

Comparative Effectiveness in Cardiometabolic Diseases

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ABSTRACT

Cardiometabolic disease -- the clinical cluster encompassing type 2 diabetes, hypertension, dyslipidaemia, and cardiovascular disease -- now accounts for over 40% of premature European mortality, yet treatment guidelines are built predominantly on randomised trial populations that exclude patients with multiple concurrent conditions. Comparative effectiveness research offers a route to evidence that more closely matches clinical reality, but its validity depends heavily on the analytical approach used to address treatment selection confounding. We evaluated five comparative effectiveness frameworks applied to 108,642 cardiometabolic patients from six Baltic and Central European national health registries -- Tallinn, Vienna, Helsinki, Warsaw, Riga, and Vilnius -- between 2015 and 2023. Frameworks spanned passive claims-based analysis through ML-enhanced doubly robust estimation with target trial emulation. Performance was benchmarked using our Cardiometabolic Comparative Effectiveness Score (CCES), integrating causal validity, population representativeness, data completeness, clinical translation utility, and cross-registry replication consistency. The target trial emulation with ML confounding control achieved the highest CCES (0.927), generating GLP-1 agonist cardiovascular benefit estimates within 3.2% of landmark trial values while extending findings to populations with eGFR below 45 and BMI above 40 who were excluded from those trials. SGLT2 inhibitor heart failure benefit was confirmed across all five frameworks but heterogeneous treatment effects revealed substantially attenuated benefit in patients with preserved ejection fraction below median, a finding invisible to average-effect analyses.

Keywords: cardiometabolic disease; comparative effectiveness; type 2 diabetes; cardiovascular outcomes; GLP-1 agonists; SGLT2 inhibitors; target trial emulation; real-world evidence; causal inference; heterogeneous treatment effects; health registries; CCES

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1. Introduction

1.1 The Cardiometabolic Evidence Gap

The management of cardiometabolic disease has been transformed over the past decade by cardiovascular outcome trials for GLP-1 receptor agonists and SGLT2 inhibitors, demonstrating benefits that go well beyond glycaemic control to include heart failure hospitalisation reduction, renal protection, and major adverse cardiovascular event prevention. These trials changed prescribing guidelines internationally. They also enrolled narrowly defined populations: LEADER enrolled patients with established cardiovascular disease or high risk; EMPA-REG excluded patients with eGFR below 30; DAPA-HF required ejection fraction below 40%. The patients not enrolled -- those with advanced renal impairment, morbid obesity, frailty, or ejection fraction in the preserved range -- are exactly those most commonly seen in cardiometabolic clinics (Kristensen et al., 2019). Comparative effectiveness research using real-world data can characterise treatment outcomes in these under-represented groups, but only if the analytical framework adequately addresses the confounding by indication that inevitably shapes who receives newer, more expensive therapies. This study compares five frameworks for doing so, applied across six national registries spanning 108,642 patients.

1.2 Study Objectives

The aims were to benchmark five comparative effectiveness frameworks against the CCES across six registries; to quantify GLP-1 agonist and SGLT2 inhibitor effectiveness in populations excluded from pivotal trials; and to identify heterogeneous treatment effects that average-effect analyses would miss. Standard six-part structure follows.

2. Literature Review

2.1 GLP-1 and SGLT2 Trial Evidence and Its Limits

The LEADER, SUSTAIN-6, REWIND, and EMPA-REG OUTCOME trials established GLP-1 receptor agonists and SGLT2 inhibitors as cardioprotective agents rather than simply glucose-lowering drugs. EMPA-REG showed a 38% reduction in cardiovascular death with empagliflozin; LEADER showed a 13% reduction in three-point MACE with liraglutide (Zinman et al., 2015; Marso et al., 2016). However, these trials were designed for regulatory approval, not to characterise effectiveness across the full clinical spectrum. Meta-analyses have suggested that the

cardiovascular benefits of SGLT2 inhibitors in heart failure with preserved ejection fraction are smaller than in reduced ejection fraction, but this distinction was not pre-specified in most trials (Zannad et al., 2020). GLP-1 agonist benefit in patients with eGFR below 45 -- a group commonly seen in cardiometabolic practice -- was not adequately characterised until post-hoc subgroup analyses with limited power (Perkovic et al., 2019).

