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Economic evaluation of direct oral anticoagulants (DOACs) versus vitamin K antagonists (VKAs) for stroke prevention in patients with atrial fibrillation: a systematic review and meta-analysis

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Abstract

Objectives To assess cost-effectiveness of direct oral anticoagulants (DOACs) compared with vitamin K antagonists (VKAs) for stroke prevention in atrial fibrillation (AF) by pooling incremental net benefits (INBs).

Design Systematic review and meta-analysis.

Setting We searched PubMed, Scopus and Centre for Evaluation of Value and Risks in Health Registry from inception to December 2019.

Participants Patients with AF.

Main outcome measures The INB was defined as a difference of incremental effectiveness multiplied by willing to pay threshold minus the incremental cost; a positive INB indicated favour treatment. These INBs were pooled (stratified by level of country income, perspective, time-horizon, model types) with a random-effects model if heterogeneity existed, otherwise a fixed effects model was applied. Heterogeneity was assessed using Q test and I^2 statistic. Risk of bias was assessed using the economic evaluations bias (ECOBIAS) checklist.

Results A total of 100 eligible economic evaluation studies (224 comparisons) were included. For high-income countries (HICs) from a third-party payer (TPP) perspective, the pooled INBs for DOAC versus VKA pairs were significantly cost-effective with INBs (95% CI) of $6632 ($2961.67 to $10 303.72; I^2=59.9%), $6353.24 ($4076.03 to $8630.45; I^2=0%), $7664.58 ($2979.79 to $12 349.37; I^2=0%) and $8573.07 ($1877.05 to $15 269.09; I^2=0%) for dabigatran, apixaban, rivaroxaban and edoxaban relative to VKA, respectively but only dabigatran was significantly cost-effective from societal perspective (SP) with an INB of $11 746.96 ($2429.34 to $21 064.59; I^2=52.4%). The pooled INBs of all comparisons for upper-middle income countries (UMICs) were not significantly cost-effective. The ECOBIAS checklist indicated that risk of bias was mostly low for most items with the exception of five items which should be less influenced on pooling INBs.

Conclusions Our meta-analysis provides comprehensive economic evidence that allows policy makers to generalise cost-effectiveness data to their local context. All DOACs may be cost-effective compared with VKA in HICs with TPP perspective. The pooling results produced moderate to high heterogeneity particularly in UMICs. Further studies are required to inform UMICs with SP.

Summary box

What is already known about this subject?

- A large number of economic evaluation studies on direct acting oral anticoagulants (DOACs) and vitamin K antagonists (VKAs) were conducted in various healthcare settings to guide health policy makers in relation to reimbursement of DOACs.
- The previous systematic reviews that compared DOACs with VKAs for stroke prevention in atrial fibrillation did not provide an overall quantitative synthesis.

What are the new findings?

- This is the first quantitative meta-analysis of 100 economic evaluations (that included 144 comparisons) of all four DOACs with VKAs applying pooled incremental net benefit.
- Our findings indicated that DOACs might be significantly more cost-effective than VKAs in high-income countries using a third-party payer perspective while no DOACs were more cost-effective in upper-middle income countries (UMICs), regardless of any perspective was used.
- We found that country socioeconomic status and the methodological approach used potentially influenced the cost-effectiveness of DOACs compared with VKAs.

Summary box

How might it impact clinical practice in the foreseeable future?

- While clinical efficacy and safety of DOACs over VKAs are established, these agents, at their current pricing, are cost-effective only in high -income countries but not in UMICs due partly to the lower socioeconomic status and the small number of studies available.
- Policy makers and pharmaceutical companies should together consider potential pathways to increase access to these useful agents by considering the impact of socioeconomic status on the cost-effectiveness for UMICs and potentially low-income and middle-income countries.

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Introduction

Atrial fibrillation (AF), the most common cardiac arrhythmia,[1] is an important global health issue[2 3] with an incidence of 596.2 cases/100 000 population in the Global Burden of Disease Study.[3] Recent projections based on various national databases suggest that the incidence has doubled or tripled in the past decade.[4–6] Complications of AF, particularly stroke, lead to significant morbidity and mortality.[2 3] Disability-adjusted life years (DALYs) lost due to AF have increased almost linearly during the past 20 years, with a current global estimate of 5·98 million DALYs lost in 2017 alone.[2]

Oral anticoagulants such as vitamin K antagonists (VKAs, eg, warfarin) and direct oral anticoagulants (DOACs) are the cornerstone of stroke prevention in AF.[7] VKAs have several limitations including the need for frequent monitoring as a consequence of numerous drug interactions.[7] DOACs (ie, dabigatran, rivaroxaban, apixaban and edoxaban) were developed to reduce these limitations. Data from controlled trials and real-world studies suggest that DOACs are non-inferior to VKAs and have some advantages[8 9] which has led to their recommendation over VKAs in the AF guidelines of many developed countries.[1 10]

Multiple cost-effectiveness studies have compared DOACs with VKAs in various healthcare settings to inform health policy including five systematic reviews (SRs) of economic evaluations.[11–15] However, none have provided an overall quantitative synthesis of their findings. Recently, SR and meta-analysis (SR–MA) of economic outcomes have been performed by converting incremental cost–effectiveness ratio (ICER) to incremental net benefit (INB), and then pooling across studies.[16–18] The ICER, estimated by dividing incremental cost with incremental effectiveness, could be interpreted that the intervention is said to be cost-effective if it is lower than the willingness to pay (WTP) threshold. However, the ICER is controversial in some state, that is, a negative ICER may be due to a lower cost but higher effectiveness, or higher cost along with lower effectiveness of the intervention. Therefore, Crespo *et al*[16] had suggested pooling the INB across studies, defined as a difference of incremental effectiveness multiplied by WTP threshold minus the incremental cost, which could be directly interpreted, that is, a positive INB indicated favour the intervention. This quantitative synthesis requires stratification by economic factors (eg, level of country income, time horizon, perspective, economic models and so on) to minimise heterogeneity.[17 18] This SR-MA summarises the cost-effectiveness of individual DOACs compared with VKAs for stroke prevention in patients with AF to inform policy decisions in countries with limited resources.

Methods

This SR-MA was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 statement and the review protocol was registered at PROSPERO.[19]

Data sources and search strategy

We performed a comprehensive search in PubMed, Scopus and Centre for Evaluation of Value and Risks in Health (CEVR) databases from inception to 7 December 2019, see online supplemental appendix 1. Studies were selected if they met the following criteria included patients with AF, primarily/secondarily aimed to compare VKAs (ie, warfarin or acenocoumarol or phenprocoumon or coumarin) with DOACs (ie, dabigatran, apixaban, rivaroxaban and edoxaban), and reported ICER, quality-adjusted life years (QALYs) or INB. Studies were excluded if they provided insufficient data for synthesis.

Data extraction

Two investigators (RN and BSB) independently extracted data. Disagreement was resolved in consultation with senior authors (SY and AT). Extracted data included study characteristics, study population, interventions, economic data (ie, perspective, WTP threshold or gross domestic product estimates from the World Bank according to the study year, time-horizon, currency, economic model) and findings. In addition, data for pooling were also extracted including mean cost, incremental cost, clinical effectiveness, incremental effectiveness and ICERs together with SE, or 95% CI. Incremental costs and effectiveness were also extracted from the cost-effective plane using Web-Plot-Digitizer software V.4.2.[20 21]

Risk of bias

We assessed risk of bias for included studies using the economic evaluations bias (ECOBIAS) checklist.[22] The first part evaluated the overall bias which consisted of the following 11 items: narrow perspective, inefficient comparator, cost measurement omission, intermittent data collection, invalid valuation, ordinal ICER, double-counting, inappropriate discounting, limited sensitivity analysis, sponsor and reporting/dissemination. The second part specifically evaluated risk of bias of the model specifications in economic evaluations consisting of three subdomains, that is, structure of the model (four items), data (six items) and consistency (one item). Each item was graded as yes, no, partly, unclear or not applicable, where yes and no referred to high and low risk of bias, respectively.

Data analysis

The primary outcome of interest was INB. Economic data were harmonised by converting all currency data using purchasing power parity for the year 2019.[23] In addition, different scenarios were applied to estimate INB and its variance based on the methods suggested by Crespo *et al*[16] (as follows: $\mathrm{INB} = \mathrm{K} \times \Delta\mathrm{E} - \Delta\mathrm{C}$, or $\mathrm{INB} = \Delta\mathrm{E} \times (\mathrm{K} - \mathrm{ICER})$ where K is the WTP threshold, ΔC the incremental cost, ΔE the incremental effectiveness, ICER the incremental cost and incremental effectiveness ratio), and our expanded methods are published previously,[17 18] see online

supplemental appendix 2. A positive INB indicated favouring treatment (ie, intervention is cost-effective), whereas a negative INB indicated favouring comparator (ie, intervention is not cost-effective).[16 24 25] Heterogeneity was assessed using the Cochrane-Q test and I^2 statistic and considered present if I^2 ≥25% or if the p value was <0.1. The INBs were pooled across studies, stratified by country income (classified by the World Bank),[20] time-horizon, economic model and perspective, using a random-effects model (Der Simonian and Laird method) if heterogeneity was present, or an inverse-variance model if not.[26]

Meta-regression, sensitivity or subgroup analyses were undertaken to explore sources of heterogeneity such as discount rate, WTP threshold, data source and funding source. Publication bias was assessed using Egger's test and funnel plots where number of studies/comparisons was 10 or more. Where a funnel plot was asymmetrical, a contour-enhanced funnel plot was constructed to assess if the asymmetry was due to missing studies or heterogeneity. All analyses were performed using STATA V.16. A two-sided p<0.05 was considered statistically significant except for heterogeneity tests, in which case p<0.10 was used.

Results

Study selection and characteristics

Of the 1585 studies identified, 100 met the inclusion criteria. List of 14 excluded studies along with reasons are provided in online supplemental appendix 3 eTable 3.1. Of those, 86, 13 and 1 study were conducted in high-income countries (HICs), upper-middle income countries (UMICs) and low/middle income country, respectively. Comparisons included dabigatran versus warfarin (N=49),[27–75] apixaban versus warfarin (N=39),[28–30 32–41 43 45 51 62 65–67 69 72 73 76–92] rivaroxaban versus warfarin (N=34)[28–30 32–38 40 41 43 45 50 51 57 62 65–69 72 73 83 93–101] and edoxaban versus warfarin (N=16)[28 30 32 38 43 45 51 62 67 72 73 102–106] (see figure 1).

