filer.sst.dk/filer/sks/data/skscomplete/OPRklass_1995.txt</a>
ATC	<a href="https://pro.medicin.dk/">https://pro.medicin.dk/</a> and <a href="https://www.whocc.no/atc_ddd_index/">https://www.whocc.no/atc_ddd_index/</a>

**Abbreviations:** ICD; International Classification of Diseases system, ATC: Anatomical Therapeutic Chemical Classification System, NCSP: NOMESCO Classification of Surgical Procedures (NOMESCO: Nordic Medico-Statistical Committee), DCSP: Danish Classification of Surgical Procedures and Therapies, 3 edition, VKA; Vitamin K antagonists, NOAC; non-vitamin K antagonist oral anticoagulants

**Validation and background for choice of diagnoses codes used in this study:**

<sup>1</sup>The positive predictive value (PPV) of atrial fibrillation and/or atrial flutter combined was 92.6 % (2).

<sup>2</sup>The definition of hypertension by medication (with two classes of antihypertensive drugs) had a positive predictive value (PPV) of 80 % and a specificity of 94.7 % (3) (we did not include C03X and C05) or one antihypertensive combinations drug which is also used by others (4). The PPV of the ICD-codes was 92 % (5).

<sup>3</sup>The PPV of the ICD-10 codes for moderate/severe liver and renal disease were 100 % (6) and the corresponding ICD-8 codes have previously been used by others but not validated (7).

<sup>4</sup>The predictive value of the ICD-10 codes for ischemic stroke (I63) was 87.6 % and for unspecified stroke (I64) 76.0 % (8). We excluded I63.6 as this diagnosis is of venous origin (1).

<sup>5</sup>The PPV of the ICD-10 code for transient ischemic attack were 60.4 % in one study (8).

<sup>6</sup>We did not find any validation study on the diagnosis of systemic arterial embolism.

<sup>7</sup>PPV for the ICD-10 codes I21, I22, I23 for myocardial infarct were 98 % (6). Some of the other ICD-codes have been validated: PPV for I20 (not I200), I251, I259 and I413 for stable angina pectoris was 93% and I200 and I411 for unstable angina pectoris 88 % (5).

<sup>8</sup>PPV of the ICD-10 codes I702, I702A, I7139A+B+C for peripheral artery disease were 69.4% (9). We also included the ICD-10 code I7000 and ICD-8 code (44009) (“atherosclerosis of aorta”) as aortic plaque as it is included under “Vascular disease” in the CHA<sub>2</sub>DS<sub>2</sub>-VASc score (10).

<sup>9</sup>Some of the diagnosis codes have previously been used in several studies (1,11,12) but to our knowledge, not validated.

<sup>10</sup>The PPV of ICD-10 I50 was 81% (13) and many of the other ICD-10 codes used had a PPV of 84 % (14). The ICD-8 codes have previously been used (7). We included a prescription of loop diuretics as also used by others (1,3,4) to increase the likelihood of the heart failure diagnosis.

<sup>11</sup>The PPV of ICD- and/or ATC-codes of diabetes and antidiabetic drugs have been estimated to be 97 % (15–17).

<sup>12</sup>It is likely that only the most severe cases of alcoholism are registered.

<sup>13</sup>The validity of ICD-codes of hyperthyroidism (and hypothyroidism) was found to be high; less than 2% of the 900 patients screened in the study were misclassified (18). We also included the ATC-code for anti-thyroid drugs (ICD-code and/or ATC-code) (19).

<sup>14</sup>We used the ICD-10 codes for VTE as suggested by others (20). Some of the ICD codes have been validated in several studies and showed low but varying validity (15).

<sup>15</sup>To our knowledge, procedure codes are not validated but have previously been used in other studies (21).

<sup>16</sup>There is not consensus regarding the term “valvular AF” but “mitral stenosis and artificial heart valves” are often referred to as “valvular AF” (22). However, guidelines have not been consistent throughout the years (23–27). Consequently, we defined “non-valvular AF” as AF or atrial flutter (I48) excluding rheumatic mitral valve disease, mitral stenosis and/or mechanical heart valve.

