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ECONOMIC EVALUATION OF *CYP2C19* GENOTYPE-GUIDED ANTIPLATELET THERAPY FOR PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION: A SYSTEMATIC REVIEW

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Abstract: Dual antiplatelet therapy with clopidogrel is essential for patients undergoing percutaneous coronary intervention, but clopidogrel's effectiveness varies due to *CYP2C19* genetic differences. This is critical in Asian populations, where *CYP2C19* loss-of-function alleles are nearly twice as prevalent as in Caucasians, increasing thrombotic risk. Alternatives such as ticagrelor and prasugrel are more effective, but costlier with higher bleeding risks, making *CYP2C19* genotype-guided therapy a potentially efficient approach. This study updates systematic reviews of economic evaluations of *CYP2C19* genotyping in coronary artery disease patients undergoing percutaneous coronary intervention to inform policy and clinical decisions. PubMed and Scopus were searched through October 2025 for full economic evaluations. Non-English or inaccessible full-text studies were excluded. Reporting and evidence quality were assessed using the Consolidated Health Economic Evaluation Reporting Standards 2022 Checklist and the Cooper hierarchy. Due to heterogeneity, results were synthesized narratively. Twenty-two studies from nine countries were included, with most conducted in high-income settings. Across extracted base-case comparisons, genotype-guided strategies were generally cost-effective or cost-saving when compared with universal clopidogrel or universal prasugrel, while results were less favorable when compared with universal ticagrelor. Key drivers of cost-effectiveness were drug prices, clinical event risks, and allele prevalence, whereas testing costs were less frequently influential. Evidence from lower-income countries was limited and results varied with local costs, testing availability, and treatment pathways. Overall, genotype-guided antiplatelet therapy appears economically favorable in many settings, but decisions should be context-specific, particularly in Asian settings with high *CYP2C19* loss-of-function burden.

Keywords: coronary artery disease, percutaneous coronary intervention, *CYP2C19* testing, clopidogrel, economic evaluation, systematic review

1. Introduction

Coronary artery disease (CAD) is a leading cause of morbidity and mortality globally, placing a significant burden on healthcare systems worldwide. The World Health Organization (WHO) reported that cardiovascular diseases, including CAD, account for approximately 17.9 million deaths annually,

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representing 32% of all global deaths (WHO, 2025). A recent systematic review and meta-analysis found that the annual direct cost per CAD patient exceeds total per capita healthcare spending in most countries and ranges from 4.9% to 137.8% of per capita GDP (Shakya *et al.*, 2025). Percutaneous coronary intervention (PCI) is the standard of care for these patients, followed by dual antiplatelet therapy (DAPT) – typically including aspirin plus a P2Y12 inhibitor (Levine *et al.*, 2016). Among P2Y12 inhibitors, clopidogrel remains the most widely used due to its affordability and established efficacy; however, its effectiveness varies depending on genetic differences, especially the *CYP2C19* enzyme, which plays a key role in clopidogrel metabolism (FDA, 2017). *CYP2C19* loss-of-function (LOF) alleles, present in roughly 30% of Caucasians and up to 60% of Asians, impair clopidogrel activation and increase the risk of major adverse cardiovascular events (MACE) by 1.5 to 3.0 times compared to normal metabolizers (Gower *et al.*, 2020; Biswas and Kali, 2021). Therefore, more potent drugs such as ticagrelor or prasugrel, which bypass the need for *CYP2C19* activation can be used as an alternative therapy; however, they are more expensive and carry a higher risk of bleeding (Huang *et al.*, 2024). *CYP2C19* genotype-guided antiplatelet therapy (*CYP2C19*-PGx) has emerged as a promising strategy to tailor treatment based on a patient's genetic profile. This strategy allows for the use of ticagrelor or prasugrel in *CYP2C19* LOF carriers and clopidogrel in non-LOF carriers, resulting in a significant reduction in MACE compared to conventional treatment (RR 0.72, 95% CI 0.55-0.95; p=0.02) without a significant increase in bleeding, while reducing unnecessary costs (Lyu *et al.*, 2020). Although *CYP2C19*-PGx can enhance efficacy, its implementation generates additional costs related to genetic testing and new antiplatelet therapy. Given the significant clinical and economic burden of CAD, evaluating the cost-effectiveness of *CYP2C19*-PGx is crucial for guiding healthcare policy and reimbursement decisions.

Previous systematic reviews synthesized economic evaluations (EEs) largely derived from pre-2020 trial data rather than real-world evidence and were conducted before the availability of cheaper generic drugs and lower-cost genetic testing, factors that could significantly affect cost-effectiveness results (AlMukdad *et al.*, 2020; Zhu *et al.*, 2020; Lim *et al.*, 2024). Furthermore, prior reviews mainly focused on acute coronary syndrome (ACS) patients undergoing PCI or on CAD populations more broadly, excluding the high-risk group of patients with chronic coronary syndrome (CCS) undergoing PCI, which may have led to biased estimates of the overall benefit. Therefore, this study aimed to systematically review recent EEs of *CYP2C19*-PGx in CAD patients undergoing PCI to inform clinical and policy decision-making.

