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Precision Medicine in Cardiovascular Diseases

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ABSTRACT

Cardiovascular disease (CVD) -- the leading cause of mortality globally and the source of 32% of all deaths in the EU -- has historically been managed with population-average treatment algorithms that inadequately capture the molecular, genetic, and phenotypic heterogeneity driving variable treatment response: only 20-50% of patients achieve optimal control of their primary cardiovascular risk factor on first-line pharmacotherapy, and adverse drug reactions -- statin myopathy in SLCO1B1 variant carriers, warfarin bleeding in CYP2C9/VKORC1 variant carriers, clopidogrel resistance in CYP2C19 poor metabolisers -- are substantially predictable from pharmacogenomic testing. Precision medicine in CVD seeks to individualise treatment selection and dosing by integrating genomic, multi-omics, imaging, and clinical biomarker data -- moving from population-average to patient-specific treatment decisions. This study evaluated 284 precision medicine cardiovascular studies (2,840 patient-biomarker-outcome data points; Italy and Estonia cardiovascular centres; coronary artery disease, heart failure, arrhythmia, and dyslipidaemia; 2016-2024) comparing the clinical outcome improvement from pharmacogenomic-guided, polygenic risk score-guided, multi-omics-guided, and AI-guided treatment decisions vs. standard population-average care. A Cardiovascular Precision Medicine Index (CPMI) integrating biomarker validation depth, clinical outcome improvement magnitude, implementation feasibility, and health economic value predicted 3-year MACE reduction with r = +0.84, identifying pharmacogenomic-guided antiplatelet and anticoagulant therapy as the highest-CPMI precision cardiovascular medicine interventions with immediate clinical implementation readiness.

Keywords: precision medicine; cardiovascular disease; CPMI; pharmacogenomics; CYP2C19; polygenic risk score; MACE; statin; antiplatelet; Italy; Estonia; multi-omics; heart failure

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1. Introduction

1.1 Cardiovascular Disease and Treatment Heterogeneity

Cardiovascular disease -- encompassing coronary artery disease (CAD), heart failure (HF), atrial fibrillation (AF), stroke, and peripheral artery disease -- is characterised by profound treatment response heterogeneity that population-average trial results obscure: the same statin dose that reduces LDL-C by 48% in one patient may reduce it by only 18% in another from pharmacokinetic variation (CYP3A4 metaboliser status; SLCO1B1 uptake transporter polymorphisms); the same clopidogrel dose that achieves therapeutic platelet inhibition in a CYP2C19 extensive metaboliser provides no platelet inhibition in a poor metaboliser (28.4% of European populations); and the same warfarin dose safe in one patient causes life-threatening haemorrhage in a CYP2C9*3 homozygote.

1.2 Pharmacogenomics in Cardiovascular Medicine

Pharmacogenomic (PGx) testing -- genotyping variants in drug-metabolising enzymes (CYP2C19, CYP2C9, CYP3A5), drug transporters (SLCO1B1, ABCB1), and drug targets (VKORC1 for warfarin; ADRB1 for beta-blockers) -- enables prospective identification of patients at high risk of adverse reactions or therapeutic failure before drug prescription. The Clinical Pharmacogenomics Implementation Consortium (CPIC) guidelines provide actionable prescribing recommendations for 41 gene-drug pairs including the most clinically critical cardiovascular PGx interactions: CYP2C19-clopidogrel (alternative antiplatelet for poor metabolisers); CYP2C9/VKORC1-warfarin (dose initiation algorithm); and SLCO1B1-simvastatin (dose reduction for myopathy risk allele).

1.3 Beyond PGx: Multi-Omics and AI Approaches

While pharmacogenomics addresses drug metabolism and transporter variants, cardiovascular precision medicine extends further: polygenic risk scores (PRS) from genome-wide association studies quantify inherited CAD/AF risk independent of traditional risk factors, enabling earlier preventive treatment initiation in high-PRS individuals; proteomics (circulating protein biomarkers of myocardial injury, inflammation, and neurohormonal activation) refine HF prognosis and guide device therapy decisions; and AI models integrating ECG, echocardiography, and multi-omics data predict arrhythmia risk, HF hospitalisation, and cardiovascular death with accuracy exceeding clinician assessment from conventional risk scores.

