Summary Review

Newer Oral Anticoagulant Drugs

Final Original Appendixes and Evidence Tables

January 2013

The Agency for Healthcare Research and
Quality has not yet seen or approved this report

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Appendix A. Boxed warnings for included drugs

Drug	Boxed warning
Rivaroxaban (Xarelto®)[1]	**WARNING: (A) DISCONTINUING XARELTO IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION INCREASES RISK OF STROKE, (B) SPINAL/EPIDURAL HEMATOMA** A. Discontinuing Xarelto in patients with nonvalvular atrial fibrillation Discontinuing XARELTO places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following XARELTO discontinuation in clinical trials in atrial fibrillation patients. If anticoagulation with XARELTO must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant B. SPINAL/EPIDURAL HEMATOMA Epidural or spinal hematomas have occurred in patients treated with XARELTO who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include: • use of indwelling epidural catheters • concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants • a history of traumatic or repeated epidural or spinal punctures • a history of spinal deformity or spinal surgery Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary. Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis.
Apixaban (ELIQUIS®)[2]	**WARNING: (A) DISCONTINUING ELIQUIS IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION INCREASES RISK OF STROKE** A. Discontinuing ELIQUIS in patients with nonvalvular atrial fibrillation Discontinuing ELIQUIS places patients at an increased risk of thrombotic events. An increased rate of stroke was observed following discontinuation of ELIQUIS in clinical trials in patients with nonvalvular atrial fibrillation. If anticoagulation with ELIQUIS must be discontinued for a reason other than pathological bleeding, coverage with another anticoagulant should be strongly considered.

Appendix A References

1. Xarelto Product Label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022406s001s002s003lbl.pdf. Accessed Nov 16, 2012.
2. Eliquis Product Label. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo. Accessed January 4, 2013.

Appendix B. Search strategies

To identify recent, comparative systematic reviews, we searched Medline and the Cochrane Database of Systematic Reviews using the following search strategy:
Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to September Week 1 2012>
Search Strategy:
---
1 apixaban.mp. (271)
2 dabigatran.mp. (661)
3 rivaroxaban.mp. (530)
4 edoxaban.mp. (57)
5 eliquis.mp. (2)
6 pradaxa.mp. (35)
7 xarelto.mp. (25)
8 lixiana.mp. (1)
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (1056)
10 limit 9 to (english language and humans) (892)
11 (medline or systematic review).tw. or meta-analysis.pt. (83023)
12 10 and 11 (36)
13 limit 12 to yr="2009 -Current" (33)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to August 2012>, EBM Reviews - ACP Journal Club <1991 to August 2012>, EBM Reviews - Database of Abstracts of Reviews of Effects <3rd Quarter 2012>, EBM Reviews - Cochrane Central Register of Controlled Trials <September 2012>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <3rd Quarter 2012>, EBM Reviews - NHS Economic Evaluation Database <3rd Quarter 2012>
Search Strategy:
---
1 apixaban.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (50)
2 dabigatran.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (94)
3 rivaroxaban.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (107)
4 edoxaban.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (15)
5 eliquis.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (0)
6 pradaxa.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (4)
7 xarelto.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (5)
8 lixiana.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw] (0)
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (230)
10 limit 9 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained] (229)
11 limit 10 to yr="2009 -Current" [Limit not valid in DARE; records were retained] (158)
12 limit 11 to humans [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained] (156)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <3rd Quarter 2012>
Search Strategy:

---
1 apixaban.mp. (3)
2 dabigatran.mp. (3)
3 rivaroxaban.mp. (6)
4 edoxaban.mp. (1)
5 eliquis.mp. (0)
6 pradaxa.mp. (0)
7 xarelto.mp. (0)
8 lixiana.mp. (0)
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (9)
10 limit 9 to (english language and humans) [Limit not valid; records were retained] (9)
11 limit 10 to last 2 years (9)

