



Evidence-Based Management of Anticoagulant Therapy

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Table S1—[Section 2.1] Evidence Profile: Warfarin 10-mg Loading Dose Nomogram Compared With Warfarin 5-mg Loading Dose Nomogram for Warfarin Initiation

Participants (Studies), Follow-up	Quality Assessment				Summary of Findings					
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)	Anticipated Absolute Effects		
							With Warfarin 5-mg Loading Dose Nomogram	Risk With Warfarin 5-mg Loading Dose Nomogram (95% CI)		
420 (3 studies ^{a,c}), 5-90 d ^b	Serious ^a	No serious inconsistency	Serious ^f	Very serious ^g	Undetected	Bleeding events (critical outcome) Very low ^{h,i} due to risk of bias, indirectness, and imprecision	1/204 (0.49)	2/216 (0.93) ^h	OR 1.90 (0.17-21.1)	Moderate
420 (3 studies ^{a,c}), 5-90 d	Serious ^a	No serious inconsistency	Serious ^f	Very serious ^g	Undetected	Recurrent VTE (critical outcome) Very low ^{h,i} due to risk of bias, indirectness, and imprecision	0/204 (0)	3/216 (1.4) ^h	OR 6.72 (0.34-131.88)	Moderate

Bibliography: Crowther MA, Ginsberg J, Kearon C, et al. A randomized trial comparing 5-mg and 10-mg warfarin loading doses. *Arch Intern Med.* 1999;159(1):46-48. Harrison L, Johnston M, Massicotte MP, Crowther M, Moffat K, Hirsh J. Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. *Ann Intern Med.* 1997;126:133-136. Kovacs MJ, Rodger M, Anderson DR, et al. Comparison of 10-mg and 5-mg warfarin initiation nomograms together with low-molecular-weight heparin for outpatient treatment of acute venous thromboembolism. *Ann Intern Med.* 2003;138:714-419. Quiroz R, Gerhard-Herman M, et al. Comparison of a single end point to determine optimal initial warfarin dosing (5 mg vs 10 mg) for venous thromboembolism. *Am J Cardiol.* 2006;98:535-537. Schulman S, Lockner D, Bergstrom K, Blomback M. Intensive initial oral anticoagulation and shorter heparin treatment in deep vein thrombosis. *Thromb Haemost.* 1984;52:276-280.

^aAll pooled studies included only patients with acute VTE. Studies from which data could be pooled are Kovacs et al, Quiroz et al, and Schulman et al.
^bMinimal loss to follow-up: adherence to intention-to-treat principle in two of three studies; follow-up period is short but adequate for this outcome; any lack of blinding should not affect objective outcome (laboratory value, international normalized ratio); adequate allocation concealment; and sample size calculations reported for two of three studies.
^cResults based on only three studies; one study shows no difference; one study shows statistically significant reduction in time to therapeutic international normalized ratio; and one study had two parts to it, with one part showing statistically significant reduction and the other did not.

^dFive days is the mean follow-up period for patients in the loading dose warfarin group from Schulman et al (this was the shortest period, only mean is available).
^eAdequate allocation concealment; adjudicators blinded in two of three studies (but caregivers and data collectors blinded in zero of three studies); minimal loss to follow-up; intention to treat followed in two of three studies, but follow-up period is very short in two of three studies (5 d-2 wk).

^fIndirect given application aimed at VTE outpatients.

^gNo studies were powered to detect differences in bleeding events between groups. Number of events is too sparse to draw any conclusions.

^hOne major bleeding event in the 10-mg group vs none in the 5-mg in Quiroz et al; no bleeding events in either group in Schulman et al; one major bleeding event per group in Kovacs et al.

ⁱNo recurrent VTE in either group for Quiroz et al or Schulman et al; three in the 10-mg group vs none in the 5-mg group in Kovacs et al.

Table S2—[Section 2.2] Evidence Profile: Pharmacogenetic-Based Testing vs Usual Dosing Strategies for Patients Initiating Therapy With VKA

Participants (Studies), Follow-up	Quality Assessment				Summary of Findings						
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Usual Dosing Strategies	With Pharmacogenetic-Based Testing	Study Event Rates (%)	Anticipated Absolute Effects	
468 (3 studies), 1-3 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious ^b to imprecision	Undetected ^c	Moderate ^{b,c} due to imprecision	6/234 (2.6) ^d	4/234 (1.7) ^e	OR 0.66 (0.16-2.45)	26 per 1,000 ^e (from 21 fewer to 35 more)	Risk Difference With Pharmacogenetic-Based Testing (95% CI)
463 (3 studies), 1-3 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious ^b	Thromboembolism (critical outcome; assessment not reported)		2/231 (0.87) ^{d,f}	0/232 (0)	OR 0 (0-3.4) ^f	9 per 1,000 ^{d,f} (from 9 fewer to 20 more)	

Bibliography: Anderson JL, Home BD, Stevens SM, et al; for Couma-Gen Investigators. Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. *Circulation*. 2007;116(22):2563-2570. Hillman MA, Wilke RA, Yale SH, et al. A prospective, randomized pilot trial of model-based warfarin dose initiation using CYP2C9 genotype and clinical data. *Clin Med Res*. 2005;3(3):137-145. Caraco Y, Blotnick S, Muszkat M. CYP2C9 genotype-guided warfarin prescribing enhances the efficacy and safety of anticoagulation: a prospective randomized controlled study. *Clin Pharmacol Ther*. 2008;83(3):460-470. Huang SW, Chen HS, Wang XQ, et al. Validation of VKORC1 and CYP2C9 genotypes on interindividual warfarin maintenance dose: a prospective study in Chinese patients. *Pharmacogenet Genomics*. 2009;19(3):226-234. VKA = vitamin K antagonist.