Characteristics are summarised in table 1 and online supplemental appendix 3 eTable 3.2. Most studies used a third-party payer (TPP) perspective (N=83),[27 29–35 37–41 43 44 46–53 55–58 60–63 65 67–73 76 78 79 81–89 91–95 97 98 100 102 103 105–126] followed by societal perspective (SP) (N=21)[28 33 36 43 54 57 59 64 72 75 77 80 96 99 101 104 113 123 125 127 128] and patient perspective (N=4).[45 57 66 74] Most studies used Markov models and a lifetime-horizon with discounting for both cost and outcomes. About 90% of studies stated no conflict of interest, and 56% were funded by pharmaceutical companies.

Clinical and utility parameters were mostly taken from published literature. Country-specific and GDP-based thresholds were used for WTP in 73[27–31 34–41 44 46–49 51 52 54 57–67 70 72 73 76–80 82–85 88 89 93 94 97 99–101 103–105 107–110 112–115 117–121 123–125 127 129] and 23 studies,[33 43 45 50 55 56 68 69 71 74 75 81 86 87 91 95 96 98 106 116 122 126 128] respectively. Eighty-four studies with 166 comparisons[29–32 34–41 44–50 52 54 56 57 60–64 66 67 69–71 73–85 87–89 91–94 96 97 99 100 102 104–129] reported increased cost-effectiveness with DOACs compared with warfarin/derivatives, in contrast to the remainder (58 comparisons from 24 studies) which did not.[27 28 33–36 38 40 43 50 51 55 58 59 62 65 68 72 86 95 98 101 103 107]

Risk of bias assessment

Across all 22 items from the ECOBIAS checklist, 17 items where more than 70% of studies were graded as low risk of bias, see online supplemental appendix 3 eTable 3.3. Therefore, risk of bias was mostly low for most items with the exception of five items including narrow perspective, double-counting, inappropriate discounting, reporting and dissemination and internal consistency. However, these biases should be less influenced on pooling INBs because they were occurred in both intervention and

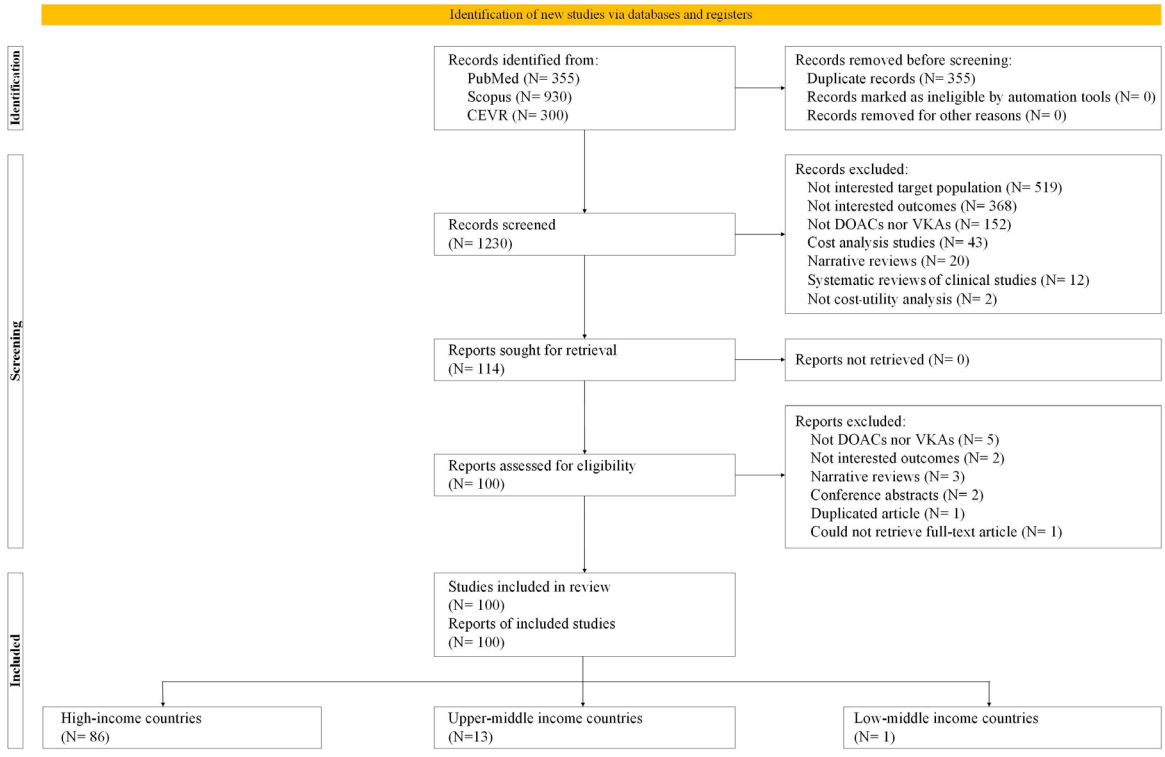

Figure 1 Study selection flow. DOACs, direct oral anticoagulants; VKAs, vitamin K antagonists;CEVR, Centre for Evaluation of Value and Risks in Health databases.

Table 1 General characteristics of the studies included (created by the authors)

Category	Number of studies (N=100)	Number of comparisons (n=224)
Perspective*		
Third-party payer	83	175
Societal	21	40
Patients	4	9
Model type		
Markov	96	216
Discrete event simulation	3	7
Economic evaluation alongside clinical trial	1	1
Time horizon		
Lifetime	96	217
Non-lifetime	4	7
Discount rate for cost		
Not reported	3	12
≤3%	53	112
›3%	44	100
Discount rate for utility*		
Not reported	3	11
≤3%	58	134
›3%	40	79
Clinical data source		
Published literature	81	181
Published literature and evidence synthesis	3	17
Published literature and registry database	11	18
Evidence synthesis	2	5
Registry database	3	3
Utility data source		
Published literature	93	209
Published literature and registry database	4	11
Survey	3	4
Currency year		
2008–2013	65	133
2014–2019	35	91
Cost-effectiveness threshold		
Country-specific	73	172
Gross domestic products-based	23	45
Others	4	7
Cost-effectiveness result*		
Cost-effective	84	166
Not cost-effective	24	58

*The total number of studies are more than 100 because individual studies applied multiple methods.

comparator, thus, should be cancelled out when calculation of the INB (a ratio of an incremental cost and QALYs).

Pooling of INB

Dabigatran versus VKAs

Based on 40 studies with 48 comparisons in HICs with lifetime-horizon, the pooled INBs were $6632.70 from a TPP (95% CI $2961.67 to $10 303.72; I^2=59.9%) and $11 746.96 from an SP (95% CI $2429.34 to $21 064.59; I^2=52.4%). The corresponding

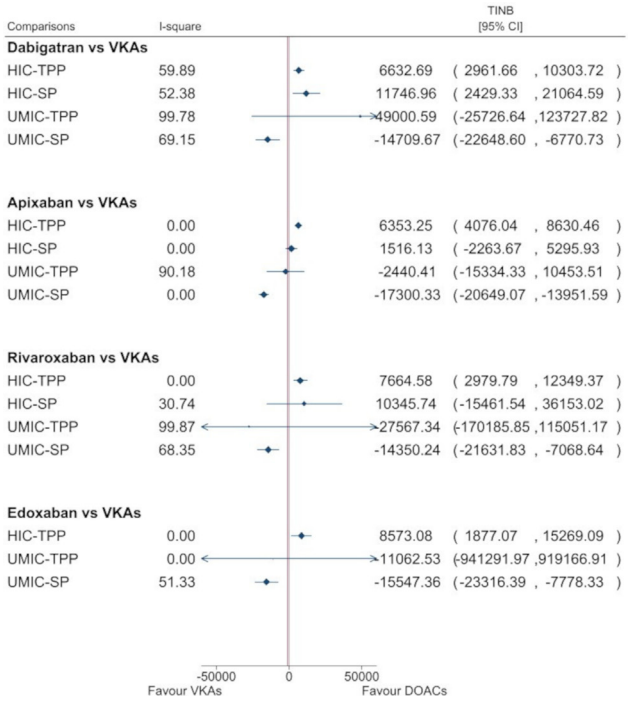

Figure 2 Summary of the pooled INBs of DOACs compared with VKAs classified by country income and perspectives. DOACs, direct oral anticoagulants; HICs, high-income countries; INBs, incremental net benefits; SP, societal perspective; TPP, third-party payer; UMICs, upper-middle income countries; VKAs, vitamin K antagonists.

pooled INBs in UMICs (nine studies with 13 comparisons) were $49 000.59 from a TPP (95% CI –$25 326.64 to $124 127.82; I^2=99.8%) and –$14 709.67 from an SP (95% CI –$22 648.61 to –$6770.74; I^2=69.2%). Dabigatran was cost-effective compared with VKAs in HICs, but not in UMICs (see figure 2, and online supplemental appendix eFigure 4.1–4.4). According to meta-regression for HICs, only funding source and WTP could partially explain heterogeneity for TPP and SP whereas heterogeneity in UMICs could not be explained (see online supplemental appendix eTable 4.1). Subgroup analysis by WTP <$50 000 and funding source from pharmaceutical companies showed that dabigatran was cost-effective compared with VKAs (online supplemental appendix 4 eFigure 4.5–4.6). Publication bias was done in the studies in HICs with TPP indicating no evidence of asymmetry, see online supplemental appendix eFigure 4.7.

Apixaban versus VKAs

Based on 31 studies (33 comparisons) in HICs, the pooled INBs were $6353.24 from a TPP (95% CI) $4076.03 to $8630.45; I^2=0%) and $1516.13 from an SP (95% CI –$2263.67 to $5295.93; I^2=0%). The corresponding pooled INBs in UMICs (eight studies with 11 comparisons) were –$2440.41 from a TPP (95% CI –$15 334.33 to $10 453.52; I^2=90.2%), and –$17 300.33 from an SP (95% CI –$20 649.07 to –$13 951.59; I^2=0%). Apixaban was cost-effective compared with VKAs in HICs with a TPP but not with an SP (see figure 2, and online supplemental appendix eFigures 5.1–5.4). According to meta-regression for UMICs, only discount rates for cost/utility and clinical data source could explain heterogeneity for a TPP whereas the other factors could not explain heterogeneity (see online supplemental appendix eTable 5.1, eFigure 5.5–5.8). There was no evidence of asymmetry using funnel plots and Egger's tests for those studies in HICs with TPP, see online supplemental appendix eFigure 5.9.

