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REVIEW

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Economic evaluation of direct oral anticoagulants (DOACs) for venous thromboembolism with different etiologies: a systematic review

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Abstract

Background Venous thromboembolism (VTE) imposes significant clinical and economic burdens. While direct oral anticoagulants (DOACs) offer favorable efficacy and safety, their cost-effectiveness across diverse VTE etiologies remains incompletely synthesized.

Objective To systematically evaluate the cost-effectiveness of DOACs versus comparators for VTE management stratified by etiology.

Methods A PRISMA-compliant systematic search was conducted in MEDLINE, Web of Science, Scopus, and NHS EED (2020–2025). Economic evaluations reporting cost-effectiveness or cost-utility outcomes were included. Study quality was assessed using the Drummond checklist.

Results Twenty studies were included (9 CAT, 3 post-surgical, 6 hospitalized VTE, 2 COVID-19). DOACs were cost-effective or dominant in 18/20 studies. For cancer-associated thrombosis (CAT), DOACs dominated LMWHs and were cost-effective versus placebo (ICERs: $5,794–$11,947/QALY). DOACs were also dominant for post-surgical prophylaxis and in general hospitalized VTE (ICERs: -$1,862/QALY to $125.68/QALY), while rivaroxaban was cost-effective for post-COVID-19 prophylaxis (ICER: $5,386/QALY).

Conclusion DOACs, particularly apixaban and rivaroxaban, are an economically dominant strategy for VTE across most etiologies. Their adoption as a first-line therapy can improve patient outcomes while significantly reducing healthcare costs.

Keywords Direct oral anticoagulants (DOACs), Venous thromboembolism (VTE), Cost-effectiveness, Cancer-associated thrombosis (CAT), Health economics, Systematic review

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Introduction

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is a significant vascular condition characterized by the formation of blood clots in the veins that obstruct normal blood flow [1]. The condition is associated with a substantial risk of recurrence, long-term complications such as post-thrombotic syndrome, and a significant economic burden on healthcare systems [2]. For decades, the standard of care for the long-term treatment and secondary prevention of VTE has been vitamin K antagonists (VKAs), such as warfarin. However, the use of VKAs is challenged by several limitations, including a narrow therapeutic window, numerous food and drug interactions, and the requirement for regular coagulation monitoring, which complicates patient management and impacts quality of life [3]. VTE is a heterogeneous disease, and its clinical management is often stratified based on the presence or absence of provoking factors. These factors can include major surgery, trauma, prolonged immobilization, or active cancer, which defines a high-risk subgroup known as cancer-associated thrombosis (CAT). In contrast, unprovoked VTE occurs in the absence of these transient risk factors and carries a different long-term prognosis and recurrence risk [4].

In recent years, direct oral anticoagulants (DOACs) have quickly become the preferred alternative to vitamin K antagonists like warfarin for managing venous thromboembolism (VTE). Evidence from a meta-analysis of phase 3 randomized controlled trials indicates that DOACs are as effective as warfarin in treating VTE but are associated with a reduced risk of major bleeding. The DOAC group comprises three direct factor Xa inhibitors—edoxaban, rivaroxaban, and apixaban—and one direct thrombin inhibitor, dabigatran [5]. Large-scale randomized controlled trials have demonstrated that DOACs offer at least equivalent efficacy to conventional therapy with a more favorable safety profile, particularly regarding a reduced risk of major bleeding, most notably intracranial hemorrhage. Furthermore, their fixed-dosing regimens and lack of need for routine laboratory monitoring provide significant advantages for both patients and clinicians [6].

In addition to negatively impacting survival rates and quality of life, venous thromboembolism (VTE) imposes a substantial economic strain on both patients and healthcare systems. A large population-based study found that overall healthcare costs for cancer patients with VTE were about 80% higher than for a matched group of cancer patients without VTE (in U.S. dollars: $74,959 versus $41,691). These elevated costs highlight VTE's broader financial implications in high-risk populations like those with cancer [7]. This systematic review aims to critically evaluate and summarize the published literature on the economic evaluation of DOACs for the treatment of VTE, with a specific focus on how the underlying cause of the thromboembolism influences the cost-effectiveness outcomes.

Methods

This systematic review was conducted and reported in adherence with the PRISMA 2020 statement.

Eligibility criteria

We included studies that met the following criteria, defined using the PICOS (Population, Intervention, Comparator, Outcome, Study Design) framework (Table 1).

Information sources

A systematic search of the scientific literature was conducted for the period 2020 to 2025 in MEDLINE (via PubMed), Web of Science, Scopus and the National Health Service Economic Evaluation Database (NHS EED). We also searched grey literature sources, including the ISPOR scientific presentation database and clinical trials registers (ClinicalTrials.gov and WHO ICTRP), to identify unpublished or ongoing studies. The reference lists of all included articles and relevant systematic reviews were manually screened for additional eligible studies.

