

## **Temporal trends in initiation of VKA, rivaroxaban, apixaban and dabigatran for the treatment of venous thromboembolism - A Danish nationwide cohort study**

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## Supplementary

**Table 1:** List of ICD-10 diagnoses codes and ATC codes

<b>Population</b>		
<b>Venous thromboembolism</b>		
<i>(Secondary and primary diagnoses codes, inpatient and outpatients)</i>		
<i>Pulmonary embolism</i>	<i>Defined from diagnosis</i>	ICD-10: DI26
<i>Deep venous thrombosis</i>	<i>Defined from diagnosis</i>	ICD10: I801-I803, I808, I809, I821-I823, I828, I829
<i>Rivaroxaban</i>	<i>Defined from ATC</i>	B01AF01
<i>Dabigatran</i>	<i>Defined from ATC</i>	B01AE07
<i>Apixaban</i>	<i>Defined from ATC</i>	B01AF02
<i>Vitamin K antagonists</i>	<i>Defined from ATC</i>	B01AA03 B01AA04
<b>Comorbidities</b>		
<i>(Secondary and primary diagnoses codes, inpatient and outpatients)</i>		
<i>Ischemic heart disease</i>	<i>Defined from diagnosis</i>	ICD-10: DI20-25
<i>Peripheral artery disease</i>	<i>Defined from diagnosis</i>	ICD-10: DI70
<i>Acute myocardial infarction</i>	<i>Defined from diagnosis</i>	ICD-10: DI21, DI22
<i>Stroke</i>	<i>Defined from diagnosis</i>	ICD-10: DI63, DI64
<i>Atrial fibrillation</i>	<i>Defined from diagnosis</i>	ICD-10: DI48
<i>Cancer</i>	<i>Defined from diagnosis</i>	ICD-10: DC
<i>Chronic kidney disease</i>	<i>Defined from diagnosis</i>	ICD-10: DE102, DE112, DE132, DE142, DI120, DN02, DN03, DNO4, DN05, DN06, DN07, DN08, DN11, DN12, DN14, DN158, DN159, DN160, DN162, DNI63, DN164, DN168, DN18, DN19, DN26, DQ61, DM300, DM313, DM319, DM321B
<i>Hypertension</i>	<i>Defined from combination treatment with at least two classes of antihypertensive drugs: adrenergic <math>\alpha</math>-antagonists, non-loop diuretics, vasodilators, beta-blockers, calcium channel blockers and renin-angiotension system</i>	ATC: C02A, C02B, C02C, C02L, C03A, C03B, C03D, C03E, C03X, C07B, C07C, C07D, C08G, C02DA, C09BA, C09DA, C02DB, C02DD, C02DG, C07A, C07B, C07C, C07D, C07F, C08, C09BB, C09DB, C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C09XA02, C09XA52
<i>Liver disease</i>	<i>Defined from diagnosis</i>	DB15, DB16, DB17, DB18, DB19, DC22, DD684C, DK70, DK71, DK72, DK73, DK74, DK75, DK76, DK77, DZ944, DQ618A

<i>Chronic obstructive pulmonary disease</i>	<i>Defined from diagnosis</i>	ICD-10: DJ42, DJ43, DJ44
<i>Chronic heart failure</i>	<i>Defined from diagnosis</i>	ICD-10: DI110, DI42, DI50, DJ81
<i>Thrombophilia</i>	<i>Defined from diagnosis</i>	ICD-10: DD685, DD686
Diabetes mellitus	Diabetes mellitus Defined from glucose lowering drugs	ATC: A10
Mechanical heart valves or rheumatic mitral stenosis	<i>Defined from diagnosis and procedure codes</i>	ICD-10: DI050, DI060 NSCP: KFKD00, KFMD00, KFG00, KFJF00
<i>Alloplastic surgery</i>	Defined from procedures	NSCP: KNFB, KNFC, KNGB, KNGC

