Non-vitamin K antagonist oral anticoagulants and Risk of Fractures: A Systematic Review and Meta-analysis

Supplementary

Table S1: The MOOSE Statement Checklist

Table S2: The search strategies used for the databases

Table S3: Risk of bias assessment of studies included in the meta-analysis by the Newcastle-Ottawa Scale

Table S4: Risk of any fractures with NOACs versus VKAs across included studies

Table S5: Results of subgroup analyses based on age, gender, and history of osteoporosis

Table S6: Sensitivity analyses: outcomes after removing individual studies (leave-one-out approach)

Table S7: Meta-regression analysis

Figure S1: Sensitivity Analysis: forest plot showing the risk ratio of any fracture outcome after adding post-hoc results of ENGAGE-AF-TIMI 48 study

Table S1. The Meta-Analysis of Observational Studies in Epidemiology (MOOSE) Statement Checklist

	Criteria	**Brief description of how the criteria were handled in the meta-analysis**
	Reporting of background should include	
✓	Problem definition	Comparative fracture risk for non-vitamin K antagonist oral anticoagulants (NOACs) and vitamin K antagonists (VKAs) among patients with atrial fibrillation (AF) remains unclear.
✓	Hypothesis statement	The use of NOACs may be associated with a lower risk of fracture compared to VKAs.
✓	Description of the study outcomes	The primary outcome was any fracture. The secondary outcomes were fractures at different skeletal sites.
✓	Types of exposure or intervention	NOAC treatment
✓	Type of study designs used	Observational studies were included.
✓	Study population	We included patients with AF that evaluated NOAC use and the risk of fracture regardless of age and sex.
	Reporting of search strategy should include	
✓	Qualifications of searchers	The credentials of all investigators are indicated in the author list.
✓	Search strategy, including time period included in the synthesis and keywords	An investigator conducted the literature search without language restriction, from 2010 to February 9, 2020.
✓	Databases and registries searched	PubMed, Embase, and the Cochrane Library
✓	Search software used, name and version, including special features	No specific search software was employed. EndNote was used to merge retrieved citations and eliminate duplications.
✓	Use of hand searching	The reference lists of the included studies, prior systematic reviews, and introduction and discussion sections of retrieved studies were handed search to identify additional relevant studies.
✓	List of citations located and those excluded, including justifications	Details of the literature review process are outlined in the PRISMA flow chart.
✓	Method of addressing articles published in languages other than English	We searched the literature without language restriction. If necessary, local scientists fluent in the original language were contacted for further information and translation.
✓	Method of handling abstracts and unpublished studies	We restricted only articles published in full-text based on quality of study and it had been peer reviewed.
✓	Description of any contact with authors	If necessary, the authors were contacted when primary outcome data was missing. If the authors did not respond, the study was excluded.

	Criteria	Brief description of how the criteria were handled in the meta-analysis
	Reporting of methods should include	
✓	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Specific inclusion and exclusion criteria were described in the methods section (Inclusion criteria).
✓	Rationale for the selection and coding of data	Data extractions from each eligible study were relevant to the general trial characteristics, population characteristics, exposure, outcome, and possible confounding factors.
✓	Assessment of confounding	Both sensitivity analysis and meta-regression analysis were assessed to address potential confounding.
✓	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	A scale explicitly addressing the quality of the study design was assessed by using the NOS.
✓	Assessment of heterogeneity	The heterogeneity was assessed by using the Cochran *Q* test and I^2 for all analyses.
✓	Description of statistical methods in sufficient detail to be replicated	All description of statistical methods, subgroup analyses, sensitivity analyses, and meta-regression are provided in the methods section.
✓	Provision of appropriate tables and graphics	Two tables and 2 figures were provided primary and secondary findings.
	Reporting of results should include	
✓	Graph summarizing individual study estimates and overall estimate	Figure 2 and figure 3.
✓	Table giving descriptive information for each study included	Table 1.
✓	Results of sensitivity testing	See results section and eTable 6 and eFigure 1.
✓	Indication of statistical uncertainty of findings	95% confidence intervals and the Cochran Q test and I^2 were reported with all summary effect estimates.
	Reporting of discussion should include	
✓	Quantitative assessment of bias	Sensitivity analyses were assessed to quantify potential biases.
✓	Justification for exclusion	Studies that provided only abstracts were excluded.
✓	Assessment of quality of included studies	The study quality was described in result sections.

