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Review Article

Economic evaluations of genotype-guided warfarin dosing in cardiovascular patients: A systematic review

Pande Made Desy Ratnasari[1,5], Tri Murti Andayani[2*], Ika Puspita Sari[2], Muhamad Taufik Ismail[3], Dwi Endarti[4]

[1] Doctoral Graduate Program, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia
[2] Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia
[3] Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Dr. Sardjito Hospital, Yogyakarta, Indonesia
[4] Department of Pharmaceutics, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia
[5] Department of Pharmacy, Faculty of Pharmacy and Health Sciences, Universitas Pendidikan Nasional, Bali, Indonesia

ABSTRACT

Genotype-guided warfarin dosing has been shown to enhance clinical outcomes. However, this method has not been widely adopted in many countries. Furthermore, economic evaluations of this strategy show promising results, highlighting the need for a more comprehensive synthesis of the available evidence. This study aims to evaluate whether genotype-based warfarin dosing is more cost-effective than standard dosing in patients with cardiovascular disease. A literature search was conducted in Scopus and PubMed up to March 2026, following PRISMA guidelines. The studies included in this review focused on patients with cardiovascular disease receiving warfarin therapy, comparing genotype-guided warfarin dosing with standard therapy, and assessing outcomes in terms of ICER/QALY, thromboembolic and/or bleeding events. The reporting quality of the included studies was assessed using the CHEERS checklist. A total of ten out of 696 articles met the inclusion criteria (577 PubMed; 119 Scopus). The majority of the studies (60.00%) used cost-effectiveness analysis from the healthcare provider's perspective, with Markov models (70.00%). The cost of genetic testing varied across countries (USD 125-550). All studies reported increases in QALY and reductions in the risk of clinical events. However, only four studies concluded that this strategy was cost-effective. In contrast, six studies indicated that the high cost of genetic testing increased the overall cost of therapy. In conclusion, while genotype-guided warfarin dosing has been associated with improved clinical outcomes, its cost-effectiveness remains inconsistent across studies. Therefore, its implementation should be considered selectively, particularly in high-risk populations or in settings with lower costs for genetic testing.

Keywords:
Warfarin; Cardiovascular disease; Cost-effectiveness; Genetic polymorphism; Genotype-guided dosing.

1. INTRODUCTION

Warfarin is an oral anticoagulant commonly prescribed to prevent and treat thromboembolic events, such as atrial fibrillation (AF), venous thromboembolism, valvular heart disease, and ischemic stroke [1]. A meta-analysis indicates that warfarin lowers the risk of stroke and systemic thromboembolism by 64% and reduces mortality by 26% when compared to a placebo [2,3]. Although warfarin is highly effective, it has a narrow therapeutic range and high interpatient variability, resulting in dosing differences of 10-20-fold to achieve the target International Normalized Ratio (INR) [4]. Higher doses may increase the risk of bleeding, whereas lower doses are insufficiently effective at preventing thromboembolic events [5].

One such form of variability is genetic polymorphism in *Cytochrome P450 2C9* (*CYP2C9*) and *Vitamin K Epoxide Reductase Complex 1* (*VKORC1*), which play a crucial role in the development of precision medicine.

***Corresponding author:**
* Tri Murti Andayani Email: trimurtia@ugm.ac.id

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Polymorphisms in the *CYP2C9* gene are associated with the pharmacokinetic phase, specifically the primary hepatic metabolism of warfarin. Polymorphisms in *VKORC1* are associated with the pharmacodynamic phase, as they are directly related to the mechanism of warfarin inhibition [6–9]. The *CYP2C9*2* and *CYP2C9*3* variants are associated with a reduced warfarin dosage requirement of approximately 5-10%, while *VKORC1* is associated with increased sensitivity to warfarin and a reduced dosage requirement of 20-25% [4,10–12].

China and Russia have shown that genotype-guided warfarin dosing (*CYP2C9* and *VKORC1*) is associated with a reduced risk of bleeding and thromboembolic complications in patients with atrial fibrillation (AF) [13–17]. Recent studies in Croatia, the United Kingdom, Sweden, and South Korea have shown that genotype-guided warfarin dosing is a cost-effective approach in patients with AF [18–20]. Although genotype-guided warfarin dosing has not been routinely implemented in some countries, this strategy plays an important role in reducing bleeding and thromboembolic events, improving time to reach the therapeutic INR range, and improving patients' quality of life. Several economic evaluations have been conducted to assess whether genotype-guided warfarin dosing is a cost-effective strategy in patients with cardiovascular disease [18–27].

Several previous studies have reviewed the economic evaluation of genotype-guided warfarin dosing, but none specifically examined warfarin [28–32]. There is one review presented as expert opinion, but it is limited to narrative articles published between 2004 and 2010. This review did not critically assess the interpretations or conclusions of the economic studies, nor did it explore cost-determining factors or other factors influencing outcomes [33]. Therefore, a comprehensive systematic review specifically focused on the economic evaluation of genotype-based warfarin dosing is still unavailable. This systematic review aims to analyze the most recent economic evaluation studies in three main areas: (1) the effectiveness of this strategy in preventing thromboembolic events or bleeding, (2) the economic evaluation methods used to assess the effectiveness of genetic testing, and (3) the factors that influence changes in the base-case scenario. Additionally, the review will determine whether this strategy is cost-effective, cost-saving, uncertain, or not cost-effective.

2. METHODS

The systematic review protocol was registered with PROSPERO, the international database for prospectively registered systematic reviews, under the identification number CRD420261367679 [34]. The results are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [35].

2.1. Review question and literature search strategy

The review questions were created using the Population, Intervention, Comparator, Outcomes, Study design (PICOS) framework, as summarized in Table 1. Literature searches were conducted to identify relevant articles published from database inception to March 2026 using Scopus and PubMed. The search strategy consisted of three groups of keywords linked by the Boolean operators "OR" and "AND." The terms used included "cost analysis" OR "cost effectiveness" OR "economic evaluation" OR pharmacoeconomics AND pharmacogenetics OR "genetic polymorphism" OR "single nucleotide polymorphism" OR mutation OR genotype AND warfarin OR coumarin OR coumadin. The screening and selection of studies were performed using the Rayyan web application (rayyan.qcri.org). The search was limited to studies involving human subjects and published in English. Publications such as editorials, letters, historical articles, abstracts, and review articles were excluded.

