Supplementary Material S4

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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We identified possible confounders *a priori* to all analyses and stratified the results by year and otherwise adjusted for the variables we considered potential confounders. We did not adjust for mediators as we believe the causal pathway between SEP and initiation of OAC is partly mediated through intermediate variables. For CHA_2DS_2-VASc- and HAS BLED components, we considered it associated with outcome (OAC) if it was included in the guidelines the respective year the patient had incident AF.

Following three things were considered when choosing confounders to adjust for:

1. The variable should be predictive of the outcome (initiation of OAC).
2. The variable should be associated with the exposure (income, education or cohabiting status).
3. The variable should not be part of the causal link between exposure (education, income or cohabiting status) and outcome (initiation of OAC). (1)

S4a. Is the variable predictive of outcome (initiation of OAC)?

Table S4a

	1999-2002 (2)	2002-2007 (3)	2007-2011 (4)	2011-2013 (5)	2013-2016 (6)
Female sex	-	-	× ˆ	× ˆ	× ˆ
Age	× (>65 y)ˆ	× (>65 y) ˆ	× ˆ	× ˆˇ	× ˆˇ
Heart failure	× ˆ	× ˆ	× ˆ	× ˆ	× ˆ
Hypertension	× ˆ	× ˆ	× ˆ	× ˆˇ	× ˆˇ
DM	× ˆ	× ˆ	× ˆ	× ˆ	× ˆ
Ischemic stroke	× ˆ	× ˆ	× ˆ	× ˆˇ	× ˆˇ
TIA	× ˆ	× ˆ	× ˆ	× ˆˇ	× ˆˇ
Systemic embolism	× ˆ	× ˆ	× ˆ	× ˆ	× ˆ
MI	× ˆ	× (CAD) ˆ	× (CAD)	× ˆ	× ˆ
CAD	× (primarily MI) ˆ	× ˆ	×	-	-

PAD/aortic plaque	-	-	-	× ˆ	× ˆ
Thyrotoxicosis	-	×ˆ	×	-[1]	-[1]
Renal disease	-	-	-	× ˇ	× ˇ
Liver disease	-	-	-	× ˇ	× ˇ
Prior bleeding	-	-	-	× ˇ	× ˇ
Alcoholism	-	-	-	× ˇ	× ˇ
NSAID	-	-	-	× ˇ	× ˇ
Antiplatelet	×[2]	× [2]	×[2]	× ˇ	× ˇ
Sociodemographic factors					
Cohabiting status	× (the reference refers to “social isolation”) (7)				
Place of residence	× (8)				
Income	× (9)				
Education	× (10)				
Other factors					
VTE[3]	X (11)				
Knee or hip arthroplasty surgery[3]	x Recent years, NOAC may be used for thromboprophylaxis after knee or hip arthroplasty. Before NOAC was implemented, other medication such as low molecular weight heparin or fondaparinux was used (12), which may also influence choice of OAC or not.				

ˆ The variable is associated with increased likelihood of OAC initiation.
ˇ The variable is associated with reduced likelihood of OAC initiation. All HAS-BLED components are considered to increase the likelihood of bleeding and thus reducing the likelihood of being initiated with OAC. Although guidelines prior to HAS-BLED was introduced state that risk of bleeding should be evaluated in relation to OAC treatment, they do not specify clearly what factors to consider.
[1]The 2010 guidelines states that it is controversial if thyrotoxicosis increases risk of stroke (5), while the 2012 guidelines says that it is not an independent risk factor of stroke (6) (and consequently also OAC).
Abbreviations: DM; diabetes mellitus, TIA; transient ischemic attack, MI; myocardial infarction, CAD; coronary artery disease, PAD; peripheral artery disease, NSAID; non-steroidal anti-inflammatory drugs, y; years
[2]Aspirin is mentioned in guidelines as an alternative to OAC treatment. Consequently, if a person receives aspirin, we consider it as a factor which makes it more unlikely to receive OAC.
[3] VTE: Within six months of baseline. Knee or hip arthroplasty surgery: Within eight weeks of AF diagnosis.

Below table is based on the relationship between the variable and exposure. We have made a short comment what the thought behind it is in the columns and some is also supported by references (if we could find any).

