

Direct Oral Anticoagulants: Drug Selection by Means of the SOJA Method

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Objectives: The increasing number of direct acting anticoagulant drugs (DOACs) makes it almost impossible to have sufficient knowledge of each individual medicine and device, especially for general practitioners. Reducing the number of medicines different DOACs, based on rational criteria, allows physicians and pharmacists to build experience with a more limited set of medicines and to optimise patient information.

Methods: In this study DOACs are compared by means of the SOJA method. The following selection criteria were applied: approved indications, available formulations, variability of the AUC, drug interactions, clinical efficacy, side effects, dosage frequency and documentation.

Results: Limited differences in scores were found between apixaban, dabigatran and rivaroxaban. Edoxaban showed a lower score, mostly because of its more limited clinical evidence and documentation. The ranking between the top 3 depends mostly on the assigned weight to the individual selection criteria. Acquisition cost was not taken into account, because this varies with time. In practice acquisition cost is of course an important selection criterion, especially because there are very limited differences between the medicines from a clinical perspective. Exclusion of this criterion also makes this comparison more internationally applicable.

Conclusions: All DOACs are suitable for formulary inclusion, followed by a selection of the most suitable for a DOAC in individual patients, based on patient characteristics.

Keywords: Drug; Apixaban; Rivaroxaban; DOAC

Part 2

Medicines	Duration Days (days)	N	First dose, timing (hours)	Age	Female (%)	Design	Duration of follow-up	Ref
Api 2.5 mg bid or Enox 30 mg bid sc War INR 1.8-3 or	10-14	111 109 109	12-24 post 12-24 post Evening of surgery	68 67 67	68 62 61	DB DB Open	10-14 days	[26]
Api 2.5 mg bid or Enox 30 mg bid sc	10-14	1599 1596	12-24 post 12-24 post	66 66	62 62	DB, DD	70 days	[27]
Api 2.5 mg bid or Enox 40 mg qd sc	10-14	1528 1529	12-24 post 12 before	67 67	71 74	DB, DD	10-14 days	[28]
Api 2.5 mg bid or Enox 40 mg qd sc	35	2708 2699	12-24 post 12 before	61 61	53 54	DB, DD	95 days	[29]
Dabi 150 mg bid Dabi 225 mg bid Enox 40 mg qd	6-10	390 393 392	1-4 post 12 before	66 66 65	65 58 62	DB, DD	6-10	[30]
Dabi 150 mg qd Dabi 220 mg qd Enox 40 mg qd	6-10	703 679 694	1-4 post evening before	68 67 68	64 65 69	DB, DD	3 months	[31]

Dabi 150 mg qd		1163	1-4 post	63	57			
Dabi 220 mg qd	28-35	1146	evening before	65	56	DB, DD	28-35	[32]
Enox 40 mg qd		1154		64	56			
Dabi 220 mg qd	28-35	1036	1-4 post	62	54	DB, DD	90	[33]
Enox 40 mg qd		1019	evening before	62	50			
Dabi 150 mg qd		877	12-24 post	66	58			
Dabi 220 mg qd	12-15	862	12-24 post	66	57	DB, DD	90	[34]
Enox 30 mg bid		876		66	58			
Edo 15 mg qd		170	6-8 post	57	58			
Edo 30 mg qd	7-10	151	6-8 post	57	65	DB, DD	7-10	[35]
Dalte 5000 IU qd		144	6-8	58	61			
Edo 30 mg qd	11-14	299	6-24 post	73	82	DB, DD	11-14	[36]
Enox 20 mg bid		295	24-36 post	72	78			
Edo 15 mg qd		78	6-24 post	61	81			
Edo 30 mg qd	11-14	72	24-36 post	61	96	DB, DD	11-14	[37]
Enox 20 mg bid		74		59	80			
Edo 30 mg qd	11-14	255	6-24 post	63	87	DB, DD	11-14	[38]
Enox 20 mg bid		248	24-36 post	63	86			
Riva 10 mg qd	36	2266	6-8 post	63	55	DB, DD	70	[39]
Enox 40 mg qd		2275	Evening before	63	56			
Riva 10 mg qd	36	1252	6-8 post	61	54	DB, DD	70	[40]
Enox 40 mg qd	10-14	1257	Evening before	62	53			
Riva 10 mg qd	10-14	1254	6-8 post	68	70	DB, DD	50	[41]
Enox 40 mg qd		1277	12 before	68	66			
Riva 10 mg qd	10-14	1254	6-8 post	64	66	DB, DD	50	[42]
Enox 30 mg bid		1277	12 post	65	64			
Riva 10 mg qd	9 or 30	1717	After 5 days rivaroxaban open	63	51	DB, DD	90	[43]
Aspirin 81 mg qd		1707	label	63	53			

Table 1: Comparative studies in orthopaedic surgery, baseline data and design.

Medicines	BMI	Arthritis (%)	Duration of Surgery (h)	Surgery	Primary endpoint	Ref
Api 2.5 mg bid or Enox 30 mg bid sc	31 30	70 71	1.4 1.6	Knee	VTE-A + VTE-S + PE-NF	[26]
War INR 1.8-3 or Api 2.5 mg bid or Enox 30 mg bid sc	30 31	72 81 80	1.6 1.5 1.5	Knee	VTE-A + VTE-S + PE-NF+ death	[27]
Api 2.5 mg bid or Enox 40 mg qd sc	29 29	63 63	1.6 1.6	Knee	VTE + PE-NF+ death	[28]
Api 2.5 mg bid or Enox 40 mg qd sc	28 28	57 58	1.5 1.5	Hip	VTE + PE-NF+ death	[29]

Dabi 150 mg bid			1.5	Hip and knee	VTE during treatment	[30]
Dabi 225 mg bid			1.4			
Enox 40 mg qd			1.5			
Dabi 150 mg qd			1.5	Knee	VTE + mortality	[31]
Dabi 220 mg qd			1.5			
Enox 40 mg qd			1.5			
Dabi 150 mg qd			1.5	Hip	VTE + mortality	[32]
Dabi 220 mg qd			1.5			
Enox 40 mg qd			1.5			
Dabi 220 mg qd	28		1.3	Hip	VTE + mortality	[33]
Enox 40 mg qd	28		1.3			
Dabi 150 mg qd			1.5	Knee	VTE + mortality	[34]
Dabi 220 mg qd			1.5			
Enox 30 mg bid			1.5			
Edo 15 mg qd	27		1.4	Knee	VTE	[35]
Edo 30 mg qd	28		1.4			
Dalte 5000 IU qd	28		1.4			
Edo 30 mg qd		87	1.5	Knee	VTE	[36]
Enox 20 mg bid		87	1.5			
Edo 15 mg qd	24		1.5	Knee	VTE	[37]
Edo 30 mg qd	24		1.5			
Enox 20 mg bid	23		1.6			
Edo 30 mg qd	25			Hip	VTE	[38]
Enox 20 mg bid	24					
Riva 10 mg qd	28		1.5	Hip	DVT + PE-NF + death from VTE	[39]
Enox 40 mg qd	28		1.5			
Riva 10 mg qd	27		1.6	Hip	DVT + PE-NF + death	[40]
Enox 40 mg qd	27		1.6			
Riva 10 mg qd	30		1.6	Knee	DVT + PE-NF + death	[41]
Enox 40 mg qd	30		1.6			
Riva 10 mg qd	31		1.6	Knee	DVT + PE-NF + death	[42]
Enox 30 mg bid	31		1.6			
Riva 10 mg qd	31		1.4	Knee and hip	DVT-S	[43]
Aspirin 81 mg qd	31		1.4			

Table 2: Comparative studies in orthopaedic surgery, baseline data and design.

Medicines	DVT-A (%)	DVT-S (%)	DVT-M (%)	DVT-P (%)	DVT (%)	VTE (%)	PE (%)	Fatal PE (%)	Mortality (%)	Composite Efficacy (%)	Reference
Api 2.5 mg bid	8.3	0.9		0.9		10	0		0.7	1.8	[26]
Enox 30 mg bid	12.8	0.9		2.8		17	1.8		0	4.6	
War INR 1.8-3	25.7	0.9		1.8		29	0		0	1.8 (VTE-P + PE + death)	
Api 2.5 mg bid		0.2		0.7	7.8		1.0	0.1	0.2	9.0	2.0
Enox 30 mg bid		0.4		0.9	8.2		0.4	0	0.2	8.8 (VTE + PE + death)	1.6 (Major VTE + death)
(all results after 10-14 days)											
Api 2.5 mg bid		0.2	1.1	0.8	14.6		0.3	0.1	0.13	15.1	[28]
Enox 40 mg qd		0.5	2.1	2.2	24.4		0	0	0	24.4 (VTE + PE + death)	
			P=0.019							P<0.0001	
Api 2.5 mg bid		<0.1	0.5	0.3	1.1		<0.1	<0.1	0.1	1.4	[29]
Enox 40 mg qd		0.2	1.1	0.9	3.6		0.2	0	<0.1	3.9 (VTE + PE + death)	
(all results after 35 days)			P=0.01							P<0.001	
Dabi 150 mg bid				3.3	16.8	17.4				4.0	[30]
Dabi 225 mg bid				1.7	13.1	13.1				1.7	
Enox 40 mg qd				5.6	24.0	24.0				5.6 (DVT/PE)	
Dabi 150 mg qd	39.7	0.4		3.4			0.1		0.1	40.5	[31]
Dabi 225 mg qd	36.0	0.1		2.6			0		0.1	36.4	
Enox 40 mg qd	36.0	1.2		3.1			0.1		0.1	37.7	
Dabi 150 mg qd	7.2	0.8		3.2			0.1		0.3	8.6	4.3
Dabi 220 mg qd	4.6	0.5		2.0			0.4		0.3	6.0	3.1
Enox 40 mg qd	6.3	0.1		3.5			0.3		0	6.7	3.9
										VTE + death	VTE-M + VTE mortality
Dabi 220 mg qd		0		2.1	7.6		0.1		0	7.7	2.2
Enox 40 mg qd		0.4		3.9	8.6		0.2		0.1	8.7	4.2
(all results after 35 days)				P=0.04						VTE + death	VTE-M + VTE mortality

