

Supplementary appendices

Economic evaluation of Direct Oral Anticoagulants (DOACs) versus Vitamin K Antagonists (VKAs) for stroke prevention in atrial fibrillation patients: a systematic review and meta-analysis

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(All figures and tables in the supplementary appendices are created by the authors)

Online Supplementary Content

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Appendix 1 Search strategies

The search terms were constructed based on domains of population, intervention, comparator, and outcome (PICO) as below. Then these search terms were combined using Boolean operator OR within the same domains, and “AND” Boolean operator between domains of PICO as described.

Domain	Search terms
P	Atrial Fibrillation
I	NOAC Oral Anticoagulants Non Vitamin K Antagonists Apixaban Rivaroxaban Dabigatran Edoxaban
C	Warfarin Vitamin K Antagonists Acenocoumarol Phenprocoumon Coumarin
O	Incremental Net Benefit Costs Quality Adjusted Life Years Incremental Cost Effectiveness Ratios
S	Economic evaluation

A) Search strategy from PubMed/Medline

DOMAIN	N of search PubMed	Search Terms
P	#1	Search "atrial fibrillation"
	#2	Search "Atrial Fibrillation"[Mesh]
	#3	#1 or #2
I	#4	Search "noac*"
	#5	Search "oral anticoagulant*"
	#6	Search "non vitamin K antagonist*"
	#7	Search apixaban
	#8	Search rivaroxaban
	#9	Search dabigatran
	#10	Search edoxaban
	#11	#4 or #5 or #6 or #7 or #8 or #9 or #10
O	#12	Search "incremental net benefit"
	#13	Search "cost*"
	#14	Search "quality adjusted life year*"
	#15	Search "incremental cost effectiveness ratio*"
	#16	Search "economic evaluation"
	#17	#12 or #13 or #14 or #15 or #16
PIO	#18	#3 and #11 and #18

B) Search strategy from Scopus

DOMAIN	N of search SCOPUS	Search Terms
P	#1	TITLE-ABS-KEY ("atrial fibrillation")
	#2	#1
I	#3	TITLE-ABS-KEY ("noac*")
	#4	TITLE-ABS-KEY ("oral anticoagulant*")
	#5	TITLE-ABS-KEY ("non vitamin k antagonist*")
	#6	TITLE-ABS-KEY (apixaban)
	#7	TITLE-ABS-KEY (rivaroxaban)
	#8	TITLE-ABS-KEY (dabigatran)
	#9	TITLE-ABS-KEY (edoxaban)
	#10	#3 or #4 or #5 or #6 or #7 or #8 or #9
O	#11	TITLE-ABS-KEY ("incremental net benefit")
	#12	TITLE-ABS-KEY ("cost*")
	#13	TITLE-ABS-KEY ("quality adjusted life year*")
	#14	TITLE-ABS-KEY ("incremental cost effectiveness ratio*")
	#15	TITLE-ABS-KEY ("economic evaluation")

DOMAIN	N of search SCOPUS	Search Terms
	#16	#11 or #12 or #13 or #14 or #15
PIO	#17	#2 and #10 and #16

C) Search strategy from CEVR registry database

DOMAIN	N of search CEVR registry	Search Terms
Method	#1	Cost Effectiveness
	#2	Cost Utility
	#3	Economic Evaluation

Appendix 2 Data hamonisation and synthesis

There were 4 steps of data hamonisation for further synthesis, namely currency conversion, data preparation, calculating INB and the variance of INB and statistical analysis by INB pooling.

A) Currency conversion

The relevant cost-effectiveness study reports economic terms in the currency units of each country at a certain time unit, so that currency conversion is needed for the standardization of monetary data. For the purposes of this analysis, all monetary units were converted to a single-year standard currency adjusted with purchasing power parity (PPP) 2019 to get PPP-adjusted US Dollars to the year of 2019. All monetary units except for country specific based threshold were adjusted to consumer price index and PPP conversion rates to 2019, using the formula:

$$Y_{ppp2019} = Y_{Ebaseyear} \times \left(\frac{cpi_{E2019}}{cpi_{Ebase\ year}} \times \frac{1}{ppp2019} \right)$$

Converting the value of the variance of monetary units using the formula:

$$Y_{ppp2019} = Y_{Ebaseyear} \times \left(\frac{cpi_{E2019}}{cpi_{Ebase\ year}} \times \frac{1}{ppp2019} \right)^2$$

B) Data Preparation

The next step is to complete the data needed to calculate the INB and its variance. In the formula for calculating the INB proposed by Crespo¹, the mean and the dispersion (up to 95% CI) of the costs and QALY are required. The data is obtained through data extraction, but many reports from cost-effectiveness studies in different forms that cause the data are not available, so to complete the lack of data, made scenarios.

There are five scenarios created based on the completeness of the data that cannot be extracted from included cost-effectiveness studies, namely:

- Scenario 1

Studies reported means along with measures of dispersion for costs, outcomes, ΔC , ΔE and Incremental Cost-Effectiveness Ratio (ICER). In this ideal situation, all the data required to calculate INB and its variance are available. Thus, the INB can be estimated as accordingly to the equation:¹

$$INB = \Delta E \times (K - ICER) \quad \text{or} \quad INB = (K \times \Delta E) - \Delta C$$

$$Var(INB) = K^2 \sigma_{\Delta E}^2 + \sigma_{ICER}^2$$

Where K is threshold, $\sigma_{\Delta E}^2$ is variance of ΔE and σ_{ICER}^2 variance of ICER

- Scenario 2

Studies reported ICER along with 95%CI, the variance of ICER is calculated by formula:

$$UL_{ICER} = \mu + 1.96 SE_{ICER}$$

$$SE_{ICER} = \frac{(UL_{ICER} - \mu)}{1.96}$$

Where UL is Upper Limit and μ is mean. Then, INB was calculated using above formula.

- Scenario 3

Studies reported mean as along with measures of dispersion (95% CI, SD or SE) of costs, outcomes, or, $\Delta C/\Delta E$ but have not provided the ICER and its variance. Monte Carlo with 1000 simulation² would be used to simulate ΔC and ΔE data. Gamma distribution is used for ΔC and normal distribution is used for ΔE . If 95% CI is given, then the variance of ΔC and ΔE would be calculated but the covariance ($\rho_{\Delta C \Delta E}$) between, ΔC and ΔE are required to estimate using the simulated data. To calculate the variance of INB using the formula:

$$\text{Var (INB)} = K^2 \sigma_{\Delta E}^2 + \sigma_{\Delta C}^2 - 2K\rho_{\Delta C \Delta E}$$

- Scenario 4

The studies have not reported any measures of dispersion but provided the Cost-Effective (CE) plane graphs for both intervention and comparator of interest as for a result of probabilistic sensitivity analysis (PSA).

The CE-plane graph is scatter plot of ΔC on Y-axis and ΔE on X-axis. data of ΔC and ΔE could be then extracted from the CE plane graph using Web-Plot Digitizer software version 4.2.³

As a result, mean of these ΔC and ΔE along with their variances and co-variances between ΔC and ΔE will be estimated leading to estimate the INB and its variance using the equation above.

- Scenario 5

Studies reported means of costs, outcomes, ΔC , ΔE or ICER but have not report neither the mean of dispersions nor the CE plane graph. The measure of dispersion would be taken from other studies that had reported data with following criteria:

1. Their ICERs were not much different, example: $\pm 70\%$ to $\pm 85\%$
2. The studies were similar in intervention, comparator, time period, counties, perspective
3. The studies were in the same level of country's income, similar model inputs (eg, discount rate, time horizon, etc.)
4. If there are more than one study met the criteria, average of variances of those studies would be used.

C) Calculate INB and the variance of INB

INB is an outcome calculated using the formula developed by Crespo¹ namely $\text{INB} = (K \times \Delta E) - \Delta C$ where K is the threshold or willingness to pay, ΔE is the incremental QALY and ΔC is the incremental cost. A positive INB value indicates favoring intervention and a negative INB value indicates favoring comparator. The variance of INB is calculated using the formula as mentioned above.

D) Statistical analysis

Furthermore, pooling is carried out from INB and stratified based on country level of income. A total INB was estimated by using the random effect model by the Der Simonian and Laird⁴ method if there is heterogeneity with the formula:

a. Random-effect model:

$$\text{INB}_p = \frac{\sum_{i=1}^S w_i^* \text{INB}_i}{\sum_{i=1}^S w_i^*}$$

$$w_i^* = \frac{1}{[K^2 \sigma_{\Delta E}^2 + \sigma_{\Delta C}^2 + 2K\rho_{\Delta E \Delta C}] + \tau^2}$$

$$\tau^2 = \frac{Q - (S - 1)}{\sum w_i - \frac{\sum w_i^2}{\sum w_i}}$$

$Q=0$ if $Q < S-1$ (Q and s is number of comparisons)

and using inverse variance method if there is N heterogeneity with the formula:

b. Fixed-effect model:

$$\text{INB}_p = \frac{\sum_{i=1}^S w_i \text{INB}_i}{\sum_{i=1}^S w_i}$$

$$w_i = \frac{1}{\text{Var}(\text{INB})}$$

$$w_1 = \frac{1}{K^2 \sigma_{\Delta E}^2 + \sigma_{\Delta C}^2 + 2K\rho_{\Delta E \Delta C}}$$

The heterogeneity was assessed using the Cochrane-Q test and I^2 statistics. There was a heterogeneity if the I^2 statistics was greater than 25% or if the Cochrane-Q test p-value was <0.1. Here is the formula for Cochrane Q test and I^2 :

c. Cochrane Q test

$$\text{Cochrane Q} = \sum_{i=1}^s w_1 (\text{INB}_i - \text{INB}_p)^2$$

Where W_1 is the inverse variance of INB_i , INB_i is the individual studies, and INB_p is the pooled INB.

d. The I^2 statistic test

$$I^2 = 100\% \times \frac{Q - \text{df}}{Q}$$

Exploration of heterogeneity sources by considering some covariables such as thresholds, time horizons, and perspectives in a meta regression model for each covariable. A sensitivity analysis or subgroup analysis was applied according to these variables.

Publication was assessed using Egger's test and funnel plot. Publication can be determined if the funnel plot shows asymmetry or the p-value from Egger's test is less than 0.05. If there is asymmetry, the source of asymmetry will be explored using a contour-enhanced funnel plot. If missing studies in statistical non-significant areas means that there is a publication bias and if missing studies in both statistical non-significance and significant areas, means that caused by other reasons. All analyzes were performed using STATA version 16. Two-sided p <0.05 was considered statistically significant except for heterogeneity tests, in which p <0.10 was used.