Table 1. A systematic review question informed by the PICOS framework**.**

Component	Description
Review question	Is genotype-guided warfarin dosing more cost-effective than standard dosing for warfarin in patients with cardiovascular disease?
Population (P)	Patients with cardiovascular disease who are receiving warfarin therapy
Intervention (I)	Genetic polymorphism testing as a guide for warfarin dose adjustment
Comparator (C)	Without genetic polymorphism testing for warfarin dose adjustment, the patient receives a standard warfarin dose based on their clinical conditions.
Outcomes (O)	1. Incremental Cost-Effectiveness Ratio (ICER) 2. Tromboemboli and or bleeding 3. International Normalized Ratio (INR) 4. Time in Therapeutic Range (TTR)
Study design	Cost-effectiveness analysis (CEA), Cost Utility Analysis (CUA) Cost benefit analysis (CBA), Markov model, decision tree model

2.2. Study selection

Two reviewers independently screened the titles of all identified articles. Studies that one reviewer considered potentially eligible were evaluated further through independent abstract screening. Full-text articles were retrieved only when both reviewers agreed that the study met the established inclusion and exclusion criteria. Any disagreements were resolved through discussion with a third, independent reviewer. In total, ten out of the 696 articles met the selection criteria and were included in this review.

2.3. Inclusion and exclusion criteria

The inclusion criteria include: 1) Adult patients (≥18 years) with cardiovascular diseases requiring warfarin therapy, such as AF, venous thromboembolism (deep vein thrombosis and pulmonary embolism), valvular heart disease, and ischemic stroke. 2) Studies that evaluate warfarin dosing based on genetic testing, particularly variants of *VKORC1*, *CYP2C9*, and/or *CYP4F2*. 3) Studies comparing warfarin dosing based on genetic testing with standard warfarin dosing (based on demographic and clinical factors without genetic testing). 4) Full economic evaluation studies, including cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA). 5) Only full-text articles are available for data extraction. The exclusion criteria are as follows: 1) Inadequate reporting of interventions or outcomes. 2) Patients who did not receive warfarin therapy. 3) Studies that focus on conditions other than cardiovascular diseases or on anticoagulants other than warfarin (such as direct oral anticoagulants, low molecular weight heparins, and fondaparinux). 4) Studies that did not assess a full economic evaluation, such as cost analyses without outcome comparisons, budget impact analyses, reviews, editorials, letters, conference abstracts without full-text, and purely clinical studies without economic outcomes. 5) Studies published in languages other than English.

2.4. Data extraction

Data were extracted into two components, consisting of general characteristics and economic evaluation results, as detailed in Tables 2 and 3. The study characteristic included the author, year of publication, country, perspective, time horizon, discount rate, currency, and type of economic evaluation. The economic evaluation results included genotyping costs, outcomes, Incremental Cost-Effectiveness Ratio (ICER), Willingness-To-Pay (WTP) thresholds, sensitivity analysis, conclusions, and decisions.

The ICERs were extracted and reported in the original currency and price year of each study. For descriptive comparison, these values were standardized to 2023 USD which was the most recent price year represented among the included studies [27], using a two-stage approach based on the Campbell and Cochrane Economics Methods Group (CCEMG) cost-conversion method. First, the values were inflated from the reported price year to 2023 in the original currency using the country-specific Consumer Price Index (CPI) from the

Table 2. The study characteristics (n=10).

Author, year	Country	Clinical Indication	Population	Type of economic evaluation	Perspective	Time horizon, discounting rate
You et al., 2009 [21]	China	Not indication-specific	≥18 years	CEA, decision tree model	Health-care providers	12 month, 3%
Patrick, et al., 2009 [22]	USA	AF	A 70-year-old patients	CEA, Markov model	Societal perspective	Lifetime, 3%
Eckman, et al., 2009 [23]	USA	Not indication-specific	60-69 years	CEA, Markov model	Societal perspective	Lifetime, 3%
Meckley et al., 2010 [26]	USA	Not indication-specific	A 65-year-old	CEA, Markov model	Health-care providers	Lifetime, 3%
Chong et al., 2014 [24]	Thailand	Not indication-specific	45 years old	CEA, decision tree and Markov model	Societal and health care providers	Lifetime, 3%
Mitropoulou et al., 2015 [19]	Kroasia	AF	≥65 years	CEA, decision tree model	Health-care providers	12 month, n/a
Verhoef et al., 2016 [20]	UK and Sweden	AF	Adult patients	CEA, Markov model	Health-care providers	Lifetime, UK:3.5%, Sweden: 3.0%
Kim et al., 2017 [18]	Korea	MHVR	Adult patient	CEA, Markov model	Health-care providers	Lifetime, 3%
Hemati et al., 2024 [25]	Iran	MPHV	≥18 years	CEA, decision tree model	Health-care providers	12 month, n/a
Anand et al., 2024 [27]	India	AF	18-65 years	CEA, Markov model	Patient's perspective	Lifetime, 3%

Notes: USA (United States of America), UK (United Kingdom), AF (Atrial Fibrillation), MHVR (Mechanical Heart Valve Replacement), MPHV (Mechanical Prosthetic Heart Valve), CEA (Cost-Effectiveness Analysis), n/a (not available)

Table 3. The economic evaluation results genotype-guide warfarin dosing (n=10).