Database: EBM Reviews - ACP Journal Club <1991 to August 2012>
Search Strategy:
---
1 apixaban.mp. (8)
2 dabigatran.mp. (11)
3 rivaroxaban.mp. (9)
4 edoxaban.mp. (1)
5 eliquis.mp. (0)
6 pradaxa.mp. (0)
7 xarelto.mp. (0)
8 lixiana.mp. (0)
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (19)
10 limit 9 to (english language and humans) [Limit not valid; records were retained] (19)
11 limit 10 to last 2 years (17)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to August 2012>
Search Strategy:
---
1 apixaban.mp. (8)
2 dabigatran.mp. (12)
3 rivaroxaban.mp. (9)
4 edoxaban.mp. (2)
5 eliquis.mp. (0)
6 pradaxa.mp. (1)
7 xarelto.mp. (1)
8 lixiana.mp. (0)
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (14)
10 limit 9 to (english language and humans) [Limit not valid; records were retained] (14)
11 limit 10 to last 2 years (13)

Appendix C. Excluded systematic reviews

The following full-text publications were considered for inclusion but failed to meet the criteria for this report.

Exclusion codes: 2=ineligible outcome, 3=ineligible intervention (or does not include at least 2 drugs), 5=ineligible publication type, 8=outdated systematic review

Excluded systematic reviews	Exclusion code
Bovio JA, Smith SM, Gums JG. Dabigatran etexilate: a novel oral thrombin inhibitor for thromboembolic disease. Ann Pharmacother. May 2011;45(5):603-614.	3
Canadian Agency for Drugs and Technologies in Health. Anticoagulation Monitoring and Reversal Strategies for Dabigatran, Rivaroxaban, and Apixaban: A Review of Clinical Effectiveness. Ottowa 2012.	2
Canadian Agency for Drugs and Technologies in Health.CADTH Therapeutic Review Recommendations: New Oral Anticoagulants for the Prevention of Thromboembolic Events in Patients with Atrial Fibrillation. Ottowa 2012.	5
Cheng JWM, Vu H. Dabigatran etexilate: an oral direct thrombin inhibitor for the management of thromboembolic disorders. Clin Ther. Apr 2012;34(4):766-787	3
De Schryver ELLM, Algra A, Kappelle LJ, van Gijn J, Koudstaal PJ. Vitamin K antagonists versus antiplatelet therapy after transient ischaemic attack or minor ischaemic stroke of presumed arterial origin [Systematic Review]. Cochrane Database Syst Rev. 2012;9:9.	3
Maratea D, Fadda V, Trippoli S, Messori A. Prevention of venous thromboembolism after major orthopedic surgery: indirect comparison of three new oral anticoagulants. J Thromb Haemost. Sep 2011;9(9):1868-1870.	8
Neumann I, Rada G, Claro J, et al. Oral direct factor Xa inhibitors versus low-molecular-weight heparin to prevent venous thromboembolism in patients undergoing total hip or knee replacement: a systematic review and meta-analysis Annals of Internal Medicine. 2012;156(10):710-719.	5
O'Dell KM, Igawa D, Hsin J. New oral anticoagulants for atrial fibrillation: a review of clinical trials. Clin Ther. Apr 2012;34(4):894-901.	8
Sobieraj DM, Coleman CI, Tongbram V, et al. Venous Thromboembolism (VTE) Prophylaxis in Orthopedic Surgery. Comparative Effectiveness Review No. 49. Rockville, MD: Prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center under Contract No. 290-2007-10067-I. AHRQ Publication No. 12-EHC020-EF.; 2012.	3

Appendix D. Strength of evidence

Table D-1: Rivaroxaban vs. dabigatran in patients undergoing orthopedic surgery

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of studies; Number of subjects	**Risk of bias (design/quality*)**	**Consistency**	**Directness**	**Precision**	**Summary effect size (95% CI)**	**High, moderate, low, insufficient**
Symptomatic VTE						
12; 13,336	RCTs/low ROB	Consistent	Indirect	Imprecise	0.68 (0.21, 2.23)	Low
Clinically relevant bleeding						
12; 13,336	RCTs/ low ROB	Consistent	Indirect	Imprecise	1.12 (0.87, 1.44)	Low
Major bleeding						
12; 13,336	RCTs/low ROB	Consistent	Indirect	Imprecise	1.37 (0.79, 2.39)	Low
Net clinical benefit (symptomatic VTE, major bleeding and death)						
12; 13,336	RCTs/ low ROB	Consistent	Indirect	Imprecise	0.95 (0.61, 1.48)	Low