	Criteria	Brief description of how the criteria were handled in the meta-analysis
	Reporting of conclusions should include	
✓	Consideration of alternative explanations for observed results	A comprehensive list of alternative explanations was described in the discussion section.
✓	Generalization of the conclusions	Our findings are generalizable since we included studies from different countries with large participants and outcomes reflected the real-world clinical practice.
✓	Guidelines for future research	We make the recommendations in the discussion sections.
✓	Disclosure of funding source	This study was not funded.

Table S2. The search strategies: PubMed database from 2010 to May 26, 2020

Search	Query	Items found
#1	Search ((((((((((((((((((((((((((((((Anticoagulants[MeSH Terms]) OR "blood thinner"[Text Word]) OR "blood thinners"[Text Word]) OR DOAC*[Text Word]) OR NOAC*[Text Word]) OR Warfarin[Text Word]) OR Apo-Warfarin[Text Word]) OR Aldocumar[Text Word]) OR Gen-Warfarin[Text Word]) OR Warfant[Text Word]) OR Coumadin[Text Word]) OR Marevan[Text Word]) OR "warfarin potassium"[Text Word]) OR "warfarin sodium"[Text Word]) OR coumadine[Text Word]) OR "vitamin K antagonist"[Text Word]) OR "vitamin K antagonists"[Text Word]) OR Antithrombin*[Text Word]) OR "direct thrombin Inhibitor"[Text Word]) OR "direct thrombin inhibitors"[Text Word]) OR "direct antithrombin"[Text Word]) OR "direct antithrombins"[Text Word]) OR Dabigatran[Text Word]) OR Pradaxa[Text Word]) OR "Factor Xa Inhibitor"[Text Word]) OR "Factor Xa Inhibitors"[Text Word]) OR "direct factor Xa inhibitor"[Text Word]) OR "direct factor Xa inhibitors"[Text Word]) OR Apixaban[Text Word]) OR Eliquis[Text Word]) OR Edoxaban[Text Word]) OR Savaysa[Text Word]) OR Rivaroxaban[Text Word]) OR Xarelto[Text Word]	113,933
#2	Search ((((Fracture[MeSH Terms]) OR Fracture*[Text Word]) OR bone*[Text Word]) OR "broken bone"[Text Word]) OR "broken bones"[Text Word]	1,111,826
#3	#1 AND #2	2166
#4	Publication date from 2010/01/01 to 2020	932

Table S2. The search strategies: EMBASE (Ovid) database from 2020 to May 26, 2020 (continued)

Item	Search terms	Items found
1	(Anticoagulants or 'blood thinner' or 'blood thinners' or DOAC* or NOAC* or Warfarin or Apo-Warfarin or Aldocumar or Gen-Warfarin or Warfant or Coumadin or Marevan or 'warfarin potassium' or 'warfarin sodium' or coumadine or 'vitamin K antagonist' or 'vitamin K antagonists' or Antithrombin* or 'direct thrombin Inhibitor' or 'direct thrombin inhibitors' or 'direct antithrombin' or 'direct antithrombins' or Dabigatran or Pradaxa or 'Factor Xa Inhibitor' or 'Factor Xa Inhibitors' or 'direct factor Xa inhibitor' or 'direct factor Xa inhibitors' or Apixaban or Eliquis or Edoxaban or Savaysa or Rivaroxaban or Xarelto).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	159,579
2	(Fracture or Fracture* or bone* or 'broken bone' or 'broken bones').mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	1,472,984
3	1 AND 2	6,054
4	limit #3 to yr="2010 -Current"	3,506
5	Limit #4 to human	3,285