Appendix 3 Characteristics of included studies and risk of bias assessment

eTable 3.1 List of excluded studies

Full-text articles excluded, with reasons (N=14 studies):

Not DOACs nor VKAs (N=5)

Not interested outcomes (N=2)

Narrative reviews (N=3)

Conference abstracts (N=2)

Duplicated article (N=1)

Cannot retrieve full-text article (N=1)

Study	Reasons for exclusion
Abdullaev SP, 2019 ⁵	Not DOACs nor VKAs
Belousov YB, 2012 ⁶	Duplicated article
Bonet Pla A, 2013 ⁷	Not interested outcomes
Kansal, 2013 ⁸	Narrative reviews
Koretsune Y, 2018 ⁹	Cannot retrieve full-text article
Monreal, 2017 ¹⁰	Conference abstract
Nedogoda, 2017 ¹¹	Not interested outcomes
Rudakova AV, 2014 ¹²	Conference abstract
Sorensen, 2013 ¹³	Narrative reviews
Uetsuka Y, 2011 ¹⁴	Narrative reviews
Vestergaard, 2015 ¹⁵	Not DOACs nor VKAs
You JHS, 2012 ¹⁶	Not DOACs nor VKAs
You JH, 2015 ¹⁷	Not DOACs nor VKAs
You JHS, 2014 ¹⁸	Not DOACs nor VKAs

eTable 3.2 Characteristics of the included studies (Created by the authors)

Category	Dabigatran versus VKAs						Rivaroxaban versus VKAs						Apixaban versus VKAs						Edoxaban versus VKAs					
	HIC		UMIC		LMIC		HIC		UMIC		LMIC		HIC		UMIC		LMIC		HIC		UMIC		LMIC	
	N	n	N	n	N	n	N	n	N	n	N	n	N	n	N	n	N	n	N	n	N	n	N	n
Perspective																								
Third-party payer	32	38	8	9	0	0	20	22	6	6	1	1	26	28	7	7	0	0	11	13	2	2	0	0
Societal	6	6	4	4	0	0	4	4	4	4	0	0	3	3	4	4	0	0	1	1	3	3	0	0
Patient	4	4	0	0	0	0	2	4	0	0	0	0	2	2	0	0	0	0	1	1	0	0	0	0
Model type																								
Markov	37	45	9	13	0	0	24	26	7	10	1	1	28	30	8	11	0	0	13	15	3	5	0	0
Discrete event simulation	3	3	0	0	0	0	2	2	0	0	0	0	2	2	0	0	0	0	0	0	0	0	0	0
EE alongside clinical trial	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0
Time horizon																								
Lifetime	39	47	8	11	0	0	26	28	7	10	1	1	31	33	7	10	0	0	13	15	3	5	0	0
Not lifetime	1	1	1	2	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0
Discount rate for cost																								
Not reported	3	4	0	0	0	0	2	3	0	0	0	0	2	3	0	0	0	0	1	2	0	0	0	0
≤3%	22	26	5	8	0	0	15	15	6	9	1	1	16	16	6	9	0	0	9	9	3	5	0	0
>3%	15	18	4	5	0	0	9	10	1	1	0	0	13	14	2	2	0	0	3	4	0	0	0	0
Discount rate for utility																								
Not reported	2	3	1	1	0	0	1	2	1	1	0	0	1	2	0	0	0	0	1	2	0	0	0	0
≤3%	23	27	5	8	0	0	16	16	6	9	1	1	17	17	6	9	0	0	9	9	3	5	0	0
>3%	15	18	3	4	0	0	9	10	0	0	0	0	13	14	2	2	0	0	3	4	0	0	0	0
Clinical data source																								
Published literature	35	42	6	8	0	0	20	21	6	8	1	1	23	24	7	9	0	0	10	11	3	5	0	0
Published literature-evidence synthesis	2	3	1	2	0	0	2	3	1	2	0	0	2	3	1	2	0	0	1	2	0	0	0	0
Published literature-registry database	2	2	1	2	0	0	2	2	0	0	0	0	4	4	0	0	0	0	1	1	0	0	0	0
Evidence synthesis	1	1	0	0	0	0	1	1	0	0	0	0	1	1	0	0	0	0	1	1	0	0	0	0
Registry database	0	0	1	1	0	0	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0
Utility data source																								
Published literature	38	46	8	11	0	0	24	26	6	8	1	1	30	32	7	9	0	0	12	14	2	3	0	0
Published literature-registry database	0	0	1	2	0	0	1	1	1	2	0	0	1	1	1	2	0	0	1	1	1	2	0	0
Survey	2	2	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Currency year																								
2008-2013	33	41	3	5	0	0	17	19	2	3	1	1	20	22	3	4	0	0	5	7	0	0	0	0
2014-2019	7	7	6	8	0	0	9	9	5	7	0	0	11	11	5	7	0	0	8	8	3	5	0	0
Cost-effectiveness threshold																								
Country specific	35	43	2	3	0	0	22	24	2	3	0	0	26	28	2	3	0	0	9	11	2	3	0	0
GDP based	4	4	7	10	0	0	3	3	5	7	1	1	3	3	6	8	0	0	2	2	1	2	0	0
Others	1	1	0	0	0	0	1	1	0	0	0	0	2	2	0	0	0	0	2	2	0	0	0	0
Cost-effectiveness result																								
Cost-effective	30	38	3	4	0	0	17	19	1	1	0	0	29	31	3	3	0	0	11	13	0	0	0	0
Not cost-effective	10	10	6	9	0	0	9	9	6	9	1	1	2	2	5	8	0	0	2	2	3	5	0	0

Abbreviations: VKAs, Vitamin K-Antagonists; EE, Economic Evaluation; GDP, Gross Domestic Product; HIC, High Income Country; UMIC, Upper-Middle Income Country; LMIC, Lower-Middle Income Country; N, number of studies; n, number of comparisons.

eTable 3.3 Risk of bias summary using the ECOBIAS checklist for each included study (Created by the authors)

Author	Part A Overall checklist for bias in economic evaluation											Part B Model-specific aspects of bias in economic evaluation										
												I ¹			II ²							III ³
	Narrow perspective bias	Inefficient comparator bias [*]	Cost measurement omission bias	Intermittent data collection bias	Invalid valuation bias	Ordinal ICER bias	Double-counting bias	Inappropriate discounting bias	Limited sensitivity analysis bias§	Sponsor bias	Reporting and dissemination bias	Structural assumptions bias	N treatment comparator bias [*]	Wrong model bias	Limited time horizon bias	Bias related to data identification	Bias related to baseline data	Bias related to treatment effects	Bias related to quality-of-life weights (utilities)	Non-transparent data incorporation bias	Limited to scope bias	Bias related to internal consistency
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Pink J, 2011 ¹⁹	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Dilokthornsaku I, P, 2019 ²⁰	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Harrington A, 2013 ²¹	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Lopez, 2017 ²²	N	Y	Y	Y	Y	Y	N	NA	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Verhoef TI, 2014 ²³	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
StevaNvic J, 2014 ²⁴	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Ademi Z, 2015 ²⁵	N	Y	P	Y	P	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	P	Y	N
Andrikopoulos GK, 2013 ²⁶	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Shah A, 2016 ²⁷	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	P	Y	Y	Y	Y	Y	N
Kamae I, 2015 ²⁸	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	P	Y	Y	Y	Y	Y	N
Lip GYH, 2014 ²⁹	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Jarungsucces S, 2014 ³⁰	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Athanasakis K, 2015 ³¹	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Coyle D, 2013 ³²	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Pletscher M, 2013 ³³	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	P	P	Y	Y	P	Y	N
Miller JD, 2014 ³⁴	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Magnuson, EA, 2015 ³⁵	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Athanasakis K, 2017 ³⁶	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Kamel H, 2012 ³⁷	Y	Y	Y	Y	Y	Y	N	NA	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Pink J, 2014 ³⁸	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Dorian P, 2014 ³⁹	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Lanitis T, 2014 ⁴⁰	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Canestaro WJ, 2013 ⁴¹	Y	P	Y	Y	Y	Y	N	N	Y	Y	P	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Wisloff , 2014 ⁴²	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Janjic A, 2014 ⁴³	N	Y	Y	Y	P	Y	N	N	Y	Y	N	Y	Y	Y	Y	P	Y	Y	Y	P	Y	N
Zheng Y, 2014 ⁴⁴	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Baron Esquivias G, 2013 ⁴⁵	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Giorgi MA, 2015 ⁴⁶	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Pradelli L, 2014 ⁴⁷	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	P	Y	P	Y	N
Li X, 2015 ⁴⁸	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Lanitis T, 2014 ⁴⁹	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Krejczyk M,	N	Y	Y	Y	Y	Y	N	N	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N

Author	Part A Overall checklist for bias in economic evaluation											Part B Model-specific aspects of bias in economic evaluation										
												I ¹				II ²						
	Narrow perspective bias	Inefficient comparator bias*	Cost measurement omission bias	Intermittent data collection bias	Invalid valuation bias	Ordinal ICER bias	Double-counting bias	Inappropriate discounting bias	Limited sensitivity analysis bias§	Sponsor bias	Reporting and dissemination bias	Structural assumptions bias	N treatment comparator bias*	Wrong model bias	Limited time horizon bias	Bias related to data identification	Bias related to baseline data	Bias related to treatment effects	Bias related to quality-of-life weights (utilities)	Non-transparent data incorporation bias	Limited to scope bias	Bias related to internal consistency
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
2014 ⁵⁰																						
Lee S, 2012 ⁵¹	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Rognoni C, 2013 ⁵²	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Kongnakorn T, 2014 ⁵³	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Mensch A, 2015 ⁵⁴	Y	Y	Y	Y	Y	Y	N	N	Y	P	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Nguyen E, 2016 ⁵⁵	Y	Y	Y	Y	Y	Y	N	N	Y	P	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Rattanakhotpanit T, 2019 ⁵⁶	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Rognoni C, 2015 ⁵⁷	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	P	Y	Y	Y	P	Y	N
Costa J, 2015 ⁵⁸	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Kleintjens J, 2013 ⁵⁹	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Sorensen SV, 2011 ⁶⁰	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Zhao YJ, 2016 ⁶¹	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Lekuona I, 2019 ⁶²	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Lanas F, 2017 ⁶³	N	Y	Y	Y	Y	Y	N	Y	Y	Y	P	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Wu B, 2014 ⁶⁴	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Langkilde LK, 2012 ⁶⁵	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	P	P	P	Y	P	Y	Y
Gonzalez-Juanatey JR, 2012 ⁶⁶	N	Y	Y	Y	Y	Y	N	N	Y	N	N	Y	Y	Y	Y	P	P	P	P	P	Y	N
Chang CH, 2014 ⁶⁷	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Kim H, 2019 ⁶⁸	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	P	Y	Y	Y	P	Y	N
Vilain KA, 2017 ⁶⁹	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Carles M, 2015 ⁷⁰	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Wang Y, 2014 ⁷¹	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Hospodar Ar, 2018 ⁷²	N	Y	Y	Y	Y	Y	N	NA	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Liu CY, 2017 ⁷³	N	Y	Y	Y	P	Y	N	N	Y	Y	N	Y	Y	Y	Y	P	P	Y	Y	P	Y	N
Lip GYH, 2015 ⁷⁴	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Hulst MV, 2017 ⁷⁵	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	P	P	P	Y	P	Y	N
Mendoza JA, 2019 ⁷⁶	N	Y	Y	Y	P	Y	N	N	Y	N	N	Y	Y	Y	P	Y	Y	Y	Y	P	Y	N
Lee S, 2012 ⁷⁷	N	P	Y	Y	Y	Y	N	N	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Wouters H, 2013 ⁷⁸	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	P	N	N	N	N	Y	N
Kourlaba G, 2014 ⁷⁹	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Kansal AR, 2012 ⁸⁰	N	Y	Y	Y	Y	Y	N	N	Y	Y	P	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Kamel H, 2012 ⁸¹	Y	Y	Y	Y	Y	Y	N	N	Y	N	P	Y	Y	Y	NA	P	Y	Y	Y	P	Y	N
Galvani G, 2015 ⁸²	Y	Y	N	Y	N	Y	N	NA	N	N	N	Y	Y	Y	Y	N	N	N	N	N	N	N
Hallinen T, 2015 ⁸³	N	Y	Y	Y	P	Y	N	N	Y	Y	N	Y	Y	Y	Y	P	Y	P	Y	P	Y	N

