SUPPLEMENTARY MATERIAL

Prophylactic anticoagulation with low molecular weight heparin in COVID-19: cohort studies in Denmark and Sweden

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Supplementary figure S1. Study design diagram.

Supplementary figure S2. Flow chart of cohort selection.

Supplementary figure S3. Monthly proportion of individuals admitted for COVID-19 who received prophylactic anticoagulation.

Supplementary figure S4. Graphical representation of covariate balance after IP-weighting.

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Supplementary table S1. Definitions and codes used for in- and exclusion criteria, exposure, outcomes and covariates.

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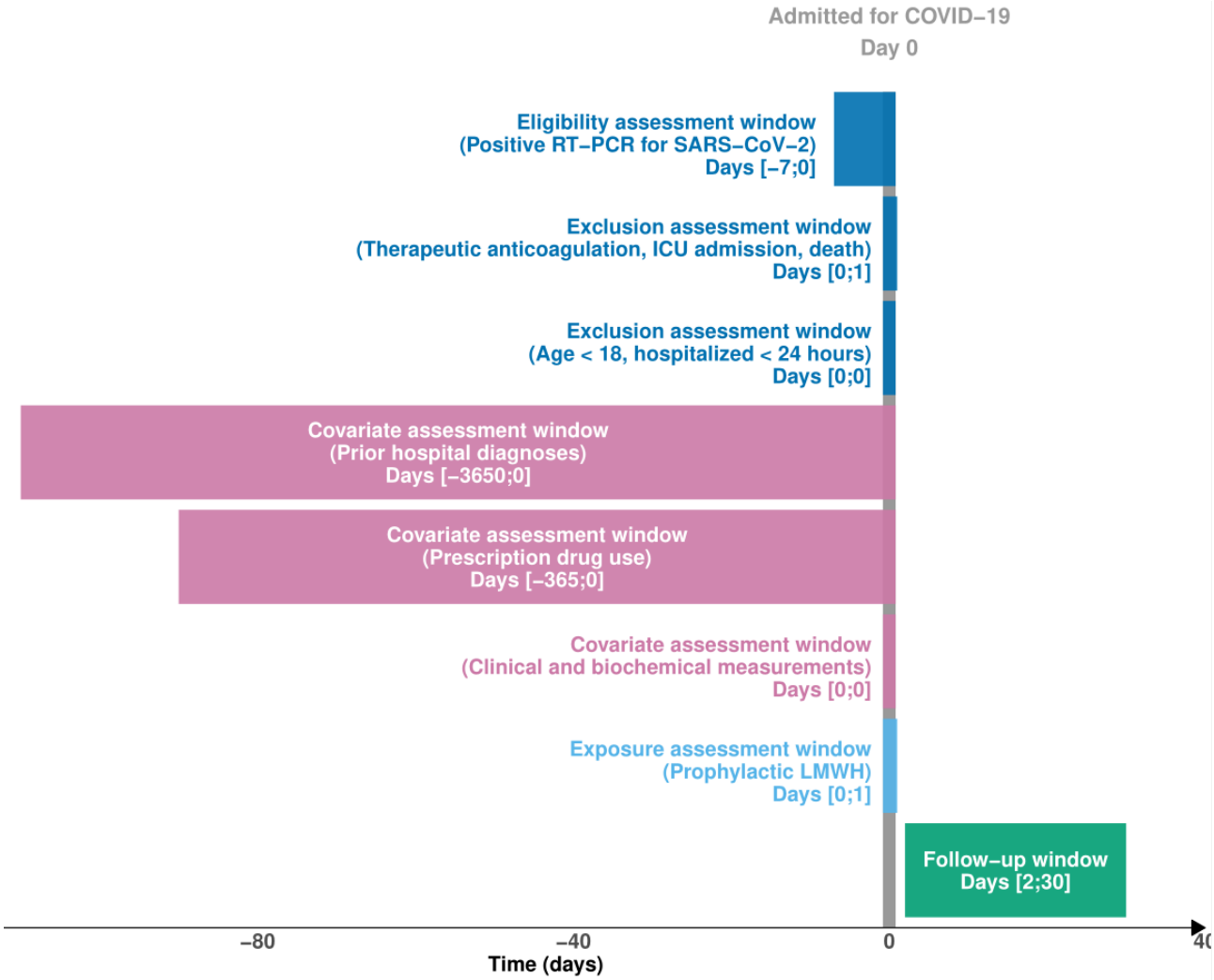
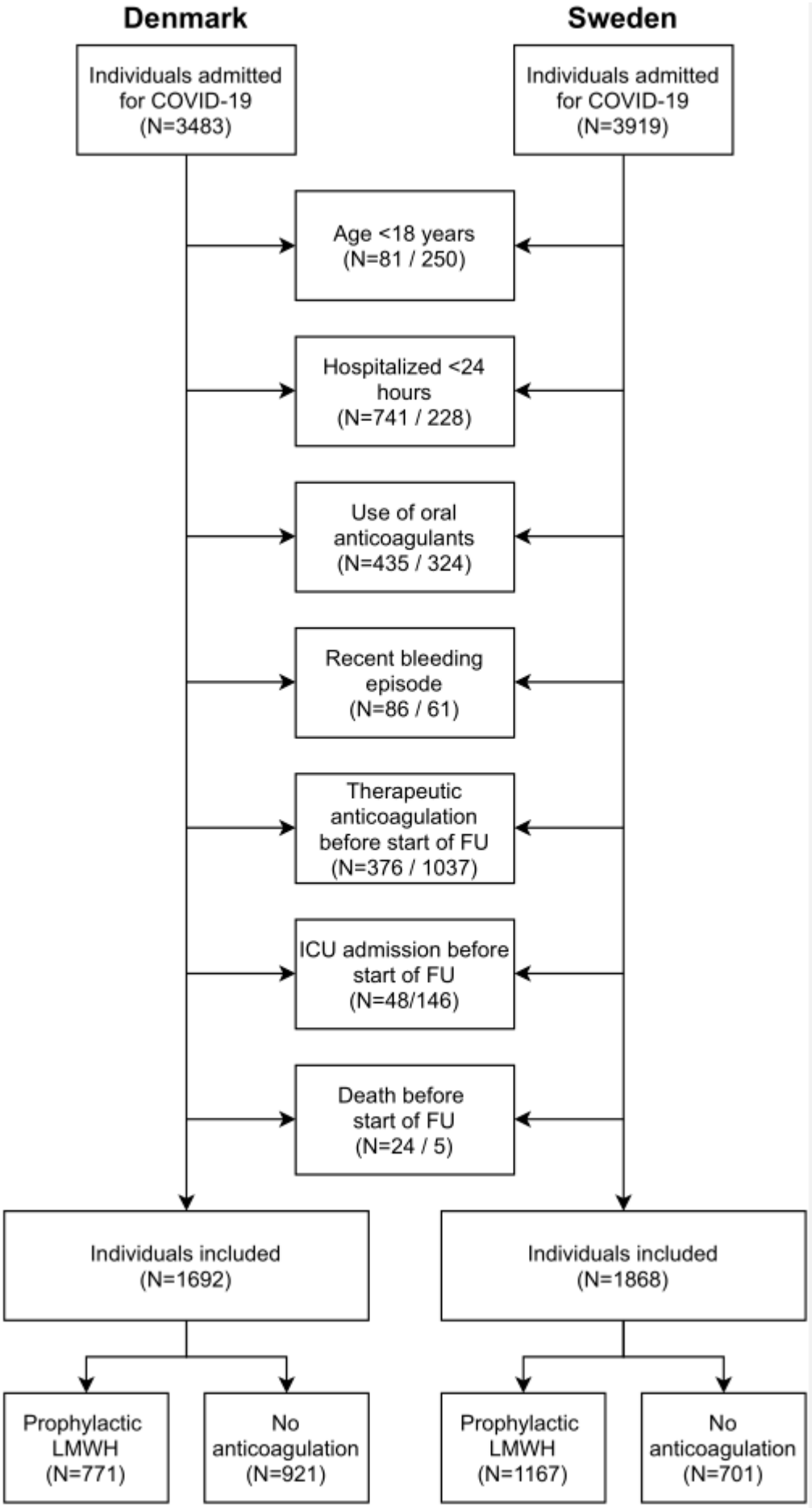
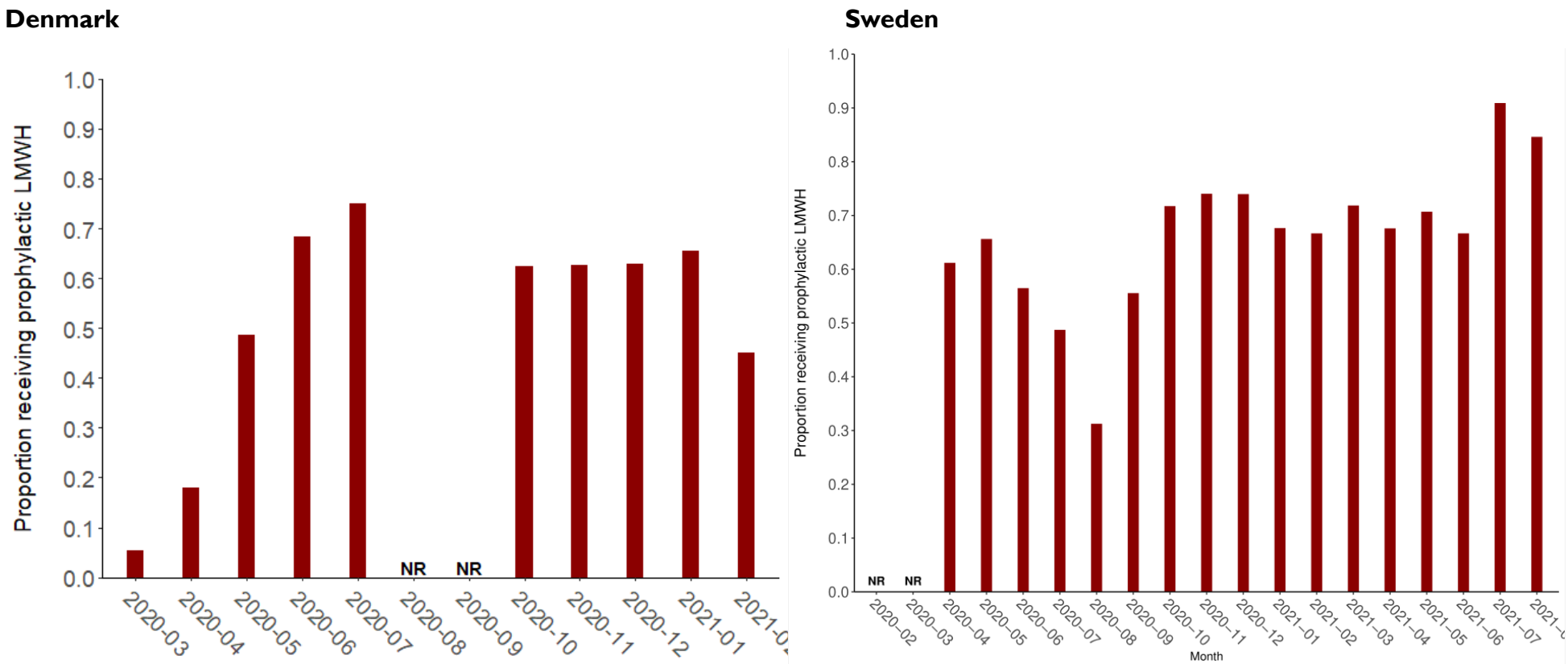
Supplementary figure S1. Study design diagram.



