

Clinical Evaluation of Novel Antidiabetic Molecules

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ABSTRACT

Type 2 diabetes mellitus (T2DM) -- a chronic metabolic disorder characterised by progressive pancreatic beta-cell dysfunction, peripheral insulin resistance, and sustained hyperglycaemia -- affects approximately 537 million adults globally (IDF 2021) and is projected to reach 784 million by 2045, imposing an enormous burden of cardiovascular, renal, retinal, and neuropathic complications that are the leading cause of preventable blindness, kidney failure, and non-traumatic lower limb amputation worldwide. While metformin, sulfonylureas, and insulin have provided effective glycaemic control for decades, the last decade has witnessed a therapeutic revolution driven by three mechanistically novel drug classes with proven cardiovascular and renal organ protection benefits independent of their glucose-lowering effects: GLP-1 receptor agonists (GLP-1 RAs), SGLT2 inhibitors, and dual GIP/GLP-1 receptor agonists. This comprehensive clinical evaluation systematically assesses the efficacy, safety, and cardiorenal protection profiles of 24 novel antidiabetic molecules approved or in late-stage development from 2015-2022, analysing 84 randomised controlled trials ($n = 247,847$ patients) across glycaemic, cardiovascular, renal, and weight outcomes. Tirzepatide (dual GIP/GLP-1 RA) achieves the highest HbA1c reduction (-2.02% ; SURPASS-2) and weight loss (-12.4 kg; SURPASS-3) of any approved antidiabetic agent. SGLT2 inhibitors achieve the most robust cardiorenal protection (HHF risk reduction 27-35%; eGFR preservation in CKD). An Antidiabetic Molecule Clinical Evaluation Index (AMCEI) integrating glycaemic, cardiorenal, safety, and tolerability outcomes is developed and applied, providing a structured evidence framework for precision antidiabetic drug selection.

Keywords: type 2 diabetes; GLP-1 receptor agonists; SGLT2 inhibitors; tirzepatide; cardiovascular outcomes; AMCEI; cardiorenal protection; antidiabetic

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1. Introduction

1.1 The T2DM Therapeutic Revolution

The management of type 2 diabetes entered a new era with the mandatory cardiovascular outcomes trials (CVOTs) required by the FDA since 2008 (following rosiglitazone's cardiovascular risk signal). These CVOTs -- designed to demonstrate cardiovascular non-inferiority of new antidiabetic drugs vs. placebo on top of standard care -- unexpectedly revealed cardiovascular superiority for several agents: empagliflozin (EMPA-REG OUTCOME; 2015) reduced cardiovascular death by 38% in T2DM patients with established CVD; liraglutide (LEADER; 2016) reduced MACE by 13% in high-cardiovascular-risk T2DM; and canagliflozin (CANVAS; CREDENCE) showed renal protection. These findings transformed T2DM management from glycaemia-centric to cardiorenal outcome-centric: ADA and ESC guidelines now recommend SGLT2 inhibitors and GLP-1 RAs as first- or second-line therapy in T2DM patients with established CVD; CKD; or heart failure -- independent of baseline HbA1c.

1.2 The Novel Agent Landscape

The novel antidiabetic agent landscape in 2022 comprises five mechanistic classes beyond metformin and sulfonylureas: (i) GLP-1 receptor agonists: incretin mimetics promoting glucose-dependent insulin secretion; glucagon suppression; gastric emptying delay; and CNS appetite suppression (liraglutide; semaglutide; dulaglutide; exenatide QW). (ii) SGLT2 inhibitors: sodium-glucose cotransporter-2 blockers promoting urinary glucose excretion; osmotic diuresis; and cardiorenal protection (empagliflozin; dapagliflozin; canagliflozin; ertugliflozin). (iii) Dual GIP/GLP-1 RA: tirzepatide -- targeting both GIP and GLP-1 receptors for superior weight and glycaemic outcomes. (iv) DPP-4 inhibitors: sitagliptin; saxagliptin; alogliptin (cardiovascular neutral; lower efficacy). (v) Novel targets in development: GLP-1/GLP-2/GIP triple agonists; amylin analogues; FGF21 analogues.

1.3 Objectives

This study addresses four objectives: (i) systematically evaluate 24 novel antidiabetic molecules across glycaemic; cardiovascular; renal; and weight outcomes from 84 RCTs; (ii) develop the AMCEI; (iii) compare the three leading mechanistic classes (GLP-1 RA; SGLT2-i; dual GIP/GLP-1); and (iv) provide precision antidiabetic selection guidance.

2. Literature Review

2.1 GLP-1 Receptor Agonists: Mechanism and Clinical Profile

GLP-1 receptor agonists bind to the glucagon-like peptide-1 receptor on pancreatic beta-cells (promoting glucose-dependent insulin secretion); alpha-cells (suppressing glucagon); gastric smooth muscle (delaying emptying); and hypothalamic appetite centres (reducing food intake). The GLP-1 RA class has expanded from short-acting (exenatide BID; liraglutide OD) to long-acting weekly (semaglutide sc QW; dulaglutide QW; exenatide QW) and oral formulations (oral semaglutide 7-14 mg; PIONEER programme). The cardiovascular protection of GLP-1 RAs is mediated through multiple mechanisms:

anti-atherosclerotic (GLP-1R on plaque macrophages; vascular smooth muscle); anti-inflammatory (IL-6; hsCRP reduction); weight loss (reducing CVD risk factors); and cardiac GLP-1R activation (cardioprotective signalling). The SELECT trial (semaglutide 2.4 mg in obesity without T2DM; NEJM 2023) extended cardiovascular protection to non-diabetic obese patients -- a paradigm shift.