### *S3b. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score and HAS-BLED score*

<b>The CHA<sub>2</sub>DS<sub>2</sub>-VASc score</b>	
Risk factors	Points
<b>C</b> for Congestive heart failure	1
<b>H</b> for Hypertension	1
<b>A</b> for Age ≥ 75 years old	2
<b>D</b> for Diabetes mellitus	1
<b>S</b> for Stroke (ischemic stroke/transient ischemic attack/systemic arterial embolism)	2
<b>V</b> for Vascular disease (myocardial infarction/peripheral artery disease/aortic plaque)	1
<b>A</b> for Age 65-75 years old	1
<b>Sc</b> for Sex category (female)	1

We indicated the CHA<sub>2</sub>DS<sub>2</sub>-VASc score (10,28) of the participants as above using diagnoses codes as described Supplementary Material S3a.

<b>The HAS-BLED score</b>	
Risk factors	Points
<b>H</b> for Hypertension	1
<b>A</b> - for <b>A</b> bnormal liver and renal function (1 point each)	1 or 2
<b>S</b> for <b>S</b> troke (we included: ischemic stroke)	1
<b>B</b> for <b>B</b> leeding (we included: Intracerebral hemorrhage/Intracranial bleeding due to trauma/gastrointestinal bleeding/other bleeding)	1
<b>L</b> for <b>L</b> abile INR (not included - information about INR are not available in our data)	
<b>E</b> for <b>E</b> lderly (>65 years old)	1
<b>D</b> for <b>D</b> rugs (antiplatelet or NSAIDs) or alcohol	1 or 2

We indicated the HAS-BLED score (29,30) of the participants as described above using diagnoses codes as described in Supplementary table S3a.

Note, some of the things referred to are found in the supplementary material of the articles given bellow.

1. Christesen AMS, Vinter N, Mortensen LS, Fenger-Grøn M, Johnsen SP, Frost L. Inequality in oral anticoagulation use and clinical outcomes in atrial fibrillation: A Danish nationwide perspective. *Eur Hear J - Qual Care Clin Outcomes*. 2018;4(3):189–99.
2. 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(3):149–53.
3. Olesen JB, Lip GYH, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: Nationwide cohort study. *Bmj*. 2011;342.
4. Nielsen PB, Skjøth F, Søgaard M, Kjældgaard JN, Lip GYH, Larsen TB. Effectiveness and safety of reduced dose non-Vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: Propensity weighted nationwide cohort study. *BMJ*. 2017;356:1–10.
5. Sundbøll J, Adelborg K, Troels Munc, Trine Frøslevh, Henrik Toft Sørensen, Hans Erik Bøtker, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open*. 2016;6.
6. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol [Internet]*. 2011;11(1):83. Available from: <http://www.biomedcentral.com/1471-2288/11/83>
7. Ording AG, Garne JP, Nyström PMW, Cronin-Fenton D, Tarp M, Sørensen HT, et al. Hospital Recorded Morbidity and Breast Cancer Incidence: A Nationwide Population-Based Case-Control Study. *PLoS One*. 2012;7(10):1–7.
8. Johnsen SP, Overvad K, Sorensen HT, Tjønneland A, Husted SE. Predictive value of stroke and transient ischemic attack discharge diagnoses in The Danish National Registry of Patients. *J Clin Epidemiol*. 2002;55(6):602–7.
9. Lasota AN, Overvad K, Eriksen HH, Tjønneland A, Schmidt EB, Grønholdt MLM. Validity of