Table S2. The search strategies: Cochrane Library database from inception to May 26, 2020 (continued)

Item	Search terms	Items found
#1	MeSH descriptor: [Anticoagulants] explode all trees	4533
#2	'blood thinner' OR 'blood thinners' OR DOAC* OR NOAC* OR Warfarin OR Apo-Warfarin OR Aldocumar OR Gen-Warfarin OR Warfant OR Coumadin OR Marevan OR 'warfarin potassium' OR 'warfarin sodium' OR coumadine OR 'vitamin K antagonist' OR 'vitamin K antagonists' OR Antithrombin* OR 'direct thrombin Inhibitor' OR 'direct thrombin inhibitors' OR 'direct antithrombin' OR 'direct antithrombins' OR Dabigatran OR Pradaxa OR 'Factor Xa Inhibitor' OR 'Factor Xa Inhibitors' OR 'direct factor Xa inhibitor' OR 'direct factor Xa inhibitors' OR Apixaban OR Eliquis OR Edoxaban OR Savaysa OR Rivaroxaban OR Xarelto	10176
#3	#1 or #2	12317
#4	MeSH descriptor: [Fractures, Bone] explode all trees	5862
#5	Fracture OR Fracture* OR bone* OR 'broken bone' OR 'broken bones'	69504
#6	#4 or #5	69516
#7	#3 AND #6 with publication year from 2010-2020	306

Table S3. Risk of bias assessment of studies included in the meta-analysis using the Newcastle-Ottawa Scale

Author (Year)	Adequacy selection of cohort				Comparability of studies		Outcome assessment			Total NOS score
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Study control for age, gender, previous fracture, osteoporosis, and glucocorticoid use	Study controls for any additional factor	Assessment of outcome	follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Norby FL, et al. (2017)[1]	1	1	1	1	0	1	1	1	1	8/9
Binding C, et al. (2019)[2]	1	1	1	1	0	1	1	1	1	8/9
Lutsey PL, et al. (2019)[3]	1	1	1	1	1	1	1	1	1	9/9
Huang HK, et al. (2020)[4]	1	1	1	1	0	1	1	1	1	8/9
Lau WC, et al. (2020)[5]	1	1	1	1	1	1	1	1	1	9/9

Abbreviation: NOS= the Newcastle-Ottawa Scale

Table S4. Risk of any fractures with NOACs versus VKAs across included studies

Author (year)	Total sample size	NOACs		VKAs		Adjusted HR (95% CI)
		Total No.	No. of cases	Total No.	No. of cases	
Norby FL, et al. (2017)[1]	77,991	32495	194	45496	408	0.83 (0.70-0.99)
Binding C, et al. (2019)[2]	37,350	25,182	606	12,168	329	0.85 (0.74-0.97)
Lutsey PL, et al. (2019)[3]	111,652	55,826	293	55,826	312	0.93 (0.88-0.98)
Huang HK, et al. (2020)[4]	19,414	9,707	737	9,707	1,009	0.84 (0.77-0.93)
Lau WCY, et al. (2020)[5]	23,515	13,974	205	9541	196	0.61 (0.48-0.77)
Total	269,922	137,184	2,035	132,738	2,254	

Abbreviations: NOACs=non-vitamin K antagonist oral anticoagulants; VKAs=vitamin K antagonists; HR=hazard ratio; CI=confidence interval

Table S5. Results of subgroup analyses based on age, gender, and history of osteoporosis