Supplementary figure S2. Flow chart of cohort selection in Denmark and Sweden.



Supplementary figure S3. Monthly proportion of individuals admitted for COVID-19 receiving prophylactic low molecular weight heparin.

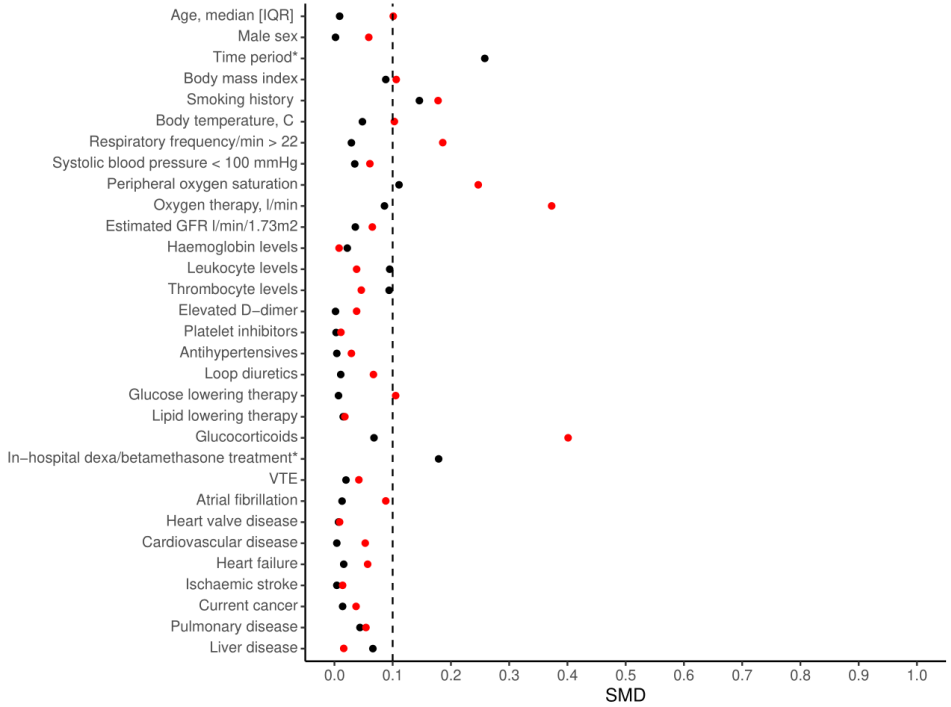


NR = Not reported due to privacy legislation (less than five individuals received prophylactic anticiagulation)

