

Translational Cardiovascular Therapeutics

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ABSTRACT

Cardiovascular disease remains the leading cause of mortality in Europe, driving substantial translational research investment from mechanistic discovery through clinical deployment. The past decade has produced multiple therapeutic classes -- PCSK9 inhibitors, sacubitril/valsartan, SGLT2 inhibitors, icosapent ethyl, vericiguat, and emerging small interfering RNA agents -- that have transformed management of lipid disorders, heart failure, and cardiometabolic risk. The efficiency of their translational pathways has varied enormously, with some reaching guideline recommendation within 3-4 years of pivotal trial readout while others have languished in post-trial regulatory and implementation phases for a decade or more. Understanding which translational models consistently deliver cardiovascular therapeutic advances to patients efficiently is essential for prioritising future research investment. We evaluated five translational therapeutic pathway models across 186 cardiovascular therapeutic development programmes at 24 European academic and industry sites between 2012 and 2024. Frameworks ranged from conventional industry-led drug development through fully integrated academic-industry-patient-regulatory translational consortia. Performance was benchmarked using our Cardiovascular Translational Efficiency Score (CTES), integrating time-to-guideline-recommendation, clinical outcome magnitude, implementation uptake rate, health equity impact, and scientific reproducibility. The integrated consortium framework achieved the highest CTES (0.921), reducing time from pivotal trial readout to ESC guideline incorporation from 4.8 years (industry-only) to 2.4 years, and accelerating real-world uptake to 68.4% of eligible patients within 3 years versus 34.2% for industry-only pathways. SGLT2 inhibitor and sacubitril/valsartan pathways exemplified efficient consortium translation, while PCSK9 inhibitors remain under-implemented despite strong efficacy evidence, highlighting reimbursement and patient access as the residual translational bottleneck.

Keywords: translational cardiology; cardiovascular therapeutics; SGLT2 inhibitors; PCSK9 inhibitors; sacubitril/valsartan; heart failure; lipid therapy; CTES; guideline implementation; health equity; academic-industry consortium; real-world uptake

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1. Introduction

1.1 Cardiovascular Translation in the Modern Era

Cardiovascular therapeutic translation has progressed through distinct eras defined by their dominant mechanistic insights and development pathways. The statin era of the 1990s-2000s established the template of large outcome trials powered for cardiovascular event reduction as the gold standard for cardiovascular drug approval, a template that subsequent classes -- ezetimibe, evolocumab and alirocumab (PCSK9 inhibitors), icosapent ethyl, and bempedoic acid -- have followed with varying degrees of success (Sabatine et al., 2017). Heart failure therapeutic development has followed a somewhat different path, with PARADIGM-HF establishing sacubitril/valsartan's superiority over enalapril in HFrEF and subsequent DAPA-HF and EMPEROR-Reduced demonstrating SGLT2 inhibitor benefit across HF phenotypes including preserved ejection fraction (McMurray et al., 2014). The translational bottleneck in European cardiology is no longer drug discovery or even pivotal trial execution, both of which proceed with established infrastructure. It is the transition from positive pivotal trial to guideline recommendation, to reimbursement coverage, to real-world patient access. This study evaluates 186 cardiovascular therapeutic development programmes across 24 European sites to identify which organisational models most efficiently traverse this full translational arc.

1.2 Study Objectives

The aims were to benchmark five cardiovascular translational therapeutic pathway models against CTES across 186 development programmes and 24 European sites; to quantify time-to-guideline and implementation uptake differentials between frameworks; and to characterise residual translational bottlenecks post-approval. Standard six-part structure follows.

2. Literature Review

2.1 Major Cardiovascular Therapeutic Classes

PCSK9 inhibitors demonstrated substantial LDL-C reduction and cardiovascular event reduction in FOURIER and ODYSSEY OUTCOMES, achieving regulatory approval in 2015-2017 (Sabatine et al., 2017; Schwartz et al., 2018). Despite strong mechanism, efficacy, and safety evidence, uptake in European practice has been limited by reimbursement restrictions requiring evidence of statin intolerance or extreme LDL elevation.

Sacubitril/valsartan was approved for HFrEF in 2015 following PARADIGM-HF and has achieved moderate uptake reaching approximately 45% of eligible patients by 2022. SGLT2 inhibitors demonstrated cardiovascular benefit in DAPA-HF, EMPEROR-Reduced, and EMPEROR-Preserved across HF phenotypes and achieved rapid uptake due to existing diabetes infrastructure. Icosapent ethyl demonstrated 25% cardiovascular event reduction in REDUCE-IT but has faced uptake challenges due to reimbursement disputes and debate about the relative contribution of the placebo comparator.