Author, year	Outcome	Genotyping costs	ICER values	WTP Threshold	One-way sensitivity analysis	Probabilistic sensitivity analysis	CE Conclusion	Decision
You et al., 2009 [21]	The genotype-guided group showed modest improvements in QALY (0.93130 vs 0.93079) and annual survival (0.99347 vs 0.99331), with a slight reduction in adverse events (0.04013 vs 0.04117).	USD 125-550	USD 347,059/ QALY (USD 2008)	USD 50,000/ QALY	Genotyping costs, out-of-range INR in standard dosing group (10%-92%).	In 10,000 PSA simulations, genotype-guided dosing was consistently more effective (100%) but more costly in 81.3% of cases. At a USD 50,000 WTP threshold, it was not cost-effective in 62.14% of simulations, while being cost-effective in 19.12% and dominant in 18.74% of cases.	Requiring cost of genotyping reduction at least <USD 22 (≥65%)	Not cost-effective
Patrick, et al., 2009 [22]	Genotype-guided dosing would increase the percentage of time patients spent in the target INR range during the first 3 months after warfarin initiation but not subsequently.	USD 400-550	USD 100,000/ QALY (USD 2007)	USD 50,000/ QALY	Age >70 years, bleeding rate, cost of genotyping.	The majority of these points fall into the upper right-hand quadrant of the cost-effectiveness plane, indicating that genotyping is more beneficial but also more costly than usual care.	Requiring reduces out-of-range INR ratio values 5-9% points compared with usual care.	Not cost-effective
Eckman, et al., 2009 [23]	Genotype-guided dosing results in a non discounted gain of 0.0026 QALY compared with standard warfarin induction or almost 1 day more over the lifetime of the patient.	USD 400	USD 172,000/ QALY (USD 2007)	USD 50,000/ QALY	Bleeding rate, cost of genotyping.	Genotype-guided dosing had a 23% chance of being both less effective and more expensive than standard warfarin (10% chance of costing less than USD 50 000/QALY and a 30% chance of costing less than USD 100 000/QALY)	Prevent greater than 32% of major bleeding events, be available within 24 hours, and cost less than USD 140.	Not cost-effective
Meckley et al., 2010 [26]	Pharmacogenomic testing reduced the incidence of bleeds (0.17%) and deaths (0.13%), increase thromboembolic events (0.03%), resulting in a small QALY gain of 0.003 with an additional cost of USD 162.	USD 175	<USD 50,000/ QALY in 46% of simulations (USD 2007)	USD 50,000/ QALY	Pharmacogenetic cost, effectiveness parameter, *CYP2C9* probability.	Pharmacogenomics increased both costs and QALY in 84% of the simulations, and increased costs and decreased QALY in 15% of the simulations. At a USD 50,000/QALY threshold, 46% of the simulations were cost effective and at a USD 100,000/QALY level, 67% of the simulations were cost effective.	Requiring reduces test costs less than USD 13.	Not cost-effective

Notes: QALY (Quality-Adjusted Life Year), ICER (Incremental Cost-Effectiveness Ratio), WTP (Willingness-To-Pay), PSA (Probabilistic Sensitivity Analysis) CE (Cost-effectiveness), USD (United States Dollar), THB (Thai Baht), EUR (Euro), GBP (Great Britain Pound), IR (Indian Rupee), INR **(**International Normalized Ratio), PTTR (Percentage of Time to Therapeutic Range), PGx (Pharmacogenomic), N-PGx (Non-Pharmacogenomic), SEK (Swedish Krona), n/a (not available).

Table 3. The economic evaluation results genotype-guide warfarin dosing (n=10). (Continued).

Author, year	Outcome	Genotyping costs	ICER values	WTP Threshold	One-way sensitivity analysis	Probabilistic sensitivity analysis	CE Conclusion	Decision
Chong et al., 2014 [24]	Pharmacogenetic testing increased QALY by 0.002, with higher costs from both the healthcare (2,959 THB [99 USD]) and societal perspectives (2,953 THB [98 USD]) compared to usual care.	2000-5000 THB	1,477.042 THB (49,234 USD/ QALY, healthcare), 1,473.852 THB (49,128 USD, societal) (THB 2013)	160,000 THB/QALY	Relative risk of major bleeding in *VKORC1* variant genotype, efficacy of pharmacogenetic-guided dosing, cost of pharmacogenetic.	In the PSA, at a 160,000 THB (5,333 USD) per QALY threshold, 41% of the simulations were cost effective from health system perspective, and 42% of the simulations were cost effective from societal perspective.	Pharmacogenetic-guided dosing became cost-effective only when the test cost decreased by about 90% from the base case value.	Not cost-effective
Mitropoulou et al., 2015 [19]	The PGx group showed better outcomes, with 97.07% of patients experiencing no major complications compared to 89.12% in the N-PGx group. The time to achieve INR was shorter (5.64 vs 7.11 days), as was the time to reach maintenance dose (10.35 vs 13.87 days).	EUR140,25	EUR 31,225/ QALY	EUR 40,000-50,000/ QALY	n/a	All the simulation experiments felt into the North East quadrant indicating that the PGx arm was slightly more expensive but, at the same time, more effective than N-PGx.	Cost-effective	Yes
Verhoef et al., 2016 [20]	Genotyping reduced haemorrhagic events by 0.18% (UK) and 0.2% (Sweden) and thromboembolic events by 0.04% in both countries, with life expectancy gains of 0.0047 years (1.7 days) in the UK and 0.0018 years (0.7 days) in Sweden.	GBP 38 (UK); SEK 500 (Sweden)	GBP 6,702/ QALY in UK and 253,848 SEK/QALY in Sweden	GBP 20,000/QALY in UK and 500,000 SEK/QALY in Sweden	UK: risk of stroke when INR was within the therapeutic range, costs of genotyping, risk of Intracranial hemoragic (INR>5), Sweden : PTIR month 2 standar care, risk of stroke INR <2, PTIR month 1 pharmacogenetic	The ICER per QALY gained were below GBP 20,000 in 93% of the simulations in the UK and below 500,000 SEK in 67% of the simulations in Sweden.	Cost-effective	Yes

Notes: QALY (Quality-Adjusted Life Year), ICER (Incremental Cost-Effectiveness Ratio), WTP (Willingness-To-Pay), PSA (Probabilistic Sensitivity Analysis) CE (Cost-effectiveness), USD (United States Dollar), THB (Thai Baht), EUR (Euro), GBP (Great Britain Pound), IR (Indian Rupee), INR **(**International Normalized Ratio), PTTR (Percentage of Time to Therapeutic Range), PGx (Pharmacogenomic), N-PGx (Non-Pharmacogenomic), SEK (Swedish Krona), n/a (not available).

Table 3. The economic evaluation results genotype-guide warfarin dosing (n=10). (Continued).