Author	Part A Overall checklist for bias in economic evaluation											Part B Model-specific aspects of bias in economic evaluation										
												I ¹			II ²							III ³
	Narrow perspective bias	Inefficient comparator bias*	Cost measurement omission bias	Intermittent data collection bias	Invalid valuation bias	Ordinal ICER bias	Double-counting bias	Inappropriate discounting bias	Limited sensitivity analysis bias§	Sponsor bias	Reporting and dissemination bias	Structural assumptions bias	N treatment comparator bias*	Wrong model bias	Limited time horizon bias	Bias related to data identification	Bias related to baseline data	Bias related to treatment effects	Bias related to quality-of-life weights (utilities)	Non-transparent data incorporation bias	Limited to scope bias	Bias related to internal consistency
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
2016 ⁸³																						
Bergh M, 2013 ⁸⁴	Y	Y	Y	Y	P	Y	N	NA	P	Y	N	Y	Y	Y	Y	N	N	N	N	N	N	N
Dwiprahasto I, 2019 ⁸⁵	N	Y	Y	Y	P	Y	N	N	Y	Y	N	Y	Y	Y	N	P	P	P	Y	P	Y	N
Cowper PA, 2017 ⁸⁶	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
De Souza CPR, 2015 ⁸⁷	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N
Salcedo J, 2019 ⁸⁸	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Salata BM, 2016 ⁸⁹	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Shah SV, 2011 ⁹⁰	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N
Freeman JV, 2011 ⁹¹	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	P	Y	Y	Y	P	Y	N
Chevalier J, 2014 ⁹²	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Nshimyumukiz a L, 2013 ⁹³	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Hernandez I, 2017 ⁹⁴	N	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Peng S, 2017 ⁹⁵	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Clemens A, 2014 ⁹⁶	N	Y	Y	Y	Y	Y	N	N	P	Y	N	Y	Y	Y	Y	P	Y	Y	N	P	P	N
Kansal AR, 2012 ⁹⁷	N	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Davidson T, 2013 ⁹⁸	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Morais J, 2014 ⁹⁹	Y	Y	Y	Y	P	Y	N	Y	Y	N	N	Y	Y	Y	Y	P	Y	Y	P	P	Y	N
Hersi AS, 2019 ¹⁰⁰	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Krejczyk M, 2014 ¹⁰¹	N	Y	Y	Y	Y	Y	N	N	Y	P	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Pink J, 2013 ¹⁰²	Y	Y	N	Y	N	Y	N	NA	Y	Y	N	Y	Y	Y	Y	P	Y	Y	Y	P	Y	N
Thom HHZ, 2019 ¹⁰³	Y	Y	Y	Y	Y	Y	N	NA	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
You JHS, 2013 ¹⁰⁴	N	Y	Y	Y	P	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	P	Y	N
Yong Fa-C, 2016 ¹⁰⁵	N	Y	Y	Y	P	Y	N	N	Y	N	N	Y	Y	Y	N	P	Y	Y	Y	P	Y	N
Fontcuberta CC, 2015 ¹⁰⁶	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Garcia-Pena AA, 2017 ¹⁰⁷	Y	Y	Y	Y	P	Y	N	N	Y	Y	P	Y	Y	Y	Y	Y	Y	Y	Y	P	Y	N
Miguel LS, 2016 ¹⁰⁸	Y	Y	Y	Y	P	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	P	Y	N
Miguel LS, 2013 ¹⁰⁹	Y	Y	Y	Y	P	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	P	Y	N
Ravasio R, 2014 ¹¹⁰	N	Y	Y	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Triana JJ, 2016 ¹¹¹	N	Y	N	Y	N	Y	N	N	Y	Y	N	Y	Y	Y	Y	N	N	N	N	N	Y	N
Rudakova AV, 2014 ¹¹²	N	Y	N	Y	N	Y	N	N	P	Y	N	Y	Y	Y	Y	N	N	N	N	N	P	N
Oyaguez I, 2019 ¹¹³	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Hori M, 2019 ¹¹⁴	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Ng SS, 2020 ¹¹⁵	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Author	Part A Overall checklist for bias in economic evaluation											Part B Model-specific aspects of bias in economic evaluation										
												I ¹			II ²							III ³
	Narrow perspective bias	Inefficient comparator bias [*]	Cost measurement omission bias	Intermittent data collection bias	Invalid valuation bias	Ordinal ICER bias	Double-counting bias	Inappropriate discounting bias	Limited sensitivity analysis bias [§]	Sponsor bias	Reporting and dissemination bias	Structural assumptions bias	N treatment comparator bias [*]	Wrong model bias	Limited time horizon bias	Bias related to data identification	Bias related to baseline data	Bias related to treatment effects	Bias related to quality-of-life weights (utilities)	Non-transparent data incorporation bias	Limited to scope bias	Bias related to internal consistency
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
De Jong LA, 2019 ¹¹⁶	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
de Pourville G, 2019 ¹¹⁷	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Taborsky M, 2019 ¹¹⁸	N	Y	Y	Y	Y	Y	N	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N

Abbreviations: N, No-high risk of bias; Y, Yes—low risk of bias; P, Partly bias; NA, Not Available.

¹ the bias related to structure

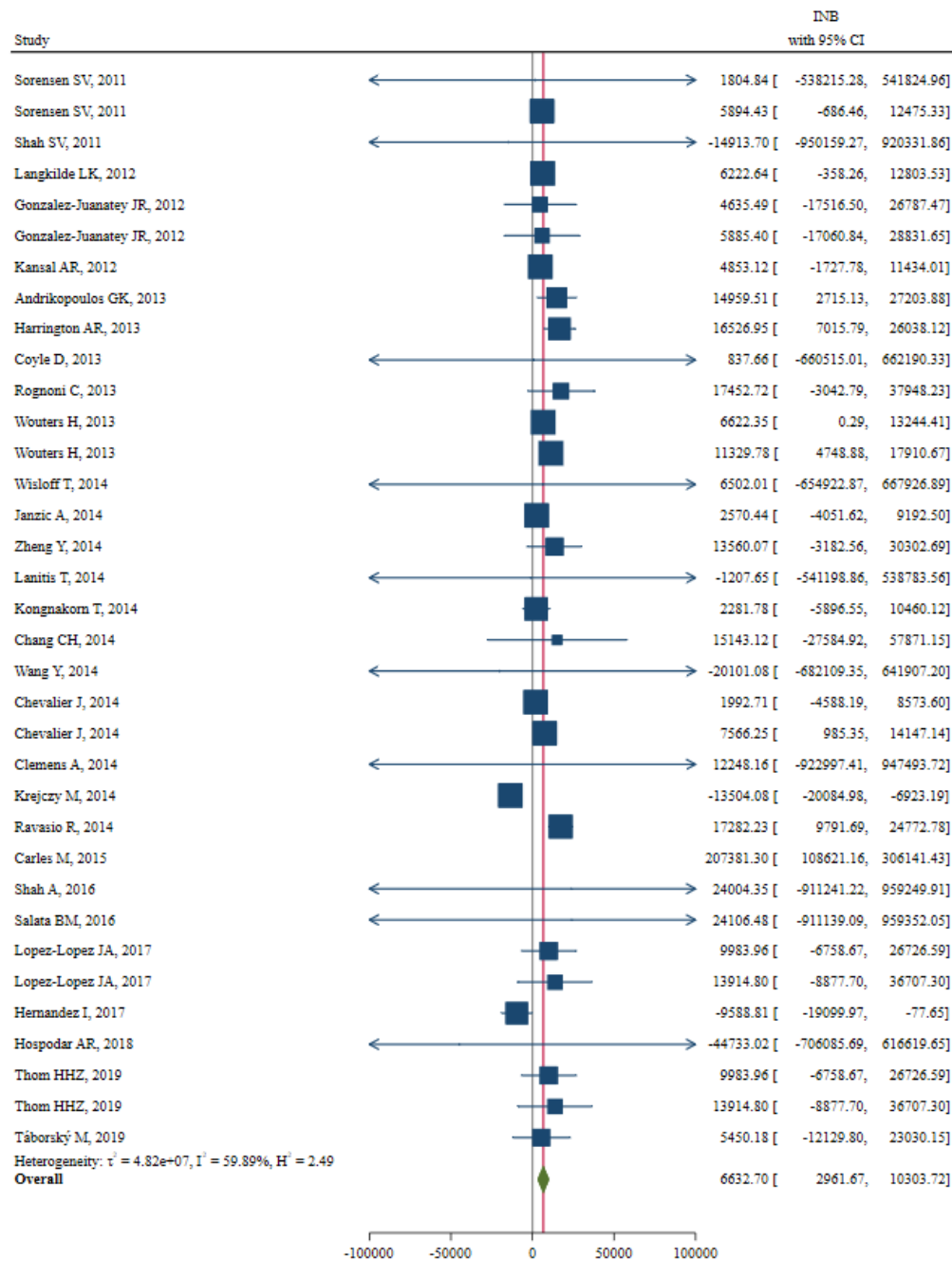
² the bias related to data

³ the bias related to consistency

Appendix 4 Results of meta-analyses: Dabigatran and Vitamin K Antagonists (VKAs)

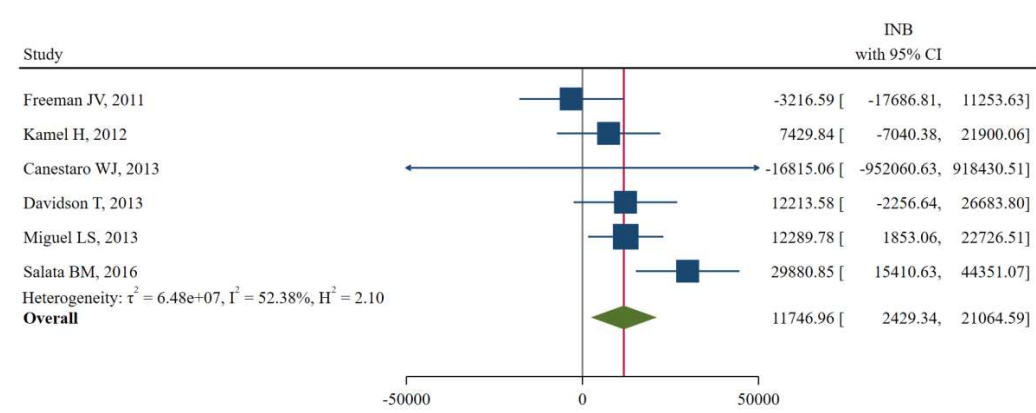
A) Pooling INBs

eFigure 4.1 Pooling INBs comparing Dabigatran with VKAs in HICs estimated by Markov model, lifetime horizon and TPP. (Created by the authors)