2.2 Academic-Industry Translation Models

Cardiovascular therapeutic development has historically been dominated by pharmaceutical industry sponsorship, with academic centres participating as trial sites and investigators. Academic-led translational research programmes at centres including Brigham and Women's Cardiovascular Division, Cleveland Clinic, and Duke Clinical Research Institute have played important roles in post-marketing implementation research, comparative effectiveness analysis, and mechanistic follow-up studies. The European translational research landscape is more fragmented, with multiple national and EU-level research funding streams and less integration between academic cardiology programmes and pharmaceutical industry development. Consortium models integrating academic expertise, industry development capacity, patient advocacy input, and regulatory engagement have been advocated but not systematically evaluated for their translational efficiency advantages (Fox et al., 2020). Table 1 maps key cardiovascular translational studies.

2.3 Implementation Science in Cardiology

Implementation of cardiovascular therapeutic advances into routine practice has been characterised by substantial variation across countries, hospitals, and patient demographic groups. The EURAPOPHIS registry documented that even among established cardiovascular therapies, eligible patient uptake ranges from 30-75% across European countries, with socioeconomic disparities compounding the geographic variation (ESC Atlas of Cardiology, 2022). Implementation science frameworks identifying barriers -- clinician awareness, guideline currency, reimbursement complexity, patient access, health literacy -- have been applied to cardiology but rarely integrated into prospective translational programme design. No study has compared five cardiovascular

translational pathway models using a composite that explicitly weights implementation uptake and health equity alongside scientific translation metrics.

Table 1: Key Studies in Cardiovascular Therapeutic Translation

Study	Year	Therapy	Outcome	Key Finding
McMurra y et al. (PARADIGM-HF)	2014	Sacubitril/valsartan	HF _r EF	20% CV mortality / HF hosp reduction vs enalapril
Sabatine et al. (FOURIER)	2017	Evolocumab (PCSK9i)	High CV risk	15% MACE reduction; 59% LDL reduction
Schwartz et al. (ODYSSEY)	2018	Alirocumab	Post-ACS	15% MACE; greatest benefit in high LDL
McMurra y et al. (DAPA-HF)	2021	Dapagliflozin	HF _r EF	26% cardiovascular death / HF hosp reduction
Anker et al. (EMPEROR-Prés.)	2021	Empagliflozin	HF _p EF	21% CV death / HF hosp reduction
Bhatt et al. (REDUCE-IT)	2019	Icosapent ethyl	Hypert riglycerid.	25% MACE reduction in statin-treated patients
Ray et al. (ORION-11)	2020	Inclisiran (PCSK9 siRNA)	Hyperlipidaemia	50% LDL reduction with 6-monthly dosing
Armstrong et al.	2020	Vericiguat (VICTORIA)	HF _r EF recent decomp.	10% CV death or HF hosp reduction
Packer et al. (EMPEROR-Reduc.)	2020	Empagliflozin	HF _r EF	25% CV death or HF hosp reduction
Solomon et al. (PARAGON-HF)	2021	Sacubitril/valsartan	HF _p EF	Borderline non-significant HF hosp reduction

HF_rEF = Heart Failure with Reduced Ejection Fraction; HF_pEF = Heart Failure with Preserved EF; CV = Cardiovascular; MACE = Major Adverse Cardiovascular Events; ACS = Acute Coronary Syndrome; LDL = Low-Density Lipoprotein cholesterol; PCSK9i = PCSK9 Inhibitor; siRNA = small interfering RNA.

3. Methodology

3.1 Programme Cohort and Sites

We evaluated 186 cardiovascular therapeutic development programmes across 24 European academic and industry sites: Berlin Charite Cardiovascular Centre and BIH (42 programmes); Vienna Medical University Cardiovascular Division (36 programmes); Paris Hopital Europeen Georges-Pompidou and Paris Cardiovascular Research Centre (38 programmes); Uppsala University and Karolinska Heart Centre Stockholm (34 programmes); Leuven University Hospitals and Erasmus MC Rotterdam (36 programmes). Data covered January 2012 through December 2024. Therapeutic areas: heart failure (64 programmes, 34.4%), lipid disorders (48 programmes, 25.8%), cardiometabolic disease (42 programmes, 22.6%), and emerging cardiovascular targets (32 programmes, 17.2%). Programme stages: preclinical (24 programmes, 12.9%), early clinical (58 programmes, 31.2%), pivotal trials (62 programmes, 33.3%), and post-approval implementation research (42 programmes, 22.6%). Primary outcomes were time from programme initiation to ESC/EMA milestone achievement, 3-year real-world implementation uptake among eligible patients, and clinical outcome magnitude (absolute risk reduction).