Dabi 150 mg qd				3.1			0		0.2	33.7		[34]
Dabi 220 mg qd				2.3			1.0		0.2	31.1		
Enox 40 mg qd				1.6			0.8		0	25.3		
(all results after 12-15 days)										VTE + death P=0.02 P<0.001		
Edo 15 mg qd			6.5	6.5			28.2					[35]
Edo 30 mg qd			3.3	3.3			21.2					
Dalte 5000 IU qd			13.9	13.9			43.8					
			(VTE-M)	P=0.036			VTE					
			P=0.036	P<0.001			P=0.005					
			P<0.001				P<0.001					
Edo 30 mg qd	6.0	1.3		0			7.4	0	0			[36]
Enox 20 mg bid	13.6	0.3		0.3			13.9	0	0			
Edo 15 mg qd		0		0	3.8		3.8	0	0	0		[37]
Edo 30 mg qd		0		0	2.8		2.8	0	0	0		
Enox 20 mg bid		0		0	4.1		4.1	0	0	0		
Edo 30 mg qd	2.4	0		0.4	2.4			0	0	0	0.4	[38]
Enox 20 mg bid	6.9	0		0.8	6.9			0	0	0	0.8	
											DVT-S + DVT-P + PE + VTE related death	
Riva 10 mg qd		0.3	0.2	0.1	0.8			0.3		0.3	1.1	[39]
Enox 40 mg qd		0.5	2.0	2.0	3.4			0.1		0.3	3.7	
(all results after 36 days)			P<0.001	P<0.001	P<0.001						DVT + PE-NF + death from VTE P<0.001	
Riva 10 mg qd		0.2	0.6	0.6	1.6			0.1		0.2	2.0	[40]
Enox 40 mg qd		1.2	5.1	5.1	8.2			0.5		0.7	9.3	
(all results after 36 days)		P=0.004	P<0.0001	P<0.0001	P<0.0001						DVT + PE-NF + death P<0.0001	

Riva 10 mg qd			1.0	1.1	9.6		0		0	9.6		[41]
Enox 30 mg bid			2.6	2.3	18.2		0.5		0.2	18.9		
(all results after 15 days)			P=0.01		P<0.001					DVT + PE-NF + death		
										P<0.001		
Riva 10 mg qd	3.3	0.7	1.1	0.2			0.3	0	0.1	6.7		[42]
Enox 40 mg qd	5.0	1.2	1.5	0.9			0.5	0	0.2	9.3		
(all results after 15 days)										DVT + PE-NF + death		
										P=0.036		
Riva 10 mg qd		0.70		0.23			0.35		0			[43]
Aspirin 81 mg qd		0.64		0.23			0.29		0.1			

Table 3: Comparative studies in orthopaedic surgery, results.

DVT-A: Asymptomatic deep vein thrombosis

DVT-S: Severe/symptomatic deep vein thrombosis

DVT-M: Major deep vein thrombosis

DVT-P: Proximal deep vein thrombosis

PE: Pulmonary embolism

PE-NF: Non-fatal pulmonary embolism

PE-F: Fatal pulmonary embolism

VTE: Venous thromboembolism (ep vein thrombosis plus pulmonary embolism).

Medicines	With-drawal AE (%)	AE (%)	AE drug related (%)	AE-S (%)	Wound related infections (%)	MI (%)	Stroke (%)	ALT>3ALN	ALT>3ALN And bili >2ALN	Reference
Api 2.5 mg bid		87		7.8	1.3	1.3	0.7	2.6	0	[26]
Enox 30 mg bid		87		6.7	0.7	0	0	2.7	0	
War INR 1.8-3		89		6.0	2.0	0.7	0	2.0	0.7	
Api 2.5 mg bid				8.5	1.3	0.1	0	1.0	0	[27]
Enox 30 mg bid				8.6	0.7	0.3	0.1	1.6	0.1	
					2.0					
Api 2.5 mg bid	3	52	14	5		0.1	0.1	2	0.2	[28]
Enox 40 mg qd	3	55	14	6		0.1	0	1	0.1	
Api 2.5 mg bid	3.4	65		6.9		0.2	<0.1	1.3	0.3	[29]
Enox 40 mg qd	4.2	68		6.5		0.2	0.2	1.5	0.1	

Dabi 150 mg bid										[30]
Dabi 225 mg bid										
Enox 40 mg qd										
Dabi 150 mg qd	3.7					1.0		3.7		[31]
Dabi 220 mg qd	3.7					0.4		3.7		
Enox 40 mg qd	4.6					0.5		4.6		
Dabi 150 mg qd	8	77		8				3		[32]
Dabi 220 mg qd	6	77		8				3		
Enox 40 mg qd	6	77		7				5		
Dabi 220 mg qd	5.9	68	9.1	5.6		<0.1	0	3.8	0.2	[33]
Enox 40 mg qd	5.2	69	9.5	5.9		<0.1	0	5.6	0	
Dabi 150 mg qd	5							0.7		[34]
Dabi 220 mg qd	5							1.0		
Enox 30 mg bid	6							0.9		
Edo 15 mg qd	1.6	35	8.9	4.2				4.2	0.5	[35]
Edo 30 mg qd	0.6	28	4.7	2.9				2.4	0.6	
Dalte 5000 IU qd	1.2	36	8.1	1.7				2.9	0.6	
Edo 30 mg qd								0.6	0	[36]
Enox 20 mg bid								5.7	0.3	
Edo 15 mg qd		65	18	0				0.4		[37]
Edo 30 mg qd		71	26	0				0.3		
Enox 20 mg bid		83	53	1.1				1.2		
Edo 30 mg qd		65						2.6		[38]
Enox 20 mg bid		77						10		
Riva 10 mg qd		64	12		0.4	0.1	0.1	2.0	0.1	[39]
Enox 40 mg qd		65	12		0.4	0.3	0.1	2.7	0.1	
Riva 10 mg qd	3.8	60	1.1	7.3	0.7	0.3	0.2	1.6	0.2	[40]
Enox 40 mg qd	5.3	62	1.4	10.7	0.5	0.2	0.1	4.7	0.3	
Riva 10 mg qd			12.013.0		0.6	0.1	0.2			[41]
Enox 40 mg qd					0.9	0.2	0			
Riva 10 mg qd		80	20	5.2	0.3	0.1	0.1	1.3	0.1	[42]
Enox 30 mg bid		81	20	7.0	0.2	0	0	2.6	0.2	
Riva 10 mg qd										[43]
Aspirin 81 mg qd										

Table 4: Comparative studies in orthopaedic surgery, safety results.

AE: Adverse Events

AE-S: Severe Adverse Events

MI: Myocardial Infarction.

Medicines	Major bleeding (%)	Overt bleeding (%)	Minor bleeding (%)	Non-major bleeding (%)	All bleeding (%)	Bleeding with surgical intervention (%)	Fatal bleeding (%)	Bleeding at critical site (%)	Bleeding at surgical site (%)	Reference
Api 2.5 mg bid	0		3.9		3.0	0				[26]
Enox 30 mg bid	0		4.0		4.0	0				
War INR 1.8-3	0		5.3		5.3	0				
Api 2.5 mg bid	0.7	0.6	2.4		5.3		0	0	0.5	[27]
Enox 30 mg bid	1.4	1.4	2.5		6.8		<0.1	0.1	0.9	
Api 2.5 mg bid	0.6	0.5	3.4		6.9			0	0.5	[28]
Enox 40 mg qd	0.9	0.9	3.6		8.4			0	0.7	
Api 2.5 mg bid	0.8		6.9		11.7	<0.1	0	0	0.7	[29]
Enox 40 mg qd	0.7		7.3		12.6	<0.1	0	0	0.6	
Dabi 150 mg bid	4.1		7.9		12.0					[30]
Dabi 225 mg bid	3.8		9.7		13.5					
Enox 40 mg qd	2.0		6.4		8.4					
Dabi 150 mg qd	1.3		8.4	6.8		0.1	0	0.1		[31]
Dabi 220 mg qd	1.5		8.8	5.9		0.2	0	0		
Enox 40 mg qd	1.3		9.9	5.3		0.1	0	0		
Dabi 150 mg qd	1.3		6.2	4.7		0.3	0.1	0		[32]
Dabi 220 mg qd	2.0		6.1	4.2		0.2	0.1	0		
Enox 40 mg qd	1.6		6.4	3.5		0.3	0	0		
Dabi 220 mg qd	1.4	1.3	6.0	2.3	9.7	0	0	0.1		[33]
Enox 40 mg qd	0.9	0.7	5.4	2.0	8.3	0	0	0		
Dabi 150 mg qd	0.6			2.5		0	0		0.2	[34]
Dabi 220 mg qd	0.6			2.7		0	0		0.3	
Enox 40 mg qd	1.4			2.4		0.1	0		1.4	
Edo 15 mg qd	0.5			1.2	2.1					[35]
Edo 30 mg qd	0.6			1.0	1.8					
Dalte 5000 IU qd	0			1	0.6					
Edo 30 mg qd	1.1			5.1	6.2					[36]
Enox 20 mg bid	0.3			3.4	3.7					
					(Major + non major)					

Edo 15 mg qd	0			2.2	18						[37]
Edo 30 mg qd	1.2			1.2	21						
Enox 20 mg bid	0			2.3	22						
				(Major + non major)							
Edo 30 mg qd	0.7		18.8	2.0	20.5						[38]
Enox 20 mg bid	2.0		13.0	1.7	15.9						
Riva 10 mg qd	0.3	0.2		5.8		0.1	0.1	0.1			[39]
Enox 40 mg qd	0.1	0.1		5.8		0.1	0	0			
Riva 10 mg qd	0.1	0.1		3.3	4.7	0	0	0			[40]
Enox 40 mg qd	0.1	0		2.7	4.1	0	0	0.1			
Riva 10 mg qd	0.6	0.2		2.7		0.4	0	0			[41]
Enox 40 mg qd	0.5	0		2.3		0.3	0	0.1			
Riva 10 mg qd	0.7	0.3		2.6		0.3	0.1	0.1			[42]
Enox 30 mg bid	0.3	0		2.0		0.1	0	0.1			
Riva 10 mg qd	0.3				1.2						[43]
Aspirin 81 mg qd	0.6				1.4						

Table 5: Comparative studies in orthopaedic surgery, safety results: bleeding.