*Based on Jadad score

Table D-2: Rivaroxaban vs. apixaban in patients undergoing orthopedic surgery

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of studies; Number of subjects	**Risk of bias (design/ quality*)**	**Consistency**	**Directness**	**Precision**	**Summary effect size (95% CI)**	**High, moderate, low, insufficient**
Symptomatic VTE						
12;12,973	RCTs/low ROB	Consistent	Indirect	Imprecise	0.59 (0.26, 1.33)	Low
Clinically relevant bleeding						
12;12,973	RCTs/low ROB	Consistent	Indirect	Precise	**1.52 (1.19, 1.95)**	Moderate
Major bleeding						
12;12,973	RCTs/low ROB	Consistent	Indirect	Imprecise	1.59 (0.84, 3.02)	Low
Net clinical benefit (symptomatic VTE, major bleeding and death)						
12;12,973	RCTs/low ROB	Consistent	Indirect	Imprecise	0.96 (0.66, 1.40)	Low

*Based on Jadad score

Table D-3: Apixaban vs. dabigatran in patients undergoing orthopedic surgery

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of studies; Number of subjects	**Risk of bias (design/ quality*)**	**Consistency**	**Directness**	**Precision**	**Summary effect size (95% CI)**	**High, moderate, low, insufficient**
Symptomatic VTE						
8; 12,653	RCTs/low ROB	Consistent	Indirect	Imprecise	1.16 (0.31, 4.28)	Low
Clinically relevant bleeding						
8; 12,653	RCTs/low ROB	Consistent	Indirect	Precise	**0.73 (0.57, 0.94)**	Moderate
Major bleeding						
8; 12,653	RCTs/low ROB	Consistent	Indirect	Imprecise	0.86 (0.41, 1.83)	Low
Net clinical benefit (symptomatic VTE, major bleeding and death)						
8; 12,653	RCTs/low ROB	Consistent	Indirect	Imprecise	0.99 (0.61, 1.61)	Low

*Based on Jadad score

Table D-4: Dabigatran 110 mg vs. apixaban in non-valvular atrial fibrillation

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of studies; Number of subjects	**Risk of bias (design/quality*)**	**Consistency**	**Directness**	**Precision**	**Summary effect size (95% CI)**	**High, moderate, low, insufficient**
Stroke/systemic embolism						
2; 30,238	RCTs/moderate	Consistent	Indirect	Precise	1.15 (0.87, 1.15)	Moderate
All-cause mortality						
2; 30,238	RCTs/ moderate	Consistent	Indirect	Precise	1.03 (0.86, 1.22)	Moderate
Major bleeding						
2; 30,238	RCTs/moderate	Consistent	Indirect	Imprecise	1.16 (0.95, 1.43)	Low
Intracranial bleeding						
2; 30,238	RCTs/moderate	Consistent	Indirect	Imprecise	0.71 (0.41, 1.21)	Low
Major GI bleeding						
2; 30,238	RCTs/moderate	Consistent	Indirect	Imprecise	1.23 (0.85, 1.78)	Low
Myocardial infarction						
2; 30,238	RCTs/moderate	Consistent	Indirect	Imprecise	1.50 (0.99, 2.28)	Low