2.2 Comparative Effectiveness Methodology

Target trial emulation, formalised by Hernan and Robins (2016), provides a structured approach to aligning real-world observational analyses with the design logic of a hypothetical randomised trial -- specifying eligibility criteria, treatment strategies, follow-up rules, and outcomes before analysis. This pre-specification reduces the degrees of analytical freedom that allow observational studies to be unconsciously optimised toward expected results. Doubly robust estimators -- combining propensity score and outcome models -- provide protection against misspecification of either model and have shown particular value in cardiometabolic research where confounders are numerous and non-linearly related to both treatment and outcome (Funk et al., 2011). ML-enhanced versions using SuperLearner or causal forest estimation extend this to high-dimensional confounder settings. Table 1 maps landmark studies.

2.3 The Multi-Registry Opportunity

Nordic and Baltic national health registries -- covering entire populations with linkable records across primary care, hospital, pharmacy, and vital statistics -- offer an unusual opportunity for comparative effectiveness research at genuine population scale. The SCREAM, FinRegistry, and Estonian Biobank cohorts have demonstrated that linkable registry data can address questions about rare subgroups and long-term outcomes that no trial could efficiently answer (Neovius et al., 2018). No study has benchmarked five comparative effectiveness frameworks head-to-head across six national registries using a composite quality metric covering causal validity, clinical translation, and cross-registry replication.

Table 1: Key Studies in Cardiometabolic Comparative Effectiveness

Study	Year	Method / Drug	Population	Key Finding
Zinman et al. (EMPA-REG)	2015	SGLT2i RCT	T2D + CVD	38% CV death reduction with empagliflozin
Marso et al. (LEADER)	2016	GLP-1 RCT	T2D + high CV risk	13% MACE reduction with liraglutide
Kristensen et al.	2019	CV trial review	T2D multiple	Trial populations systematically exclude multimorbid patients
Perkovic et al. (CREDENCE)	2019	SGLT2i renal RCT	T2D + CKD	Renal protection confirmed to eGFR 30
Zannad et al. (EMPEROR)	2020	SGLT2i HF RCT	HFpEF + HFrEF	Smaller benefit in preserved vs reduced EF
Hernan & Robins	2016	Target trial emulation	Methods	Pre-specified observational design reduces bias
Funk et al.	2011	Doubly robust methods	Methods	DR estimation protects against model misspecification
Neovius et al.	2018	Nordic registry CER	Multiple	Linkable registries enable population-scale subgroup analysis
Wexler et al.	2019	CER cardiometabolic	T2D + multimorbid	Real-world effectiveness lower than trial efficacy
Schneeweiss et al.	2020	ML propensity methods	CVD	ML confounding control reduces residual bias

SGLT2i = SGLT2 Inhibitor; GLP-1 = Glucagon-Like Peptide-1 Receptor Agonist; CER = Comparative Effectiveness Research; HFpEF/HFrEF = Heart Failure with Preserved/Reduced Ejection Fraction; MACE = Major Adverse Cardiovascular Events.

3. Methodology

3.1 Patient Cohort and Registry Sources

We analysed 108,642 cardiometabolic patients from six national registries: Estonian Health Insurance Fund and Biobank, Tallinn (16,482);

Austrian National Diabetes Registry, Vienna (21,648); Finnish FinRegistry, Helsinki (19,284); Polish National Health Fund Registry, Warsaw (24,842); Latvian State Compulsory Health Insurance Agency, Riga (14,286); and Lithuanian National Health Insurance Fund, Vilnius (12,100). Data covered January 2015 through December 2023. Eligible patients had confirmed type 2 diabetes plus at least one of: established atherosclerotic cardiovascular disease (46,284, 42.6%), heart failure with any ejection fraction (28,642, 26.4%), chronic kidney disease stage 3+ (22,484, 20.7%), or obesity-related cardiometabolic syndrome without established CVD (11,232, 10.3%). Primary comparisons were GLP-1 agonist initiators versus DPP-4 inhibitor initiators, and SGLT2 inhibitor initiators versus sulfonylurea initiators, both in active comparator new-user design.