2. Materials and Methods

2.1 Search strategy

A systematic literature review was performed using two search databases, including MEDLINE via PubMed and Scopus to identify relevant articles from inception to October 2025. The search strategy followed the PICO(S) framework as follows: population (P) included patients with CAD undergoing PCI, intervention (I) was *CYP2C19* genotype-guided antiplatelet therapy, and study (S) included full EEs (i.e., cost-effectiveness analysis (CEA), cost-utility analysis (CUA), or cost-benefit analysis (CBA)). Since this review focused on studies assessing the implementation of *CYP2C19* genetic testing,

all included studies were required to evaluate *CYP2C19* genetic testing or pharmacogenomic tests that included *CYP2C19* variants as the primary intervention. Therefore, the "Intervention" domain (I) was limited to *CYP2C19*-specific search terms and broader genetic-testing terms, excluding individual antiplatelet drug names to avoid irrelevant results related to them while ensuring relevant results. Keywords were tailored to database-specific indexing terms, e.g., the use of Medical Subject Heading (MeSH) terms in MEDLINE via PubMed database. Search terms within the same domain were combined using OR, while terms across different domains were linked using AND. In the population domain (P), P1 - CAD and P2 - PCI were combined using OR instead of AND to avoid missing relevant studies, as some abstracts may not explicitly state all conditions of the target population - CAD patients undergoing PCI. Additionally, the Boolean operator OR was applied to combine terms and identify overlaps. Redundant terms, including variations such as singular/plural forms or subgroup disease terms, were removed to achieve comprehensive coverage while minimizing redundancy. Searching was updated every 3 months, and the reference lists of relevant studies were also explored. The search terms are detailed in Table 1 and Table 2.

Table 1: PubMed search terms

No.	Domain	Terms	Results
#1	P1- Coronary artery disease	Coronary	2,226,826
#2		Cardiovascular	2,352,937
#3	P2 - Percutaneous coronary intervention	“Percutaneous Coronary Intervention”[MeSH]	70,380
#4		"Percutaneous Coronary Intervention*"	63,849
#5		Stent	154,827
#6		Revascularization	86,778
#7	P – CAD patients undergoing PCI	#1 OR #2 OR #3 OR #4 OR #5 OR #6	3,527,091
#8	I - Intervention	*CYP2C19*	7,229
#9		"Cytochrome P-450 *CYP2C19*"[MeSH]	3,832
#10		"Genotype"[MeSH]	489,320
#11		"Pharmacogenetics"[MeSH]	14,377
#12		Pharmacogenetics	28,703
#13		"Genetic Testing"[MeSH]	59,014
#14		"Pharmacogenomic Testing"[MeSH]	1,486
#15		"Pharmacogenomic Testing"	1,907
#16		#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	786,009
#17	S - Study designs	"Economic evaluation"	16,721
#18		"Cost-Effectiveness Analysis"[MeSH]	1,653
#19		"cost utility"	7,600
#20		"cost benefit"	108,631

#21		pharmacoeconomic	37,810
#22		#17 OR #18 OR #19 OR #20 OR #21	148,422
#23	RESULTS	#7 AND #16 AND #22	516

Table 2: Scopus search terms

No.	Domain	Terms	Results
#1	P1- Coronary artery disease	Coronary	840,086
#2		Cardiovascular	1,362,230
#3	P2 - Percutaneous coronary intervention	Percutaneous Coronary Intervention*	115,532
#4		Stent	198,422
#5		Revascularization	125,721
#6	P – CAD patients undergoing PCI	#1 OR #2 OR #3 OR #4 OR #5	2,103,637
#7	I - Intervention	*CYP2C19*	8,346
#8		Cytochrome P-450 *CYP2C19*	4,190
#9		Genotype*	733,215
#10		Pharmacogenetic*	37,806
#11		Genetic Testing	181,412
#12		Pharmacogenomic*	22,337
#13		#7 OR #8 OR #9 OR #10 OR #11 OR #12	918,285
#14	S - Study designs	Economic evaluation	213,455
#15		Cost effective*	1,272,190
#16		cost utilit*	120,704
#17		cost benefit*	624,923
#18		pharmacoeconomic*	17,012
#19		#14 OR #15 OR #16 OR #17 OR #18	1,861,167
#20	RESULTS	#6 AND #13 AND #19	853

2.2 Eligibility criteria

The inclusion and exclusion of articles were conducted by two independent reviewers (H.C. and T.A.) through an initial screening of titles and abstracts, followed by a full-text review. Disagreements were resolved through discussion with a third reviewer (Turongkaravee S.) until consensus. Eligibility criteria were also based on the PICO(S) framework. We included patients with CAD, encompassing both acute and chronic coronary syndrome undergoing PCI. The intervention of interest was *CYP2C19*-PGx compared against any standard strategy (e.g., clopidogrel, ticagrelor, prasugrel), clinician- or pharmacist-guided selection without genotyping, or a platelet function test-guided strategy. Only full EEs were included. Exclusion criteria consisted of non-English language studies and those where the full text was inaccessible.