**Table 2:** list of ATC-codes

<i>ADP-receptor blockers</i>	Defined from ATC-codes	B01AC except B01AC06/ B01AC56
<i>Aspirin</i>	Defined from treatment with acetylsalicylic acid	B01AC06, N02BA01, B01AC56
<i>Ulcer medication</i>	Defined from ATC-codes	A02
<i>Lipid modifying drugs</i>	Defined from ATC-codes	C10
<i>Non steroidal anti-inflammatory drugs</i>	Defined from ATC-codes	M01A
<i>Contraceptives</i>	Defined from treatment with hormonal contraceptives for systemic use	G03A
<i>Hormone replacement therapy</i>	Defined from treatment with estrogens, progestogens, androgens	G03C, G03D, G03E, G03F
<i>Diuretics</i>	Defined from ATC-codes	C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C02DA, C09BA, C09DA, C09xa52
<i>Loop</i>	Defined from ATC-codes	C03C
<i>Diuretics+ other antihypertensive drugs</i>	Defined from ATC-codes	C02L
<i>Beta- blocking agents</i>	Defined from ATC-codes	C07A
<i>Beta blocking agents combined with diuretics</i>	Defined from ATC-codes	C07B , C07C, C07D
<i>Beta blocking agents combined with calcium channel antagonists</i>	Defined from ATC-codes	C07F
<i>Calcium channel antagonists</i>	Defined from ATC-codes	C08
<i>Calcium channel antagonists and diuretics</i>	Defined from ATC-codes	C08G
<i>Renin angiotensin system</i>	Defined from ATC-codes	C09XA02

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*inhibitors*

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<i>Renin angiotensin system inhibitors + diuretics</i>	Defined from ATC-codes	C09BA, C09DA
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<i>Renin angiotensin system inhibitors + calcium channel blockers</i>	Defined from ATC-codes	C09BB, C09DB
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**Table 3:** Factors associated with initiation of rivaroxaban, apixaban, or dabigatran, vs. VKA in patients with deep venous thromboembolism. Odds ratio below 1 indicates in favor of VKA and above 1 in favor of rivaroxaban, apixaban or dabigatran

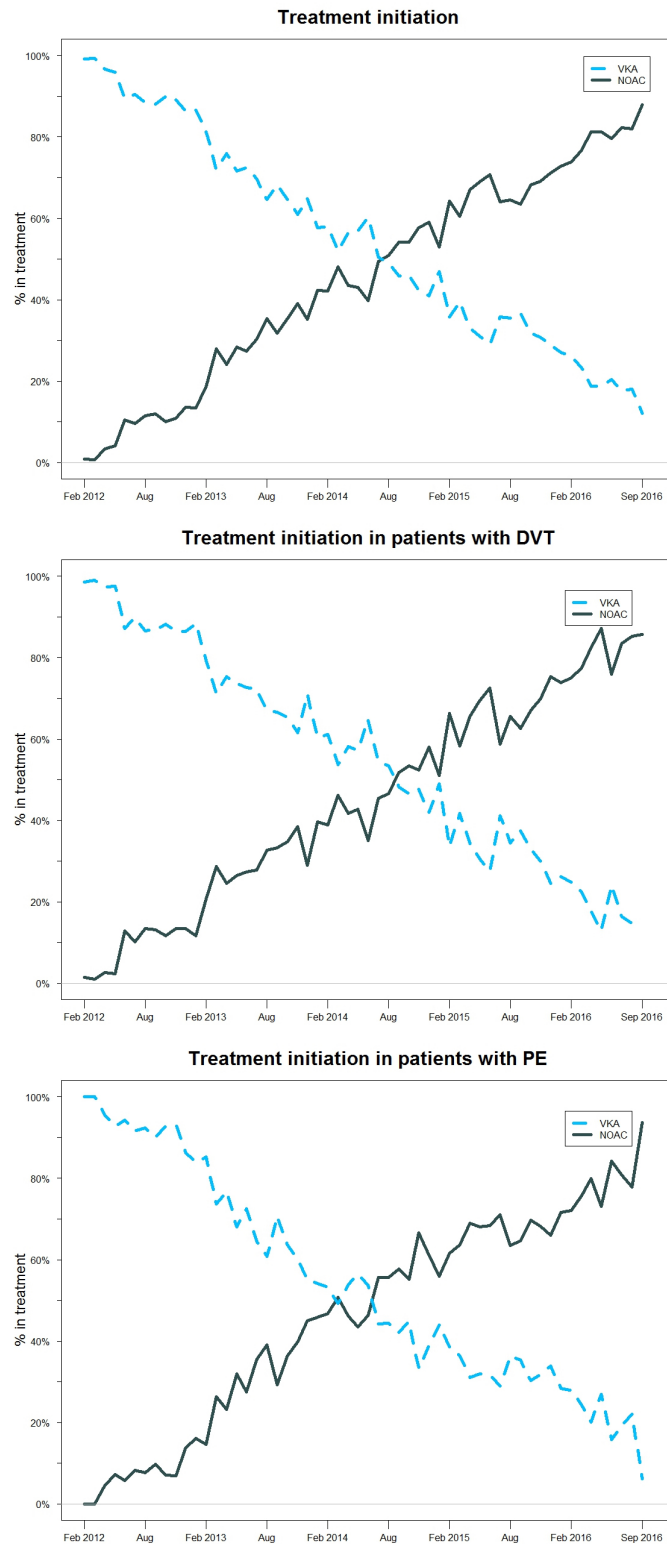
	Odds ratios		
	Rivaroxaban vs. VKA	Apixaban vs. VKA	Dabigatran vs. VKA
<b>Sex</b>			
Female	Ref	Ref	Ref
Male	1.02 (0.93-1.11)	1.11 (0.89-1.39)	0.92 (0.52-1.65)
<b>Age groups</b>			
<65	Ref	Ref	Ref
65-75	0.96 (0.86-1.07)	0.96 (0.86-1.07)	1.25 (0.58-2.58)
>75	1.00 (0.90-1.23)	1.00 (0.90-1.23)	1.66 (0.81-3.35)
<b>Index event</b>			
Deep venous thrombosis	NA	NA	NA
Pulmonary embolism	NA	NA	NA
<b>Comorbidities</b>			
Previous VTE	0.73 (0.64-0.82)*	0.71 (0.50-0.99)*	0.54 (0.18-1.26)
Previous bleeding	1.14 (0.97-1.24)	0.95 (0.63-1.40)	1.18 (0.43-2.73)
Alloplastic surgery	1.02 (0.75-1.40)	0.88 (0.35-1.96)	1.88 (0.29-6.61)
Chronic kidney disease	0.42 (0.32-0.54)*	0.63 (0.35-1.07)	NA
Liver disease	0.83 (0.60-1.48)	1.07 (0.48-2.19)	NA
Heart failure	1.50 (1.14-1.96)*	0.92 (0.46-1.76)	0.79 (0.04-4.36)
Ischemic heart disease	0.94 (0.77-1.14)	1.55 (0.98-2.39)	0.54 (0.08-1.92)
Vascular disease	0.89 (0.64-1.21)	1.17 (0.55-2.30)	1.83 (0.29-6.40)
Hypertension	0.86 (0.77-0.96)*	0.85 (0.63-1.22)	0.50 (0.19-1.07)
Acute myocardial infarction	0.73 (0.47-1.50)	0.49 (0.18-1.38)	NA
Cancer	0.71 (0.61-0.82)*	0.70 (0.49-0.99)*	0.77 (0.29-1.74)
Diabetes	1.16 (0.98-1.38)	1.33 (0.87-1.98)	0.95 (0.22-2.74)
Stroke	0.75 (0.62-0.91)*	1.04 (0.66-1.58)	1.54 (0.51-3.74)
COPD	0.78 (0.65-0.94)*	0.91 (0.57-1.41)	2.71 (0.85-4.84)
Thrombophilia	0.61 (0.43-0.86)*	0.17 (0.03-0.60)*	NA
Year (with 1 year increments)	2.28 (2.20-2.36)*	5.24 (4.62-5.98)	2.71 (2.12-3.53)

