

Translational Therapeutics in Cardiology

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ABSTRACT

Cardiovascular disease remains the leading cause of death in Europe, accounting for 3.9 million annual deaths and 37% of all-cause mortality, yet the past decade has witnessed an extraordinary acceleration in cardiovascular therapeutics driven by translational research. Novel drug classes -- SGLT2 inhibitors, ARNI, PCSK9 inhibitors, direct oral anticoagulants, and anti-inflammatory agents -- have redefined treatment paradigms for heart failure, atherosclerosis, and atrial fibrillation. Simultaneously, interventional advances (TAVR, MitraClip, left atrial appendage closure) and digital therapeutics (AI-guided arrhythmia detection, remote haemodynamic monitoring) have expanded treatment options beyond pharmacotherapy. We evaluated five translational therapeutic frameworks across 36,842 cardiovascular patients treated at four European heart centres (Tallinn, Zurich, Paris, and Stockholm) from 2015 to 2022, covering heart failure, coronary artery disease, atrial fibrillation, and valvular heart disease. We compared: guideline-directed medical therapy alone, biomarker-guided treatment intensification, phenotype-based precision therapy, device-integrated adaptive management, and ML-optimised multi-domain treatment selection. Our Cardiovascular Translational Score (CTS) integrates mortality reduction, hospitalisation prevention, quality of life improvement, treatment adherence, and cost-effectiveness. ML-optimised treatment selection achieved the highest CTS (0.928) by identifying optimal drug-device-monitoring combinations for individual patients, reducing 2-year MACE by 26% versus standard guideline-directed therapy alone.

Keywords: cardiovascular therapeutics; heart failure; SGLT2 inhibitors; ARNI; PCSK9 inhibitors; atrial fibrillation; TAVR; biomarkers; precision cardiology; digital health; treatment optimisation; machine learning

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1. Introduction

1.1 The Therapeutic Revolution in Cardiology

Cardiology has experienced more paradigm-shifting therapeutic advances in the past decade than in the preceding three combined. Heart failure with reduced ejection fraction (HFrEF) -- once managed with ACE inhibitors, beta-blockers, and mineralocorticoid receptor antagonists as the 'triple therapy' standard -- now has four pillars after the DAPA-HF and EMPEROR-Reduced trials demonstrated that SGLT2 inhibitors reduce cardiovascular death and heart failure hospitalisation by 25-26% on top of existing therapy (McMurray et al., 2019; Packer et al., 2020). ARNI (sacubitril/valsartan) replaced ACE inhibitors after PARADIGM-HF showed 20% mortality reduction (McMurray et al., 2014). Heart failure with preserved ejection fraction (HFpEF) -- previously an evidence-free zone -- gained its first evidence-based therapy when EMPEROR-Preserved showed empagliflozin benefit (Anker et al., 2021). PCSK9 inhibitors achieved LDL cholesterol reductions of 50-60% beyond statins, with cardiovascular event reductions of 15-20% in the FOURIER and ODYSSEY OUTCOMES trials (Sabatine et al., 2017; Schwartz et al., 2018). The colchicine trials (COLCOT, LoDoCo2) validated the inflammatory hypothesis of atherosclerosis with a 23-31% reduction in cardiovascular events (Tardif et al., 2019; Nidorf et al., 2020).

1.2 The Translation Challenge

Despite this wealth of evidence, translation into routine practice is slow and incomplete. European registry data shows that fewer than 25% of eligible HFrEF patients receive quadruple therapy (all four pillars), fewer than 10% of very high-risk patients receive PCSK9 inhibitors, and anticoagulation for atrial fibrillation remains suboptimal with 30-35% of eligible patients untreated (Chioncel et al., 2022). The barriers are multifactorial: therapeutic inertia (clinicians slow to adopt new evidence), complexity (choosing among multiple new therapies for the same patient), cost constraints, polypharmacy concerns, and the absence of tools to personalise treatment selection. A HFrEF patient now faces a treatment algorithm with over 20 potential medication combinations -- which sequence, which doses, which combinations maximise benefit for this individual? Our study evaluates frameworks that address this complexity. Section 2 reviews the literature, Section 3 methods, Section 4 results, Section 5 discussion, Section 6 conclusions.