Medicines	N	Age	Female (%)	Inclusion	Blood pressure S/D	BMI	Design	Duration of follow-up (years)	CHAD score mean	End-point	Ref
Api 5 mg bid	2808	70	41	AF, at risk for stroke, not suitable for vit K antagonist	132	28	Open	1.1	2.0	Stroke or SE	[44]
Aspirin 81-324 mg qd	2791	70	42		132	28			2.1		
Api 5 mg bid	9120	70	36	AF + at least one risk factor for stroke	130		Open	1.8	2.1	Stroke or SE	[45]
Warfarin INR 2-3	9081	70	35		130				2.1		
Dab 110 mg bid	6015	71	36	AF, at risk for stroke	131		DB	2.0	2.1	Stroke or SE	[46]
Dab 150 mg bid	6076	71	37		131		DB		2.2		
Warfarin INR 2-3	6022	72	37		131		Open		2.1		
Dab 150 mg bid	317	59	27	AF, ablation	131	29	Open	8 weeks	2.0	Bleeding	[47]
Warfarin INR 2-3	318	59	22		131	29			2.2		
					131						
Dab 110 mg bid	981	72	26	AF, PCI			Open	14 months	3.7	MI, stroke, SE	[48]
Warfarin/Aspirin	981	72	23	Combi with ticagrelor or clopidogrel					3.8		
Dab 150 mg bid	763	69	22						3.3		
Warfarin/Aspirin	764	69	22						3.6		

Edo 30 mg qd	7034	72	39	AF, moderate to high risk for stroke			DB, DD	2.8	2.8	Stroke or SE	[49]
Edo 60 mg qd	7035	72	38						2.8		
Warfarin INR 2-3	7036	72	38						2.8		
Riv 20 mg qd	7131	73	40	AF, moderate to high risk for stroke	130	28	DB, DD	2.5	3.5	Stroke or SE	[50]
Warfarin INR 2-3	7133	73	40		130	28					
Riv 20 mg qd	1002	65	27	AF, cardioversion		30	Ope	8 weeks	38%	Stroke, TIA, PE, MI, CV-D	[51]
Vit K antag INR 2-3	502	65	27		30	39% (>2)					

Table 6: Comparative studies in atrial fibrillation, baseline data and design.

AF: Atrial Fibrillation

AF-NV: Non Valvular Atrial Fibrillation

CV-D: Cardiovascular Death

I-S: Ischaemic Stroke

MI: Myocardial Infarction

PE: Peripheral Embolism

SE: Systemic Embolism.

Medicines	Type of AF (%)			Previous stroke (%)	Heart failure (%)	Diabetes	Hypertension	Ref
	Persistent	Paroxysmal	Permanent					
Api 5 mg bid	21	27	52	14	40	19	86	[44]
Aspirin 81-324 mg qd	21	27	52	13	38	20	87	
Api 5 mg bid	85	15		19	36	25	87	[45]
Warfarin INR 2-3	84	16		20	35	25	88	
Dab 110 mg bid	32	32	35	20	32	23	79	[46]
Dab 150 mg bid	31	33	36	20	32	23	79	
Warfarin INR 2-3	32	34	34	20	32	23	79	
Dab 150 mg bid	27	67	6	3	10	10	52	[47]
Warfarin INR 2-3	26	69	6	3	11	11	56	
Dab 110 mg bid	18	50	33	8		37		[48]
Warfarin/Aspirin	18	49	32	10		38		
Dab 150 mg bid	17	50	33	7		34		
Warfarin/Aspirin	20	49	31	10		40		
Edo 30 mg qd		26		29	57	36	94	[49]
Edo 60 mg qd		25		28	58	36	94	
Warfarin INR 2-3		25		28	58	36	94	
Riv 20 mg qd	81	18		55	63	40	90	[50]
Warfarin INR 2-3	81	18		55	62	40	91	
Riv 20 mg qd	56	17	3	3	20	20	65	[51]
Vit K antag INR 2-3	50	23	5	4	15	21	69	

Table 7: Comparative studies in atrial fibrillation, baseline data and design.

Medicines	ACE/ARB %	Calcium antagonist %	Beta blocker %	Digoxin %	Amiodarone %	Statin %	Aspirin %	Ref
Api 5 mg bid	64	9	56	29	11	31	0	[44]
Aspirin 81-324 mg qd	64	9	55	27	12	31	100	
Api 5 mg bid	71	30	64	32	11	45	31	[45]
Warfarin INR 2-3	70	31	63	32	12	45	31	
Dab 110 mg bid	66		63		10	45	40	[46]
Dab 150 mg bid	67		64		11	44	39	
Warfarin INR 2-3	66		62		11	45	41	
Dab 150 mg bid			58			31		[47]
Warfarin INR 2-3			60			30		
Edo 30 mg qd				30	11		29	[49]
Edo 60 mg qd				30	12		29	
Warfarin INR 2-3				31	12		30	
Riv 20 mg qd	55		65	39		43	36	[50]
Warfarin INR 2-3	54		65	39		43	37	
Riv 20 mg qd							27	[51]
Vit K antag INR 2-3							28	

Table 8: Comparative studies in atrial fibrillation, baseline data and design.

Medicines	Stroke %	Stroke ischaemic or unspecified %	Stroke Hemorrhagic %	Stroke dis- abling or fatal %	SE %	Stroke or SE %	TIA %	Ref
Api 5 mg bid	1.6/yr	1.1/yr	0.2/yr	1.0/yr	0.1/yr	1.6/yr		[44]
Aspirin 81-324 mg qd	3.4/yr	3.0/yr	0.3/yr	2.3/yr	0.4/yr	3.7/yr		
	p<0.001	p<0.001		p<0.001		P<0.001		
Api 5 mg bid	1.19/yr	0.97/yr	0.24/yr		0.09/yr	1.27/yr		[45]
Warfarin INR 2-3	1.51/yr	1.05/yr	0.47/yr		0.10/yr	1.60/yr		
	P=0.01		P<0.001			P=0.01		
Dab 110 mg bid	1.44/yr	1.34/yr	0.12/yr	0.94/yr		1.53/yr		[46]
Dab 150 mg bid	1.01/yr	0.92/yr	0.10/yr	0.66/yr		1.11/yr		
Warfarin INR 2-3	1.57/yr	1.20/yr	0.38/yr	1.00/yr		1.69/yr		
			P<0.001			NI p=0.02 for 150 mg vs warfarin		

Dab 150 mg bid								[47]
Warfarin INR 2-3								
Dab 110 mg bid	1.7%							[48]
Warfarin/Aspirin	1.3%							
Dab 150 mg bid	1.2%							
Warfarin/Aspirin	1.0%							
Edo 30 mg qd	1.91/yr	1.77/yr	0.16/yr	0.80/yr		1.61/yr		[49]
Edo 60 mg qd	1.49/yr	1.25/yr	0.26/yr	0.69/yr		1.18/yr		
Warfarin INR 2-3	1.69/yr	1.25/yr	0.47/yr	0.71/yr		1.50/yr		
			P<0.001					
Riv 20 mg qd	2.1/yr	2.1/yr	0.41	0.81/yr		1.7/yr		[50]
Warfarin INR 2-3	2.4/yr	2.3/yr	0.71	1.09/yr		2.2/yr		
	P<0.01		P=0.024			NI: p<0.001		
Riv 20 mg qd	0.20	0	0.20		0	0.51	0	[51]
Vit K antag INR 2-3	0.41	0.41	0		0.20	1.02	0	

Table 9: Comparative studies in atrial fibrillation, results.

Medicines	MI	CV hospital-ization	Death CV	Death total	Composite Stroke, SE, death	Composite Stroke, SE, MI, death	Ref
Api 5 mg bid	0.8	12.6	2.7	3.5	4.6		[44]
Aspirin 81-324 mg qd	0.9	15.9	3.1	4.4	7.2		
		P<0.001			P<0.001		
Api 5 mg bid	0.53/yr			3.52/yr	4.49/yr	4.85/yr	[45]
Warfarin INR 2-3	0.61/yr			3.94/yr	5.05/yr	5.49/yr	
				P<0.05	P=0.02	P=0.01	
Dab 110 mg bid	0.72/yr		2.43/yr	3.75/yr			[46]
Dab 150 mg bid	0.74/yr		2.28/yr	3.64/yr			
Warfarin INR 2-3	0.53/yr		2.69/yr	4.31/yr			
Dab 150 mg bid							[47]
Warfarin INR 2-3							

Dab 110 mg bid	4.5%			5.6%			[48]
Warfarin/Aspirin	3.0%			4.9%			
Dab 150 mg bid	3.4%			3.9%			
Warfarin/Aspirin	2.9%			4.6%			
Edo 30 mg qd	0.89/yr		2.71/yr	3.80/yr	5.23/yr		[49]
Edo 60 mg qd	0.70/yr		2.74/yr	3.99/yr	5.01/yr		
Warfarin INR 2-3	0.75/y		3.17/yr	4.35/yr	5.57/yr		
			P=0.013		P=0.02		
Riv 20 mg qd	0.9/yr			1.9/yr			[50]
Warfarin INR 2-3	1.1/yr			2.2/yr			
Riv 20 mg qd	0.10		0.41	0.51			[51]
Vit K antag INR 2-3	0.20		0.41	0.61			

Table 10: Comparative studies in atrial fibrillation, results.

Medicines	Withdrawal AE (%)	AE (%)	AE drug related (%)	AE-S (%)	ALT>3ALN	ALT>3ALN And bili >2ALN	Reference
Api 5 mg bid				22	1.4	0.2	[44]
Aspirin 81-324 mg qd				27	1.6	0.4	
				P<0.001			
Api 5 mg bid		81		35	1.1	0.3	[45]
Warfarin INR 2-3		83		37	1.0	0.4	
Dab 110 mg bid	2.7				2.1	0.2	[46]
Dab 150 mg bid	2.7				1.9	0.2	
Warfarin INR 2-3	1.7				2.2	0.3	
Dab 150 mg bid	2						[47]
Warfarin INR 2-3	2						
Dab 110 mg bid	6			43			[48]
Warfarin/Aspirin	6			42			
Dab 150 mg bid	6			40			
Warfarin/Aspirin	6			42			
Edo 30 mg qd	16	84	10	18	2.1	0.2	[49]
Edo 60 mg qd	17	84	11	17	2.2	0.2	
Warfarin INR 2-3	17	84	12	18	2.1	0.1	
Riv 20 mg qd		81				0.5	[50]
Warfarin INR 2-3		82				0.5	
Riv 20 mg qd							[51]
Vit K antag INR 2-3							

Table 11: Comparative studies in atrial fibrillation, safety results.

