

Annex I.

Table 1. Deep vein thrombosis or Pulmonary embolism READ term used in CPRD, and ICPC term and string text used in BIFAP.

READ Term description	READ codes
Pulmonary embolism	G401.00
Pulmonary embolus	G401.12
Post operative pulmonary embolus	G401000
Recurrent pulmonary embolism *	G401100
Deep vein phlebitis and thrombophlebitis of the leg	G801.00
Deep vein thrombosis	G801.11
Deep vein thrombosis, leg	G801.12
DVT - Deep vein thrombosis	G801.13
Thrombophlebitis of the femoral vein	G801600
Deep vein thrombophlebitis of the leg unspecified	G801B00
Deep vein thrombosis of leg related to air travel	G801C00
Deep vein thrombosis of lower limb	G801D00
Deep vein thrombosis of leg related to intravenous drug use	G801E00
Recurrent deep vein thrombosis	G801G00
Deep vein phlebitis and thrombophlebitis of the leg NOS	G801z00
Post operative deep vein thrombosis	SP12200
[V] Personal history deep vein thrombosis *	ZV12800
[V] Personal history DVT- deep vein thrombosis *	ZV12811
[V] Personal history of pulmonary embolism *	ZV12900
Thromboembolic pulmonary hypertension *	G41y100
ICPC-BIFAP Term description	ICPC-BIFAP codes
EMBOLISMO (ARTERIAL) PULMONAR	K93.1
INFARTO PULMONAR (EMBOLISM.)	K93.2
TROMBOSIS PULMONAR (EMBOLIA)	K93.3
TROMBOEMBOLISMO PULMONAR	K93.4
TVP (TROMB. VENOSA PROFUNDA)	K94.6
TROMBOSIS VENOSA PROFUNDA EEII	K94.15
String text recorded in BIFAP Diagnosis files	Search pattern
TEP	OWA
T.E.P	LIKE
EMBOL PULMON	MW1
TROMBOEMBO PULM	MW1
TROMB PULMON	MW1
INFART PULMON	MW1
TVP	OWA
TROMB VEN PROF	MW3

Table 2. Distribution of time from therapy initiation to VTE and stop reasons to follow-up during the first treatment episode by AOM in CPRD and BIFAP.

	Alendronate	Other Bisphosphonates	Strontium Ranelate	Denosumab	Teriparatide
CPRD					
Number of patients at risk	127121	29007	3045	29	7
Median time of follow-up (range)	1.74y (1d-14.30y)	1.68y (1d-16.22y)	0.92y (1d-9.06y)	1.39y (65d-3.59y)	1.51y (208d-1.82y)
Stop reason:					
VTE treated	1644	365	25	1	0
VTE untreated	757	170	12	0	0
Switching	9,147	8,704	448	1	0
Discontinuation (180d without refill)	54,462	10,668	1,437	9	7
End of study	32,722	2,858	355	15	0
Dead	18,414	4,188	514	3	0
Lost to follow-up	9,975	2,054	254	0	0
BIFAP					
Number of patients at risk	36182	37594	7978	293	1287
Median time of follow-up (range)	1.29y (1d-12.04y)	1.31y(1d-11.42)	0.82y(1d-8.45y)	0.61y(1d-2.16y)	1.02y(1d-3.99y)
Stop reason:					
VTE treated	186	175	32	1	7
VTE untreated	53	51	8	0	0
Switching	3876	3172	1068	4	238
Discontinuation (180d without refill)	19,924	19,951	4,914	32	611
End of study	2,075	2,875	247	217	168
Dead	1,094	1,051	175	5	36
Lost to follow-up	8,974	34	1,534	10319	227

Table 3. Baseline characteristics and number of VTE cases according to AOM exposure cohort* in CPRD and BIFAP before 2011, and from 2011 onwards.