Rivaroxaban versus VKAs

Based on 26 studies with 28 comparisons in HICs, the pooled INBs were $7664.58 from a TPP (95% CI $2979.79 to $12 349.37; I^2=0%) and $10 345.74 from an SP (95% CI −$15 461.54, $36 153.02; I^2=30.7%). The corresponding pooled INBs in UMICs (seven studies with 10 comparisons) were −$27 567.34 from a TPP (95% CI −$170 185.85 to $115 051.17; I^2=99.9%), and −$14 350.24 from an SP (95% CI −$21 631.83 to −$7068.64; I^2=68.3%). Rivaroxaban was cost-effective compared with VKAs in HICs with lifetime-horizon from TPP, but not from SP, see figure 2, and online supplemental appendix eFigure 6.1–6.4. Furthermore, rivaroxaban was significantly not cost-effective compared with VKAs in UMICs. According to meta-regression for UMICs with TPP, none of economic factors could explain heterogeneity (see online supplemental appendix eTable 6.1). There was no evidence of asymmetry for pooling INBs in HICs and TPP, see online supplemental appendix eFigure 6.5.

Edoxaban versus VKAs

Based on 13 studies with 15 comparisons in HICs, the pooled INBs (95% CI) were $8573.07 from a TPP (95% CI $1877.05 to $15 269.09; I^2=0%). The pooled INBs in UMICs (three studies with five comparisons) were −$11 062.53 from a TPP (95% CI −$941 291.97 to $919 166.9; I^2=0%) and −$15 547.36 from an SP (95% CI −$23 316.39 to −$7778.33; I^2=51.3%). Edoxaban was cost-effective compared with VKAs from TPP only in HICs, but not cost-effective in UMICs in both TPP and SP, see figure 2, and online supplemental appendix eFigure 7.1–7.3. Source of heterogeneity could be not explored for pooling in UMICs and SP due to very small number of studies.

Discussion

This SR-MA assessed whether DOACs were more cost-effective than VKAs for preventing stroke in patients with AF. The INBs were pooled, stratified by country income, economic models, time-horizon, as well as perspective. Data from 100 studies with 224 comparisons of DOACs to VKAs were included. The pooled INBs associated with four DOACs (ie, dabigatran, apixaban, rivaroxaban and edoxaban) from a TPP were significantly more cost-effective in HICs compared with VKAs. However, outcomes varied if the evaluation was conducted from an SP; with only dabigatran remaining cost-effective compared with VKAs. Conversely, all DOACs were not cost-effective compared with VKAs in UMICs with SP.

To our knowledge, this is the first SR-MA of cost-effectiveness that includes all four commonly used DOACs providing quantitative economic evidence. Given the variable reporting of economic outcomes, the use of INBs provides direct interpretation and supporting evidence for policy decision making. To minimise the heterogeneity across economic studies, we initially pooled INBs from similar studies based on strata including country incomes, economic model, perspectives and time-horizon. Heterogeneity was therefore reduced in studies from HICs but remained moderate to high in UMICs. This may be due to variation in the characteristics and assumptions that underlie the key model features, different reporting mechanisms, and measures of dispersion for point estimates within individual studies. As such, different approaches, data simulations and variance values were considered from similar studies in our analyses.[17 18]

Our study found that country socioeconomic status and methodological approach used potentially influenced the cost-effectiveness of DOACs versus VKAs. DOACs were cost-effective in HICs when the evaluation was conducted using Markov models and lifetime-horizon from TPP-perspective but only dabigatran was cost-effective when using SP. This paradox could be explained by the much smaller number of previous studies analysed from SP in HICs. Moreover, many of them originated from the USA where the WTP thresholds were higher than those from other HICs. Hence, even though DOACs were cost-effective in comparison to VKAs in some individual studies, once their INBs were pooled, the effect was lost.

It is noteworthy that subgroup analyses highlighted that dabigatran was significantly cost-effective compared with VKAs from TPP when WTP thresholds were less than $50 000. Therefore, policy makers in HICs should consider these conditions in their decision making especially when the SP is preferred or the WTP threshold is less than $50 000 per QALY.

Our findings confirm the individual economic evaluations in UMICs that all DOACs were less cost-effective than VKAs particularly with SP and low WTP thresholds. However, apixaban might be more cost-effective than VKAs when considered according to WTP threshold. In general, DOACs would not be the optimum choice compared with VKAs in UMICs. Many of the economic evaluations of DOACs versus VKAs for stroke prevention in patients with AF are represented by diverse methods.

Strengths and weaknesses of the study

Our study provides comprehensive economic evidence for policy makers to assess cost-effectiveness data in their local context, considering perspectives, time horizons, discounting, sources of data and WTP thresholds. Our study had several limitations. Pooling INBs produced moderate to high heterogeneity particularly in UMICs. A meta-regression could be performed in a few pooling because of small number of studies particularly in UMIC, only a few factors could identify leading to subgroup analysis. Although we considered data from variable scenarios, we were still left with some estimated INBs that had no variances, and we had to 'borrow' the variances from similar studies. Although we limited the extent of heterogeneity by using several simulation methods, this was not possible for studies from UMICs. This highlights a need for uniformity of data reporting in economic analyses, particularly measures of dispersion, to enable SR-MA of economic evaluations. Our findings for rivaroxaban and edoxaban may be limited given the small number of evaluations published. Furthermore, the analyses from UMICs may also be affected by the quality of VKA monitoring; there is evidence that time in therapeutic range is lower in developing countries[130–133] leading to higher rates of stroke and major bleeding with VKAs.[131 134] Since clinical trial data under controlled conditions were used in the modelling, DOACs might potentially offer lower benefit in real-world practice for UMICs. The costs relative to hospitalisation are also much lower while drug prices tend to be more expensive in UMICs than HICs which may affect the cost-effectiveness balance of DOACs in UMICs. Changes in DOACs pricing such as the introduction of generic products may also influence our findings. In summary, our findings suggested that DOACs may be cost-effective relative to VKAs in HICs with TPP perspective given that DOACs are clinically non-inferior to VKAs. Our findings are based on studies with low risk of bias for most items, high risk in minor items should be less influenced and cancelled out in INB calculation. Further clinical and cost-effectiveness studies based on real-world clinical data from UMICs are clearly needed.

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Contributors RN, BSB, SY and AT conceived and designed the work. RN and BSB did the analysis. RN wrote the first draft of the manuscript with input from SY and AT. All authors interpreted the data, provided critical revision for important intellectual content and approved the final version to be published.

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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

Noviyani R, Youngkong S, Nathisuwan S, Bagepally BS, Chaikledkaew U, Chaiyakunapruk N, McKay G, Attia J, Thakkinstian A

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

Online Supplementary Content

Contents

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:

$$Y_{\text{ppp2019}} = Y_{\epsilon\text{baseyear}} \times \left(\frac{\text{cpi}_{\epsilon 2019}}{\text{cpi}_{\epsilon\text{base year}}} \times \frac{1}{\text{ppp2019}} \right)$$

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

$$Y_{\text{ppp2019}} = Y_{\epsilon\text{baseyear}} \times \left(\frac{\text{cpi}_{\epsilon 2019}}{\text{cpi}_{\epsilon\text{base year}}} \times \frac{1}{\text{ppp2019}} \right)^2$$

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 Crespo[1], 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]

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

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

Where K is threshold, $\sigma^2_{\Delta E}$ is variance of ΔE and σ^2_{ICER} variance of ICER

- **Scenario 2**

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

$$\text{UL}_{\text{ICER}} = \mu + 1.96\ \text{SE}_{\text{ICER}}$$

$$\text{SE}_{\text{ICER}} = \frac{(\text{UL}_{\text{ICER}} - \mu)}{1.96}$$

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, ΔC/ΔE but have not provided the ICER and its variance. Monte Carlo with 1000 simulation[2] 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:

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

- **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: ±70% to ±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 Crespo[1] namely INB = (K x Δ E) -ΔC 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 Laird [4] method if there is heterogeneity with the formula:

a. Random-effect model:

$$\text{INB}_p = \frac{\sum_{1-1}^{S} w_1^* - \text{INB}_1}{\sum_{1-1}^{S} w_1^*}$$

$$w_1^* = \frac{1}{[K^2\sigma^2_{\Delta E} + \sigma^2_{\Delta C} + 2K\rho_{\Delta E\Delta C}] + \tau^2}$$

$$\tau^2 = \frac{Q - (S-1)}{\sum W_1 - \frac{\sum w_1^2}{\sum w_1}}$$

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:

$$\text{INB}_p = \frac{\sum_{1-1}^{S} w_1 - \text{INB}_1}{\sum_{1-1}^{S} w_1}$$

$$w_1 = \frac{1}{\text{Var(INB)}}$$

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

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

$$\text{Cochrane Q} = \sum_{i-1}^{s} w_1(\text{INB}_1 - \text{INBp})^2$$

Where W_1 is the inverse variance of INB_1, INB_1 is the individual studies, and INB_p is the pooled INB.

d. The I^2 statistic test

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

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
Dilokthornsakul, 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
Jarungsuccess 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
Janzic 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
Krejczy 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]							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
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
Rattanachotpanit 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,	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
Nshimyumukiza 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
Krejczy 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 Pouvourville 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