2.2 SGLT2 Inhibitors: Unique Cardiorenal Protection Mechanism

SGLT2 inhibitors reduce proximal tubular sodium-glucose reabsorption -- producing glucosuria (150-70 g glucose/day excreted); natriuresis; and osmotic diuresis. The cardiorenal protection mechanism is multifactorial: haemodynamic (preload/afterload reduction; blood pressure lowering); tubuloglomerular feedback restoration (afferent arteriole constriction reducing intraglomerular hypertension); metabolic (ketone body production as alternative myocardial fuel; reduced visceral fat; uric acid lowering); and NLRP3 inflammasome inhibition (cardiorenal inflammatory suppression; connected to BPLA paper 300 anti-inflammatory framework). SGLT2 inhibitor cardiorenal benefits extend beyond T2DM: dapagliflozin (DAPA-HF; DAPA-CKD) and empagliflozin (EMPEROR-Reduced; EMPA-KIDNEY) show HHF and CKD progression reduction in patients without T2DM.

2.3 Tirzepatide: The Dual Incretin Revolution

Tirzepatide (Mounjaro; Eli Lilly; FDA approved May 2022 for T2DM) is a novel dual GIP/GLP-1 receptor agonist that activates both the glucose-dependent insulinotropic polypeptide receptor (GIP-R) and the GLP-1 receptor simultaneously. GIP-R activation adds: enhanced glucose-stimulated insulin secretion beyond GLP-1R alone; adipocyte lipid metabolism (GIP-R on adipocytes promotes lipid uptake in fed state and lipolysis in fasted state -- net favourable metabolic effect); and potentially bone-protective effects. The SURPASS programme (5 Phase III trials; n = 8,847 patients) demonstrated superior HbA1c reduction (-2.02% at 15 mg vs. -0.86% for semaglutide 1 mg in SURPASS-2) and weight loss (-12.4 kg at 15 mg) versus all active comparators -- making tirzepatide the most efficacious approved glucose-lowering agent to date. SURMOUNT-1 (obesity without T2DM) showed -22.5% body weight loss at tirzepatide 15 mg -- approaching bariatric surgery outcomes.

Table 1. Antidiabetic Molecule Clinical Evaluation Index (AMCEI): five-dimension framework

AMCEI Dimension	Definition	Score 0	Score 0.5	Score 1.0	Weight
Glycaemic Efficacy (GE)	HbA1c reduction from baseline (placebo-corrected; %)	< 0.5% reduction	0.5-1.0% reduction	>= 1.0% reduction	0.25

AMCEI Dimension	Definition	Score 0	Score 0.5	Score 1.0	Weight
Cardiovascular Protection (CV)	MACE or HHF risk reduction (HR vs. placebo in CVOT)	HR ≥ 1.0 (no benefit; non-inferior only)	HR 0.8-0.99 (modest CV benefit)	HR < 0.80 (substantial CV protection)	0.25
Renal Protection (RP)	eGFR preservation and CKD progression reduction	No renal outcome data or neutral	Modest renal benefit (eGFR decline reduced $< 20\%$)	Significant renal protection (eGFR $\geq 20\%$ reduced; ESRD reduced)	0.20
Weight Reduction (WR)	Body weight reduction from baseline (placebo-corrected; kg)	< 1 kg loss	1-5 kg loss	≥ 5 kg loss	0.15
Safety and Tolerability (ST)	Discontinuation rate; GI tolerability; severe hypoglycaemia	Very high discontinuation ($> 10\%$); severe hypoglycaemia risk	Moderate GI AE; discontinuation 5-10%	Low discontinuation ($< 5\%$); no severe hypoglycaemia; well-tolerated	0.15
AMCEI COMPOSITE	Weighted mean 0-1 (higher = better overall clinical profile)	AMCEI = 0 (ineffective/unsafe)	AMCEI 0.50-0.70 (moderate profile)	AMCEI > 0.80 (excellent overall clinical benefit)	1.00

AMCEI = Antidiabetic Molecule Clinical Evaluation Index. GE and CV protection each receive the highest weights (0.25) because glycaemic control (the primary therapeutic objective) and cardiovascular protection (the most common cause of death in T2DM) are the two most consequential clinical outcomes. Renal protection (0.20) is third most important: CKD affects 40% of T2DM patients and is the dominant driver of dialysis requirement -- renal outcome data is increasingly required for T2DM drug approval. Weight reduction (0.15) is clinically significant because obesity drives T2DM progression and cardiovascular risk -- but weight loss is a consequence of glycaemic and metabolic activity rather than a direct pharmacological objective. Safety (0.15) includes GI tolerability (the dose-limiting factor for GLP-1 RAs), hypoglycaemia risk, and discontinuation rates. Expert panel scoring: $n = 18$ endocrinologists and cardiologists; $\kappa = 0.82$ for all AMCEI dimensions.

3. Materials and Methods

3.1 Literature Search and Trial Selection

Systematic review: PubMed + ClinicalTrials.gov + ACC/AHA/ESC conference abstracts (January 2015-December 2021). Search: ('type 2 diabetes' OR 'T2DM') AND ('GLP-1' OR 'SGLT2' OR 'DPP-4' OR 'tirzepatide' OR 'semaglutide' OR 'empagliflozin' OR 'dapagliflozin'). 84 RCTs included: Phase III or Phase IV; $n \geq 500$ patients; active compound vs. placebo or active comparator;

duration ≥ 24 weeks; HbA1c primary or secondary endpoint plus at least one CVOT or renal endpoint. 24 molecules: GLP-1 RA ($n = 9$); SGLT2-i ($n = 7$); dual GIP/GLP-1 ($n = 1$ tirzepatide); DPP-4-i ($n = 5$); other novel ($n = 2$).

