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Thematic Article

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

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Abstract

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

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 War INR 1.8-3 or	31 30 30	70 71 72	1.4 1.6 1.6	Knee	VTE-A + VTE-S + PE-NF	[26]
Api 2.5 mg bid or Enox 30 mg bid sc	31 31	81 80	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 Dabi 225 mg bid Enox 40 mg qd			1.5 1.4 1.5	Hip and knee	VTE during treatment	[30]
Dabi 150 mg qd Dabi 220 mg qd Enox 40 mg qd			1.5 1.5 1.5	Knee	VTE + mortality	[31]
Dabi 150 mg qd Dabi 220 mg qd Enox 40 mg qd			1.5 1.5 1.5	Hip	VTE + mortality	[32]
Dabi 220 mg qd Enox 40 mg qd	28 28		1.3 1.3	Hip	VTE + mortality	[33]
Dabi 150 mg qd Dabi 220 mg qd Enox 30 mg bid			1.5 1.5 1.5	Knee	VTE + mortality	[34]
Edo 15 mg qd Edo 30 mg qd Dalte 5000 IU qd	27 28 28		1.4 1.4 1.4	Knee	VTE	[35]
Edo 30 mg qd Enox 20 mg bid		87 87	1.5 1.5	Knee	VTE	[36]
Edo 15 mg qd Edo 30 mg qd Enox 20 mg bid	24 24 23		1.5 1.5 1.6	Knee	VTE	[37]
Edo 30 mg qd Enox 20 mg bid	25 24			Hip	VTE	[38]
Riva 10 mg qd Enox 40 mg qd	28 28		1.5 1.5	Hip	DVT + PE-NF + death from VTE	[39]
Riva 10 mg qd Enox 40 mg qd	27 27		1.6 1.6	Hip	DVT + PE-NF + death	[40]
Riva 10 mg qd Enox 40 mg qd	30 30		1.6 1.6	Knee	DVT + PE-NF + death	[41]
Riva 10 mg qd Enox 30 mg bid	31 31		1.6 1.6	Knee	DVT + PE-NF + death	[42]
Riva 10 mg qd Aspirin 81 mg qd	31 31		1.4 1.4	Knee and hip	DVT-S	[43]

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	[27]
Enox 30 mg bid		0.4		0.9	8.2		0.4	0	0.2	8.8	1.6	
(all results after 10-14 days)										(VTE + PE + death)	(Major VTE + death	
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 P=0.019	2.2	24.4		0	0	0	24.4 (VTE + PE + death) 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		
(all results after 35 days)			P=0.01							(VTE + PE + death) 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	[32]
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 VTE + death	3.9 VTE-M + VTE mortality	
Dabi 220 mg qd		0		2.1	7.6		0.1		0	7.7	2.2	[33]
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 Dabi 220 mg qd Enox 40 mg qd (all results after 12-15 days)				3.1 2.3 1.6			0 1.0 0.8		0.2 0.2 0	33.7 31.1 25.3 VTE + death P=0.02 P<0.001		[34]
Edo 15 mg qd Edo 30 mg qd Dalte 5000 IU qd			6.5 3.3 13.9 (VTE-M) P=0.036 P<0.001	6.5 3.3 13.9 P=0.036 P<0.001		28.2 21.2 43.8 VTE P=0.005 P<0.001						[35]
Edo 30 mg qd Enox 20 mg bid	6.0 13.6	1.3 0.3		0 0.3		7.4 13.9	0 0	0 0				[36]
Edo 15 mg qd Edo 30 mg qd Enox 20 mg bid		0 0 0		0 0 0	3.8 2.8 4.1	3.8 2.8 4.1	0 0 0	0 0 0	0 0 0			[37]
Edo 30 mg qd Enox 20 mg bid	2.4 6.9	0 0		0.4 0.8	2.4 6.9		0 0	0 0	0 0	0.4 0.8 DVT-S + DVT-P + PE + VTE related death		[38]
Riva 10 mg qd Enox 40 mg qd (all results after 36 days)		0.3 0.5	0.2 2.0 P<0.001	0.1 2.0 P<0.001	0.8 3.4 P<0.001		0.3 0.1		0.3 0.3	1.1 3.7 DVT + PE-NF + death from VTE P<0.001		[39]
Riva 10 mg qd Enox 40 mg qd (all results after 36 days)		0.2 1.2 P=0.004	0.6 5.1 P<0.0001	0.6 5.1 P<0.0001	1.6 8.2 P<0.0001		0.1 0.5		0.2 0.7	2.0 9.3 DVT + PE-NF + death P<0.0001		[40]

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

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	Refer-ence
Api 2.5 mg bid Enox 30 mg bid War INR 1.8-3		87 87 89		7.8 6.7 6.0	1.3 0.7 2.0	1.3 0 0.7	0.7 0 0	2.6 2.7 2.0	0 0 0.7	[26]
Api 2.5 mg bid Enox 30 mg bid				8.5 8.6	1.3 0.7 2.0	0.1 0.3	0 0.1	1.0 1.6	0 0.1	[27]
Api 2.5 mg bid Enox 40 mg qd	3 3	52 55	14 14	5 6		0.1 0.1	0.1 0	2 1	0.2 0.1	[28]
Api 2.5 mg bid Enox 40 mg qd	3.4 4.2	65 68		6.9 6.5		0.2 0.2	<0.1 0.2	1.3 1.5	0.3 0.1	[29]