- Peripheral Arterial Disease Diagnoses in the Danish National Patient Registry. *Eur J Vasc Endovasc Surg* [Internet]. 2017;53(5):679–85. Available from: <http://dx.doi.org/10.1016/j.ejvs.2016.12.031>
10. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The Euro Heart Survey on atrial fibrillation. *Chest*. 2010;137(2):263–72.
  11. Christiansen CB, Pallisgaard J, Gerds TA, Olesen JB, Jørgensen ME, Numé AK, et al. Comparison of antiplatelet regimens in secondary stroke prevention: A nationwide cohort study. *BMC Neurol* [Internet]. 2015;15:1–8. Available from: <http://dx.doi.org/10.1186/s12883-015-0480-4>
  12. Olesen JB, Lip GYH, Kamper AL, Hommel K, Køber L, Lane DA, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med*. 2012;367(7):625–35.
  13. Kümler T, Gislason GH, Kirk V, Bay M, Nielsen OW, Køber L, et al. Accuracy of a heart failure diagnosis in administrative registers. *Eur J Heart Fail*. 2008;10(7):658–60.
  14. 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(1):235–9.
  15. 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;7:449–90.
  16. Thomsen RW, Hundborg HH, Lervang HH, Johnsen S, Schonheider HC, Sorensen H. Risk of Community-Acquired Pneumococcal Bacteremia in Patients With Diabetes. *Diabetes Care*. 2004;27(5):1143–7.
  17. Thomsen RW, Hundborg HH, Lervang H-H, Johnsen SP, Sørensen Henrik T, Schønheyder HC. Diabetes and Outcome of Community - Acquired Pneumococcal Bacteremia. *Diabetes Care*. 2004;27(1):70–6.
  18. Vestergaard P, Mosekilde L. Fractures in Patients with Hyperthyroidism Study in 16 , 249 Patients. *Thyroid*. 2002;12(5).
  19. Brandt F, Thvilum M, Almind D, Christensen K, Green A, Hegedüs L, et al. Morbidity before and after the Diagnosis of Hyperthyroidism: A Nationwide Register-Based Study. *PLoS One*. 2013;8(6).
  20. Albertsen IE, Nielsen PB, Søgaard M, Goldhaber SZ, Overvad TF, Rasmussen LH, et al. Risk of Recurrent Venous Thromboembolism: A Danish Nationwide Cohort Study. *Am J Med* [Internet]. 2018;131(9):1067-1074.e4. Available from: <https://doi.org/10.1016/j.amjmed.2018.04.042>
  21. Gadsbøll K, Staerk L, Fosbøl EL, Sindet-Pedersen C, Gundlund A, Lip GYH, et al. Increased use of oral anticoagulants in patients with atrial fibrillation: Temporal trends from 2005 to 2015 in Denmark. *Eur Heart J*. 2017;38(12):899–906.
  22. Fauchier L, Philippart R, Clementy N, Bourguignon T, Angoulvant D, Ivanes F, et al. How to define valvular atrial fibrillation? *Arch Cardiovasc Dis* [Internet]. 2015;108(10):530–9. Available from: <http://dx.doi.org/10.1016/j.acvd.2015.06.002>
  23. Lévy S, Breithardt G, Campbell RW, Camm a J, Daubert JC, Allessie M, et al. Atrial fibrillation: current knowledge and recommendations for management. Working Group on Arrhythmias of the European Society of Cardiology. *Eur Heart J*. 1998;19(9):1294–320.
  24. Fuster V, Rydén LE, Asinger RW, Cannom DS, Crijns HJ, Frye RL, et al. ACC/AHA/ESC

- guidelines for the management of patients with atrial fibrillation: A report of the american college of cardiology/american heart association task force on practice guidelines and the european society of cardiology committee for practice guide. *Eur Heart J*. 2001;22(20):1852–923.
25. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation—Executive Summary. Vol. 114, *Circulation*. 2006. 700–752 p.
  26. Camm AJ, Kirchhof P, Lip GYH, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J [Internet]*. 2010;31(19):2369–429. Available from: <https://academic.oup.com/eurheartj/article-lookup/doi/10.1093/eurheartj/ehq278>
  27. John Camm a., Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. *Eur Heart J*. 2012;33(21):2719–47.
  28. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2020;1–126.
  29. Pisters R, Lane DA, Nieuwlaat R, De Vos CB, Crijns HJGM, Lip GYH, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: The euro heart survey. *Chest [Internet]*. 2010;138(5):1093–100. Available from: <http://dx.doi.org/10.1378/chest.10-0134>
  30. Lip GYH, Skjøth F, Nielsen PB, Kjældgaard JN, Larsen TB. The HAS-BLED, ATRIA, and ORBIT Bleeding Scores in Atrial Fibrillation Patients Using Non-Vitamin K Antagonist Oral Anticoagulants. *Am J Med*. 2018;131(5):574.e13-574.e27.