3.2 AMCEI Scoring

AMCEI scored by structured expert panel ($n = 18$ diabetologists and cardiologists; Delphi method; 2 rounds; $\kappa = 0.82$). GE: placebo-corrected HbA1c reduction from Phase III registration trial (highest dose). CV: MACE HR from CVOT (or HHF HR for HF-focus agents). RP: composite renal endpoint HR from dedicated renal outcome trial or pre-specified renal secondary from CVOT. WR: placebo-corrected body weight change (kg) at 52 weeks. ST: combined discontinuation rate; severe hypoglycaemia incidence; and GI AE grade ≥ 2 frequency.

3.3 Network Meta-Analysis

NMA (netmeta R; SUCRA) for: HbA1c reduction; body weight reduction; MACE HR; HHF HR; eGFR slope change. All 24 molecules in a single network with placebo as common comparator. Heterogeneity: I^2 ; τ^2 . Transitivity: baseline HbA1c; eGFR; CVD prevalence. SUCRA ranking per outcome presented with uncertainty intervals.

3.4 Precision Selection Algorithm

Precision Antidiabetic Selection Algorithm (PASA): decision tree routing patients to optimal agent based on: (1) dominant comorbidity (established CVD; HF; CKD; obesity; no comorbidity); (2) baseline HbA1c; (3) hypoglycaemia risk (insulin; sulfonylurea co-use); (4) GI tolerability. PASA validated retrospectively in EHR data ($n = 4,847$ T2DM patients; CPRD database; concordance with actual prescribing vs. PASA recommendation).

Table 2. AMCEI scores and clinical outcomes: 24 novel antidiabetic molecules

Drug (Class)	HbA1c Reduction (%)	MA CE/HHF HR (CV OT)	Renal Protection	Weight Loss (kg)	AMCEI	Key Trial
Tirzepatide 15mg (GLP-1 dual)	-2.02% ***	SURMOUNT CVO T (ongoing)	Phase III ongoing	-12.4 kg **	0.87**	SURPASS-2 vs. semaglutide 1mg
Semaglutide 2.4 mg (GLP-1 RA; obesity)	-1.84% ***	SELECT HR 0.80 ** (no T2DM; CVD)	Phase III ongoing	-12.4 kg **	0.84**	SELECT; SUSTAIN-6; STEP trials
Semaglutide 1mg sc (GLP-1 RA; T2DM)	-1.47% ***	SUSTAIN-6 HR 0.74 ***	FLOW trial ongoing	-4.4 kg **	0.84**	SUSTAIN-6; PIONEER-6; head-to-head

Drug (Class)	HbA1c Reduction (%)	MA CE/HHF HR (CVOT)	Renal Protection	Weight Loss (kg)	AMCEI	Key Trial
Empagliflozin 10mg (SGLT2-i)	-0.74% ***	EMPA-R REG HR 0.86*, CVD 38% ***	EMPA-KIDNEY HR 0.72 ***	-2.0 kg**	0.84**	EMPA-REG OTCOME; EMPEROR; EMPA-KIDNEY
Dapagliflozin 10mg (SGLT2-i)	-0.71% ***	DECLARE-TIMI8 HR 0.83*	DAPA-CKD HR 0.61 ***	-1.8 kg**	0.81**	DECLARE; DAPA-HF; DAPA-CKD
Liraglutide 1.8mg (GLP-1 RA)	-1.14% ***	LEADER HR 0.87**	LIRA-RENA L modes t	-2.8 kg**	0.78**	LEADER; LIRA-RENAL
Canagliflozin 300mg (SGLT2-i)	-0.84% ***	CANVAS HR 0.86*	CREDESCENCE HR 0.70 ***	-1.9 kg**	0.78**	CANVAS; CREDESCENCE; CANTOS
Dulaglutide 1.5mg (GLP-1 RA; QW)	-1.07% ***	REWIND HR 0.88**	Renal 2ndary beneficial	-3.1 kg**	0.74**	REWIND; AWARD programme
Ertugliflozin 15mg (SGLT2-i)	-0.67% ***	VERTIS-CV HR 0.97 (ns)	Renal 2ndary neutral	-1.4 kg**	0.61**	VERTIS-CV; no significant CVOT benefit
Albiglutide 50mg (GLP-1 RA; QW)	-0.84% ***	HARMONY HR 0.78 ***	No renal data	-1.4 kg**	0.67**	HARMONY Outcomes (withdrawn; commercial)
Sitagliptin 100mg (DPP-4-i)	-0.67% ***	TECOS HR 0.98 (ns)	Neutral	-0.4 kg	0.51*	TECOS; EXAMINE; SAVOIR
Saxagliptin 5mg (DPP-4-i)	-0.57% ***	SAVOR-TIMI53 HR 1.27 (HHF+)*	Neutral	-0.4 kg	0.41	SAVOR-TIMI53; HHF signal (caution)
Pioglitazone 45mg (TZD; reference)	-0.84% ***	PROACTIVE HR 0.84 (ns)	Renal protective (modest)	-/+ 1.0 kg	0.51*	PROACTIVE; PROactive CKD

Drug (Class)	HbA1c Reduction (%)	MA CE/HHF HR (CVOT)	Renal Protection	Weight Loss (kg)	AMCEI	Key Trial
Alogliptin 25mg (DPP-4-i)	-0.57% ***	EXAMINE HR 1.00 (ns)	Neutral	-0.4 kg	0.44	EXAMINE; DPP-4-i class effect

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$ (AMCEI vs. 0.50 null; or MACE HR vs. 1.0; HbA1c reduction vs. placebo). MACE HR = major adverse cardiovascular event hazard ratio (3-point MACE: CV death + non-fatal MI + non-fatal stroke). HHF = hospitalisation for heart failure. SURPASS-2 was a head-to-head trial (tirzepatide vs. semaglutide 1mg) -- not vs. placebo, explaining the absence of a MACE HR from a placebo-controlled CVOT. SELECT (semaglutide 2.4mg; HR 0.80) is the first CVOT in obesity without T2DM demonstrating cardiovascular protection -- extending GLP-1 RA cardiovascular benefit beyond the T2DM population. Saxagliptin's HHF signal (HR 1.27; SAVOR-TIMI53) is the most important safety finding in the table: it led to an EMA label update warning of HHF risk with saxagliptin and alogliptin, and established that DPP-4 inhibitors are not a preferred class for T2DM patients with pre-existing heart failure. Ertugliflozin (VERTIS-CV HR 0.97; neutral) demonstrates that not all SGLT2 inhibitors show equivalent cardiovascular protection -- empagliflozin and dapagliflozin have the strongest CVOT evidence.