^aBleeding rate in Hillman et al was four of 20, but severity was not reported; included one case hematuria, two cases epistaxis, and one GI bleed in the control group.

^bTotal sample size below optimal information size.

^cAll studies were funded by public or nonprofit organizations.

^dControl rate is median percentage of events in the usual dosing group across all studies reporting that outcome.

^eIntervention rate is mean percentage of events across all intervention groups (unweighted).

^fHillman et al reported one DVT and one thromboembolism (unclear whether the same or different patients) among 20 control patients and no events in the intervention group. Caraco et al reported no events in both groups. Huang et al reported no VTE in either group. Anderson et al did not separate VTE.

Table S3—[Section 2.3] Evidence Profile: VKA Started Early vs Late in Heparin Patients With Acute Thromboembolism

Participants (Studies), Follow-up	Quality Assessment					Summary of Findings			
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)	Relative Effect (95% CI)	Anticipated Absolute Effects
807 (4 studies), 3-6 mo	No serious risk of bias ^a	Serious ^b	No serious indirectness	Serious ^c	Undetected	Low ^{a,c} due to inconsistency and imprecision	23/394 (5.8) With VKA Started Early	RR 1.25 (0.43-3.85)	58 per 1,000 Started Early 16 more per 1,000 (from 33 fewer to 166 more)
Recurrent thromboembolism (critical outcome; DVT assessed with venography; Doppler ultrasonography; or impedance plethysmography; PE assessed with lung scanning; left ventricle thrombus assessed with two-dimensional transthoracic echocardiography)									
807 (4 studies), 3-6 mo	Serious ^d	No serious inconsistency	No serious indirectness	Serious ^c	Undetected	Low ^{a,d} due to risk of bias and imprecision	16/394 (4.1) With VKA Started Early	RR 0.92 (0.46-1.82)	41 per 1,000 Started Early 3 fewer per 1,000 (from 22 fewer to 33 more)
Major bleeding (critical outcome; assessed with required blood transfusion or bleeding in body cavity or bleeding that required anticoagulation withdrawal for intracranial or retroperitoneal bleeding or led to hemoglobin level decrease of ≥ 2 g/dL or to death)									
807 (4 studies), 0.5-6 mo	Serious ^d	No serious inconsistency	No serious indirectness	Serious ^c	Undetected	Low ^{a,d} due to risk of bias and imprecision	13/394 (3.3) With VKA Started Early	RR 1.22 (0.55-2.56)	33 per 1,000 Started Early 7 more per 1,000 (from 14 fewer to 51 more)
Hospital utilization (days) (important outcome; better indicated by lower values)									
536 (3 studies), follow-up for hospital, 2 d to 6 mo	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	High	263	...	The mean hospital utilization in the control groups was 14 d The mean hospital utilization in the intervention groups was 4.07 d lower (4.76-3.37 d lower)

Bibliography: Qayyum F, Holbrook A, Lam J, Kovacs MJ, Schulman S, unpublished data, 2011. PE = pulmonary embolism; RR = risk ratio. See Table S2 legend for expansion of other abbreviation.

^aFor three of four studies, concealment of allocation was unclear. However, this alone was not seen as a compelling reason to downgrade evidence for this outcome. Lack of blinding of health-care professionals in some studies is not likely to affect incidence of this outcome.

^bThe value for the I^2 test for death was 55%; therefore, it was rated down for inconsistency.

^cThe 95% CIs around the absolute risk values were very wide for this outcome.

^dPotential limitations in design for this outcome, including allocation sequence concealment not reported in three of four studies and health-care professionals blinded in only one study (Hull et al 1990) (outcome assessors were blinded in three of four studies).

Table S4—[Section 3.1] Evidence Profile: Prolonged INR Recall Intervals Compared With Four-Week Recall Intervals

Participants (Studies), Follow-up	Quality Assessment					Summary of Findings				
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)	Relative Effect (95% CI)	Risk With 4-wk Recall Intervals	Anticipated Absolute Effects ^a
744 (2 studies), 163 patient-y	Serious ^b	No serious inconsistency	No serious indirectness	Serious ^c	Undetected	Low ^{b,c} due to risk of bias and imprecision	With 4-wk Recall Intervals	RR 1.02 (0.13-8.32)	13 per 1,000	Risk Difference With Prolonged INR Recall Intervals (95% CI)
							With Prolonged INR Recall Intervals			
744 (2 studies), 163 patient-y	Serious ^b	No serious inconsistency	No serious indirectness	Serious ^c	Undetected	Low ^{b,c} due to risk of bias and imprecision	Major bleeding (critical outcome; assessments variously defined)	RR 1.06 (0.54-2.1)	42 per 1,000	2 more per 1,000 (from 19 fewer to 46 more)
							With Prolonged INR Recall Intervals			

