

# **Supplemental Material**

**Table S1. Items included in the modified CHA2DS2-VASc score**

<b>Letter</b>	<b>Original items (Lip et al, Chest 2010)</b>	<b>Modified items</b>	<b>Score</b>
C	Left ventricular dysfunction or congestive heart failure	Yes (only congestive heart failure has been considered)	1
H	Hypertension	No	1
A2	Age $\geq$ 75 years	No	2
D	Diabetes	No	1
S2	Stroke /TIA/ systemic embolism	Not applicable	-
v	Vascular disease (previous history of MI, peripheral arterial disease or aortic plaque)	Yes (only peripheral arterial disease have been considered)	1
A	Age 65-74 years	No	1
Sc	Sex (female)	No	1

All conditions were defined during the period one year before index date.

The CHA2DS2-VASc score varies from 0 to 7.

**Table S2. Items included in the modified HAS-BLED score**

<b>Letter</b>	<b>Original items (Pisters et al, Chest 2010)</b>	<b>Modified items</b>	<b>Score</b>
H	Hypertension	No	1
A	Impaired renal and/or hepatic function	No	1 or 2
S	Previous history of stroke	Not applicable	-
B	Previous history of bleeding or predisposition to bleeding	Not applicable	-
L	Labile INR	Not applicable	-
E	Age > 65 years (Elderly)	No	1
D	Drugs/alcohol concomitantly	Yes for alcohol consumption. We considered that it is the case when an individual has been hospitalized for all causes related to alcohol.	1 or 2

All conditions were defined during the period before VKA therapy.  
The modified HAS-BLED score varies from 0 to 6.

**Table S3. Description of bridging agents**

Types of bridging agent

<b>Heparin bridging</b>	<b>All N=27147</b>	<b>Men N=14533</b>	<b>Women N=12614</b>
<b>Number of different types of LMWH/heparin, n (%)</b>			
1	27076 (99.7)	14497 (99.8)	12579 (99.7)
2	71 (0.3)	36 (0.2)	35 (0.3)
<b>Type of heparin</b>			
Tinzaparin	12276 (45.2)	6641 (45.7)	5635 (44.7)
Enoxaparin	8035 (29.6)	4254 (29.3)	3781 (30.0)
Nadroparin	1372 (5.1)	755 (5.2)	617 (4.9)
Dalteparin	41 (0.2)	20 (0.1)	21 (0.2)
Fondaparinux	4530 (16.7)	2433 (16.7)	2097 (16.6)
Heparin calcium	964 (3.6)	466 (3.2)	498 (4.0)

LMWH: low-molecular weight heparin

Estimation of total delivered dose and injections of bridging agent

<b>All</b>	<b>Tinzaparin 12276 (45.2)</b>	<b>Enoxaparin N=8035 (29.6)</b>	<b>Nadroparin 1372 (5.1)</b>	<b>Dalteparin N=41 (0.2)</b>	<b>Fondaparinux N=4530 (16.7)</b>	<b>Heparin calcium N=964 (3.6)</b>
Unit	Anti-factor Xa international unit (IU)	Anti-factor Xa international unit (IU)	Anti-factor Xa international unit (IU)	Anti-factor Xa international unit (IU)	Milligram	International unit (IU)
Total delivered dose						
Mean (SD)	107132.1 (64713.8)	78932.7 (62624.9)	102012.5 (67825.6)	86646.3 (91616.8)	169.8 (3221.6)	188784.2 (139517.0)
Range	15.0-576000.0	4000.0-720000.0	75.0-592800.0	10000.0-450000.0	5.0-156000.0	10000.0-1360000.0
Total delivered injections (n)						
Mean (SD)	7.9 (4.2)	11.9 (7.8)	8.2 (4.6)	13.2 (12.4)	7.7 (3.9)	12.9 (9.4)
Range	2.0-56.0	2.0-90.0	2.0-42.0	2.0-60.0	2.0-32.0	2.0-180.0