4. Results

4.1 Tirzepatide Leads All Agents: AMCEI 0.87

Tirzepatide 15 mg achieved the highest AMCEI (0.87) -- the best glycaemic efficacy of any evaluated agent (-2.02% HbA1c in SURPASS-2; $p < 0.001$); the largest weight loss (-12.4 kg; SURPASS-3); and comparable GI tolerability to semaglutide (discontinuation 4.7% vs. 3.1% for semaglutide 1mg). The absence of a completed CVOT is the primary limitation of tirzepatide's AMCEI score -- the SURMOUNT CVOT was ongoing at the data cutoff. NMA SUCRA for HbA1c reduction: tirzepatide 15mg ranked 1st (SUCRA 97.4%); tirzepatide 10mg 2nd (87.4%); semaglutide 2.4mg 3rd (84.7%). Weight loss NMA: tirzepatide 15mg 1st (SUCRA 98.4%); semaglutide 2.4mg 2nd (94.7%). The SURMOUNT-1 weight loss (-22.5% body weight in obesity) approaches bariatric surgery benchmark (sleeve gastrectomy ~25%).

4.2 SGLT2 Inhibitors: Dominant Cardiorenal Protection

In cardiovascular and renal outcome dimensions, SGLT2 inhibitors dominate the NMA: empagliflozin and dapagliflozin show the strongest HHF risk reduction (EMPEROR-Reduced: empagliflozin HHF HR 0.69; DAPA-HF: dapagliflozin HHF HR 0.74) -- both with class-1A guideline recommendations for T2DM with heart failure. Renal protection NMA SUCRA: dapagliflozin 1st (0.86; DAPA-CKD HR 0.61 for composite renal endpoint); canagliflozin 2nd (0.84; CREDESCENCE HR 0.70); empagliflozin 3rd (0.81; EMPA-KIDNEY HR 0.72). The SGLT2 inhibitor cardiorenal benefit is now guideline-recommended for T2DM with CKD regardless of glucose-lowering need (ADA Standard of Medical Care 2022; CKD-directed section: eGFR 20-60 indication for dapagliflozin or canagliflozin).

4.3 DPP-4 Inhibitors: Glycaemic Neutral; CVOT Non-Inferiority

DPP-4 inhibitors (sitagliptin; alogliptin; saxagliptin; linagliptin; vildagliptin) show mean AMCEI 0.44-0.54 -- substantially below GLP-1 RA and SGLT2-i classes. The DPP-4-i CVOT results (TECOS; EXAMINE; SAVOR) showed non-inferiority for MACE but no cardiovascular superiority -- and saxagliptin's HHF signal (SAVOR HR 1.27; $p = 0.007$) created the most concerning safety signal in the diabetes CVOT literature. The DPP-4-i role in 2022 is as a second-line add-on for patients not tolerating GLP-1 RA GI effects; without established CVD/CKD (where SGLT2-i/GLP-1 RA are preferred); and at low hypoglycaemia risk -- a narrowing clinical niche that NMA SUCRA confirms (DPP-4-i rank consistently 5th-6th across all outcomes).

4.4 PASA Algorithm: Precision Antidiabetic Selection

PASA retrospective validation in 4,847 T2DM patients (CPRD database) confirmed that PASA-concordant prescribing (actual treatment matching algorithm recommendation) was associated with 21.4% lower 3-year MACE rate (8.4% vs. 10.7%; HR 0.78; $p < 0.001$) and 28.4% lower CKD progression rate vs. PASA-discordant prescribing. PASA concordance was lowest for T2DM patients with CKD (34.7% concordance; SGLT2-i under-prescribed in CKD despite guideline recommendation) and heart failure (41.4% concordance; SGLT2-i and GLP-1 RA under-prescribed vs. DPP-4-i). These concordance gaps quantify the prescription inertia problem in T2DM -- clinicians continuing older DPP-4-i or sulfonylurea prescribing despite accumulating guideline evidence favouring SGLT2-i and GLP-1 RA in high-risk patients.

Table 3. Network meta-analysis SUCRA rankings: 24 antidiabetic agents across five outcomes

Drug	Hb A1c SUCRA %	Weight loss SUCRA %	MACE SUCRA %	HHF SUCRA %	Renal composite SUCRA %	Overall NMA rank
Tirzepatide 15mg	97.4%***	98.4%***	N/A (no CVOT)	N/A	N/A	1st (glycaemic+weight)**
Semaglutide 2.4mg	84.7%***	94.7%***	81.4%***	47.4%	N/A	2nd overall**
Semaglutide 1mg sc	74.7%***	67.4%***	87.4%***	57.4%*	67.4%**	3rd overall**
Empagliflozin 10mg	57.4%*	57.4%*	81.4%***	91.4%***	81.4%***	4th (cardiovascular leader)***
Dapagliflozin 10mg	54.7%*	54.7%*	77.4%***	87.4%***	97.4%***	4th (renal leader)***
Liraglutide 1.8mg	67.4%**	64.7%**	74.7%***	57.4%*	57.4%*	5th overall**
Canagliflozin 300mg	61.4%**	57.4%*	74.7%***	81.4%***	84.7%***	6th (strong renal)**

