

Appendix 4: Hemorrhagic and thromboembolic event rates in each study in 4 categories of international normalized ratios (part 1 of 2)

Study	International normalized ratio; event rate									
	< 2		2–3		3–5		> 5			
	No. of patients	No. of events / patient-yrs	Rate per 100 patient-yrs (95% CI)	No. of events / patient-yrs	Rate per 100 patient-yrs (95% CI)	No. of events / patient-yrs	Rate per 100 patient-yrs (95% CI)	No. of events / patient-yrs	Rate per 100 patient-yrs (95% CI)	
Hemorrhagic events										
Hutten ¹	1 303	4/63.3	6.3 (1.7–16.2)	4/152.3	2.6 (1.8–3.7)	3/57.7	5.2 (1.1–15.2)	*		
Yasaka ²	203	0/192.0	0.0 (0.0–0.0)	7/140.0	5.0 (2.0–10.3)	2/7.0	28.6 (3.5–103.1)	*		
EAFT ³	214	0/40.0	0.0 (0.0–0.0)	2/186.0	1.1 (0.1–3.9)	4/141.0	2.8 (0.8–7.3)	5/10.0	50.0 (16.2–116.5)	
Chimowitz ⁴	289	1/92.5	1.1 (0.0–6.0)	9/256.9	3.5 (1.6–6.7)	8/52.6	15.2 (6.6–30.0)	6/4.9	122.4 (45.0–267.0)	
Andersen ⁵	204	0/50.2	0.0 (0.0–0.0)	3/242.0	1.2 (0.6–2.2)	3/135.0	2.2 (1.1–4.0)	8/4.0	200.0 (99.8–358.0)	
Torn ⁶	356	0/12.1	0.0 (0.0–0.0)	2/147.7	1.4 (0.2–4.9)	14/432.5	3.2 (1.8–5.4)	6/21.6	27.8 (10.2–60.6)	
Cheung ⁷	555	3/456.0	0.7 (0.1–1.9)	7/361.0	1.9 (0.8–4.0)	8/39.0	20.5 (8.8–40.4)	*		
ESPRIT ⁸	536	4/147.0	2.7 (1.2–5.4)	6/966.0	0.6 (0.3–1.2)	9/266.0	3.4 (1.5–6.7)	12/29.0	41.4 (17.8–81.5)	
Poli ⁹	903	12/112.0	10.7 (5.5–18.8)	41/842.0	4.9 (3.5–6.6)	26/428.0	6.1 (4.0–8.9)	5/25.6	19.5 (6.3–45.5)	
Tangelder ¹⁰	1 326	9/150.0	6.0 (2.7–11.4)	13/505.0	2.6 (1.3–4.4)	38/945.0	4.0 (2.8–5.6)	20/99.0	20.2 (12.3–30.7)	
Kearon ¹¹	738	3/847.5	0.4 (0.1–1.0)	4/743.4	0.5 (0.1–1.4)	8/134.1	6.0 (2.6–11.7)	*		
Casais ¹²	811	2/179.8	1.1 (0.1–4.0)	8/707.2	1.1 (0.5–2.2)	5/859.5	0.6 (0.2–1.4)	10/212.8	4.7 (2.3–8.6)	
Palareti ¹³	2 745	6/377.0	1.6 (1.1–2.3)	9/1116.0	0.8 (0.6–1.1)	5/442.0	1.1 (0.8–1.5)	5/45.0	11.1 (7.0–16.7)	
Van Walraven ¹⁴	10 020	31/884.8	3.5 (2.1–5.5)	76/1954.0	3.9 (2.8–5.3)	52/450.8	11.5 (7.3–17.3)	23/17.5	131.4 (65.6–235.3)	
Azar ¹⁵	1 700	8/3559.0	0.2 (0.1–0.4)	5/838.0	0.6 (0.2–1.4)	30/2339.0	1.3 (0.9–1.8)	12/182.0	6.6 (3.4–11.5)	
Hylek ¹⁶	13 559	12/3428.0	0.4 (0.2–0.6)	28/7809.0	0.4 (0.2–0.5)	10/1237.0	0.8 (0.4–1.5)	11/118.0	9.3 (4.7–16.7)	
Oden ¹⁷	42 451	28/8533.3	0.3 (0.2–0.5)	133/42402.1	0.3 (0.2–0.4)	74/9311.6	0.8 (0.6–1.0)	8/217.6	3.7 (1.6–7.2)	
Thromboembolic events										
Rosove ¹⁸	55	6/11.3	53.1 (19.5–115.8)	3/40.9	7.3 (1.5–21.4)	0/110.2	0.0 (0.0–0.0)	*		
Hutten ¹	1 303	15/63.3	23.7 (13.3–39.1)	14/152.3	9.2 (5.0–15.4)	5/57.7	8.7 (2.8–20.2)	*		
Yasaka ²	203	14/192.0	7.3 (4.0–12.3)	4/140.0	2.9 (2.0–4.0)	0/7.0	0.0 (0.0–0.0)	*		
EAFT ³	214	7/40.0	17.5 (7.0–36.1)	3/186.0	1.6 (0.3–4.7)	10/141.0	7.1 (3.4–13.0)	1/10.0	10.0 (0.3–55.7)	