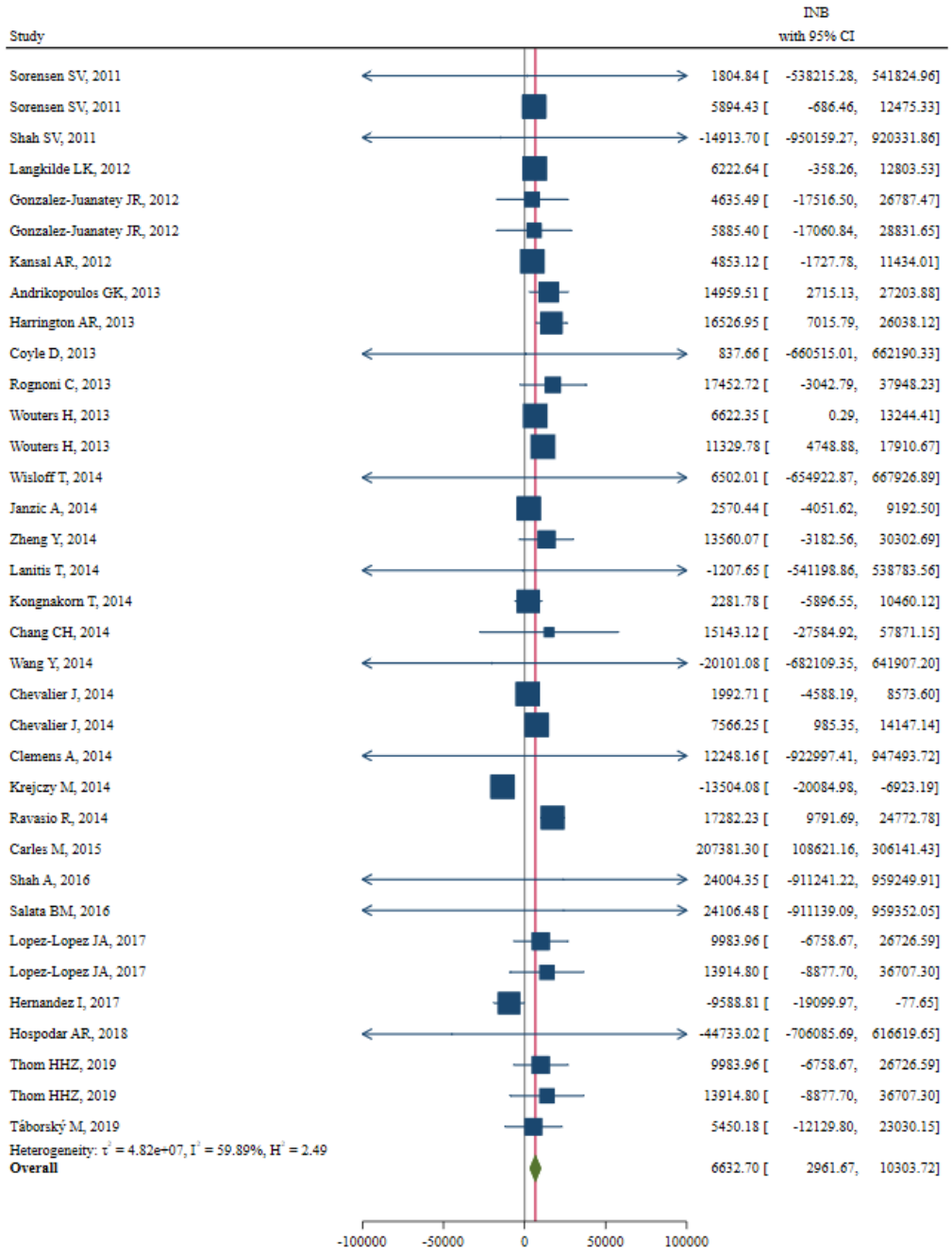
[2] the bias related to data

[3] the bias related to consistency

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

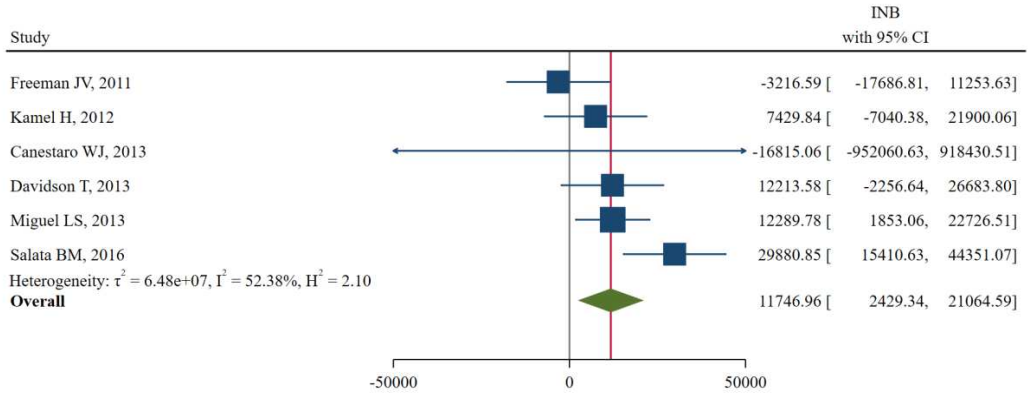
A) Pooling INBs

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



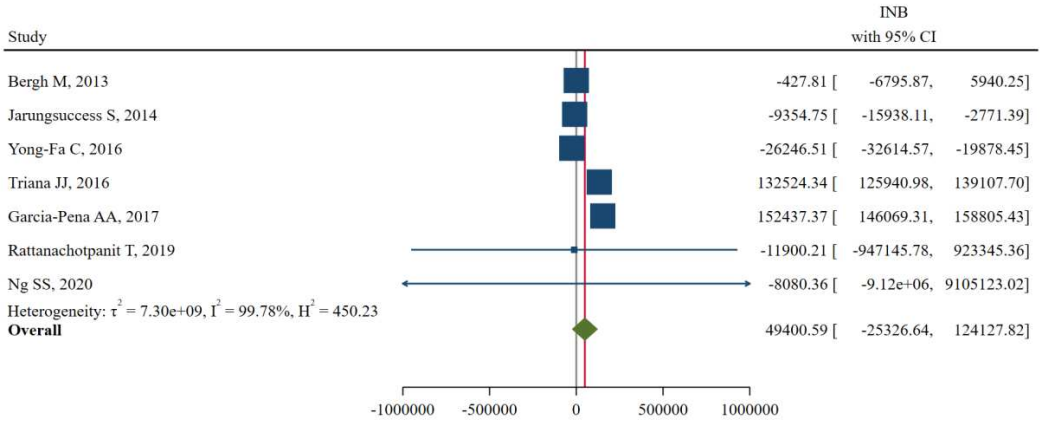
Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; HICs, High-Income Countries; TPP, Third-party payer perspective.

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



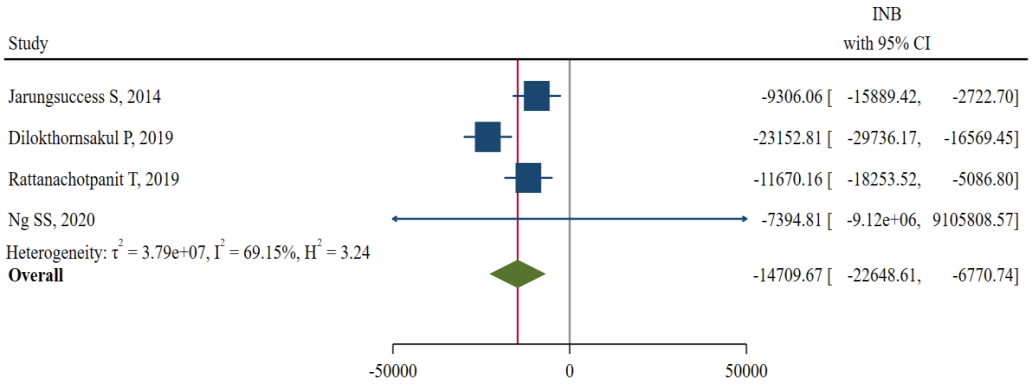
Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; HICs, High-Income Countries; SP, Societal perspective**.**

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)

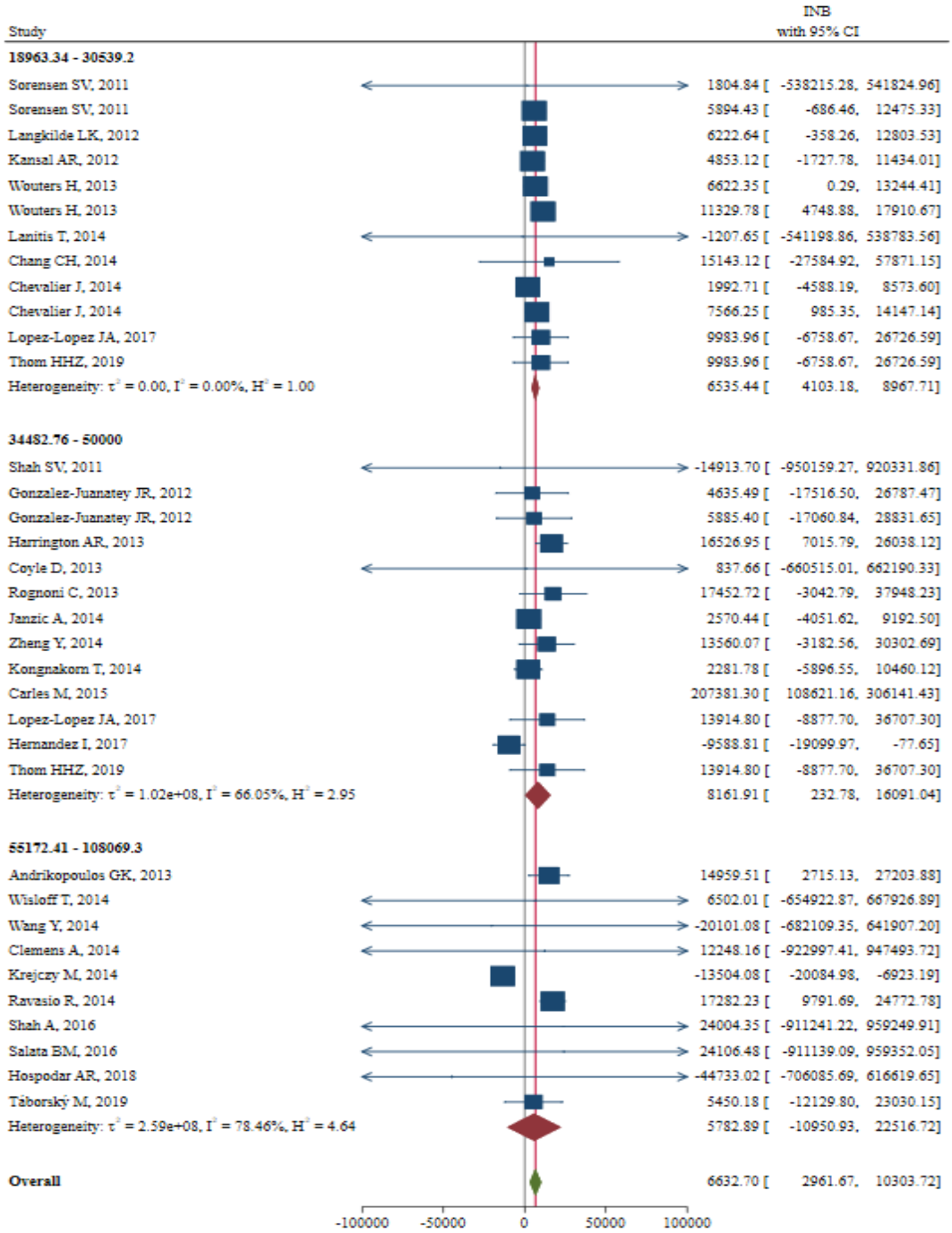
Factors	**Coefficient**	**SE**	**P-value**	**I^2 (%)**
Dabigatran vs VKAs in HICs Markov-TPP-LT				
Model without factors	6,632.695	1,873.005	0.001	59.89
WTP Threshold				
18,963.34-30,539.2 vs >50,000	303.4636	4,365.701	0.945	60.92
34,482.76-50,000 vs >50,000	-1,828.197	5,370.961	0.736	
Discount cost				
≥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.

