Supplemental material – Sensitivity analysis – Cohort 1 - patients newly treated with an anticoagulant combined with an antiarrhythmic agent or a rate control treatment excluding beta-blockers, within a time window of +/- 30 days

Table 1 – Characteristics of Patients and Prescribers at Anticoagulant Treatment Initiation (2011-2015)

	VKA*	DOACs[†]
	N = 289,430	N = 199,016
Demographic characteristics		
Mean age (sd[§])	76.1 (11.2)	73.7 (11.3)
Male	49.8%	52.5%
Clinical characteristics[‖]		
High blood pressure	91.9%	88.7%
Ischemic heart disease	26.3%	16.6%
Heart failure	34.4%	21.6%
Diabetes	21.9%	18.6%
Cancer	16.1%	13.0%
Renal failure	9.7%	2.4%
Liver failure	1.3%	0.7%
Dementia	4.6%	2.7%
History Ischemic stroke	8.5%	6.2%
History of bleeding	5.5%	2.9%
HAS-BLED score, mean (sd)	2.6 (0.9)	2.4 (0.9)
CHA_2DS_2- $VASc_2$ score, mean (sd)	3.9 (1.5)	3.4 (1.5)
Other treatment at cohort entry[¶]		
Aspirin	45.9%	42.2%
Nonsteroidal anti-inflammatory drugs	13.8%	15.9%
Antiplatelet Agents (other than Aspirin)	14.4%	10.9%
Corticosteroids	13.9%	12.8%
Prescriber of first anticoagulant		
General Practitioner	59.7%	46.7%
Among general practitioners	*65.0%*	*35.0%*
Cardiologist	27.7%	43.8%
Among cardiologists	*47.9%*	*52.1%*
Other specialist	4.2%	3.8%
Unknown	8.4%	5.6%

Vitamin K agonist; † Direct oral anticoagulants; ‡, p value comparing VKA vs DOACs; § sd: standard deviation; ‖ defined in the 12 months prior to cohort entry; ¶ defined in the 3 months prior to cohort entry

Supplemental material – Sensitivity analysis – Cohort 1 - patients newly treated with an anticoagulant combined with an antiarrhythmic agent or a rate control treatment excluding beta-blockers, within a time window of +/- 30 days

Table 2 – Characteristics of Patients and Prescribers at Anticoagulant Treatment Initiation in the Sub-Group of Patients Receiving a Direct Oral Anticoagulant (2011-2015)

	Dabigatran N = 65,851	Rivaroxaban N = 104,936	Apixaban N = 28,229
Demographic characteristics			
Mean age (sd[†])	73.7 (11.4)	73.0 (11.3)	76.0 (11.0)
Male	52.3%	53.4%	49.6%
Clinical characteristics[‡]			
High blood pressure	88.7%	87.8%	91.8%
Ischemic heart disease	17.9%	15.8%	17.0%
Heart failure	22.8%	19.9%	25.2%
Diabetes	18.6%	18.3%	20.0%
Cancer	14.0%	12.8%	11.3%
Renal failure	2.1%	2.2%	3.8%
Liver failure	0.7%	0.6%	0.6%
Dementia	2.8%	2.6%	2.9%
History of ischemic stroke	7.2%	5.4%	7.1%
History of bleeding	2.7%	2.7%	3.6%
HAS-BLED score, mean (sd)	2.4 (0.9)	2.3 (0.9)	2.5 (0.9)
CHA_2DS_2- $VASc_2$, mean (sd)	3.4 (1.5)	3.2 (1.5)	3.6 (1.4)
Other treatments at cohort entry[§]			
Aspirin	43.0%	41.4%	43.2%
Nonsteroidal anti-inflammatory drugs	16.6%	16.1%	13.2%
Antiplatelet Agents (other than Aspirin)	11.3%	10.4%	12.1%
Corticosteroids	12.8%	12.8%	12.6%
Prescriber of first anticoagulant			
General Practitioner	47.0%	46.3%	47.5%
Cardiologist	43.1%	44.9%	41.7%
Other specialist	3.7%	3.8%	4.1%
Unknown	6.2%	5.0%	6.7%

* *Direct oral anticoagulants*, † Standard deviation, ‡ defined in the 12 months prior to cohort entry, § defined in the 3 months prior to cohort entry

Supplemental material – Sensitivity analysis – Cohort 1 - patients newly treated with an anticoagulant combined with an antiarrhythmic agent or a rate control treatment excluding beta-blockers, within a time window of +/- 30 days

Table 3 – Multivariate analysis of the determinants associated with DOAC initiation according to year of therapy initiation

