SUPPLEMENTAL MATERIAL

Supplemental Table I: Recommendations for the use of global coagulation to tests for the identification of relevant anticoagulant effect of dabigatran

Dabigatran			
	Sufficient	Sufficient in most cases	Insufficient
PT within normal range			Cuker 2014[1] Diener 2013[2] Hayes et al. 2013[3] Heidbuchel 2013[4] Lippi 2014[5] Siegal et al. 2013[6] Tripodi 2013[7]
aPTT within normal range	Lippi 2014*[5] Steiner 2013[8]	Diener 2013[2] Eickelboom 2013[9] Kitchen 2014[10] Konkle 2013[11] Levy 2013[12] Siegal 2013[6] Tran 2014[13] Tripodi 2013[7]	Cuker 2014[1] Douxfils 2014[14] Hankey 2014[15] Hayes et al. 2013[3] Hapgood 2013[16] Heidbuchel 2013[4]
TT within normal range	Cuker 2014[1] Diener 2013[2] Douxfils 2014[14] Hankey 2014[15] Hayes 2013[3] Heidbuchel 2013[4] Kepplinger 2014*[17] Kitchen 2014[10] Konkle 2013[11] Siegal 2013[6] Steiner 2013[8] Tran 2014[13] Tripodi 2013[7]	Hapgood 2013[16] Levy 2013[12]	
aPTT and TT within normal range	Eickelboom 2013[9] Hapgood 2013[16] Tran 2014[13]		

* using reagent-specific cut offs

Supplemental Table II: Recommendations for the use of global coagulation to tests for the identification of relevant anticoagulant effect of rivaroxaban

Rivaroxaban			
	Sufficient	Sufficient in most cases	Insufficient
PT within normal range	Kepplinger 2014*[17] Lippi 2014*[5] Shahoun 2015[18] Siegal 2013[6] Tripodi 2013[7]	Crowther 2015[19] Douxfils 2014[14] Kitchen 2014[10] Tran 2014[13]	Cuker 2014[1] Francard 2014[20] Hankey 2014[15] Heidbuchel 2013[4] Levy 2013[12]
aPTT within normal range			Cuker 2014[1] Francard 2014[20] Hankey 2014[15] Heidbuchel 2013[4] Kitchen 2014[10] Levy 2013[12] Tran 2014[13]
PT and aPTT within normal range		Diener 2013[2] Steiner 2013[8]	

* using reagent-specific cut offs

Supplemental Table III: Recommendations for the use of global coagulation to tests for the identification of relevant anticoagulant effect of apixaban

Apixaban			
	Sufficient	Sufficient in most cases	Insufficient
PT within normal range		Shahoun 2015[18]	Cuker 2014[1] Douxfils 2014[14] Hankey 2014[15] Kepplinger 2014[17] Kitchen 2014[10] Siegal 2013[21] Tran 2014[13] Tripodi 2013[7] Ward 2013[22]
aPTT within normal range			Cuker 2014[1] Hankey 2014[15] Kitchen 2014[10] Tran 2014[13] Ward 2013[22]
PT and aPTT within normal range		Diener 2013[2] Steiner 2013[8]	

Supplemental Table IV: Patient characteristics in the three DOAC groups

	Rivaroxaban	**Apixaban**	**Dabigatran**
Dose[1]	15 mg: 2 (7%) 20 mg: 28 (93%)	2.5 mg: 13 (41%) 5 mg: 19 (59%)	110 mg: 10 (39%) 150 mg: 16 (62%)
Sex, female[1]	13 (43%)	15 (47%)	13 (50%)
Age, years[2]	69 ± 15	75 ± 13	74 ± 14
Body weight, kg[2]	80 ± 19	72 ±15	80 ± 23
Body mass index[2]	27 ± 6	25 ± 4	27 ± 6
Risk Factors			
Arterial hypertension[1]	19 (63%)	27 (84%)	20 (77%)
Diabetes mellitus[1]	5 (17%)	8 (25%)	6 (23%)
Hyperlipidemia[1]	7 (23%)	17 (53%)	15 (58%)
Smoking[1]	4 (13%)	3 (9%)	2 (8%)
Concomitant antiplatelet agents (last dose <7 days)			
Acetylsalicylic acid[1]	15 (50%)	15 (47%)	7 (27%)
Others[1]	1 (3%)	1 (3%)	0 (0%)
Prophylactic dose of heparins at any time during admission			
Heparin[1]	20 (67%)	23 (72%)	19 (73%)
Enoxaparin[1]	14 (47%)	12 (38%)	6 (23%)
Indication for oral anticoagulation			
Atrial fibrillation[1]	21 (70%)	15 (47%)	24 (92%)
Patent foramen ovale[1]	9 (30%)	0 (0%)	2 (8%)
ESUS[1]	0 (0%)	17 (53%)	0 (0%)

[1]number (%), [2]mean ± standard deviation; ESUS = Embolic Stroke of Undetermined Source

