



Republic of the Philippines  
Department of Health  
**OFFICE OF THE SECRETARY**

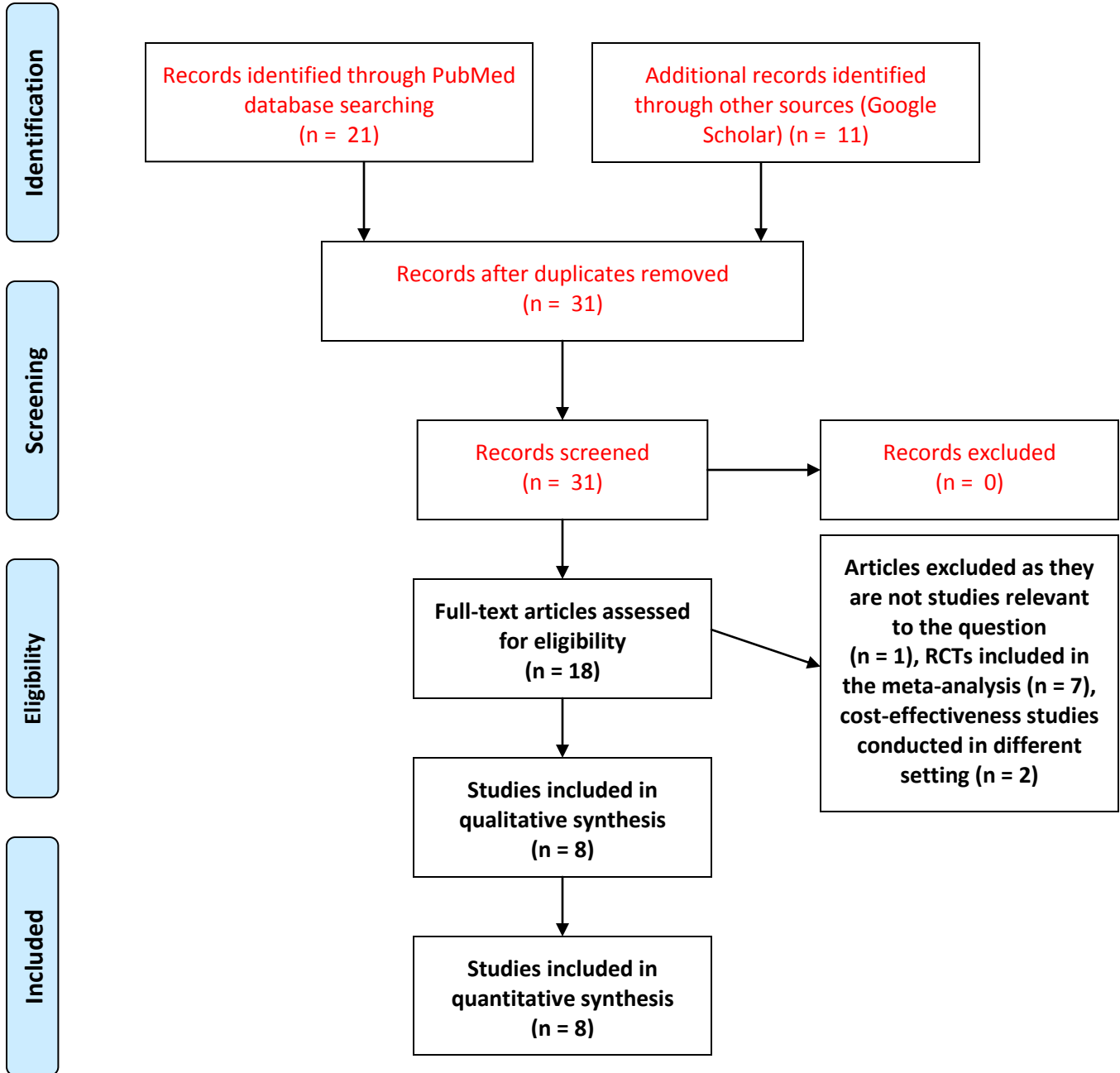
<b>Name of medicine (INN):</b>	<b>Dabigatran 75 mg, 110 mg and 150 mg capsule</b>
<b>Indication:</b>	For the prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation.
<b>Date of deliberation:</b>	01 July 2015
<b>Recommendation:</b>	<b>DISAPPROVAL</b>
<b>Clinical evidence:</b>	<p>The Council noted that dabigatran has similar efficacy with warfarin in the treatment of venous thromboembolism (VTE) as the primary endpoint. With regard to its safety, dabigatran was also found to be similar with warfarin in terms of major bleeding. On the other hand, indirect comparisons showed that there is no statistically significant difference among dabigatran and other new oral anticoagulants (NOACs) (i.e., apixaban/rivaroxaban) in the prevention of mortality, stroke or systemic emboli.</p> <p>The Council noted that the only advantage of dabigatran is it would not require frequent prothrombin time monitoring but its treatment cost is significantly higher than that of warfarin even when the cost of monitoring is already incorporated.</p> <p><i>(See Attachment for the full ERG evaluation)</i></p>
<b>Cost data:</b>	<p>The Council acknowledged the cost of treatment presented in the report of the Evidence Review Group (<i>See Attachment</i>). The FEC noted that the average monthly treatment cost with dabigatran is Php 1,718.10 which is significantly higher than the total monthly treatment and pro-thrombin time monitoring cost with warfarin ranging between Php 1,028 to Php 1,100.</p> <p>The FEC concluded that given the fact that dabigatran is as effective and safe as warfarin, there is insufficient evidence and weak justification to</p>