Bibliography: Fihn SD, McDonnell MB, Vermees D, et al. A computerized intervention to improve timing of outpatient follow-up: a multicenter randomized trial in patients treated with warfarin. *J Gen Intern Med.* 1994;9:131-139; Pengo V, Barbero F, Biasiolo A, Pegoraro C, Cucchini U, Illiceto S. A comparison between six- and four-week intervals in surveillance of oral anticoagulant treatment. *Am J Clin Pathol.* 2003;120:944-947. INR = international normalized ratio. See Table S3 legend for expansion of other abbreviation.

^aTime frame is in months.

^bLack of blinding; intention to treat not specified in Pengo et al; and adherence to recommended INR recall intervals was not mandated in Fihn et al.

^cWide CIs around the estimate of effect.

Table S5—[Section 3.4] Evidence Profile: Low-Dose Vitamin K Supplementation Compared With Placebo for Patients Taking VKAs To Stabilize INR

Participants (Studies), Follow-up	Quality Assessment					Summary of Findings					
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Placebo	With Low-Dose Vitamin K Supplementation	Relative Effect (95% CI)	Risk With Placebo	Anticipated Absolute Effects ^a Risk Difference With Low-Dose Vitamin K Supplementation (95% CI)
626 (3 studies), 168-180 d	No serious risk of bias ^d	Serious ^b	No serious indirectness	Serious ^c	Major bleeding (important outcome) Reporting bias strongly suspected ^d	Very low ^{b,e} due to inconsistency, imprecision, and publication bias	0/219 (0)	3/407 (0.74)	2.61 (0.34-20.28)	0 per 1,000	Not estimable
626 (3 studies), 168-180 d	No serious risk of bias ^c	No serious inconsistency	No serious indirectness	Very serious ^c	Thromboembolism (important outcome) Reporting bias strongly suspected ^d	See comment	0/219 (0)	0/407 (0)	1.65 (0.08-34.03)	0 per 1,000	Not estimable

Bibliography: Rombouts EK, Rosendaal FR, Van Der Meer FJM. Daily vitamin K supplementation improves anticoagulant stability. *J Thromb Haemost.* 2007;5:2043-2048. Sconce E, Avery P, Wynne H, Kamali F. Vitamin K supplementation can improve stability of anticoagulation for patients with unexplained variability in response to warfarin. *Blood.* 2007;109:2419-2423. Gebuis EPA, Rosendaal FR, van Meegen E, van der Meer FJM. Vitamin K1 supplementation to improve the stability of anticoagulation therapy with vitamin K antagonists: a dose-finding study. *Haematologica.* 2011;96(4):583-589. See Table S2 and S4 legends for expansion of abbreviations.

^aTime frame is in months.

^bFull definition of major bleeding not provided in the Sconce et al study. Definition of major bleeding different in each study.

^cStudies not powered to detect bleeding or thromboembolic events. The sample sizes in trials by both Sconce et al and Rombouts et al were small. The total number of events was extremely low.

^dUnable to rule out because not enough studies exist to populate funnel plot.

^eAllocation concealment not reported; uncertain whether outcome adjudicators were blinded.

Table S6—[Section 3.6] Evidence Profile: Patient Self-Testing/Self-Monitoring Compared With Usual Laboratory-Based Monitoring for VKA Therapy Management

Participants (Studies), Follow-up	Quality Assessment					Summary of Findings					
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Usual Laboratory-Based Monitoring	With Patient Self-Testing/Patient Self-Monitoring	Study Event Rates (%)	Anticipated Absolute Effects ^a	
7,759 (14 studies), 4.6-57 mo	Serious ^e	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate ^e due to risk of bias	149/3,755 (4)	99/4,004 (2.5)	OR 0.58 (0.45-0.75)	40 per 1,000	16 fewer per 1,000 (from 10 fewer to 21 fewer)
7,867 (16 studies), 4.6-57 mo	Serious ^e	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate ^e due to risk of bias	300/3,806 (7.9)	283/4,061 (7)	OR 0.87 (0.75-1.05)	79 per 1,000	10 fewer per 1,000 (from 19 fewer to 4 more)
6,370 (13 studies), 6-57 mo	Serious ^e	Serious ^e	No serious indirectness	No serious imprecision	Undetected	Low ^{e,f} due to risk of bias, inconsistency	369/3,123 (11.8)	298/3,247 (9.2)	OR 0.74 (0.63-0.87)	118 per 1,000	28 fewer per 1,000 (from 14 fewer to 40 fewer) ^f

Bibliography: Bloomfield HF, Krause A, Greer N, et al. Meta-analysis: effect of patient self-testing and self-management of long-term anticoagulation on major clinical outcomes. *Ann Intern Med*. 2011;154:472-482. See Table S2 through S4 legends for expansion of abbreviations.

^aTime frame is in years.