Characteristics at treatment initiation	2011 N = 101,817		2012 N = 110,571		2013 N = 103,594		2014 N = 94,180		2015 N = 78,284	
	Adjusted OR	CI 95%*	Adjusted OR	CI 95%	Adjusted OR	CI 95%	Adjusted OR	CI 95%	Adjusted OR	CI 95%
Demographic characteristics										
Age										
< 65 years	0.89	0.78 – 1.01	0.93	0.88 – 0.97	1.02	0.98 – 1.06	1.15	1.10 – 1.21	1.08	1.03 – 1.14
65 –74 years	1.0		1.0		1.0		1.0		1.0	
>= 75 years	1.15	1.04 – 1.27	0.98	0.94 – 1.01	0.69	0.67 – 0.71	0.59	0.57 – 0.61	0.65	0.63 – 0.68
Sex (Male)	0.86	0.79 – 0.94	0.97	0.94 – 1.01	1.09	1.06 – 1.13	1.10	1.06 – 1.13	1.08	1.05 – 1.12
Clinical characteristics[†]										
High blood pressure	0.87	0.76 – 1.00	0.82	0.78 – 0.86	0.79	0.75 – 0.83	0.78	0.74 – 0.82	0.79	0.74 – 0.84
Ischemic heart disease	0.88	0.79 – 0.97	0.83	0.80 – 0.86	0.76	0.74 – 0.79	0.74	0.72 – 0.77	0.76	0.72 – 0.79
Heart failure	0.60	0.55 – 0.67	0.70	0.68 – 0.72	0.61	0.59 – 0.63	0.59	0.57 – 0.61	0.63	0.60 – 0.65
Diabetes	0.88	0.79 – 0.98	0.89	0.86 – 0.93	0.88	0.85 – 0.91	0.93	0.89 – 0.96	0.92	0.89 – 0.96
Cancer	0.98	0.88 – 1.10	0.96	0.92 – 1.00	0.85	0.81 – 0.88	0.85	0.81 – 0.88	0.84	0.80 – 0.89
Renal failure	0.50	0.39 – 0.63	0.34	0.31 – 0.36	0.23	0.22 – 0.25	0.22	0.20 – 0.23	0.24	0.23 – 0.26
Liver failure	0.59	0.33 – 1.05	0.74	0.63 – 0.88	0.59	0.52 – 0.68	0.58	0.50 – 0.66	0.49	0.41 – 0.58
Dementia	0.96	0.77 – 1.19	0.84	0.77 – 0.92	0.75	0.70 – 0.80	0.81	0.76 – 0.88	0.74	0.68 – 0.81
History of Ischemic Stroke	1.01	0.87 – 1.16	0.99	0.94 – 1.05	0.88	0.84 – 0.93	0.88	0.84 – 0.93	0.92	0.86 – 0.98
History of bleeding	1.28	1.06 – 1.55	0.70	0.64 – 0.76	0.52	0.48 – 0.55	0.52	0.49 – 0.56	0.57	0.53 – 0.61
Prescriber of first anticoagulant										
General Practitioner	1.0		1.0		1.0		1.0		1.0	
Cardiologist	1.30	1.19 – 1.42	2.33	2.25 – 2.41	2.63	2.55 – 2.71	2.57	2.49 – 2.65	2.46	2.37 – 0.56
Other specialists/Unknown	1.72	1.52 – 1.93	1.03	0.97 – 1.08	1.00	0.96 – 1.05	1.03	0.98 – 1.07	1.03	0.98 – 1.08
Other treatments at cohort entry[‡]										
Aspirin	1.28	1.18 – 1.42	1.16	1.12 – 1.19	0.98	0.85 – 1.00	0.93	0.90 – 0.95	0.87	0.84 – 0.90
NSAID	1.37	1.24 – 1.52	1.16	1.11 – 1.21	1.18	1.13 – 1.22 1	1.21	1.17 – 1.27	1.20	1.14 – 1.26
Antiplatelet Agents	1.30	1.15 – 1.46	1.06	1.01 – 1.11	0.85	0.82 – 0.89	0.73	0.70 – 0.76	0.78	0.74 – 0.82
Corticosteroids	0.90	0.79 – 1.02	0.96	0.92– 1.00	0.93	0.89 – 0.96	0.98	0.94 – 1.02	0.92	0.88 – 0.96
Time of anticoagulant intiation										
1st term of the year	1.0		1.0		1.0		1.0		1.0	
2nd term of the year	1.13	0.96 – 1.32	3.17	2.98 – 3.37	1.00	0.96 -1.04	1.08	1.04 – 1.13	1.11	1.06 – 1.15
3rd term of the year	2.05	1.77 – 2.37	9.37	8.84 – 9.94	0.93	0.89 – 0.96	1.09	1.05 – 1.14	1.17	1.11 – 1.22
4th term of the year	4.71	4.14 – 5.36	31.06	29.34 – 32.88	0.54	0.52 – 0.56	1.35	1.30 – 1.40	1.39	1.33 – 1.45

* 95% Confidence interval; † defined in the 12 months prior to cohort entry; ‡ defined in the 3 months prior to cohort entry