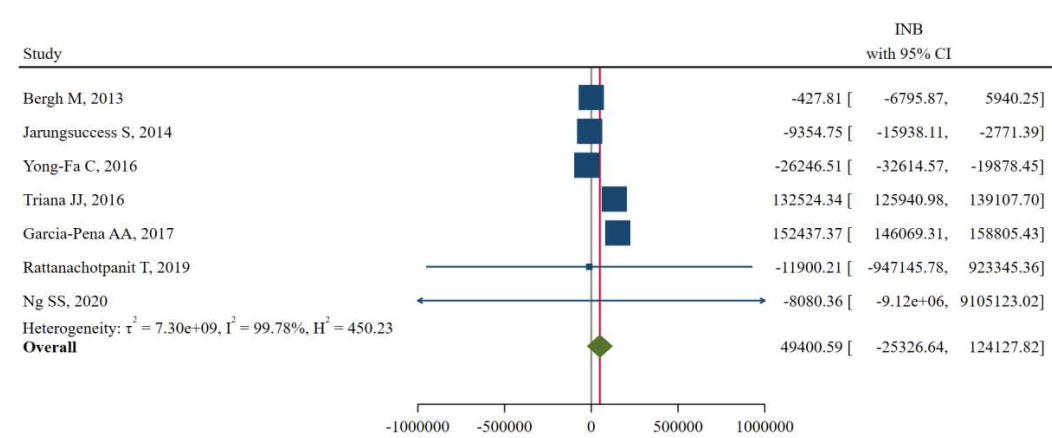
Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; HICs, High-Income Countries; TPP, Third-party payer perspective.

eFigure 4.2 Pooling INBs comparing Dabigatran with VKAs in HICs estimated by Markov model, lifetime horizon and SP. (Created by the authors)



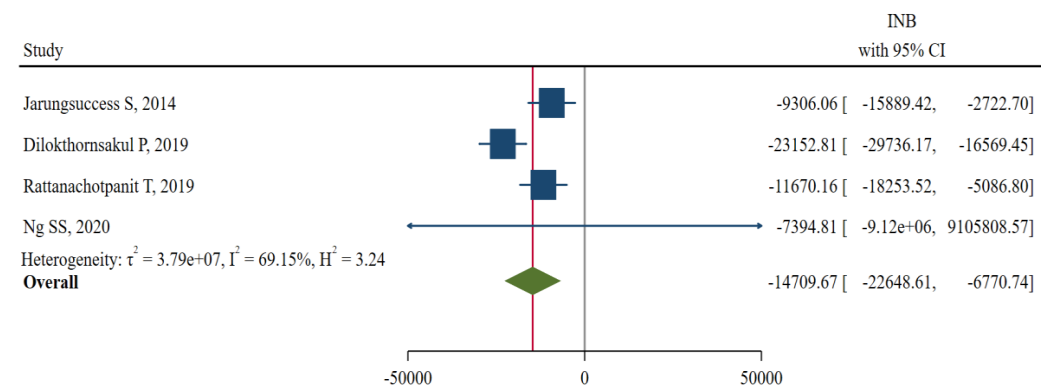
Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; HICs, High-Income Countries; SP, Societal perspective.

eFigure 4.3 Pooling INBs comparing Dabigatran with VKAs in UMICs estimated by Markov model, lifetime horizon and TPP. (Created by the authors)



Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; UMICs, Upper Middle-Income Countries; TPP, Third-party payer perspective.

eFigure 4.4 Pooling INBs comparing Dabigatran with VKAs in UMICs estimated by Markov model, lifetime horizon and SP. (Created by the authors)



Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; UMICs, Upper Middle-Income Countries; SP, Societal perspective.

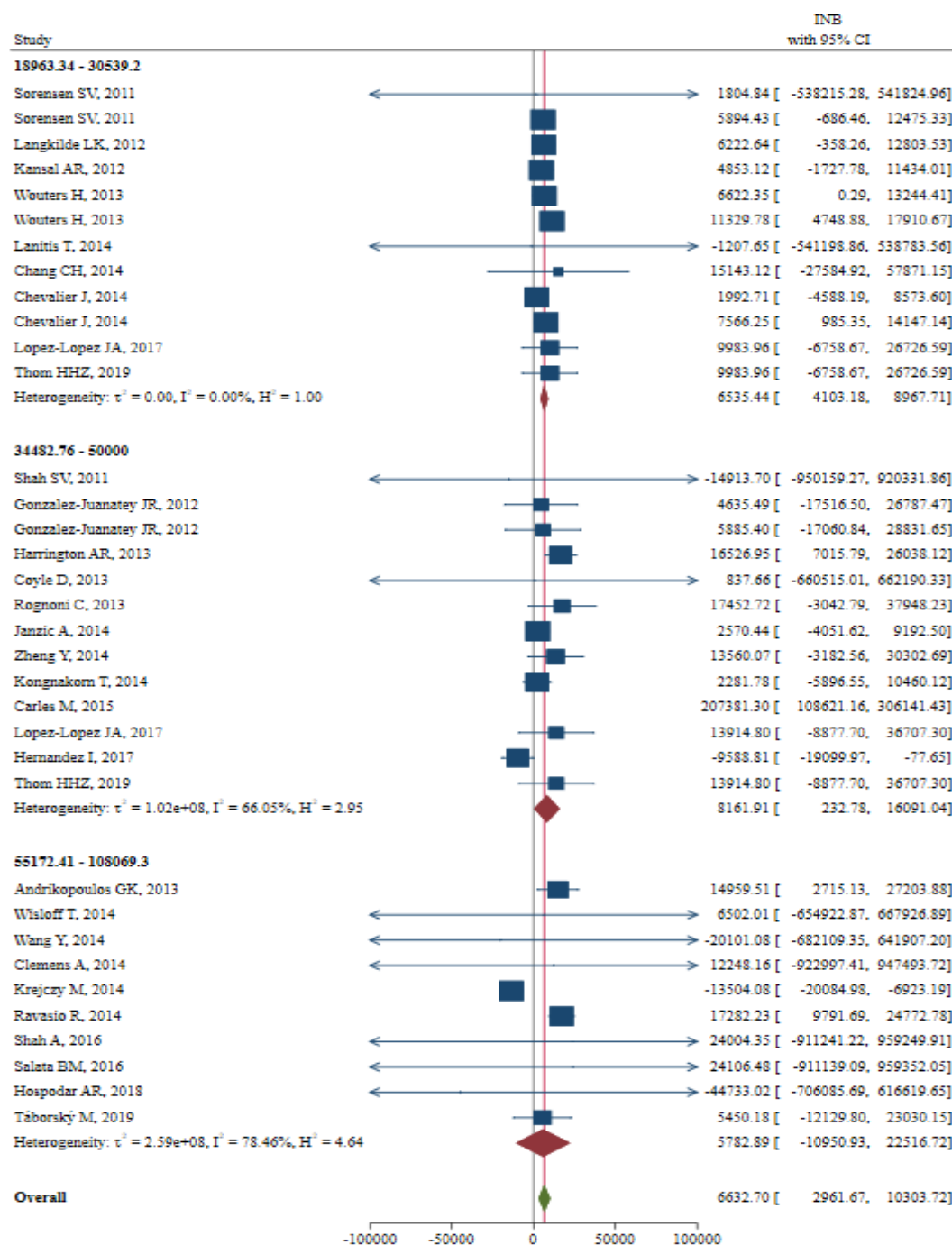
B) Meta-regression analysis**eTable 4.1 Exploring sources of heterogeneity by a meta-regression analysis.** (Created by the authors)

Factors	Coefficient	SE	P-value	I ² (%)
Dabigatran vs VKAs in HICs Markov-TPP-LT				
Model without factors	6,632.695	1,873.005	0.001	59.89
WTP Threshold				
18,963.34-30,539.2 vs >50,000	303.4636	4,365.701	0.945	60.92
34,482.76-50,000 vs >50,000	-1,828.197	5,370.961	0.736	
Discount cost				
≥3% vs <3%	-1,541.342	4,002.778	0.703	61.02
Discount utility				
≥3% vs <3%	-1,541.342	4,002.778	0.703	61.02
Clinical data source				
PL Evidence Synthesis vs PL	5,208.721	8,893.681	0.562	61.81
PL Registry database vs PL	8,760.234	23,161.07	0.708	61.81
Funding source				
Pharma-grant vs no data	7,222.606	3,850.02	0.070	51.89
Non-pharma-grant vs no data	10,405.1	6,655.359	0.128	
Dabigatran vs VKAs in HICs Markov SP LT				
Model without factors	11,746.96	4,753.977	0.056	52.38
WTP Threshold				
50,704.23-100,000 vs < 50,704.23	14,627.96	8,058.964	0.144	30.72
Discount cost				
≥3% vs <3%	718.2315	13,759.11	0.961	61.86
Discount utility				
≥3% vs <3%	718.2315	13,759.11	0.961	61.86
Dabigatran vs VKAs in UMICs Markov TPP LT				
Model without factors	49,400.59	38,126.84	0.243	99.78

Factors	Coefficient	SE	P-value	I ² (%)
WTP Threshold				
43,695.49-770,414.2 vs 12959.5-18498.4	91,224.38	73,396.51	0.269	99.72
Discount cost				
≥3% vs <3%	-34,678.48	86,468.17	0.705	99.80
Discount utility				
≥3% vs <3%	-3,606.83	104,057.4	0.974	99.80
Clinical data source				
PL-Evidence synthesis vs PL	-50,572.68	111,273.6	0.673	99.77
Registry database vs PL	91,306.41	111,273.6	0.458	99.77
Utility data source				
PL-Registry database vs PL	-61,682.35	486,276.7	0.904	99.81
Grant source				
Pharma-grant vs No data	27,106.04	89,094.74	0.776	99.85
Non-pharma-grant vs No data	-50,839.9	490,291.6	0.922	99.85