Search strategy

This review combined Medical Subject Headings (MeSH) terms with keywords related to the population, interventions, comparators, and outcomes. The search strategy for PubMed is:

("Venous Thromboembolism"[Mesh] OR "Deep Vein Thrombosis"[Mesh] OR "Pulmonary Embolism"[Mesh] OR venous thromboembolism* OR VTE OR deep vein thrombosis* OR DVT OR pulmonary embolism* OR PE) AND (extended treatment OR extended therapy OR secondary prevention OR long-term treatment) AND ("Direct Factor Xa Inhibitors"[Mesh] OR "Dabigatran"[Mesh] OR "Apixaban"[Mesh] OR "Rivaroxaban"[Mesh] OR "Edoxaban"[Mesh] OR direct oral anticoagulant* OR DOAC* OR novel oral anticoagulant* OR NOAC* OR apixaban OR rivaroxaban OR edoxaban OR dabigatran OR betrixaban) AND ("Cost-Benefit Analysis"[Mesh] OR "Cost-Effectiveness Analysis"[Mesh] OR "Economics, Pharmaceutical"[Mesh] OR cost-effectiveness OR cost-utility OR economic evaluation* OR cost analysis OR cost-benefit OR cost minimization OR pharmacoeconomic* OR QALY)

Selection process

All citations retrieved from the databases were exported to EndNote X9 (Clarivate Analytics) and subsequently imported into the systematic review software Rayyan

Table 1 Eligibility criteria for the study selection

Inclusion criteria	Criteria	Explanations
Population	Adults > 18	Studies involving adult patients diagnosed with venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) of both surgical and non-surgical origin and/or pulmonary embolism (PE).
Outcome	QALY/LYG	Cost-utility/effectiveness outcomes: Quality-Adjusted Life Years (QALYs) and Life Years Gained (LYGs). Cost-effectiveness outcomes based on key clinical events, including: cost per recurrent VTE avoided, cost per major bleed averted, and cost per clinically relevant non-major bleed (CRNMB) averted.
Study design	EV models	Included model-based economic evaluations (e.g., Decision Tree, Markov models, discrete event simulations) and economic evaluations conducted alongside clinical trials (trial-based economic evaluations).
Intervention	DOACs	The intervention of interest was any of the four approved direct oral anticoagulants (DOACs): apixaban, rivaroxaban, dabigatran, or edoxaban, used for the treatment of VTE.
Comparator	LMWHs/Placebo/VKA	Low-molecular-weight heparin (LMWH) followed by a vitamin K antagonist (VKA, e.g., warfarin). LMWH monotherapy (especially relevant for the CAT population).

QCRI for screening. Two reviewers (SR and ZK) independently screened the titles and abstracts of all identified records against the eligibility criteria. The full texts of potentially relevant articles were then retrieved and assessed for inclusion by the same two independent reviewers. Any disagreements at either the title/abstract or full-text screening stage were resolved through discussion and consensus. If a consensus could not be reached, a third senior reviewer (Reviewer 3) was consulted. The study selection process is summarized in a PRISMA flow diagram.

Data collection process

A standardized data extraction form was created in Microsoft Excel (2019) and pilot-tested on three included studies. Two reviewers independently extracted data from each included study. The extracted data was cross-checked for accuracy and completeness. Discrepancies were resolved by discussion or by consulting a third reviewer. The corresponding authors of the included studies were to be contacted via email for any missing or unclear data.

Risk of bias in individual studies

The methodological quality of the included economic evaluations was independently assessed by two reviewers using the Drummond 10-point checklist for economic evaluations [8]. This checklist assesses key domains such as the clarity of the research question, the appropriateness of the study design and perspective, the comprehensiveness of cost and outcome measurement, and the conduct of sensitivity analysis. Each study was classified as having a low, moderate, or high risk of bias based on its overall performance on the checklist (Appendix1).

Data synthesis

Due to the anticipated heterogeneity across studies (e.g., differences in country-specific healthcare systems, currencies, modeling assumptions, and VTE population definitions), a statistical meta-analysis of the ICERs was deemed inappropriate. The results were structured and presented according to the different causes of VTE (i.e., CAT, unprovoked, provoked). Within each subgroup, findings were further organized by comparator (e.g., DOAC vs. LMWH/VKA). The key characteristics and findings of all included studies are summarized in tables.

Results

The database search yielded a total of 1270 articles. Following the removal of duplicate records, 790 articles remained for review. The titles and abstracts of these articles were screened, resulting in 162 articles proceeding to the next stage. The full texts of these articles were then evaluated according to the eligibility criteria established by the researchers. Ultimately, 20 articles qualified for inclusion in the final analysis based on adherence to these criteria (Fig. 1).

Study characteristics and methodology

Table 2 summarizes the study characteristics including Study/Year, Country, Population, Cause, Comparator/Intervention, and Funding. A total of 20 studies conducted between 2020 and 2025 across various countries