Author, year	Outcome	Genotyping costs	ICER values	WTP Threshold	One-way sensitivity analysis	Probabilistic sensitivity analysis	CE Conclusion	Decision
Kim et al., 2017 [18]	The genotype-guided approach increased QALYs marginally (0.005; approximately 2 days of perfect health) and increased costs by USD 6.8 compared with standard warfarin therapy.	USD 140	USD 1,356.2/ QALY (USD 2016)	USD 50,000/ QALY	Effect of genotype-guide warfarin dosing (%TTR increased), cost of sequelae (long term treatment), cost of genotyping	Genotype-guided dosing was dominant in 82.7% of simulations and more effective but more costly in 17.3%, with a 99.8% probability of being cost-effective at a WTP threshold of USD 50,000/QALY gained	Cost-effective	Yes
Hemati et al., 2024 [25]	Genotype-guided dosing increases QALY by 0.07 and costs by approximately USD 177.	USD 246	USD 2,474/ QALY (USD 2022)	USD 1,500/ QALY	PTTR (genotype-guided dosing group), PTTR (standar dosing group)	Pharmacogenetic-guided dosing was not cost-effective in 86.1% of simulations, suggesting robust findings.	This requires lowering the test cost to below USD 118 and raising the utility to 0.86.	Not cost-effective
Anand et al., 2024 [27]	The genotype-guided group had a significantly higher median time in therapeutic INR (42.85% vs 8.8%; p< 0.00001) and a shorter time to reach target range (17.85 vs 33.92 days; p=0.002) compared with standard care.	n/a	IR 71,630/ QALY (IR 2023)	IR150,000/ QALY	n/a	Genotype-guided dosing consistently improved health outcomes across all simulations, with 82.8% showing increased costs alongside QALY gains and 17.2% indicating cost savings with improved effectiveness. The cost-effectiveness acceptability curve further showed a 90% probability of cost-effectiveness at a willingness-to-pay threshold of IR 71,630, which is below the commonly accepted threshold in the Indian setting, indicating a high likelihood that the intervention is cost-effective.	Cost-effective	Yes

Notes: QALY (Quality-Adjusted Life Year), ICER (Incremental Cost-Effectiveness Ratio), WTP (Willingness-To-Pay), PSA (Probabilistic Sensitivity Analysis) CE (Cost-effectiveness), USD (United States Dollar), THB (Thai Baht), EUR (Euro), GBP (Great Britain Pound), IR (Indian Rupee), INR **(**International Normalized Ratio), PTTR (Percentage of Time to Therapeutic Range), PGx (Pharmacogenomic), N-PGx (Non-Pharmacogenomic), SEK (Swedish Krona), n/a (not available).

International Monetary Fund (IMF) World Economic Outlook Database. Second, the inflation-adjusted values were converted to USD using the 2023 Purchasing Power Parity (PPP) conversion factor rather than the market exchange rate, to better reflect differences in purchasing power across countries [36,37]. When the price year was not reported, the publication year was used as a proxy (Supplementary Table S1). Given the substantial heterogeneity in the standardized values across studies, the results were synthesized narratively rather than quantitatively pooled.

2.5. Reporting quality assessment

The quality of reporting was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS), as summarized in Table 4 with a 28-item checklist. Overall reporting quality was expressed as a percentage of relevant items. Studies with a score above the 85% threshold were categorized as having high reporting quality. The quality assessment for each item is discussed in more detail in the narrative. CHEERS is a reporting guideline and was used accordingly: it evaluates whether specific items were reported, not the methodological quality, internal validity, or risk of bias of the underlying economic model [38].

3. RESULTS

3.1. Literature search results

A total of 577 articles were identified from PubMed and 119 articles from Scopus, resulting in a total of 696 articles. After screening the titles, abstracts, and full texts, ten articles were included in this review. The reasons for exclusion are summarized in Figure 1.

3.2. Study characteristics of the included studies

The study characteristics presented in Table 2 show that most studies were conducted in Asia (50.00%), followed by America (30.00%) and Europe (20.00%). Among the 10 included studies, four focused on patients with AF[19,20,22,27], two in patients with mechanical heart valves[18,25], and four examined broader cardiovascular populations without restricting eligibility to a specific clinical indication[21,23,24,26]. Among studies involving patients with AF, genotype-guided dosing

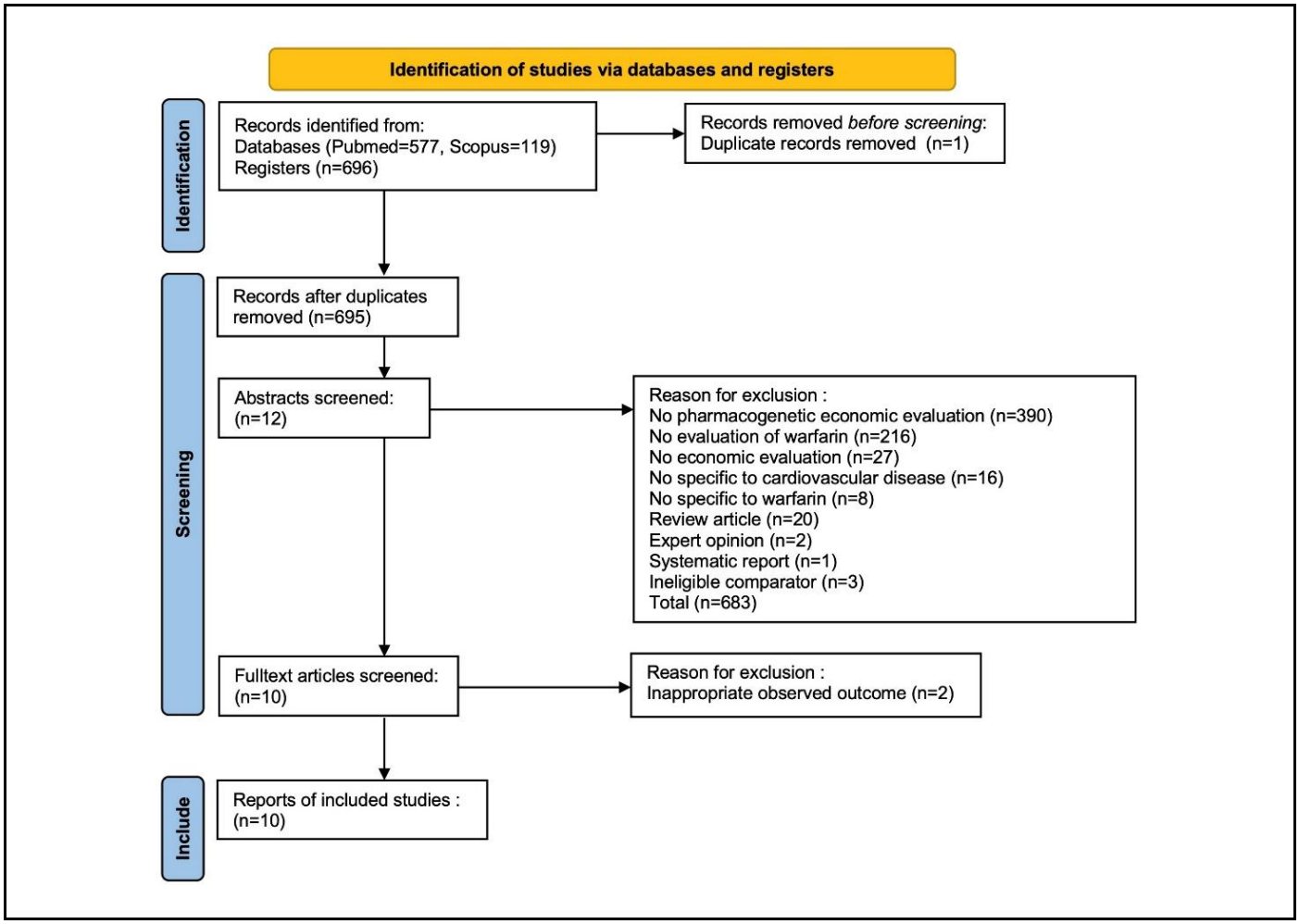


Figure 1. PRISMA flow chart of the literature search.