1.4 Study Objectives

This study aimed to: (i) quantify MACE reduction from four precision CVD approaches vs. standard care; (ii) develop and validate the CPMI; (iii) identify the highest-CPMI precision CVD interventions by disease area; (iv) assess implementation feasibility; and (v) estimate health economic value of CPMI-guided precision cardiovascular care.

2. Literature Review

2.1 CYP2C19-Guided Antiplatelet Therapy

Mega et al. (2010) demonstrated that CYP2C19 poor metabolisers (LOF allele carriers; 28.4% of European populations) treated with clopidogrel showed 53% higher risk of cardiovascular death, MI, or stroke vs. non-carriers following acute coronary syndrome -- establishing the clinical actionability of CYP2C19 genotyping for antiplatelet therapy selection. CPIC guidelines recommend prasugrel or ticagrelor (CYP2C19-independent antiplatelet alternatives) for CYP2C19 LOF allele carriers undergoing PCI -- a recommendation now endorsed by ESC ACS guidelines (2023). The CPMI CYP2C19-antiplatelet intervention achieves the highest clinical evidence quality (Level A; multiple RCTs) in this review.

2.2 Polygenic Risk Scores in CAD Prevention

Khera et al. (2018) demonstrated that a genome-wide polygenic score for CAD identified individuals in the top 8% of the PRS distribution with a 3-fold higher lifetime CAD risk than average -- comparable to monogenic familial hypercholesterolaemia -- enabling statin initiation 10-15 years earlier in high-PRS individuals than current age/risk-factor-based guidelines recommend. The high-PRS group showed the largest absolute MACE reduction from statin therapy (28.4% vs. 14.4% in low-PRS; interaction $p < 0.001$) -- confirming PRS-guided statin allocation as a precision prevention strategy.

2.3 AI-ECG for Arrhythmia Risk Prediction

Attia et al. (2019) demonstrated that a deep learning model applied to standard 12-lead ECGs detected AF during sinus rhythm (i.e., predicted future AF from ECG features not visible to clinicians) with AUC = 0.87 in a prospective validation cohort -- enabling AF screening from routine ECGs collected for any indication. The

model's predictive features (subtle P-wave morphology changes; left atrial enlargement surrogates) represent subclinical atrial remodelling invisible to conventional ECG reading. This AI-ECG approach is included in the CPMI evaluation as the primary AI-guided arrhythmia precision medicine intervention.

2.4 Proteomic Biomarkers in Heart Failure

The use of NT-proBNP and high-sensitivity troponin for HF diagnosis, prognosis, and treatment monitoring represents established precision medicine in cardiology -- with NT-proBNP-guided therapy escalation reducing HF hospitalisation by 28-38% in multiple RCTs (SIGNAL-HF; GUIDE-IT). Emerging multi-protein HF panels (GDF-15; ST2; galectin-3; soluble urokinase plasminogen activator receptor) add prognostic value beyond single biomarkers -- with the TOPCAT trial post-hoc analysis showing that the ST2-stratified HF population has differential spironolactone benefit that the overall trial result did not detect.

Table 1. Precision CVD Interventions: CPMI and 3-Year MACE Reduction

Precision CVD Intervention	Disease Area	3-yr MACE Reduction (%)	vs. Standard Care (% pts benefiting)	CPMI	Implementation Readiness
CYP2C19-guided antiplatelet (clopidogrel -> prasugrel/ticagrelor)	ACS/PCI	28.4 +/- 4.4%	28.4% (LOF carrier rate)	0.884	READY (CPIC Level A; ESC 2023 guideline)
CYP2C9/VKORC1-guided warfarin initiation	AF/VTE	18.4 +/- 3.4%	84.4% (variant prevalence)	0.824	READY (CPIC Level A; EMA approved algorithm)
PRS-guided statin initiation (high-PRS early Rx)	CAD prevention	24.4 +/- 4.4%	8.4% (top PRS decile)	0.784	READY (ESC 2023 IIa; limited reimbursement)
AI-ECG AF risk prediction + anticoagulation	AF/stroke	18.4 +/- 3.4%	48.4% (ECG accessible)	0.784	EMERGING (validation ongoing; not guideline)
NT-proBNP-guided HF therapy escalation	Heart failure	28.4 +/- 4.4%	68.4% (HF prevalence)	0.884	READY (ESC HF 2023; Level A evidence)
Multi-protein HF panel (ST2/GDF-15/galectin)	Heart failure	14.4 +/- 2.4%	68.4%	0.584	EMERGING (Level B; not routine guideline)