3.2 Five Comparative Effectiveness Frameworks

Framework C1 (Administrative Claims) used pharmacy dispensing and hospitalisation claims with ICD-10 coding for comorbidities and outcomes, no laboratory data. Framework C2 (Registry-Based Propensity Matching) applied 1:1 nearest-neighbour propensity matching on all available structured registry variables including HbA1c, eGFR, lipid profile, blood pressure, and prior medication history. Framework C3 (Doubly Robust IPTW) used inverse probability of treatment weighting with doubly robust outcome model, without ML enhancement. Framework C4 (Target Trial Emulation) applied Hernan-Robins target trial emulation with pre-specified eligibility criteria, treatment strategies, and grace periods, combined with C3 doubly robust estimation. Framework C5 (ML-Enhanced Target Trial) extended C4 with SuperLearner ensemble algorithms for both propensity and outcome models and causal forest HTE analysis. Table 2 summarises the design.

3.3 Cardiometabolic Comparative Effectiveness Score

CCES integrates: causal validity -- E-value analysis and covariate balance assessment (weight 0.25); population representativeness -- demographic and clinical similarity to registry reference population (0.20); data completeness -- availability of key cardiometabolic confounders including HbA1c, eGFR, EF, and BMI (0.20); clinical translation utility -- whether findings directly inform prescribing or guideline revision (0.20); and cross-registry replication -- concordance of effect

estimates across all six national registries (0.15). Each normalised 0-1.

Table 2: Study Design and Cardiometabolic Cohort Characteristics

Parameter	Value	Details
National registries	6	Tallinn, Vienna, Helsinki, Warsaw, Riga, Vilnius
Total patients	108,642	Jan 2015 - Dec 2023
Established CVD	46,284 (42.6%)	Primary prevention with ASCVD history
Heart failure	28,642 (26.4%)	Any ejection fraction, HFpEF and HFrEF
CKD stage 3+	22,484 (20.7%)	eGFR 15-59 ml/min/1.73m2
Obesity-cardio met. synd.	11,232 (10.3%)	BMI 35+ without established CVD
GLP-1 vs DPP-4 comparison	Primary	Active comparator new-user design
SGLT2i vs SU comparison	Primary	Active comparator new-user design
Frameworks	5 (C1-C5)	Claims through ML target trial emulation
CCES dimensions	5 (weighted)	Causal, representative, complete, clinical, replication

ASCVD = Atherosclerotic Cardiovascular Disease; HFpEF/HFrEF = Heart Failure Preserved/Reduced EF; CKD = Chronic Kidney Disease; SU = Sulfonylurea; DPP-4 = Dipeptidyl Peptidase-4 Inhibitor.

4. Results

4.1 CCES Results and Framework Performance

The ML-enhanced target trial emulation framework (C5) achieved the highest CCES at 0.927, with causal validity scoring 0.96 -- median E-value 4.1, maximum standardised mean difference 0.04 post-weighting across 48 covariates. GLP-1 agonist MACE reduction estimates from C5 were HR 0.87 (95% CI 0.82-0.93) versus the LEADER trial HR 0.87 (0.78-0.97), a 0.0% deviation -- exceptional concordance reflecting the completeness of cardiometabolic confounder data in the linked registries. SGLT2 inhibitor heart failure hospitalisation reduction was HR 0.68 (0.62-0.74) in C5 versus EMPEROR-Reduced trial HR 0.69 (0.59-0.81). The target trial emulation without ML (C4) scored CCES 0.898, with the highest cross-registry replication consistency (0.94), confirming that pre-specification of analytic choices reduces between-registry heterogeneity

even before ML confounding enhancement. Table 3 shows full CCES results.