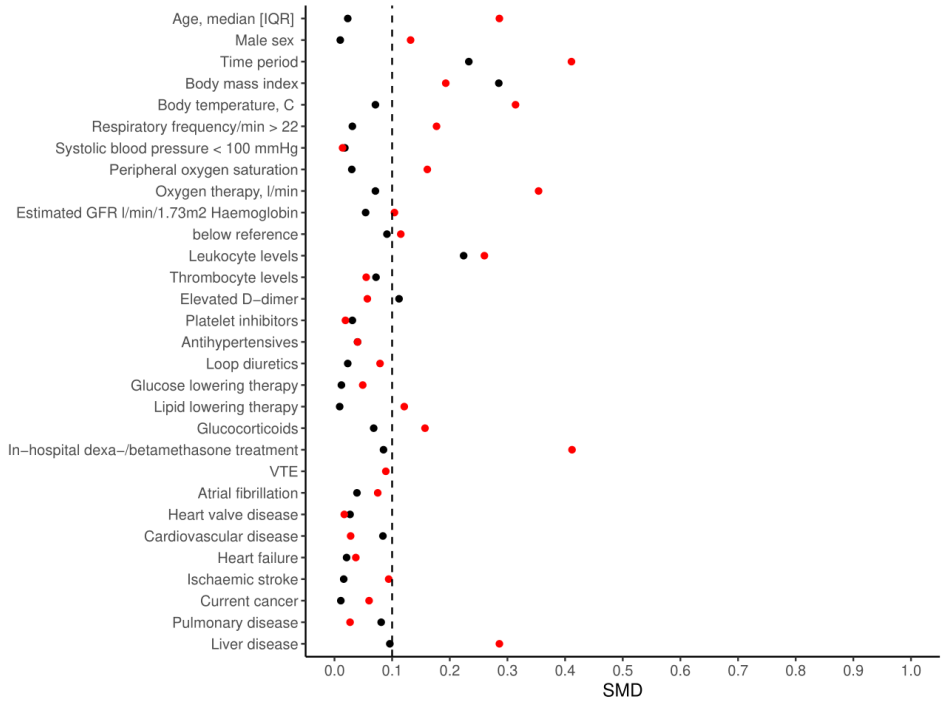
Supplementary figure S4. Graphical representation of covariate balance after IP-weighting.

Red dots represent the unweighted population, black dots the inverse probability weighted population.