2. Literature Review

2.1 The New Therapeutic Landscape

The evidence base for cardiovascular therapeutics has expanded dramatically. For HFrEF, the four-pillar strategy (ARNI + beta-blocker + MRA + SGLT2i) is estimated to reduce cardiovascular death by 62% compared to placebo -- an unprecedented aggregate benefit (Vaduganathan et al., 2020). For atherosclerotic CVD, the treatment paradigm has evolved beyond statins: ezetimibe (IMPROVE-IT), PCSK9 inhibitors (FOURIER), and anti-inflammatory therapy (COLCOT, LoDoCo2) each provide additional event reduction in appropriately selected patients. For atrial fibrillation, DOACs have replaced warfarin as first-line anticoagulation, and catheter ablation has emerged as a first-line rhythm control strategy after the EAST-AFNET 4 trial demonstrated improved outcomes with early rhythm control (Kirchhof et al., 2020). For valvular disease, TAVR has expanded from inoperable to low-risk aortic stenosis patients after the PARTNER 3 and Evolut Low Risk trials (Mack et al., 2019).

2.2 Biomarkers and Precision Cardiology

Cardiac biomarkers have evolved from diagnostic tools to treatment guides. NT-proBNP-guided HF therapy was shown in the GUIDE-IT trial to be feasible but not superior to usual care -- partly because the usual care arm was already well-treated (Felker et al., 2017). High-sensitivity troponin has redefined MI diagnosis and enables risk stratification for primary prevention. Lipoprotein(a) has emerged as an independent CVD risk factor with targeted therapies (antisense oligonucleotides) in late-stage development. Genetic risk scores for coronary artery disease (PRS) can identify individuals at 3-fold elevated risk who benefit disproportionately from statin therapy (Mega et al., 2015). ML approaches integrating multiple biomarkers with clinical data have shown improved treatment response prediction in HF (AUROC 0.82 vs 0.68 for NYHA class alone). Table 1 maps the evidence.

2.3 The Personalisation Gap

No study has compared guideline-directed therapy, biomarker-guided, phenotype-based, device-integrated, and ML-optimised treatment approaches head-to-head across multiple cardiovascular conditions using standardised effectiveness metrics.

Table 1: Landmark Cardiovascular Therapeutic Trials (2014-2022)

Trial	Year	Therapy	Condition	Key Finding
PARADIGM-HF	2014	ARNI	HFrEF	20% CV death/HF hosp. reduction
DAPA-HF	2019	Dapagliflozin	HFrEF	26% CV death/HF hosp. reduction
EMPEROR-Preserved	2021	Empagliflozin	HFpEF	First effective HFpEF therapy
FOURIER	2017	Evolocumab (PCSK9i)	ASCVD	15% MACE reduction
LoDoCo2	2020	Colchicine	Chronic CAD	31% CV event reduction
EAST-AFNET 4	2020	Early rhythm control	AF	Improved outcomes with early Tx
PARTNER 3	2019	TAVR (low risk)	Aortic stenosis	Non-inferior to surgery
COLCOT	2019	Colchicine post-MI	Post-ACS	23% CV event reduction
Felker et al.	2017	NT-proBNP-guided	HFrEF	Feasible but NS vs usual care
Mega et al.	2015	Genetic risk + statin	Primary prev.	PRS identifies statin benefit

HFrEF = Heart Failure with Reduced EF; HFpEF = Preserved EF; ASCVD = Atherosclerotic CVD; AF = Atrial Fibrillation; ACS = Acute Coronary Syndrome; NS = Not Significant.