was considered cost-effective in three studies[19,20,27], but not cost-effective in one[22]. Similarly, findings among patients with mechanical heart valves were inconsistent, with genotype-guided dosing considered cost-effective in one study[18] not cost-effective in another[25]. Overall, the variation in cost-effectiveness findings does not appear to be explained solely by the clinical indication. The majority of studies simulated individuals aged under 60 years (60.00%) and over 60 years (40.00%), and used pharmacogenetic testing of *CYP2C9* and *VKORC1* to determine warfarin dosing. Overall, most studies conducted CEA from the healthcare provider's perspective (70.00%), with the majority using Markov models and a lifetime time horizon (70.00%). The discount rates used ranged from 3% to 3.5% in most studies (80.00%), while two studies did not report them (20.00%)".

3.3. Economic evaluation results of study

Based on the economic evaluation data in Table 3, the most commonly assessed outcomes were Quality-Adjusted Life Years (QALYs), bleeding events, thromboembolism, and total costs from each study's perspective. The cost of genetic testing varied across countries, ranging from $125-$550. Of the ten studies, only four reported that genotype-guided warfarin dosing was cost-effective. All studies indicated that pharmacogenetic testing for warfarin dosing improved QALYs and reduced the risk of thromboembolic events and major bleeding. However, six studies highlighted that the high cost of genetic testing significantly increased the overall cost of therapy.

3.4. Reporting quality

The completeness of reporting quality assessed using the CHEERS checklist showed a mean score of 89.29, as shown in Table 4. Overall, all studies (100%) demonstrated high reporting completeness (CHEERS score >75%). Sensitivity analysis reporting was varied, with evidence that both univariate deterministic and multivariate probabilistic sensitivity analyses had been conducted.

4. DISCUSSION

4.1. Study characteristics of included studies

The study characteristics of the studies analyzed, as presented in Table 2, show significant variations in geographic settings, populations, and methodological approaches. These differences are influenced by factors such as health care systems, cost structures, and WTP thresholds, which can affect the economic evaluation results of an intervention. As a result, findings from one country may not apply to another [40,41]. Thus, it is essential to consider the specific conditions and characteristics of each country's health system when interpreting these results [42].

Most studies simulate patients of various ages, including those <60 and those >60, with a significant focus on cases of AF, as shown in Table 2. Atrial fibrillation is a primary indication for the use of warfarin, as it is associated with an increased risk of stroke or thromboembolism. This condition serves as a foundation for evaluating the effectiveness of warfarin therapy. The prevalence of atrial fibrillation increases 2 to 3 times with advancing age [43,44]. From a clinical perspective, age is a critical factor in determining the balance of benefits and risks of therapy. Older patients have a higher risk of thromboembolism, which means they have the potential to gain greater benefits from warfarin therapy. However, this increased benefit comes with a heightened risk of bleeding. Cohort studies indicate that patients aged 75 and older face a major bleeding risk approximately 1.5 to 2 times higher than that of younger patients [45,46].

In the studies analyzed, pharmacogenetic testing focused on the *CYP2C9* and *VKORC1* genes was used to guide warfarin dosing (see Table 2). The selection of these two genes was based on their significant roles in influencing individual variability in response to warfarin, which involves both metabolism and drug sensitivity. Genetic variations in *CYP2C9* are known to affect the rate of warfarin metabolism, while polymorphisms in *VKORC1* are associated with the degree of sensitivity to anticoagulant effects. By considering these genetic factors, a genotype-based approach is expected to improve dosing accuracy from the start of therapy [10–12,47,48].

Several findings indicate that a *genotype-guided warfarin dosing* approach can improve anticoagulation control and reduce clinical complications compared with conventional approaches. A multicenter randomized clinical trial in the United States involving patients undergoing knee or hip replacement surgery showed that the use of genotype-based warfarin dosing can reduce clinical events such as major bleeding (2 vs 8; RR, 0.24; 95% CI, 0.05-1.15), INR ≥4 (56 vs. 77; RR, 0.71; 95% CI, 0.51-0.99), venous thromboembolism (33 vs. 38; RR, 0.85; 95% CI, 0.54-1.34) [49]. Similar results were observed in a randomized clinical trial in an Asian population, showing that using genetic information improves warfarin dose stability and reduces the need for dose adjustments during the early phase of therapy compared with traditional methods [50]. Furthermore, updated international guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC) confirm that the use of genetic information such as *CYP2C9*, *VKORC1*, *CYP4F2*, and rs12777823 can help determine warfarin dosing more accurately,

Table 4. Reporting quality assessment based on CHEERS cheklist (n=10).