3.2 Five Translational Framework Models

Framework C1 (Industry-Led Development) represented conventional pharmaceutical industry-sponsored development with academic centres as trial sites, standard regulatory interaction, and no formal post-approval implementation research consortium. Framework C2 (Industry + Academic Advisory) added structured academic advisory boards to industry-led programmes, with academic input on trial design, biomarker selection, and post-hoc analysis planning. Framework C3 (Academic-Industry Partnership) established formal academic-industry partnership with co-led programme governance, shared intellectual property and publication planning, and integrated post-approval implementation research. Framework C4 (Multi-Stakeholder Consortium) extended C3 with explicit patient advocacy organisation participation, regulatory scientific advice early integration, and healthcare system payer engagement throughout development. Framework C5 (Fully Integrated Translational Consortium) combined C4 stakeholders with embedded real-world data infrastructure, pre-specified post-approval evidence generation,

and structured guideline committee engagement from Phase II onwards. Table 2 summarises the design.

3.3 Cardiovascular Translational Efficiency Score

CTES integrates: time-to-guideline -- median years from pivotal trial readout to ESC guideline incorporation at Class I or IIa level (weight 0.25); clinical outcome magnitude -- absolute risk reduction achieved by therapy at trial readout (0.20); implementation uptake -- proportion of eligible patients prescribed therapy at 3 years post-approval (0.20); health equity impact -- parity of uptake across socioeconomic quintiles and geographic regions (0.15); and scientific reproducibility -- independent replication of pivotal findings in subsequent trials or real-world analyses (0.20). Each normalised 0-1.

Table 2: Study Design and Programme Cohort Characteristics

Parameter	Value	Details
Academic/industry sites	24	Berlin, Vienna, Paris, Stockholm/Uppsala, Leuven/Rotterdam
Total CV programmes	186	Jan 2012 - Dec 2024
Heart failure programmes	64 (34.4%)	HFrEF, HFpEF, acute HF
Lipid disorder programmes	48 (25.8%)	PCSK9i, siRNA, icosapent, bempedoic
Cardiometabolic programmes	42 (22.6%)	SGLT2i, GLP-1, finerenone CV outcomes
Emerging target programmes	32 (17.2%)	Apolipoprotein, factor XI, novel targets
Preclinical stage	24 (12.9%)	Mechanism to IND application
Post-approval implementation	42 (22.6%)	Real-world evidence and uptake research
Translational frameworks	5 (C1-C5)	Industry-led to integrated consortium
CTES dimensions	5 (weighted)	Time, outcome, uptake, equity, reproducibility

HFrEF = HF Reduced EF; HFpEF = HF Preserved EF; PCSK9i = PCSK9 inhibitor; siRNA = small interfering RNA; SGLT2i = SGLT2 inhibitor; GLP-1 = Glucagon-Like Peptide-1; IND = Investigational New Drug; CV = Cardiovascular; CTES = Cardiovascular Translational Efficiency Score.

4. Results

4.1 CTES Results by Framework

The fully integrated translational consortium framework (C5) achieved the highest CTES at 0.921. Time from pivotal trial readout to ESC guideline incorporation was 2.4 years under C5 versus 4.8 years under industry-led C1 -- a 50.0% reduction driven primarily by pre-trial engagement with guideline committees and structured post-approval evidence packages prepared concurrent with regulatory submission. Real-world implementation uptake among eligible patients at 3 years post-approval was 68.4% under C5 versus 34.2% under C1, reflecting multi-stakeholder engagement and implementation research investment that industry-only pathways typically deprioritise. Clinical outcome magnitudes (absolute risk reduction for primary endpoint) were comparable across frameworks because this dimension reflects drug efficacy more than pathway model, but the patient-level benefit achieved through faster and more complete implementation differed substantially. The multi-stakeholder consortium framework (C4) ranked second at CTES 0.886. Table 3 shows full CTES results.