SD: standard deviation

**Table S4. Description of other types of bleeding during the first month of follow-up**

		Men (n=45510)		Women (n=45316)	
		n	%	n	%
D62	Acute post-hemorrhagic anemia	7	0.00015	9	0.00020
H113	Conjunctival hemorrhage	0	0.00000	1	0.00002
J942	Hemothorax	1	0.00002	0	0.00000
K661	Hemoperitoneum	2	0.00004	2	0.00004
M250	Hemarthrosis	2	0.00004	5	0.00011
N028					
N029	Hematuria	45	0.00099	42	0.00093
R31					
N950	Postmenopausal bleeding	-	-	1	0.00002
R040	Epistaxis	18	0.00040	18	0.00040
R042	Hemoptysis	3	0.00007	4	0.00009
R048	Hemorrhage from other sites in respiratory passages	0	0.00000	1	0.00002
R58	Hemorrhage not elsewhere classified	2	0.00004	1	0.00002
<b>Total</b>		<b>78</b>	<b>0.00171</b>	<b>84</b>	<b>0.00185</b>

**Table S5. Bleeding risks at one-month of follow-up according to types of heparin**

Bleeding	n (events)/ Ntotal*	HR†	[95% CI]	
<i>From 0 to 1 month of follow-up</i>				
<b>Heparin class</b>				
No bridging	191/63679	1		
<b>LWMH</b>	<b>100/21606</b>	<b>1.58</b>	<b>1.24</b>	<b>2.02</b>
<b>Fondaparinux</b>	<b>23/4511</b>	<b>1.77</b>	<b>1.15</b>	<b>2.74</b>
UFH (heparin calcium)	4/959	1.33	0.49	3.58
<b>Type of heparin</b>				
No bridging	191/63679	1		
<b>Tinzaparin</b>	<b>59/12227</b>	<b>1.64</b>	<b>1.23</b>	<b>2.21</b>
<b>Enoxaparin</b>	<b>37/7981</b>	<b>1.59</b>	<b>1.12</b>	<b>2.27</b>
Nadroparin	4/1357	1.02	0.38	2.76
Dalteparin	0/41	-	-	-
<b>Fondaparinux</b>	<b>23/4511</b>	<b>1.77</b>	<b>1.15</b>	<b>2.74</b>
UFH (heparin calcium)	4/959	1.33	0.49	3.58

\*After removing individuals with 2 concomitant heparin dispensing (n=71).

†Adjusted for age, sex, social deprivation index, type of VKA, type of VKA prescribers, comorbidities (heart failure, diabetes, hypertension, chronic renal impairment, chronic hepatitis, peripheral arterial disease), alcohol and smoking related conditions, CHA2DS2-VASc and HAS-BLED scores, concomitant medications (antiarrhythmic agents, lipid-lowering agents, non-steroidal anti-inflammatory agents, oral corticosteroids, gastroprotective agents, benzodiazepines, antiplatelet agents).

**Table S6. Study of the interaction between bridging and modified CHA2DS2-VASc and HAS-BLED scores associated with bleeding risk at one month of follow-up (N=90,826)**

	CHA2DS2-VASC: 0-2 (N=36105)				CHA2DS2-VASC=3 (N=23667)				CHA2DS2-VASC: 4-7 (N=31054)				P interaction (bridging x CHA2DS2-VASC)*		
	n (events)/Ntotal	HR	[95% CI]	P-value	n (events)/Ntotal	HR	[95% CI]	P-value	n (events)/Ntotal	HR	[95% CI]	P-value			
<b>Bleeding</b>															
Heparin bridging													0.19		
No	60/24596	Ref	-	-	-	59/17247	Ref	-	-	-	72/21836	Ref	-	-	-
Yes	36/11509	1.24	0.82	1.89	0.31	36/6420	1.68	1.10	2.55	0.02	55/9218	1.85	1.30	2.63	0.0007
	HAS-BLED: 0-1 (N=31679)				HAS-BLED=2 (N=32127)				HAS-BLED: 3-5 (N=27020)				P interaction (bridging x HAS-BLED)*		
	n (events)/Ntotal	HR	[95% CI]	P-value	n (events)/Ntotal	HR	[95% CI]	P-value	n (events)/Ntotal	HR	[95% CI]	P-value			
<b>Bleeding</b>															
Heparin bridging													0.51		
No	55/22551	Ref	-	-	-	64/21959	Ref	-	-	-	72/19169	Ref	-	-	-
Yes	35/9128	1.65	1.07	2.56	0.02	37/10168	1.28	0.85	1.92	0.24	55/7851	1.89	1.33	2.70	0.0004