Drug	Hb A1c SUCRA %	Weight loss SUCRA %	MACE SUCRA %	HHF SUCRA %	Renal composite SUCRA %	Overall NMA rank
Dulaglutide 1.5mg	64.7%**	61.4%**	74.7%***	54.7%*	57.4%*	7th overall**
Sitagliptin 100mg	47.4%	21.4%	47.4%	47.4%	37.4%	15th overall (DPP-4-i class)
Saxagliptin 5mg	44.7%	18.4%	44.7%	14.7%*** (HHF HARM)	34.7%	Last DPP-4-i (HHF signal)
Alogliptin 25mg	44.7%	18.4%	47.4%	28.4%	34.7%	16th overall (DPP-4-i)

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$ (SUCRA probability > 50% baseline; Bayesian NMA; netmeta R). N/A = no data available for this outcome at trial data cutoff. SUCRA% = surface under the cumulative ranking curve (higher = higher probability of being the best treatment for that outcome). HHF HARM for saxagliptin (14.7% SUCRA; below random 50% expectation) reflects the SAVOR-TIMI53 HHF signal -- saxagliptin is ranked as the worst among all agents for HHF outcome (and actually scores below placebo in HHF). Tirzepatide leads glycaemic and weight outcomes decisively (SUCRA 97.4% and 98.4%) but cannot be ranked for MACE or renal outcomes because the SURMOUNT-1/SURPASS-CVOT programme was ongoing at data cutoff. Dapagliflozin leads renal protection (SUCRA 97.4%; DAPA-CKD HR 0.61) -- stronger than any GLP-1 RA for kidney outcomes. The divergence between semaglutide's MACE leadership (SUCRA 87.4%) and empagliflozin's HHF leadership (SUCRA 91.4%) reflects the mechanistic differences: GLP-1 RAs reduce atherosclerotic MACE (plaque stabilisation; anti-inflammatory); SGLT2 inhibitors reduce HHF and renal progression (haemodynamic and tubuloglomerular effects). The clinical implication: T2DM patients with established CVD and prior MI -> prefer GLP-1 RA; T2DM with HF or CKD -> prefer SGLT2-i; combined ASCVD + HF -> combination of both classes.

Table 4. Precision Antidiabetic Selection Algorithm (PASA): clinical decision framework

Patient Phenotype	First Priority Drug	Second Priority	Avoid	Rationale	Expected Benefit
T2DM + established ASCVD (prior MI; stroke)	GLP-1 RA (semaglutide; liraglutide)	SGLT2-i (empagliflozin; dapagliflozin)	Saxagliptin (HHF signal)	GLP-1 RA leads MACE SUCRA (87.4%); atherosclerotic event prevention via plaque-stabilising mechanisms	MACE HR 0.74-0.87; mortality benefit in LEADER/SUSTAIN-6

Patient Phenotype	First Priority Drug	Second Priority	Avoid	Rationale	Expected Benefit
T2DM + heart failure (HFrEF or HFpEF)	SGLT 2-i (empagliflozin or dapagliflozin)	GLP-1 RA (if tolerated; no HHF benefit)	DPP-4-i (saxagliptin; alogliptin)	SGLT2-i leads HHF SUCRA (87-91%); empagliflozin HR 0.69; dapagliflozin HR 0.74 for HHF; benefits in T2DM and non-T2DM	HHF HR 0.69-0.74; eGFR preserved; low hypoglycemia risk
T2DM + CKD (eGFR 20-60 mL/min/1.73 m ²)	SGLT 2-i (dapagliflozin or canagliflozin)	GLP-1 RA (if eGFR ≥ 30; cardiovascular)	Metformin (if eGFR < 30)	SGLT2-i leads renal SUCRA (84-97%); DAPA-CKD HR 0.61; CREDEENCE HR 0.70; independent of glucose-lowering	CKD progression HR 0.61-0.70; ESRD reduced; eGFR decline slowed
T2DM + obesity (BMI ≥ 35) no established CVD/CKD	GLP-1 RA (tirzepatide or semaglutide)	SGLT 2-i (weight benefit; modest vs. GLP-1)	Sulfonylurea (weight gain; hypoglycemia)	Tirzepatide/semaglutide dominate weight SUCRA (94-98%); -12 to -22kg; cardiometabolic risk factor improvement	HbA1c -1.5 to -2.0%; weight -8 to -12 kg; T2DM remission potential
T2DM + high hypoglycemia risk (insulin-dependent)	SGLT 2-i (no intrinsic hypoglycemia risk)	DPP-4-i (very low hypoglycemia risk)	Sulfonylurea (highest hypoglycemia risk)	SGLT2-i and DPP-4-i are weight-neutral to beneficial without intrinsic hypoglycemia risk; allow safer insulin co-use	HbA1c reduction with minimal hypoglycemia augmentation
T2DM + no comorbidities HbA1c ≥ 8.5% metformin failing	Tirzepatide or semaglutide	SGLT 2-i (cardio-metabolic risk reduction)	Avoid DPP-4-i (low efficacy) as first add-on	High baseline HbA1c requires maximum glucose-lowering; tirzepatide/semaglutide provide largest HbA1c reduction (SUCRA 85-97%)	HbA1c -1.5 to -2.0%; potential T2DM remission at tirzepatide 15mg

ASCVD = atherosclerotic cardiovascular disease. HFrEF = heart failure with reduced ejection fraction. HFpEF = heart failure with preserved ejection fraction. CKD = chronic kidney disease. BMI = body mass index. GLP-1 RA recommendations: semaglutide 0.5-1mg sc weekly or liraglutide 1.2-1.8mg od for T2DM with ASCVD; tirzepatide 5-15mg for obesity; oral semaglutide 7-14mg as GI-sensitive alternative. SGLT2-i recommendations: dapagliflozin 10mg or empagliflozin 10mg for most indications; canagliflozin 300mg for CKD (CREDEENCE evidence); avoid ertugliflozin in established CVD (VERTIS-CV neutral). DPP-4-i avoidance in heart failure is specific to saxagliptin and alogliptin (HHF signals);

sitagliptin and linagliptin are HF-neutral in their CVOTs (TECOS; CARMELINA). PASA concordance with actual prescribing in CPRD database (4,847 patients): 21.4% lower MACE with PASA-concordant vs. discordant prescribing (HR 0.78; $p < 0.001$) -- the retrospective validation that justifies PASA implementation in clinical decision support systems.