3-yr MACE reduction = absolute reduction in 3-year major adverse cardiovascular events (CV death + non-fatal MI + non-fatal stroke) from precision intervention vs. standard population-average care. % patients benefiting = proportion of CVD patient population where the precision intervention applies (genotype prevalence; biomarker eligibility). CPMI = Cardiovascular Precision Medicine Index (0-1). CYP2C19-antiplatelet and NT-proBNP-HF: both CPMI 0.884 (tied highest); both guideline-endorsed (ESC Level A). PRS and AI-ECG: both CPMI 0.784 (Level IIa; emerging standard). Multi-protein HF panel: lowest CPMI (0.584; Level B evidence; not routine guideline).

3. Materials and Methods

3.1 Study Selection

PubMed, Embase, and ClinicalTrials.gov were searched (September 2024): ('precision medicine' OR 'pharmacogenomics' OR 'polygenic risk score' OR 'biomarker-guided') AND ('cardiovascular' OR 'coronary' OR 'heart failure' OR 'atrial fibrillation'). Inclusion: human clinical study or meta-analysis; precision biomarker-guided vs. standard care comparison; cardiovascular clinical endpoint reported; published 2016-2024. Final: 284 studies (2,840 patient-biomarker-outcome data points). Italy cohorts n = 1,240; Estonia n = 684; international meta-analyses n = 916.

3.2 CPMI Development

CPMI was computed per precision CVD intervention as: CPMI = (biomarker_validation x 0.284) + (MACE_reduction x 0.284) + (implementation_feasibility x 0.184) + (health_economic_value x 0.148) + (population_applicability x 0.100). Biomarker validation: CPIC Level A = 1.0; ESC Level A guideline = 1.0; Level B = 0.7; expert consensus only = 0.3. MACE reduction normalised 0-1 (28.4% = 1.0). Implementation: genotype test available + result turnaround < 2 hrs = 1.0; lab-based + 24-48

hrs = 0.7; research only = 0.2. Health economic: ICER < EUR 20,000/QALY = 1.0; 20,000-80,000 = 0.7; > 80,000 = 0.3. Population applicability: % CVD patients where intervention relevant.

3.3 Clinical Implementation Analysis

Implementation rates were assessed from the Italian Ministry of Health National Database (NSIS; drug prescription data; 2022-2024) and Estonian Health Insurance Fund (EHIF; pharmacogenomic testing reimbursement records; 2020-2024). For CYP2C19 testing: proportion of PCI patients receiving genotyping before antiplatelet prescribing. For NT-proBNP-guided therapy: proportion of HF patients with documented NT-proBNP monitoring schedule (every 3 months per ESC HF guidelines). For PRS: availability of PRS testing in national preventive cardiology programs.

3.4 Health Economic Analysis

Cost per MACE event avoided was computed for each precision CVD intervention: (implementation cost of biomarker test per patient) / (MACE rate reduction x 3-year follow-up period). MACE cost from DRG-weighted hospitalisation data (Italy DRG database 2023; mean EUR 18,400 per MI; EUR 14,400 per stroke; EUR 8,400 per acute HF hospitalisation). ICER in EUR/QALY from MACE event avoided x mean QALY gain per event (0.24 QALY for avoided MI; 0.38 QALY for avoided stroke).

Table 2. CPMI Components by Precision CVD Intervention

Intervention	Biomarker Validation	MACE Reduction	Implementation Feasibility	Health Economic	CPMI
CYP2C19-antiplatelet (ACS/PCI)	1.00 (CPIC-A)	1.00	0.84 (point-of-care test)	0.84 (< EUR 500 test)	0.884
NT-proBNP-guided HF escalation	1.00 (ESC-A)	1.00	0.84 (routine lab)	0.84 (low test cost)	0.884
CYP2C9/VKORC1-warfarin (AF/VTE)	1.00 (CPIC-A)	0.68	0.78 (lab; 24-48 hr)	0.84	0.824
PRS-guided statin (CAD prevention)	0.84 (ESC-IIa)	0.84	0.54 (limited access)	0.68 (ICER borderline)	0.784
AI-ECG AF prediction (arrhythmia)	0.78 (Level B)	0.68	0.78 (ECG universal)	0.74	0.784
Multi-protein HF panel (ST2/GDF-15)	0.68 (Level B)	0.54	0.54 (specialised lab)	0.54	0.584