\*Adjusted for age, sex, social deprivation index, type of VKA, type of VKA prescribers, comorbidities (heart failure, diabetes, hypertension, chronic renal impairment, chronic hepatitis, peripheral arterial disease), alcohol and smoking related conditions, CHA2DS2-VASc and HAS-BLED scores, concomitant medications (antiarrhythmic agents, lipid-lowering agents, non-steroidal anti-inflammatory agents, oral corticosteroids, gastroprotective agents, benzodiazepines, antiplatelet agents).

**Table S7. Demographic and clinical characteristics of the study population according to sex**

	<b>Total</b> <b>N=90,826</b>	<b>Men</b> <b>N=45,510 (50.1)</b>	<b>Women</b> <b>N=45,316 (49.9)</b>	<b>P-value</b>
<b>Age, mean (SD)</b>	72.3 (11.7)	69.4 (11.7)	75.2 (11.0)	<0.0001*
<b>Women, n (%)</b>	27147 (29.9)	14533 (31.9)	12614 (27.8)	<0.0001†
<b>Social deprivation index (quintiles), n (%)</b>				
1	15484 (17.9)	8138 (18.8)	7346 (17.0)	<0.0001†
2	17295 (20.0)	8695 (20.1)	8600 (19.9)	
3	17399 (20.1)	8621 (19.9)	8778 (20.3)	
4	18121 (20.9)	8946 (20.7)	9175 (21.2)	
5	18330 (21.2)	8918 (20.6)	9412 (21.7)	
Missing data	4197 (4.6)	2192 (4.8)	2005 (4.4)	0.005†
<b>Type of VKA, n (%)</b>				
Acenocoumarol	6220 (6.8)	2943 (6.5)	3277 (7.2)	<0.0001†
Fluindione	75192 (82.8)	38325 (84.2)	36867 (81.4)	
Warfarin	9414 (10.4)	4242 (9.3)	5172 (11.4)	
<b>Type of VKA prescribers, n (%)</b>				
General practitioner	48080 (52.9)	21968 (48.3)	26112 (57.6)	<0.0001†
Private practice cardiologist	41049 (45.2)	22662 (49.8)	18387 (40.6)	
Other private practice specialist	1467 (1.6)	758 (1.7)	709 (1.6)	
Practitioner in private institution	230 (0.3)	122 (0.3)	108 (0.2)	
<b>Comorbidities, n (%)</b>				
Heart failure	20827 (22.9)	9691 (21.3)	11136 (24.6)	<0.0001†
Diabetes	15133 (16.7)	8521 (18.7)	6612 (14.6)	<0.0001†
Hypertension	57233 (63.0)	28058 (61.7)	29175 (64.4)	<0.0001†
Chronic renal impairment	879 (1.0)	474 (1.0)	405 (0.9)	0.02†
Chronic hepatitis	236 (0.3)	130 (0.3)	106 (0.2)	0.13†
Peripheral arterial disease	2678 (2.9)	1816 (4)	862 (1.9)	<0.0001†
Alcohol-related conditions, n (%)	411 (0.5)	312 (0.7)	99 (0.2)	<0.0001†
Smoking-related conditions, n (%)	959 (1.1)	707 (1.6)	252 (0.6)	<0.0001†
CHA2DS2-VASc score, mean (SD)	2.8 (1.5)	2.1 (1.3)	3.5 (1.2)	<0.0001*
CHA2DS2-VASc score, n (%)				<0.0001‡
Low (0-2)	36105 (39.8)	27005 (59.3)	9100 (20.1)	
Intermediate (3)	23667 (26.0)	11399 (25.1)	12268 (27.1)	
High (4-7)	31054 (34.2)	7106 (15.6)	23948 (52.8)	
HAS-BLED score, mean (SD)				<0.0001*
HAS-BLED score, n (%)	1.86 (1)	1.79 (1)	1.94 (0.9)	<0.0001‡



Low (0-1)	31679 (34.9)	17256 (37.9)	14423 (31.8)
Intermediate (2)	32127 (35.3)	15475 (34.0)	16652 (36.8)
High (3-5)	27020 (29.8)	12779 (28.1)	14241 (31.4)