S4b. Is the variable associated with the exposure (does the variable influence the risk of the income/education/cohabiting status)?

Table S4b			
Variable	**Education**	**Household income**	**Cohabiting status**
Female sex	Yes (13). Female sex influences level of education but it probably varies with time (more common today than, for example, 70 years ago).	Yes (14).	Probably, the meaning of the association probably differs between men and women (15). Furthermore, as women normally lives longer than men, older women are probably more often alone than older men.
Age	Yes, longer education is more common today than before (13). Hence, older age is associated with lower education.	Yes. For example, old age increases the risk of lower income (retirement).	Yes, older are more likely to be alone as it is more likely that a partner has died.
Heart failure	Probably not, heart failure is very rare in young people and it is therefore unlikely that it will influence the education of a person (which is normally finished early in life).	Probably yes. It is reasonable to believe that heart failure can cause work disability and consequently a lower income.	Possible yes. Cardiac diseases may cause distress in marriage but it can also bring couples closer together (16).
Hypertension	Probably not, same argument as above.	Possible. Although hypertension is not a condition which cause symptoms itself, it increases the risk of several cardiovascular diseases which may influence work ability and income. Furthermore, drug expenses may influence the income for people who already have low income.	Possible. Although hypertension is more a condition than a diseases, it may possibly influence cohabiting status in line with other diseases.
DM	Probably yes, diabetes mellitus type I may occur in	Probably yes (17).	Probably. A diagnosis of DM may cause, for example, marital stress

	young people and might influence choice of education.		(18) and influence cohabiting status.
Ischemic stroke	Probably not, same argument as for heart failure and hypertension.	Probably yes (19).	Probably yes. It is likely that a stroke diagnoses causes disability and morbidity, and this may influence cohabiting status.
TIA	Probably not, as above.	Possible, TIA may cause people to become disabled (20) and consequently stop working and hereby lower income.	Possible, yes.
Systemic embolism	Probably not, as above.	Probably yes.	Possible, yes.
MI	Probably not, as above.	Probably yes (21).	Possible, yes. Cardiac diseases may cause distress in marriage but it can also bring couples closer together (16). Overall, it may influence cohabiting status.
CAD	Probably not, as above.	Probably yes (21).	Possible, yes, as above (16).
PAD/aortic plaque	Probably not, as above.	Probably yes.	Possible, yes.
Thyrotoxicosis	Possible, although hyperthyroidism are most common in older ages it may also occur in young (22) and influence choice of education.	Probably yes (23).	Possible, yes.
Renal disease	Probably not, as above.	Probably yes (24).	Probably, yes.
Liver disease	Probably not, as above.	Probably yes, we only included ICD codes which is considered to be of severe or moderate severity and it is likely to believe that persons with those	Probably yes,

		diagnoses influence work ability and therefor income.	
Bleeding	Probably not, although young people might experience bleeding episodes, we find it unlikely that it will be so severe/persistent that it affects choice of education.	Probably yes. It depends on the bleeding type, but many types of bleeding included here can cause work disability and lower income, for example, intracranial hemorrhage.	Possible yes.
Alcoholism	Possible, alcoholism may occur in young age and affect educational achievement.	Probably yes.	Probably yes (25).
NSAID	Possible.	Possible.	Possible.
Antiplatelet	Probably not, it is unlikely for young people to receive antiplatelet drugs.	Possible.	Possible.
Cohabiting status	Probably yes, it is reasonable to believe, that cohabiting status may influence educational level (26).	Probably yes.	
Place of residence	Probably yes.	Yes, probably.	Probably yes.
Household income	Probably yes.		Probably yes.
Education		Probably yes	Probably yes.
VTE	Although incidence increases with age, it may occur in young age and influence educational path (27)	Probably yes	Probably yes
Hip or knee arthroplasty	Probably not as hip and knee	Probably yes	Probably yes

	arthroplasty is rare among young and it is therefore unlikely that it influences educational choice.		