Denmark



Sweden

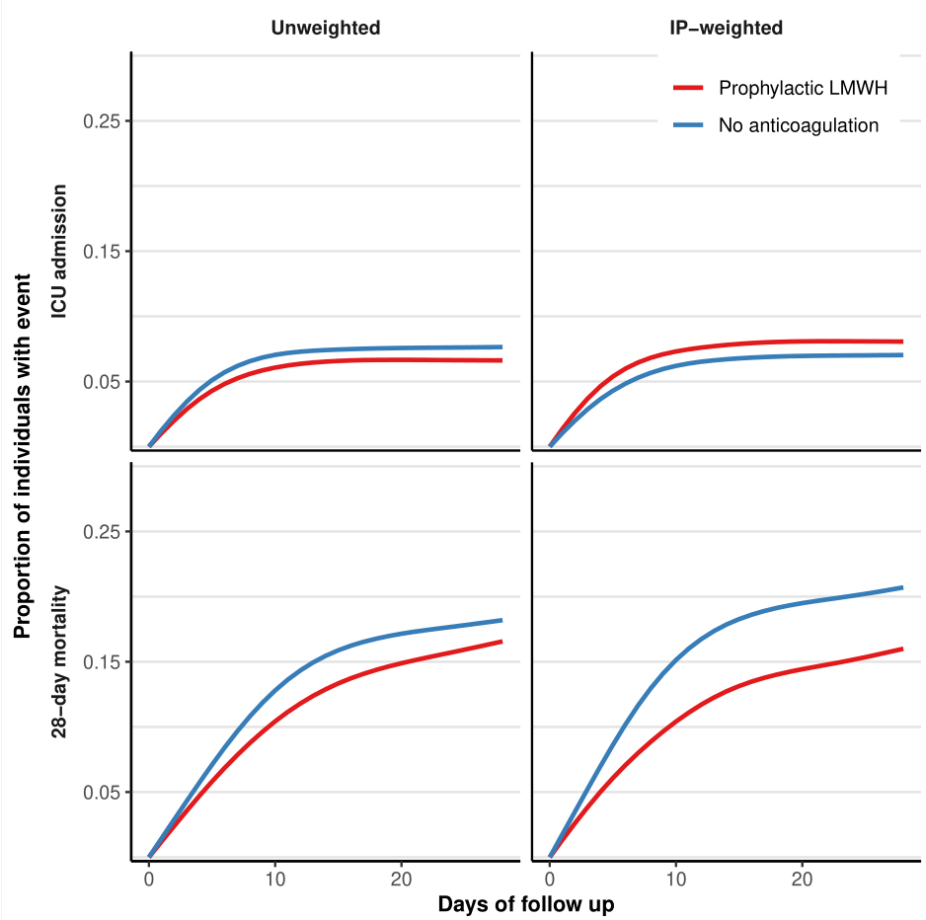


*Unweighted standardised mean difference > 1.0

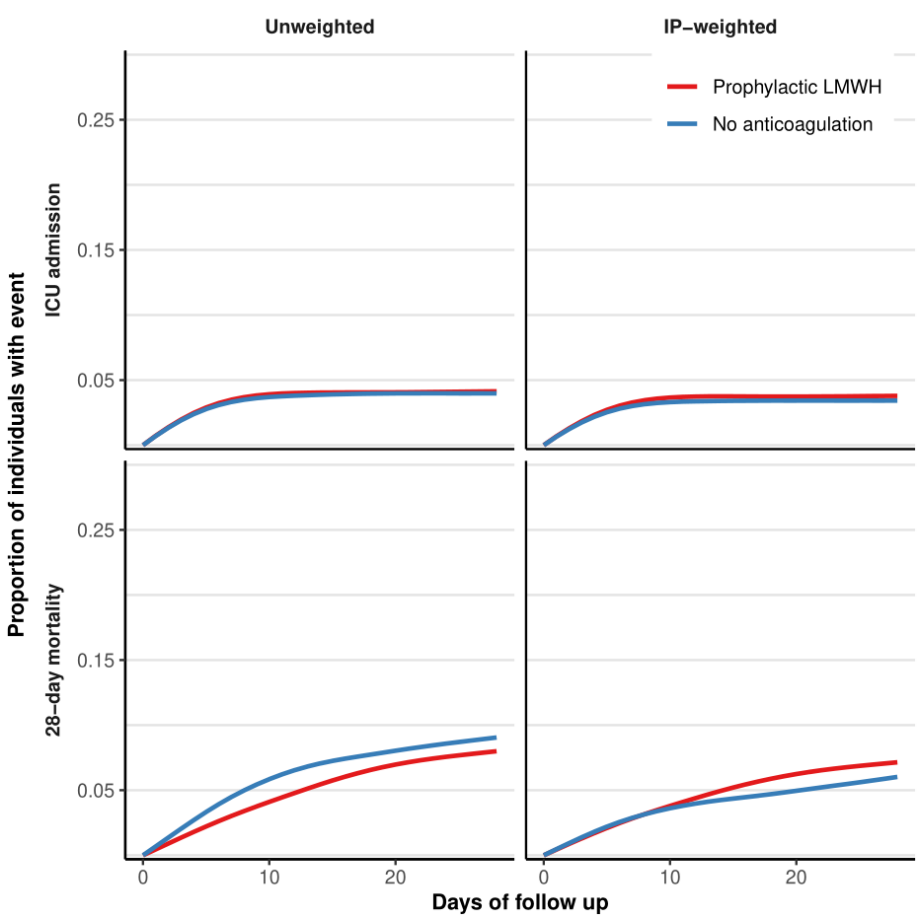
Supplementary figure S5. Unweighted and IP-weighted cumulative incidence plots for ICU admission and death in Denmark and Sweden.

Cumulative incidence curves were smoothed using cubic splines and a smoothing parameter of 0.7 to comply with local privacy regulation.

Denmark



Sweden



Supplementary table S1. Definitions of clinical entities used in the study.

Condition	Coding system	Codes	Window	Variable type
Exclusion criteria				
Major bleeding	ICD-10	D62 I60-I62 J942 K250 K252 K254 K256 K260 K262 K264 K270 K272 K274 K276 K280 K282 K284 K286 K290 K298A K625 K638C K920-K922 N02 N93 R04 R31 S064-S066	[-365; -1]	Binary
Oral anticoagulant use	ATC	B01AA03 B01AA04 B01AF01-B01AF03 B01AE07	[-365; 0]	Binary
Intensive care unit admission	SKS	NABB NABE	[0; 1]	Binary
Low-molecular weight heparin therapy (therapeutic dose)	ATC	B01AB04 B01AB05 B01AB10	[0; 1]	Binary
Other heparin therapy	ATC	B01AB01 B01AB02 B01AB03 B01AB06-B01AB09 B01AB11 B01AB12 B01AB51	[0; 1]	Binary
Exposure				
Low-molecular weight heparin (prophylactic dose)	ATC	B01AB04 B01AB05 B01AB10	[0; 1]	Binary
Outcome				
Low-molecular weight heparin (therapeutic dose)	ATC	B01AB04 B01AB05 B01AB10	[2; 29]	Binary
Venous thromboembolism	ICD-10	I801 I802 I803 I26	[2; 29]	Binary
Major bleeding	ICD-10	D62 I60-I62 J942 K250 K252 K254 K256 K260 K262 K264 K270 K272 K274 K276 K280 K282 K284 K286 K290 K298A K625 K638C K920-K922 N02 N93 R04 R31 S064-S066	[2; 29]	Binary
All-cause mortality	EHR	-	[2; 29]	Binary