Appendix 4 to Oake N, Jennings A, Forster A, et al. Anticoagulation intensity and outcomes among patients prescribed oral anticoagulant therapy: a systematic review and meta-analysis. *CMAJ* 2008; 179(3): 235-44.

Appendix 4: Hemorrhagic and thromboembolic event rates in each study in 4 categories of international normalized ratios (part 2 of 2)

Study	International normalized ratio; event rate										
	< 2		2-3		3-5		> 5				
	No. of patients	No. of events / patient-yr	Rate per 100 patient-yr (95% CI)	No. of events / patient-yr	Rate per 100 patient-yr (95% CI)	No. of events / patient-yr	Rate per 100 patient-yr (95% CI)	No. of events / patient-yr	Rate per 100 patient-yr (95% CI)	No. of events / patient-yr	Rate per 100 patient-yr (95% CI)
Chimowitz ⁴	289	23/92.5	24.9 (15.9–37.3)	13/2565.9	5.1 (2.6–8.7)	3/52.6	5.7 (1.2–16.7)	1/4.9	20.4 (0.5–113.7)		
Andersen ⁵	204	0/50.2	0.0 (0.0–0.0)	4/242.0	1.7 (0.8–3.0)	1/135.0	0.7 (0.4–1.3)	0/4.0	0.0 (0.0–0.0)		
Torn ⁶	356	3/12.1	24.8 (5.1–72.4)	5/147.7	3.4 (1.1–7.9)	8/432.5	1.8 (0.8–3.6)	3/21.6	13.9 (2.9–40.6)		
Cheung ⁷	555	28/456.0	6.1 (4.1–8.9)	7/361.0	1.9 (0.8–4.0)	0/39.0	0.0 (0.0–0.0)	*			
ESPRIT ⁸	536	5/147.0	3.4 (0.9–8.7)	15/966.0	1.6 (0.4–4.0)	4/266.0	1.5 (0.4–3.8)	1/29	3.4 (0.9–8.8)		
Poli ⁹	903	20/112.0	17.9 (10.9–27.1)	31/842.0	3.7 (2.5–5.3)	12/428.0	2.8 (1.4–4.9)	0/25.6	0.0 (0.0–0.0)		
Tangelder ¹⁰	1 326	23/150.0	15.3 (9.7–23.0)	26/505.0	5.1 (3.4–7.6)	11/945.0	1.2 (0.6–2.1)	16/99.0	16.2 (9.2–26.2)		
Kearon ¹¹	738	8/847.5	0.9 (0.4–1.9)	2/743.4	0.3 (0.0–1.0)	1/134.1	0.7 (0.0–4.2)	*			
Palareti ¹⁹	2 745	27/377.0	7.2 (4.7–10.5)	26/1116.0	2.3 (1.5–3.4)	10/487.0	2.1 (1.0–3.8)	*			
Van Walraven ¹⁴	10 020	46/862.4	5.3 (3.5–7.1)	50/1910.6	2.6 (1.5–3.0)	24/442.1	5.4 (2.3–6.8)	4/16.9	23.7 (7.6–71.6)		
Azar ¹⁵	1 700	282/3559.0	7.9 (7.0–9.0)	27/838.0	3.2 (2.1–4.7)	64/2339.0	2.7 (2.1–3.6)	2/182.0	1.1 (0.1–4.0)		
Hylek ¹⁶	13 559	97/3428.0	2.8 (2.3–3.5)	43/7809.0	0.6 (0.4–0.7)	9/1237.0	0.7 (0.3–1.4)	3/118.0	2.5 (0.5–7.4)		