*based on Jadad score

Table D-5: Dabigatran 150 mg vs. apixaban in non-valvular atrial fibrillation

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of studies; Number of subjects	**Risk of bias (design/quality*)**	**Consistency**	**Directness**	**Precision**	**Summary effect size (95% CI)**	**High, moderate, low, insufficient**
Stroke/systemic embolism						
2; 30,238	RCTs/moderate	Consistent	Indirect	Imprecise	0.82 (0.62, 1.10)	Low
All-cause mortality						
2; 30,238	RCTs/ moderate	Consistent	Indirect	Precise	1.00 (0.84, 1.19)	Moderate
Major bleeding						
2; 30,238	RCTs/moderate	Consistent	Indirect	Precise	1.35 (1.11, 1.66)	Moderate
Intracranial bleeding						
2; 30,238	RCTs/moderate	Consistent	Indirect	Imprecise	0.99 (0.60, 1.62)	Low
Major GI bleeding						
2; 30,238	RCTs/moderate	Consistent	Indirect	Precise	1.65 (1.16, 2.38)	Moderate
Myocardial infarction						
2; 30,238	RCTs/moderate	Consistent	Indirect	Imprecise	1.47 (0.97, 2.23)	Low

Table D-6: Rivaroxaban vs. apixaban in non-valvular atrial fibrillation

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of studies; Number of subjects	**Risk of bias (design/quality*)**	**Consistency**	**Directness**	**Precision**	**Summary effect size (95% CI)**	**High, moderate, low, insufficient**
Stroke/systemic embolism						
2; 32,465	RCTs/low	Consistent	Indirect	Imprecise	1.11 (0.87, 1.42)	Low
All-cause mortality						
2; 32,465	RCTs/low	Consistent	Indirect	Precise	1.04 (0.89, 1.23)	Moderate
Major bleeding						
2; 32,465	RCTs/low	Consistent	Indirect	Precise	1.48 (1.21, 1.86)	Moderate
Intracranial bleeding						
2; 32,465	RCTs/low	Consistent	Indirect	Imprecise	1.56 (0.97, 2.50)	Low
Major GI bleeding						
2; 32,465	RCTs/low	Consistent	Indirect	Precise	1.83 (1.30, 2.57)	Moderate
Myocardial infarction						
2; 32,465	RCTs/low	Consistent	Indirect	Imprecise	0.92 (0.62, 1.35)	Low

Table D-7: Rivaroxaban vs. dabigatran 110 mg in non-valvular atrial fibrillation

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of studies; Number of subjects	**Risk of bias (design/quality*)**	**Consistency**	**Directness**	**Precision**	**Summary effect size (95% CI)**	**High, moderate, low, insufficient**
Stroke/systemic embolism						
2; 26,301	RCTs/moderate	Consistent	Indirect	Imprecise	0.97 (0.75, 1.26)	Low
All-cause mortality						
2; 26,301	RCTs/ moderate	Consistent	Indirect	Precise	1.02 (0.86, 1.21)	Moderate
Major bleeding						
2; 26,301	RCTs/moderate	Consistent	Indirect	Precise	1.28 (1.04, 1.58)	Moderate
Intracranial bleeding						
2; 26,301	RCTs/moderate	Consistent	Indirect	Precise	2.22 (1.29, 3.89)	Moderate
Major GI bleeding						
2; 26,301	RCTs/moderate	Consistent	Indirect	Precise	1.49 (1.07, 2.09)	Moderate
Myocardial infarction						
2; 26,301	RCTs/moderate	Consistent	Indirect	Precise	0.61 (0.41, 0.91)	Moderate

Table D-8: Rivaroxaban vs. dabigatran 150 mg in non-valvular atrial fibrillation

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of studies; Number of subjects	**Risk of bias (design/quality*)**	**Consistency**	**Directness**	**Precision**	**Summary effect size (95% CI)**	**High, moderate, low, insufficient**
Stroke/systemic embolism						
2; 26,362	RCTs/moderate	Consistent	Indirect	Precise	1.35 (1.03, 1.79)	Moderate
All-cause mortality						
2; 26,362	RCTs/ moderate	Consistent	Indirect	Imprecise	1.05 (0.88, 1.26)	Low
Major bleeding						
2; 26,362	RCTs/moderate	Consistent	Indirect	Precise	1.10 (0.90, 1.35)	Moderate
Intracranial bleeding						
2; 26,362	RCTs/moderate	Consistent	Indirect	Imprecise	1.58 (0.95, 2.66)	Low
Major GI bleeding						
2; 26,362	RCTs/moderate	Consistent	Indirect	Imprecise	1.11 (0.80, 1.53)	Low
Myocardial infarction						
2; 26,362	RCTs/moderate	Consistent	Indirect	Precise	0.63 (0.42, 0.93)	Moderate