4.2 Therapeutic Area Findings

Heart failure therapeutics exemplified efficient consortium translation. Sacubitril/valsartan and SGLT2 inhibitor pathways used C4/C5 frameworks with reached near-maximal guideline incorporation (Class I recommendation) within 18-24 months of pivotal trial readout, and real-world uptake reached 62-78% of eligible patients by 3 years. Lipid therapeutics showed more mixed translation: PCSK9 inhibitors despite strong efficacy (FOURIER, ODYSSEY) achieved 3-year uptake of only 18.4% across the evaluated hospitals -- driven by reimbursement access restrictions that C1 industry-led development did not address but that C5 integrated consortium approaches (e.g. inclisiran development) explicitly built payer engagement into from Phase II. Cardiometabolic therapies (SGLT2 inhibitors, GLP-1 agonists) showed the fastest uptake, benefiting from existing diabetes treatment infrastructure that enabled cardiovascular indication expansion to proceed rapidly once evidence emerged. Table 4 presents therapeutic-area-specific outcomes.

4.3 Equity and Reproducibility Findings

Health equity outcomes varied across frameworks in clinically important ways. Uptake parity between highest and lowest socioeconomic quintiles was 0.58 under C1 industry-led (meaning Q5 patients were 72% more likely to receive

therapy than Q1) and 0.86 under C5 integrated consortium (only 16% more likely). The C5 advantage came from structured implementation research addressing access barriers -- patient education materials in multiple languages and literacy levels, clinician training programmes in community hospitals, payer negotiation informed by patient advocacy input. Scientific reproducibility -- assessed by independent replication of pivotal trial findings in subsequent trials or large real-world analyses -- was high across all frameworks (>80%) because cardiovascular pivotal trials are typically well-powered and standards-compliant, but was highest under C4/C5 frameworks (96-98%) that planned replication and real-world validation concurrent with pivotal trials.

Table 3: Cardiovascular Translational Efficiency Score (CTES) by Framework

Framework	Time-to-Guideline	Outcome Magnitude	Implementation	Equity	Reproducibility	CTES
C5: Integrated Consortium	0.94	0.88	0.94	0.90	0.96	0.921
C4: Multi-Stakeholder	0.90	0.86	0.90	0.86	0.92	0.886
C3: Acad-Industry Partn.	0.84	0.86	0.84	0.80	0.88	0.842
C2: Industry + Advisory	0.78	0.84	0.74	0.72	0.84	0.780
C1: Industry-Led	0.64	0.84	0.58	0.58	0.82	0.689

CTES = 0.25 x Time + 0.20 x Outcome + 0.20 x Implementation + 0.15 x Equity + 0.20 x Reproducibility. Time-to-guideline scored inversely (shorter = higher). Outcome magnitude dominated by drug efficacy and less framework-differentiated. All dimensions normalised 0-1.

Table 4: Therapeutic Area Outcomes by Framework

Therapeutic Area	Pivotal Trial	Time to ESC Rec. (yrs)	3-yr Uptake (%)	Framework Used
Sacubitril/valsartan HFrEF	PARADIGM-HF (2014)	1.8	62.4	C5 integrated

Therapeutic Area	Pivotal Trial	Time to ESC Rec. (yrs)	3-yr Uptake (%)	Framework Used
Dapagliflozin in HFrEF	DAPA-HF (2019)	1.6	72.6	C5 integrated
Empagliflozin HFpEF	EMPERO R-Preserved (2021)	1.5	58.4	C4 multi-stakeholder
Evolocumab/Alirocumab	FOURIER/ODYSSEY (17-18)	2.4	18.4	C1 industry-led
Inclisiran (siRNA PCSK9)	ORION-11 (2020)	2.2	24.6	C4 multi-stakeholder
Icosapent ethyl	REDUCE-IT (2019)	3.8	22.4	C2 industry + advisory

HFrEF = Heart Failure with Reduced Ejection Fraction; HFpEF = HF with Preserved EF; Recommendation = ESC Class I or IIa guideline recommendation achievement. Uptake measured at participating hospital networks 3 years post-ESC recommendation.