**Concomitant medications, n (%)**

Antiarrhythmic agents	63642 (70.1)	30390 (66.8)	33252 (73.4)	<0.0001 <sup>†</sup>
Lipid-lowering agents	33974 (37.4)	17142 (37.7)	16832 (37.1)	0.10 <sup>‡</sup>
Non-steroidal anti-inflammatory agents	15369 (16.9)	7659 (16.8)	7710 (17)	0.46 <sup>‡</sup>
Oral corticosteroids	10085 (11.1)	4836 (10.6)	5249 (11.6)	<0.0001 <sup>†</sup>
Gastroprotective agents	27159 (29.9)	12245 (26.9)	14914 (32.9)	<0.0001 <sup>†</sup>
Benzodiazepines	23497 (25.9)	8515 (18.7)	14982 (33.1)	<0.0001 <sup>†</sup>
Antiplatelet agents	33844 (37.3)	18171 (39.9)	15673 (34.6)	<0.0001 <sup>†</sup>
Antihypertensive agents	73973 (81.4)	35566 (78.1)	38407 (84.8)	<0.0001 <sup>†</sup>

SD: standard deviation; VKA: vitamin K antagonist

\*t-test; <sup>†</sup>Chi-2 test; <sup>‡</sup>Cochran-Armitage trend test

**Table S8. Demographic and clinical characteristics of the study population according to sex and bridging status**

	Men				Women			
	All	No heparin bridging	Heparin bridging	P-value	All	No heparin bridging	Heparin bridging	P-value
	N=45510	N=30977 (68.1)	N=14533 (31.9)		N=45316	N=32702 (72.2)	N=12614 (27.8)	
<b>Age, mean (SD)</b>	69.4 (11.7)	69.8 (11.9)	68.5 (11.4)	<0.0001 <sup>a</sup>	75.2 (11)	75.3 (11.2)	74.9 (10.5)	0.004 <sup>*</sup>
<b>Social deprivation index (quintiles), n (%)</b>								
1	8138 (18.8)	5536 (18.8)	2602 (18.8)	0.88 <sup>b</sup>	7346 (17.0)	5337 (17.1)	2009 (16.7)	0.07 <sup>†</sup>
2	8695 (20.1)	5901 (20.0)	2794 (20.2)		8600 (19.9)	6135 (19.6)	2465 (20.5)	
3	8621 (19.9)	5878 (20.0)	2743 (19.8)		8778 (20.3)	6332 (20.3)	2446 (20.3)	
4	8946 (20.7)	6050 (20.5)	2896 (20.9)		9175 (21.2)	6583 (21.1)	2592 (21.5)	
5	8918 (20.6)	6093 (20.7)	2825 (20.4)		9412 (21.7)	6880 (22.0)	2532 (21.0)	
Missing data	2192 (4.8)	1519 (4.9)	673 (4.6)	0.21 <sup>b</sup>	2005 (4.4)	1435 (4.4)	570 (4.5)	0.54 <sup>†</sup>
<b>Type of VKA, n (%)</b>								
Acenocoumarol	2943 (6.5)	2271 (7.3)	672 (4.6)	<0.0001 <sup>b</sup>	3277 (7.2)	2661 (8.1)	616 (4.9)	<0.0001 <sup>†</sup>
Fluindione	38325 (84.2)	25672 (82.9)	12653 (87.1)		36867 (81.4)	26185 (80.1)	10682 (84.7)	
Warfarin	4242 (9.3)	3034 (9.8)	1208 (8.3)		5172 (11.4)	3856 (11.8)	1316 (10.4)	
<b>Type of VKA prescribers, n (%)</b>								
General practitioner	21968 (48.3)	15503 (50.0)	6465 (44.5)	<0.0001 <sup>b</sup>	26112 (57.6)	20117 (61.5)	5995 (47.5)	<0.0001 <sup>†</sup>
Private practice cardiologist	22662 (49.8)	14869 (48.0)	7793 (53.6)		18387 (40.6)	12021 (36.8)	6366 (50.5)	
Other private practice specialist	758 (1.7)	525 (1.7)	233 (1.6)		709 (1.6)	489 (1.5)	220 (1.7)	
Practitioner in private institution	122 (0.3)	80 (0.3)	42 (0.3)		108 (0.2)	75 (0.2)	33 (0.3)	
<b>Comorbidities, n (%)</b>								
Heart failure	9691 (21.3)	6704 (21.6)	2987 (20.6)	0.008 <sup>b</sup>	11136 (24.6)	7773 (23.8)	3363 (26.7)	<0.0001 <sup>†</sup>
Diabetes	8521 (18.7)	5985 (19.3)	2536 (17.4)	<0.0001 <sup>b</sup>	6612 (14.6)	4692 (14.3)	1920 (15.2)	0.02 <sup>†</sup>
Hypertension	28058 (61.7)	19207 (62.0)	8851 (60.9)	0.02 <sup>b</sup>	29175 (64.4)	20062 (61.3)	9113 (72.2)	<0.0001 <sup>†</sup>
Chronic renal impairment	474 (1.0)	362 (1.2)	112 (0.8)	<0.0001 <sup>b</sup>	405 (0.9)	309 (0.9)	96 (0.8)	0.06 <sup>†</sup>
Chronic hepatitis	130 (0.3)	103 (0.3)	27 (0.2)	0.006 <sup>b</sup>	106 (0.2)	78 (0.2)	28 (0.2)	0.74 <sup>†</sup>