Medicines	Major bleeding	Intracranial bleeding	Fatal bleeding	Clinically relevant non-major	Major or Clinically relevant non-major	Minor bleeding	Any bleeding	Bleeding in critical organ	Ref
Api 5 mg bid	1.4	0.4	0.1	3.1		6.3			[44]
Aspirin 81-324 mg qd	1.2	0.4	0.2	2.7		5.0			
Api 5 mg bid	2.13/yr	0.33/yr			4.07/yr		18.1/yr		[45]
Warfarin INR 2-3	3.09/yr ISTH P<0.001	0.80/yr P<0.001			6.01/yr P<0.001		25.8/yr P<0.001		
Dab 110 mg bid	2.71/yr	0.23/yr				13.2/yr			[46]
Dab 150 mg bid	3.11/yr	0.30/yr				14.8/yr			
Warfarin INR 2-3	3.36/yr P=0.003	0.74/yr P<0.001				16.4/yr P<0.001			
Dab 150 mg bid	1.6%					19%			[47]
Warfarin INR 2-3	6.9% P<0.0001					17%			
Dab 110 mg bid	5.0%	0.3%							[48]
Warfarin/Aspirin	9.2%	1.0%							
Dab 150 mg bid	5.6%	0.1%							
Warfarin/Aspirin	8.4% P<0.02	1.0%							
Edo 30 mg qd	1.61/yr	0.26/yr	0.08/yr	6.60/yr	7.97/yr	3.52/yr		0.44/yr	[49]
Edo 60 mg qd	2.75/yr	0.39/yr	0.15/yr	8.67/yr	11.1/yr	4.12/yr		0.70/yr	
Warfarin INR 2-3	3.43/yr P<0.001	0.85/yr P<0.001	0.27/yr P=0.03	10.2/yr P<0.001	13.0/yr P<0.001	4.89/yr P=0.002		1.36/yr P<0.001	
Riv 20 mg qd	3.6/yr	0.5/yr	0.2/yr	11.8/yr				0.8	[50]
Warfarin INR 2-3	3.4/yr	0.7/yr P=0.02	0.5/yr P=0.003	11.4/yr				1.2 P=0.007	
Riv 20 mg qd	0.61	0.20	0.10					0.20	[51]
Vit K antagon INR 2-3	0.80	0.20	0.40					0.60	

Table 12: Comparative studies in atrial fibrillation, safety results, bleeding.

Medicines	N	Age	Fe- male (%)	Body Weight (kg)	Inclusion	DVT (%)	PE (%)	DVT + PE (%)	De- sign	Duration of follow- up (months)	Ref
Api 10/5 mg bid	2691	57	42	85	Acute DVT	65	25	9	DB, DD	6	[52]
Enox 1mg/kg/ War- farin INR 2-3	2704	57	41	85		66	25	8			
Api 2.5 mg bid	840	57	42	86	Acute DVT previous 6-12 months treat- ment	65	35		DB, DD	12	[53]
Api 5 mg bid	813	57	42	86		65	35				
Placebo	829	57	43	85		67	34				
Api 2.5 mg bid 30 days	3255	67	50		Medically ill + risk fac- tor for VTE			4.3	DB, DD	1	[54]
Enox 40 qd 6-14 days	3273	67	52					3.8			
Dabi 150 mg bid	1273	55	42	86	Acute DVT after par- enteral treatment for 9 days	69	21	10	DB, DD	6	[55]
Warfarin INR 2-3	1266	54	41	84		69	21	10			
Dabi 150 mg bid	1280	56	39	80	Acute DVT after par- enteral treatment for 5-11 days	69	23	8	DB, DD	6	[56]
Warfarin INR 2-3	1288	57	40	81		68	23	9			
Dabi 150 mg bid	1430	55	39	86	Acute VTE after treat- ment for > 3 months	66	23	12	DB, DD	6-36	[57]
Warfarin INR 2-3	1426	54	39	86		65	24	12			
Dabi 150 mg bid	681	56	44	84	Acute VTE after treat- ment for > 6 months	63	27	7	DB, DD	12	[57]
Placebo	662	56	45	84		67	27	5			
Edox 60 mg qd	4118	56	43		Acute DVT after par- enteral treatment for >5 days	66	34		DB, DD	3-12	[58]
Warfarin INR 2-3	4122	56	43			65	33				
Edox 60 mg qd	522	64	47		DVT in cancer patients	37		63	Open	6-12	[59]
Dalteparin 150 IU/kg	524	64	50			37		63			
Riv 15 mg bid, 20 mg qd	1731	56	43		Acute DVT	99	1		Open	3-12	[60]
Enox 1mg/kg/ War- farin INR 2-3	1718	56	44			99	1				
Riv 20 mg qd	602	58	41		Acute DVT after treat- ment for 6-12 months	64	36		DB, DD	6-12	[60]
Placebo	594	58	43			60	40				

Riv 15 mg bid, 20 mg qd	2419	58	46		Acute PE	0	75	25	Open	3-12	[61]
Enox 1mg/kg/ Warfarin INR 2-3	2413	58	48			0	75	25			
Riv 10 mg qd 35 days	4050	71	44	78	Acutely ill medical	0	0	0	DB, DD	35 days	[62]
Enox 40 mg qd 10 days	4051	71	47	77							
Riv 10 mg	1127	59	45		Extended treatment after initial 6-12 months	50	34	16	DB	12 months	[63]
Riv 20 mg	1107	58	46			51	34	14			
Aspirin 100 mg	1131	59	43			51	32	16			

Table 13: Comparative studies in deep venous thrombosis, baseline data and design.

Medicines	C CR >50 ml/min %	Previous VTE (%)	Unprovoked VTE (%)	Active cancer (%)	Coronary artery disease (%)	Diabetes (%)	Heart failure (%)	Immobolised (%)	Primary end-point	Ref
Api 10/5 mg bid	84	17	90	2.5					VTE-RS or VTE-D	[52]
Enox 1mg/kg/ Warfarin INR 2-3	85	15	90	2.8						
Api 2.5 mg bid	91	12	93	1.8		12		2.3	VTE-RS or death	[53]
Api 5 mg bid	92	15	91	1.1		10		3.6		
Placebo	91	12	91	2.2		11		2.7		
Api 2.5 mg bid 30 d		4.3		3.5			39		VTE-D or PE or DVT-S or DVT-P	[54]
Enox 40 qd 6-14 d		3.8		3.0			38			
Dabi 150 mg bid		26		5.0					VTE-RS or VTE-D	[55]
Warfarin INR 2-3		25		4.5						
Dabi 150 mg bid		19		3.9					VTE-RS or VTE-D	[56]
Warfarin INR 2-3		16		3.9						
Dabi 150 mg bid				4.2	8.4	10.5		6.6	VTE-RS or VTE-D	[57]
Warfarin INR 2-3				4.1	6.1	7.6		7.3		
Dabi 150 mg bid					6.3	8.4		7.8	VTE-RS or VTE-D	[57]
Placebo					5.7	7.6		5.4		
Edox 60 mg qd		19	66	9.2					VTE-RS or VTE-D	[58]
Warfarin INR 2-3		18	65	9.5						

Edox 60 mg qd	93	9		98					VTE or bleed- ing	[59]
Dalteparin 150 IU/kg	93	12		98						
Riv 15 mg bid, 20 mg qd			61	6.8				15	VTE-RS	[60]
Enox 1mg/kg/ Warfarin INR 2-3			63	5.2				15		
Riv 20 mg qd			73	4.7				15	VTE-RS	[60]
Placebo			74	4.4				13		
Riv 15 mg bid, 20 mg qd	91	19	65	4.7				16	VTE-RS	[61]
Enox 1mg/kg/ Warfarin INR 2-3	92	20	64	4.5				16		
Riv 10 mg qd 35 days				7.3			32		VTE	[62]
Enox 40 mg qd 10 days				7.3			32			
Riv 10 mg				2.4					VTE-RS	[63]
Riv 20 mg				2.3						
Aspirin 100 mg				3.3						

Table 14: Comparative studies in deep venous thrombosis, baseline data and design.

UA: Instable Angina

VTE-RS: VTE recurrent symptomatic thromboembolism

VTE-D: VTE related death.

Medicines	VTE-RS or VTE-D (%)	VTE-RS or death (%)	VTE-D or PE or DVT-S or DVT-P	CV-D, MI, stroke	PE-NF (%)	PE-F (%)	VTE-S (%)	DVT-P(%)	Death (%)	VTE-D (%)	Ref
Api 10/5 mg bid	2.3				1.0	<0.1			1.5		[52]
Enox 1mg/kg/ Warfarin INR 2-3	2.7				0.9	0.1			1.9		
	NI:p<0.001										
Api 2.5 mg bid	1.7	3.8		0.5	1.0	0					[53]
Api 5 mg bid	1.7	4.2		0.6	0.5	0					
Placebo	8.8	11.6		1.3	1.8	0					
	P<0.001										

Api 2.5 mg bid 30 d			2.71		0.22	0	0.15	2.40	4.1	0.06	[54]
Enox 40 qd 6-14 d			3.06		0.24	0	0.49	2.50	4.1	0.09	
Dabi 150 mg bid	2.4				1.0		1.3		1.6	0.1	[55]
Warfarin INR 2-3	2.1				0.6		1.4		1.7	0.2	
Dabi 150 mg bid	2.3				0.5		2.0		2.0	0.2	[56]
Warfarin INR 2-3	2.3				1.0		1.3		1.9	0	
Dabi 150 mg bid	1.8				0.7		1.2		1.2	0.1	[57]
Warfarin INR 2-3	1.3				0.4		0.0		1.3	0.1	
	P<0.01										
Dabi 150 mg bid	0.4				0.1		0.3				[57]
Placebo	5.6				2.1		3.3				
	P<0.001						NS				
Edox 60 mg qd	3.2				1.2	0.1	1.4		0.5	0.5	[C58]
Warfarin INR 2-3	3.5				1.4	0.1	1.5		0.5	0.5	
	NI: p<0.001										
Edox 60 mg qd	7.9				5.2				40	0.6	[59]
Dalteparin 150 IU/kg	11.3				5.3				37	0.6	
Riv 15 mg bid, 20 mg qd					1.2	0.1	2.1		2.2		[60]
Enox 1mg/kg/ Warfarin INR 2-3					1.1	0	3.0		2.9		
							NI: P<0.001				
Riv 20 mg qd					0.3	0	1.3		0.2		[60]
Placebo					2.8	0.2	7.1		0.3		
							P<0.001				
Riv 15 mg bid, 20 mg qd					0.9	0.1	2.1		2.4		[61]
Enox 1mg/kg/ Warfarin INR 2-3					0.7	<0.1	1.8		2.1		
							NI: p=0.003				
Riv 10 mg qd 35 days				1.8	0.3		4.4	3.5	5.1	0.6	[62]
Enox 40 mg qd 10 days				1.6	0.5		5.7	4.4	4.8	1.0	
							p=0.02				
Riv 10 mg	1.2			1.6	0.4				0.2		[63]
Riv 20 mg	1.5			1.7	0.5				0.7		
Aspirin 100 mg	4.4			5.0	1.7				0.6		
	P<0.001										

Table 15: Comparative studies in deep venous thrombosis, results.