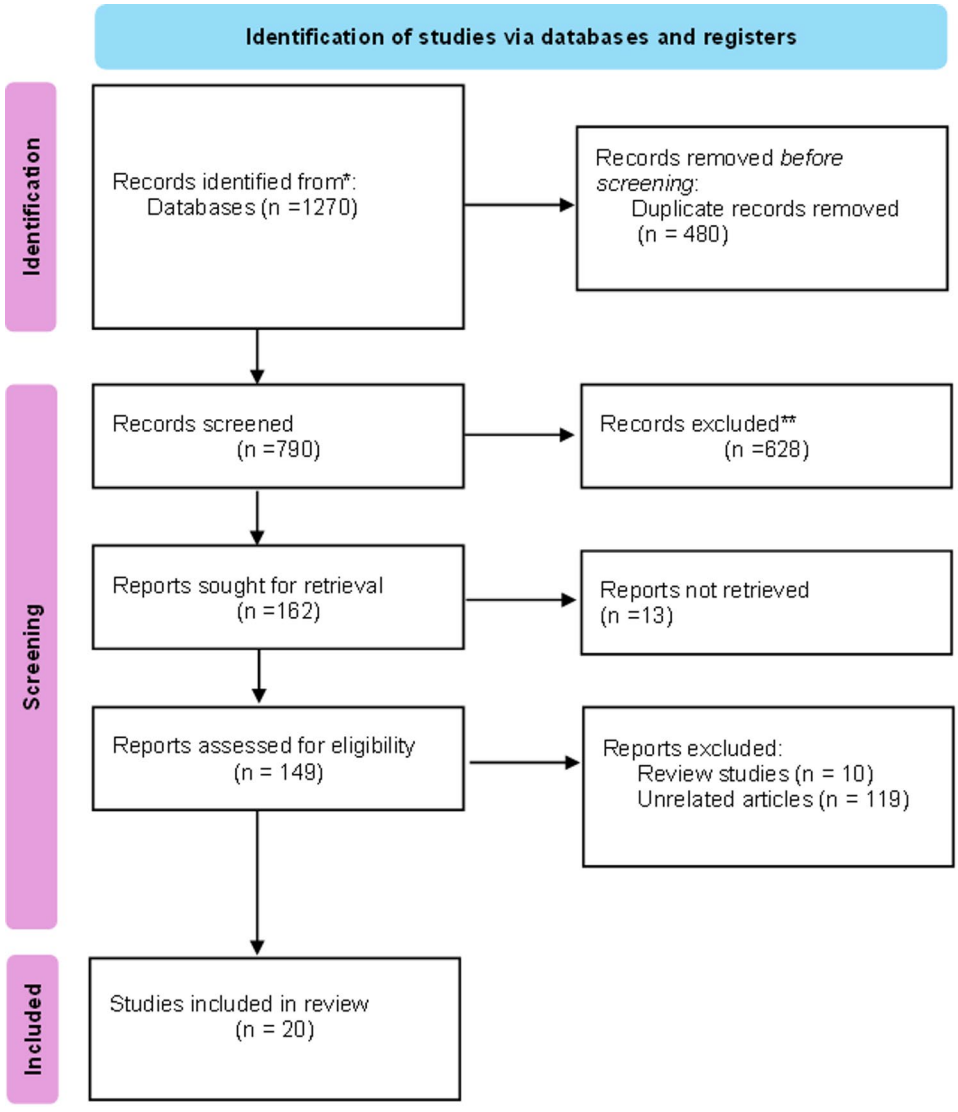

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow diagram

were included in the analysis. The evidence base comprised 20 studies across diverse healthcare settings in North America [9–14], Europe [15–18], Asia [19–24], Africa [25, 26] and South America [27, 28], encompassing a wide range of venous thromboembolism (VTE)–related indications including deep vein thrombosis (DVT), cancer-associated thrombosis, post-surgical prophylaxis, COVID-19–related VTE risk and unprovoked VTE.

Most studies compared direct oral anticoagulants (DOACs) with low-molecular-weight heparins (LMWHs) [10, 13–16, 19, 20, 22, 24–27] or vitamin K antagonists (VKAs) [18, 21], although several evaluations used placebo [9, 11] or no thromboprophylaxis [12, 17, 23, 28] as comparators, particularly in ambulatory cancer populations, trauma patients, and high-risk post-discharge cohorts. DOACs were cost-effective in 90% (18/20) of studies. Across all etiologies, DOACs reduced costs by $828–$9,135 and increased QALYs by 0.003–0.44. ICERs ranged from dominant to $269,809/QALY, with apixaban most frequently cost-effective.

Most of the included economic evaluations adopted a healthcare system perspective [9–13, 16–18, 20, 21, 24],], with a smaller number using a societal [13, 15, 22, 25] or payer [19, 23] perspective, and nearly all reported outcomes in terms of quality-adjusted life years using Markov state-transition or decision tree models over time horizons ranging from months to lifetime. Time horizons were typically aligned with disease progression or intervention effects, and a few studies also reported life years gained or avoided complications in addition to QALYs (Table 3).

The key methodological pattern in uncertainty handling was extensive use of deterministic and probabilistic sensitivity analyses, particularly one-way sensitivity