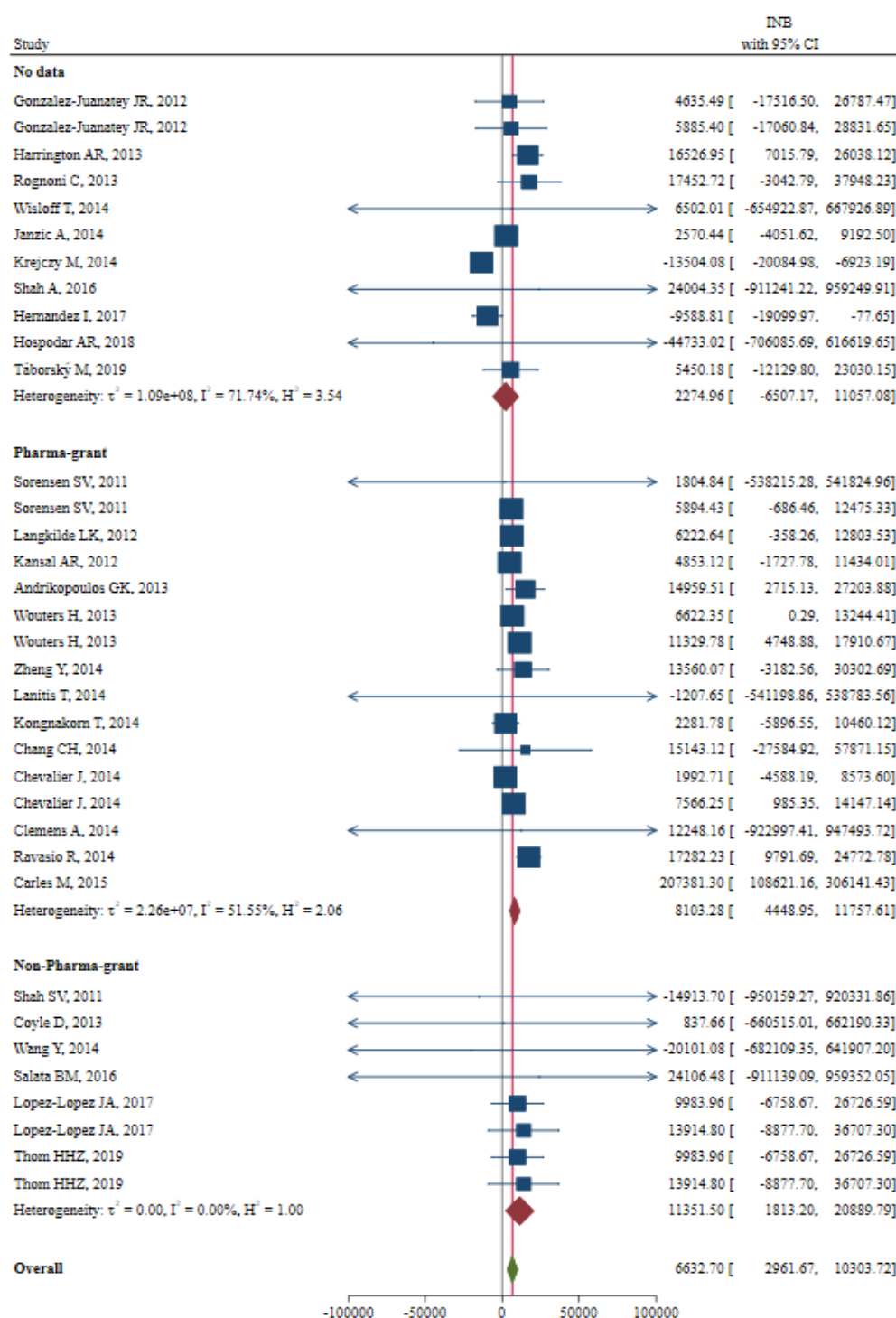
Abbreviations: HICs, High-Income Countries; LT, lifetime; PL, Published Literature; SE, Standard Error; SP, Societal Perspective; TPP, Third-party payer perspective; UMICs, Upper Middle-Income Countries; VKAs, Vitamin K Antagonists, VS, versus; WTP, Willingness-to-Pay.

C) Sub-group Analysis

Figure 4.5 Sub-group analysis by threshold of INB comparing Dabigatran with VKAs that estimated by Markov models with lifetime horizon and TPP in HICs. (Created by the authors)

Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; HICs, High-Income Countries; TPP, Third-party payer perspective.

eFigure 4.6 Sub-group analysis by grant source of INB comparing Dabigatran with VKAs that estimated by Markov models with lifetime horizon and TPP in HICs. (Created by the authors)



Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; HICs, High-Income Countries; TPP, Third-party payer perspective.

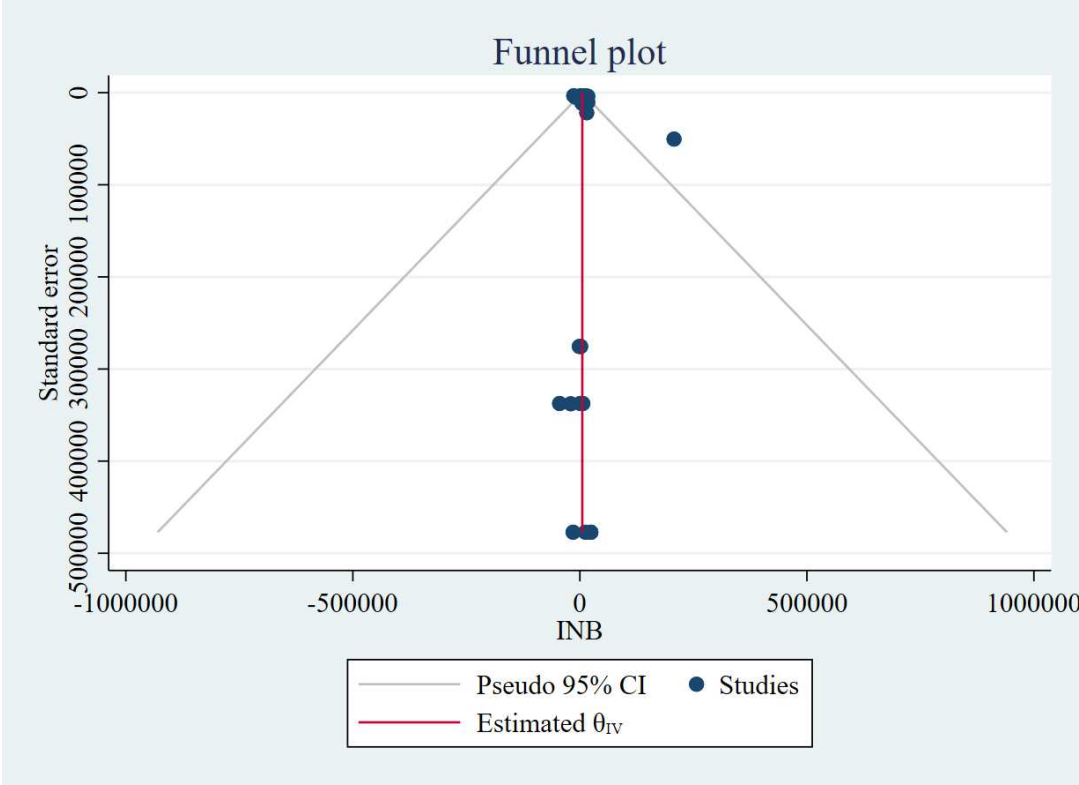
D) Publication Bias

Publication bias was assessed in each group of studies compared Dabigatran versus VKAs with similar in the level of country’s income, Markov model, perspectives used and lifetime horizon, yielded the results:

High-income countries (HICs)

Assessment for the evidence of publication bias of those studies in HICs with Markov model, lifetime horizon and perspectives indicated a symmetry of the funnel plot (eFigure 4.7) as well as the Egger’s test resulted coefficient=0.42, SE=0.27, p=0.130 in HICs with Markov model, lifetime horizon in TPP.

eFigure 4.7 Funnel plot comparing Dabigatran with VKAs that estimated by Markov models with lifetime horizon and TPP in HICs. (Created by the authors)

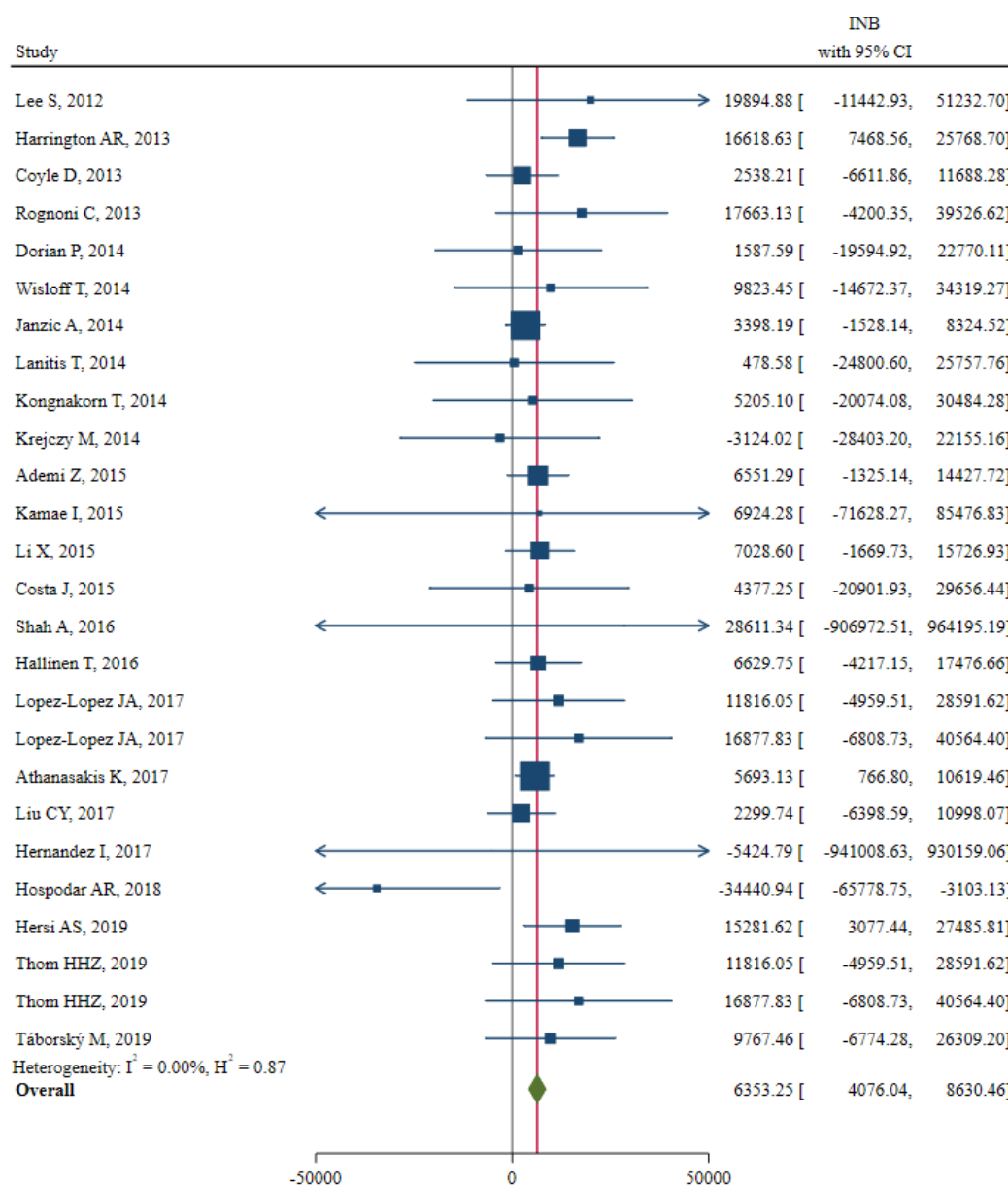


Abbreviations: VKAs, Vitamin K Antagonists; HICs, High-Income Countries; TPP, Third-party payer perspective.