Variable	No. of studies	Pooled RR (95% CI)	P-value	Heterogeneity test			
				X2	P-value	I^{2}-index	τ^{2}
Gender							
Female							
Overall NOACs	2[3-5]	0.82 (0.72-0.95)	0.006	6.12	0.047	67.3%	0.0092
Dabigatran	2[3,5]	0.86 (0.67-1.11)	0.251	2.28	0.131	56.2%	0.0221
Rivaroxaban	2[3,5]	0.68 (0.43-1.07)	0.099	3.93	0.048	74.5%	0.0841
Apixaban	2[3,5]	0.76 (0.56-1.05)	0.094	1.90	0.169	47.3%	0.0287
Male							
Overall NOACs	2[3-5]	0.82 (0.65-1.02)	0.077	10.44	0.005	80.8%	0.0290
Dabigatran	2[3,5]	0.83 (0.54-1.28)	0.391	3.57	0.059	72.0%	0.0755
Rivaroxaban	2[3,5]	0.76 (0.54-1.06)	0.105	1.94	0.164	48.4%	0.0364
Apixaban	2[3,5]	0.85 (0.70-1.03)	0.090	0.26	0.609	0.0%	0.0000
Age							
< 75 years							
Overall NOACs	2[3,4]	0.94 (0.87-1.01)	0.100	0.08	0.778	0.0%	0.0000
Dabigatran	1[3]	0.97 (0.88-1.07)	NR	NA	NA	NA	NA
Rivaroxaban	1[3]	0.83 (0.73-0.93)	NR	NA	NA	NA	NA
Apixaban	1[3]	0.87 (0.70-1.07)	NR	NA	NA	NA	NA
≥ 75 years							
Overall NOACs	2[3,4]	0.89 (0.77-1.02)	0.096	3.21	0.073	68.9%	0.0076
Dabigatran	1[3]	0.96 (0.88-1.05)	NR	NA	NA	NA	NA
Rivaroxaban	1[3]	0.83 (0.74-0.91)	NR	NA	NA	NA	NA
Apixaban	1[3]	0.86 (0.73-1.02)	NR	NA	NA	NA	NA
History of osteoporosis							
Without history of osteoporosis							
Overall NOACs	1[3]	0.95 (0.89-1.02)	NR	NA	NA	NA	NA
Dabigatran	1[3]	1.01 (0.93-1.10)	NR	NA	NA	NA	NA
Rivaroxaban	1[3]	0.82 (0.74-0.91)	NR	NA	NA	NA	NA
Apixaban	1[3]	0.86 (0.73-1.02)	NR	NA	NA	NA	NA
With history of osteoporosis							
Overall NOACs	1[3]	0.9 (0.83-0.98)	NR	NA	NA	NA	NA
Dabigatran	1[3]	0.89 (0.81-0.99)	NR	NA	NA	NA	NA
Rivaroxaban	1[3]	0.82 (0.73-0.93)	NR	NA	NA	NA	NA
Apixaban	1[3]	0.84 (0.68-1.04)	NR	NA	NA	NA	NA

Abbreviations: NOACs=non-vitamin K antagonist oral anticoagulants; RR=relative risk; CI=confidence interval; NR=not reported; NA=not applicable

Table S6. Sensitivity analyses: outcomes after removing individual studies (leave-one-out approach)

Studies	**Incidence of any fractures** **RR (95% CI)**
All studies	0.83 (0.75-0.92)
Norby FL, et al. (2017) omitted	0.83 (0.74-0.94)
Binding C, et al. (2019) omitted	0.82 (0.72-0.94)
Lutsey PL, et al. (2019) omitted	0.80 (0.72-0.89)
Huang HK, et al. (2020) omitted	0.82 (0.71-0.95)
Lau WCY, et al. (2017) omitted	0.88 (0.82-0.94)

Abbreviations: RR=relative risk, CI=confidence interval

Table S7. Meta-regression analysis

Variable	P-value
Year of publication	0.625
Continent that study was taken place (Asia vs Europe vs North American)	0.290
Duration of study	0.150
Individual NOACs vs NOACs group	0.963