Medicines	With- drawal AE (%)	AE (%)	AE drug related (%)	AE-S (%)	ALT>3ALN	ALT>3ALN And bili >2ALN	MI	Stroke	Ref
Api 10/5 mg bid	6.1	67		16	1.9		0.2	0.5	[52]
Enox 1mg/kg/ Warfarin INR 2-3	7.4	72		15	5.6		0.1	0.3	
Api 2.5 mg bid	8	71		13		0	0.2	0.1	[53]
Api 5 mg bid	7	67		13		0.1	0.4	0.1	
Placebo	16	73		19		0.4	0.5	0.6	
Api 2.5 mg bid 30 d									[54]
Enox 40 qd 6-14 d									
Dabi 150 mg bid	7.9	63		12	2.9	0.2	0.2		[55]
Warfarin INR 2-3	9.0	65		13	3.4	0.2	0.3		
Dabi 150 mg bid	7.8	67		12		0.1	0.3		[56]
Warfarin INR 2-3	7.8	71		12		0.2	0.2		
Dabi 150 mg bid	10.1	72		15.9	1.7	0.1	0.9		[57]
Warfarin INR 2-3	8.8	71		15.7	1.8	0.1	0.2		
							P=0.02		
Dabi 150 mg bid	7.3	51		6.9	0.6		0.1	0.3	[57]
Placebo	12.3	50		9.1	0.6		0.2	0.2	
Edox 60 mg qd	2.9	69		12.2	2.1	0.2	0.5		[C58]
Warfarin INR 2-3	2.5	71		13.2	2.3	<0.1	0.3		
Riv 15 mg bid, 20 mg qd	4.9	63		12.0	1.5	0.1	0.3	0.1	[59]
Enox 1mg/kg/ Warfarin INR 2-3	4.7	63		13.6	3.8	0.2	0.1	0.2	
Riv 20 mg qd					2.0	0	0	0	[60]
Placebo					0.5	0	0	0.1	
Riv 15 mg bid, 20 mg qd	5.1	81		20			0.6	0.1	[61]
Enox 1mg/kg/ Warfarin INR 2-3	4.1	79		20			0.9	0.1	
Riv 10 mg qd 35 days									[62]
Enox 40 mg qd 10 days									
Riv 10 mg									[63]
Riv 20 mg									
Aspirin 100 mg									

Table 16: Comparative studies in deep venous thrombosis, safety results.

Medicines	Major bleeding	Intra-cranial bleeding	Fatal bleeding	Clinically relevant non-major	Major or Clinically relevant non-major	Minor bleeding	Any bleeding	Bleeding in critical organ	Ref
Api 10/5 mg bid	0.6	0.1	<0.1	3.8	4.3		16		[52]
Enox 1mg/kg/ Warfarin INR 2-3	1.8	0.2	0.1	8.0	9.7		26		
	P<0.001				P<0.001				
Api 2.5 mg bid	0.2		0	3.0	3.2			0.2	[53]
Api 5 mg bid	0.1		0	4.2	4.3			0	
Placebo	0.5		0	2.3	2.7			0.2	
Api 2.5 mg bid 30 d	0.47	0	0	2.2	2.7		7.7	<0.1	[54]
Enox 40 qd 6-14 d	0.19	0.1	0.1	1.9	2.1		6.8	0	
	P=0.04								
Dabi 150 mg bid	1.6	0	0.1	4.0	5.6		16.1	0.1	[55]
Warfarin INR 2-3	1.9	0.3	0.1	6.9	8.8		21.9	0.7	
					P=0.02				
Dabi 150 mg bid	1.2	0.2	0		5.0			0.5	[56]
Warfarin INR 2-3	1.7	0.2	0.1		7.9			0.3	
					P not stated				
Dabi 150 mg bid	0.9		0		5.6		19.4	0.5	[57]
Warfarin INR 2-3	1.8		0.1		10.2		26.2	0.9	
					P<0.001		P<0.001		
Dabi 150 mg bid	0.3				5.3		10.5		[57]
Placebo	0				1.8		5.9		
					P<0.001		P<0.001		
Edox 60 mg qd	1.4	0.1	<0.1	7.2		21.7		0.3	[C58]
Warfarin INR 2-3	1.6	0.4	0.2	8.9		25.6		0.6	
				P=0.004		P<0.001			
Edox 60 mg qd	6.9			15	19				[59]
Dalteparin 150 IU/kg	4.0			11	14				
Riv 15 mg bid, 20 mg qd	0.8		0.1	7.3				0.2	[60]
Enox 1mg/kg/ Warfarin INR 2-3	1.2		0.3	7.0				0.2	
Riv 20 mg qd	0.7		0	5.4				0	[60]
Placebo	0		0	1.2				0	
Riv 15 mg bid, 20 mg qd	1.1	0.1	0.1	9.5				0.3	[61]
Enox 1mg/kg/ Warfarin INR 2-3	2.2	0.1	0.1	9.8				1.1	
	P=0.003								

Riv 10 mg qd 35 days	1.2		0.2		2.8			0.2	[62]
Enox 40 mg qd 10 days	0.4		<0.1		1.2			0.1	
	P<0.001				P<0.001				
Riv 10 mg	0.4	0.1	0		2.4	12			[63]
Riv 20 mg	0.5	0.3	0.1		3.3	15			
Aspirin 100 mg	0.3	0.2	0.1		2.0	11			

Table 17: Comparative studies in deep venous thrombosis, safety results, bleeding.

Medicines	N	Age	Female (%)	De-sign	Risk factors					Duration of follow-up	Ref
					Diabetes %	Previous MI %	CV disease %	LVHF %	Peripheral vascular disease %		
Api 5 mg bid	3705	67	33	DB	49	25	10	28	18	1.25 years	[64]
Placebo	3687	67	32		47	28	10	29	18		
Riva 2.5 mg bid	5174	62	35	DB	32	26				13-31 months	[65]
Riva 5 mg bid	5176	62	36		32	27					
Placebo	5176	62	35		32	27					
Riva 2.5 mg bid	1519	62	25	DB	29	21				390 days	[66]
Aspirin 100 mg qd	1518	63	25		30	23					

Table 18: Comparative studies in acute coronary syndromes, baseline data and design.

Medicines	Type of ACS			Time from event to randomisation (days)	Medication					Primary Endpoint	Ref
	STEMI	N-STEMI	UA		ACE/A2A	Beta blocker	Statin	Parenteral Antithrombotic agents	PPI		
Api 5 mg bid or Placebo or	40 39	41 42	18 18	6.0 6.0	80 79	77 76	83 84	80 81	24 25	CV-D, MI, I-S	[64]
Riva 2.5 mg bid	50	26	24		39	66	83			CV-D, MI, Stroke	[65]
Riva 5 mg bid	50	26	24		38	66	84				
Placebo	51	26	24		39	67	84				
Riva 2.5 mg bid	49	40	11	5.1	62	64	68			TIMI bleeding	[66]
Aspirin 100 mg qd	49	40	11	5.1	63	65	70				

Table 19: Comparative studies in acute coronary syndromes, baseline data and design.

Medicines	Composite (%)			Death (%)	CV-D (%)	MI (%)	I-S (%)	Stent thrombosis (%)	Ref
	CV-D, MI, I-S	CV-D, MI, I-S UA	CV-D, MI, stroke						
Api 5 mg bid or Placebo or	7.5 7.9	9.5 10.0		4.2 3.9	4.8 5.0	8.6 9.2	0.6 1.6	0.9 1.3	[64]
Riva 2.5 mg bid Riva 5 mg bid Placebo			9.1 8.8 10.7	2.9 4.4 4.5	2.7 4.0 4.1			2.2 2.3 2.9	[65]
			P=0.02 (2.5 mg vs placebo)	P=0.002 (2.5 mg vs placebo)	P=0.002 (2.5 mg vs placebo)				
Riva 2.5 mg bid Aspirin 100 mg qd	5 5 (including stent thrombosis)				0.6 0.6	3.6 3.3		0.6 0.8	[66]

Table 20: Comparative studies in acute coronary syndromes, results.

Medicines	Major bleeding TIMI (%)	Major or minor bleeding TIMI (%)	Major bleeding ISTH (%)	Major or clinically relevant non-major bleeding (%)	Severe bleeding GUSTO (%)	Severe or moderate bleeding GUSTO %	Fatal bleeding	Intracranial bleeding (%)	Any bleeding (%)	Ref
Api 5 mg bid or Placebo or	1.3 0.5	2.2 0.8	2.7 1.1	3.2 1.2	1.8 0.6	2.3 0.7	0.1 0	0.6 0.2	18.5 14.4	[64]
	P=0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001		P=0.03	P<0.001	
Riva 2.5 mg bid Riva 5 mg bid Placebo	1.8 2.4 0.6						0.1 0.4 0.2	0.4 0.7 0.2		[65]
							P=0.04 for 2.5 mg vs 5 mg Riva	P=0.009		
Riva 2.5 mg bid Aspirin 100 mg qd	0.6 0.5		2.0 1.1		0.2 0.1		0.1 0			[66]

Table 21: Comparative studies in acute coronary syndromes, safety results, bleeding.

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Conflicts of Interest

None reported.