Appendix 5 Results of meta-analyses: Apixaban and Vitamin K Antagonists (VKAs)

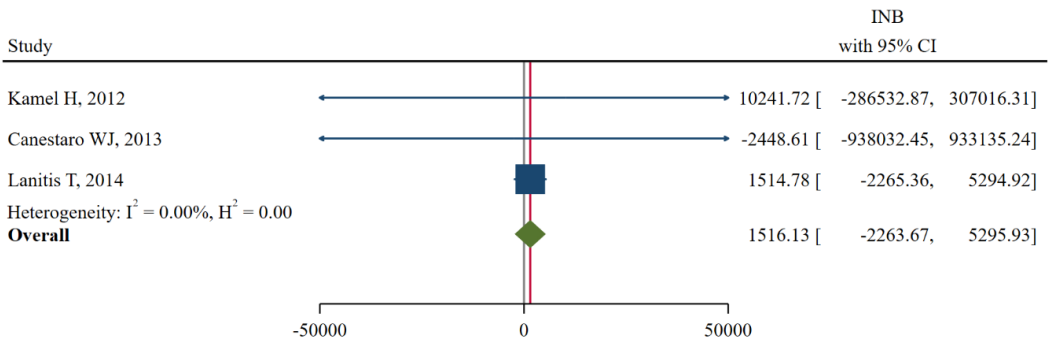
A) Pooling INB

eFigure 5.1 Pooling INBs comparing Apixaban with VKAs in HICs estimated by Markov model, lifetime horizon and TPP. (Created by the authors)



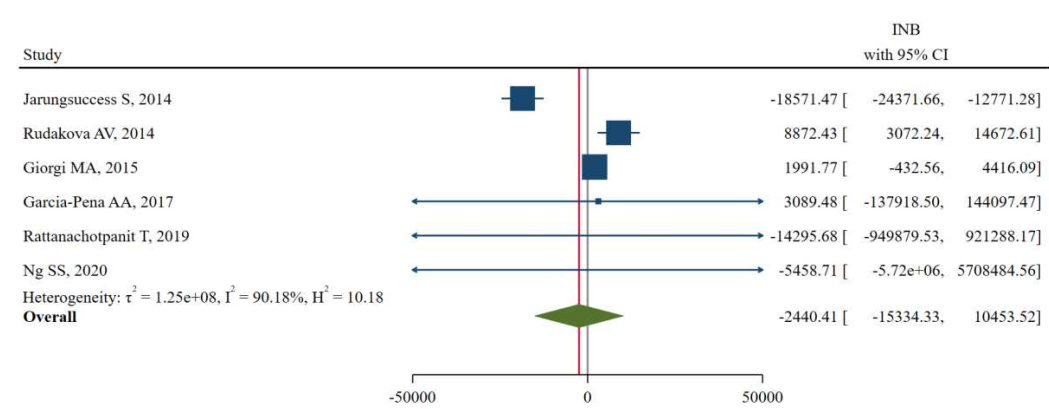
Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; HICs, High-Income Countries; TPP, Third-party payer perspective.

eFigure 5.2 Pooling INBs comparing Apixaban with VKAs in HICs estimated by Markov model, lifetime horizon and SP. (Created by the authors)



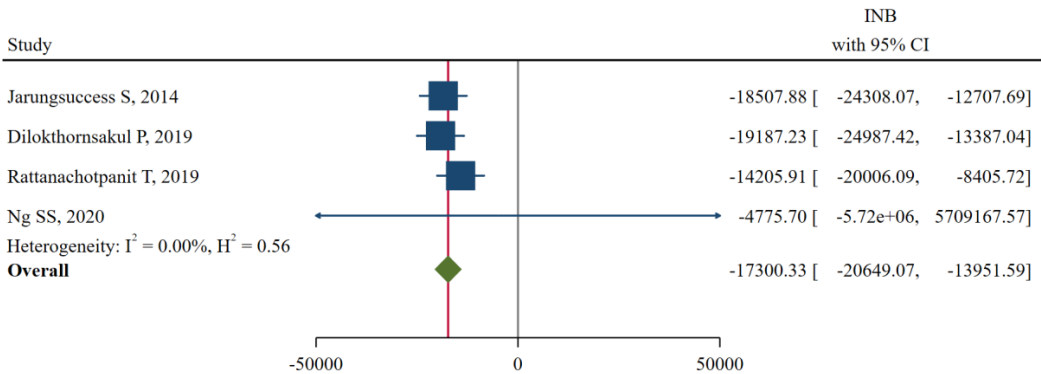
Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; HICs, High-Income Countries; SP, Societal perspective.

eFigure 5.3 Pooling INBs comparing Apixaban with VKAs in UMICs estimated by Markov model, lifetime horizon and TPP. (Created by the authors)



Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; UMICs, Upper Middle-Income Countries; TPP, Third-party payer perspective.

eFigure 5.4 Pooling INBs comparing Apixaban with VKAs in UMICs estimated by Markov model, lifetime horizon and SP. (Created by the authors)



Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; UMICs, Upper Middle-Income Countries; SP, Societal perspective.

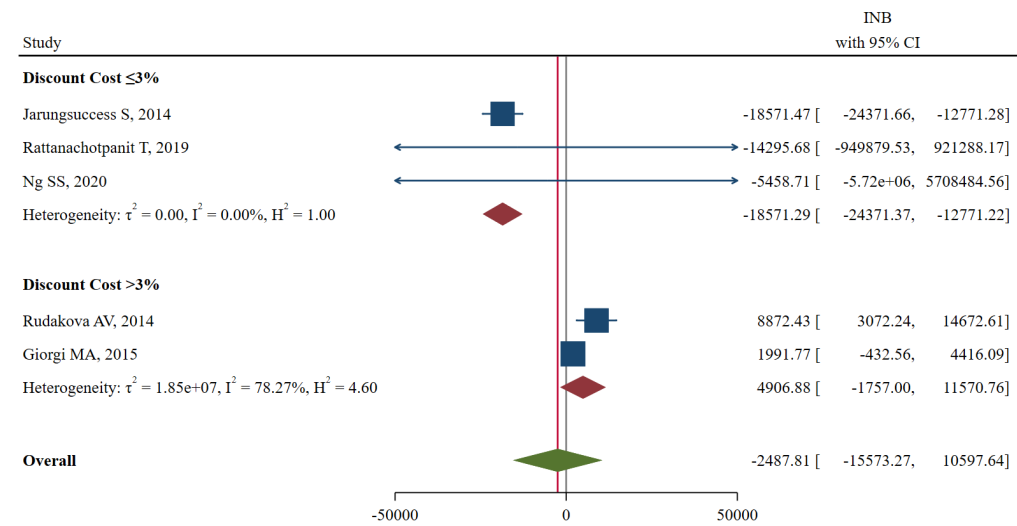
B) Meta-regression analysis**eTable 5.1 Exploring source of heterogeneity using a meta-regression analysis.** (Created by the authors)

Factors	Coefficient	SE	P-value	I ² (%)
Apixaban vs VKAs in UMICs M TPP LT				
Model without factors	-2,440.41	6,578.654	0.726	90.18
WTP Threshold in USD				
16,389.31-770,414.2 vs 12424.11-16285.37	16,745.97	17,022.31	0.381	90.27
Discount cost				
≥3% vs <3%	22,522.73	3,985.208	0.005	14.76
Discount utility				
≥3% vs <3%	22,522.73	3,985.208	0.005	14.76
Clinical data source				
PL-Evidence synthesis vs PL	-22,494.21	3,896.37	0.004	13.11
Utility data source				
PL-Registry database vs PL	-11,856.68	477,527.1	0.981	92.15

Abbreviations: HICs, High-Income Countries; LT, lifetime; PL, Published Literature; SE, Standard Error; SP, Societal Perspective; TPP, Third-party payer perspective; UMICs, Upper Middle-Income Countries; VKAs, Vitamin K Antagonists, VS, versus; WTP, Willingness-to-Pay.

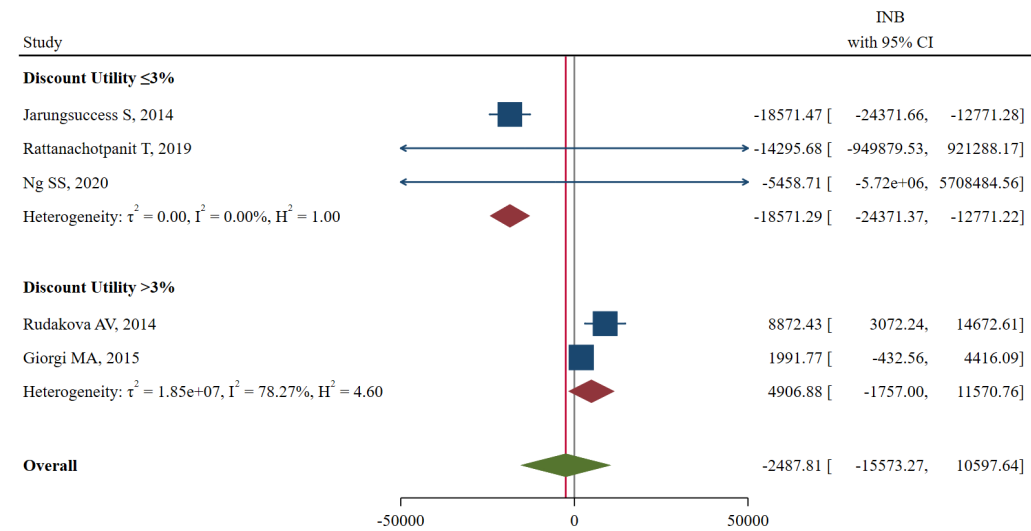
C) Sub-group Analysis

eFigure 5.5 Sub-group analysis by discount cost of INB comparing Apixaban with VKAs that estimated by Markov models with lifetime horizon and TPP in UMICs. (Created by the authors)



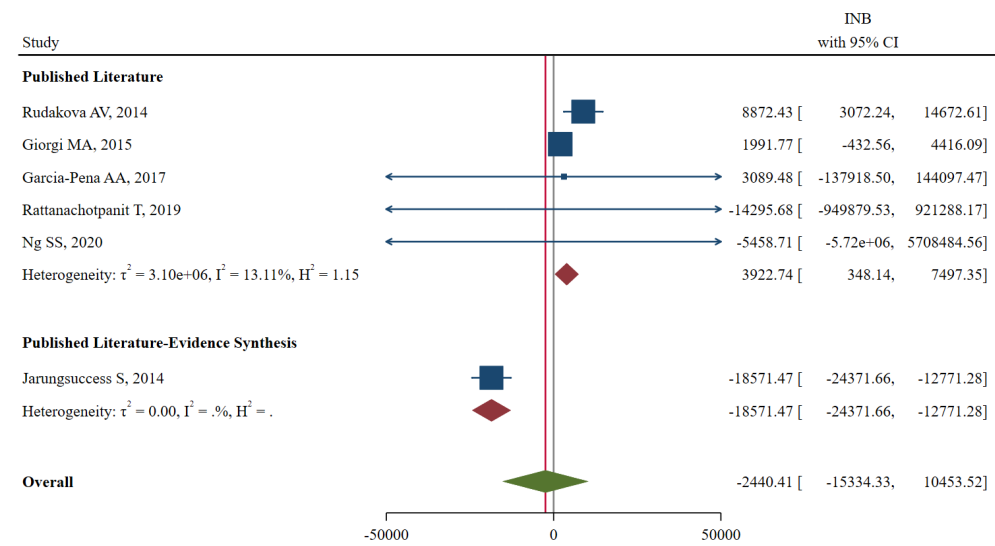
Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; UMICs, Upper Middle-Income Countries; TPP, Third-party payer perspective.

eFigure 5.6 Sub-group analysis by discount utility of INB comparing Apixaban with VKAs that estimated by Markov models with lifetime horizon and TPP in UMICs. (Created by the authors)



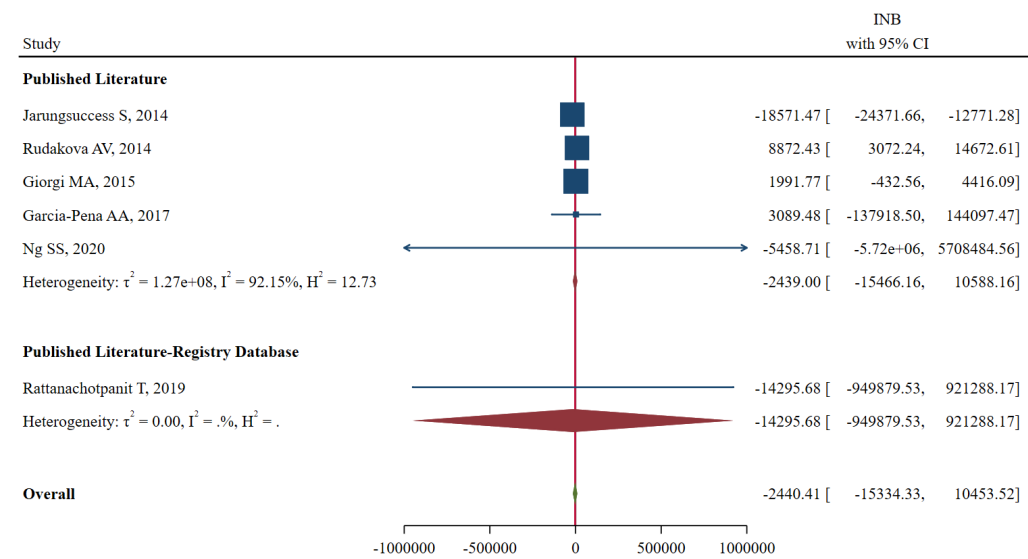
Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; UMICs, Upper Middle-Income Countries; TPP, Third-party payer perspective.

eFigure 5.7 Sub-group analysis by clinical data source of INB comparing Apixaban with VKAs that estimated by Markov models with lifetime horizon and TPP in UMICs. (Created by the authors)



Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; UMICs, Upper Middle-Income Countries; TPP, Third-party payer perspective.

eFigure 5.8 Sub-group analysis by utility data source of INB comparing Apixaban with VKAs that estimated by Markov models with lifetime horizon and TPP in UMICs. (Created by the authors)



Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; UMICs, Upper Middle-Income Countries; TPP, Third-party payer perspective.