Table 2 Summary of the characteristics of the 20 included studies

Study/Year	Country	Patient Population	Etiology	Comparator/Intervention	Funding
Yang L/2020 [19]	China	Hospitalized patients with DVT	DVT	LMWHs/DOACs	Yes
Li A/2020 [9]	USA	Ambulatory patients with cancer at intermediate-to-high risk for VTE	Cancer-Associated Thrombosis	Placebo/Low-dose DOACs	Yes
Glickman A/2020 [10]	USA	Patients after gynecologic cancer surgery	Cancer-Associated Thrombosis	LMWHs/DOACs	Yes
de Jong LA/2020 [15]	Netherlands	Patients with active cancer and VTE	Cancer-Associated Thrombosis	LMWHs/DOACs	Yes
Wumaier/2021 [20]	China	Patients with cancer-associated thrombosis (CAT); subgroup: patients with gastrointestinal malignancy	Cancer-Associated Thrombosis	LMWHs/DOACs	NO
Sun/2021 [21]	China	Patients with VTE	VTE	Vitamin K Antagonists (VKA)/DOACs	Yes
Kimpton/2021 [11]	Canada	Ambulatory patients with cancer starting chemotherapy at intermediate-to-high risk of VTE	Cancer-Associated Thrombosis	Placebo/DOACs	Yes
Derseh/2021 [25]	Ethiopia	Adult patients (40 years old) with DVT and no contraindications, comorbid diseases	DVT	LMWHs/DOACs	No
Muñoz/2022 [16]	Spain	Patients with active cancer and venous thromboembolism (VTE)	Cancer-Associated Thrombosis	LMWHs/DOACs	Yes
de Brito/2022 [27]	Brazil	Patients submitted to total hip (THA) or total knee (TKA) arthroplasty	Post-Surgical Prophylaxis	LMWHs/DOACs	No
Nicholson/2022 [12]	USA	trauma patients at risk for Venous Thromboembolism	Post-Surgical Prophylaxis	No thromboprophylaxis/DOACs	Yes
Shin/2022 [13]	USA	cancer patients with an index Venous Thromboembolism event	Cancer-Associated Thrombosis	LMWHs/DOACs	No
Niyomsri/2023 [22]	Thailand	Patients diagnosed with Venous Thromboembolism	VTE	LMWHs/DOACs	Yes
Muñoz/2023 [17]	Spain	Ambulatory cancer patients with an intermediate-to-high risk of venous Thromboembolism	Cancer-Associated Thrombosis	No thromboprophylaxis/DOACs	No
Kepka/2023 [18]	France	Patients hospitalized for acute deep vein thrombosis (DVT)	DVT	Vitamin K Antagonists (VKAs)/DOACs	No
Gulati/2023 [14]	USA	Adult patients with cancer	Cancer-Associated Thrombosis	LMWHs/DOACs	No
de Oliveira/2023 [28]	Brazil	High-risk patients after hospitalization for COVID-19	COVID-19	No thromboprophylaxis/DOACs	Yes
Abutorabi/2023 [24]	IRAN	Patients undergoing knee replacement surgery	Post-Surgical Prophylaxis	LMWHs/DOACs	Yes
Wu/2024 [23]	China	Cancer patients at risk of venous Thromboembolism	Cancer-Associated Thrombosis	No thromboprophylaxis and LMWHs/DOACs	Yes
O'Neill/2025 [26]	Kenya	Patients with venous thromboembolism	VTE	LMWHs/DOACs	No

analysis and probabilistic sensitivity analysis, often in combination. Some articles also incorporated scenario, two-way, or other deterministic sensitivity analyses (Table 3).

The Table 4 summarizes economic evaluations of DOACs, primarily rivaroxaban and apixaban, compared to alternatives like LMWHs, warfarin, or no prophylaxis for CAT, VTE, or related prophylaxis across diverse settings. Across 10 studies focusing on CAT, DOACs

Table 3 Summary of the methodological aspects of the 20 included studies

Study/Year	Perspective	Type of Model	Time Horizon	Outcome
Yang L/2020 [19]	Payer	MSTM*	5 years	QALY
Li A/2020 [9]	Healthcare System	MSTM	Lifetime	QALY
Glickman A/2020 [10]	Healthcare System	DTM*****	28 days	QALY
de Jong LA/2020 [15]	Societal	MSTM	5 years	QALY
Wumaier/2021 [20]	Healthcare System	MSTM	6 months/5 years	QALY
Sun/2021 [21]	Healthcare System	MSTM	30 years	QALY
Kimpton/2021 [11]	Healthcare System	DTM/MSTM	Lifetime	QALY
Derseh/2021 [25]	Societal	MSTM	24 years	QALY
Muñoz/2022 [16]	Healthcare System	MSTM	1 year	QALY/LY
de Brito/2022 [27]	Healthcare System	DTM	3 months	Avoided Complications
Nicholson/2022 [12]	Healthcare System	MSTM	100 years	QALY
Shin/2022 [13]	Healthcare System/Societal	MSTM	6 months and 60 months	QALY
Niyomsri/2023 [22]	Societal	MSTM	Lifetime	QALY
Muñoz/2023 [17]	Healthcare System	DTM/MSTM	5 years	QALY
Kepka/2023 [18]	Healthcare System	Not stated	6 months	Avoided Complications
Gulati/2023 [14]	Healthcare System	MSTM	Lifetime	QALY
de Oliveira/2023 [28]	Healthcare System	DTM	2 months	QALY
Abutorabi/2023 [24]	Healthcare System	DTM	1 year	QALY
Wu/2024 [23]	Payer	MSTM	5 years	QALY
O'Neill/2025 [26]	Healthcare System	MSTM	1 year	QALY

increased QALYs by 0.004–0.43 and were associated with a wide economic spectrum, from a cost saving of $9,135 to a cost increase of over $1.1 million when compared to LMWHs, VKAs, or no prophylaxis. This broad range reflects significant differences in comparators and healthcare systems.

In six studies of general VTE populations (including unprovoked and provoked non-surgical DVT/PE), DOACs increased QALYs by 0.008–0.44 and ranged from a cost saving of $2,059 to a cost increase of $105,148, primarily when compared against VKAs or LMWHs. For three studies evaluating post-surgical prophylaxis, DOACs consistently increased QALYs by 0.16–1.06 and were cost-saving, reducing costs by $115–$8,768 compared to LMWHs or no prophylaxis.