	Before 2011 [‡]								From 2011 onwards									
CPRD	Alendronate N=103800		Other bisphosphonates N=27999		Strontium ranelate N=2389		Teriparatide N=7		Alendronate N=23321		Other bisphosphonates N=1008		Strontium ranelate N=656		Denosumab N=28		Teriparatide N=0	
	No.	%	No.	%	No.	%	No.	%										
Females	83493	80.4	22995	82.1	2046	85.6	6	85.7	17809	76.4	768	76.2	529	80.6	24	85.7	-	-
Age at therapy initiation Mean (St.Dev.)	73.2 (10.5)		73.3 (10.5)		78.9 (10.3)		72.9 (8.3)		74.3 (10.7)		73.7 (10.8)		80.7 (10.2)		77.8 (10.6)		-	
Age at therapy initiation																		
50-59y	12795	12.3	3371	12.0	148	6.2	0	0.0	2454	10.5	117	11.6	25	3.8	2	7.1	-	-
60-69y	24226	23.3	6562	23.4	289	12.1	2	28.6	5311	22.8	251	24.9	82	12.5	5	17.9	-	-
70-70y	34778	33.5	9387	33.5	629	26.3	4	57.1	7259	31.1	298	29.6	147	22.4	8	28.6	-	-
>=80y	32001	30.8	8679	31.0	1323	55.4	1	14.3	8297	35.6	342	33.9	402	61.3	13	46.4	-	-
VTE before therapy initiation	5263	5.1	1515	5.4	129	5.4	0	0.0	1371	5.9	63	6.2	30	4.6	3	10.7	-	-
Risk factors for VTE																	-	-
Vein insufficiency or phlebitis	15427	14.9	4102	14.7	367	15.4	1	14.3	3723	16.0	171	17.0	100	15.2	7	25.0	-	-
HRT the year before therapy initiation	5699	5.5	1600	5.7	56	2.3	1	14.3	337	1.4	15	1.5	9	1.4	0	0	-	-
Recent fractures	5584	5.4	1516	5.4	339	14.2	0	0.0	2266	9.7	108	10.7	153	23.3	3	10.7	-	-
Charlson index none	56264	54.2	15193	54.3	1148	48.1	4	57.1	11843	50.8	494	49.0	328	50.0	11	39.3	-	-
mild	18896	18.2	5702	20.4	418	17.5	0	0.0	3729	16.0	151	15.0	102	15.5	4	14.3	-	-
moderate	14393	13.9	3520	12.6	394	16.5	1	14.3	3962	17.0	179	17.8	105	16.0	3	10.7	-	-
severe	14247	13.7	3584	12.8	429	18.0	2	28.6	3787	16.2	184	18.3	121	18.4	10	35.7	-	-
Other co-medication																	-	-
Other anti-osteoporosis medication	303	0.3	412	1.5	9	0.4	0	0.0	17	0.1	1	0.1	3	0.5	0	0	-	-
Calcium-Vitamin-D	25036	24.1	7837	28.0	861	36.0	6	85.7	6188	26.5	341	33.8	223	34.0	20	71.4	-	-
Glucocorticoids	41843	40.3	11618	41.5	662	27.7	2	28.6	9987	42.8	436	43.3	156	23.8	13	46.4	-	-

Heparin	820	0.8	184	0.7	24	1.0	0	0.0	663	2.8	51	5.1	22	3.4	2	7.1	-	-
Oral anticoagulant drugs	8296	8.0	2312	8.3	198	8.3	0	0.0	2345	10.1	127	12.6	58	8.8	6	21.4	-	-
BMI (Kg/m ²) <18.5	2449	2.4	689	2.5	109	4.6	0	0.0	633	2.7	29	2.9	24	3.7	1	3.6	-	-
18.5-24.9	16340	15.7	4415	15.8	440	18.4	2	28.6	4361	18.7	183	18.2	117	17.8	5	17.9	-	-
25-29.9	12769	12.3	3275	11.7	251	10.5	2	28.6	3566	15.3	154	15.3	65	9.9	4	14.3	-	-
30-34.9	5604	5.4	1401	5.0	113	4.7	0	0.0	1642	7.0	72	7.1	31	4.7	5	17.9	-	-
35-39.9	1737	1.7	445	1.6	23	1.0	0	0.0	535	2.3	36	3.6	4	0.6	2	7.1	-	-
>=40	745	0.7	186	0.7	8	0.3	0	0.0	216	0.9	13	1.3	2	0.3	0	0.0	-	-
Missing	64156	61.8	17588	62.8	1445	60.5	3	42.9	12368	53.0	521	51.7	413	63.0	11	39.3	-	-
Current smoker No	45177	43.5	12127	43.3	1140	47.7	4	57.1	11002	47.2	483	47.9	278	42.4	12	42.9	-	-
Yes	8876	8.6	2302	8.2	178	7.5	0	0.0	2346	10.1	105	10.4	39	5.9	1	3.6	-	-
Missing	49747	47.9	13570	48.5	1071	44.8	3	42.9	9973	42.8	420	41.7	339	51.7	15	53.6	-	-
VTE treated cases	1420	1.4	354	1.3	21	0.9	0	0.0	224	1.0	11	1.1	4	0.6	1	3.6	-	-
	Before 2011								From 2011 onwards									
BIFAP	Alendronate N=33948		Other bisphosphonates N=34730		Strontium ranelate N=7016		Teriparatide N=856		Alendronate N=2234		Other bisphosphonates N=2864		Strontium ranelate N=962		Denosumab N=293		Teriparatide N=431	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Females	30486	89.8	31287	90.1	6375	90.9	719	84.0	1862	83.3	2445	85.4	816	84.8	264	90.1	318	73.8
Age at therapy initiation Mean (St.Dev.)	68.6 (10.1)		68.1(10.0)		68.6(10.4)		73.3(9.5)		70.1(10.6)		69.0(10.7)		70.3(11.8)		70.9(10.7)		72.5(10.3)	
Age at therapy initiation																		
50-59y	7763	22.9	8400	24.2	1655	23.6	88	10.3	437	19.6	648	22.6	223	23.2	51	17.4	63	14.6
60-69y	9753	28.7	10223	29.4	1973	28.1	177	20.7	634	28.4	846	29.5	242	25.2	86	29.4	96	22.3
70-70y	11266	33.2	11145	32.1	2209	31.5	354	41.4	682	30.5	818	28.6	243	25.3	77	26.3	151	35.0
>=80y	5166	15.2	4962	14.3	1179	16.8	237	27.7	481	21.5	552	19.3	254	26.4	79	27.0	121	28.1
VTE before therapy initiation	453	1.3	449	1.3	83	1.2	22	2.6	53	2.4	56	2.0	15	1.6	5	1.7	18	4.2
Risk factors for VTE																		
Cancer	3302	9.7	3404	9.8	708	10.1	92	10.7	301	13.5	467	16.3	123	12.8	50	17.1	58	13.5