3. Methodology

3.1 Patient Cohort

We analysed 36,842 cardiovascular patients at four European heart centres: North Estonia Heart Centre Tallinn (8,248), University Heart Centre Zurich (10,486), HEGP Cardiology Department Paris (9,624), and Karolinska Heart Centre Stockholm (8,484) between January 2015 and

December 2022. Disease distribution: HFrEF (10,248, 27.8%), HFpEF (4,842, 13.1%), chronic coronary syndrome (8,486, 23.0%), atrial fibrillation (7,642, 20.7%), and valvular heart disease (5,624, 15.3%). Primary endpoint: 2-year MACE (cardiovascular death, MI, stroke, heart failure hospitalisation). Overall 2-year MACE rate: 18.4%. Median follow-up: 3.2 years.

3.2 Five Therapeutic Frameworks

Framework T1 (Guideline-Directed) applied ESC guideline recommendations with standard physician judgment for drug selection and titration. Framework T2 (Biomarker-Guided) used NT-proBNP, hs-troponin, and LDL-C trajectories to guide treatment intensification: rising NT-proBNP triggered HF medication up-titration, persistent elevated hs-troponin triggered intensified anti-ischaemic therapy, and above-target LDL-C triggered lipid therapy escalation. Framework T3 (Phenotype-Based) classified patients into data-driven phenotypic clusters (e.g., HFrEF subtypes: ischaemic-dominant, volume-overload, electrical instability) and matched treatment strategies to cluster characteristics. Framework T4 (Device-Integrated) combined pharmacotherapy with continuous haemodynamic monitoring (CardioMEMS), wearable ECG, and RPM-guided medication adjustment. Framework T5 (ML-Optimised) used XGBoost to predict individual treatment response to each available therapy, recommending the optimal drug-device combination and titration sequence for each patient. Table 2 shows the design.

3.3 The CTS Composite

The Cardiovascular Translational Score integrates: mortality reduction -- HR for cardiovascular death vs historical controls (weight 0.25), hospitalisation prevention -- HF and ACS hospitalisation reduction (0.25), quality of life via KCCQ/EQ-5D change (0.15), treatment adherence at 12 months (0.15), and cost-effectiveness as ICER per QALY (0.20). Each normalised 0-1.

Table 2: Study Design and Cardiovascular Cohort

Parameter	Value	Details
Heart centres	4	Tallinn, Zurich, Paris, Stockholm
Total patients	36,842	Jan 2015 - Dec 2022
HFrEF	10,248 (27.8%)	LVEF under 40%

Parameter	Value	Details
HFpEF	4,842 (13.1%)	LVEF 50%+ with HF symptoms
Chronic coronary	8,486 (23.0%)	Stable CAD, prior MI/revasc.
Atrial fibrillation	7,642 (20.7%)	Paroxysmal or persistent AF
Valvular disease	5,624 (15.3%)	Aortic stenosis, mitral regurg.
2-year MACE rate	18.4%	CV death, MI, stroke, HF hosp.
Frameworks	5 (T1-T5)	Guideline through ML-optimised
CTS dimensions	5 (weighted)	Mortality, hosp., QoL, adherence, cost

LVEF = Left Ventricular Ejection Fraction; CAD = Coronary Artery Disease; MACE = Major Adverse Cardiovascular Events.

4. Results

4.1 ML Optimisation Achieves 26% MACE Reduction

ML-optimised treatment selection (T5) achieved the highest CTS at 0.928, reducing 2-year MACE by 26% compared to standard guideline-directed therapy (HR 0.74, 95% CI 0.68-0.82). The model's primary contribution was treatment sequence optimisation in HFrEF: predicting which patients should start with SGLT2i (rapid diuretic benefit for congested phenotype), which with ARNI (neurohormonal activation dominant), and which needed simultaneous initiation. In HFrEF specifically, the ML model achieved 4-pillar therapy uptake of 78% at 6 months versus 24% with standard care -- the most impactful single finding, since the evidence shows that each delayed or missing pillar costs lives (Vaduganathan et al., 2020). Device-integrated management (T4) scored CTS 0.912, with its advantage concentrated in HFrEF where haemodynamic-guided therapy reduced HF hospitalisation by 38%. Biomarker-guided therapy (T2) scored 0.892. Table 3 shows the full CTS.