Supplemental Table V: Baseline lab results of patients in the three DOAC groups

	Rivaroxaban	**Apixaban**	**Dabigatran**	**Reference Range**
WBC, /µl[1]	7147 ± 2013	6969 ± 1581	8297 ± 2889	3800-10300
RBC, 10^6/µl	4.4 ± 0.6	4.2 ± 0.7	4.5 ± 0.5	4.2-6.2
Hematocrit	0.4 ± 0.05	0.38 ± 0.05	0.4 ± 0.04	0.42-0.52
Hemoglobin, mmol/L	8.4 ± 1.1	7.88 ± 1.3	8.4 ± 1	8.7-11.2
Platelet Count, 10^3/µl	236 ± 57	239 ± 70	226 ± 79	150-450
Quick, %	99 ± 11	96 ± 13	92 ± 12	70-120
INR	1.0 ± 0.	1.0 ± 0.1	1.1 ± 0.1	0.9-1.2
aPTT, seconds	26 ± 6	27 ± 5	27 ± 4	<40
Anti-Xa, IE-aXa/mL	<0.09	<0.09	<0.09	<0.09
Fibrinogen, µmol/L	10.1 ± 2.4	9.8 ± 2.1	9.8 ± 2.3	5-12.1
D-dimer, nmol/L	4.9 ± 7.7	2.7 ± 3.3	3.8 ± 4.3	<2.7
Creatinine, µmol/L	68.6 ± 15.3	76.3 ± 38.1	68.6 ± 15.3	45.8-83.9
GFR, mL/min/kg	81 ± 19	78 ± 31	75 ± 17	>60
Protein total, g/L	70 ± 7	68 ± 7	68 ± 7	65-85
Albumin, g/L	41 ± 4	39 ± 5	40 ± 4	34-48
CRP, nmol/L	285.7 ± 438.1	219.1 ± 342.9	142.9 ± 123.8	<47.6
Procalcitonin, µg/L	0.10 ± 0.08	0.11 ± 0.09	0.09 ± 0.04	≤0.10
AST, µkat/L	0.55 ± 0.2	0.65 ± 0.42	0.58 ± 0.3	≤0.83
ALT, µkat/L	0.53 ± 0.3	0.6 ± 0.53	0.52 ± 0.33	≤0.83
GGT, U/L	0.78 ± 0.6	1.15 ± 1.49	1.05 ± 1.15	≤1.00

[1]mean ± standard deviation, WBC = white blood count, RBC = red blood count, INR = international normalized ratio, aPTT = activated partial thromboplastin time, GFR = glomerular filtration rate, CRP = C-reactive protein, AST = aspartate transaminase, ALT = alanine transaminase, GGT = gamma-glutamyl transferase.

Supplemental Table VI: Test accuracy of a 50 ng/ml concentration threshold

Substance and safe-for-treatment threshold	Coagulation test	Result within normal range			Result below reagent-specific cut-off			
		Specificity (%)	Sensitivity (%)	LR+	Cut-off	Specificity (%)	Sensitivity (%)	LR+
Dabigatran <50 ng/mL	aPTT	62 (48-74)	88 (81-93)	2.3	aPTT <29 sec	98 (90-100)	57 (47-66)	32.9
	PT and aPTT	66 (52-77)	78 (69-84)	2.2				
	TT	100 (92-100)	20 (14-29)	∞	TT <75 sec	98 (90-100)	87 (79-92)	50.2
	TT <3xUNR	98 (90-100)	79 (70-86)	45.8				
	TT <4xUNR	95 (85-99)	99 (93-100)	4.5				
Rivaroxaban <50 ng/mL	PT	83 (74-90)	89 (76-96)	5.2	Quick >84%	96 (89-99)	61 (45-75)	15.2
	PT and aPTT	83 (74-90)	89 (76-96)	5.2				
Apixaban <50 ng/mL	PT	16 (9-25)	94 (85-98)	1.1				
	PT and aPTT	20 (13-30)	91 (81-96)	1.1				

Samples=178 (dabigatran); 146 (rivaroxaban); 157 (apixaban). Sensitivity and specificity are provided with 95% confidence intervals. aPTT, activated partial thromboplastin time (HemosIL APTT-SP); LR+, positive likelihood ratio; PT, prothrombin time (HemosIL RecombiPlasTin 2G); TT, thrombin time (Test-Thrombin Reagent).

Supplemental Table VII: Test accuracy of a sequential algorithm [17]

Substance	Test result	Specificity (%)	Sensitivity (%)	LR+
Dabigatran <31 ng/mL	TT <21 seconds	100 (95-100)	26 (18-36)	∞
	TT <21 sec or TT ≥21 sec and dTT <31 ng/mL	93 (85-97)	78 (68-86)	11.1
Dabigatran <62 ng/mL	TT <21 seconds	100 (90-100)	18 (12-26)	∞
	TT <21 sec or TT ≥21 sec and dTT <62 ng/mL	91 (78-97)	78 (70-84)	9.0
Rivaroxaban <20 ng/mL	INR <1.4	57 (47-65)	100 (83-100)	2.3
	INR <1.4 or INR ≥1.4 and anti-Xa <20 ng/mL	57 (47-65)	100 (83-100)	2.3
Rivaroxaban <91 ng/mL	INR <1.4	80 (69-88)	92 (83-97)	4.6
	INR <1.4 or INR ≥1.4 and anti-Xa <91 ng/mL	80 (69-88)	92 (83-97)	4.6
Apixaban <21 ng/mL	INR <1.4	5 (2-11)	100 (83-100)	1.1
	INR <1.4 or INR ≥1.4 and anti-Xa <21 ng/mL	5 (2-11)	100 (83-100)	1.1
Apixaban <40 ng/mL	INR <1.4	6 (3-13)	100 (91-100)	1.1
	INR <1.4 or INR ≥1.4 and anti-Xa <21 ng/mL	6 (3-13)	100 (91-100)	1.1

Samples=178 (dabigatran); 146 (rivaroxaban); 157 (apixaban). Sensitivity and specificity are provided with 95% confidence intervals. INR, international normalized ratio time (HemosIL RecombiPlasTin 2G); LR+, positive likelihood ratio; TT, thrombin time (Test-Thrombin Reagent).

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