2.3 Data extraction

Two reviewers (H.C. and T.A.) extracted data independently using a data extraction form to ensure data reliability and trustworthiness. Any disagreements were discussed with the third reviewer (Turongkaravee S.). The extracted data included four main parts as follows: (1) study characteristics (i.e., authors, year of publication, country, country income level, target populations, % LOF alleles), (2) study design (type of EEs, trial or model-based EEs, perspective, time horizon, discounting, willingness-to-pay (WTP), uncertainty analysis), (3) target treatments, and (4) study results (i.e., incremental cost-effectiveness ratio (ICER), uncertainty analysis findings and conclusions).

2.4 Quality assessment of economic evaluation reporting

Reporting quality was assessed using the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) checklist (Husereau *et al.*, 2022). Each item was rated as "Reported," "Not reported," or "Not applicable." Two reviewers (H.C. and T.A.) independently assessed the reporting quality and involved a third reviewer (Turongkaravee S.) where agreement could not be reached.

2.5 Quality assessment of evidence used

The quality of evidence for input parameters used in EEs, such as clinical effect sizes, baseline clinical data, resource use, costs, and utilities (for CUA) was assessed using the hierarchy of data sources developed by Cooper *et al.* (Cooper *et al.*, 2005). Each item was evaluated and given a rank ranging from 1 to 6. Two reviewers (H.C. and T.A.) independently ranked the data sources, resolving disagreements through discussion with the third reviewer (Turongkaravee S.) and percentages of agreement and disagreement by input parameter was also calculated.

2.6 Presentation of results

Due to the heterogeneity present in the study designs across the sample, this study synthesized the results using a narrative method.

3. Results and Discussion

The search strategy identified a total of 1,369 records, with 516 from MEDLINE via PubMed and 853 from Scopus. After removing 236 duplicate records, 1,133 records underwent title and abstract screening, resulting in the exclusion of 1,090 records. Of the 43 reports sought for retrieval, 3 were excluded because they were in Chinese and full text could not be accessed. Ultimately, we identified 22 studies for data extraction, as detailed in Figure 1.