**Remarks:**

include the drug in the Formulary as an alternative to warfarin because of its prohibitive cost.

The Secretary of Health has officially disapproved the proposal to include dabigatran in the PNF. There was no appeal received within the set deadline, thus the recommendation of the Council still remains.

PRISMA Table



1. What is the comparative efficacy and safety profile of dabigatran vs. warfarin and other new oral anticoagulants?

**EVIDENCE TABLE 1**

NO	TITLE/ AUTHOR YEAR/JOURNAL	STUDY DESIGN	PARTICIPANT DESCRIPTION	INTERVENTION	RESULTS/OUTCOMES					GRADE OF EVIDENCE	REMARKS
					EVENTS (including adverse events)	Dabigatran		Warfarin			
						No. of events *	Total # of patients	No. of events *	Total # of patients		
	Roskell et al. Thromb Haemost. 2010	Network Meta-analysis	RCTs on AF to prevent stroke	Dabigatran vs anti-platelets	Any stroke  Mortality					High	RR=0.25 (95%CI; 0.12 and 0.51)  RR=0.64 (95%CI; 0.45 and 0.91)
	Schulman et al. Circulation. 2014	Pooled analysis of 2 trials	2 RCTs on acute venous thromboembolism	Dabigatran vs warfarin	Mortality or recurrent VTE  Major bleeding	30  15	1,279	28  22	1,289	High	RR=1.08 (95%CI; 0.64 and 1.80)  RR=0.69 (95%CI; 0.36 and 1.32)
	Providência et al. Heart. 2014	Meta-analysis	RCTs on patients with AF	Dabigatran vs. warfarin	Thromboembolic events  Major bleeding	10  27	1,823	5  40	2,959	High	RR = 1.78 (95% CI; 0.66 and 4.80)  RR = 1.07 (95% CI; 0.51 and 2.26)
	Majeed et al. Circulation. 2013	Pooled analysis of 5 RCTs	Phase III RCTs	Dabigatran vs. warfarin	Major bleeding  Mortality (OR)	627	16,755	407	10,002	Moderate	RR = 0.66 (95% CI; 0.44 and 1.0)
	Marijon et al. Circulation. 2013	RCT (post-hoc analysis)	RCT on patients with long-term use	Dabigatran vs. warfarin	Vascular-related mortality  Cardiac mortality					Moderate	RR = 0.63 (95% CI; 0.45 and 0.88)  RR = 0.96 (95% CI; 0.80 and 1.15)
	Capodanno et al. Int J Cardiol. 2013	Meta-analysis	3 major RCTs on patients with AF	Dabigatran vs warfarin (RELY)  Rivaroxaban vs. warfarin	Stroke or systemic embolism  Stroke or systemic embolism	316  269	12,091  7,081	199  306	6,022  7,090	High	RR=0.78 (95%CI;0.65 and 0.94)  RR=0.87 (95%CI; 0.74 and 1.0)