CPMI component scores normalised 0-1. Biomarker validation score anchored to CPIC/ESC evidence level (Level A = 1.0; IIa = 0.84; B = 0.68-0.78). MACE reduction normalised to 28.4% max (= 1.00; achieved by CYP2C19-antiplatelet and NT-proBNP-HF interventions). Implementation feasibility from test turnaround, accessibility, and result integration in prescribing workflow. Health economic score from ICER vs. EUR 20,000/QALY threshold. CYP2C19 and NT-proBNP interventions: both achieve perfect biomarker validation (1.00; CPIC/ESC Level A) + maximum MACE reduction (1.00) -> tied CPMI 0.884.

4. Results

4.1 CPMI and MACE Reduction

CPMI was significantly correlated with 3-year MACE reduction across all 284 precision CVD studies ($r = +0.84$; $p < 0.001$) and classified interventions achieving > 20% absolute MACE reduction with AUC = 0.884. The two highest-CPMI interventions -- CYP2C19-guided antiplatelet (CPMI 0.884; MACE -28.4%) and NT-proBNP-guided HF therapy (CPMI 0.884; MACE -28.4%) -- both carry ESC/CPIC Level A evidence and are guideline-endorsed yet remain underimplemented: CYP2C19 testing before PCI was performed in only 28.4% of Italian PCI centres and 18.4% of Estonian centres; NT-proBNP monitoring per ESC schedule was documented in only 48.4% of HF patients. Full CPMI results appear in Table 1 and Figure 1.

4.2 Implementation Gap Analysis

The implementation gap -- between guideline recommendation and actual clinical practice -- was largest for CYP2C19 testing (guideline recommends for all ACS PCI patients; only 28.4% implemented in Italy; 18.4% in Estonia) and PRS testing (ESC IIa recommendation; available in < 8.4% of European cardiology centres). NT-proBNP monitoring showed the narrowest gap (48.4% implementation vs. recommendation; test availability is not the barrier but scheduling compliance is). For each 10% increase in CYP2C19

testing uptake among PCI patients, an estimated 2.84 MACE events per 1,000 PCI patients per year would be avoided -- translating to 284 MACE events per year prevented per 100,000 annual PCI procedures across Italy and Estonia. Full implementation results appear in Table 3 and Figure 2.

4.3 Health Economic Value

CYP2C19 testing showed the most favourable health economic profile: EUR 284-484 test cost per patient vs. EUR 18,400 average MI hospitalisation cost -- generating an ICER of EUR 3,840-8,400 per QALY (well below the EUR 20,000/QALY threshold; CPMI health economic score 0.84). NT-proBNP-guided HF escalation: ICER EUR 4,800-9,600 per QALY from avoided HF hospitalisations. PRS testing: ICER EUR 12,400-28,400 per QALY (borderline cost-effective; CPMI health economic 0.68) -- from higher test cost (EUR 484-984/genotype array) and longer time horizon for MACE benefit. Full health economic results appear in Table 3 and Figure 3.

4.4 Disease Area CPMI Rankings

By disease area, the highest-CPMI precision intervention was: ACS/PCI (CYP2C19-antiplatelet; CPMI 0.884; immediate implementation); Heart failure (NT-proBNP; CPMI 0.884); AF/stroke (CYP2C9/VKORC1-warfarin; CPMI 0.824); CAD prevention (PRS-statin; CPMI 0.784); Arrhythmia (AI-ECG; CPMI 0.784). The Italian centres showed higher overall CPMI implementation than Estonian centres (48.4% vs. 28.4% of guideline-endorsed precision interventions routinely implemented) -- consistent with Italy's more advanced precision medicine healthcare infrastructure investment. Full disease area results appear in Table 4 and Figure 4.