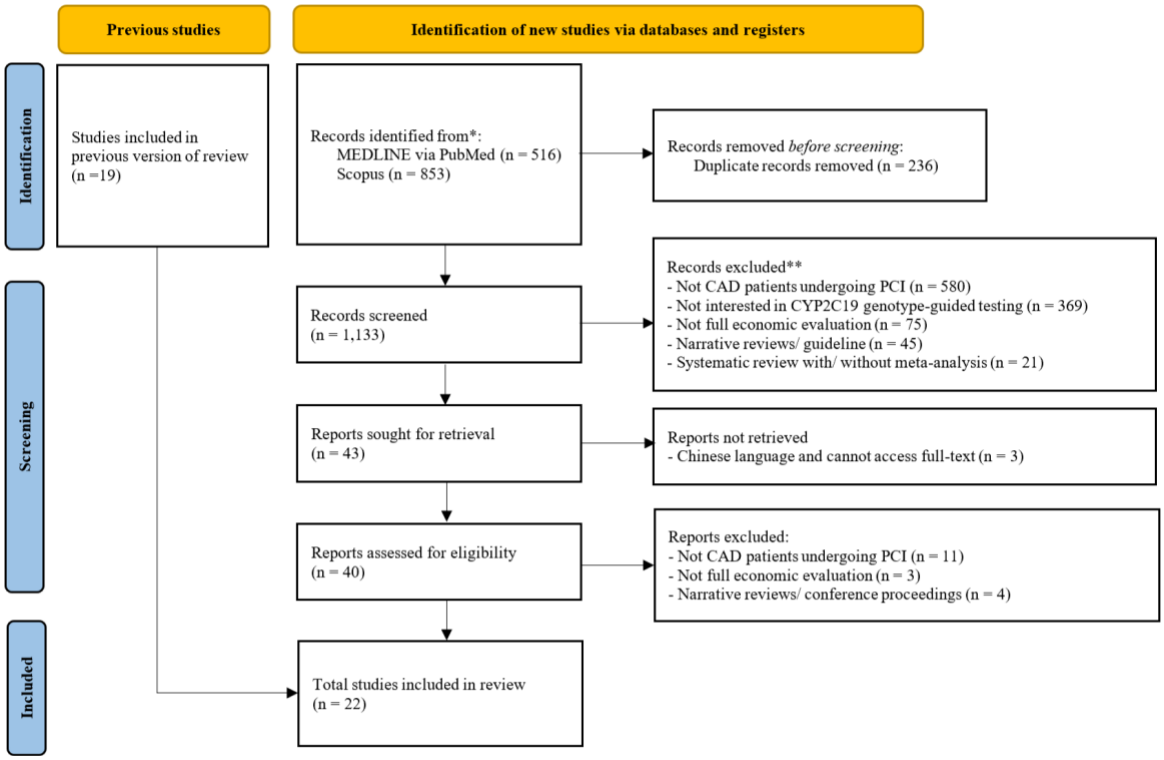

Figure 1: PRISMA 2020 flow diagram for updated systematic review, including searches of databases, registers and other sources. The flowchart shows the number of records identified from databases (MEDLINE via PubMed and Scopus), duplicate records removed, records screened, full-text reports assessed for eligibility, reasons for exclusion at each stage, and the final number of included studies, including studies carried over from a previous review (n = 22).

Table 3: Characteristics of included studies

No.	Author (Year)	Country	Population	Target treatment	EE type
1	Reese *et al.* (2012)	USA	ACS/PCI	C, P, PGx-P	CEA
2	Lala *et al.* (2013)	USA	ACS/PCI	C, P, PGx-P	CUA
3	Sorich *et al.* (2013)	Australia	ACS/PCI	C, T, PGx-T	CUA
4	Kazi *et al.* (2014)	USA	ACS/PCI	C, P, T, PGx-P, PGx-T	CUA
5	Patel *et al.* (2014)	USA	ACS/PCI	C, P, PGx-P	CUA
6	Jiang *et al.* (2015)	USA	ACS/PCI	C, P+T, PGx-PRT	CUA
7	Deiman *et al.* (2016)	Netherlands	CAD/PCI	C, P, T, PGx-P-PM; PGx-P-IM/PM	CUA
8	Jiang *et al.* (2016)	USA	ACS/PCI	C, P+T, PGx-P+T, PRT	CUA
9	Jiang *et al.* (2017)	USA	ACS/PCI	C, P+T, PGx-P+T	CUA
10	Borse *et al.* (2017)	USA	CAD/PCI	C, P, PGx-P	CEA
11	Okere *et al.* (2018)	USA	ACS/PCI	MTM-C, MTM-T, PGx-T	CUA
12	Wang *et al.* (2018)	Hong Kong	ACS/PCI	C, T, PGx-T	CUA
13	K. Kim *et al.* (2019)	USA	ACS/PCI	T, C, PGx-T-PM, PGx-T-PM/IM, PGx-PRT	CUA

No.	Author (Year)	Country	Population	Target treatment	EE type
14	Fragoulakis *et al.* (2019)	Spain	CAD/PCI	Esca, PGx	CUA
15	Fu *et al.* (2020)	China	ACS/PCI	C, T, PGx-T	CUA
16	Limdi *et al.* (2020)	USA	ACS/PCI	C, T, PGx-T	CUA
17	J. H. Kim *et al.* (2021)	Singapore	ACS/PCI	C, T, PGx-T	CUA
18	AlMukdad *et al.* (2021)	Qatar	ACS/PCI	C, T, PGx-T	CEA + CUA
19	Claassens *et al.* (2022)	Netherlands	STEMI/PCI	C, P+T, PGx-P+T	CUA
20	Dong *et al.* (2023)	USA	ACS/PCI	Esca, PGx	CUA
21	Suh *et al.* (2024)	Korea	ACS/PCI	C, P, PGx-P	CEA
22	van den Broek *et al.* (2025)	Netherlands	ACS/PCI	Esca, PGx	CUA

***ACS/PCI**: Acute coronary syndrome undergoing percutaneous coronary intervention; **CAD/PCI**: Coronary artery disease undergoing percutaneous coronary intervention; **STEMI/PCI**: ST-elevation myocardial infarction undergoing percutaneous coronary intervention*

***PGx-T**: Genetic testing followed by ticagrelor for LOF carriers; **PGx-P**: Genetic testing followed by prasugrel for LOF carriers; **PGx-P+T**: Genetic testing followed by either ticagrelor or prasugrel for LOF carriers; **PGx-PRT**: Genetic testing combined with platelet reactivity testing; **PGx-P-PM**: Genetic testing followed by prasugrel for poor metabolizers; **PGx-P-IM/PM**: Genetic testing followed by prasugrel for intermediate and poor metabolizers; **PGx-T-PM**: Genetic testing followed by ticagrelor for poor metabolizers; **PGx-T-PM/IM**: Genetic testing followed by ticagrelor for intermediate and poor metabolizers; **C**: Universal clopidogrel; **P**: Universal prasugrel; **T**: Universal ticagrelor, **MTM-C**: Face-to-face comprehensive medication therapy management (MTM) followed by universal clopidogrel; **MTM-T**: Face-to-face comprehensive medication therapy management (MTM) followed by universal ticagrelor; **Esca**: Non-guided escalation, patients receiving ticagrelor or prasugrel or clopidogrel without testing*