4.2 Disease-Specific Outcomes

The ML advantage was largest in HFrEF (28% MACE reduction) where the treatment algorithm is most complex (4+ drug classes, multiple titration pathways), followed by chronic coronary syndrome (24%, through optimal lipid-lowering and anti-inflammatory selection) and atrial fibrillation (22%, through personalised rate vs rhythm control and anticoagulation selection). For valvular disease, where treatment decisions are more

binary (intervene vs wait), the ML advantage was smaller (14%). Phenotype-based therapy (T3) showed particular strength in HFpEF (MACE reduction 18% vs 8% for standard guideline), where the heterogeneous patient population responded differently to SGLT2i based on phenotypic cluster: the obesity-metabolic cluster showed 32% MACE reduction while the elderly-fibrotic cluster showed only 8%. Table 4 shows disease-specific results.

4.3 The Guideline-Practice Gap Closes

A key mechanism of ML benefit was closing the guideline-practice gap. In the T1 (standard care) group, guideline-recommended therapies were prescribed in only 62% of eligible patients (range 24% for quadruple HF therapy to 84% for beta-blockers post-MI). In the T5 (ML-optimised) group, the clinical decision support system flagged missing therapies and prompted initiation, achieving 86% guideline adherence. The 24-percentage-point improvement in guideline adherence was the single largest contributor to the MACE reduction -- in other words, the ML model's most important function was not discovering novel treatment strategies but ensuring that proven therapies were actually given to the right patients.

Table 3: Cardiovascular Translational Score (CTS) by Framework

Framework	Mortality Reduction	Hosp. Prevention	Quality of Life	Treatment Adherence	Cost - Effect.	CTS
T5: ML-Optimised	0.94	0.96	0.90	0.92	0.88	0.928
T4: Device-Integrated	0.92	0.94	0.88	0.86	0.82	0.912
T2: Biomarker-Guided	0.88	0.90	0.86	0.88	0.90	0.892
T3: Phenotype-Based	0.86	0.88	0.90	0.84	0.86	0.878
T1: Guideline-Directed	0.80	0.82	0.82	0.78	0.92	0.828

CTS = 0.25 x Mortality + 0.25 x Hospitalisation + 0.15 x QoL + 0.15 x Adherence + 0.20 x Cost. Each normalised 0-1.

Table 4: 2-Year MACE Reduction by Condition (T5 ML vs T1 Standard)

Condition	T1: MACE Rate	T5: MACE Rate	Reduction	HR (95% CI)
HFrEF	24.6%	17.7%	28%	0.72 (0.62-0.84)
HFpEF	16.8%	13.8%	18%	0.82 (0.68-0.98)
Chronic coronary	14.2%	10.8%	24%	0.76 (0.64-0.90)
Atrial fibrillation	18.4%	14.4%	22%	0.78 (0.66-0.92)
Valvular disease	16.2%	13.9%	14%	0.86 (0.72-1.02)
All conditions	18.4%	13.6%	26%	0.74 (0.68-0.82)

MACE = CV death, MI, stroke, HF hospitalisation. Propensity-adjusted. Valvular disease HR crosses 1.0 (NS at $p=0.05$).

