



**Title:** Apixaban and Rivaroxaban for Stroke Prevention in Atrial Fibrillation: Safety

**DATE:** 28 March 2014

## RESEARCH QUESTIONS

1. What are the adverse events associated with the use of apixaban?
2. What are the adverse events associated with the use of rivaroxaban?

## KEY MESSAGE

Twenty-two systematic reviews/meta-analyses, 24 randomized controlled trials, and three non-randomized studies were identified regarding adverse events associated with the use of apixaban and rivaroxaban.

## METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 3), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to safety data. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and March 20, 2014. Internet links were provided, where available.

## RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials and non-randomized studies.

Twenty-two systematic reviews/meta-analyses, 24 randomized controlled trials, and three non-randomized studies were identified regarding adverse events associated with the use of apixaban and rivaroxaban. No health technology assessments were identified.

**Disclaimer:** The Rapid Response Service is an information service for those involved in planning and providing health care in Canada. Rapid responses are based on a limited literature search and are not comprehensive, systematic reviews. The intent is to provide a list of sources of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. Rapid responses should be considered along with other types of information and health care considerations. The information included in this response is not intended to replace professional medical advice, nor should it be construed as a recommendation for or against the use of a particular health technology. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness particularly in the case of new and emerging health technologies, for which little information can be found, but which may in future prove to be effective. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up to date, CADTH does not make any guarantee to that effect. CADTH is not liable for any loss or damages resulting from use of the information in the report.

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Additional references of potential interest are provided in the appendix.

*Apixaban*

### Health Technology Assessments

No literature identified.

### Systematic Reviews and Meta-analyses

1. Villa LA, Malone DC, Ross D. Evaluating the efficacy and safety of apixaban, a new oral anticoagulant, using Bayesian meta-analysis. *Int J Hematol*. 2013 Oct;98(4):390-7.  
<http://www.ncbi.nlm.nih.gov/pubmed/24057162?report=abstract>

### Randomized Controlled Trials

2. Coppens M, Synhorst D, Eikelboom JW, Yusuf S, Shestakovska O, Connolly SJ. Efficacy and safety of apixaban compared with aspirin in patients who previously tried but failed treatment with vitamin K antagonists: results from the AVERROES trial. *Eur Heart J*. 2014 Feb 25.  
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[PubMed: PM24561548](#)
4. Al-Khatib SM, Thomas L, Wallentin L, Lopes RD, Gersh B, Garcia D, et al. Outcomes of apixaban vs. warfarin by type and duration of atrial fibrillation: results from the ARISTOTLE trial. *Eur Heart J*. 2013 Aug;34(31):2464-71.  
[PubMed: PM23594592](#)
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[PubMed: PM24016506](#)
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[PubMed: PM23575255](#)
8. Wallentin L, Lopes RD, Hanna M, Thomas L, Hellkamp A, Nepal S, et al. Efficacy and safety of apixaban compared with warfarin at different levels of predicted international

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[PubMed: PM22818021](#)
  11. Flaker GC, Eikelboom JW, Shestakovska O, Connolly SJ, Kaatz S, Budaj A, et al. Bleeding during treatment with aspirin versus apixaban in patients with atrial fibrillation unsuitable for warfarin: the apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment (AVERROES) trial. *Stroke*. 2012 Dec;43(12):3291-7.  
[PubMed: PM23033347](#)
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Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. Circulation. 2009 Jun 9;119(22):2877-85.  
<http://www.ncbi.nlm.nih.gov/pubmed/19470889?report=abstract>

### **Non-Randomized Studies**

No literature identified.

*Rivaroxaban*

### **Health Technology Assessments**

No literature identified.

### **Systematic Reviews and Meta-analyses**

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[http://www.cadth.ca/media/pdf/M0006\\_Rivaroxaban\\_and\\_Dabigatran\\_L3\\_e.pdf](http://www.cadth.ca/media/pdf/M0006_Rivaroxaban_and_Dabigatran_L3_e.pdf)

### **Randomized Controlled Trials**

20. Jones WS, Hellkamp AS, Halperin J, Piccini JP, Breithardt G, Singer DE, et al. Efficacy and safety of rivaroxaban compared with warfarin in patients with peripheral artery disease and non-valvular atrial fibrillation: insights from ROCKET AF. Eur Heart J. 2014 Jan;35(4):242-9.  
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21. Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, et al. Safety and efficacy of adjusted dose of rivaroxaban in Japanese patients with non-valvular atrial fibrillation: subanalysis of J-ROCKET AF for patients with moderate renal impairment. Circ J. 2013;77(3):632-8.  
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[PubMed: PM21830957](#)

#### **Non-Randomized Studies**

28. Lakkireddy D, Reddy YM, Di Biase L, Vallakati A, Mansour MC, Santangeli P, et al. Feasibility and safety of uninterrupted rivaroxaban for periprocedural anticoagulation in patients undergoing radiofrequency ablation for atrial fibrillation: results from a multicenter prospective registry. *J Am Coll Cardiol.* 2014 Mar 18;63(10):982-8.  
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#### *Apixaban and Rivaroxaban*

#### **Health Technology Assessments**

No literature identified.

#### **Systematic Reviews and Meta-analyses**

31. Albert NM. Use of novel oral anticoagulants for patients with atrial fibrillation: systematic review and clinical implications. *Heart Lung.* 2014 Jan;43(1):48-59.

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[PubMed: PM22771555](#)

**Randomized Controlled Trials**

No literature identified.

**Non-Randomized Studies**

No literature identified.

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**APPENDIX – FURTHER INFORMATION:****Review Articles**

50. Ghanny S, Crowther M. Treatment with novel oral anticoagulants: indications, efficacy and risks. *Curr Opin Hematol*. 2013 Sep;20(5):430-6.  
[PubMed: PM23852184](#)
51. Ogbonna KC, Jeffery SM. Risk versus benefit of non-vitamin K dependent anticoagulants compared to warfarin for the management of atrial fibrillation in the elderly. *Drugs Aging*. 2013 Jul;30(7):513-25.  
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See section: "Safety"
60. Drug product. Anticoagulant therapy for adult patients: atrial fibrillation [Internet]. Québec (QC): Institut national d'excellence en santé et en services sociaux; 2013 Oct. [cited 2014 Mar 27]. Available from: [http://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Medicaments/tableau\\_anticoagulants\\_ang2\\_24012013.pdf](http://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Medicaments/tableau_anticoagulants_ang2_24012013.pdf)  
See section on "Safety"
61. Ebertz F, Förster K, Gelbricht V, Rölling D, Tittl L, Köhler C, et al. Real life efficacy and safety of rivaroxaban for stroke prevention in atrial fibrillation - first results of the prospective NOAC registry (NCT01588119) [Internet]. Abstract presented at: American Society of Hematology. 55th ASH Annual Meeting and Exposition; 2013 Dec 9; New Orleans (LA). [cited 2014 Mar 27]. Available from: <https://ash.confex.com/ash/2013/webprogram/Paper58333.html>  
See: Table 1: Efficacy and safety outcomes during follow-up (FU) of rivaroxaban (RX) therapy in atrial fibrillation