**Table 4:** Factors associated with initiation of rivaroxaban, apixaban, or dabigatran, vs. VKA in patients with pulmonary embolism Odds ratio below 1 indicates in favor of VKA and above 1 in favor of rivaroxaban, apixaban or dabigatran

Variables	Odds ratios		
	Rivaroxaban vs. VKA	Apixaban vs. VKA	Dabigatran vs. VKA
<b>Sex</b>			
Male	Ref	Ref	Ref
Female	1.09 (0.98-1.22)	0.97 (0.80-1.20)	0.88 (0.48-1.62)
<b>Age groups</b>			
<65	Ref	Ref	Ref
65-75	1.06 (0.93-1.22)	1.63 (1.26-2.11)	1.63 (0.75-3.53)
>75	1.02 (0.89-1.17)	1.06 (0.80-1.40)	1.64 (0.77-3.55)
<b>Index event</b>			
Deep venous thrombosis	NA	NA	NA
Pulmonary embolism	NA	NA	NA
<b>Comorbidities</b>			
Previous VTE	0.87 (0.74-1.02)	0.75 (0.52-1.05)	0.87 (0.29-2.11)
Previous bleeding	0.87 (0.74-1.03)	0.92 (0.67-1.25)	0.87 (0.15-1.40)
Alloplastic surgery	1.51 (1.06-2.16)	1.13 (0.56-2-15)	NA
Chronic kidney disease	0.41 (0.31-0.54)	0.37 (0.21-0.62)*	NA
Liver disease	0.61 (0.39-0.93)	0.85 (0.39-1-72)	NA
Heart failure	1.12 (0.90-1.40)	0.75 (0.47-1.17)	1.10 (0.24-3.51)
Ischemic heart disease	0.81 (0.67-0.98)	1.04 (0.73-1.47)	0.42 (0.06-1.47)
Vascular disease	0.93 (0.65-1.32)	0.43 (0.17-0.97)*	1.00 (0.05-5.06)
Hypertension	0.93 (0.82-1.05)	0.99 (0.78-1.25)	0.47 (0.21-1.00)
Acute myocardial infarction	0.93 (0.60-1.46)	3.24 (1.27-9.17)*	2.06 (0.15-5.75)
Cancer	0.78 (0.67-0.90)	0.79 (0.59-1.04)	1.08 (0.48-2.22)
Diabetes	0.83 (0.68-1.02)	0.76 (0.51-1.10)	0.94 (0.27-2.49)
Stroke	1.00 (0.82-1.24)	1.32 (0.91-1.90)	1.05 (0.25-3.03)
COPD	0.96 (0.82-1.12)	1.16 (0.86-1.53)	1.48 (0.65-3.05)
Thrombophilia	0.51 (0.26-0.94)	0.50 (0.08-1.88)	NA
Year (with 1 year increments)	2.12 (2.03-2.22)	4.01 (3.60-4.49)	2.79 (2.14-3.75)