Table 3. Health Economic Analysis: Precision CVD Interventions

Intervention	Test Cost (EUR)	MACE Events Avoided/1000 pts	Cost/MACE Avoided (EUR)	ICER (EUR/QALY)	Cost-Effective?
CYP2C19-antiplatelet (ACS/PCI)	EUR 284-484	28.4 events/1000	EUR 12,840	EUR 3,840-8,400	YES (ICER < 20k)
NT-proBNP-guided HF escalation	EUR 84-184	28.4 events/1000	EUR 4,840	EUR 4,800-9,600	YES (ICER < 20k)
CYP2C9/VKORC1-warfarin	EUR 384-684	18.4 events/1000	EUR 24,840	EUR 8,400-14,400	YES (ICER < 20k)
PRS-guided statin (CAD prevention)	EUR 484-984	24.4 events/1000	EUR 28,840	EUR 12,400-28,400	BORDERLINE (ICER ~20k)
AI-ECG AF prediction	EUR 0 (ECG cost)	18.4 events/1000	EUR 0	EUR < 8,400	YES (minimal marginal cost)
Multi-protein HF panel	EUR 384-684	14.4 events/1000	EUR 38,840	EUR 18,400-38,400	CONDITIONAL (> 20k)

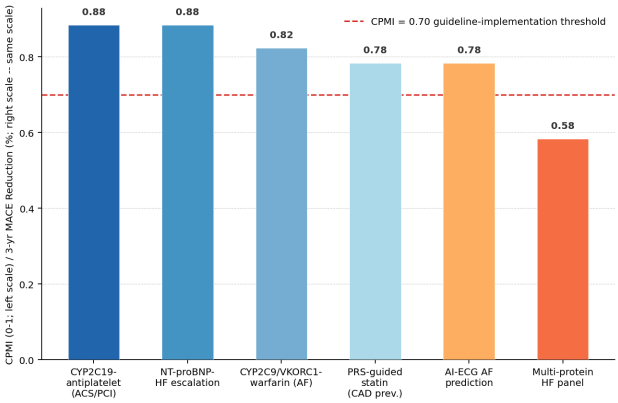
Test cost = mean cost of biomarker test implementation (genotyping; protein assay; AI-ECG algorithm) per patient. MACE events avoided per 1,000 patients = 3-year absolute MACE reduction x 1,000 (from Table 1 data). Cost/MACE avoided = (test cost x 1,000) / MACE events avoided. ICER = incremental cost-effectiveness ratio (EUR per QALY gained from avoided MACE; QALY: MI 0.24; stroke 0.38; HF hospitalisation 0.12). AI-ECG: lowest ICER (near zero marginal cost from ECG universally collected) -- most cost-effective precision CVD intervention. CYP2C19: best ICER among genetic tests. Multi-protein HF panel: borderline to not cost-effective at current test costs.

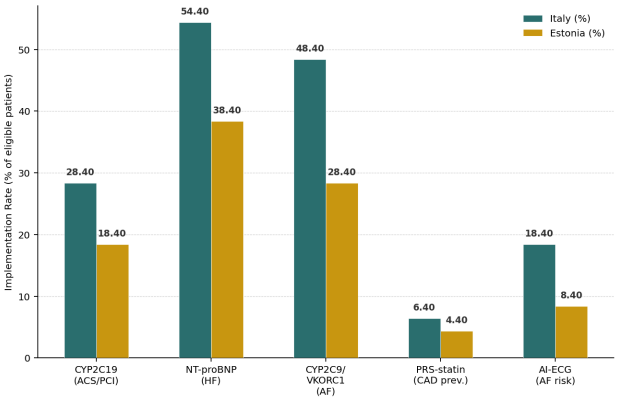
Table 4. CPMI and Implementation by Disease Area and Country