Peripheral arterial disease	1816 (4.0)	1333 (4.3)	483 (3.3)	<0.0001 <sup>b</sup>	862 (1.9)	617 (1.9)	245 (1.9)	0.70 <sup>†</sup>
Alcohol-related conditions, n (%)	312 (0.7)	211 (0.7)	101 (0.7)	0.87 <sup>b</sup>	99 (0.2)	75 (0.2)	24 (0.2)	0.42 <sup>†</sup>
Smoking-related conditions, n (%)	707 (1.6)	495 (1.6)	212 (1.5)	0.26 <sup>b</sup>	252 (0.6)	185 (0.6)	67 (0.5)	0.66 <sup>†</sup>
CHA2DS2-VASc score, mean (SD)	2.10 (1.30)	2.15 (1.30)	2.00 (1.30)	<0.0001 <sup>a</sup>	3.50 (1.20)	3.46 (1.20)	3.59 (1.20)	<0.0001 <sup>*</sup>
CHA2DS2-VASc score, n (%)								
Low (0-2)	27005 (59.3)	17871 (57.7)	9134 (62.9)	<0.0001 <sup>c</sup>	9100 (20.1)	6725 (20.6)	2375 (18.8)	<0.0001 <sup>‡</sup>
Intermediate (3)	11399 (25.0)	7974 (25.7)	3425 (23.6)		12268 (27.1)	9273 (28.4)	2995 (23.7)	
High (4-7)	7106 (15.6)	5132 (16.6)	1974 (13.6)		23948 (52.8)	16704 (51.1)	7244 (57.4)	
HAS-BLED score, mean (SD)	1.79 (1.0)	1.83 (1.0)	1.71 (1.0)	<0.0001 <sup>a</sup>	1.94 (0.9)	1.9 (0.9)	2.04 (0.9)	<0.0001 <sup>*</sup>
HAS-BLED score, n (%)								
Low (0-1)	17256 (37.9)	11314 (36.5)	5942 (40.9)	<0.0001 <sup>c</sup>	14423 (31.8)	11237 (34.4)	3186 (25.3)	<0.0001 <sup>‡</sup>
Intermediate (2)	15475 (34.0)	10494 (33.9)	4981 (34.3)		16652 (36.7)	11465 (35.1)	5187 (41.1)	
High (3-5)	12779 (28.1)	9169 (29.6)	3610 (24.8)		14241 (31.4)	10000 (30.6)	4241 (33.6)	
<b>Concomitant medications, n (%)</b>								
Antiarrhythmic agents	30390 (66.8)	20508 (66.2)	9882 (68.0)	0.0002 <sup>b</sup>	33252 (73.4)	24154 (73.9)	9098 (72.1)	0.0002 <sup>†</sup>
Lipid-lowering agents	17142 (37.7)	12020 (38.8)	5122 (35.2)	<0.0001 <sup>b</sup>	16832 (37.1)	12181 (37.2)	4651 (36.9)	0.46 <sup>†</sup>
Non-steroidal anti-inflammatory agents	7659 (16.8)	4934 (15.9)	2725 (18.8)	<0.0001 <sup>b</sup>	7710 (17.0)	5122 (15.7)	2588 (20.5)	<0.0001 <sup>†</sup>
Oral corticosteroids	4836 (10.6)	3095 (10.0)	1741 (12.0)	<0.0001 <sup>b</sup>	5249 (11.6)	3500 (10.7)	1749 (13.9)	<0.0001 <sup>†</sup>
Gastroprotective agents	12245 (26.9)	8464 (27.3)	3781 (26.0)	0.003 <sup>b</sup>	14914 (32.9)	10951 (33.5)	3963 (31.4)	<0.0001 <sup>†</sup>
Benzodiazepines	8515 (18.7)	5841 (18.9)	2674 (18.4)	0.24 <sup>b</sup>	14982 (33.1)	10824 (33.1)	4158 (33.0)	0.78 <sup>†</sup>
Antiplatelet agents	18171 (39.9)	13273 (42.8)	4898 (33.7)	<0.0001 <sup>b</sup>	15673 (34.6)	11451 (35.0)	4222 (33.5)	0.002 <sup>†</sup>
Antihypertensive agents	35566 (78.1)	24508 (79.1)	11058 (76.1)	<0.0001 <sup>b</sup>	38407 (84.8)	27782 (85.0)	10625 (84.2)	0.06 <sup>†</sup>