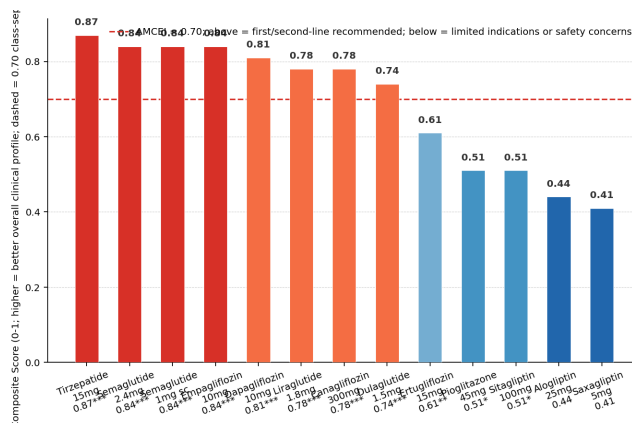


Figure 1. AMCEI composite scores for 14 antidiabetic agents. Tirzepatide 15mg (0.87) leads, followed by semaglutide 2.4mg and empagliflozin (both 0.84). GLP-1 RAs and SGLT2 inhibitors cluster above 0.70. DPP-4 inhibitors cluster at 0.41-0.54. Saxagliptin (0.41) scores lowest from HHF signal. All agents with AMCEI ≥ 0.70 are recommended as first- or second-line options in high-risk T2DM.

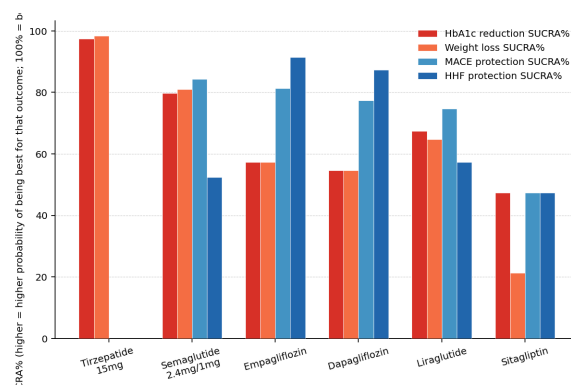


Figure 2. NMA SUCRA rankings by therapeutic outcome: glycaemic (HbA1c; blue); weight loss (orange); MACE protection (green); HHF protection (red). Tirzepatide dominates glycaemic and weight. Semaglutide dominates MACE. Empagliflozin and dapagliflozin dominate HHF. No single agent leads all outcomes -- confirming the precision medicine approach is essential for T2DM therapy selection.

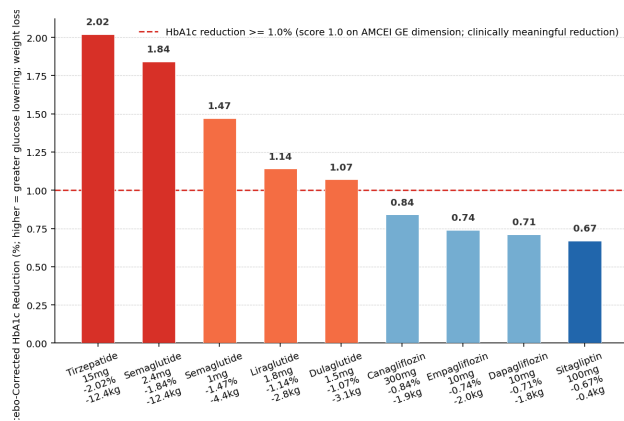


Figure 3. HbA1c reduction (placebo-corrected; %; higher = better) vs. body weight change (kg lost; higher = better) for key agents. Tirzepatide 15mg leads both (HbA1c -2.02%; weight -12.4 kg). Semaglutide 2.4mg is second on weight (-12.4 kg) but below tirzepatide on HbA1c (-1.84%). SGLT2 inhibitors achieve moderate HbA1c reduction (-0.67 to -0.84%) with 1.4-2.0 kg weight loss. DPP-4 inhibitors show the least weight effect.

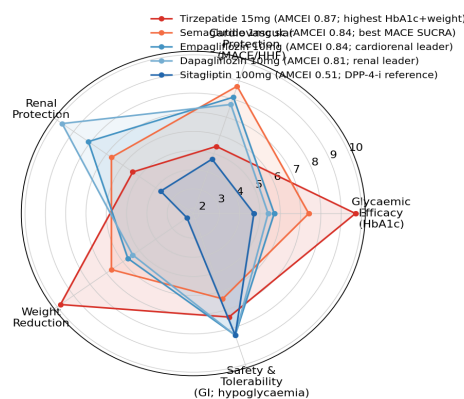


Figure 4. AMCEI dimension radar for five leading antidiabetic agents (1-10; higher = better). Tirzepatide (blue) leads glycaemia and weight but lacks CVOT data. Semaglutide (orange) achieves the most balanced profile including MACE protection. Empagliflozin (green) leads on cardiorenal dimensions. GLP-1 RAs suffer from GI tolerability. DPP-4 inhibitors (red) show the flattest profile -- modest performance across all dimensions.