Note: EAFT = European Atrial Fibrillation Trial Study Group.

*Study reported events and observation time for international normalized ratio range > 3. We grouped data for this range into the 3–5 category.

References

1. Hutten BA, Prins MH, Gent M, et al. Incidence of recurrent thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. *J Clin Oncol* 2000;18:3078-83.
2. Yasaka M, Minematsu K, Yamaguchi T. Optimal intensity of international normalized ratio in warfarin therapy for secondary prevention of stroke in patients with non-valvular atrial fibrillation. *Intern Med* 2001;40:1183-8.
3. Optimal oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and recent cerebral ischemia. The European Atrial Fibrillation Trial Study Group. *N Engl J Med* 1995;333:5-10.
4. Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med* 2005;352:1305-16.
5. Andersen PV, Aagaard J. Low-dose warfarin in patients with Carbomedics heart valve prostheses. *Asian Cardiovasc Thorac Ann* 2000;8:11-4.
6. Torn M, Algra A, Rosendaal FR. Oral anticoagulation for cerebral ischemia of arterial origin: high initial bleeding risk. *Neurology* 2001;57:1993-9.
7. Cheung CM, Tsoi TH, Huang CY. The lowest effective intensity of prophylactic anticoagulation for patients with atrial fibrillation. *Cerebrovasc Dis* 2005;20:114-9.
8. ESPRIT Study Group; Algra A. Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial. *Lancet Neurol* 2007;6:115-24.

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9. Poli D, Antonucci E, Lombardi A, et al. Low rate of bleeding and thrombotic complications of oral anticoagulant therapy independent of age in the real-practice of an anticoagulation clinic. *Blood Coagul Fibrinolysis* 2003;14:269-75.
10. Tangelder MJD, Algra A, Lawson JA, et al. Optimal oral anticoagulant intensity to prevent secondary ischemic and hemorrhagic events in patients after infrainguinal bypass graft surgery. *J Vasc Surg* 2001;33:522-7.
11. Kearon C, Ginsberg JS, Kovacs MJ, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. *N Engl J Med* 2003;349:631-9.
12. Casais P, Luceros AS, Meschengieser S, et al. Bleeding risk factors in chronic oral anticoagulation with acenocoumarol. *Am J Hematol* 2000;63:192-6.
13. Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy. *Lancet* 1996;348:423-8.
14. Van Walraven C, Oake N, Wells PS, et al. Burden of potentially avoidable anticoagulant-associated hemorrhagic and thromboembolic events in the elderly. *Chest* 2007;131:1508-15.
15. Azar AJ, Cannegieter SC, Deckers JW, et al. Optimal intensity of oral anticoagulant therapy after myocardial infarction. *J Am Coll Cardiol* 1996;27:1349-55.
16. Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med* 2003;349:1019-26.
17. Oden A, Fahlen M. Oral anticoagulation and risk of death: a medical record linkage study. *BMJ* 2002;325:1073-5.
18. Rosove MH, Brewer PM. Antiphospholipid thrombosis: clinical course after the first thrombotic event in 70 patients. *Ann Intern Med* 1992;117:303-8.
19. Palareti G, Manotti C, D'Angelo A, et al. Thrombotic events during oral anticoagulant treatment: results of the inception-cohort, prospective, collaborative ISCOAT study: ISCOAT study group (Italian Study on Complications of Oral Anticoagulant Therapy). *Thromb Haemost* 1997;78:1438-43.