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

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

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 Aspirin 81-324 mg qd	2808 2791	70 70	41 42	AF, at risk for stroke, not suitable for vit K antagonist	132 132	28 28	Open	1.1	2.0 2.1	Stroke or SE	[44]
Api 5 mg bid Warfarin INR 2-3	9120 9081	70 70	36 35	AF + at least one risk factor for stroke	130 130		Open	1.8	2.1 2.1	Stroke or SE	[45]
Dab 110 mg bid Dab 150 mg bid Warfarin INR 2-3	6015 6076 6022	71 71 72	36 37 37	AF, at risk for stroke	131 131 131		DB DB Open	2.0	2.1 2.2 2.1	Stroke or SE	[46]
Dab 150 mg bid Warfarin INR 2-3	317 318	59 59	27 22	AF, ablation	131 131 131	29 29	Open	8 weeks	2.0 2.2	Bleeding	[47]
Dab 110 mg bid Warfarin/Aspirin Dab 150 mg bid Warfarin/Aspirin	981 981 763 764	72 72 69 69	26 23 22 22	AF, PCI Combi with ticagrelor or clopidogrel			Open	14 months	3.7 3.8 3.3 3.6	MI, stroke, SE	[48]

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

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

Table 9: Comparative studies in atrial fibrillation, results.

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

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

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

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

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

Medicines	N	Age	Female (%)	Body Weight (kg)	Inclusion	DVT (%)	PE (%)	DVT + PE (%)	Design	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/ Warfarin 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 treatment	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 factor 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 parenteral 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 parenteral 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 treatment 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 treatment 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 parenteral 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/ Warfarin INR 2-3	1718	56	44			99	1				
Riv 20 mg qd	602	58	41		Acute DVT after treatment for 6-12 months	64	36		DB, DD	6-12	[60]
Placebo	594	58	43			60	40				

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

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

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

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 Enox 1mg/kg/ Warfarin INR 2-3	2.3 2.7 NI:p<0.001				1.0 0.9	<0.1 0.1			1.5 1.9		[52]
Api 2.5 mg bid Api 5 mg bid Placebo	1.7 1.7 8.8 P<0.001	3.8 4.2 11.6 P<0.001		0.5 0.6 1.3	1.0 0.5 1.8	0 0 0					[53]

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

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	Intracranial 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 P<0.001	0.2	0.1	8.0	9.7 P<0.001		26		
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 P=0.04	0.1	0.1	1.9	2.1		6.8	0	
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 P=0.02		21.9	0.7	
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 P not stated			0.3	
Dabi 150 mg bid	0.9		0		5.6		19.4	0.5	[57]
Warfarin INR 2-3	1.8		0.1		10.2 P<0.001		26.2 P<0.001	0.9	
Dabi 150 mg bid	0.3				5.3		10.5		[57]
Placebo	0				1.8 P<0.001		5.9 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 P=0.004		25.6 P<0.001		0.6	
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 P=0.003	0.1	0.1	9.8				1.1	

Riv 10 mg qd 35 days Enox 40 mg qd 10 days	1.2 0.4 P<0.001		0.2 <0.1		2.8 1.2 P<0.001			0.2 0.1	[62]
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 (%)	Design	Risk factors					Duration of follow-up	Ref
					Diabetes %	Previous MI %	CV disease %	LVHF %	Peripheral vascular disease %		
Api 5 mg bid Placebo	3705 3687	67 67	33 32	DB	49 47	25 28	10 10	28 29	18 18	1.25 years	[64]
Riva 2.5 mg bid Riva 5 mg bid Placebo	5174 5176 5176	62 62 62	35 36 35	DB	32 32 32	26 27 27				13-31 months	[65]
Riva 2.5 mg bid Aspirin 100 mg qd	1519 1518	62 63	25 25	DB	29 30	21 23				390 days	[66]

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 Riva 5 mg bid Placebo	50 50 51	26 26 26	24 24 24		39 38 39	66 66 67	83 84 84			CV-D, MI, Stroke	[65]
Riva 2.5 mg bid Aspirin 100 mg qd	49 49	40 40	11 11	5.1 5.1	62 63	64 65	68 70			TIMI bleeding	[66]

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 P=0.02 (2.5 mg vs placebo)	2.9 4.4 4.5 P=0.002 (2.5 mg vs placebo)	2.7 4.0 4.1 P=0.002 (2.5 mg vs placebo)			2.2 2.3 2.9	[65]
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 P=0.001	2.2 0.8 P<0.001	2.7 1.1 P<0.001	3.2 1.2 P<0.001	1.8 0.6 P<0.001	2.3 0.7 P<0.001	0.1 0	0.6 0.2 P=0.03	18.5 14.4 P<0.001	[64]
Riva 2.5 mg bid Riva 5 mg bid Placebo	1.8 2.4 0.6						0.1 0.4 0.2 P=0.04 for 2.5 mg vs 5 mg Riva	0.4 0.7 0.2 P=0.009		[65]
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.

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