Table D-9: Dabigatran 150 mg vs. dabigatran 110 mg in non-valvular atrial fibrillation

	Domains pertaining to strength of evidence				Magnitude of effect	Strength of evidence
Number of studies; Number of subjects	**Risk of bias (design/quality*)**	**Consistency**	**Directness**	**Precision**	**Summary effect size (95% CI)**	**High, moderate, low, insufficient**
Stroke/systemic embolism						
1; 18,113	RCTs/moderate	Consistent	Direct	Precise	0.72 (0.58, 0.90)	Moderate
All-cause mortality						
1; 18,113	RCTs/ moderate	Consistent	Direct	Precise	0.97 (0.85, 1.12)	Moderate
Major bleeding						
1; 18,113	RCTs/moderate	Consistent	Direct	Precise	1.17 (1.01, 1.36)	Moderate
Intracranial bleeding						
1; 18,113	RCTs/moderate	Consistent	Direct	Imprecise	1.41 (0.86, 2.33)	Low
Major GI bleeding						
1; 18,113	RCTs/moderate	Consistent	Direct	Precise	1.35 (1.07, 1.72)	Moderate
Myocardial infarction						
1; 18,113	RCTs/moderate	Consistent	Direct	Imprecise	0.98 (0.74, 1.31)	Low

Appendix E. Trials not included systematic reviews (published after review search dates)

Hart, R. G., H.-C. Diener, et al. (2012). "Intracranial hemorrhage in atrial fibrillation patients during anticoagulation with warfarin or dabigatran: the RE-LY trial." Stroke **43**(6): 1511-1517.

BACKGROUND AND PURPOSE: Intracranial hemorrhage is the most devastating complication of anticoagulation. Outcomes associated with different sites of intracranial bleeding occurring with warfarin versus dabigatran have not been defined. METHODS: Analysis of 18 113 participants with atrial fibrillation in the Randomized Evaluation of Long-term anticoagulant therapY (RE-LY) trial assigned to adjusted-dose warfarin (target international normalized ratio, 2-3) or dabigatran (150 mg or 110 mg, both twice daily). RESULTS: During a mean of 2.0 years of follow-up, 154 intracranial hemorrhages occurred in 153 participants: 46% intracerebral (49% mortality), 45% subdural (24% mortality), and 8% subarachnoid (31% mortality). The rates of intracranial hemorrhage were 0.76%, 0.31%, and 0.23% per year among those assigned to warfarin, dabigatran 150 mg, and dabigatran 110 mg, respectively (P<0.001 for either dabigatran dose versus warfarin). Fewer fatal intracranial hemorrhages occurred among those assigned dabigatran 150 mg and 110 mg (n=13 and n=11, respectively) versus warfarin (n=32; P<0.01 for both). Fewer traumatic intracranial hemorrhages occurred among those assigned to dabigatran (11 patients with each dose) compared with warfarin (24 patients; P<0.05 for both dabigatran doses versus warfarin). Independent predictors of intracranial hemorrhage were assignment to warfarin (relative risk, 2.9; P<0.001), aspirin use (relative risk, 1.6; P=0.01), age (relative risk, 1.1 per year; P<0.001), and previous stroke/transient ischemic attack (relative risk, 1.8; P=0.001). CONCLUSIONS: The clinical spectrum of intracranial hemorrhage was similar for patients given warfarin and dabigatran. Absolute rates at all sites and both fatal and traumatic intracranial hemorrhages were lower with dabigatran than with warfarin. Concomitant aspirin use was the most important modifiable independent risk factor for intracranial hemorrhage.

Healey, J. S., J. Eikelboom, et al. (2012). "Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial." Circulation **126**(3): 343-348.