Intensive care unit admission	EHR	-	[2; 29]	Binary
Mechanical ventilation	EHR	-	[2; 29]	Binary
Covariates				
Age	-	-	[0; 0]	Continuous
Sex	-	-	[0; 0]	Binary
Prescription drug use				
Antihypertensive drug use	ATC	C03A C07 C08 C09	[-365; 0]	Binary
Glucose lowering drugs	ATC	A10	[-365; 0]	Binary
Platelet inhiubitors	ATC	B01AC N02BA01 N02BA51	[-365; 0]	Binary
Loop diuretics	ATC	C03C	[-365; 0]	Binary
Glucose lowering drugs	ATC	A10	[-365; 0]	Binary
Lipid lowering drugs	ATC	C10AA C10AB	[-365; 0]	Binary
Glucocorticoids	ATC	H02AB	[-365; 0]	Binary
Glucocorticoids (intravenous)	ATC	H02AB	[0; 1]	Binary
Prior medical history				
Venous thromboembolism	ICD-10	I801 I802 I803 I26	[-365; -1]	Binary
Atrial fibrillation	ICD-10	I48	[-365; -1]	Binary
Thrombophilia	ICD-10	D685 D686	[-3650; -1]	Binary
Cancer	ICD-10	C00-C43 C45-C97	[-365; -1]	Binary
Myeloproliferative disease	ICD-10	D45 D46 D47	[-3650; -1]	Binary
Heart valve disease	ICD-10	I05-I08 I098 I34-I37 I39 I511A Q22 Q23	[-3650; -1]	Binary
Obesity	ICD-10	E66	[-3650; -1]	Binary
Cardiovascular disease	ICD-10	I20-I26 I30-I32 I40-I43 I47-I50	[-3650; -]	Binary
Heart failure	ICD-10	I50	[-3650; -1]	Binary
Pulmonary disease	ICD-10	J40-J47 J80-J99	[-3650; -1]	Binary
		B18 K700-K703 K709 K71 K73 K74 K760		
Liver disease	ICD-10	B150 B160 B162 B190 K704 K72 K766 I85	[-3650; -1]	Binary

Biochemical and clinical measurements at admission				
Leukocyte count at admission (<3.5 or >8.8*10^9/l)	NPU	NPU02593	[0; 0]	Discrete
Thrombocyte count at admission (<145 or >390*10^9/l)	NPU	NPU03568	[0; 0]	Discrete
Hemoglobin* (Female: <7.3, male: <8.3 mmol/l)	NPU	NPU02319 NPU28289 NPU18684 NPU28289 NPU19767	[0; 0]	Discrete
Elevated D-dimer*	NPU	NPU02044	[0; 0]	Binary
Estimated glomerular filtration rate, ml/min/1.73m^2	NPU	DNK35301 DNK35302 DNK35304 DNK35303 DNK35131	[0; 0]	Categorical, ordered
Respiratory frequency	EHR	-	[0; 0]	Binary (above or below 22)
Peripheral oxygen saturation (<88, 88-92, >92%)	EHR	-	[0; 0]	Categorical, ordered
Hypotension (systolic blood pressure <100 mmHg)	EHR	-	[0; 0]	Binary
Body temperature (<37.5, 37.5-38.4, 38.5+ C)			[0; 0]	Categorical
Maximum oxygen supplementation (0, 1-4, 5+ l/min)	EHR	-	[0; 1]	Categorical
Body mass index	EHR	-	[-365; 0]	Continuous
Smoking status	EHR	-	[-365; 0]	Categorical

* Age-specific cut-offs between 0.5 and 0.8 FEU/l

Supplementary table S2. Model specifications for inverse probability weighting.

Independent variable	Type
Treatment model	
Age	Continuous (linear)
Sex	Binary
Date of admission	Continuous (natural spline, 3 knots)
Estimated glomerular filtration rate*†	Categorical
Peripheral oxygen saturation (%)†	Categorical
Oxygen supplementation (l/min.) †	Categorical
Body temperature†	Categorical
Hypotension†	Categorical
Respiratory frequency†	Categorical
Recent VTE diagnosis	Binary
Atrial fibrillation	Binary
Cancer	Binary
Cardiovascular disease	Binary
Ischaemic stroke	Binary
Heart valve disease	Binary
In-hospital intravenous beta-/dexamethasone	Binary
Platelet inhibitors	Binary
Loop diuretics	Binary
Glucose lowering drugs	Binary
Oral glucocorticoids	Binary
Antihypertensives	Binary
Lipid lowering therapy	Binary

* Calculated according to CKD-EPI formula

† Not included in the missing data model

Supplementary table S3. Baseline characteristics of individuals with missing and complete information on variables included in the missing data model.