No	CHEERS Cheklist	Author, Year									
		You et al., 2009	**Patrick, et al., 2009**	**Eckman, et al., 2009**	**Meckley et al., 2010**	**Chong et al., 2014**	**Mitropoulou et al., 2015**	**Verhoef et al., 2016**	**Kim et al., 2017**	**Hemati et al., 2024**	**Anand et al., 2024**
1	Title	1	1	1	1	1	1	1	1	1	1
2	Abstract	1	1	1	1	1	1	0	1	1	1
3	Backround and objectives	1	1	1	1	1	1	1	1	1	1
4	Health economic analysis plan	0	0	0	0	0	0	0	0	0	0
5	Study population	1	1	1	1	1	1	1	1	1	1
6	Setting and location	1	1	1	1	1	1	1	1	1	1
7	Comparators	1	1	1	1	1	1	1	1	1	1
8	Perspective	1	1	1	1	1	1	1	1	1	1
9	Time horizon	1	1	1	1	1	1	1	1	1	1
10	Discount rate	1	1	1	1	1	0	1	1	0	1
11	Selection of outcomes	0	1	1	1	1	1	1	1	1	1
12	Measurement of outcomes	1	1	1	1	1	1	1	1	1	1
13	Valuation of outcomes	1	1	1	1	1	1	1	1	1	1
14	Measurement and valuation of resources and costs	1	1	1	1	1	1	1	1	1	1
15	Currency, price date and conversion	1	1	1	1	1	0	0	1	1	1
16	Rationale and description of model	1	1	1	1	1	1	1	1	1	1
17	Analytics and assumptions	1	1	1	1	1	1	1	1	1	1
18	Characterizing heterogeneity	1	1	1	1	0	1	1	1	0	1
19	Characterizing distributional effects	1	1	1	1	1	1	1	1	1	1
20	Characterizing uncertainty	1	1	1	1	1	1	1	1	1	1

Notes: reporting quality assessment of included articles; high reporting completeness (>75%), moderate reporting completeness (50-75%), poor reporting completeness (<50%), CHEERS (Consolidated Health Economic Evaluation Reporting Standards)

Table 4. Reporting quality assessment based on CHEERS cheklist (n=10).

No	CHEERS Cheklist	Author, Year									
		You et al., 2009	**Patrick, et al., 2009**	**Eckman, et al., 2009**	**Meckley et al., 2010**	**Chong et al., 2014**	**Mitropoulou et al., 2015**	**Verhoef et al., 2016**	**Kim et al., 2017**	**Hemati et al., 2024**	**Anand et al., 2024**
21	Approach to engagement with patient and others affected by the study	0	0	0	0	0	0	1	0	1	0
22	Study parameters	1	1	1	1	1	1	1	1	1	
23	Summary of main results	1	1	1	1	1	1	1	1	1	1
24	Effect of uncertainty	1	1	1	1	1	1	1	1	1	1
25	Effect of engagement with patient and others affected by the study	1	1	1	1	1	1	1	1	1	1
26	Study findings, limitations, generalizability and current knowledge	1	1	1	1	1	1	1	1	1	1
27	Source of funding	1	1	1	1	1	1	1	1	1	1
28	Conflicts of interest	1	1	1	1	1	1	1	1	1	1
	Total score	25	26	26	26	25	24	25	26	25	26
	Percentage (%)	89.29	92.86	92.86	92.86	89.29	85.71	89.29	92.86	89.29	92.86

Notes: reporting quality assessment of included articles; high reporting completeness (>75%), moderate reporting completeness (50-75%), poor reporting completeness (<50%), CHEERS (Consolidated Health Economic Evaluation Reporting Standards)

accelerate the achievement of therapeutic INR, and improve the safety of anticoagulant therapy [47].

4.2. Methodological approaches in economic evaluations

Overall, all studies in this review used CEA, with the majority adopting the healthcare provider perspective, as presented in Table 2. This perspective is commonly used because it focuses on direct medical costs that are critical to the healthcare system, such as medications, diagnostic tests, hospitalizations, and the management of complications. A methodological analysis of economic evaluation publications from 1974 to 2018 indicates that approximately 74% of CEA studies used the healthcare sector or payer perspective, as these perspectives yield results more readily applicable to health policy decision-making [51]. However, the provider perspective has limitations because it typically excludes indirect costs, such as lost productivity and other socioeconomic impacts, and thus cost-effectiveness results may differ from those of the societal perspective, which assesses the economic burden more broadly [52,53].

The majority of studies use Markov models with a lifetime horizon (70.00%), a common approach in the economic evaluation of chronic diseases (see Table 2). Markov models allow for the simulation of repeated transitions between health states—such as stable conditions, thromboembolic events, bleeding, and death—thereby enabling a more realistic depiction of the disease course. The use of a lifetime horizon is also considered important because it captures all long-term consequences of interventions, including costs and health outcomes [54]. Regarding economic parameters, most studies use a discount rate of 3-3.5% (77.78%), in line with recommendations from international health economic evaluation guidelines, namely the World Health Organization (WHO) and the National Institute for Health and Care Excellence (NICE) [55,56]. The application of discounting aims to reflect the present value of future health costs and benefits, consistent with the concept of time preference in health economic evaluation [42,57].

4.3. Economic and clinical outcomes of genotype-guided warfarin dosing

According to the economic evaluation data presented in Table 3, the outcomes most commonly assessed across all studies were QALYs, the incidence of bleeding and thromboembolism, and total costs from the perspective of each study [18–21,23–27,39]. QALYs are the most widely used primary outcome measure because they capture both the increase in life expectancy and the improvement in quality of life resulting from a health intervention [58]. All studies included in this review indicated that genotype-guided warfarin dosing increased QALYs compared to standard therapy, although the increase was relatively small [18,21,23–26]. The study by You et al. (2009) reported an increase in QALYs from 0.93079 to 0.93130 in the genotype-guided dosing group, which corresponds to an increase of 0.00051 QALYs [21]. Similarly, Eckman et al. (2009) found an additional 0.0026 QALYs, equivalent to nearly one additional day of quality-adjusted life, compared to standard therapy [23].

The study by Meckley et al. (2010) also reported an increase of 0.003 QALYs, while Chong et al. (2014) demonstrated an increase of 0.002 QALYs from both the healthcare system and societal perspectives. In more recent studies, the increase in QALYs tends to be greater [24,26]. Kim et al. (2017) found an increase of 0.005 QALYs at minimal additional cost, approximately United States Dollar (USD) 6.8, compared with standard warfarin therapy [18]. Hemati et al. (2024) even reported an increase of 0.07 QALY, the largest increase among studies [25]. However, although all studies show an increase in QALY, most of these increases are relatively small in absolute terms. This explains why some studies still yield high ICERs and conclude that the strategy is not yet cost-effective [21,23–26,39].