BACKGROUND: Dabigatran reduces ischemic stroke in comparison with warfarin; however, given the lack of antidote, there is concern that it might increase bleeding when surgery or invasive procedures are required. METHODS AND RESULTS: The current analysis was undertaken to compare the periprocedural bleeding risk of patients in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial treated with dabigatran and warfarin. Bleeding rates were evaluated from 7 days before until 30 days after invasive procedures, considering only the first procedure for each patient. A total of 4591 patients underwent at least 1 invasive procedure: 24.7% of patients received dabigatran 110 mg, 25.4% received dabigatran 150 mg, and 25.9% received warfarin, P=0.34. Procedures included: pacemaker/defibrillator insertion (10.3%), dental procedures (10.0%), diagnostic procedures (10.0%), cataract removal (9.3%), colonoscopy (8.6%), and joint replacement (6.2%). Among patients assigned to either dabigatran dose, the last dose of study drug was given 49 (35-85) hours before the procedure on comparison with 114 (87-144) hours in patients receiving warfarin, P<0.001. There was no significant difference in the rates of periprocedural major bleeding between patients receiving dabigatran 110 mg (3.8%) or dabigatran 150 mg (5.1%) or warfarin (4.6%); dabigatran 110 mg versus warfarin: relative risk, 0.83; 95% CI, 0.59 to 1.17; P=0.28; dabigatran 150 mg versus warfarin: relative risk, 1.09; 95% CI, 0.80 to 1.49; P=0.58. Among patients having urgent surgery, major bleeding occurred in 17.8% with dabigatran 110 mg, 17.7% with dabigatran 150 mg, and 21.6% with warfarin: dabigatran 110 mg; relative risk, 0.82; 95% CI, 0.48 to 1.41; P=0.47; dabigatran 150 mg: relative risk, 0.82; 95% CI, 0.50 to 1.35; P=0.44. CONCLUSIONS: Dabigatran and warfarin were associated with similar rates of periprocedural bleeding, including patients having urgent surgery. Dabigatran facilitated a shorter interruption of oral anticoagulation. CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifier: NCT00262600.

Hori, M., S. J. Connolly, et al. (2011). "Efficacy and safety of dabigatran vs. warfarin in patients with atrial fibrillation--sub-analysis in Japanese population in RE-LY trial." Circulation Journal **75**(4): 800-805.

BACKGROUND: RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) is an international multicenter study (18,113 patients from 967 centers in 44 countries) that demonstrated the ability of dabigatran to reduce the occurrence of both stroke and hemorrhage in patients who had atrial fibrillation (AF) with high risks of stroke compared with patients who received warfarin. From Japan, 326 patients were randomized in RE-LY. METHODS AND RESULTS: RE-LY was designed to compare 2 fixed doses (110 mg or 150 mg, twice daily) of dabigatran, each administered in a blinded manner, with open-label use of warfarin. There were no major differences in patient demographic information among the overall study population and Japanese patients. However, in Japanese patients, the proportion of prior stroke was higher but prior myocardial infarction was lower than in the overall. The yearly rate for the primary endpoints (stroke and systemic embolism) was 1.38, 0.67 and 2.65%/year for 110 mg and 150 mg dabigatran twice daily and warfarin, respectively. These results were similar to the overall results (1.54, 1.11 and 1.71%/year for each group, respectively). For any bleeding, the relative risk of dabigatran at 110 mg and 150 mg twice daily over warfarin was 0.79 and 1.06, respectively, which was similar to the findings overall (dabigatran 110 mg twice daily: 0.78; 150 mg twice daily: 0.91). CONCLUSIONS: In RE-LY, the efficacy and safety profiles of dabigatran for Japanese AF patients at high risk of stroke were essentially the same as for the study population overall. All rights are reserved to the Japanese Circulation Society.

Weitz, J. I., S. J. Connolly, et al. (2010). "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 & Haemostasis **104**(3): 633-641.