	Missing information (N=176)	Complete cases (N=1516)	SMD	Missing information (N=397)	Complete cases (N=1471)	SMD
Demographics						
Age, median [IQR]	60.00 [37.00, 76.25]	73.00 [59.00, 81.00]	0.46	38.00 [30.00, 57.00]	62.00 [49.50, 74.00]	0.98
Male sex	64 (36)	813 (54)	0.60	138 (35)	869 (59.1)	0.50
Time period			0.35			0.25
Before June 2020	51 (29)	568 (37)		161 (41)	616 (42)	
June to October 2020	24 (14)	169 (11)		68 (17)	148 (10)	
November 2020 to February 2021	101 (57)	779 (51)		89 (22)	443 (30)	
March 2021 to June 2021				71 (18)	235 (16)	
July 2021 to August 2021				8 (2)	29 (2)	
Prescription drug use						
Platelet inhibitors	36 (20)	383 (25)	0.12	35 (9)	161 (11)	0.07
Antihypertensives	50 (28)	696 (46)	0.37	82 (21)	405 (28)	0.16
Loop diuretics	17 (10)	214 (14)	0.14	26 (7)	132 (9)	0.09
Glucose lowering therapy	24 (14)	323 (21)	0.20	46 (12)	271 (18)	0.19
Lipid lowering therapy	35 (20)	473 (31)	0.26	34 (9)	239 (16)	0.24
Glucocorticoids	16 (9)	266 (18)	0.25	74 (19)	325 (22)	0.09
In-hospital dexa-/betamethasone treatment	31 (18)	632 (42)	0.55	57 (14)	432 (29)	0.37
Medical history						
VTE	n<5	NR	-	0 (0)	0 (0)	-
Atrial fibrillation	6 (3)	40 (3)	0.05	n<5	NR	-
Heart valve disease	10 (6)	63 (4)	0.07	n<5	NR	-
Cardiovascular disease	31 (18)	361 (24)	0.15	38 (10)	222 (15)	0.17
Heart failure	9 (5)	103 (7)	0.07	11 (3)	83 (6)	0.14
Ischaemic stroke	7 (4)	117 (8)	0.16	n<5	NR	-
Current cancer	22 (12)	135 (9)	0.12	35 (9)	128 (9)	0.00

NR: Not reported due to local privacy regulation

Supplementary table S4. IP-weighted baseline characteristics for the Danish and Swedish cohort.

Binary variables are presented as counts and percentages in the form N (%) and continuous variables as median and interquartile range.

	Denmark			Sweden		
	Prophylactic LMWH (N=696)	**No anticoagulation** (N=823)	**SMD**	**Prophylactic LMWH** (N=1258)	**No anticoagulation** (N=549)	**SMD**
Demographics						
Age, median [IQR]	73.00 [58.00, 81.74]	74.00 [57.93, 82.00]	0.01	59.00 [46.00, 72.00]	61.00 [43.00, 74.48]	0.02
Male sex	350 (50)	415 (50)	0.00	706 (56)	305 (56)	0.01
Time period			0.26			0.23
Before June 2020	201 (29)	331 (40)		538 (43)	217 (40)	
June to October 2020	82 (12)	103 (13)		104 (8)	83 (15)	
November 2020 to February 2021	413 (59)	389 (47)		389 (31)	164 (30)	
March to June 2021	-	-		200 (16)	79 (14)	
July 2021 and onwards	-	-		28 (2)	6 (1)	
Clinical measurements						
Body mass index*			0.09			0.29
<18.5	28 (5)	27 (4)		26 (4)	-†	
18.5-24	198 (32)	229 (34)		229 (34)	128 (47)	
25-34	328 (54)	365 (55)		379 (56)	125 (46)	
35+	58 (9)	48 (7)		42 (6)	18 (7)	
Smoking history*			0.15			
Ex-smoker	260 (53)	274 (46)		-	-	
Current smoker	53 (11)	76 (13)		-	-	
Body temperature, C			0.05			0.07
37.5-38.4	190 (27)	242 (29)		392 (31)	171 (31)	
38.5+	158 (23)	182 (22)		364 (29)	143 (26)	
Respiratory frequency/min > 22	248 (36)	282 (34)	0.03	562 (45)	237 (43)	0.03
Systolic blood pressure < 100 mmHg	25 (4)	35 (4)	0.04	52 (4)	25 (4)	0.02
Low peripheral oxygen saturation, %			0.11			0.03

<88	27 (4)	17 (2)		59 (5)	23 (4)	
88-92	84 (12)	110 (13)		198 (16)	84 (15)	
Oxygen therapy, l/min			0.09			0.07
1-4	209 (30)	229 (28)		413 (33)	163 (30)	
5+	54 (8)	51 (6)		109 (9)	47 (8)	
Biochemical measurements						
Reduced kidney function, eGFR l/min/1.73m2			0.04			0.05
30-59	97 (14)	118 (14)		228 (18)	110 (20)	
15-29	28 (4)	38 (5)		64 (5)	30 (6)	
<15	8 (1)	11 (1)		26 (2)	12 (2)	
Haemoglobin below reference*	258 (37)	296 (36)	0.02	403 (32)	160 (30)	0.09
Leukocyte levels*			0.10			0.22
Below reference	161 (23)	215 (26)		100 (8)	46 (8)	
Above reference	37 (5)	54 (7)		234 (19)	151 (28)	
Thrombocyte levels*			0.09			0.07
Below reference	104 (15)	101 (12)		192 (16)	90 (17)	
Above reference	62 (9)	88 (11)		61 (5)	19 (4)	
Elevated D-dimer*	332 (66)	305 (66)	0.00	760 (71)	212 (66)	0.11
Prescription drug use						
Platelet inhibitors	170 (24)	200 (24)	0.00	136 (11)	65 (12)	0.03
Antihypertensives	319 (46)	375 (46)	0.00	341 (27)	159 (29)	0.04
Loop diuretics	96 (14)	111 (13)	0.01	118 (9)	55 (10)	0.02
Glucose lowering therapy	139 (20)	162 (20)	0.01	221 (18)	94 (17)	0.01
Lipid lowering therapy	200 (29)	242 (29)	0.02	187 (15)	80 (15)	0.01
Glucocorticoids	122 (18)	124 (15)	0.07	280 (22)	107 (20)	0.07
In-hospital dexa-/betamethasone treatment	298 (43)	282 (34)	0.18	337 (27)	127 (23)	0.09
Medical history						
VTE	7 (1)	10 (1)	0.02	0 (0)	0 (0)	-
Atrial fibrillation	27 (4)	30 (4)	0.01	19 (1)	11 (2)	0.04
Heart valve disease	34 (5)	42 (5)	0.01	21 (2)	11 (2)	0.03