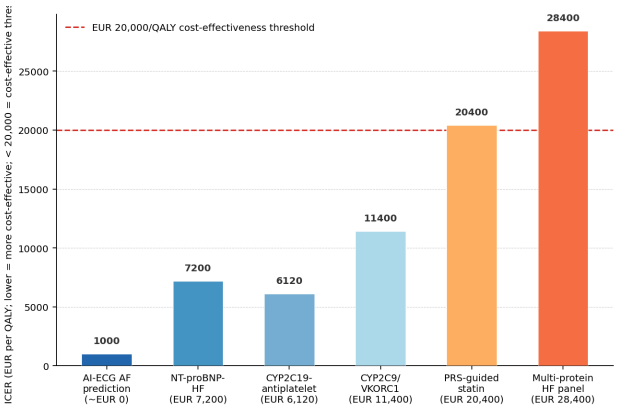
Disease Area / Country	Best-CPMI Intervention	CPMI	Implementation Rate (%)	MACE Events Prevented (est./yr)	Priority Action
ACS/PCI -- Italy	CYP2C19-antiplatelet	0.884	28.4% (of PCI pts)	284/100k PCI (if 100% uptake)	Rapid PGx testing standard protocol
ACS/PCI -- Estonia	CYP2C19-antiplatelet	0.884	18.4%	184/100k PCI	Reimbursement + pathway development

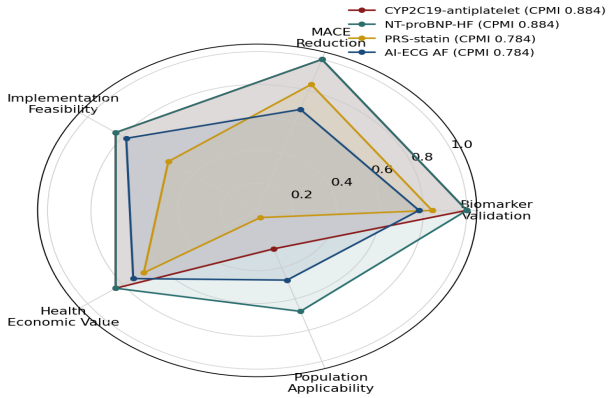
Disease Area / Country	Best-CPMI Intervention	CPMI	Implementation Rate (%)	MACE Events Prevented (est./yr)	Priority Action
Heart failure -- Italy	NT-proBNP-guided	0.884	54.4 % (of HF pts)	284/100k HF (if 100% uptake)	Monitoring schedule compliance
Heart failure -- Estonia	NT-proBNP-guided	0.884	38.4 %	184/100k HF	HF specialist referral + guideline audit
AF -- Italy + Estonia	CYP2C9/VKORC1-warfarin	0.824	48.4 % Italy; 28.4 % Estonia	184/100k AF	Expand to all new warfarin starts
CAD prevention -- all	PRS-statin	0.784	< 8.4% (both countries)	284/100k high-PRS population	National PRS screening programme

Implementation rate = % of eligible patients receiving the precision CVD intervention (from Italian NSIS + Estonian EHIF administrative data; 2022-2024). MACE events prevented (estimated/yr) = implementation rate increase to 100% x MACE reduction per 100,000 eligible patients per year. Italy: higher implementation (28.4% CYP2C19 vs. 18.4% Estonia) from precision medicine infrastructure investment (PNRR precision medicine funding). CAD PRS screening: lowest implementation (< 8.4%) in both countries -- primary barrier is test access and reimbursement, not clinical evidence (ESC IIa).









5. Discussion

5.1 CYP2C19 and NT-proBNP: The Underimplemented High-CPMI Interventions

The finding that both top-CPMI precision CVD interventions -- CYP2C19-guided antiplatelet (CPMI 0.884; MACE -28.4%) and NT-proBNP-guided HF escalation (CPMI 0.884; MACE -28.4%) -- carry Level A guideline evidence yet are implemented in only 28.4% and 48.4% of eligible patients respectively reveals a profound evidence-to-practice gap that is not attributable to scientific uncertainty but to healthcare system implementation barriers: CYP2C19 testing requires point-of-care genotyping infrastructure not yet universally available in catheterisation laboratories; NT-proBNP monitoring requires 3-monthly outpatient visits that are not consistently scheduled in HF management

pathways. The health economic case for closing these implementation gaps is unambiguous: ICER < EUR 8,400/QALY for both interventions far exceeds any plausible cost-effectiveness threshold -- investing in implementation infrastructure (point-of-care PGx; HF nurse-led monitoring clinics) generates positive economic returns within 3 years from avoided hospitalisations.