***CUA**: cost-utility analysis; **CEA**: cost-effectiveness analysis*

Table 4: Methodological characteristics of included economic evaluations

No.	Author (Year)	Perspective	Model type	Time horizon	Discount rate (%)	SA	WTP
1	Reese *et al.* (2012)	Payer	D	15 months	5	OSA; PSA; Scenario	NR
2	Lala *et al.* (2013)	Payer	M	15 months & Lifetime	3	OSA+TSA ; PSA	$100,000
3	Sorich *et al.* (2013)	Healthcare	D+M	Lifetime	5	OSA; PSA; Scenario	AUD 30,000-50,000
4	Kazi *et al.* (2014)	Societal	M	Lifetime	3	OSA; PSA; Scenario	$50,000
5	Patel *et al.* (2014)	Payer	D+M	Lifetime	5	OSA; PSA	$100,000
6	Jiang *et al.* (2015)	Payer	D+M	Lifetime	3	OSA+TSA ; PSA	$50,000
7	Deiman *et al.* (2016)	Hosp-expense	Trial-based	Lifetime	NA	NR	€65,000
8	Jiang *et al.* (2016)	Payer	D+M	Lifetime	3	OSA; PSA	$50,000

No.	Author (Year)	Perspective	Model type	Time horizon	Discount rate (%)	SA	WTP
9	Jiang *et al.* (2017)	Payer	D+M	Lifetime	3	OSA; PSA	$50,000
10	Borse *et al.* (2017)	Payer	D	30 days & 1 year	NA	OSA; PSA	$50,000
11	Okere *et al.* (2018)	Healthcare	D+M	Lifetime	3.5	OSA; PSA	$50,000-$200,000
12	Wang *et al.* (2018)	Healthcare	D+M	Lifetime	3	OSA; PSA	$42,423
13	K. Kim *et al.* (2019)	Healthcare	D+M	Lifetime	3	OSA; PSA	$100,000
14	Fragoulakis *et al.* (2019)	Healthcare	Trial-based	1 year	NA	PSA	NR
15	Fu *et al.* (2020)	Healthcare	D+M	Lifetime	5	OSA; PSA	RMB 59,660
16	Limdi *et al.* (2020)	Payer	D	1 year	NA	OSA; PSA	$100,000
17	J. H. Kim *et al.* (2021)	Payer	D	1 year	NA	OSA; PSA	SGD 88,991
18	AlMukdad *et al.* (2021)	Healthcare	D+M	1 year & Lifetime	3.5	OSA; PSA	$150,000
19	Claassens *et al.* (2022)	Healthcare	D+M	Lifetime	4 (Costs) & 1.5 (Utilities)	OSA; PSA	€20,000-€80,000
20	Dong *et al.* (2023)	Payer	D	1 year	NA	OSA; PSA	$150,000
21	Suh *et al.* (2024)	Societal	D	1 year	NA	OSA; PSA	NR
22	van den Broek *et al.* (2025)	Healthcare	D+M	Lifetime	3	OSA; PSA	€20,000

***Hosp-expense**: Hospital-level pharmaceutical expenses*

***D**: Decision tree; **M**: Markov model*

***OSA**: One-way sensitivity analysis; **TSA**: two-way sensitivity analysis; **PSA**: probabilistic sensitivity analysis; **Scenario**: scenario analysis*

***AUD**: Australian dollar; **RMB**: Renminbi/Chinese yuan; **SGD**: Singapore dollar*

***WTP**: Willingness-to-pay threshold; **NA**: not applicable; **NR**: not reported*

A total of 22 EE studies published between 2012 and 2025 were included, as shown in Table 3. Most of the studies were conducted in the United States, accounting for over half of the studies (n=12, 54.5%) (Reese *et al.*, 2012; Lala *et al.*, 2013; Kazi *et al.*, 2014; Patel *et al.*, 2014; Jiang and You, 2015, 2016, 2017; Borse *et al.*, 2017; Okere *et al.*, 2018; K. Kim *et al.*, 2019; Limdi *et al.*, 2020; Dong *et al.*, 2023). Other represented countries included the Netherlands (Deiman *et al.*, 2016; Claassens *et al.*, 2022; van den Broek *et al.*, 2025) (n=3), Australia (Sorich *et al.*, 2013), Hong Kong (Wang *et al.*, 2018), Spain (Fragoulakis *et al.*, 2019), China (Fu *et al.*, 2020), Singapore (J. H. Kim *et al.*, 2021), Qatar (AlMukdad *et al.*, 2021), and Korea (Suh *et al.*, 2024) (n=1 each). Nearly all evaluations (n=21, 95.5%) were performed in high-income countries (HICs), with only one study conducted in an upper-middle-income country (UMIC; China). The predominant target population was patients with ACS undergoing PCI, which represented 18 of the 22 studies (81.8%). Three studies focused more broadly on CAD patients (CAD/PCI), and one focused specifically on ST-segment elevation myocardial infarction (STEMI/PCI).