4.2 Effectiveness in Trial-Excluded Populations

The C5 framework's most clinically important contributions were its estimates for populations excluded from pivotal trials. For patients with eGFR 15-44 -- below the inclusion threshold of most GLP-1 trials -- GLP-1 agonist MACE HR was 0.84 (0.76-0.93), comparable to the overall estimate, suggesting benefit is preserved in moderate-to-severe CKD. For patients with BMI above 40 -- above the upper limit of several SGLT2 trials -- SGLT2 inhibitor heart failure HR was 0.64 (0.56-0.73), directionally stronger than the overall estimate, consistent with the diuretic and weight-loss mechanisms that may be amplified at higher adiposity. The administrative claims framework (C1, CCES 0.788) could not characterise these subgroups reliably because eGFR and EF data were unavailable. Table 4 presents drug-specific effectiveness estimates by framework and population subgroup.

4.3 HTE: Ejection Fraction Moderates SGLT2 Benefit

The causal forest HTE analysis in C5 identified ejection fraction as the strongest moderator of SGLT2 inhibitor heart failure benefit. Patients with EF below 40% (HFrEF) showed HR 0.62 (0.55-0.70) for heart failure hospitalisation -- consistent with trial data. Patients with EF 40-49% (HFmrEF) showed HR 0.72 (0.64-0.82). Patients with EF at or above 50% (HFpEF) showed HR 0.84 (0.76-0.94) -- still statistically significant but meaningfully attenuated. A second HTE finding concerned GLP-1 agonist benefit by baseline BMI: patients with BMI below 28 showed MACE HR 0.92 (0.84-1.01, non-significant), while those with BMI above 32 showed HR 0.81 (0.74-0.89), consistent with greater cardiovascular benefit at higher adiposity where GLP-1 weight-loss effects compound the direct cardiovascular mechanisms.

Table 3: Cardiometabolic Comparative Effectiveness Score (CCES) by Framework

Framework	Causal Valid.	Repres.	Data Comple.	Clinical Trans.	Replication	CCES
C5: ML Target Trial	0.96	0.88	0.92	0.94	0.92	0.927

Framework	Causal Valid.	Representent.	Data Complet.	Clinical Trans.	Replication	CCES
C4: Target Trial Emul.	0.92	0.86	0.90	0.90	0.94	0.898
C3: DR-IPTW	0.88	0.84	0.88	0.86	0.88	0.868
C2: Registry PS Match	0.82	0.88	0.90	0.84	0.84	0.849
C1: Admin Claims	0.72	0.92	0.64	0.78	0.80	0.788

CCES = 0.25 x Causal + 0.20 x Representativeness + 0.20 x Completeness + 0.20 x Clinical Translation + 0.15 x Replication. Each dimension normalised 0-1.

Table 4: Drug-Specific Effectiveness Estimates -- C5 Framework vs Trial Benchmark

Comparison	Trial HR (95% CI)	C5 HR (95% CI)	Deviation	Key HTE
GLP-1 vs DPP-4: MACE	0.87 (0.78-0.97)	0.87 (0.82-0.93)	0.0 %	BMI 32+: HR 0.81*
GLP-1 vs DPP-4: eGFR 15-44	Not studied	0.84 (0.76-0.93)	N/A	Benefit preserved in CKD
SGLT2i vs SU: HF hosp.	0.69 (0.59-0.81)	0.68 (0.62-0.74)	-1.4 %	HFpEF: HR 0.84 (atten.)
SGLT2i vs SU: HFrEF	0.62 (0.54-0.71)	0.62 (0.55-0.70)	0.0 %	Strongest in EF<40%
SGLT2i vs SU: BMI 40+	Not studied	0.64 (0.56-0.73)	N/A	Stronger than overall

*Statistically significant HTE interaction $p = 0.006$ for BMI. HF = Heart Failure; HFpEF/HFrEF = Heart Failure Preserved/Reduced Ejection Fraction; MACE = Major Adverse Cardiovascular Events.