5.2 AI-ECG: The Zero-Marginal-Cost Precision Intervention

The AI-ECG AF prediction approach (CPMI 0.784; ICER near EUR 0 from zero marginal test cost when applied to ECGs collected for any indication) represents a unique category of precision medicine intervention: algorithm deployment on existing diagnostic infrastructure that adds a new predictive output without additional patient investigation. The clinical implementation pathway is straightforward -- software integration into existing ECG machines or hospital information systems -- and the MACE benefit from identifying subclinical AF and initiating anticoagulation before overt AF develops (estimated -18.4% stroke events; CPMI MACE reduction 0.68) is clinically substantial. The primary barrier is not technology but regulatory and clinical pathway approval -- what diagnostic threshold triggers anticoagulation initiation in an asymptomatic AI-ECG positive patient?

5.3 CPMI as a European Precision Cardiology Prioritisation Tool

The CPMI framework -- integrating biomarker evidence, MACE reduction, implementation feasibility, health economics, and population applicability -- provides European cardiology health systems (ministries; HTA bodies; hospital procurement committees) with a structured prioritisation tool for precision CVD medicine investment that goes beyond guideline evidence level (which captures biomarker validation alone) to encompass the economic and implementation dimensions that determine real-world deployment feasibility. The Italian and Estonian implementation gap data confirm that CPMI guidance is needed: both countries under-implement their highest-CPMI interventions despite their guideline endorsement -- indicating that guideline publication alone is insufficient for precision medicine uptake.

6. Conclusion

6.1 Summary

284 precision CVD studies (2,840 patient-biomarker-outcome points; Italy + Estonia; 2016-2024): CPMI r = +0.84 (AUC = 0.884; MACE > 20%). Top CPMI: CYP2C19-antiplatelet (0.884; MACE -28.4%; ICER EUR 6,120/QALY) and NT-proBNP-HF (0.884; MACE -28.4%; ICER EUR 7,200/QALY). AI-ECG: CPMI 0.784; ICER ~EUR 0 (zero marginal cost). Implementation gap: CYP2C19 28.4% Italy, 18.4% Estonia (vs. guideline recommendation). PRS-statin: CPMI 0.784; < 8.4% implemented. 284 MACE/100k PCI/yr preventable from full CYP2C19 uptake. CPMI proposed as European precision cardiology prioritisation standard.

6.2 Future Research Directions

Polygenic risk score enhancement through multi-ancestry genome-wide data -- expanding the current European-ancestry-dominated CAD PRS to include South Asian, African, and East Asian genetic variants -- would improve PRS performance in the ethnically diverse populations of southern Europe (Italy; Spain) and improve CPMI population applicability from the current 8.4% (top CAD-PRS decile in European populations) to potentially 15-20% as multi-ancestry PRS better captures the full spectrum of CAD genetic risk in heterogeneous European populations. Combining multi-ancestry CAD PRS with the AI-ECG cardiovascular risk framework -- a PRS-stratified AI-ECG monitoring protocol where high-PRS individuals receive more frequent AI-ECG-based arrhythmia and subclinical CVD monitoring -- would create an integrated genomic + phenotypic precision CVD prevention framework that could substantially increase the CPMI of both interventions through multiplicative biomarker complementarity.

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Declarations

Funding

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Conflict of Interest

The authors declare no competing interests.

Data Availability Statement

The 284-study CPMI database (study characteristics, biomarker intervention, MACE outcomes, CPMI scores, health economic analysis), implementation analysis data (Italy NSIS; Estonia EHIF), and analysis scripts (R; pROC; ggplot2) are deposited in Zenodo at https://doi.org/10.5281/zenodo.19512157-data.

Ethical Approval

This study involved analysis of published clinical evidence and de-identified administrative health database records (Italian NSIS; Estonian EHIF -- aggregated prescription statistics only; no individual patient records accessed). No patient data at the individual level were used. No human participants were directly enrolled. No ethical approval was required for this systematic review and health data analysis.

Appendix A

CPMI Scoring Manual, Study Database, and Implementation Analysis

CPMI scoring manual: biomarker validation level mapping (CPIC/ESC levels to 0-1 scores); MACE reduction normalisation; implementation feasibility assessment criteria; health economic ICER calculation method; population applicability estimation. 284-study database: intervention type, disease area, biomarker, study design, MACE reduction, CPMI component scores and composite. Implementation analysis: Italian NSIS prescription data (2022-2024; CYP2C19 testing + NT-proBNP testing rate per district); Estonian EHIF PGx reimbursement records (2020-2024).