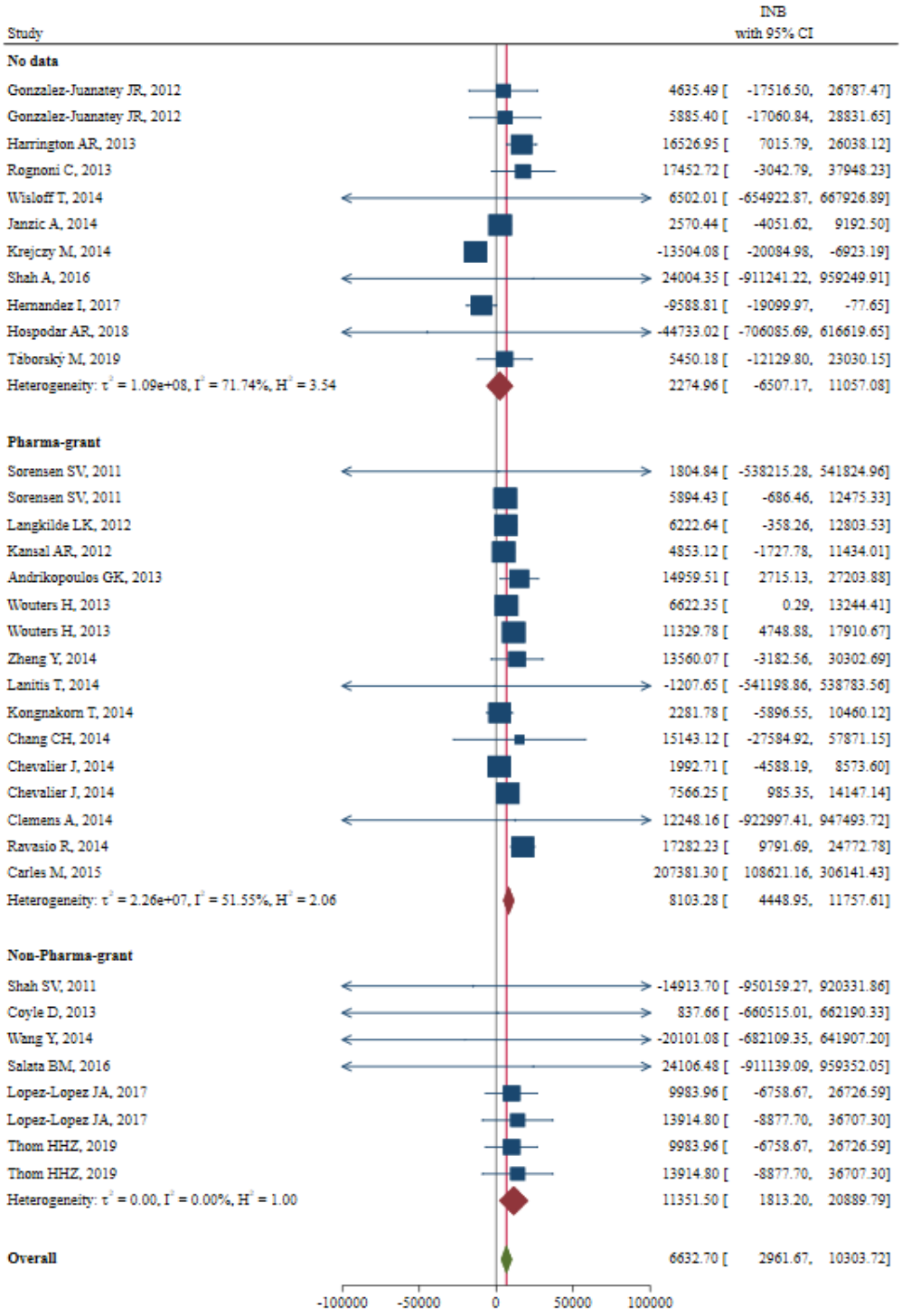
C) Sub-group Analysis

eFigure 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.

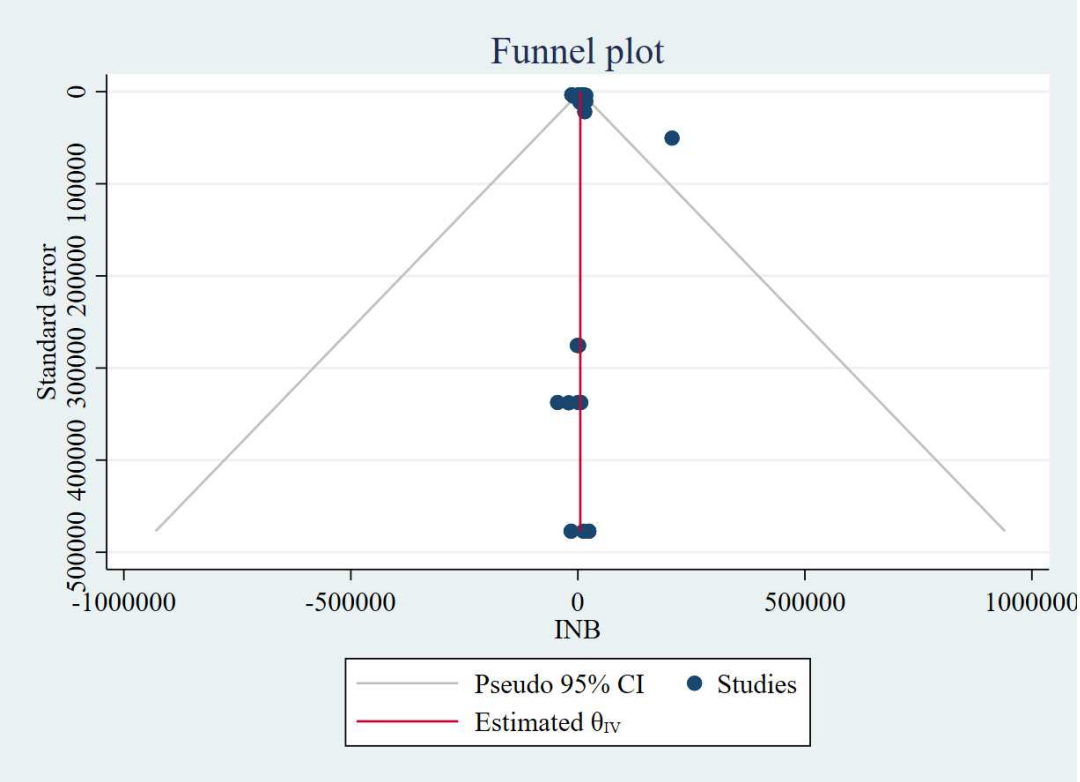
D) Publication Bias

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)