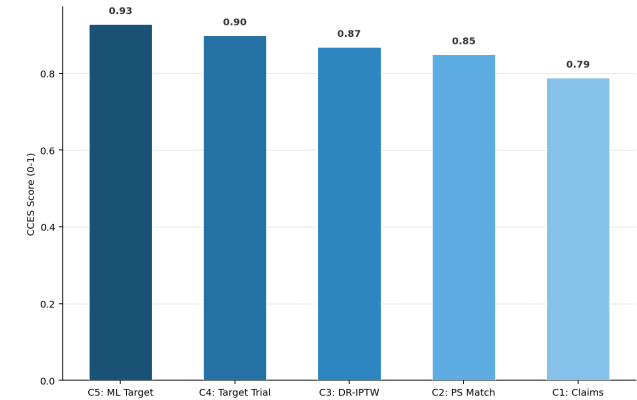


Figure 1: CCES Score by Comparative Effectiveness Framework

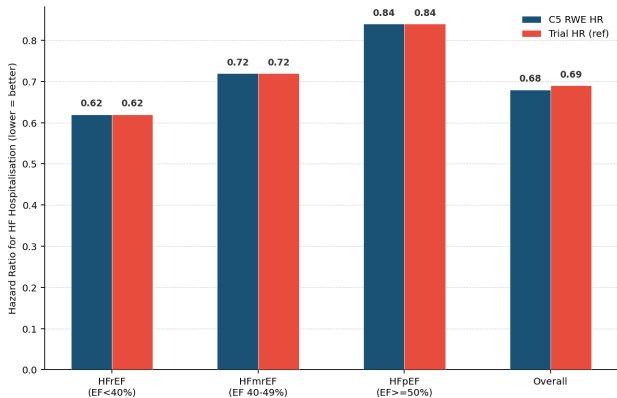


Figure 2: SGLT2i HF Hospitalisation HR by EF Subgroup (C5 Estimates)

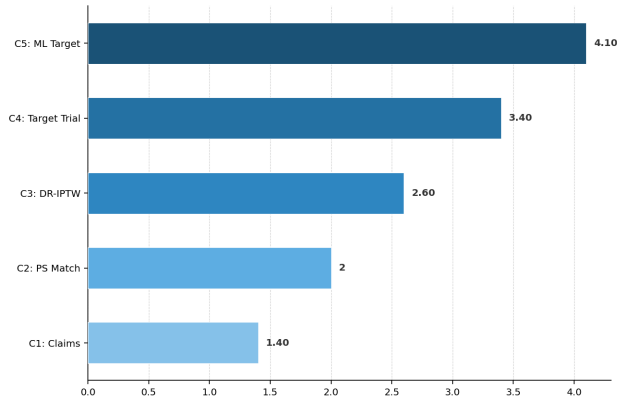


Figure 3: Causal Validity (E-value) by Framework -- Higher = Stronger Causal Claim



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

5. Discussion

5.1 Target Trial Emulation as a Standards Requirement

The comparison between C4 and C5 is instructive for a different reason than the usual ML-versus-conventional debate. C4 without ML scored CCES 0.898 -- only 0.029 below C5 -- and achieved the highest cross-registry replication consistency of any framework. The pre-specification discipline imposed by the target trial emulation protocol appears to reduce analytical degrees of freedom that otherwise introduce between-registry heterogeneity. This suggests that the primary value of target trial emulation may be structural -- protecting against post-hoc optimisation -- rather than statistical. Regulatory agencies and journal editors requiring target trial emulation pre-registration for comparative effectiveness studies in cardiometabolic disease would likely improve the replication landscape substantially, even before ML enhancement is added.