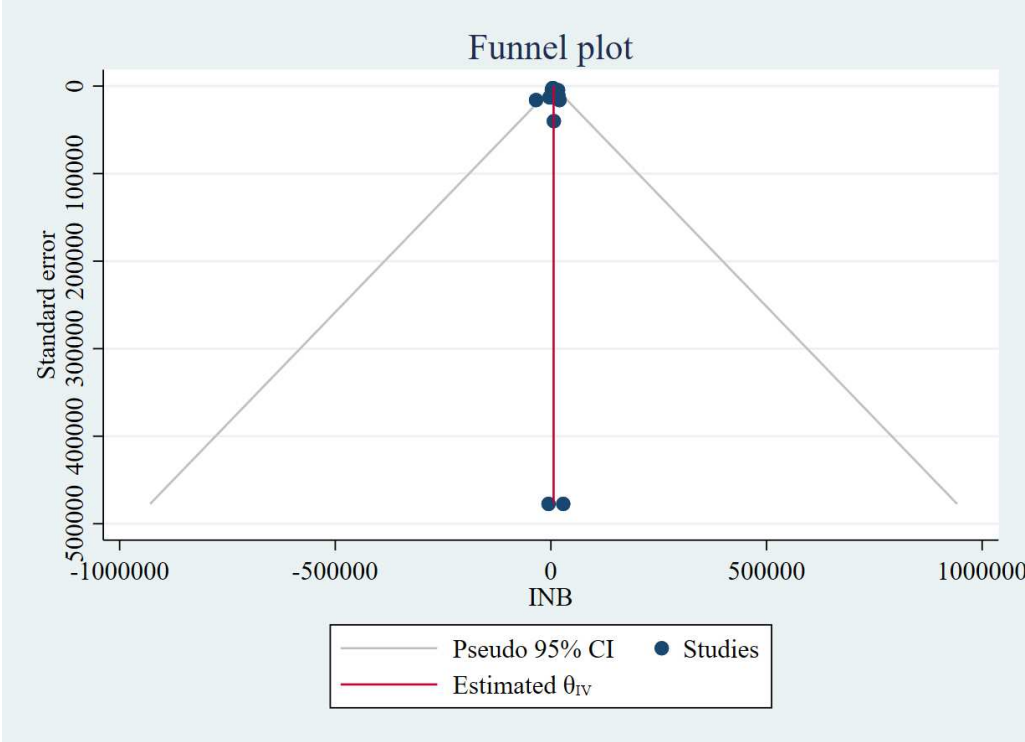
D) Publication Bias

Publication bias was assessed in each group of studies compared apixaban versus VKAs with similar in the level of country’s income, Markov model, perspectives used and lifetime horizon, yielded the results:

High Income Countries (HICs)

Assessment for the evidence of the publication bias of those studies in HICs with Markov, lifetime and perspectives indicated a symmetry of the funnel plot (eFigure 5.9) as well as the Egger’s test resulted coefficient= 0.20, SE=0.33, p=0.538 in HICs with Markov lifetime with TPP.

eFigure 5.9 Funnel plot comparing Apixaban with VKAs that estimated by Markov models with lifetime horizon and TPP in HICs. (Created by the authors)

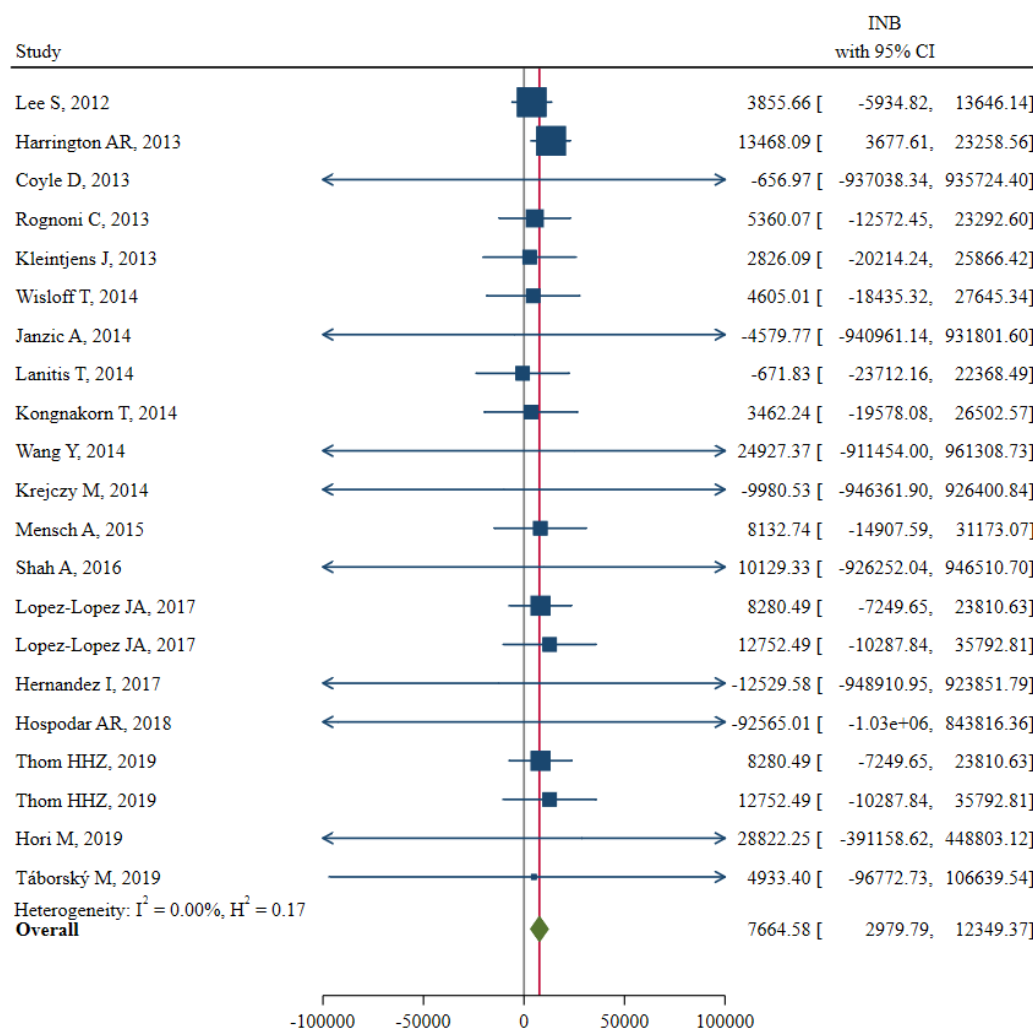


Abbreviations: VKAs, Vitamin K Antagonists; HICs, High-Income Countries; TPP, Third-party payer perspective.

Appendix 6 Results of meta-analyses: Rivaroxaban and Vitamin K Antagonists (VKAs)

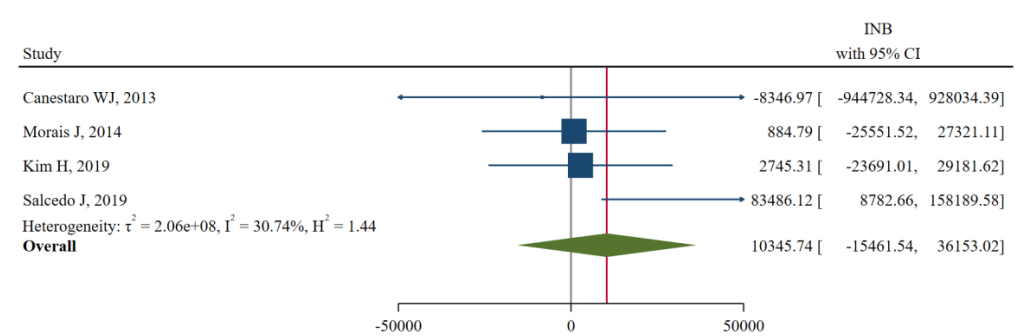
A) Pooling INB

eFigure 6.1 Pooling INBs comparing Rivaroxaban with VKAs in HICs estimated by Markov model, lifetime horizon, and TPP. (Created by the authors)



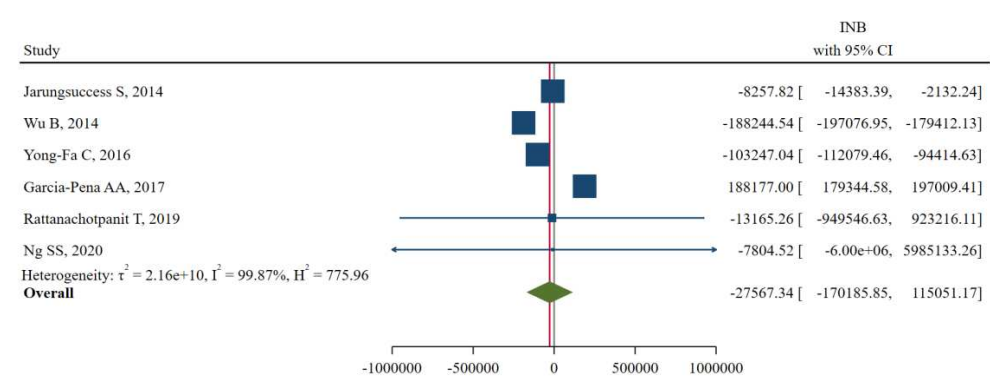
Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; HICs, High-Income Countries; TPP, Third-party payer perspective.

eFigure 6.2 Pooling INBs comparing Rivaroxaban with VKAs in HICs estimated by Markov model, lifetime horizon, and SP. (Created by the authors)



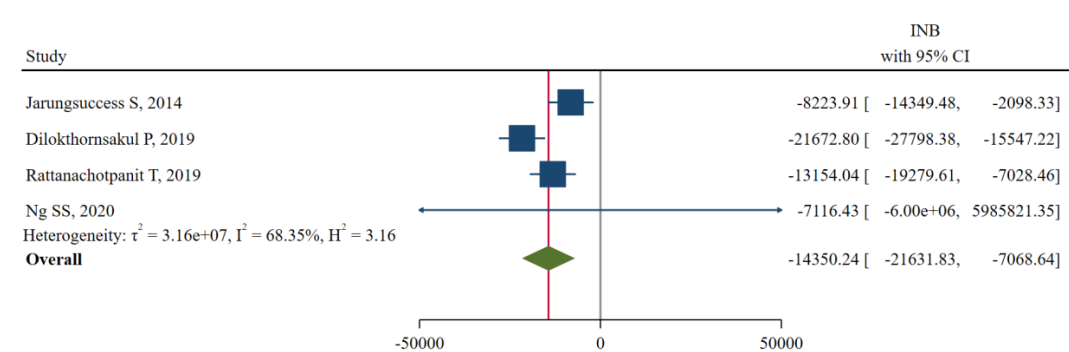
Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; HICs, High-Income Countries; SP, Societal perspective.

eFigure 6.3 Pooling INBs comparing Rivaroxaban with VKAs in UMICs estimated by Markov model, lifetime horizon, and TPP. (Created by the authors)



Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; UMICs, Upper Middle-Income Countries; TPP, Third-party payer perspective.

eFigure 6.4 Pooling INBs comparing Rivaroxaban with VKAs in UMICs estimated by Markov model, lifetime horizon, and SP. (Created by the authors)



Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; UMICs, Upper Middle-Income Countries; SP, Societal perspective.