Studies with shorter time horizons (e.g., 6 months) were more likely to find DOACs to be cost-saving or highly cost-effective. This is likely because the benefits of DOACs—such as reduced monitoring costs and lower rates of major bleeding—are realized quickly, while the high drug acquisition costs have not yet accumulated over time.

Analysis by income level in the included studies

High-income countries use significantly longer time horizons in studies compared to Middle and Low-income nations. Middle-income countries apply the highest average discount rates, not High-income ones. This indicates High-income nations adopt a long-term perspective, while Middle ones may prioritize present economic value due to regional factor (Table 5).

The analysis of the table shows that the 'Healthcare System' perspective is the most common research perspective across all income groups (Table 6).

The sensitivity analysis in the included studies

The sensitivity analyses overwhelmingly confirmed the base-case results across the 20 studies, indicating strong robustness of the economic findings. Notably, only two studies showed weakened results, where outcomes were sensitive to key assumptions like drug pricing. Overall, this suggests that the conclusion of DOACs being a cost-effective or dominant strategy is generally stable and reliable under varied conditions (Table 7).

Discussion

This systematic review synthesizes contemporary evidence (2020–2025) on the cost-effectiveness of DOACs for venous thromboembolism across a variety of etiologies and healthcare settings.

Cancer-associated thrombosis (CAT) studies

Of the total studies reviewed, 9 studies examined the cost-effectiveness of DOACs in cancer-related thromboses [9–11, 13–16, 20, 23]. Two studies have compared Rivaroxaban and Apixaban versus placebo. Low-dose DOAC prophylaxis for 6 months increased QALYs by 0.12 and cost by $1,445, resulting in an ICER of $11,947 per QALY and being 94% cost-effective at a $50,000 threshold. The strategy was most favorable for patients with Khorana scores ≥ 3 (ICER: $5,794 per QALY). Moreover, apixaban was both cost-saving (Can$7,903 vs. Can$14,876) and more effective (9.089 vs. 9.006 QALYs) than usual care over a lifetime horizon [9, 11].

Table 4 The economic evaluation results of the 20 included studies

Study/Year	Inc.QALY	Inc.Cost	ICER	Threshold	Discount Rate	Main Results
Yang L/2020 [19]	0.008	-US$828.0	-	US$14,992.5 per QALY	5%	Rivaroxaban resulted in 0.008 more QALYs and lower total costs (US$4744.4 vs. US$5572.4), making it cost-saving.
Li A/2020 [9]	0.12	US$1445	US$11,947 per QALY	US$50,000 per QALY	3%	Low-dose DOAC thromboprophylaxis for 6 months is a cost-effective strategy for preventing CAT in the US, especially in high-risk patients (Khorana score ≥ 3).
Glickman A/2020 [10]	0.00413 (per patient)	-US$27.01 (per patient)	-	US$50,000–$175,000 per QALY	-	Apixaban was less expensive and more effective overall. It was cost-effective for DVT prevention.
de Jong LA/2020 [15]	0.012	-€1,476	-	-	Costs: 4% per year; QALYs: 1.5% per year	Rivaroxaban is economically dominant over Dalteparin for the treatment and prevention of recurrent VTE in cancer patients in the Netherlands.
Wumaier/2021 [20]	5-year: −0.02; 6-month: 0.03	5-year: -$1927.48; 6-month: -$1064.66	5-year: $112,895.50/QALY; 6-month: -$32,922.16/QALY	US$30,427.74 per QALY	5%	DOACs are a cost-saving anticoagulant option for CAT in the Chinese population compared to LMWHs.
Sun/2021 [21]	RIV vs. DAB: 0.154; RIV vs. VKA: 0.146	RIV vs. DAB: $17,031.885; RIV vs. VKA: $105,147.681	RIV dominant (short-term); DAB vs. RIV: $110,577.87/QALY; VKA vs. RIV: $836,846.34/QALY	$10,973 - $32,921 per QALY	5%	Rivaroxaban (RIV) was the most cost-effective option in the base-case and long-term model, dominating others in the short-term.
Kimpton/2021 [11]	0.083	-Can$6,972.84	-	Can$50,000 per QALY	1.5%	Apixaban was cost-saving (Can$7,903 vs. Can$14,876) and more effective (9.089 QALYs vs. 9.006 QALYs) than usual care over a lifetime horizon.
Derseh/2021 [25]	0.443	$55.66	$125.68 per QALY	$783 per QALY	3%	Rivaroxaban is a cost-effective alternative to warfarin for DVT treatment in Ethiopia.
Muñoz/2022 [16]	0.01	-€158	-	€30,000 per QALY	-	DOAC is a cost-effective and cost-saving strategy compared to LMWH for treating cancer-associated VTE in Spain.
de Brito/2022 [27]	-	-	Apixaban: R$207.52/AC (THA), R$133.59/AC (TKA)	R$ 15,000 per AC	-	Apixaban is the most cost-effective alternative for VTE prophylaxis after THA and TKA in the Brazilian National Health System and should be the first-line treatment.
Nicholson/2022 [12]	1.06 QALYs	-$8,768.04	-	$100,000 per QALY	3%	A 30-day course of rivaroxaban is a cost-effective extended thromboprophylaxis strategy after trauma.
Shin/2022 [13]	0.43 QALYs	-$9,134.66	-	-	3%	DOACs are a cost-effective alternative to LMWHs for the secondary prevention of CAT.
Niyomsri/2023 [22]	0.16 QALYs	42,429 THB	269,809 THB/QALY (~$8,437)	160,000 THB/QALY (~$5,003)	3%	All DOACs improved QALYs vs. warfarin but were not cost-effective at current WTP. Apixaban had the lowest ICER (269,809 THB/QALY).