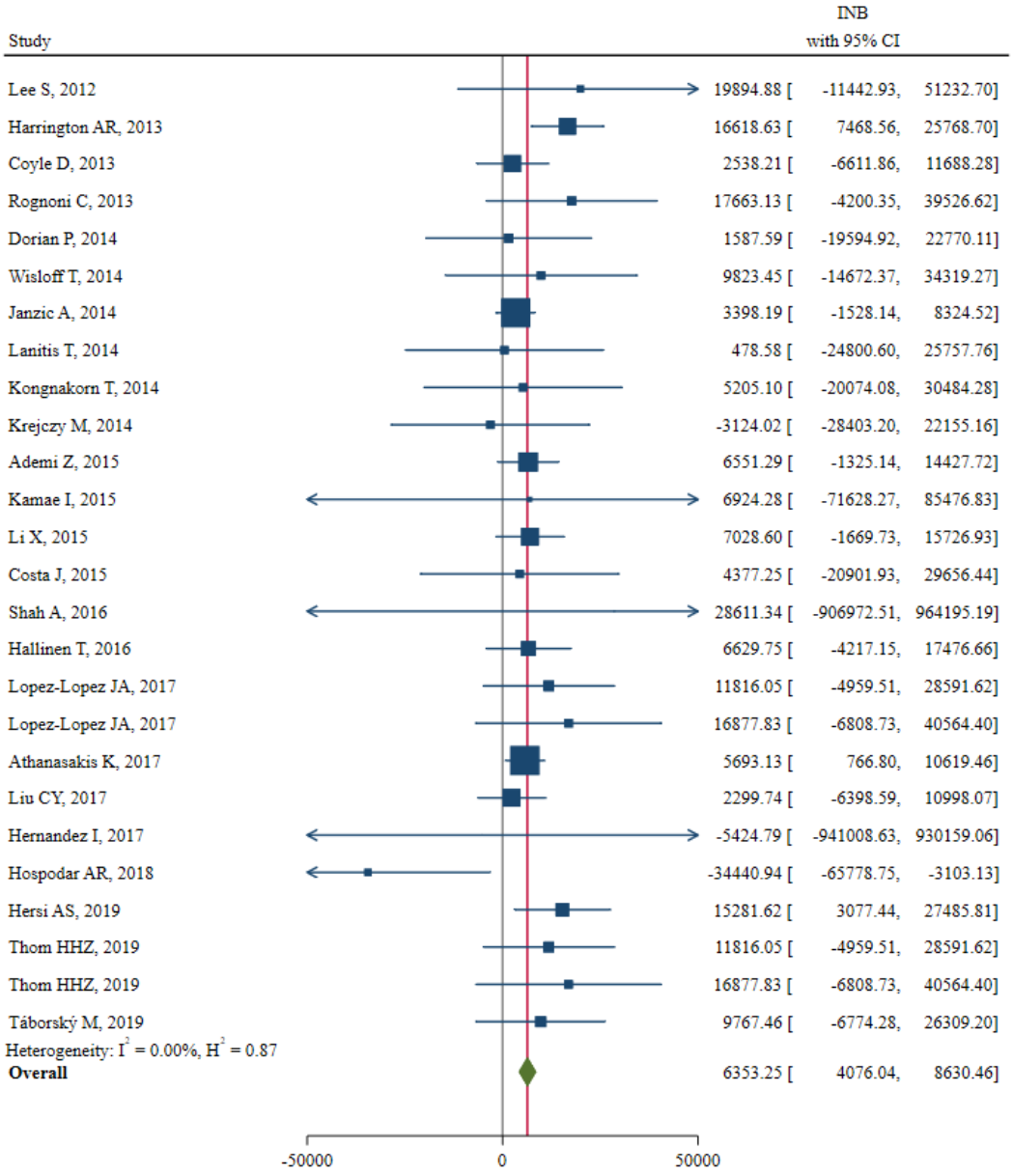


Abbreviations: VKAs, Vitamin K Antagonists; HICs, High-Income Countries; TPP, Third-party payer perspective**.**

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

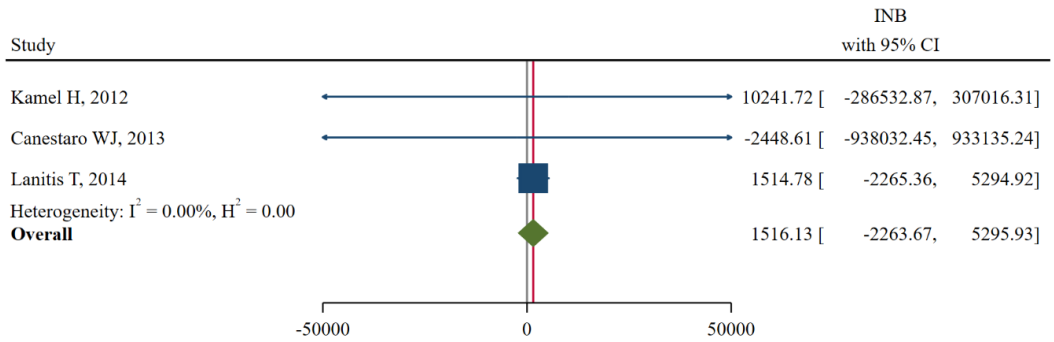
A) Pooling INB

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



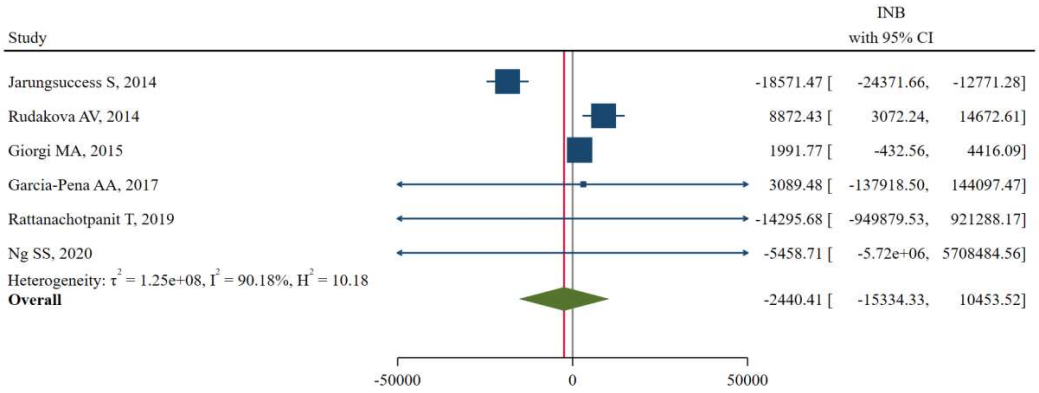
Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; HICs, High-Income Countries; TPP, Third-party payer perspective**.**

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



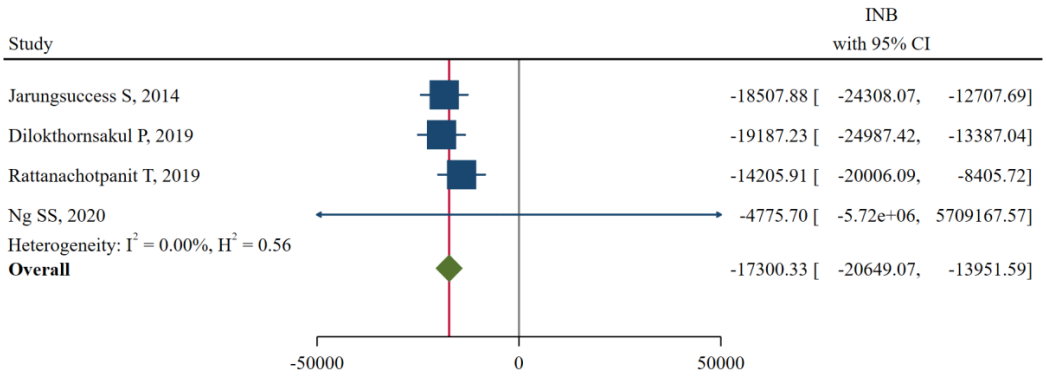
Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; HICs, High-Income Countries; SP, Societal perspective**.**

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

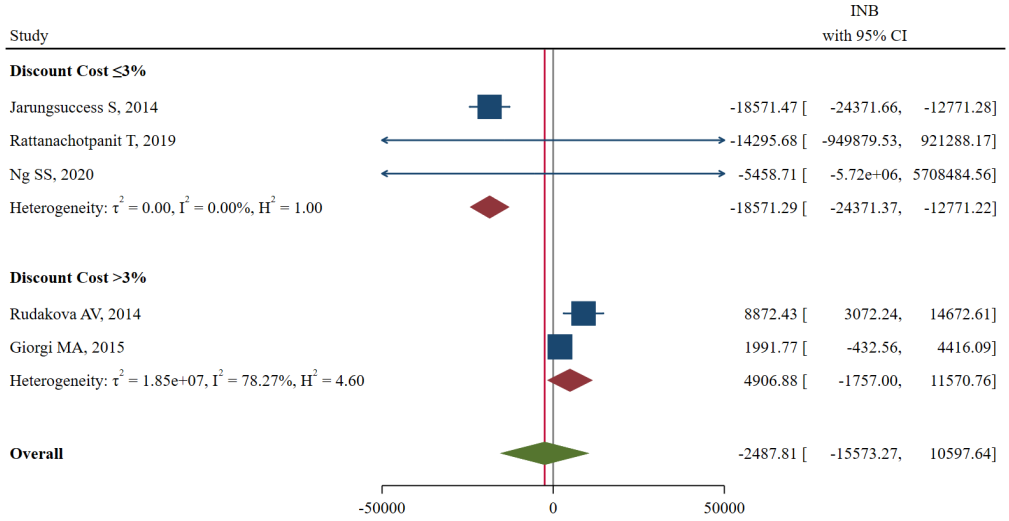
eTable 5.1 Exploring source of heterogeneity using a meta-regression analysis. (Created by the authors)

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.

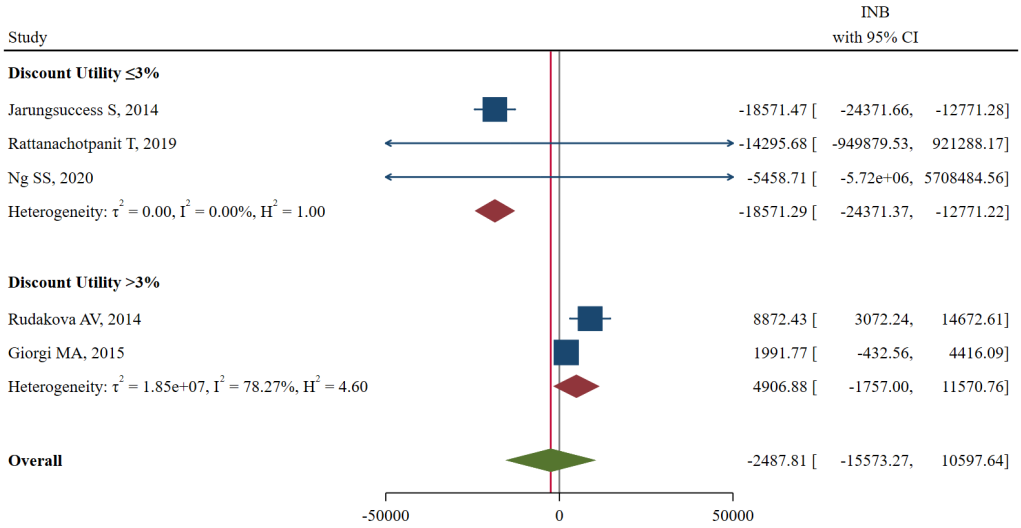
C) Sub-group Analysis

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)