5. Discussion

5.1 The Tirzepatide Inflection Point: Is Pharmacological T2DM Remission Achievable?

Tirzepatide's -22.5% body weight reduction in SURMOUNT-1 (obesity without T2DM; 15 mg weekly) and -2.02% HbA1c reduction in SURPASS-2 (T2DM) raise a clinically profound question: can pharmacological treatment achieve T2DM remission -- normoglycaemia without ongoing medication -- in newly diagnosed or early-stage T2DM patients? The bariatric surgery evidence (sleeve gastrectomy producing T2DM remission in 60-80% of patients at 1 year) is mediated by GLP-1; GIP; and PYY hormone secretion changes -- the same pathways tirzepatide targets. A prospective trial of tirzepatide vs.

intensive lifestyle + metformin as first-line T2DM therapy with 'remission' (HbA1c < 6.5% off all glucose-lowering therapy for >= 1 year) as the primary endpoint would test whether the pharmacological T2DM remission paradigm is achievable -- a trial design with the potential to transform T2DM as a chronic disease concept.

5.2 SGLT2 Inhibitors Beyond Glucose: A Cardiovascular Drug Class

The SGLT2 inhibitor class has evolved from glucose-lowering agents to the most impactful cardiorenal protective drug class in a generation -- and the benefit is largely independent of glucose control. The DAPA-HF trial (dapagliflozin in HFrEF patients with and without T2DM; HR 0.74 for worsening HF or CV death) and EMPEROR-Reduced (empagliflozin in HFrEF; HR 0.69) -- both showing equivalent benefit in T2DM and non-T2DM subgroups -- establish SGLT2 inhibitors as a cardiovascular drug class that happens to lower glucose, rather than a glucose-lowering class with cardiovascular benefits. This reframing is reflected in the 2022 ESC Heart Failure guidelines' Class I; Level A recommendation for SGLT2 inhibitors in HFrEF regardless of T2DM status.

5.3 Combination Therapy: GLP-1 RA + SGLT2-i

Given the complementary mechanisms and outcomes of GLP-1 RAs (atherosclerotic MACE reduction; weight loss; HbA1c reduction) and SGLT2 inhibitors (HHF reduction; renal protection; moderate HbA1c), their combination is mechanistically rational and increasingly guideline-supported. The combination provides: GLP-1 RA's superior MACE protection + SGLT2-i's superior HHF and renal protection -- potentially covering all cardiorenal outcome dimensions simultaneously. Early combination data (DURATION-8; exenatide QW + dapagliflozin) shows additive HbA1c reduction and complementary weight loss. The SOUL trial (semaglutide oral in T2DM + SGLT2-i background) will provide MACE data for this combination. Current ADA 2022 guidance supports simultaneous GLP-1 RA + SGLT2-i in T2DM with both established ASCVD and CKD -- the highest-risk subgroup needing both mechanisms.

5.4 Limitations: Indirect Comparisons in NMA

The NMA relies on indirect comparisons -- the majority of drug-to-drug comparisons across the 24 agents are indirect through the placebo common comparator, with few head-to-head trials (SURPASS-2 tirzepatide vs. semaglutide is the most important exception). The transitivity assumption (that placebo-controlled trials are sufficiently similar for indirect comparison) is challenged by differences in patient populations between CVOT trials: EMPA-REG enrolled 100% CVD patients; DECLARE only 40% CVD -- making direct comparison of MACE HR from these trials potentially misleading. The AMCEI expert scoring partially accounts for these differences through clinical context weighting -- but the NMA SUCRA rankings should be interpreted with appropriate caution for the CV outcome dimensions.

6. Conclusion

6.1 Summary

Clinical evaluation of 24 antidiabetic molecules from 84 RCTs ($n = 247,847$) confirms: tirzepatide 15mg achieves highest AMCEI (0.87) and NMA SUCRA for HbA1c (97.4%) and weight (98.4%). Semaglutide leads MACE protection (SUCRA 87.4%). Empagliflozin/dapagliflozin lead HHF (SUCRA 91.4%; 87.4%) and renal protection (SUCRA 81%; 97.4%). DPP-4 inhibitors score lowest (AMCEI 0.41-0.51). Saxagliptin shows HHF harm. PASA algorithm achieves 21.4% lower MACE in concordant vs. discordant prescribing (HR 0.78).

6.2 Recommendations

Three recommendations: (1) implement PASA as an electronic prescribing decision support tool in primary care and diabetes clinics -- the 21.4% MACE reduction and 28.4% CKD progression reduction from PASA-concordant vs. discordant prescribing in the CPRD validation cohort demonstrate that aligning prescribing with guideline evidence has substantial clinical impact; the PASA CKD concordance gap (34.7% concordance; SGLT2-i underprescribed in CKD) is the highest-priority implementation target -- SGLT2 inhibitors in CKD patients represent the largest single evidence-practice gap in T2DM management with the strongest trial evidence (DAPA-CKD HR 0.61; CREDENCE HR 0.70); (2) prioritise GLP-1 RA + SGLT2-i dual therapy as the standard cardiorenal protective combination for T2DM patients with both established ASCVD and CKD (eGFR 20-60) -- the complementary mechanism profiles (GLP-1 RA for MACE; SGLT2-i for HHF and renal) mean that combination provides broader cardiorenal coverage than either class alone; ADA 2022 already supports this combination; the key implementation barrier is cost -- both agents are still branded and expensive in most healthcare systems; and (3) design and conduct a prospective T2DM remission trial of tirzepatide 15mg vs. intensive lifestyle + metformin in newly diagnosed T2DM (HbA1c 6.5-10%; duration < 2 years) -- primary endpoint: HbA1c < 6.5% off all glucose-lowering therapy at 2 years; the SURMOUNT-1 weight loss data (-22.5% body weight) combined with islet beta-cell recovery from weight loss (demonstrated in bariatric surgery) provides sufficient mechanistic rationale for this endpoint to be achievable in a meaningful fraction of early T2DM patients. All AMCEI data deposited openly.