B) Meta-regression analysis**eTable 6.1 Exploring source of heterogeneity by a meta-regression analysis.** (Created by the authors)

Factors	Coefficient	SE	P-value	I ² (%)
Rivaroxaban vs VKAs in UMICs M TPP LT				
Model without factor	-27,567.34	72,765.88	0.720	99.87
WTP Threshold				
34,210.87-770,414.2 vs 12959.46-16389.31	-25,560.01	216,442.7	0.912	99.90
Clinical data source				
PL-Evidence synthesis vs PL	25,160.73	226,510.4	0.917	99.90
Utility data source				
PL-Registry database vs PL	14,713.85	505,271.6	0.978	99.90

Abbreviations: HICs, High-Income Countries; LT, lifetime; PL, Published Literature; SE, Standard Error; SP, Societal Perspective; TPP, Third-party payer perspective; UMICs, Upper Middle-Income Countries; VKAs, Vitamin K Antagonists, VS, versus; WTP, Willingness-to-Pay.

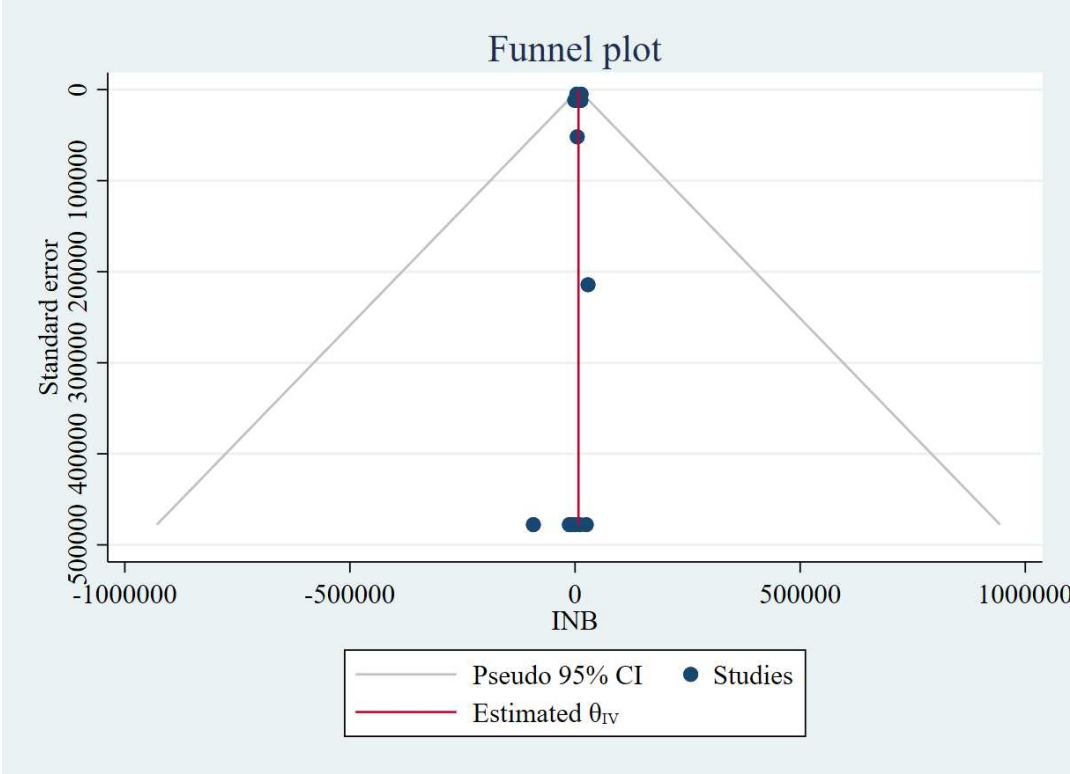
C) Publication Bias

Publication bias was assessed in each group of studies compared rivaroxaban versus VKAs with similar in the level of country’s income, Markov model, perspectives used and lifetime horizon, yielded the results:

High-Income Countries (HICs)

Assessment for the evidence of publication bias of those studies in HICs with Markov, lifetime and perspectives indicated a symmetry of the funnel plot as well as the (eFigure 6.5) as well as the Egger’s test resulted coefficient=-0.08, SE=0.32, p=0.805 in HICs and Markov model, lifetime horizon with TPP.

eFigure 6.5 Funnel plot comparing Rivaroxaban with VKAs that estimated by Markov models with lifetime horizon and TPP in HICs. (Created by the authors)

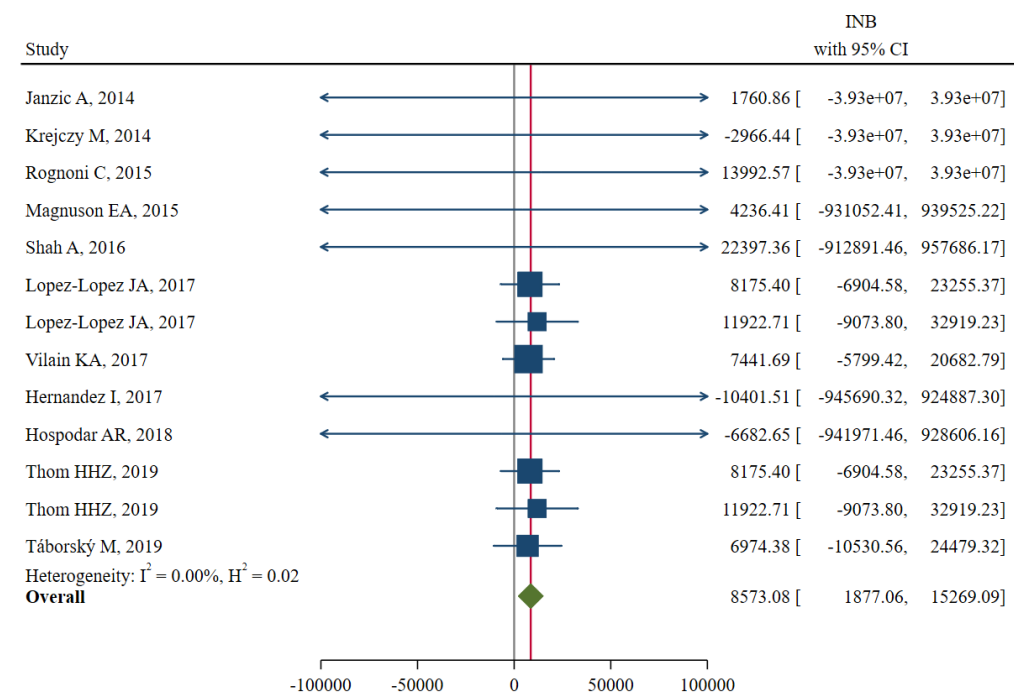


Abbreviations: VKAs, Vitamin K Antagonists; HICs, High-Income Countries; TPP, Third-party payer perspective.

Appendix 7 Results of meta-analyses: Edoxaban and Vitamin K Antagonists (VKAs)

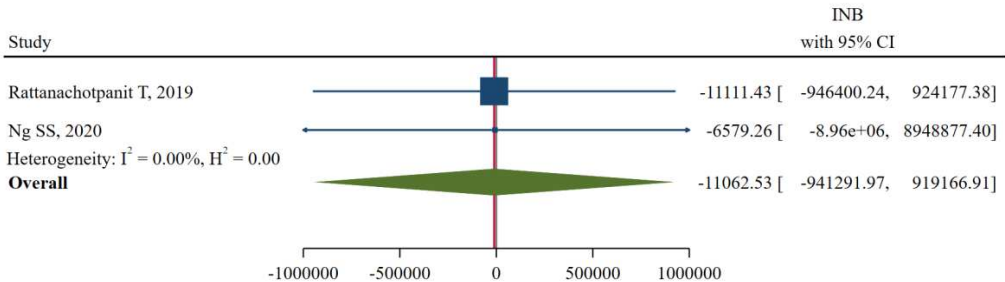
A) Pooling INB

eFigure 7.1 Pooling INBs comparing Edoxaban with VKAs in HICs estimated by Markov model, lifetime horizon, and TPP. (Created by the authors)



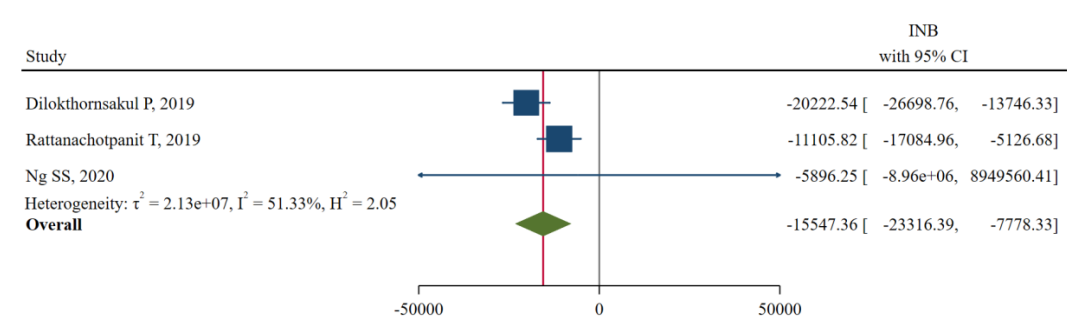
Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; HICs, High-Income Countries; TPP, Third-party payer perspective.

eFigure 7.2 Pooling INBs comparing Edoxaban with VKAs in UMICs estimated by Markov model, lifetime horizon, and TPP. (Created by the authors)



Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; UMICs, Upper Middle-Income Countries; TPP, Third-party payer perspective.

eFigure 7.3 Pooling INBs comparing Edoxaban with VKAs in UMICs estimated by Markov model, lifetime horizon, and SP. (Created by the authors)



Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; UMICs, Upper Middle-Income Countries; SP, Societal perspective.

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