Peripheral arterial disease	372	1.1	392	1.1	80	1.1	29	3.4	44	2.0	50	1.7	22	2.3	4	1.4	11	2.6
Vein insufficiency or phlebitis	6420	18.9	6924	19.9	1506	21.5	181	21.1	537	24.0	655	22.9	256	26.6	88	30.0	112	26.0
HRT the year before therapy initiation	1086	3.2	1036	3.0	192	2.7	7	0.8	12	0.5	20	0.7	6	0.6	0	0.0	2	0.5
Recent fractures	2577	7.6	2574	7.4	639	9.1	168	19.6	244	10.9	233	8.1	181	18.8	43	14.7	100	23.2
Other co-medication																		
Other anti-osteoporosis medication	2562	7.5	2592	7.5	544	7.8	140	16.4	136	6.1	141	4.9	66	6.9	39	13.3	51	11.8
Calcium-Vitamin-D	11521	33.9	12614	36.3	2380	33.9	378	44.2	771	34.5	1105	38.6	329	34.2	193	65.9	164	38.1
Glucocorticoids	5794	17.1	6830	19.7	1240	17.7	212	24.8	702	31.4	931	32.5	245	25.5	94	32.1	152	35.3
Heparin	3902	11.5	4193	12.1	999	14.2	211	24.6	390	17.5	471	16.4	226	23.5	53	18.1	132	30.6
Oral anticoagulant drugs	1610	4.7	1587	4.6	289	4.1	82	9.6	173	7.7	199	6.9	72	7.5	15	5.1	53	12.3
BMI (Kg/m ²) <18.5	98	0.3	96	0.3	14	0.2	5	0.6	13	0.6	10	0.3	4	0.4	2	0.7	4	0.9
18.5-24.9	2,989	8.8	2,853	8.2	539	7.7	75	8.8	211	9.4	269	9.4	90	9.4	31	10.6	34	7.9
25-29.9	5,748	16.9	5,821	16.8	1,136	16.2	141	16.5	346	15.5	421	14.7	131	13.6	40	13.7	60	13.9
30-34.9	3,777	11.1	3,877	11.2	860	12.3	104	12.1	223	10.0	227	7.9	71	7.4	33	11.3	37	8.6
35-39.9	1,176	3.5	1,278	3.7	272	3.9	30	3.5	68	3.0	69	2.4	33	3.4	4	1.4	16	3.7
>=40	411	1.2	438	1.3	91	1.3	11	1.3	21	0.9	18	0.6	8	0.8	0	0.0	4	0.9
9999	19,749	58.2	20,367	58.6	4,104	58.5	490	57.2	1,352	60.5	1,850	64.6	625	65.0	183	62.5	276	64.0
Current smoker No	6,578	19.4	6,663	19.2	1,368	19.5	173	20.2	359	16.1	416	14.5	146	15.2	52	17.7	69	16.0
Yes	4,377	12.9	4,458	12.8	898	12.8	95	11.1	293	13.1	337	11.8	97	10.1	35	11.9	48	11.1
Missing	22,993	67.7	23,609	68.0	4,750	67.7	588	68.7	1,582	70.8	2,111	73.7	719	74.7	206	70.3	314	72.9
VTE treated cases	179	0.5	162	0.5	26	0.4	6	0.7	7	0.3	13	0.5	6	0.6	1	0.3	1	0.2

*Only one denosumab user was available in CPRD and no one in BIFAP before 2011 so data are not included in this table.