In terms of methods, CUA was the most common economic evaluation type, utilized in 18 studies (81.8%). Three studies applied only CEA and one study performed both CEA and CUA.

Most models adopted either a payer perspective (n=10, 45.5%) or a healthcare system perspective (n=9, 40.9%). Only two studies utilized a broader societal perspective, suggesting that direct non-medical costs were rarely considered, and one study adopted a hospital-level perspective. A hybrid approach combining a decision tree with a Markov model (D+M) with a lifetime horizon was the most frequently employed model to capture long-term costs and clinical consequences (n=12, 54.5%). Six studies used only a decision tree and applied shorter time horizons, most commonly 1 year to align with the DAPT duration or trial follow-up periods. Of the remaining four studies, two used only a Markov model, and two utilized trial-based models. Regarding uncertainty analysis, 20 of the 22 included studies (90.9%) adopted a comprehensive approach by conducting both one-way sensitivity analysis (SA) and probabilistic sensitivity analysis (PSA). More advanced forms of uncertainty assessment were less frequent; specifically, only two studies (9.1%) included two-way SA, while three studies (13.6%) performed scenario analyses. Only one study (1/22; 4.5%) did not report any SA, and one study (1/22; 4.5%) reported PSA alone without assessing one-way SA. Details are presented in Table 4.

Across the 22 included studies, we extracted 42 base-case comparisons evaluating *CYP2C19*-PGx against alternative treatment strategies as shown in Figure 2. Overall findings were comparator dependent. When *CYP2C19*-PGx strategies were compared with universal clopidogrel (n = 20 comparisons), the results were predominantly favorable: 18/20 (90%) comparisons reported *CYP2C19*-PGx as dominant or cost-effective, while 2/20 found *CYP2C19*-PGx to be dominated. Against universal prasugrel (n = 6), all comparisons were favorable (6/6; 100%). In contrast, when compared with universal ticagrelor (n = 5), *CYP2C19*-PGx strategies were frequently unfavorable, being not cost-effective in 3/5 (60%) comparisons. Comparisons against mixed P2Y12 inhibitor strategies (prasugrel/ticagrelor) and non-guided mixed strategies also yielded favorable outcomes (100% dominant), whereas comparisons involving face-to-face comprehensive medication therapy management (MTM) were more often unfavorable, with two-thirds dominated.

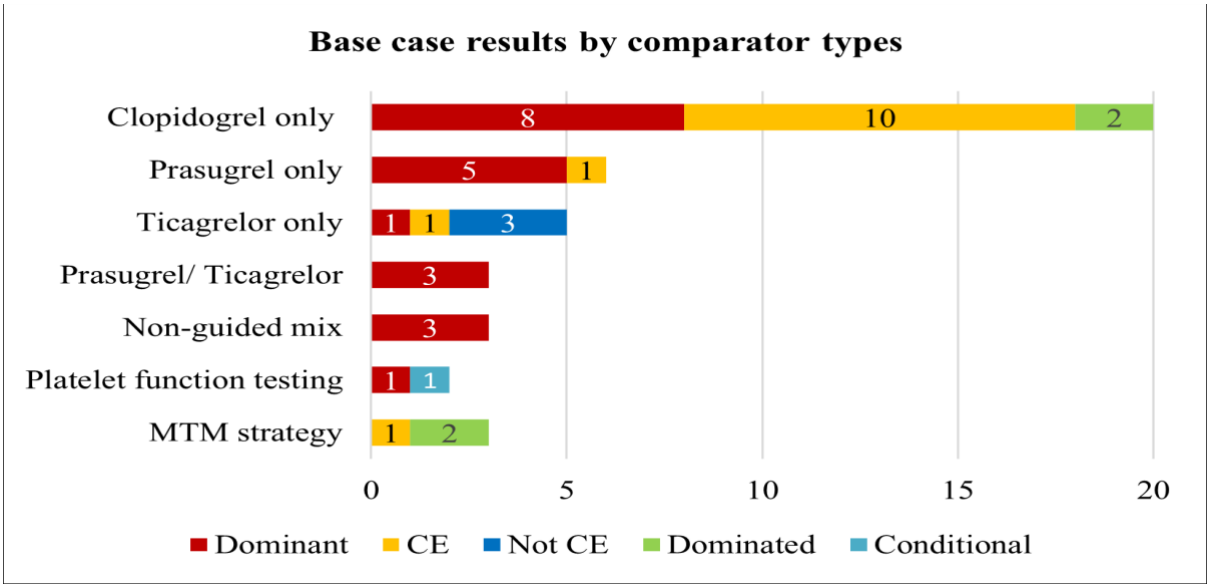

Figure 2: Base-case cost-effectiveness results of CYP2C19 genotype-guided antiplatelet therapy by comparator type (n = 42 comparisons). Stacked bars show the distribution of conclusions across comparator categories (universal clopidogrel, universal prasugrel, universal ticagrelor, mixed P2Y12 strategies, non-guided mix, platelet function testing, and MTM). Colors indicate whether CYP2C19-PGx was dominant, cost-effective (CE), not cost-effective, dominated, or conditional. Readers should note the strong comparator dependence: findings were predominantly favorable versus universal clopidogrel and universal prasugrel, but less favorable versus universal ticagrelor and MTM. Abbreviations: MTM: Face-to-face comprehensive medication therapy; CE: cost-effective