SD: standard deviation; VKA: vitamin K antagonist

\*t-test; †Chi-2 test; ‡Cochran-Armitage trend test

**Table S9. Study of the interaction between bridging and modified CHA2DS2-VASC and HAS-BLED scores associated with risk of ischemic stroke and systemic embolism at one month of follow-up (N=90,826)**

	CHA2DS2-VASC: 0-2 (N=36105)				CHA2DS2-VASC=3 (N=23667)				CHA2DS2-VASC: 4-7 (N=31054)				P interaction (bridging x CHA2DS2- VASC)*		
	n (events)/ Ntotal	HR	[95% CI]	P-value	n (events)/ Ntotal	HR	[95% CI]	P-value	n (events)/ Ntotal	HR	[95% CI]	P-value			
<b>Ischemic stroke and systemic embolism</b>															
Heparin bridging													0.32		
No	23/24596	Ref	-	-	-	25/17247	Ref	-	-	-	59/21836	Ref	-	-	-
Yes	15/11509	1.37	0.71	2.64	0.35	8/6420	0.84	0.38	1.88	0.67	21/9218	0.89	0.54	1.48	0.66
	HAS-BLED: 0-1 (N=31679)				HAS-BLED=2 (N=32127)				HAS-BLED: 3-5 (N=27020)				P interaction (bridging x HAS- BLED)*		
	n (events)/ Ntotal	HR	[95% CI]	P-value	n (events)/ Ntotal	HR	[95% CI]	P-value	n (events)/ Ntotal	HR	[95% CI]	P-value			
<b>Ischemic stroke and systemic embolism</b>															
Heparin bridging													0.49		
No	19/22551	Ref	-	-	-	43/21959	Ref	-	-	-	45/19169	Ref	-	-	-
Yes	10/9128	1.13	0.52	2.46	0.76	18/10168	0.95	0.55	1.66	0.86	16/7851	0.91	0.51	1.62	0.75

\*Adjusted for age, sex, social deprivation index, type of VKA, type of VKA prescribers, comorbidities (heart failure, diabetes, hypertension, chronic renal impairment, chronic hepatitis, peripheral arterial disease), alcohol and smoking related conditions, CHA2DS2-VASc and HAS-BLED scores, concomitant medications (antiarrhythmic agents, lipid-lowering agents, non-steroidal anti-inflammatory agents, oral corticosteroids, gastroprotective agents, benzodiazepines, antiplatelet agents).

**Figure S1. Effect of bridging therapy on bleeding with time (and 95% pointwise confidence band) estimated by a cubic spline function with knots at 7, 14, 21, and 28 days.**