Abbreviations: DM, diabetes mellitus; TIA, transient ischemic attack; MI, myocardial infarction; CAD, coronary artery disease; PAD, peripheral artery disease; NSAID, non-steroidal anti-inflammatory drugs; VTE, venous thromboembolism; y, years

S4c. Does exposure (education, income or cohabiting status) influence the risk of the variable?

Table S4c

Variable	**Education**	**Household income**	**Cohabiting status**
Female sex	No	No	No
Age	No	No	No
Heart failure	Probably yes (28)	Probably yes (28)	Probably yes.
Hypertension	Probably yes (29)	Possibly yes	Possible yes (30)
DM	Probably yes(31)	Probably yes (31)	Probably yes (30)
Ischemic stroke	Probably yes (32)	Probably yes (33)	Probably yes (34)
TIA	Probably yes	Probably yes	Possible yes
Systemic embolism	Probably yes	Probably yes	Possible yes
MI	Probably yes(35)	Probably yes (reference refers to CAD) (36)	Probably yes (37)
CAD	Probably yes (MI) (35)	Probably yes (36)	Probably yes (37)
PAD/aortic plaque	Probably yes (38)	Probably yes (38)	Probably yes
Thyrotoxicosis	Possible (39)	Possible yes	Possible yes
Renal disease	Probably yes (40)	Possible yes	Possible yes
Liver disease	Probably yes, for example alcohol related liver diseases (41)	Probably yes, for example alcohol related liver diseases (41)	Possible yes
Bleeding	Possible yes (42)	Probably yes (43)	Possible yes
Alcoholism	Probably yes (41)	Probably yes (41)	Probably yes (44)
NSAID	Possible yes	Possible yes	Probably yes
Antiplatelet	Possible yes	Possible yes	Possible yes
Cohabiting status	Probably	Probably	-
Place of residence	Probably	Probably	Probably yes
Household income	Probably	-	Yes
Education	-	Probably	Probably yes.
VTE	Probably yes (45)	Probably yes (45)	Probably yes (45)

Hip or knee arthroplasty	Probably yes	Probably yes (46)	Probably yes.

Abbreviations: DM, diabetes mellitus; TIA, transient ischemic attack; MI, myocardial infarction; CAD, coronary artery disease; PAD, peripheral artery disease; NSAID, non-steroidal anti-inflammatory drugs; y, years

S4d. Is it an intermediate variable (mediator) or confounder?

Variable	**Education**	**Household income**	**Cohabiting status**
Female sex	Possible confounder	Possible confounder	Possible confounder
Age	Possible confounder	Possible confounder	Possible confounder
Heart failure	Mediator	Possible confounder	Possible confounder
Hypertension	Mediator	Possible confounder	Possible confounder
DM	Possible confounder	Possible confounder	Possible confounder
Ischemic stroke	Mediator	Possible confounder	Possible confounder
TIA	Mediator	Possible confounder	Possible confounder
Systemic embolism	Mediator	Possible confounder	Possible confounder
MI	Mediator	Possible confounder	Possible confounder
CAD	Mediator	Possible confounder	Possible confounder
PAD/aortic plaque	Mediator	Possible confounder	Possible confounder
Thyrotoxicosis	Possible confounder	Possible confounder	Possible confounder
Renal disease	Mediator	Possible confounder	Possible confounder
Liver disease	Mediator	Possible confounder	Possible confounder
Bleeding	Mediator	Possible confounder	Possible confounder
Alcoholism	Possible confounder	Possible confounder	Possible confounder
NSAID	Possible confounder	Possible confounder	Possible confounder
Antiplatelet	Mediator	Possible confounder	Possible confounder
Cohabiting status	Possible confounder	Possible confounder	-
Place of residence	Possible confounder	Possible confounder	Possible confounder
Household income	Possible confounder	-	Possible confounder
Education	-	Possible confounder	Possible confounder
VTE	Possible confounder	Possible confounder	Possible confounder
Hip or knee arthroplasty	Mediator	Possible confounder	Possible confounder

Abbreviations: DM, diabetes mellitus; TIA, transient ischemic attack; MI, myocardial infarction; CAD, coronary artery disease; PAD, peripheral artery disease; NSAID, non-steroidal anti-inflammatory drugs; y, years

S4e. We adjusted for potential confounders in different steps:

Education	
Crude	The unadjusted analysis.
Model 1	Adjusted for age

Model 2	Adjusted for sociodemographic factors: age, household income, cohabiting status and place of residence.
Model 3	Model 2 and 1999-2002: Diabetes mellitus, VTE. 2002-2007: Diabetes mellitus, thyrotoxicosis, VTE. 2007-2011: Diabetes mellitus, thyrotoxicosis, VTE. 2011-2013: Diabetes mellitus, alcoholism, NSAID, VTE. 2013-2016: Diabetes mellitus, alcoholism, NSAID, VTE.