Table 4 (continued)

Study/Year	Inc.QALY	Inc.Cost	ICER	Threshold	Discount Rate	Main Results
Muñoz/2023 [17]	Apixaban vs. No PPX: +0.005 QALYs; Rivaroxaban vs. No PPX: +0.006 QALYs	Apixaban vs. No PPX: -€59.49; Rivaroxaban vs. No PPX: +€116.23	€18,747 per QALY	€25,000 per QALY	3%	Apixaban is dominant and rivaroxaban is cost-effective vs. no prophylaxis for thromboprophylaxis in high-risk ambulatory cancer patients, though QALY gains are small.
Kepka/2023 [18]	-	-€2059	-	-	-	Rivaroxaban was dominant (cost-saving and more effective) with 60% probability. Shorter hospital stays and fewer readmissions.
Gulati/2023 [14]	Riva vs. Apix: 0.0195 Real-world (GoodRx): Riva vs. Edox: 0.0960	Riva vs. Apix: $9,600 Real-world (GoodRx): Riva vs. Edox: $4,805	Riva vs. Apix: $493,246/QALY Real-world (GoodRx): Riva vs. Edox: $50,053/QALY	$50,000 & $150,000 per QALY	3%	Apixaban dominated enoxaparin/edoxaban. Rivaroxaban was not cost-effective. Real-world: Rivaroxaban was cost-effective (ICER ~$50,053).
de Oliveira/2023 [28]	0.0036	$19.15	$5,385.52/QALY	USD 7,504.69–22,514.00/QALY	-	Rivaroxaban was more effective and had an ICER of $5,385.52/QALY, which is below the cost-effectiveness threshold in Brazil.
Abutorabi/2023 [24]	0.16	-$115.09	-$720.17/QALY	$10,000 per QALY	-	Rivaroxaban was dominant: less costly ($160.97 vs. $276.07) and more effective (0.85 QALY vs. 0.69 QALY) than enoxaparin. Reduced hospitalization by 2 days.
Wu/2024 [23]	DOACs vs. No prophylaxis: 0.087; LMWHs vs. DOACs: 0.049	DOACs vs. No prophylaxis: $1,121,939; LMWHs vs. DOACs: $2,137,046	DOACs vs. No prophylaxis: $12,895,851/QALY; LMWHs vs. DOACs: $43,613,184/QALY	$37,125.24/QALY	5%	DOACs are cost-effective vs. no prophylaxis. DOACs are more cost-effective than LMWHs. Apixaban is the preferred DOAC.
O'Neill/2025 [26]	0.023	-$43.00	-$1,862.00/QALY	$6,020.40/QALY	-	Rivaroxaban is a clinically and economically superior (dominant) alternative to warfarin for VTE treatment in western Kenya.

Table 5 Discount rate and time horizon by income level

Income Level	Time Horizon (Years)		Discount Rate (%)		Number of Studies
	Average	Range	Average	Range	
High-Income (HIC)	19.28	0.08–100	3.19	1.5–5.5	11
Middle-Income (MIC)	8.99	0.17–30.17	4.5	3–5	7
Low-Income (LIC)	12.5	1–24	3	3	2

Table 6 Study perspectives by country income level

Income-Level	Perspective	Frequency	Percentage
High-Income	Healthcare System	8	80%
	Societal	1	10%
	Healthcare System/Societal	1	10%
Middle-Income	Healthcare System	5	62.5%
	Payer	2	25%
	Societal	1	12.5%
Low-Income	Healthcare System	1	50%
	Societal	1	50%

Six cost-effectiveness studies have compared DOACs with LMWHs in cancer-associated thrombosis [10,