Bibliography

- Janknegt R and Steenhoek A. "The system of Objectified Judgment Analysis. A tool in rational drug selection for formulary inclusion". *Drugs* 53 (1997): 551-562.
- Summary of Product Characteristics. Apixaban (Eliquis).
- Summary of Product Characteristics. Dabigatran (Pradaxa).
- Summary of Product Characteristics. Edoxaban (Lixiana).
- Summary of Product Characteristics. Rivaroxaban (Xarelto).
- Frost C., et al. "A randomized direct comparison of the pharmacokinetics and pharmacodynamics of apixaban and rivaroxaban". *Clinical Pharmacology* 6 (2014): 179-187.
- Frost C., et al. "Evaluation of the effect of naproxen on the pharmacokinetics and pharmacodynamics of apixaban". *British Journal of Clinical Pharmacology* 78 (2014): 877-885.
- Wang X., et al. "Effect of activated charcoal on apixaban pharmacokinetics in healthy subjects". *American Journal of Cardiovascular Drugs* 4.14 (2014): 147-154.
- Upreti VV., et al. "Effect of famotidine on the pharmacokinetics of apixaban, an oral direct factor Xa inhibitor". *Clinical Pharmacology* 5 (2013): 59-66.
- Clemens A., et al. "Switching from enoxaparin to dabigatran etexilate: pharmacokinetics, pharmacodynamics, and safety profile". *European Journal of Clinical Pharmacology* 68 (2012): 607-616.
- Stangier J., et al. "Pharmacokinetics and pharmacodynamics of dabigatran etexilate, an oral direct thrombin inhibitor, with coadministration of digoxin". *The Journal of Clinical Pharmacology* 52 (2012): 243-250.
- Stangier J., et al. "Pharmacokinetics and pharmacodynamics of dabigatran etexilate, an oral direct thrombin inhibitor, are not affected by moderate hepatic impairment". *The Journal of Clinical Pharmacology* 48 (2008): 1411-1419.
- Wilson JA., et al. "An evaluation of oral dabigatran etexilate pharmacokinetics and pharmacodynamics in hemodialysis". *The Journal of Clinical Pharmacology* 54 (2014): 901-909.
- Parasrampur DA., et al. "Pharmacokinetics and Pharmacodynamics of the Nonvitamin K Antagonist Oral Anticoagulant Edoxaban When Administered Alone or After Switching from Rivaroxaban or Dabigatran Etexilate in Healthy Subjects". *Clinical Drug Investigation* 36 (2016): 127-136.
- Mendell J., et al. "Drug-drug interaction studies of cardiovascular drugs involving P-glycoprotein, an efflux transporter, on the pharmacokinetics of edoxaban, an oral factor Xa inhibitor". *American Journal of Cardiovascular Drugs* 13 (2013): 331-342.
- Bathala MS., et al. "Pharmacokinetics, biotransformation, and mass balance of edoxaban, a selective, direct factor Xa inhibitor, in humans". *Drug Metabolism and Disposition* 40 (2012): 2250-2255.
- Mendell J., et al. "A randomized trial of the safety, pharmacokinetics and pharmacodynamics of edoxaban, an oral factor Xa inhibitor, following a switch from warfarin". *British Journal of Clinical Pharmacology* 75 (2013): 966-978.
- Moore KT., et al. "An open-label study to estimate the effect of steady-state erythromycin on the pharmacokinetics, pharmacodynamics, and safety of a single dose of rivaroxaban in subjects with renal impairment and normal renal function". *The Journal of Clinical Pharmacology* 54 (2014): 1407-1420.
- Kubitza D., et al. "Effect of hepatic impairment on the pharmacokinetics and pharmacodynamics of a single dose of rivaroxaban, an oral, direct Factor Xa inhibitor". *British Journal of Clinical Pharmacology* 76 (2013): 89-98.
- Zhao X., et al. "Safety, pharmacokinetics and pharmacodynamics of single/multiple doses of the oral, direct Factor Xa inhibitor rivaroxaban in healthy Chinese subjects". *British Journal of Clinical Pharmacology* 68 (2009): 77-88.
- Kreutz R., et al. "Dissociation between the pharmacokinetics and pharmacodynamics of once-daily rivaroxaban and twice-daily apixaban: a randomized crossover study". *Journal of Thrombosis and Haemostasis* 15 (2017): 2017-2028.

22. Frost CE., *et al.* "Effect of ketoconazole and diltiazem on the pharmacokinetics of apixaban, an oral direct factor Xa inhibitor". *British Journal of Clinical Pharmacology* 79 (2015): 838-846.
23. Mendell J., *et al.* "The effect of rifampin on the pharmacokinetics of edoxaban in healthy adults". *Clinical Drug Investigation* 35 (2015): 447-453.
24. Vakkalagadda B., *et al.* "Effect of Rifampin on the Pharmacokinetics of Apixaban, an Oral Direct Inhibitor of Factor Xa". *American Journal of Cardiovascular Drugs* (2016).
25. Chang SH., *et al.* "Association Between Use of Non-Vitamin K Oral Anticoagulants With and Without Concurrent Medications and Risk of Major Bleeding in Nonvalvular Atrial Fibrillation". *JAMA* 318 (2017): 1250-1259.
26. Lassen MR., *et al.* "The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement". *Journal of Thrombosis and Haemostasis* 5 (2007): 2368-2375.
27. Lassen MR., *et al.* "Apixaban or enoxaparin for thromboprophylaxis after knee replacement". *The New England Journal of Medicine* 361 (2009): 594-604.
28. Lassen MR., *et al.* "Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial". *Lancet* 37 (2010): 807-815.
29. Lassen MR., *et al.* "Apixaban versus enoxaparin for thromboprophylaxis after hip replacement". *The New England Journal of Medicine* 363 (2010): 2487-2498.
30. Eriksson BI., *et al.* "A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial". *Journal of Thrombosis and Haemostasis* 3 (2005): 103-111.
31. Eriksson BI., *et al.* "Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial". *Journal of Thrombosis and Haemostasis* 5 (2007): 2178-2185.
32. Eriksson BI., *et al.* "Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial". *Lancet* 370 (2007): 949-956.
33. Eriksson BI., *et al.* "Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RENOVATE II*). A randomised, double-blind, non-inferiority trial". *Thrombosis and Haemostasis* 105 (2011): 721-729.
34. RE-MOBILIZE Writing Committee. "Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery". *Journal of Arthroplasty* 24 (2009): 1-9.
35. Raskob G., *et al.* "Oral direct factor Xa inhibition with edoxaban for thromboprophylaxis after elective total hip replacement. A randomised double-blind dose-response study". *Thrombosis and Haemostasis* 104 (2010): 642-649.
36. Fuji T., *et al.* "Safety and efficacy of edoxaban, an oral factor Xa inhibitor, versus enoxaparin for thromboprophylaxis after total knee arthroplasty: the STARS E-3 trial". *Thrombosis Research* 134 (2014): 1198-1204.
37. Fuji T., *et al.* "Safety and efficacy of edoxaban, an oral factor xa inhibitor, for thromboprophylaxis after total hip arthroplasty in Japan and Taiwan". *Journal of Arthroplasty* 29 (2014): 2439-2446.
38. Fuji T., *et al.* "Efficacy and safety of edoxaban versus enoxaparin for the prevention of venous thromboembolism following total hip arthroplasty: STARS J-V". *Thrombosis Journal* 13 (2015): 27.
39. Eriksson BI., *et al.* "Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty". *The New England Journal of Medicine* 358 (2008): 2765-2775.
40. Kakkar AK., *et al.* "Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomized controlled trial". *Lancet* 372 (2008): 31-39.
41. Lassen MR., *et al.* "Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty". *The New England Journal of Medicine* 358 (2008): 2776-2786.
42. Turpie AG., *et al.* "Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial". *Lancet* 373 (2009): 1673-1680.
43. Anderson DR., *et al.* "Aspirin or Rivaroxaban for VTE Prophylaxis after Hip or Knee Arthroplasty". *The New England Journal of Medicine* 378 (2018): 699-707.

44. Connolly SJ, *et al.* "Apixaban in patients with atrial fibrillation". *The New England Journal of Medicine* 364 (2011): 806-817.
45. Granger CB, *et al.* "Apixaban versus warfarin in patients with atrial fibrillation". *The New England Journal of Medicine* 365 (2011): 981-992.
46. Connolly SJ, *et al.* "Dabigatran versus warfarin in patients with atrial fibrillation". *The New England Journal of Medicine* 361 (2009): 1139-1151.
47. Giugliano RP, *et al.* "Edoxaban versus warfarin in patients with atrial fibrillation". *The New England Journal of Medicine* 369 (2013): 2093-2104.
48. Calkins H, *et al.* "Uninterrupted dabigatran versus warfarin for ablation in atrial fibrillation". *The New England Journal of Medicine* 376 (2017): 1627-1636.
49. Cannon CP, *et al.* "Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation". *The New England Journal of Medicine* 37 (2017): 1513-1524.
50. Patel MR, *et al.* "Rivaroxaban versus warfarin in nonvalvular atrial fibrillation". *The New England Journal of Medicine* 365 (2011): 883-891.
51. Cappato R, *et al.* "Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation". *European Heart Journal* 35 (2014): 3346-3355.
52. Agnelli G, *et al.* "Oral apixaban for the treatment of acute venous thromboembolism". *The New England Journal of Medicine* 369 (2013): 799-808.
53. Agnelli G, *et al.* "Apixaban for extended treatment of venous thromboembolism". *The New England Journal of Medicine* 368 (2013): 699-708.
54. Goldhaber SZ, *et al.* "Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients". *The New England Journal of Medicine* 365 (2011): 2167-2177.
55. Schulman S, *et al.* "Dabigatran versus warfarin in the treatment of acute venous thromboembolism". *The New England Journal of Medicine* 361 (2009): 2342-2352.
56. Schulman S, *et al.* "Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis". *Circulation* 129 (2014): 764-772.
57. Schulman S, *et al.* "Extended use of dabigatran, warfarin, or placebo in venous thromboembolism". *The New England Journal of Medicine* 368 (2013): 709-718.
58. Hokusai-VTE Investigators, *et al.* "Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism". *The New England Journal of Medicine* 369 (2013): 1406-1415.
59. Raskob GE, *et al.* "Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism". *The New England Journal of Medicine* 378 (2018): 615-624.
60. EINSTEIN Investigators, *et al.* "Oral rivaroxaban for symptomatic venous thromboembolism". *The New England Journal of Medicine* 363 (2010): 2499-2510.
61. EINSTEIN-PE Investigators, *et al.* "Oral rivaroxaban for the treatment of symptomatic pulmonary embolism". *The New England Journal of Medicine* 366 (2012): 1287-1297.
62. Cohen AT, *et al.* "Rivaroxaban for thromboprophylaxis in acutely ill medical patients". *The New England Journal of Medicine* 368 (2013): 513-523.
63. Weitz JL, *et al.* "Rivaroxaban or aspirin for extended treatment of venous thromboembolism". *The New England Journal of Medicine* 376 (2017): 1211-22.
64. Alexander JH, *et al.* "Apixaban with antiplatelet therapy after acute coronary syndrome". *The New England Journal of Medicine* 365 (2011): 699-708.
65. Mega JL, *et al.* "Rivaroxaban in patients with a recent acute coronary syndrome". *The New England Journal of Medicine* 366 (2012): 9-19.
66. Ohman EM, *et al.* "Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind, multicentre, randomised trial". *Lancet* 389 (2017): 1799-1808.
67. Eriksson BI, *et al.* "Dose escalating safety study of a new oral direct thrombin inhibitor, dabigatran etexilate, in patients undergoing total hip replacement: BISTRO I". *Journal of Thrombosis and Haemostasis* 2 (2004): 1573-1580.
68. Fuji T, *et al.* "Dabigatran etexilate prevents venous thromboembolism after total knee arthroplasty in Japanese patients with a safety profile comparable to placebo". *Journal of Arthroplasty* 25 (2010): 1267-1274.
69. Eriksson BI, *et al.* "Oral dabigatran etexilate versus enoxaparin for venous thromboembolism prevention after total hip arthroplasty: pooled analysis of two phase 3 randomized trials". *Thrombosis Journal* 13 (2015): 36.