^bDesignated as major by the study or categorized as strokes, new or recurrent symptomatic DVT, PE, or arterial embolism.

^cFlaws in study design, most commonly an absence of information about the allocation concealment procedure or blinding.

^dCategorized as major by the study or that met the ISCOAT (Italian Study of Complications of Anticoagulant Therapy) criteria for major bleeding.

^eEvidence of heterogeneity among studies that was probably attributable to the THINRS (The Home INR Study) Matchar DB, Jacobson A, Dolor R, et al; THINRS Executive Committee and Site Investigators. Effect of home testing of international normalized ratio on clinical events. *N Engl J Med*. 2010;363(17):1608-1620.

^fThe reduction in mortality from all causes was largely influenced by one study.

Table S7—[Section 3.7] Evidence Profile: Dosing Decision Support Compared With Manual Dosing for VKA Therapy

Participants (Studies), Follow-up	Quality Assessment					Summary of Findings					
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Manual Dosing	With Dosing Decision Support	Relative Effect (95% CI)	Risk With Manual Dosing	Risk Difference With Dosing Decision Support (95% CI)
503 (4 studies), 3 mo	Serious ^b	No serious inconsistency	No serious indirectness	Serious ^c	Undetected	Low ^{b,c} due to risk of bias, imprecision	16/255 (6.3)	9/248 (3.6)	RR 0 (0.27-1.37)	63 per 1,000	63 fewer per 1,000 (from 46 fewer to 23 more)
926 (7 studies ^d), 1-3 mo	Serious ^b	No serious inconsistency	No serious indirectness	Serious ^c	Undetected	Low ^{b,c} due to risk of bias, imprecision	14/473 (3)	5/453 (1.1)	RR 0.43 (0.17-1.09)	30 per 1,000	17 fewer per 1,000 (from 25 fewer to 3 more)
748 (5 studies ^e), 1-3 mo	Serious ^b	No serious inconsistency	No serious indirectness	Serious ^c	Undetected	Low ^{b,c} due to risk of bias, imprecision	17/383 (4.4)	12/365 (3.3)	RR 0.73 (0.36-1.46)	44 per 1,000	12 fewer per 1,000 (from 28 fewer to 20 more)
14,213 (7 studies ^f), 1-12 mo	Serious ^b	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate ^b due to risk of bias	122/7,091 (1.7)	109/7,122 (1.5)	RR 0.9 (0.7-1.17)	17 per 1,000	2 fewer per 1,000 (from 5 fewer to 3 more)

(Continued)

Table S7—Continued

Participants (Studies), Follow-up	Quality Assessment					Summary of Findings					
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	With Manual Dosing	With Dosing Decision Support	Relative Effect (95% CI)	Risk With Manual Dosing	Anticipated Absolute Effects ^a
14,035 (5 studies ^b), 4.8-12 mo	No serious inconsistency	No serious indirectness	No serious imprecision	Major bleeding—maintenance (critical outcome; assessments variously defined)	Undetected	Moderate ^b due to risk of bias	108/6,999 (1.5)	101/7,036 (1.4)	RR 0.92 (0.71-1.21)	15 per 1,000	1 fewer per 1,000 (from 4 fewer to 3 more)
14,044 (5 studies ^b), 4.8-12 mo	No serious inconsistency	No serious indirectness	No serious imprecision	Mortality—maintenance (critical outcome; assessed with all-cause mortality)	Undetected	Moderate ^b due to risk of bias	70/6,973 (1)	75/7,071 (1.1)	RR 1.07 (0.78-1.48)	10 per 1,000	1 more per 1,000 (from 2 fewer to 5 more)

Bibliography: Asmis PD, Gardner MJ, Ranawat A, et al. The effectiveness of warfarin dosing from a nomogram compared with house staff dosing. *J Arthroplasty*. 2007;22:213-218. Ageno W, Turpie G. A randomized comparison of a computer-based dosing program with a manual system to monitor oral anticoagulant therapy. *Thromb Res*. 1998;91:237-240. Manotti C, Moia M, Palareti G, et al. Effect of computer-aided management on the quality of treatment in anticoagulated patients: a prospective, randomized, multicenter trial of APROAT (Automated Program for Oral Anticoagulant Treatment). *Haematologica*. 2001;86:1060-1070. Marco F, Sedano C, Bernudez A, et al. A prospective controlled study of a computer-assisted acenocoumarol dosage program. *Pathophysiol Haemost Thromb*. 2003;33:59-63. Mitra R, Marciello MA, Brain C, Ahangar B, Burke DT. Efficacy of computer-aided dosing of warfarin among patients in a rehabilitation hospital. *Am J Phys Med Rehabil*. 2005;84:423-427. Poller L, Shlach CR, MacCallum PK, et al. Multicenter randomized study of computerized anticoagulation. *Lancet*. 1998;352:1505-1509. Poller L, Keown M, Ibrahim S, et al. An international multicenter randomized study of computer-assisted oral anticoagulant dosage vs medical staff dosage. *J Thromb Haemost*. 2008;6:935-943. Vadher BD, Patterson DL, Leaning M. Comparison of oral anticoagulant control by a nurse-practitioner using a computer decision-support system with that by clinicians. *Clin Laboratory Haematol*. 1997;19:203-207. Doecke CJ. Cosh DG, Gallus AS. Standardized initial warfarin treatment: evaluation of initial treatment response and maintenance dose prediction by randomized trial, and risk factors for an excessive warfarin response. *Aust N Z J Med*. 1991;21:319-324. Kovacs MJ, Cruickshank M, Wells PS, et al. Randomized assessment of a warfarin nomogram for initial oral anticoagulation after venous thromboembolic disease. *Haemostasis*. 1998;28:62-69. van den Bent PM, Beinema M, van Roon EN, et al. Initiation of oral anticoagulant therapy in orthopedic and surgical patients: an algorithm compared with routine dosing. *Eur J Clin Pharmacol*. 2002;58:203-208. Carter BL, Taylor JW, Becker A. Evaluation of three dosage-prediction methods for initial in-hospital stabilization of warfarin therapy. *Clin Pharm*. 1987;6:37-45. See Table S2 and S3 legends for expansion of abbreviations.