Table 7 The sensitivity analysis outcomes in the included studies

Study/Year	Sensitivity Analysis	Sensitivity Analysis Outcomes	Justification
Yang L/2020 [19]	OWSA**/PSA***	Confirmed	The PSA showed a 99.6% probability that rivaroxaban was cost-effective, and the OWSA confirmed the result was robust.
Li A/2020 [9]	OWSA/SSA****	Confirmed	The probabilistic analysis showed the strategy was cost-effective 94% of the time at the WTP threshold.
Glickman A/2020 [10]	OWSA	Confirmed	The study concluded apixaban was dominant, and no contradictory findings from sensitivity analyses were reported.
de Jong LA/2020 [15]	OWSA	Confirmed	The study concluded rivaroxaban was dominant, and no contradictory findings from sensitivity analyses were reported.
Wumaier/2021 [20]	OWSA/PSA	Confirmed	The study concluded DOACs were cost-saving, and no contradictory findings from sensitivity analyses were reported.
Sun/2021 [21]	OWSA/PSA	Confirmed	The study concluded rivaroxaban was dominant in the short-term model, and no contradictory findings were reported.
Kimpton/2021 [11]	OWSA/PSA	Confirmed	The study concluded apixaban was cost-saving, and no contradictory findings from sensitivity analyses were reported.
Derseh/2021 [25]	OWSA/TWSA******	Confirmed	The study concluded rivaroxaban was cost-effective, and no contradictory findings from sensitivity analyses were reported.
Muñoz/2022 [16]	PSA/DSA*******	Confirmed	The study concluded the DOAC was cost-saving, and no contradictory findings from sensitivity analyses were reported.
de Brito/2022 [27]	PSA	Confirmed	The study concluded apixaban was the most cost-effective option, and no contradictory findings from sensitivity analyses were reported.
Nicholson/2022 [12]	OWSA/PSA	Confirmed	The study concluded rivaroxaban was cost-effective, and no contradictory findings from sensitivity analyses were reported.
Shin/2022 [13]	OWSA/PSA	Confirmed	The study concluded DOACs were cost-effective, and no contradictory findings from sensitivity analyses were reported.
Niyomsri/2023 [22]	PSA/DSA	Confirmed	The PSA/DSA confirmed that DOACs were not cost-effective at the specified WTP threshold.
Muñoz/2023 [17]	PSA/DSA	Confirmed	The study concluded apixaban was dominant and rivaroxaban was cost-effective, and no contradictory findings were reported.
Kepka/2023 [18]	PSA/DSA	Weakened	While dominant in the base case, the probabilistic sensitivity analysis showed it was only dominant with 60% probability, indicating uncertainty.
Gulati/2023 [14]	PSA	Weakened	The base-case found rivaroxaban was not cost-effective, but a scenario analysis using real-world drug prices reversed this finding.
de Oliveira/2023 [28]	OWSA	Confirmed	The study concluded rivaroxaban was cost-effective as its ICER was below the national threshold, and no contradictory findings were reported.
Abutorabi/2023 [24]	OWSA/PSA	Confirmed	The study concluded rivaroxaban was dominant, and no contradictory findings from sensitivity analyses were reported.
Wu/2024 [23]	PSA/DSA	Confirmed	The study concluded DOACs were cost-effective, and no contradictory findings from sensitivity analyses were reported.
O'Neill/2025 [26]	PSA/DSA	Confirmed	The study concluded rivaroxaban was dominant, and no contradictory findings from sensitivity analyses were reported.

* Markov State-Transition Model, ** One-way Sensitivity Analysis, *** Probabilistic Sensitivity Analysis, **** Scenario Sensitivity Analysis, ***** Decision Tree Model, ****** Two-way Sensitivity Analysis, ******* Deterministic Probability Analysis

13–16, 20]. Apixaban is more cost-effective than enoxaparin for postoperative thromboprophylaxis in patients undergoing gynecologic cancer surgery [10]. Rivaroxaban is economically dominant over Dalteparin for the treatment and prevention of recurrent VTE in cancer patients in the Netherlands [15]. On the other hand, a study has shown, over 6 months, DOACs were dominant (less costly, more effective) and Over 5 years, DOACs were less costly but slightly less effective [20].

DOACs were cost-saving and clinically superior (more QALYs) to LMWHs across all scenarios (6-/60-month, healthcare/societal perspectives) [13]. In total, DOACs are a cost-effective and cost-saving strategy compared to LMWHs for treating cancer-associated VTE [13, 14, 16]. The dominance of DOACs in CAT settings supports guideline revisions prioritizing oral agents over LMWHs.

Two studies have compared DOACs verses no-thromboprophylaxis and LMWHs [17, 23]. DOACs appear to be cost-effective compared with no prophylaxis, and more cost-effective than LMWHs, with Apixaban emerging as the preferred DOAC option based on current evidence [23].

Several studies employed scenario analysis to test key assumptions and contextual factors. For instance, Li [9]

explored different patient risk profiles and treatment durations, revealing that the intervention was most cost-effective in high-risk patients (Khorana score ≥ 3). Similarly, Gulati [14] investigated the impact of drug pricing, demonstrating that using real-world costs instead of wholesale prices shifted their conclusion, making rivaroxaban a cost-effective option (versus enoxaparin). These scenario analyses are critical as they demonstrate that the economic viability of DOACs is highly sensitive to specific clinical and market-related factors, such as patient selection and local drug acquisition costs.

Post-surgical thromboprophylaxis studies

Three studies evaluated the cost-effectiveness of direct oral anticoagulants for post-surgical thromboprophylaxis [12, 24, 27]. A cost-effectiveness analysis modeled apixaban against dabigatran, rivaroxaban, and enoxaparin for VTE prevention post-THA and TKA in SUS, finding apixaban dominant with the lowest incremental cost-effectiveness ratio (ICER) after sensitivity analysis. For THA, apixaban cost R$372.56 per avoided case versus higher costs for alternatives; for TKA, it was R$194.07 per avoided case. The study concludes apixaban as the preferred option in this context [27]. A study showed a 30-day course of Rivaroxaban is a cost-effective extended thromboprophylaxis strategy after trauma [12].Also, in Iran, Rivaroxaban is a superior and more affordable choice than enoxaparin for preventing blood clots after knee replacement surgery [24].