As shown in Figure 3, among the studies reporting one-way sensitivity analyses, the parameters most frequently identified as key drivers influencing cost-effectiveness were drug costs (18 studies), clinical event risks (15 studies), and allele prevalence (13 studies). Genotyping cost was a less influential parameter (6 studies), while utilities (or QALYs) and other inputs played a minor role (3 studies each).

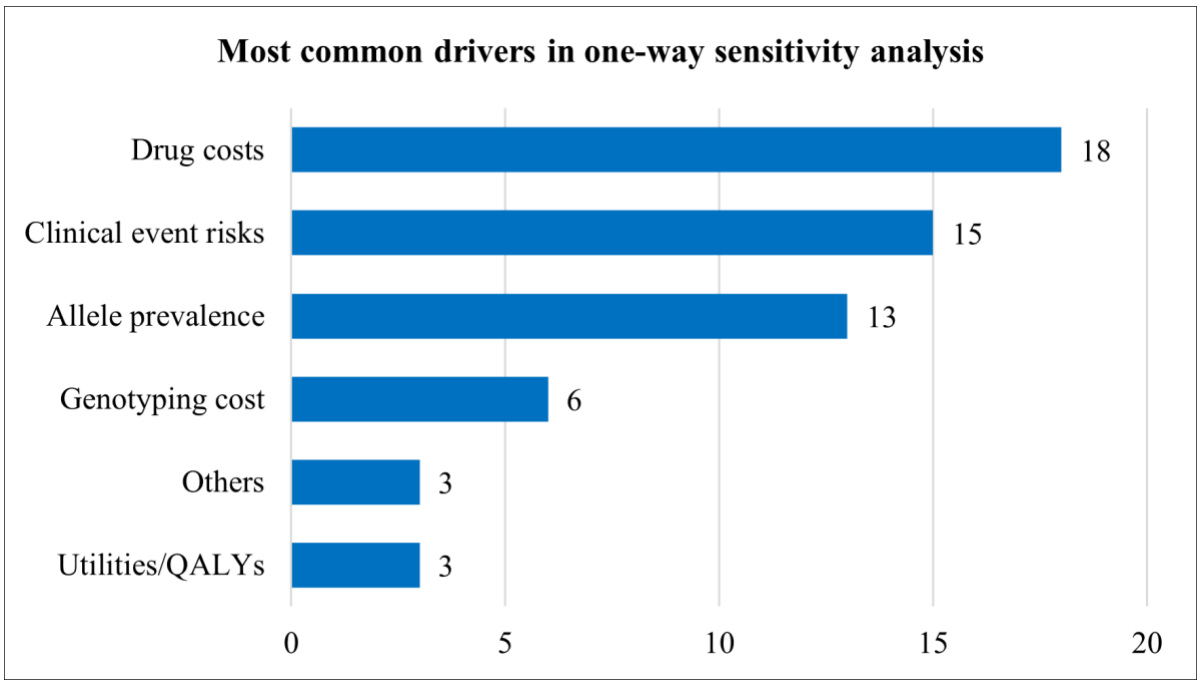

Figure 3: The most common drivers in one-way sensitivity analysis reported in the included studies. The bars indicate the number of studies identifying each parameter as a key driver of incremental cost-effectiveness. Drug cost, clinical event risk, and CYP2C19 allele prevalence were most frequently the most influential, while genotyping cost and utility/QALY inputs were less commonly reported as the primary influencing factors. Abbreviations: QALYs: Quality-Adjusted Life Years

Overall, the 22 included studies demonstrated strong reporting standards for basic health economic criteria; however, some noticeable gaps remained in areas highlighted by recent reporting guidelines, such as patient engagement and equity (Table 5). All included studies (22/22) fully reported the core structural elements of the EE, including the Title, Abstract, and Introduction. In the Methods and Results sections, the studies also addressed most items. Only a few studies omitted the discount rate (n=17, 77% reported), typically justified by applying a short-term time horizon appropriate for the duration of DAPT treatment. Furthermore, all studies thoroughly discussed their findings, limitations, and generalizability. Most studies performed well in describing the rationale of the model, characterizing uncertainty, and

detailing the impact of that uncertainty (all at 95%). Reporting on conflicts of interest (95%), outcome valuation (n=19, 86%), and funding sources (n=18, 82%) was also generally high, although these items were lacking in a few studies. Conversely, only half of the studies (n=11, 50%) described heterogeneity in their models, and very few (n=3, 14%) mentioned a predefined health economic analysis plan. Furthermore, none of the 22 studies addressed distributional effects (Item 19) or discussed any engagement with patients or external stakeholders (Items 21 and 25).