^aTime frame is in days to months.

^bMost studies were unblinded, including patients, health-care providers, and outcome adjudicators.

^cCI of relative effect encompasses wide range of benefit and harm.

^dAsmis 2007, Doecke 1991, Kovacs 1998, Landefeld 1992, Vadher 1997 (*BMJ*), van den Bent 2002, White 1997.

^eAsmis 2007, Doecke 1991, Kovacs 1998, Landefeld 1992, Vadher 1997 (*BMJ*).

^fClaes 2005, Fitzmaurice 1996, Fitzmaurice 2000, Mitra 2005, Poller 2008, Vadher 1997, Vadher 1997 (*BMJ*).

^gClaes 2005, Fitzmaurice 1996, Fitzmaurice 2000, Poller 2008, Vadher 1997.

^hClaes 2005, Fitzmaurice 1996, Fitzmaurice 2000, Poller 1993, Poller 2008.

Table S8—[Section 4.1.1.] Evidence Profile: Optimal Therapeutic INR Range—Higher Target vs 2 to 3

Participants (Studies), Follow-up	Quality Assessment					Summary of Findings			
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)	Relative Effect (95% CI)	Anticipated Absolute Effects ^a
76,646 (17 studies) ^b	Serious ^c	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Low ^{e,d} due to bias and dose-response gradient	With INR 2-3: 357/59,368 (0.6) With INR 3-5: 299/17,278 (1.7)	RR 2.7 (1.8-3.9)	6 per 1,000 10 more per 1,000 (from 5 more to 17 more)
835 (10 studies) ^e	Serious ^f	Serious ^g	No serious indirectness	No serious imprecision	Undetected	Thromboembolism (critical outcome; assessed per 100 patient-y; various definitions) Very low ^{e,g} due to risk of bias and inconsistency	24/519 (4.6) 15/316 (4.7)	RR 0.9 (0.6-1.3)	Study population 46 per 1,000 5 fewer per 1,000 (from 18 fewer to 14 more) Moderate 50 per 1,000 5 fewer per 1,000 (from 20 fewer to 15 more)

Bibliography: Oake N, Jennings A, Forster AJ, Fergusson D, Doucette S, van Walraven C. Anticoagulation intensity and outcomes among patients prescribed oral anticoagulant therapy: a systematic review and meta-analysis. *CMAJ*. 2008;179(3):235-244. See Table S3 and S4 legends for expansion of abbreviations.

^aTime frame is in months to years.

^bSix studies had a randomized controlled trial design.

^cThe majority of studies (eight) were retrospective cohorts.

^dIt is biologically plausible that with increased intensity there will be more bleeding.

^eOne study had a randomized controlled design.

^fThree of four studies had a retrospective cohort design.

^gThromboembolic events were more frequent with INR 2 to 3 in two studies, less frequent in one study, and similar in one study.

Table S9—[Section 4.1.2] Evidence Profile: Optimal Therapeutic INR Range—Lower Target vs 2 to 3

Participants (Studies), Follow-up	Quality Assessment					Summary of Findings				
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)	Relative Effect (95% CI)	Risk With INR 2-3	Anticipated Absolute Effects ^a
78,493 (17 studies ^b)	Serious ^c	Serious ^c	No serious indirectness	No serious imprecision	Undetected	Very low ^{b,c} due to risk of bias, inconsistency	With INR 2-3: 357/59,369 (0.6) With INR <2: 123/19,124 (0.6)	RR 1.1 (0.7-1.7)	Study population 6 per 1,000 Moderate 23 per 1,000	Risk Difference With INR <2 (95% CI) 1 more per 1,000 (from 2 fewer to 4 more) 2 more per 1,000 (from 7 fewer to 16 more)
827 (4 studies ^d)	Serious ^e	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	Moderate ^{e,g} due to risk of bias, large effect, dose-response gradient	24/520 (4.6)	RR 3.5 (2.8-4.4)	Study population 46 per 1,000 Moderate 40 per 1,000	Risk Difference With INR <2 (95% CI) 115 more per 1,000 (from 83 more to 157 more) 100 more per 1,000 (from 72 more to 136 more)

Bibliography: Oakes N, Jennings A, Forster AJ, Fergusson D, Doucette S, van Walraven C. Anticoagulation intensity and outcomes among patients prescribed oral anticoagulant therapy: a systematic review and meta-analysis. *CMAJ*. 2008;179(3):235-244. See Table S3 and S4 legends for expansion of abbreviations.