Major bleeding events are a critical outcome because they represent the primary complication of warfarin therapy and are associated with increased mortality, hospitalizations, and a significant healthcare cost burden [59,60]. All studies in this review indicate that genotype-guided dosing tends to reduce the risk of bleeding compared to standard therapy. The study by You et al. (2009) reported a reduction in total adverse events from 0.04117 to 0.04013 in the genotype-guided dosing group [21]. Meckley et al. (2010) demonstrated that pharmacogenomic testing reduced the incidence of bleeding by 0.17% and mortality by 0.13% [26]. Chong et al. (2014) found that a reduction significantly influenced the strategy's effectiveness in the risk of major bleeding in patients with the VKORC1 variant [24]. Mitropoulou et al. (2015) reported that 97.07% of patients in the pharmacogenomic group did not experience major complications compared to 89.12% in the non-pharmacogenomic group [19]. Verhoef et al. (2016) demonstrated a 0.18% reduction in the risk of hemorrhagic events in the United Kingdom (UK) and a 0.2% reduction in Sweden [20]. Additionally, Patrick et al. (2009) stated that genotype-guided dosing increases the time patients spend within the therapeutic INR range during the early phase of therapy, thereby potentially reducing the risk of supratherapeutic INR levels and major bleeding [39]. Anand et al. (2024) also demonstrated a significant increase in therapeutic INR in the genotype-guided group (42.85% vs. 8.8%; $p<0.00001$), which is clinically associated with a reduced risk of bleeding complications [27].

In addition to bleeding, thromboembolism is also a primary outcome in the economic evaluation of warfarin because failure to achieve a therapeutic INR can increase the risk of stroke and systemic embolism [61]. However, this outcome was not consistently assessed across all studies. Out of the ten studies analyzed, only two reported thromboembolic events as an outcome: Meckley et al. (2010) and Verhoef et al. (2016) [20,26]. Verhoef et al. (2016) found that genotype-guided dosing reduced the risk of thromboembolism by 0.04% in both the UK and Sweden [20]. In contrast, Meckley et al. (2010) reported a slight increase in thromboembolic events by 0.03%, although their overall strategy still resulted in increased QALYs and reduced mortality. This indicates that the impact of genotype-guided dosing on thromboembolism is likely smaller than its effect on bleeding [26].

Several studies have shown that genotype-guided warfarin dosing can improve INR stability and Time in Therapeutic Range (TTR), and reduce the risk of major bleeding and thromboembolism compared to the standard approach. A meta-analysis encompassing 27 randomized controlled trials involving a total of 9,906 patients reported that the genotype-based approach significantly increased TTR, achieved therapeutic INR levels more quickly, reached a stable dose in a shorter time, and reduced the risk of major bleeding and thromboembolic events compared to the standard warfarin group [62]. Similar findings were observed in the Genetic Informatics Trial, which showed that the genotype-guided group experienced a reduction in the composite clinical outcome of major bleeding (2 vs 8; RR 0.24; 95% CI, 0.05-1.15), venous thromboembolism (33 vs. 38; RR, 0.85; 95% CI, 0.54-1.34), and death compared to the standard therapy group. A genotype-based approach is also associated with faster achievement of therapeutic INR and more stable anticoagulation control during the early phase of warfarin therapy [49]. In Asian populations, an open-label randomized trial showed that genotype-guided dosing significantly reduced the need for dose adjustments during the first two weeks of therapy compared to the traditional approach (1.77 vs 2.93 dose titrations; $p<0.001$). The genotype-based group also demonstrated more stable INR values during therapy, potentially reducing the risk of both bleeding and thromboembolic complications [50,63].

4.4. Factors influencing cost-effectiveness and sensitivity analysis

The ICERs reported in the analyzed studies (see Table 3) showed considerable variation, reflecting differences in health system contexts, model assumptions, and the costs of genetic testing. Overall, the ICERs ranged from USD 1,356/QALY to USD 347,059/QALY in the original currencies and price years reported by the studies. For descriptive comparison, all ICERs were standardized to a common currency and price year (2023 USD, adjusted using PPP), which represented the most recent price year among the included studies [36,37]. After standardization, the ICERs still ranged from approximately USD 1,721/QALY to more than USD 491,123/QALY (Supplementary Table S1), suggesting that the observed heterogeneity was primarily driven by differences in study populations, model structures, and country-specific WTP thresholds rather than by currency or price-year differences alone. Compared with the commonly used WTP threshold of approximately USD 50,000/QALY, only a few studies reported that the genotype-guided warfarin dosing strategy fell below this threshold and could be considered cost-effective. Meanwhile, most other studies reported ICERs exceeding the WTP threshold, indicating the intervention was deemed not cost-effective [18,21,23–26].

To further contextualize the standardized ICERs in relation to each country's economic capacity, ICER-to-GDP-per-capita ratios were calculated using 2023 GDP per capita at current prices from the International Monetary Fund World Economic Outlook Database (Supplementary Table S1). This relative comparison revealed a markedly different pattern from the absolute ICER comparison. You et al. (2009, China) had both the highest absolute ICER (USD 491,123/QALY) and the highest ICER-to-GDP-per-capita ratio (38.98 times GDP per capita), whereas Kim et al. (2017, South Korea) had a low absolute ICER (USD 1,721/QALY) and a substantially lower relative ratio (0.05 times GDP per capita). Notably, Eckman et al. (2009, USA) and Anand et al. (2024, India) showed a substantial difference in absolute ICERs (USD 243,397 vs. USD 3,142/QALY), despite their ICER-to-GDP-per-capita ratios providing a more context-specific basis for comparison. These findings illustrate that direct cross-country comparisons of ICERs based solely on absolute monetary values may be misleading without considering differences in the economic context of each country.

One-way sensitivity analysis indicates that the base-case results across all studies are highly influenced by economic and clinical parameters, particularly the cost of genetic testing, bleeding risk, INR/TTR/PTTR control, treatment effectiveness, and the probability of thromboembolic events (see Table 3). Genotyping cost is the factor that most consistently influences the ICER. Several studies indicate that genotype-guided warfarin dosing strategy becomes cost-effective only if testing costs are substantially reduced, such as to below USD 22 in the study by You et al. (2009), below USD 13 in Meckley et al. (2010),

or by approximately 90% from the initial cost in Chong et al. (2014) [21,24,26]. Similar findings were also reported by Eckman et al. (2009), who showed that the cost of testing must be below USD 140 for the intervention to be cost-effective [23].