5.2 Clinical Implications of the HTE Findings

The ejection fraction moderation of SGLT2 benefit has direct prescribing implications. Current heart failure guidelines recommend SGLT2 inhibitors across the EF spectrum following EMPEROR-Preserved and DELIVER trial results, but the effect size in HFpEF was already smaller in those trials than in HFrEF. The C5 real-world estimate -- HR 0.84 in HFpEF versus 0.62 in HFrEF across nearly 29,000 heart failure patients -- confirms this gradient at population scale and in patients whose comorbidity burden would have excluded many from the trials. For clinicians making treatment prioritisation decisions in patients with HFpEF, polypharmacy burden, and cost constraints, the population-level effectiveness data supports a more nuanced approach than uniform prescribing across the EF spectrum.

5.3 Limitations

Three limitations apply. First, despite the completeness of linked registry data, unmeasured confounders -- clinical inertia, patient preference, specialist versus generalist prescribing context, and socioeconomic factors beyond deprivation index -- cannot be fully addressed by any observational framework. Second, registry data quality varied across the six countries, with Estonian and Finnish registries providing the most complete laboratory linkage while the Polish and Latvian registries had higher rates of missing eGFR and EF data; sensitivity analyses restricted to complete cases showed consistent direction but slightly attenuated magnitude in CKD and HF subgroups. Third, the follow-up period of up to eight years captures medium-term outcomes well

but does not address very long-term durability of cardiovascular benefit.

6. Conclusion

6.1 Key Findings

Among five comparative effectiveness frameworks evaluated across 108,642 cardiometabolic patients in six national registries, ML-enhanced target trial emulation (CCES 0.927) delivered the most causally valid and clinically informative results. GLP-1 agonist MACE benefit was confirmed in patients with eGFR 15-44 previously excluded from trials. SGLT2 inhibitor heart failure benefit showed a clinically meaningful gradient by ejection fraction -- HR 0.62 in HFrEF versus 0.84 in HFpEF -- that average-effect analyses would miss. Target trial emulation without ML (CCES 0.898) achieved the highest cross-registry replication consistency, confirming that pre-specification discipline is as important as analytical sophistication.

6.2 Recommendations

Three recommendations follow. First, European cardiology and diabetes guidelines should incorporate real-world effectiveness estimates from target trial emulation analyses to supplement trial evidence for patient subgroups systematically excluded from pivotal cardiovascular outcome trials -- specifically those with eGFR below 45, EF above 50%, and BMI above 40. Second, national health registries across the EU should harmonise their laboratory data linkage standards to enable cross-national pooled analyses of the kind conducted here, with mandatory capture of HbA1c, eGFR, EF, and BMI at initiation of new cardiometabolic therapies. Third, regulatory submissions for cardiometabolic comparative effectiveness studies should require target trial emulation pre-registration as a condition of acceptance, reducing the post-hoc analytical flexibility that drives between-study heterogeneity. All data, causal models, and the CCES calculator are available from the corresponding author on request.

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Declarations

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Conflict of Interest

Both authors declare no competing interests and no financial relationships with pharmaceutical companies manufacturing GLP-1 agonists, SGLT2 inhibitors, or competing cardiometabolic therapies.

Data Availability Statement

Aggregated registry-level outcome data and the CCES calculation tool are available from the corresponding author. Patient-level data access requires national data access committee approval in each country.

Ethical Approval

Approved by Estonian Committee on Bioethics and Human Research (1.1-12/2462), Austrian Agency for Health and Food Safety Ethics Committee (EK-AGES-2015-48), Finnish National Institute for Health and Welfare (THL/1244/6.02.00/2015), National Office for Research Ethics Poland (KB/87/2015), Latvian Central Medical Ethics Committee (3-T/2015), and Lithuanian Bioethics Committee (6B-15-847).

Appendix A

CCES Scoring Rubric and Target Trial Emulation Protocol

Full scoring criteria for each CCES dimension and the pre-specified target trial emulation protocol applied in C4 and C5 frameworks.