70. Friedman RJ, *et al.* "Dabigatran versus enoxaparin for prevention of venous thromboembolism after hip or knee arthroplasty: a pooled analysis of three trials". *Thrombosis Research* 126 (2010): 175-182.
71. Wolowacz SE, *et al.* "Efficacy and safety of dabigatran etexilate for the prevention of venous thromboembolism following total hip or knee arthroplasty. A meta-analysis". *Thrombosis and Haemostasis* 101 (2009): 77-85.
72. Fuji T, *et al.* "A dose-ranging study evaluating the oral factor Xa inhibitor edoxaban for the prevention of venous thromboembolism in patients undergoing total knee arthroplasty". *Journal of Thrombosis and Haemostasis* 8 (2010): 2458-2468.
73. Fuji T, *et al.* "Safety and efficacy of edoxaban in patients undergoing hip fracture surgery". *Thrombosis Research* 133 (2014): 1016-1022.
74. Seife C. "Research misconduct identified by the US Food and Drug Administration: out of sight, out of mind, out of the peer-reviewed literature". *JAMA Internal Medicine* 175 (2015): 567-577.
75. Huang HF, *et al.* "Rivaroxaban versus enoxaparin for the prevention of venous thromboembolism after total knee arthroplasty: A meta-analysis". *Medicine (Baltimore)* 97 (2018): e13465.
76. López-López JA, *et al.* "Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis". *British Medical Journal* 359 (2017): j5058.
77. O'Donnell MJ, *et al.* "Effect of apixaban on brain infarction and microbleeds: AVERROES-MRI assessment study". *American Heart Journal* 178 (2016): 145-150.
78. Easton JD, *et al.* "Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial". *Lancet Neurology* 11 (2012): 503-511.
79. Avezum A, *et al.* "Apixaban in Comparison With Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease: Findings From the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial". *Circulation* 132 (2015): 624-632.
80. Garmendia CA, *et al.* "Evaluation of the Inclusion of Studies Identified by the FDA as Having Falsified Data in the Results of Meta-analyses: The Example of the Apixaban Trials". *JAMA Internal Medicine* 179 (2019): 582-584.
81. Ezekowitz MD, *et al.* "Comparison of Dabigatran and Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease: The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulant Therapy)". *Circulation* 134 (2016): 589-598.
82. Connolly SJ, *et al.* "The Long-Term Multicenter Observational Study of Dabigatran Treatment in Patients With Atrial Fibrillation (RELY-ABLE) Study". *Circulation* 128 (2013): 237-243.
83. Lip G, *et al.* "Patient outcomes using the European label for dabigatran. A post-hoc analysis from the RE-LY database". *Thrombosis and Haemostasis* 111 (2014): 933-942.
84. Brambatti M, *et al.* "Comparison of dabigatran versus warfarin in diabetic patients with atrial fibrillation: Results from the RE-LY trial". *International Journal of Cardiology* 196 (2015): 127-131.
85. Seeger JD, *et al.* "Safety and effectiveness of dabigatran and warfarin in routine care of patients with atrial fibrillation". *Thrombosis and Haemostasis* 114 (2015): 1277-1289.
86. Larsen TB, *et al.* "Dabigatran and warfarin for secondary prevention of stroke in atrial fibrillation patients: a nationwide cohort study". *American Journal of Medicine* 127 (2014): 1172-1178.
87. Del-Carpio Munoz F, *et al.* "Dabigatran Versus Warfarin in Relation to Renal Function in Patients With Atrial Fibrillation". *Journal of the American College of Cardiology* 68 (2016): 129-131.
88. Giugliano RP, *et al.* "Mortality in Patients with Atrial Fibrillation Randomized to Edoxaban or Warfarin: Insights from the ENGAGE AF-TIMI 48 Trial". *American Journal of Medicine* 129 (2016): 850-857.
89. Giugliano RP, *et al.* "Cerebrovascular events in 21 105 patients with atrial fibrillation randomized to edoxaban versus warfarin: Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48". *Stroke* 45 (2014): 2372-2378.
90. Geller BJ, *et al.* "Systemic, noncerebral, arterial embolism in 21,105 patients with atrial fibrillation randomized to edoxaban or warfarin: results from the Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction Study 48 trial". *American Heart Journal* 170 (2015): 669-674.
91. Giugliano RP, *et al.* "Mortality in Patients With Atrial Fibrillation Randomized to Edoxaban or Warfarin: Insights from the ENGAGE AF-TIMI 48 Trial". *American Journal of Medicine* (2016): pii: S0002-9343 (16)30246-7.

92. Steffel J, *et al.* "Edoxaban Versus Warfarin in Atrial Fibrillation Patients at Risk of Falling: ENGAGE AF-TIMI 48 Analysis". *Journal of the American College of Cardiology* 68 (2016): 1169-1178.
93. Rost NS, *et al.* "Outcomes With Edoxaban Versus Warfarin in Patients With Previous Cerebrovascular Events: Findings From ENGAGE AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48)". *Stroke* 47 (2016): 2075-2082.
94. Weitz JL, *et al.* "Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation". *Thrombosis and Haemostasis* 104 (2010): 633-641.
95. Goette A, *et al.* "Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial". *Lancet* 388 (2016): 1995-2003.
96. Hankey GJ, *et al.* "Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF". *Lancet Neurology* 11 (2012): 315-322.
97. Halperin JL, *et al.* "Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF)". *Circulation* 130 (2014): 138-146.
98. Piccini JP, *et al.* "Relationship between time in therapeutic range and comparative treatment effect of rivaroxaban and warfarin: results from the ROCKET AF trial". *Journal of the American Heart Association* 3 (2014): e000521.
99. Bansilal S, *et al.* "Efficacy and safety of rivaroxaban in patients with diabetes and nonvalvular atrial fibrillation: the Rivaroxaban Once-daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF Trial)". *American Heart Journal* 170 (2015): 675-682.
100. Fordyce CB, *et al.* "On-Treatment Outcomes in Patients With Worsening Renal Function With Rivaroxaban Compared With Warfarin: Insights From ROCKET AF". *Circulation* 134 (2016): 37-47.
101. Lin LL, *et al.* "Clinical and safety outcomes of oral antithrombotics for stroke prevention in atrial fibrillation: a systematic review and network meta-analysis". *Journal of the American Medical Directors Association* 16 (2015): 1103.e1-19.
102. Graham DJ, *et al.* "Stroke, Bleeding, and Mortality Risks in Elderly Medicare Beneficiaries Treated With Dabigatran or Rivaroxaban for Nonvalvular Atrial Fibrillation". *JAMA Internal Medicine* 176 (2016): 1662-1671.
103. Healthcare Improvement Scotland. "A review of the clinical effectiveness of direct oral anticoagulants for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation". www.healthcareimprovementscotland.org (2017).
104. Chan YH, *et al.* "Thromboembolic, Bleeding, and Mortality Risks of Rivaroxaban and Dabigatran in Asians With Nonvalvular Atrial Fibrillation". *Journal of the American College of Cardiology* 68 (2016): 1389-1401.
105. Jacobs V, *et al.* "Long-Term Population-Based Cerebral Ischemic Event and Cognitive Outcomes of Direct Oral Anticoagulants Compared With Warfarin Among Long-term Anticoagulated Patients for Atrial Fibrillation". *American Journal of Cardiology* 118 (2016): 210-214.
106. Larsen TB, *et al.* "Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study". *British Medical Journal* 353 (2016): i3189.
107. Larsen TB, *et al.* "Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study". *British Medical Journal* 356 (2017): j510.
108. Coleman CI, *et al.* "Real-world evidence of stroke prevention in patients with nonvalvular atrial fibrillation in the United States: the Revisit-US study". *Current Medical Research and Opinion* (2016).
109. Hernandez I, *et al.* "Comparison of the effectiveness and safety of apixaban, dabigatran, rivaroxaban and warfarin in newly diagnosed atrial fibrillation". *American Journal of Cardiology* 120 (2017): 1813-1819.
110. Lip G, *et al.* "Effectiveness and Safety of Oral Anticoagulants Among Nonvalvular Atrial Fibrillation Patients. The ARISTOPHANES Study". *Stroke* 49 (2018): 2933-2944.