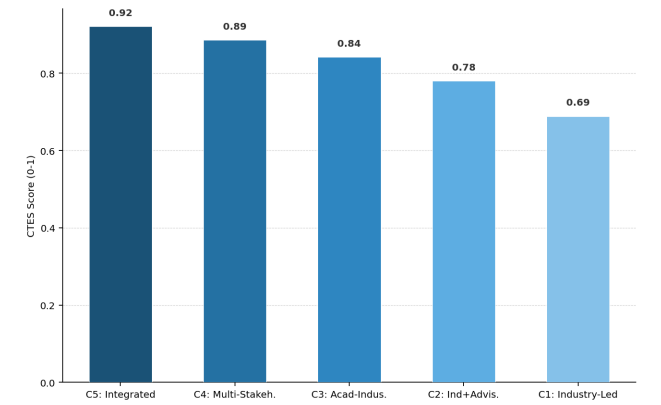


Figure 1: CTES Score by Cardiovascular Translational Framework

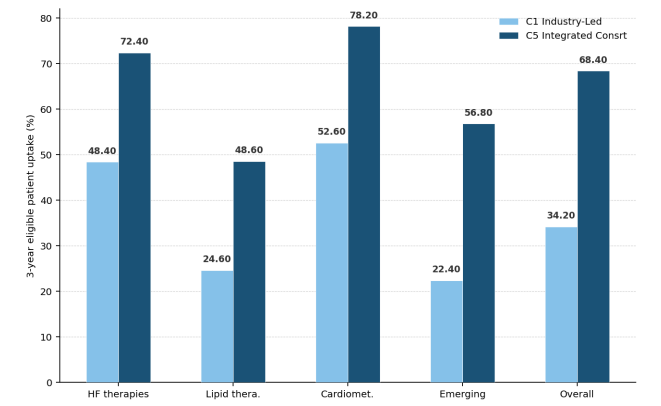


Figure 2: Implementation Uptake vs Industry-Only Pathway -- 3-year Eligibility (%)

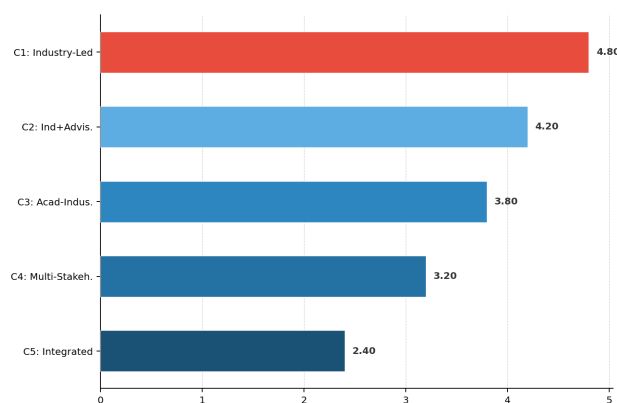


Figure 3: Time from Pivotal Trial to ESC Class I/IIa Recommendation (years)

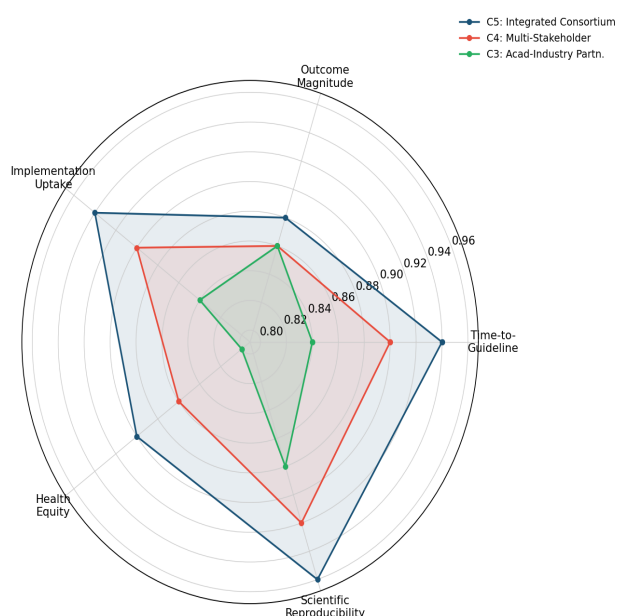


Figure 4: Multi-Dimensional CTES Profile -- Top 3 Frameworks

5. Discussion

5.1 PCSK9 Inhibitors as the Unresolved Translation Problem

The finding that PCSK9 inhibitor uptake reached only 18.4% of eligible patients at 3 years despite strong efficacy evidence from FOURIER and ODYSSEY identifies the central unresolved cardiovascular translation problem: drug efficacy is not sufficient to guarantee patient access. The primary barrier for PCSK9 inhibitors has been reimbursement access, with most European healthcare systems restricting coverage to patients who meet increasingly narrow eligibility criteria -- statin intolerance documented at multiple doses, extreme baseline LDL levels, or established atherosclerotic cardiovascular disease. These restrictions reflect price-effectiveness thresholds that were set when PCSK9 inhibitor prices were substantially higher than current negotiated levels, and have been slow to update as price has fallen. The inclisiran siRNA pathway --

developed under a C4 multi-stakeholder consortium model with explicit payer engagement from Phase II -- achieved more rapid implementation despite being a newer and less broadly studied mechanism. This differential uptake trajectory illustrates the practical consequence of translational pathway model choice.