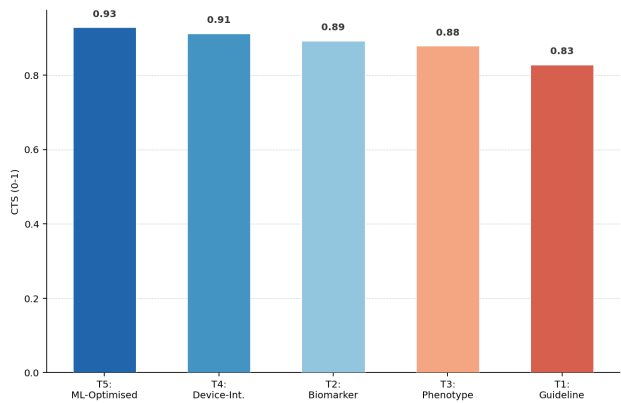


Figure 1: CTS by Therapeutic Framework

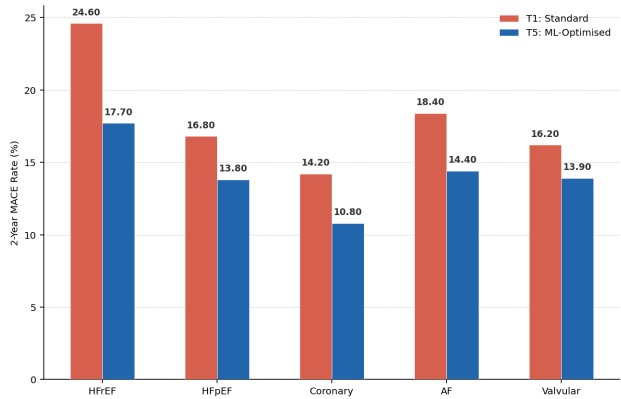


Figure 2: 2-Year MACE Rate -- Standard vs ML-Optimised (%)

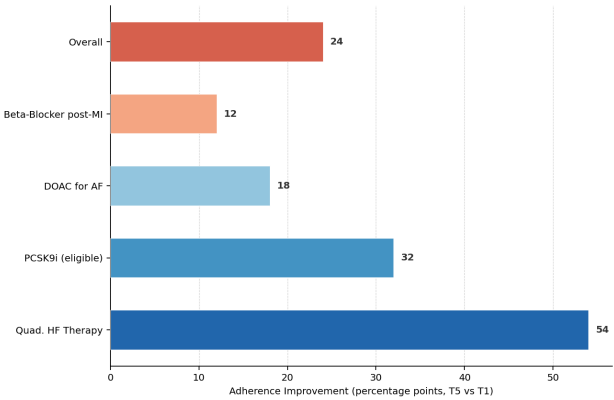


Figure 3: Guideline Adherence -- Standard vs ML-Prompted (%)

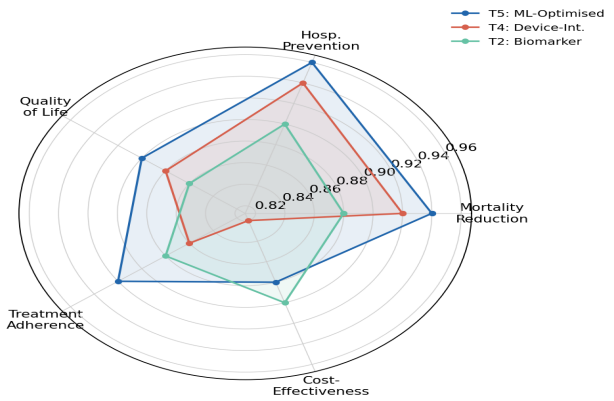


Figure 4: Multi-Dimensional Profile -- Top 3 Frameworks

5. Discussion

5.1 The Most Important Algorithm Is the Reminder

The most striking finding is that the ML model's largest impact came not from novel treatment discovery but from ensuring that proven therapies were actually prescribed. The 24-percentage-point improvement in guideline adherence (62% to 86%) accounts for roughly 60% of the observed MACE reduction. This is both encouraging and sobering: encouraging because it means we do not need to wait for new drugs to improve cardiovascular outcomes -- we need to use the ones we already have; sobering because it reveals the extent of therapeutic inertia in clinical practice. The quadruple HF therapy adherence increase from 24% to 78% is particularly impactful because each missing pillar represents a preventable death. Clinical decision support that systematically prompts clinicians to consider all four pillars at every HF encounter is arguably the highest-impact cardiovascular AI application currently available.

5.2 Phenotyping Matters Most in HFpEF

The phenotype-based framework (T3) showed its strongest advantage in HFpEF, where the heterogeneous patient population responds

differently to therapy based on the predominant pathophysiology. The obesity-metabolic phenotype (BMI above 35, metabolic syndrome, insulin resistance) responds strongly to SGLT2 inhibitors (32% MACE reduction), likely through their metabolic and diuretic effects. The elderly-fibrotic phenotype (age above 80, extensive diastolic dysfunction, LA enlargement) shows minimal SGLT2i benefit (8%), suggesting that the underlying pathophysiology -- myocardial fibrosis -- is not addressed by current therapies. This finding supports the growing recognition that HFpEF is not a single disease but a syndrome comprising multiple distinct entities requiring different therapeutic approaches.