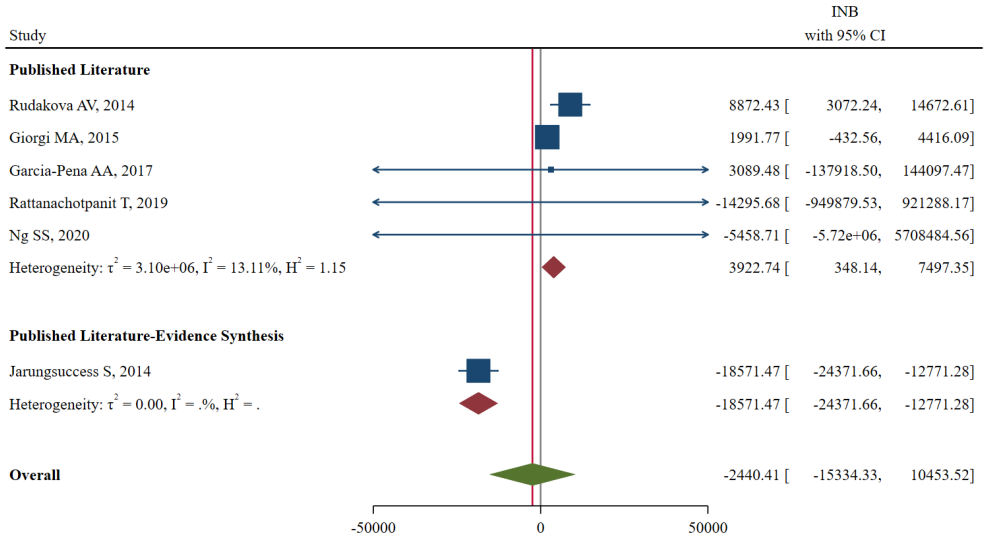
Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; UMICs, Upper Middle-Income Countries; TPP, Third-party payer perspective**.**

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)



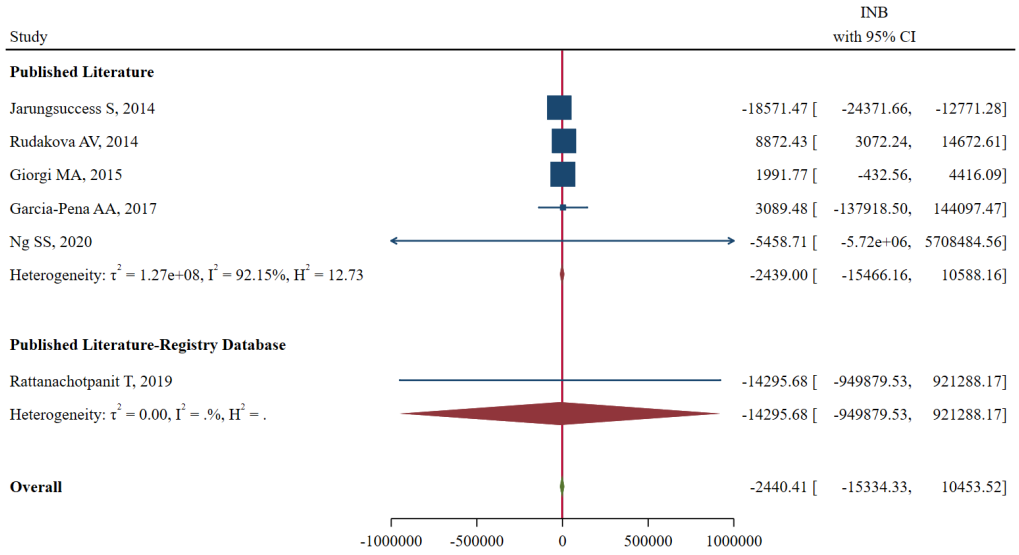
Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; UMICs, Upper Middle-Income Countries; TPP, Third-party payer perspective**.**

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**.**

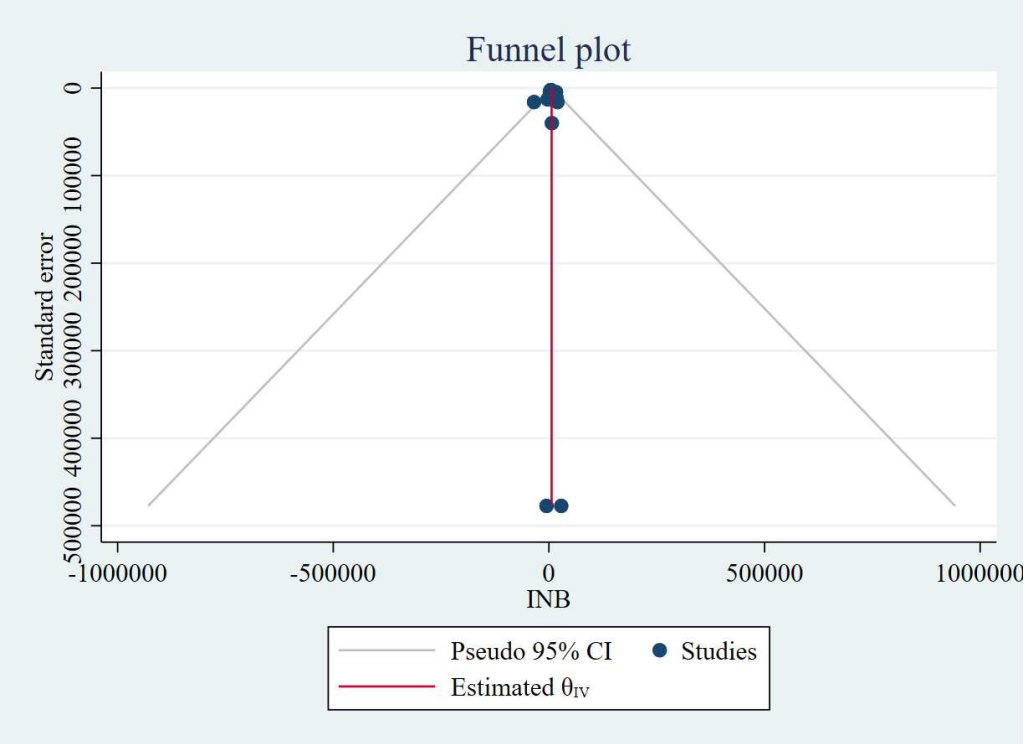
D) Publication Bias

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)

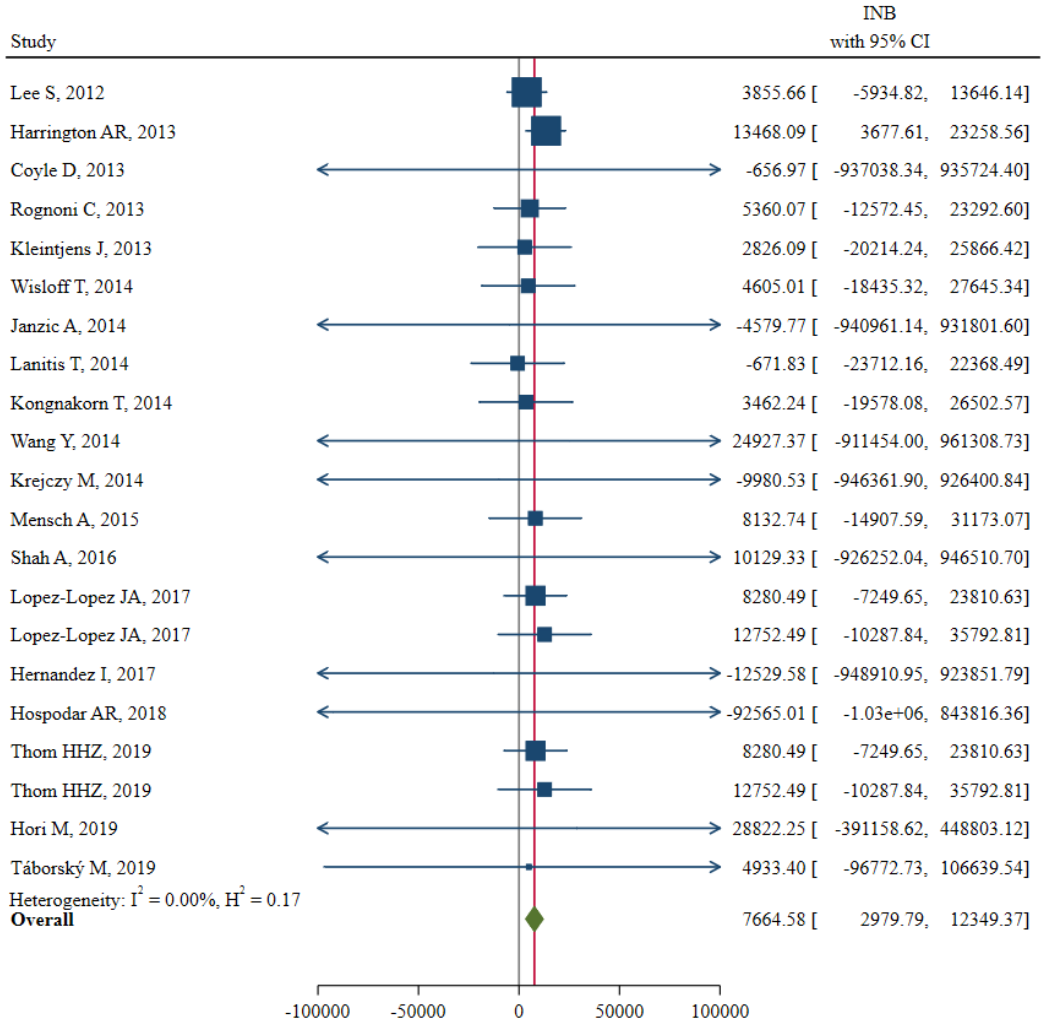


Abbreviations: VKAs, Vitamin K Antagonists; HICs, High-Income Countries; TPP, Third-party payer perspective.