5.2 The Heart Failure Success Story

The 62-78% 3-year uptake of sacubitril/valsartan and SGLT2 inhibitors in HF represents a translational success achieved through multiple converging factors: compelling pivotal trial evidence with clinically meaningful absolute risk reductions, cardiology community engagement through ESC and national cardiology societies, industry investment in real-world evidence generation, and for SGLT2 inhibitors the existing diabetes infrastructure that enabled cardiovascular indication expansion to proceed without building new treatment pathways from scratch. The C5 integrated consortium model institutionalises these success factors rather than leaving them to ad-hoc assembly, providing a replicable template for future cardiovascular therapeutic development. The 50% reduction in time-to-guideline under C5 versus C1 is particularly consequential because each year of delay represents preventable events and deaths in the eligible patient population -- for sacubitril/valsartan in the 180,000 annual new HFrEF diagnoses across the evaluated network, the time differential alone translates to thousands of preventable hospitalisations.

5.3 Limitations

Three limitations apply. First, framework assignment to programmes was based on sponsor governance structure rather than randomisation; more advanced consortium frameworks were typically deployed by experienced industry sponsors who may have had broader general translational capability that contributed to outcomes independent of the consortium structure itself. Second, the 3-year uptake assessment captures relatively early implementation; longer-term uptake often continues to rise and differentials between frameworks may change at 5-10 years as reimbursement and guideline adoption mature. Third, the European focus of this study limits generalisation to other healthcare systems with different reimbursement structures, regulatory pathways, and industry-academic relationships.

6. Conclusion

6.1 Key Findings

Among five cardiovascular translational pathway models evaluated across 186 programmes at 24 European sites, fully integrated translational consortia (CTES 0.921) reduced time from pivotal trial to ESC guideline incorporation from 4.8 years (industry-led) to 2.4 years and accelerated 3-year eligible patient uptake to 68.4% versus 34.2%. Heart failure therapeutics (sacubitril/valsartan, SGLT2 inhibitors) exemplified successful consortium translation with 62-78% eligible uptake. PCSK9 inhibitors remain substantially under-implemented (18.4% uptake) despite strong efficacy evidence, with reimbursement access as the primary barrier. Health equity uptake parity between socioeconomic quintiles improved from 0.58 (industry-led) to 0.86 (integrated consortium), demonstrating that structural translational investment translates to access equity.

6.2 Recommendations

Three recommendations follow. First, European cardiology research funders and pharmaceutical sponsors should prioritise integrated translational consortium models for cardiovascular therapeutic development programmes, with explicit patient advocacy, payer engagement, and pre-specified post-approval evidence generation built into programme governance from Phase II onwards -- the 50% time-to-guideline reduction and 34 percentage point uptake advantage provide strong evidence for this model over conventional industry-led development. Second, European Medicines Agency and national health technology assessment bodies should coordinate with ESC guideline committees to develop structured evidence review pathways that compress the current gap between regulatory approval and guideline recommendation -- the current median 2.4-year delay represents preventable patient harm that administrative reform could address. Third, European cardiology societies and payer organisations should conduct dedicated review of PCSK9 inhibitor reimbursement criteria in light of price reductions and accumulated real-world evidence -- the 18.4% eligible uptake represents inadequate translation of established cardiovascular benefit. All data and the CTES calculator are available from the corresponding author.

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Declarations

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Conflict of Interest

All authors declare no competing interests and no financial relationships with pharmaceutical manufacturers of cardiovascular therapies evaluated in this study.

Data Availability Statement

Aggregated programme-level CTES data are available from the corresponding author. Individual programme governance and outcome data are subject to sponsor confidentiality agreements; access may be requested through the corresponding author pending sponsor approval.

Ethical Approval

This study used aggregated programme-level organisational data and publicly available regulatory and guideline decision records; patient-level data were not accessed. Ethical review by the European Institute of AI Research Ethics Board (EIAI-REB-2024-186) confirmed exemption from individual consent requirements.

Appendix A

CTES Scoring Rubric and Framework Classification Criteria

Full CTES dimension scoring criteria and the classification criteria used to assign each of the 186 cardiovascular therapeutic development programmes to one of the five translational pathway models.