				(ROCKET-AF) Apixaban vs. warfarin (ARISTOTLE)	Stroke or systemic embolism	212	9,120	265	9,081		RR=0.79 (95%CI; 0.66 and 0.95)
	Baker et al. Circ Cardiovasc Qual Outcomes. 2012	Systematic review	RCTs on patients with AF	Dabigatrab vs. rivaroxaban (Indirect comparison)	Stroke or systemic emboli Ischemic stroke Hemorrhagic stroke Mortality Major bleeding					Moderate	RR = 0.75 (95% CI; 0.57 and 1.0) RR = 0.67 (95% CI; 0.48 and 0.93) RR = 0.45 (95% CI; 0.45 and 0.99) RR=1.06 (95%CI; 0.86 and 1.33) RR=0.91 (95%CI; 0.75 and 1.11)
				Apixaban vs. Dabigatrab (Indirect comparison)	Stroke or systemic emboli Ischemic stroke Mortality Major bleeding						RR=1.19 (95%CI; 0.92 and 1.58) RR=1.19 (95% CI; 0.86 and 1.64) RR=1.01 (95%CI; 0.85 and 1.18) RR = 0.75 (95% CI; 0.62 and 0.92)
	Assiri et al. Clin Ther. 2013	Meta-analysis	RCTs on patients receiving oral anticoagulants	Indirect comparison with placebo	Reduction of stroke (Warfarin) Reduction of stroke (Dabigatran) Reduction of stroke (Apixaban)					Moderate	RR = 0.43 (95% CI; 0.33 and 0.57) RR = 0.34 (95% CI; 0.21 and 0.57) RR = 0.37 (95% CI; 0.27 and 0.54)

					Reduction of stroke (Rivaroxaban)						RR = 0.36 (95% CI; 0.22 and 0.60)
					All-cause mortality (Dabigatran)						RR = 0.61 (95% CI; 0.39 and 0.89)
					All-cause mortality (Apixaban)						RR = 0.60 (95% CI; 0.42 and 0.84)
					All-cause mortality (Rivaroxaban)						RR = 0.56 (95% CI; 0.35 and 0.84)

\*group means with standard deviations may be reported if the data are continuous

**EVIDENCE TABLE 2: GRADE EVIDENCE PROFILE TABLE**

QUALITY ASSESSMENT							SUMMARY OF FINDINGS				Over-all Quality	Importance
							No. of patients		Effect			
No. of Studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute MD		
<b>Outcome: Mortality or recurrent VTE</b>												
1	Meta-analyses	None	None	None	None		Dabigatran	Warfarin	1.08 (95% CI; 0.64 and 1.80)		High	Critical
<b>Outcome: Thromboembolic events</b>												
1	Meta-analyses	None	None	None	None		Dabigatran	Warfarin	1.78 (95% CI; 0.66 and 4.80)		High	Critical
<b>Outcome: Major bleeding</b>												
1	Meta-analyses	None	None	None	None		Dabigatran	Warfarin	1.07 (95% CI; 0.51 and 2.26)		High	Critical
<b>Outcome: Mortality</b>												
1	Meta-analyses	Yes	None	Yes	None	Indirect comparison	Dabigatran	Rivaroxaban	1.06 (95% CI; 0.86 and 1.33)		Moderate	Critical
1	Meta-analyses	Yes	None	Yes	None	Indirect comparison	Apixaban	Dabigatran	1.01 (95% CI; 0.85 and 1.18)		Moderate	Critical
<b>Outcome: Stroke or systemic emboli</b>												
1	Meta-analyses	Yes	None	Yes	None	Indirect comparison	Dabigatran	Rivaroxaban	1.01 (95% CI; 0.85 and 1.18)		Moderate	Critical
1	Meta-analyses	Yes	None	Yes	None	Indirect comparison	Apixaban	Dabigatran	1.19 (95% CI; 0.92 and 1.58)		Moderate	Critical