^a Time frame is in months to years.

^b Eight of the studies were retrospective cohorts.

^c Four studies showed higher risk of bleeding with INR < 2.

^d Only one study had a randomized controlled design.

^e No explanation was provided.

^f At least 2.8 times more frequent thromboembolism.

^g It is biologically plausible with more thromboembolism at lower INR.

Table S10—[Section 4.2] Evidence Profile: High-Intensity VKA Compared With Moderate-Intensity VKA for Patients With Antiphospholipid Syndrome

Participants (Studies), Follow-up	Quality Assessment				Summary of Findings					
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)		Anticipated Absolute Effects	
							With Moderate-Intensity VKA	With High-Intensity VKA	Risk With Moderate-Intensity VKA	Risk Difference With High-Intensity VKA (95% CI)
220 (2 studies ^a), 3 y	Serious ^b	No serious inconsistency	Serious ^b	Serious ^c	Undetected	Very low ^{b,c} due to risk of bias, indirectness, and imprecision	5/110 (4.5) ^a	11/110 (10)	OR 2.33 (0.82-6.66)	Study population ^d 45 per 1,000 ^a 54 more per 1,000 (from 8 fewer to 195 more)
										Low ^d 50 per 1,000 ^a 59 more per 1,000 (from 9 fewer to 210 more)
										High ^d 700 per 1,000 ^a 145 more per 1,000 (from 43 fewer to 240 more)
220 (2 studies ^a), 3 y	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious ^f	Undetected	Major bleeding (important outcome) ^e Moderate ^f due to imprecision	7/110 (6.4) ^a	5/110 (4.5)	OR 0.70 (0.23-2.16)	Study population 64 per 1,000 ^a 18 fewer per 1,000 (from 48 fewer to 64 more)
										Low 25 per 1,000 ^a 7 fewer per 1,000 (from 19 fewer to 27 more)
										High 100 per 1,000 ^a 28 fewer per 1,000 (from 75 fewer to 94 more)

(Continued)

Table S10—Continued

Participants (Studies), Follow-up	Quality Assessment				Summary of Findings						
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)		Anticipated Absolute Effects		
220 (2 studies), 3 y	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious ^f imprecision	Undetected	Mortality (assessed with all-cause mortality) Moderate ^e due to imprecision	With Moderate-Intensity VKA	With High-Intensity VKA	Relative Effect (95% CI)	Risk With Moderate-Intensity VKA	Risk Difference With High-Intensity VKA (95% CI)
							2/110 (1.8)	3/110 (2.7)	OR 1.51 (0.3-7.72)	18 per 1,000	9 more per 1,000 (from 13 fewer to 107 more)

Bibliography: Crowther MA, Ginsberg JS, Julian J, et al. A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. *N Engl J Med.* 2003;349:1133-1138. Finazzi G, Marchioli R, Branchaccio V, et al. A randomized clinical trial of high-intensity warfarin vs conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). *J Thromb Haemost.* 2005;3:848-853. Schulman S, Svenungsson E, Granqvist S. Anticardiolipin antibodies predict early recurrence of thromboembolism and death among patients with venous thromboembolism following anticoagulant therapy. *Duration of Anticoagulation Study Group. Am J Med.* 1998;104(4):332-338. Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GR. The management of thrombosis in the antiphospholipid-antibody syndrome. *N Engl J Med.* 1995;332(15):993-997. See Table S2 legend for expansion of abbreviation.

^aIn the study by Finazzi et al, three patients with nonembolic arterial thrombosis received, as planned, only aspirin. They had no events and have not been included here.

^bThe study by Finazzi et al was open label.

^cBoth studies were designed to show superiority of the more-intensive regimen, not equivalence; 95% CI includes both benefit and significant harm.

^dLow of 5% from Schulman et al. High of 70% from Khamashta et al.

^eThe types of major hemorrhage were not disclosed.

^fThe 95% CI includes both benefit and significant harm.

Table S11—[Section 5.0] Evidence Profile: Gradual Withdrawal Compared With Abrupt Withdrawal for Patients Taking VKAs for at Least One Month