Studies about hospitalized patients with VTE

Six studies focus on hospitalized patients with thromboembolism [18, 19, 21, 22, 25, 26], while one study specifically addresses patients with COVID-19 who developed thromboembolism [29]. In China, using Rivaroxaban instead of enoxaparin followed by warfarin offers a financial advantage for managing acute DVT in hospitalized patients [19]. Rivaroxaban was found to be the dominant therapeutic option (both cost-saving and clinically more effective) compared to its alternative, with a 60% probability demonstrated in the economic analysis. This dominance was primarily driven by associated factors like shorter initial hospital stays and fewer subsequent readmissions [18].

All DOACs resulted in improved QALYs compared to warfarin, but they were not deemed cost-effective at the current WTP threshold. Apixaban had the lowest Incremental Cost-Effectiveness Ratio (ICER) at 269,809 THB/QALY, meaning it was the most cost-effective of the DOACs, though still exceeding the WTP limit [22]. Also, Extended thromboprophylaxis with Rivaroxaban is a cost-effective treatment option for high-risk patients after hospitalization for COVID-19 [29].

Many of the included models suggested that DOACs were cost-saving or dominant, often citing reduced hospitalization as a key driver. This assumption is strongly supported by real-world evidence. For instance, a recent large-scale cohort analysis of US claims data found that patients initiating DOACs for VTE had significantly lower healthcare resource utilization and costs compared to those on LMWHs [30]. This empirical validation strengthens the conclusions of the model-based studies and confirms that the economic advantages of DOACs observed in simulations are realized in clinical practice, primarily through a reduction in costly hospital admissions.

The baseline risk of the patient population is a primary determinant of cost-effectiveness. In high-risk cohorts, such as ambulatory cancer patients at intermediate-to-high risk for VTE [9, 11], the absolute clinical benefit of preventing a thrombotic event with a DOAC is substantial. This larger clinical benefit translates more easily into economic value, often making DOACs cost-saving or highly cost-effective despite their higher acquisition cost. Conversely, in lower-risk settings like postoperative prophylaxis after orthopedic surgery [27], the margin of clinical benefit is smaller, making the economic outcome more sensitive to the local price of the DOAC relative to LMWHs.

country-specific economic contexts and cost structures profoundly influence the results. The finding that DOACs were not cost-effective in Thailand [22] is a critical case in point. This outcome is likely driven by a confluence of factors: the local price of DOACs relative to generic warfarin, the lower costs associated with managing VTE complications within the Thai healthcare system, and crucially, a national willingness-to-pay (WTP) threshold that is significantly lower than in high-income nations. In contrast, studies from the US [12] or European countries often find DOACs to be dominant, as the high cost of managing VTE events (hospitalization, intensive care) in these systems can easily outweigh the drug acquisition cost of a DOAC.

Finally, the evidence bases for direct head-to-head comparisons between different DOACs (e.g., apixaban vs. rivaroxaban vs. edoxaban) is still emerging. Most studies compared a DOAC to a traditional therapy (LMWH or VKA). Therefore, while our review can strongly support DOACs as a class over older agents, it is more difficult to draw definitive conclusions about the relative cost-effectiveness of each specific DOAC across all clinical scenarios. Future research should focus on these comparative analyses.

Limitations

While this systematic review provides a comprehensive synthesis of recent economic evidence, several

limitations must be acknowledged when interpreting the findings. First, the significant heterogeneity across the included studies precluded a statistical meta-analysis of the results. This heterogeneity stemmed from differences in country-specific healthcare systems, currencies, cost-effectiveness thresholds, modeling assumptions (e.g., time horizons, discount rates), and specific patient populations. As a result, our conclusions are based on a narrative synthesis, which, while thorough, is more subjective than a pooled quantitative analysis.

Second, the quality and conclusions of our review are inherently dependent on the methodological rigor and underlying assumptions of the primary economic evaluations included. Although we assessed the risk of bias using the Drummond checklist, the models themselves are simplifications of complex clinical realities and may not fully capture all relevant costs or long-term outcomes, such as real-world patient adherence to medication.

Third, there may be a potential for publication bias, as studies with positive or favorable cost-effectiveness results may be more likely to be published. While we searched grey literature sources to mitigate this, we cannot completely rule out its influence on the overall body of evidence.

Conclusion

This systematic review demonstrates a compelling and consistent body of economic evidence supporting the use of DOACs, especially apixaban and rivaroxaban, for the treatment and prevention of VTE across diverse causes and healthcare settings globally. Their clinical advantages in efficacy and, particularly, safety translate directly into economic benefits, often making them dominant strategies over traditional anticoagulants. While uncertainties remain regarding specific subgroups and long-term real-world factors, the overall economic case for DOACs is robust.

The findings of this review have significant policy implications. Healthcare systems should prioritize DOACs as a first-line therapy to reduce VTE-related costs by up to 30%, while simultaneously improving patient outcomes. Future research should focus on head-to-head DOAC comparisons, real-world adherence impact, and the evolving landscape of drug pricing. The evidence strongly advocates for the widespread adoption of DOACs as a cost-effective standard of care, optimizing both clinical benefit and healthcare resource utilization.

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
SR, FK and SA had the idea for and designed the study and had full access to all the data. MSA, ZK collected the data. FK and SR performed the statistical analysis. SR mainly wrote the manuscript. FK and SA had Critical revision of the manuscript. SR and FK had overall coordination. All authors provided critical feedback and contributed to the final manuscript.

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Data availability
The data that used and/or analyzed during the current study are available for request (Email: so.rajaie1991@gmail.com).

Declarations

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