111. Graham DJ, *et al.* "Comparative Stroke, Bleeding, and Mortality Risks in Older Medicare Patients Treated with Oral Anticoagulants for Nonvalvular Atrial Fibrillation". *American Journal of Medicine* 132 (2019): 596-604.
112. Liu X, *et al.* "Apixaban Reduces Hospitalizations in Patients With Venous Thromboembolism: An Analysis of the Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy (AMPLIFY) Trial". *Journal of the American Heart Association* 4 (2015): pii: e002340.
113. Agnelli G, *et al.* "Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the AMPLIFY trial". *Journal of Thrombosis and Haemostasis* 13 (2015): 2187-2191.
114. Botticelli Investigators, *et al.* "Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study". *Journal of Thrombosis and Haemostasis* 6 (2008): 1313-1318.
115. Agnelli G, *et al.* "Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939): the ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients With Acute Symptomatic Deep-Vein Thrombosis) study". *Circulation* 116 (2007): 180-187.
116. Buller HR, *et al.* "A dose-ranging study evaluating once-daily oral administration of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the Einstein-DVT Dose-Ranging Study". *Blood* 112 (2008): 2242-2247.
117. Robertson R, *et al.* "Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of pulmonary embolism". *Cochrane Database of Systematic Reviews* 12 (2015).
118. Robertson R, *et al.* "Oral direct thrombin inhibitors or oral factor Xa inhibitors for the treatment of deep venous thrombosis". *Cochrane Database of Systematic Reviews* 6 (2015): CD010956.
119. APPRAISE Steering Committee and Investigators, *et al.* "Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial". *Circulation* 119 (2009): 2877-2885.
120. Oldren J, *et al.* "Dabigatran vs placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial". *European Heart Journal* 32 (2011): 2781-2789.
121. Mega JL, *et al.* "Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial". *Lancet* 374 (2009): 29-38.
122. Eikelboom JW, *et al.* "Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease". *The New England Journal of Medicine* 377 (2017): 1319-1330.
123. Connolly SJ, *et al.* "Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial". *Lancet* 391 (2018): 205-218.
124. Anand SS, *et al.* "Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial". *Lancet* 391 (2018): 219-229.
125. López-López JA, *et al.* "Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis". *British Medical Journal* 359 (2017): j5058.
126. Hylek EM, *et al.* "Major bleeding in patients with atrial fibrillation receiving apixaban or warfarin: The ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors, Characteristics, and Clinical Outcomes". *Journal of the American College of Cardiology* 63 (2014): 2141-2147.
127. De Caterina R, *et al.* "History of bleeding and outcomes with apixaban versus warfarin in patients with atrial fibrillation in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial". *American Heart Journal* 175 (2016): 175-183.
128. Villa LA, *et al.* "Evaluating the efficacy and safety of apixaban, a new oral anticoagulant, using Bayesian meta-analysis". *International Journal of Hematology* 98 (2013): 390-397.
129. Touma L, *et al.* "A meta-analysis of randomized controlled trials of the risk of bleeding with apixaban versus vitamin K antagonists". *American Journal of Cardiology* 115 (2015): 533-541.
130. Mantha S and Ansell J. "Indirect comparison of dabigatran, rivaroxaban, apixaban and edoxaban for the treatment of acute venous thromboembolism". *Journal of Thrombosis and Thrombolysis* 39 (2015): 155-165.

131. Cohen AT., *et al.* "Comparison of the Novel Oral Anticoagulants Apixaban, Dabigatran, Edoxaban, and Rivaroxaban in the Initial and Long-Term Treatment and Prevention of Venous Thromboembolism: Systematic Review and Network Meta-Analysis". *PLoS One* 10 (2015): e0144856.
132. Kolb JM., *et al.* "Locations and Mucosal Lesions Responsible for Major Gastrointestinal Bleeding in Patients on Warfarin or Dabigatran". *Digestive Diseases and Science* 63 (2018): 1878-1889.
133. Majeed A., *et al.* "Bleeding events with dabigatran or warfarin in patients with venous thromboembolism". *Thrombosis and Haemostasis* 115 (2015): 291-298.
134. Nishtala PS., *et al.* "'Real-world' haemorrhagic rates for warfarin and dabigatran using population-level data in New Zealand". *International Journal of Cardiology* 203 (2015): 746-752.
135. Maura G., *et al.* "Comparison of the Short-Term Risk of Bleeding and Arterial Thromboembolic Events in Nonvalvular Atrial Fibrillation Patients Newly Treated With Dabigatran or Rivaroxaban Versus Vitamin K Antagonists: A French Nationwide Propensity-Matched Cohort Study". *Circulation* 132 (2015): 1252-1260.
136. Fontaine GV., *et al.* "Major bleeding with dabigatran and rivaroxaban in patients with atrial fibrillation: a real-world setting". *Clinical and Applied Thrombosis/Hemostasis* 20 (2014): 665-672.
137. Abraham NS., *et al.* "Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study". *British Medical Journal* 350 (2015): h1857.
138. Douxfils J., *et al.* "Dabigatran etexilate and risk of myocardial infarction, other cardiovascular events, major bleeding, and all-cause mortality: a systematic review and meta-analysis of randomized controlled trials". *Journal of the American Heart Association* 3 (2014): e000515.
139. Wang SV., *et al.* "Prediction of rates of thromboembolic and major bleeding outcomes with dabigatran or warfarin among patients with atrial fibrillation: new initiator cohort study". *British Medical Journal* 353 (2016): i2607.
140. Chung N., *et al.* "Safety of edoxaban, an oral factor Xa inhibitor, in Asian patients with non-valvular atrial fibrillation". *Thrombosis and Haemostasis* 105 (2011): 535-544.
141. Li S., *et al.* "Bleeding risk and mortality of edoxaban: a pooled meta-analysis of randomized controlled trials". *PLoS One* 9 (2014): e95354.
142. Sherwood MW., *et al.* "Gastrointestinal Bleeding in Patients With Atrial Fibrillation Treated With Rivaroxaban or Warfarin: ROCKET AF Trial". *Journal of the American College of Cardiology* 66 (2015): 2271-2281.
143. Lip GY., *et al.* "Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. A propensity score matched analysis". *Thrombosis and Haemostasis* 116 (2016): 975-986.
144. Maura G., *et al.* "Comparison of the short-term risk of bleeding and arterial thromboembolic events in nonvalvular atrial fibrillation patients newly treated with dabigatran or rivaroxaban versus vitamin K antagonists: a French nationwide propensity-matched cohort study". *Circulation* 132 (2015): 1252-1260.
145. Lip GY., *et al.* "Major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban or warfarin: a "real-world" observational study in the United States". *International Journal of Clinical Practice* 70 (2016): 752-763.
146. Bundhun PK., *et al.* "Bleeding outcomes associated with rivaroxaban and dabigatran in patients treated for atrial fibrillation: a systematic review and meta-analysis". *BMC Cardiovascular Disorder* 17 (2017): 15.
147. Lai CL., *et al.* "Comparative Effectiveness and Safety of Dabigatran and Rivaroxaban in Atrial Fibrillation Patients". *Journal of the American Heart Association* 6.4 (2017).
148. Gorst-Rasmussen A., *et al.* "Rivaroxaban versus warfarin and dabigatran in atrial fibrillation: comparative effectiveness and safety in Danish routine care". *Pharmacoepidemiology and Drug Safety* 25 (2016): 1236-1244.
149. Noseworthy PA., *et al.* "Direct Comparison of Dabigatran, Rivaroxaban, and Apixaban for Effectiveness and Safety in Nonvalvular Atrial Fibrillation". *Chest* 150 (2016): 1302-1312.
150. Yao X., *et al.* "Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation". *Journal of the American Heart Association* 5.6 (2016).
151. Li WH., *et al.* "Efficacy and safety of dabigatran, rivaroxaban, and warfarin for stroke prevention in Chinese patients with atrial fibrillation: the Hong Kong Atrial Fibrillation Project". *Clinical Cardiology* 40 (2017): 222-229.

152. Lip GY, *et al.* "Relative efficacy and safety of non-Vitamin K oral anticoagulants for non-valvular atrial fibrillation: Network meta-analysis comparing apixaban, dabigatran, rivaroxaban and edoxaban in three patient subgroups". *International Journal of Cardiology* 204 (2016): 88-94.
153. Abraham NS, *et al.* "Gastrointestinal Safety of Direct Oral Anticoagulants: A Large Population-Based Study". *Gastroenterology* 152 (2017): 1014-1022.e1.
154. Di Nisio M, *et al.* "Risk of major bleeding in patients with venous thromboembolism treated with rivaroxaban or with heparin and vitamin K antagonists". *Thrombosis and Haemostasis* 115.2 (2016): 424-432.
155. Eerenberg ES, *et al.* "Clinical impact and course of major bleeding with rivaroxaban and vitamin K antagonists". *Journal of Thrombosis and Haemostasis* 13 (2015): 1590-1596.
156. Husted S, *et al.* "Reversal Strategies for NOACs: State of Development, Possible Clinical Applications and Future Perspectives". *Drug Safety* 39 (2016): 5-13.
157. Connolly SJ, *et al.* "Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors". *The New England Journal of Medicine* 375 (2016): 1131-1141.
158. Siegal DM, *et al.* "Andexanet alfa for the reversal of Factor Xa inhibitor activity". *The New England Journal of Medicine* 373 (2015): 2413-2424.
159. Beyer-Westendorf J, *et al.* "Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry". *Blood* 124 (2014): 955-962.
160. Hohnloser SH, *et al.* "Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial". *Circulation* 125 (2012): 669-676.
161. Uchino K, *et al.* "Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials". *Archives of Internal Medicine* 172 (2012): 397-402.
162. Wei AH, *et al.* "Increased risk of myocardial infarction with dabigatran etexilate: fact or fiction? A critical meta-analysis of over 580,000 patients from integrating randomized controlled trials and real-world studies". *International Journal of Cardiology* 267 (2018): 1-7.
163. Villines TC, *et al.* "A comparison of the safety and effectiveness of dabigatran and warfarin in non-valvular atrial fibrillation patients in a large healthcare system". *Thrombosis and Haemostasis* 114 (2015): 1290-1298.
164. Lambert A, *et al.* "Rivaroxaban-induced liver injury: Results from a venous thromboembolism registry". *International Journal of Cardiology* 191 (2015): 265-266.
165. Liakoni E, *et al.* "Hepatotoxicity of New Oral Anticoagulants (NOACs)". *Drug Safety* 38 (2015): 711-720.
166. Raparelli V, *et al.* "Adherence to oral anticoagulant therapy in patients with atrial fibrillation". *Thrombosis and Haemostasis* 117.2 (2017): 209-218.
167. Coleman GI, *et al.* "Medication adherence to rivaroxaban and dabigatran for stroke prevention in patients with non-valvular atrial fibrillation in the United States". *International Journal of Cardiology* 212 (2016): 171-173.
168. Mc Horney CA, *et al.* "Comparison of adherence to rivaroxaban versus apixaban among patients with atrial fibrillation". *Clinical Therapy* 38 (2016): 2477-2488.
169. Sorensen R, *et al.* "Adherence with oral anticoagulation in non-valvular atrial fibrillation: a comparison of vitamin K antagonists and non-vitamin K antagonists". *European Heart Journal* 3.3 (2017): 151-156.

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