Cardiovascular disease	169 (24)	202 (24)	0.00	187 (15)	98 (18)	0.08
Heart failure	51 (7)	57 (7)	0.02	68 (5)	32 (6)	0.02
Ischaemic stroke	49 (7)	58 (7)	0.00	35 (3)	17 (3)	0.02
Current cancer	65 (9)	74 (9)	0.01	114 (9)	52 (9)	0.01
Pulmonary disease	150 (22)	193 (23)	0.04	156 (12)	83 (15)	0.08
Liver disease	10 (1)	20 (2)	0.07	43 (3)	30 (5)	0.10

LMWH: Low molecular weight heparin; GFR: Glomerular filtration rate; VTE: Venous thromboembolism, SMD: Standardised mean difference.

*Age-specific cut-offs between 0.5 and 0.8 FEU/l

* Information not available for all individuals in the IP-weighted cohorts, not included in the treatment model.

†Bmi < 25, categories combined due to local privacy regulations.

Supplementary table S5. Crude risk estimates for Denmark and Sweden.

		Risk, % (Events)		Comparison	
		LMWH	**Ref.**		
Outcome		**(N=771/1167)**	**(N=921/701)**	**RR (95% CI)**	**RD (95% CI)**
Mortality		16 (123)	17.7 (163)	0.90 (0.73, 1.11)	-1.7 (-5.3, 1.8)
		7.5 (88)	8.3 (58)	0.91 (0.67, 1.26)	-0.7 (-3.3, 1.8)
ICU admission		6.5 (50)	7.2 (66)	0.90 (0.63, 1.29)	-0.7 (-3.1, 1.8)
		3.9 (46)	3.4 (24)	1.15 (0.72, 1.9)	+0.5 (-1.3, 2.2)
VTE diagnosis		0.8 (6)	0.5 (5)	1.43 (0.43, 4.96)	+0.2 (-0.6, 1.1)
		2.4 (28)	3 (21)	0.80 (0.46, 1.42)	-0.6 (-2.2, 0.9)
Bleeding		0.6 (5)	0.5 (5)	1.19 (0.33, 4.28)	+0.1 (-0.7, 0.9)
		2.4 (28)	5.1 (36)	0.47 (0.29, 0.76)	-2.7 (-4.7, -1.0)

LMWH: Low molecular weight heparin; Ref.: Reference cohort not receiving anticoagulation; RR: Risk ratio; RD: Risk difference; ICU: Intensive care unit; VTE: Venous thromboembolism

Supplementary table S6. IP-weighted risk estimates for sensitivity analyses with a shortened exposure assessment windows, matching data availability in Denmark and Sweden, body mass index adjusted estimates and when restricting to individuals who received in-hospital corticosteroid treatment.

		RR (95% CI)				
Outcome		**Main analysis**	**Exposure window: 24 hours**	**Shortened inclusion period* (Feb 2020-2021)**	**BMI-adjusted**	**In-hospital corticocosteroid treatment**
Mortality		0.76 (0.58-1.01)	0.87 (0.66-1.15)	0.76 (0.58-1.01)	0.83 (0.61-1.11)	0.61 (0.40-0.92)
		1.12 (0.72-1.74)	0.83 (0.58-1.20)	0.99 (0.62-1.58)	1.18 (0.66-2.09)	1.11 (0.49-2.52)
ICU admission		1.13 (0.70-1.84)	1.00 (0.63-1.57)	1.13 (0.70-1.84)	1.07 (0.67-1.7)	0.60 (0.28-1.29)
		1.11 (0.57-2.13)	1.06 (0.70-1.61)	1.16 (0.60-2.24)	0.74 (0.31-1.8)	NR
VTE diagnosis		NR	NR	NR	NR	NR
		0.68 (0.33-1.38)	0.83 (0.49-1.40)	0.68 (0.30-1.57)	0.68 (0.25-1.89)	NR
Bleeding		1.53 (0.32-7.39)	NR	1.53 (0.32-7.39)	NR	NR
		0.33 (0.17-0.63)	0.31 (0.16-0.60)	0.31 (0.15-0.64)	0.23 (0.10-0.56)	NR
Therapeutic LMWH		0.99 (0.63-1.57)	-	-	-	
		1.52 (0.87-2.67)	-			

NR: Not reported due to local privacy regulations (less than five events in one of the exposure groups).

* Study period only shortened in Sweden, corresponds to Danish study period.