**DETAILS REQUIRED FOR COST-EFFECTIVENESS ANALYSIS**

<p align="center"><b>PARAMETER</b> (Indicate information for intended recipient)* <i><u>INTENDED RECIPIENT:</u></i></p>	<p align="center"><b>NEW MEDICINE OR PROPOSED NEW INDICATION/ FORMULATION/ ROUTE OF ADMINISTRATION</b></p>	<p align="center"><b>CURRENTLY LISTED MEDICINE FOR SAME INDICATION IN THE PNF</b> <i>(*where there is no comparator medicine in the formulary, use the cost of the best existing standard of care)</i></p>	<p align="center"><b>REFERENCES</b></p>
<p>COST PER DOSAGE UNIT (in PhP)</p> <p>a. Proposed list price to the government</p> <p>b. Current prevailing market price</p>	<p>Dabigatran (Pradaxa) P 2,272 per 110 mg tablet (30s)</p>	<p>Warfarin P 10 per 5 mg tablet</p>	<p>Dabigatran price from MIMS</p> <p>Warfarin price from DPRI</p>
<p>NUMBER OF DOSAGE UNITS PER UNIT COURSE</p>	<p align="center">30</p>	<p align="center">60</p>	
<p>TOTAL DIRECT COST PER PATIENT PER TREATMENT COURSE (in PhP)</p>	<p align="center">2,272</p>	<p align="center">300</p>	
<p>ADDITIONAL COST PER PATIENT PER TREATMENT COURSE: (n PhP)</p> <p>a. Implementation costs: (cost of drug administration, monitoring, additional diagnostic services, additional equipment, travel, caregiver, etc.)</p>		<p align="center">500</p>	
<p>TOTAL COST PER PATIENT PER TREATMENT COURSE (in PhP) Total Direct + Additional Costs</p>	<p align="center">2,272 monthly</p>	<p align="center">800 monthly</p>	
<p>ESTIMATED NUMBER OF PATIENTS WITH THE DISEASE/CONDITION WHO WILL USE THE MEDICINE</p>			
<p>QUALITY ADJUSTED LIFE YEARS (IF AVAILABLE)</p>			
<p>DISABILITY ADJUSTED LIFE YEARS (IF AVAILABLE)</p>			