Table 5: Quality assessment results of economic evaluation reporting

CHEERS 2022 Checklist	No.	Item	Number of studies met the recommendations	Percentage (%)
Title	1	Title	22/22	100
Abstract	2	Abstract	22/22	100
Introduction	3	Background and objectives	22/22	100
	3.1	Give the context for the study	22/22	100
	3.2	Give the study question	22/22	100
	3.3	Give study's practical relevance for decision making in policy or practice	22/22	100
Methods	4	Health economic analysis plan	3/22	14
	5	Study population	22/22	100
	6	Setting and location	22/22	100
	7	Comparators	22/22	100
	8	Perspective	22/22	100
	9	Time horizon	22/22	100
	10	Discount rate	17/22	77
	11	Selection of health outcomes	22/22	100
	12	Measurement of outcomes	22/22	100
	13	Valuation of outcomes	19/22	86
	14	Measurement and valuation of resources and costs	22/22	100
	15	Currency, price date, and conversion	22/22	100
	16	Rationale and description of model	21/22	95
	17	Analytics and assumptions	22/22	100
	18	Characterizing heterogeneity	11/22	50
	19	Characterizing distributional effects	0/22	0
	20	Characterizing uncertainty	21/22	95
	21	Approach to engagement with patients and others affected by the study	0/22	0
Results	22	Study parameters	22/22	100

CHEERS 2022 Checklist	No.	Item	Number of studies met the recommendations	Percentage (%)
	23	Summary of main results	22/22	100
	24	Effect of uncertainty	21/22	95
	25	Effect of engagement with patients and others affected by the study	0/20	0
Other relevant information	26	Study findings, limitations, generalizability, and current knowledge	22/22	100
	27	Source of funding	18/22	82
	28	Conflicts of interest	21/22	95

Table 6: Quality assessment results of evidence used based on the hierarchy of data sources by Cooper et al.

Input parameters	Hierarchy of data sources					
	1	2	3	4	6	NA
Clinical effect sizes	18 (82%)	0 (0%)	0 (0%)	4 (18%)	0 (0%)	0 (0%)
Baseline clinical data	7 (32%)	2 (9%)	0 (0%)	13 (59%)	0 (0%)	0 (0%)
Costs	7 (32%)	15 (68%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Resource use	8 (36%)	9 (41%)	0 (0%)	4 (18%)	1 (5%)	0 (0%)
Utility	2 (9%)	0 (0%)	17 (77%)	0 (0%)	0 (0%)	3 (14%)

Our findings are broadly consistent with prior systematic reviews. Overall, *CYP2C19*-PGx strategies were generally cost-effective, particularly against universal clopidogrel or prasugrel, though less favorable versus universal ticagrelor. This underscores that economic conclusions are highly comparator-dependent. Furthermore, our uncertainty analysis revealed that economic outcomes are no longer driven by genotyping costs, but rather by medication prices and population risk profiles. As generic potent P2Y12 inhibitors become cheaper, the economic advantage of genotyping may diminish unless the population has a high prevalence of risk alleles or significant local clinical risk. These findings support the use of *CYP2C19*-PGx strategies as a potentially effective method for personalizing antiplatelet therapy after PCI. Future research should prioritize context-specific evaluations in UMIC and low and middle income country (LMIC) settings, incorporate distributional and equity considerations and assess real-world costs and outcomes. Where feasible, studies should use locally derived event rates and utilities and explicitly consider heterogeneity across subgroups to better inform reimbursement and clinical decision-making. Finally, we acknowledge certain limitations in this review. First, limiting our search to English-language studies may have caused some language bias by omitting relevant non-English local evidence. Moreover, due to high heterogeneity in study designs, we report qualitative economic patterns rather than pooled effects.

4. Conclusion

This review synthesized evidence from 22 EE studies (2012–2025) assessing *CYP2C19*-PGx in CAD patients undergoing PCI. The collective evidence demonstrates that *CYP2C19*-PGx is a potentially cost-

effective strategy for personalizing antiplatelet therapy, particularly when evaluated against universal clopidogrel or universal prasugrel in high-income settings. However, cost-effectiveness remains highly sensitive to the chosen comparator and the declining prices of generic P2Y12 inhibitors. Future context-specific evaluations, especially in lower-income settings and utilizing real-world data, are essential to fully inform global clinical guidelines and equitable reimbursement policies.

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Declaration of Interest Statement

The authors declare that they have no conflict of interests.

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