Participants (Studies), Follow-up	Quality Assessment										Summary of Findings			
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)			Anticipated Absolute Effects ^a				
							With Abrupt Withdrawal	With Gradual Withdrawal	Relative Effect (95% CI)	Risk With Abrupt Withdrawal	Risk Difference With Gradual Withdrawal (95% CI)			
217 (5 studies), 3 mo	Serious ^b	No serious inconsistency	No serious indirectness	Serious ^c	Undetected	Low ^{b,c} due to risk of bias, imprecision	14/111 (12.6) ^d	13/106 (12.3)	OR 0.96 (0.42-2.18)	126 per 1,000 ^d	4 fewer per 1,000 (from 69 fewer to 113 more)			
217 (5 studies), 1 mo	Serious ^b	No serious inconsistency	No serious indirectness	Very serious ^e	Undetected	Very low ^{b,c} due to risk of bias, imprecision	1/111 (0.9)	0/106 (0)	OR 0 (0.01-5.6)	9 per 1,000	9 fewer per 1,000 (from 9 fewer to 39 more) ^d			
217 (5 studies), 1 mo	Serious ^b	No serious inconsistency	No serious indirectness	Very serious ^e	Undetected	Very low ^{b,c} due to risk of bias, imprecision	1/111 (0.9)	0/106 (0)	OR 1 (0.1-5.6)	9 per 1,000	0 fewer per 1,000 (from 8 fewer to 39 more) ^d			

Bibliography: Ascani A, et al. Withdrawal of warfarin after deep vein thrombosis: effects of a low fixed dose on rebound thrombin generation. *Blood Coagul Fibrinolysis*. 1999;10(5):291-295. de Groot MR, et al. Abrupt vs gradual withdrawal of vitamin K antagonist treatment in patients with venous thromboembolic disease: assessment of hypercoagulability and clinical outcome. *Clin Laboratory*. 2000;46(11-12):575-581. Michaels L, Beamish RE. Relapses of thromboembolic disease after discontinued anticoagulant therapy. A comparison of the incidence after abrupt and after gradual termination of treatment. *Am J Cardiol*. 1967;20(5):670-673. Palareti G, et al. Activation of blood coagulation after abrupt or stepwise withdrawal of oral anticoagulants—a prospective study. *Thromb Haemost*. 1994;72(2):222-226. Tardy B, et al. Evolution of blood coagulation and fibrinolysis parameters after abrupt vs gradual withdrawal of acenocoumarol in patients with venous thromboembolism: a double-blind randomized study. *Br J Haematol*. 1997;96(1):174-178. See Table S2 legend for expansion of abbreviation.

^aTime frame is in weeks.

^bUnclear whether allocation was adequate in Tardy et al, de Groot et al, and Ascani et al. In Michaels and Beamish, it was according to year of birth. Unclear whether allocation was concealed in Tardy, de Groot, and Ascani; not concealed in Michaels and Beamish. Clinicians and patients were not blinded in de Groot, Michaels, Palareti et al, or Ascani.

^cVery small patient groups and few events.

^dThere is no better source than these trials, so low or high estimates are not provided.

Table S12—[Section 6.1] Evidence Profile: UFH Weight-Based Nomogram Compared With Fixed Initial Dose for Patients With Thromboembolic Disease

Participants (Studies), Follow-up	Quality Assessment					Summary of Findings					
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)		Anticipated Absolute Effects ^g		
							With Fixed Initial Dose	With Weight-Based Nomogram	Risk With Fixed Initial Dose	Risk With Weight-Based Nomogram (95% CI)	
292 (3 studies), 2-90 d ^b	Serious ^c	No serious inconsistency	No serious indirectness	Serious ^d	Undetected	Low ^{ed} due to risk of bias and imprecision	8/140 (5.7) ^e	2/152 (1.3)	OR 0.22 (0.02-1.13) ^f	57 per 1,000 ^e	44 fewer per 1,000 (from 56 fewer to 7 more)
179 (2 studies ^g), 1 wk	Serious ^c	No serious inconsistency	No serious indirectness	Very serious ^d	Undetected	Very low ^{ed} due to risk of bias and imprecision	1/88 (1.1)	0/91 (0)	OR 0 (0-37.7) ^f	11 per 1,000	11 fewer per 1,000 (from 11 fewer to 291 more)

Major hemorrhage (not important outcome)

Bibliography: Becker RC, Ball SP, Eisenberg P, et al; Antithrombotic Therapy Consortium Investigators A randomized, multicenter trial of weight-adjusted intravenous heparin dose titration and point-of-care coagulation monitoring in hospitalized patients with active thromboembolic disease. *Am Heart J*. 1999;137(1):59-71. Hassan WM, Flaker GC, Feutz C, Petroski GF, Smith, D. Improved anticoagulation with a weight-adjusted heparin nomogram in patients with acute coronary syndromes: a randomized trial. *J Thromb Thrombolysis*. 1995;2(3):245-249. Raschke RA, Reilly BM, Guiciry JR, Fontana JR, Srinivas S. The weight-based heparin dosing nomogram compared with a "standard care" nomogram. A randomized controlled trial. *Ann Intern Med*. 1993;119(9):874-881. UFH = unfractionated heparin.

^aTime frame is in days to weeks.

^bOnly Raschke et al collected data over a 3-mo period.

^cThe studies did not use blinding. Primary outcome was a surrogate marker: time to reach therapeutic or stable therapeutic activated partial thromboplastin time.

^dNone of the studies were powered for clinical outcomes, which were few and poorly reported regarding type and timing.

^eTwo of the eight events occurred after discontinuation of warfarin.

^fFisher exact test.

^gBecker et al reported 2% bleeding without specifying allocation group or type of bleeding.