**Table 5:** Factors associated with initiation of NOACs vs. VKA in patients with venous thromboembolism, Deep venous thromboembolism or pulmonary embolism

	NOAC vs VKA in patients with VTE	NOAC vs VKA in patients with DVT	NOAC vs VKA in patients with PE
<b>Sex</b>			
Female	Ref		
Male	1.05 (0.98-1.12)	1.02 (0.93-1.11)	1.07 (0.97-1.19)
<b>Age groups</b>			
<65	Ref		
65-75	1.01 (0.92-1.10)	1.01 (0.90-1.13)	1.07 (0.94-1.24)
>75	1.00 (0.92-1.09)	0.97 (0.89-1.01)	1.09 (0.95-1.22)
<b>Index event</b>			
Deep venous thrombosis	Ref	NA	NA
Pulmonary embolism	1.10 (1.03-1.18)*	NA	NA
<b>Comorbidities</b>			
Previous VTE	0.78 (0.71-0.85)*	0.73 (0.64-0.82)*	0.86 (0.74-1.00)
Previous bleeding	1.00 (0.90-1.12)	1.14 (0.98-1.33)	0.87 (0.74-1.02)
Alloplastic surgery	1.22 (0.97-1.53)	1.03 (0.76-1.40)	1.48 (1.05-2.10)*
Chronic kidney disease	0.42 (0.35-0.51)*	0.44 (0.34-0.56)*	0.41 (0.31-0.53)*
Liver disease	0.75 (0.59-0.97)*	0.84 (0.61-1.15)	0.65 (0.43-0.97)*
Heart failure	1.22 (1.03-1.44)*	1.45 (1.11-1.89)*	1.08 (0.87-1.34)
Ischemic heart disease	0.90 (0.78-1.02)	0.98 (0.81-1.19)	0.84 (0.70-1.01)
Vascular disease	0.88 (0.70-1.11)	0.93 (0.68-1.26)	0.85 (0.60-1.20)
Hypertension	0.89 (0.82-0.97)*	0.85 (0.76-0.95)*	0.93 (0.83-1.05)
Acute myocardial infarction	0.91 (0.67-1.23)	0.69 (0.45-1.07)	1.11 (0.72-1.72)
Cancer	0.75 (0.68-0.82)*	0.71 (0.62-0.81)*	0.78 (0.67-0.90)
Diabetes	1.01 (0.89-1.14)	1.17 (0.99-1.40)	0.89 (0.69-1.12)
Stroke	0.90 (0.78-1.03)	0.78 (0.65-0.94)*	1.05 (0.86-1.24)
COPD	0.91 (0.81-1.03)	0.82 (0.68-0.98)*	0.99 (0.85-1.15)
Thrombophilia	0.56 (0.41-0.75)*	0.58 (0.41-0.81)*	0.50 (0.26-0.95)*
Year (with 1 year increments)	2.37 (2.31-2.44)*	2.41 (2.32-2.50)*	2.33 (2.23-2.44)*



**Figure 1:** Graph of temporal trend over initiation of oral anticoagulation therapy in patients with venous thromboembolism (VTE). Percentage per month of patients with VTE, pulmonary embolism (PE) or deep venous thromboembolism (DVT) initiating VKA or NOAC, between February 2012 and September 2016. VKA: p- value for decreasing trend < 0.001, NOAC: p-value for increasing trend < 0.001.