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

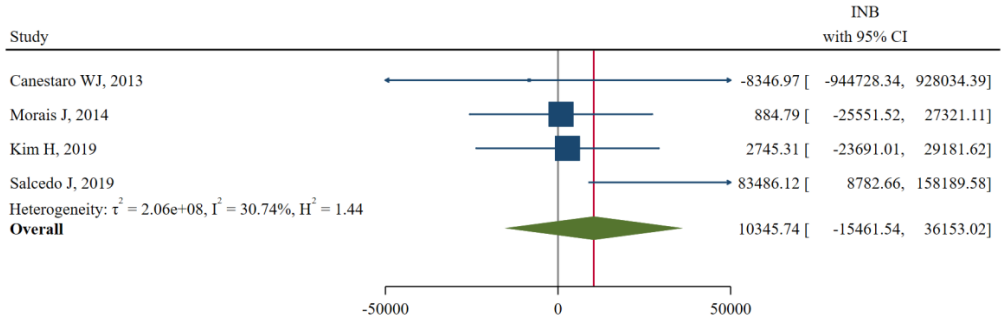
A) Pooling INB

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



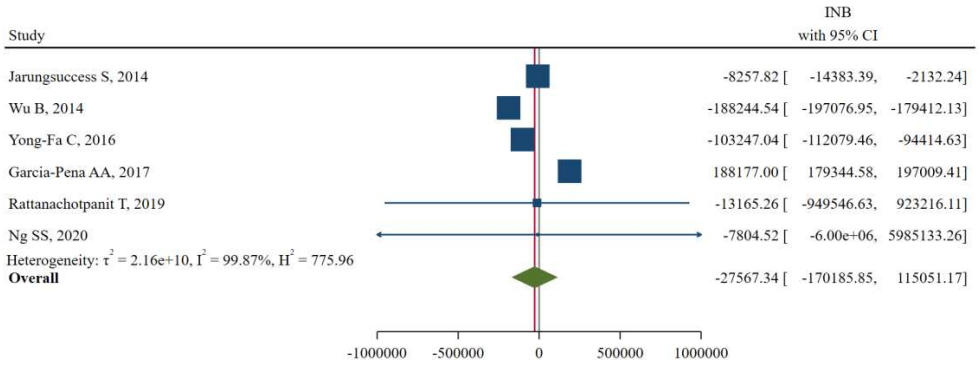
Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; HICs, High-Income Countries; TPP, Third-party payer perspective.

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



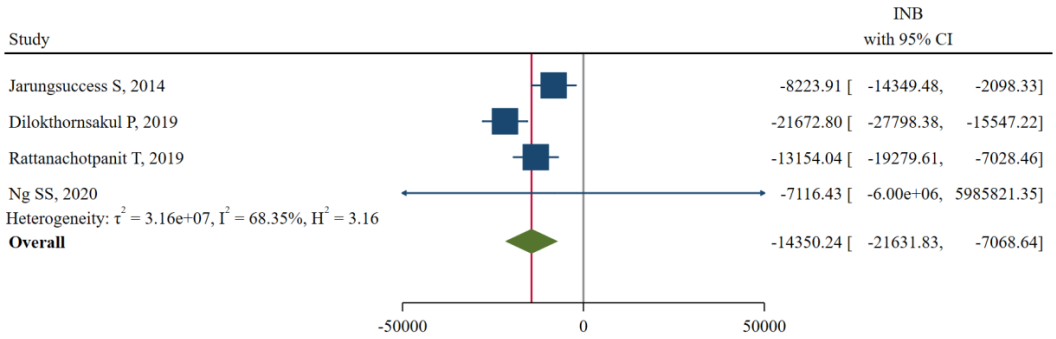
Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; HICs, High-Income Countries; SP, Societal perspective**.**

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.

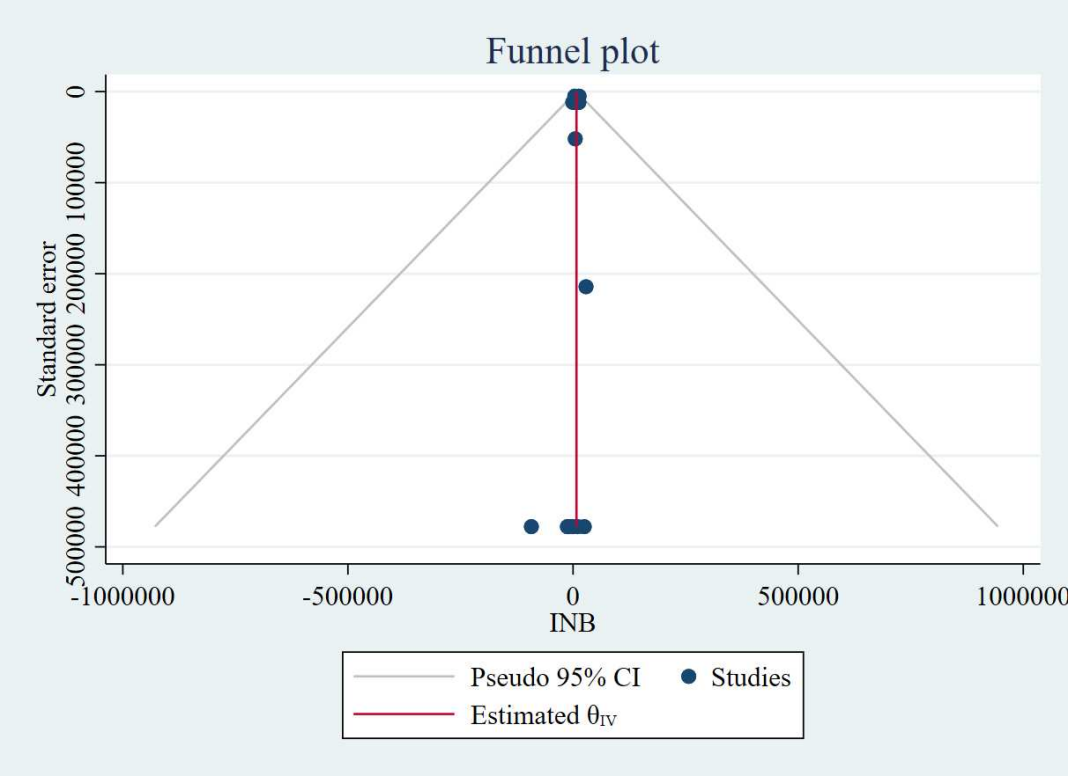
C) Publication Bias

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)

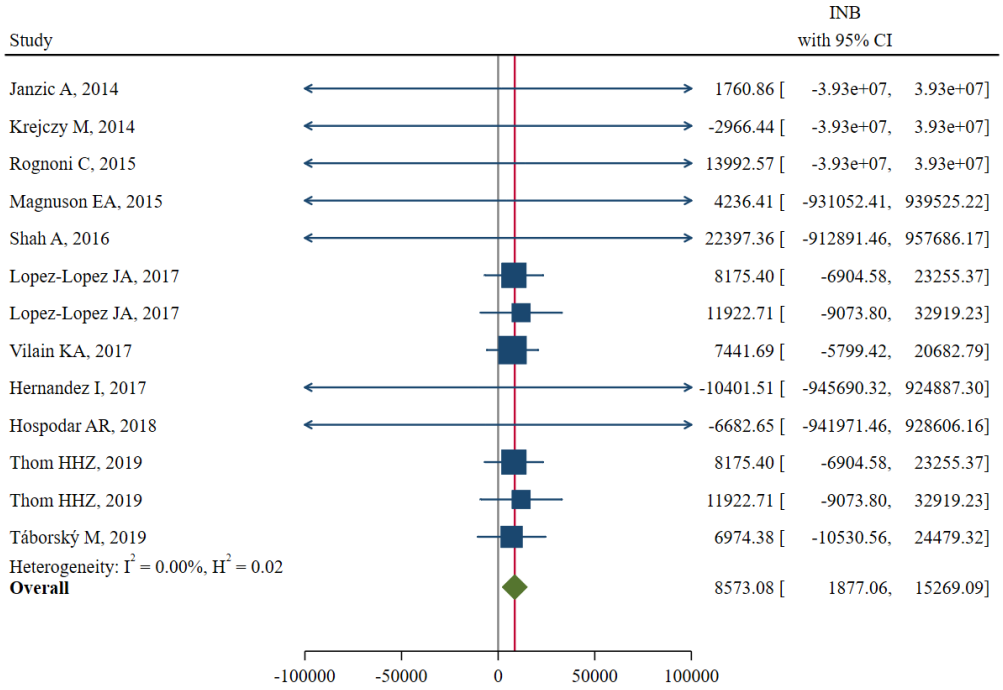


Abbreviations: VKAs, Vitamin K Antagonists; HICs, High-Income Countries; TPP, Third-party payer perspective**.**

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

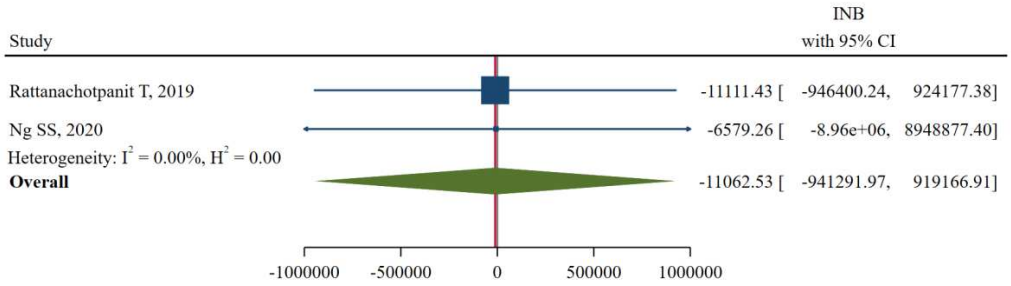
A) Pooling INB

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



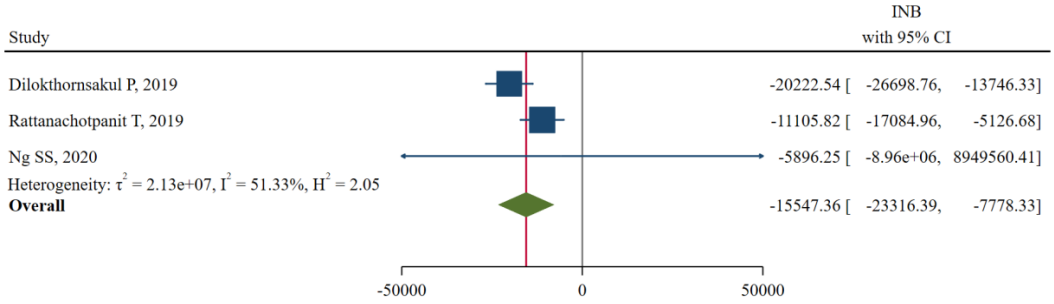
Abbreviations: INBs, Incremental Net Benefits; VKAs, Vitamin K Antagonists; HICs, High-Income Countries; TPP, Third-party payer perspective.

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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