Abbreviations: NOACs=non-vitamin K antagonist oral anticoagulants

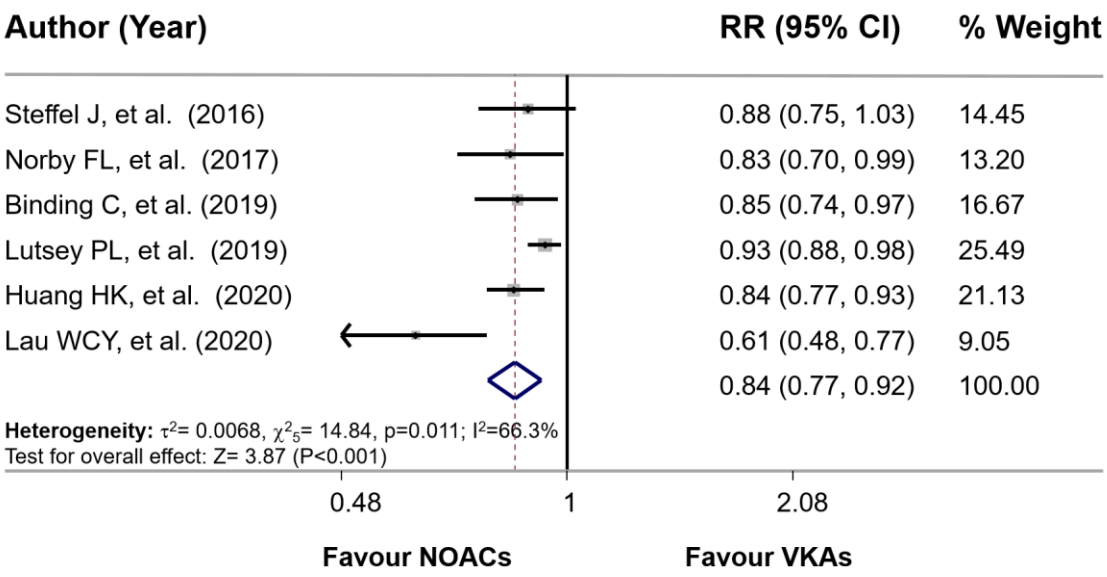

Figure S1. Sensitivity Analysis: forest plot showing the risk ratio of any fracture outcome after adding post-hoc results of ENGAGE-AF-TIMI 48 study

Abbreviations: RR=relative risk, CI=confidence interval, NOACs= Non-vitamin K antagonist oral anticoagulants, VKAs=vitamin K antagonists

References

1. Norby FL, Bengtson LGS, Lutsey PL, et al. Comparative effectiveness of rivaroxaban versus warfarin or dabigatran for the treatment of patients with non-valvular atrial fibrillation. *BMC Cardiovascular Disorders.* 06 Sep 2017;17 (1) (no pagination)(238).
2. Binding C, Bjerring Olesen J, Abrahamsen B, Staerk L, Gislason G, Nissen Bonde A. Osteoporotic Fractures in Patients With Atrial Fibrillation Treated With Conventional Versus Direct Anticoagulants. *Journal of the American College of Cardiology.* 29 October 2019;74(17):2150-2158.
3. Lutsey PL, Norby FL, Ensrud KE, et al. Association of Anticoagulant Therapy with Risk of Fracture among Patients with Atrial Fibrillation. *JAMA Internal Medicine.* 2019.
4. Huang HK, Liu PP, Hsu JY, et al. Fracture risks among patients with atrial fibrillation receiving different oral anticoagulants: a real-world nationwide cohort study. *European heart journal.* Feb 1 2020.
5. Lau WCY. Cheung CL MK. Association between treatment with apixaban, dabigatran, rivaroxaban, or warfarin and the risk of osteoporotic fractures among patients with atrial fibrillation: A population-based cohort study. *Ann Intern Med.* 2020;In press.