In addition to cost parameters, clinical effectiveness in improving anticoagulation control also significantly affects the results of economic evaluations (Table 3). Patrick et al. (2009) demonstrated that a 5-9% reduction in the proportion of INRs outside the therapeutic range can increase the likelihood of an intervention being cost-effective, while Eckman et al. (2009) reported that preventing >32% of major bleeding events can significantly improve the ICER [23,39]. Studies by Verhoef et al. (2016), Kim et al. (2017), Hemati et al. (2024), and Anand et al. (2024) also indicate that improvements in TTR/PTTR and reductions in the risk of stroke and bleeding are the parameters most strongly influencing sensitivity results [18,20,25,27]. Meanwhile, Mitropoulou et al. (2015) demonstrated that therapy effectiveness and the costs of pharmacogenetics are the primary factors in determining the probability that an intervention is cost-effective. Overall, these results indicate that the cost-effectiveness of genotype-guided warfarin dosing depends heavily on the balance between the cost of genetic testing and the magnitude of clinical benefits from improved INR control and reduced bleeding and thromboembolic complications [19].

The results of the probabilistic sensitivity analysis (PSA) across all studies indicate that the probability of genotype-guided warfarin dosing being cost-effective still varies across countries and is strongly influenced by the WTP threshold, the cost of genetic testing, and the clinical effectiveness of the intervention (Table 3). Most studies indicate that genotype-based strategies tend to yield better health outcomes than standard therapy, though they are often associated with higher costs. In the study by You et al. (2009), genotype-guided dosing was reported to be more effective in all PSA simulations, but also more expensive in 81.3% of simulations, meaning that only 19.12% of simulations were deemed cost-effective at a WTP threshold of USD 50,000/QALY [21]. Similar findings were reported by Patrick et al. (2009), who found that the majority of simulation results fell into the more effective but more costly quadrant [39].

Several studies indicate a relatively low to moderate probability of cost-effectiveness. Meckley et al. (2010) reported that the intervention was cost-effective in only 46% of simulations using a threshold of USD 50,000/QALY, although this increased to 67% at a threshold of USD 100,000/QALY [26]. Chong et al. (2014) also found a probability of cost-effectiveness of approximately 41-42% from both the health system and societal perspectives. In contrast, more recent studies show better results [24]. Verhoef et al. (2016) reported that the probability of the intervention falling below the accepted cost threshold reached 93% in the UK and 67% in Sweden [20]. Kim et al. (2017) showed a probability of cost-effectiveness of 99.8% at a threshold of USD 50,000/QALY, while Anand et al. (2024) reported a probability of 90% at a threshold of Indian Rupee (IR) 71,630/QALY [18,27].

However, not all studies have shown consistent results supporting cost-effectiveness. Hemati et al. (2024) reported that the pharmacogenetic approach was not cost-effective in 86.1% of PSA simulations, indicating that economic evaluation results remain highly sensitive to changes in model parameters [25]. Meanwhile, Mitropoulou et al. (2015) showed that all simulations fell in the northeast quadrant, indicating that the intervention was more effective but also more expensive compared to standard therapy [19]. Overall, the PSA results suggest that genotype-guided warfarin dosing could be cost-effective, particularly in healthcare systems with low genetic testing costs and high therapeutic efficacy in improving INR control and reducing clinical complications [18–21,23–27,39].

In general, the cost-effectiveness conclusions from the 10 studies vary. Four studies concluded that genotype-guided warfarin dosing is cost-effective [18–20,27], while the other six studies found that this intervention is not yet cost-effective compared to standard therapy [21,23–26,39]. This variation in conclusions reflects differences in healthcare system contexts, cost structures, population characteristics, and the economic model assumptions used in each study. Studies concluding that the approach is cost-effective generally demonstrate a combination of lower genetic testing costs and more pronounced clinical benefits, particularly improvements in INR/TTR control and reductions in warfarin therapy complications. Conversely, studies concluding that the approach is not cost-effective are generally influenced by the high cost of genetic testing relative to the additional health benefits gained. Nevertheless, nearly all studies demonstrate that a genotype-based approach yields better clinical outcomes than standard therapy, including increased QALYs, improved INR stability, and reduced risks of bleeding and thromboembolism [18–21,23–27,39].

The findings indicate that the clinical effectiveness of genotype-guided dosing has been generally consistent; however, its cost-effectiveness remains highly dependent on each country's specific circumstances and the healthcare system's capacity to provide affordable genetic testing. Therefore, this strategy is likely to be more cost-effective in countries or healthcare facilities with low genotyping costs, rapid access to testing, and relatively high rates of warfarin-related complications [18–21,23–27,39].

4.5. Limitation

This systematic review has several limitations that should be considered when interpreting the study results. First, the number of studies meeting the inclusion criteria remains limited to 10, so the findings cannot yet be broadly generalized. Additionally, there is variation across studies in terms of economic evaluation design, analytical perspective, time horizon, population characteristics, and the clinical and economic parameters used. These differences make it difficult to compare cost-effectiveness results across studies directly. Second, most studies used data and model assumptions tailored to each country's health system. Differences in healthcare and genetic testing costs, and in WTP thresholds, can influence ICER values and cost-effectiveness conclusions. Therefore, the results of this review may not be fully applicable to different countries or healthcare systems.

Third, some studies used short-term clinical efficacy data, particularly regarding INR control and TTR, so the long-term benefits of genotype-guided warfarin dosing in reducing bleeding and thromboembolic complications may not yet be fully captured. Additionally, the clinical outcomes reported across studies are not always consistent, which limits a comprehensive comparison of results. Fourth, rapid advances in genetic technology and declining genotyping costs may affect the relevance of results from older studies. Some of the studies included in this review were conducted when the cost of genetic testing was still relatively high, potentially resulting in ICER estimates that do not accurately reflect current conditions. Therefore, recent economic evaluation studies using current genotyping costs and more representative clinical data are needed to assess cost-effectiveness more accurately. Fifth, we were unable to conduct formal subgroup analyses stratified by baseline thromboembolic or bleeding risk because these variables were not consistently reported across the included studies.

5. CONCLUSIONS

This systematic review indicates that genotype-guided warfarin dosing is associated with improved clinical outcomes compared with standard therapy, particularly enhanced INR/TTR control, increased QALYs, and reduced risks of bleeding and thromboembolism. However, from an economic perspective, its cost-effectiveness remains inconsistent and is influenced by factors such as genetic testing costs, patient characteristics, and the healthcare system context. Therefore, this approach may be more appropriately applied in high-risk populations or in settings with lower genetic testing costs.

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Author contribution

PMDR was responsible for the conception and design of the study, conducted the literature search, study selection, data extraction, data analysis, and drafted the manuscript. TMA and DE contributed to the study design, provided methodological guidance, and were involved in data extraction and analysis. IPS and MTI contributed to data interpretation, manuscript development and critically revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

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Conflict of interest

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