## REVIEWERS' RECOMMENDATIONS

### Literature Search

- We search PubMed database searched last December 2014 using the search terms “dabigatran” and “warfarin” and “meta-analysis”. The yield was 12 articles. We also search Google Scholar for the same search terms and yielded 11 articles.
- We reviewed the available full text articles. The retrieved full text articles are a mixed of meta-analysis and primary RCTs. The meta-analysis also includes the big RCTs on dabigatran so we prioritized the review of meta-analysis articles. These are the articles included in this review.
  - Providência R(1), Albenque JP, Combes S, Bouzeman A, Casteigt B, Combes N, Narayanan K, Marijon E, Boveda S. Safety and efficacy of dabigatran versus warfarin in patients undergoing catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *Heart*. 2014 Feb;100(4):324-35. doi: 10.1136/heartjnl-2013-304386. Epub 2013 Jul 22.
  - Baker WL(1), Phung OJ. Systematic review and adjusted indirect comparison meta-analysis of oral anticoagulants in atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2012 Sep 1;5(5):711-9. Epub 2012 Aug 21.
  - Capodanno D(1), Capranzano P, Giacchi G, Calvi V, Tamburino C. Novel oral anticoagulants versus warfarin in non-valvular atrial fibrillation: a meta-analysis of 50,578 patients. *Int J Cardiol*. 2013 Aug 20;167(4):1237-41. doi: 10.1016/j.ijcard.2012.03.148. Epub 2012 Apr 10.
  - Roskell NS(1), Lip GY, Noack H, Clemens A, Plumb JM. Treatments for stroke prevention in atrial fibrillation: a network meta-analysis and indirect comparisons versus dabigatran etexilate. *Thromb Haemost*. 2010 Dec;104(6):1106-15. doi: 10.1160/TH10-10-0642. Epub 2010 Oct 21.
  - Schulman S(1), Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, Christiansen AV, Friedman J, Le Maulf F, Peter N, Kearon C; RE-COVER II Trial Investigators. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation*. 2014 Feb 18;129(7):764-72. doi: 10.1161/CIRCULATIONAHA.113.004450. Epub 2013 Dec 16.
  - Majeed A(1), Hwang HG, Connolly SJ, Eikelboom JW, Ezekowitz MD, Wallentin L, Brueckmann M, Fraessdorf M, Yusuf S, Schulman S. Management and outcomes of major bleeding during treatment with dabigatran or warfarin. *Circulation*. 2013 Nov 19;128(21):2325-32. doi: 10.1161/CIRCULATIONAHA.113.002332. Epub 2013 Sep 30.
  - Marijon E(1), Le Heuzey JY, Connolly S, Yang S, Pogue J, Brueckmann M, Eikelboom J, Themeles E, Ezekowitz M, Wallentin L, Yusuf S; RE-LY Investigators. Causes of death and influencing factors in patients with atrial fibrillation: a competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. *Circulation*. 2013 Nov 12;128(20):2192-201. doi: 10.1161/CIRCULATIONAHA.112.000491. Epub 2013 Sep 9.
  - Assiri A(1), Al-Majzoub O, Kanaan AO, Donovan JL, Silva M. Mixed treatment comparison meta-analysis of aspirin, warfarin, and new anticoagulants for stroke prevention in patients with nonvalvular atrial fibrillation. *Clin Ther*. 2013 Jul;35(7):967-984.e2. doi: 10.1016/j.clinthera.2013.05.011.

### Effectiveness/Efficacy

- Although not so relevant to the clinical question of NCPAM, previous meta-analysis has shown that dabigatran is better than anti-platelets in terms of preventing mortality and stroke. When compared to warfarin, dabigatran has similar effect in terms of mortality or recurrent venous thromboembolism (RR=1.08 (95%CI; 0.64 and 1.80)). This is based on high quality meta-analysis.
- A more recent high quality meta-analysis that included RCTs on patients with atrial fibrillation, the incidence of thromboembolic events (RR = 1.78 (95% CI; 0.66 and 4.80))
- There are indirect comparison between dabigatran, rivaroxiban and apixaban. These studies showed that in terms of preventing mortality, stroke or systemic emboli, there are no statistically significant difference between the three.

## Safety

- In terms of safety dabigatran was also found to be similar with warfarin in terms of major bleeding in two meta-analysis (RR=0.69 (95%CI; 0.36 and 1.32) Schulman, 2014 ) and (RR = 1.07 (95% CI; 0.51 and 2.26) in Providencia, 2014)

## Summary of Review

- Overall, our review showed dabigatran to be as effective and safe as warfarin and other newer oral anticoagulants (apixaban and rivaroxiban).