Household income	
Crude	The unadjusted analysis.
Model 1	Adjusted for age
Model 2	Adjusted for sociodemographic factors: Age, education, cohabiting status and place of residence.
Model 3	Model 2 and 1999-2002: Heart failure, hypertension, diabetes mellitus, ischemic stroke/TIA/systemic embolism, myocardial infarction, antiplatelet drugs, VTE and hip and knee arthroplasty. 2002-2006: Heart failure, hypertension, diabetes mellitus, ischemic stroke/TIA/systemic embolism, myocardial infarction, coronary artery disease, thyrotoxicosis, antiplatelet drugs, VTE and hip and knee arthroplasty. 2007-2011: Heart failure, hypertension, diabetes mellitus, ischemic stroke/TIA/systemic embolism, myocardial infarction, coronary artery disease thyrotoxicosis, antiplatelet drugs, VTE and hip and knee arthroplasty. 2011-2013: Heart failure, hypertension, diabetes mellitus, ischemic stroke/TIA/systemic embolism, myocardial infarction, peripheral artery disease/aortic plaque, renal disease, liver disease, bleeding, alcoholism, NSAID, antiplatelet drugs, VTE and hip and knee arthroplasty. 2013-2016: Heart failure, hypertension, diabetes mellitus, ischemic stroke/TIA/systemic embolism, myocardial infarction, peripheral artery disease/aortic plaque, renal disease, liver disease, bleeding, alcoholism, NSAID, antiplatelet drugs, VTE and hip and knee arthroplasty.

Abbreviations: DM, diabetes mellitus; TIA, transient ischemic attack; MI, myocardial infarction; CAD, coronary artery disease; PAD, peripheral artery disease; NSAID, non-steroidal anti-inflammatory drugs; y, years

Cohabiting status	
Crude	The unadjusted analysis.
Model 1	Adjusted for age, education, household income and place of residence.

Model 3	Adjusted for sociodemographic factors: Age, education, cohabiting status and place of residence.
Model 3	Model 2 and 1999-2002: Heart failure, hypertension, diabetes mellitus, ischemic stroke/TIA/systemic embolism, myocardial infarction, antiplatelet drugs, VTE and hip and knee arthroplasty. 2002-2006: Heart failure, hypertension, diabetes mellitus, ischemic stroke/TIA/systemic embolism, myocardial infarction, coronary artery disease, thyrotoxicosis, antiplatelet drugs, VTE and hip and knee arthroplasty. 2007-2011: Heart failure, hypertension, diabetes mellitus, ischemic stroke/TIA/systemic embolism, myocardial infarction, coronary artery disease thyrotoxicosis, antiplatelet drugs, VTE and hip and knee arthroplasty. 2011-2013: Heart failure, hypertension, diabetes mellitus, ischemic stroke/TIA/systemic embolism, myocardial infarction, peripheral artery disease/aortic plaque, renal disease, liver disease, bleeding, alcoholism, NSAID, antiplatelet drugs, VTE and hip and knee arthroplasty. 2013-2016: Heart failure, hypertension, diabetes mellitus, ischemic stroke/TIA/systemic embolism, myocardial infarction, peripheral artery disease/aortic plaque, renal disease, liver disease, bleeding, alcoholism, NSAID, antiplatelet drugs, VTE and hip and knee arthroplasty.

Abbreviations: DM, diabetes mellitus; TIA, transient ischemic attack; MI, myocardial infarction; CAD, coronary artery disease; PAD, peripheral artery disease; NSAID, non-steroidal anti-inflammatory drugs; y, years.

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