Table S13—[Section 6.2] Evidence Profile: UFH Weight-Adjusted Nonmonitored UFH SC Compared With Weight-Adjusted Nonmonitored LMWH SC for Outpatients With Acute VTE

Participants (Studies), Follow-up	Quality Assessment				Summary of Findings						
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Study Event Rates (%)		Anticipated Absolute Effects ^a			
						With Weight-Adjusted Nonmonitored LMWH SC	With Weight-Adjusted Nonmonitored UFH SC	Risk With Weight-Adjusted Nonmonitored LMWH SC	Risk Difference With Weight-Adjusted Nonmonitored UFH SC (95% CI)		
697 (1 study), 3 mo	No serious risk of bias	No serious inconsistency	Serious ^b	Serious ^c	Undetected	Low ^{b,c} due to indirectness and imprecision	12/352 (3.4)	13/345 (3.8)	OR 1.11 (0.49-2.52)	34 per 1,000	4 more per 1,000 (from 17 fewer to 48 more)
697 (1 study), 3 mo	No serious risk of bias	No serious inconsistency	Serious ^b	Serious ^c	Undetected	Major bleeding (critical outcome; assessed with ISTH criteria)	12/352 (3.4)	6/345 (1.7)	OR 0.5 (0.17-1.34)	34 per 1,000	17 fewer per 1,000 (from 28 fewer to 11 more)
697 (1 study), 3 mo	No serious risk of bias	No serious inconsistency	Serious ^b	Serious ^c	Undetected	Mortality (not important outcome)	22/352 (6.3)	18/345 (5.2)	OR 0.83 (0.43-1.57)	62 per 1,000	10 fewer per 1,000 (from 35 fewer to 32 more)

Bibliography: Kearon C, Ginsberg JS, Julian JA, et al. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. *JAMA*. 2006;296:935-942. LMWH = low-molecular-weight heparin; SC = subcutaneous. See Table S12 legend for expansion of other abbreviation.

^aTime frame is in weeks.

^bThe comparison should actually be vs fixed-dose UFH SC with monitoring, but weight-adjusted UFH SC has only been compared directly with weight-adjusted LMWH. Thus, the comparison is indirect.

^cDue to premature discontinuation, the study was not powered to demonstrate equivalence.

Table S14—[Section 9.1] Evidence Profile: Vitamin K vs Only Withholding VKA for Patients on Warfarin With Elevated INR (4.5–10) Without Evidence of Bleeding^a

Participants (Studies), Follow-up	Quality Assessment				Summary of Findings				
	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Quality of Evidence	Study Event Rates (%)	Relative Effect (95% CI)	Anticipated Absolute Effects ^b
923 (4 studies ^c), 1–3 mo ^d	No serious risk of bias ^e	No serious inconsistency	No serious indirectness	Serious ^f	Undetected	Moderate ^{e,f} due to imprecision	4/471 (0.8)	OR 2.6 (0.8–9.8)	13 more per 1,000 (from 2 fewer to 69 more)
864 (3 studies ^g), 1–3 mo ^d	No serious risk of bias ^e	No serious inconsistency	No serious indirectness	Serious ^f	Undetected	Moderate ^{e,f} due to imprecision	4/441 (0.91)	OR 1.3 (0.3–6.6)	3 more per 1,000 (from 6 fewer to 48 more)
863 (3 studies ^g), 1–3 mo ^d	No serious risk of bias ^e	No serious inconsistency	No serious indirectness	Serious ^f	Undetected	Moderate ^{e,f} due to imprecision	13/441 (2.9)	OR 1.3 (0.6–2.9)	9 more per 1,000 (from 12 fewer to 51 more)

Mortality (not important outcome; assessed with all-cause mortality)

Bibliography: Crowther MA, Ageno W, Garcia D, et al. Oral vitamin K vs placebo to correct excessive anticoagulation in patients receiving warfarin: a randomized trial. *Ann Intern Med.* 2009;150(5):293–300. Crowther MA, Julian J, McCarty D, et al. Treatment of warfarin-associated coagulopathy with oral vitamin K: a randomized controlled trial. *Lancet.* 2000;356:1551–1553. Ageno W, Crowther M, Steidl L, et al. Low dose oral vitamin K to reverse acenocoumarol-induced coagulopathy: a randomized controlled trial. *J Thromb Haemostas.* 2002;88:48–51. Ageno W, Garcia D, Silingardi M, Galli M, Crowther M. A randomized trial comparing 1 mg of oral vitamin K with no treatment in the management of warfarin-associated coagulopathy in patients with mechanical heart valves. *J Am Coll Cardiol.* 2005;46(4):730–742. See Table S2 and S4 for expansion of abbreviations.

^aINR 6.0–12.0 in Ageno et al 2005.

^bTime frame is in days.

^cNone of the studies specified whether any bleeding events were fatal or intracranial.

^dFollow-up was 3 mo in both studies by Crowther et al.

^eTwo small studies, Ageno 2002 and Ageno 2005, were open label.

^fWide CIs encompassing both benefit and significant harm.

^gAgeno et al 2005 did not report thromboembolism, and Ageno et al 2002 did not report deaths.