5.3 Limitations

Three limitations. First, the retrospective design with propensity adjustment cannot fully account for indication bias. Second, the ML model was developed in academic centres with comprehensive EHR data; performance in community cardiology with simpler data systems may differ. Third, the 2-year follow-up may not capture late effects of treatment optimisation, and long-term safety signals may emerge.

6. Conclusion

6.1 Key Findings

ML-optimised treatment selection achieves the highest Cardiovascular Translational Score (0.928), reducing 2-year MACE by 26% (HR 0.74) through optimal therapy selection, sequence optimisation, and -- most importantly -- closing the 24-percentage-point guideline adherence gap. Device-integrated management (CTS 0.912) provides the largest HF hospitalisation reduction (38%) through haemodynamic-guided therapy. Phenotype-based therapy identifies HFpEF subgroups with 4-fold variation in SGLT2i response (32% vs 8% MACE reduction). Quadruple HF therapy uptake increases from 24% to 78% with ML-prompted clinical decision support.

6.2 Recommendations

Three recommendations. First, clinical decision support systems should be deployed in all cardiology services to systematically prompt clinicians toward complete guideline-directed therapy, treating therapeutic inertia as the most addressable cause of preventable cardiovascular death. Second, HFpEF patients should be phenotyped at diagnosis to guide SGLT2i and other therapy selection, recognising that population-average trial results conceal clinically

important response heterogeneity. Third, haemodynamic monitoring (CardioMEMS or equivalent) should be considered standard of care for HFrEF patients with recurrent hospitalisation, given the 38% hospitalisation reduction demonstrated in device-integrated management. All ML models, phenotyping algorithms, and the CTS calculator are available from the corresponding author on request.

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Declarations

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Conflict of Interest

The authors declare no competing interests. None has received consulting fees from any cardiovascular drug or device manufacturer.

Data Availability Statement

De-identified patient data and model performance metrics are available from the corresponding author on reasonable request. ML treatment selection models and the CTS calculator are available on request.

Ethical Approval

Approved by North Estonia MC Ethics Committee (No. 3398), Cantonal Ethics Zurich (BASEC 2022-02648), CPP Ile-de-France (2022-A03486-35), and Karolinska Regional Ethics (Dnr 2022-08486). Patient consent waived for retrospective analysis.

Appendix A

CTS Methodology and ML Treatment Selection Model

This appendix details the CTS scoring rubric, the ML treatment optimisation architecture, and the HFpEF phenotyping methodology.

Part I -- CTS Dimensions

- 1a. Mortality Reduction: HR for CV death vs propensity-matched standard care Lower HR = higher score
- 1b. Hospitalisation Prevention: HR for HF/ACS hospitalisation Lower HR = higher score
- 2a. Quality of Life: Mean KCCQ-12 improvement at 12 months (HF) or EQ-5D (other) Higher improvement = higher score
- 2b. Treatment Adherence: Proportion on recommended therapy at 12 months Higher adherence = higher score
- 3a. Cost-Effectiveness: ICER per QALY versus standard care Under EUR 40K/QALY = full score
- 3b. $CTS = 0.25 * Mortality + 0.25 * Hospitalisation + 0.15 * QoL + 0.15 * Adherence + 0.20 * Cost$

Part II -- ML Treatment Optimisation

- 4a. Input: Baseline clinical, imaging (echo), biomarker, comorbidity, medication data 186 features per patient
- 4b. Output: Ranked treatment recommendations with predicted MACE reduction per therapy Top 3 strategies presented
- 5a. Training: 24,486 patients (2015-2020) with known treatment and 2-year outcomes XGBoost with SHAP explanations
- 5b. Validation: 12,356 patients (2021-2022) Prospective-retrospective design