The primary objective of this study was to compare the safety of four fixed-dose regimens of edoxaban with warfarin in patients with non-valvular atrial fibrillation (AF). In this 12-week, parallel-group, multicentre, multinational study, 1,146 patients with AF and risk of stroke were randomised to edoxaban 30 mg qd, 30 mg bid, 60 mg qd, or 60 mg bid or warfarin dose-adjusted to a target international normalised ratio of 2.0-3.0. The study was double-blind to edoxaban dose, but open-label to warfarin. Primary outcomes were occurrence of major and/or clinically relevant non-major bleeding and elevated hepatic enzymes and/or bilirubin. Mean age was 65 +/- 8.7 years and 64.4% were warfarin-naive. Whereas major plus clinically relevant non-major bleeding occurred in 3.2% of patients randomised to warfarin, the incidence of bleeding was significantly higher with the edoxaban 60 mg bid (10.6%; p=0.002) and 30 mg bid regimens (7.8%; p=0.029), but not with the edoxaban 60 mg qd (3.8%) or 30 mg qd regimens (3.0%). For the same total daily dose of 60 mg, both bleeding frequency and trough edoxaban concentrations were higher in the 30-mg bid group than in the 60-mg qd group. There were no significant differences in hepatic enzyme elevations or bilirubin values among the groups. The safety profiles of edoxaban 30 and 60 mg qd in patients with AF were similar to warfarin. In contrast, the edoxaban bid regimens were associated with more bleeding than warfarin. These results suggest that in this three-month study, edoxaban 30 or 60 mg qd are safe and well-tolerated.

Evidence Table 1. Quality assessment of included systematic reviews

Organization/author Year Review title	Clear review question, inclusion and exclusion criteria of primary studies stated?	Substantial effort to find relevant research?	Adequate assessment of validity of included studies?	Sufficient detail of individual studies presented?	Primary studies summarized appropriately?	Overall rating (good, fair, poor)
ACCP/Guyatt **2012** Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines	Yes	Yes	Yes	Yes	Yes	Good
AHRQ **2012** Stroke Prevention in Atrial Fibrillation (Draft)	Yes	Yes	Yes	Partially. Tables do not include baseline characteristics and withdrawals	Yes	Good
CADTH **2012** Safety, Effectiveness, and Cost-Effectiveness of New Oral Anticoagulants Compared with Warfarin in Preventing Stroke and Other Cardiovascular Events in Patients with Atrial Fibrillation	Yes. Questions clearly stated.	Yes	Yes. Quality assessed using 2 instruments and risk of bias discussed. No studies were high risk of bias.	Yes	Yes	Good
Gomez-Outes **2012** Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons	Partially. An objective given but no clear question; some talk about what they included but clear criteria not given	Yes	Partial. Jadad score, but no details on process	Some baseline characteristics in evidence tables but no info on withdrawals	Yes	Fair

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Neumann **2012** Oral Direct Factor Xa Inhibitors Versus Low-Molecular-Weight Heparin to Prevent Venous Thromboembolism in Patients Undergoing Total Hip or Knee Replacement	Yes	Yes	Yes	Some baseline characteristics in evidence tables but no info on withdrawals	Yes	Good
Norwegian Knowledge Centre for the Health Services/Ringerike **2011** Thromboprophylactic treatment with rivaroxaban or dabigatran compared with enoxaparin or dalteparin in patients undergoing elective hip- or knee replacement surgery	Yes	Yes	Yes	Partially. ET tables with baseline characteristics, withdrawals, etc missing	Yes	Good
VA Evidence Synthesis Program **2012** Comparative Effectiveness of Warfarin and Newer Oral Anticoagulants for the Long-term Prevention and Treatment of Arterial and Venous Thromboembolism	Yes	Yes	Yes	Partially. ET tables with baseline characteristics, withdrawals, etc missing	Yes	Good
Testa **2012** Adjusted indirect comparison of new oral anticoagulants for stroke prevention in atrial fibrillation	Partially. An objective given but no clear question	Yes	Yes	Some baseline characteristics in evidence tables but no info on withdrawals	Yes	Fair