## Cost Data

- In terms of cost, we found dabigatran to be almost 3 times more expensive than warfarin even if we include the laboratory cost.

## Overall Recommendation

- In summary we found dabigatran to be as effective and safe as warfarin but 3 times more expensive. There is not enough evidence and justification to include dabigatran in the PNF as alternative to warfarin in terms of cost.
- Note – Compared to LMW heparin, dabigatran is as effective and safe and lesser cost for the prevention of thromboembolism. Newer oral anticoagulants may be useful in situation where laboratory determination for INR of pro-time is not available. Please refer to our review on apixaban.

## References

1. Spencer FA, Emery C, Lessard D, et al. The Worcester Venous Thromboembolism study: a population-based study of the clinical epidemiology of venous thromboembolism. *J Gen Intern Med* 2006;21: 722-7.
2. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;133:Suppl:454S-545S.
3. Ezekowitz MD, Connolly S, Parekh A, et al. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. *Am Heart J* 2009;157:805-10, 810.e1-2.
4. Providência R(1), Albenque JP, Combes S, Bouzeman A, Casteigt B, Combes N, Narayanan K, Marijon E, Boveda S. Safety and efficacy of dabigatran versus warfarin in patients undergoing catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *Heart*. 2014 Feb;100(4):324-35. doi: 10.1136/heartjnl-2013-304386. Epub 2013 Jul 22.
5. Baker WL(1), Phung OJ. Systematic review and adjusted indirect comparison meta-analysis of oral anticoagulants in atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2012 Sep 1;5(5):711-9. Epub 2012 Aug 21.
6. Capodanno D(1), Capranzano P, Giacchi G, Calvi V, Tamburino C. Novel oral anticoagulants versus warfarin in non-valvular atrial fibrillation: a meta-analysis of 50,578 patients. *Int J Cardiol*. 2013 Aug 20;167(4):1237-41. doi: 10.1016/j.ijcard.2012.03.148. Epub 2012 Apr 10.
7. Roskell NS(1), Lip GY, Noack H, Clemens A, Plumb JM. Treatments for stroke prevention in atrial fibrillation: a network meta-analysis and indirect comparisons versus dabigatran etexilate. *Thromb Haemost*. 2010 Dec;104(6):1106-15. doi: 10.1160/TH10-10-0642. Epub 2010 Oct 21.
8. Schulman S(1), Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, Christiansen AV, Friedman J, Le Maulf F, Peter N, Kearon C; RE-COVER II Trial Investigators. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation*. 2014 Feb 18;129(7):764-72. doi: 10.1161/CIRCULATIONAHA.113.004450. Epub 2013 Dec 16.

9. Majeed A(1), Hwang HG, Connolly SJ, Eikelboom JW, Ezekowitz MD, Wallentin L, Brueckmann M, Fraessdorf M, Yusuf S, Schulman S. Management and outcomes of major bleeding during treatment with dabigatran or warfarin. *Circulation*. 2013 Nov 19;128(21):2325-32. doi: 10.1161/CIRCULATIONAHA.113.002332. Epub 2013 Sep 30.
10. Marijon E(1), Le Heuzey JY, Connolly S, Yang S, Pogue J, Brueckmann M, Eikelboom J, Themeles E, Ezekowitz M, Wallentin L, Yusuf S; RE-LY Investigators. Causes of death and influencing factors in patients with atrial fibrillation: a competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. *Circulation*. 2013 Nov 12;128(20):2192-201. doi: 10.1161/CIRCULATIONAHA.112.000491. Epub 2013 Sep 9.
11. Assiri A(1), Al-Majzoub O, Kanaan AO, Donovan JL, Silva M. Mixed treatment comparison meta-analysis of aspirin, warfarin, and new anticoagulants for stroke prevention in patients with nonvalvular atrial fibrillation. *Clin Ther*. 2013 Jul;35(7):967-984.e2. doi: 10.1016/j.clinthera.2013.05.011.