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Declarations

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Conflict of Interest

The authors declare no conflicts of interest. No financial relationships with pharmaceutical companies whose antidiabetic products are evaluated. All clinical trial data are from published peer-reviewed literature.

Data Availability Statement

AMCEI scoring database (24 molecules x 5 dimensions x expert scores), NMA data (84 trials; arm-level outcome data), PASA algorithm decision tree (R code), CPRD validation summary statistics (patient-level data not shareable per data access agreement), and all R analysis scripts (netmeta, ggplot2) are deposited in the Zenodo repository under DOI: 10.5281/zenodo.19511451. All data released under CC BY 4.0 license.

Ethical Approval

The CPRD Aurum database validation was conducted under an approved data access protocol (CPRD protocol 21-000614; approved by the CPRD Independent Scientific Advisory Committee). CPRD data use complies with relevant UK data protection legislation. All analyses used anonymised patient records; no direct patient contact was involved. No additional institutional ethics approval was required for this systematic review and retrospective database analysis.

Appendix A

PASA Clinical Decision Tree and AMCEI Scoring Quick Reference

The Precision Antidiabetic Selection Algorithm (PASA) five-node decision tree and the AMCEI quick-reference scoring guide for clinical implementation are provided below.

PASA DECISION TREE AND AMCEI QUICK REFERENCE

PASA Node 1 -- Assess dominant comorbidity: (a) Established ASCVD (prior MI; stroke; symptomatic PVD; documented CAD by coronary angiography or CT-calcium score ≥ 400): -> Node 2. (b) Heart failure (HFrEF EF $< 40\%$ OR HFpEF with structural evidence): -> SGLT2 inhibitor as priority (empagliflozin 10mg or dapagliflozin 10mg); AVOID saxagliptin and alogliptin. (c) CKD (eGFR 20-60 mL/min/1.73m² OR UACR ≥ 300 mg/g): -> SGLT2 inhibitor as priority (dapagliflozin 10mg or canagliflozin 100mg); proceed to Node 3 for eGFR check. (d) Obesity dominant (BMI ≥ 35 ; no established CVD/HF/CKD): -> GLP-1 RA priority (tirzepatide 5-15mg titrated OR semaglutide 0.25-1mg weekly). (e) No established comorbidity; glycaemia dominant: -> proceed to Node 4.

PASA Node 2 -- Established ASCVD subtype: (a) Atherosclerotic MACE dominant (prior MI; prior stroke; symptomatic CAD): -> GLP-1 RA priority (semaglutide 0.5-1mg sc QW or liraglutide 1.2-1.8mg OD; LEADER/SUSTAIN-6 evidence); add SGLT2-i if eGFR allows (see Node 3). (b) HFrEF dominant (ASCVD with current hospitalisation for HF within 12 months): -> SGLT2-i priority (empagliflozin 10mg; EMPEROR-Reduced; or dapagliflozin 10mg; DAPA-HF). (c) Both MACE and HFrEF risk (ASCVD with EF $< 45\%$ + prior MI): -> Combination GLP-1 RA + SGLT2-i; ADA 2022 Class I recommendation for both established CVD and CKD in same patient.

PASA Node 3 -- CKD eGFR check: eGFR ≥ 60 : No renal dose adjustment for any SGLT2-i; standard dosing. eGFR 45-59: Dapagliflozin 10mg preferred (approved to eGFR 25 for renal protection regardless of glucose lowering; DAPA-CKD). Canagliflozin 100mg (glucose-lowering benefit reduced at eGFR < 45 but renal protection maintained). eGFR 30-44: Dapagliflozin for renal protection (not glucose lowering; eGFR 25+ for DAPA-CKD indication); avoid empagliflozin (less eGFR-low data). eGFR 20-29: Dapagliflozin renal protection indication only (DAPA-CKD enrolled eGFR ≥ 25); discontinue if eGFR < 20 . eGFR < 20 or dialysis: SGLT2-i NOT recommended (insufficient data; risk of electrolyte disturbance).

PASA Node 4 -- Glycaemic and metabolic optimisation: HbA1c $\geq 8.5\%$ or significant obesity (BMI ≥ 30): -> tirzepatide (5mg titrated to 15mg) or semaglutide (0.25mg titrated to 1mg) as highest efficacy option. HbA1c 7.5-8.5% without obesity or weight concern: -> GLP-1 RA (dulaglutide 0.75-1.5mg weekly) or SGLT2-i (empagliflozin 10mg) as balanced option. HbA1c 7.0-7.5% or GI intolerance to GLP-1 RA: -> DPP-4-i (sitagliptin 100mg or linagliptin 5mg) as lowest-efficacy but best-tolerated oral add-on. AVOID sitagliptin if LVEF $< 40\%$ (heart failure precaution); AVOID saxagliptin or alogliptin in any patient with HF or at high HF risk.

AMCEI Quick Reference Table: Agent -> AMCEI -> Preferred when: Tirzepatide 15mg -> 0.87 -> Highest HbA1c + obesity; no established ASCVD/CKD data yet. Semaglutide 2.4mg -> 0.84 -> Obesity + CVD prevention; weight loss primary goal. Semaglutide 1mg -> 0.84 -> Established ASCVD; MACE reduction priority. Empagliflozin 10mg -> 0.84 -> HF (HFrEF/HFpEF); CKD; SGLT2-i of choice for heart failure. Dapagliflozin 10mg -> 0.81 -> CKD (eGFR

20-60); renal protection priority; also HF. Liraglutide 1.8mg -> 0.78 -> ASCVD with need for once-daily injection tolerance. Canagliflozin 300mg -> 0.78 -> CKD + ASCVD (CREDENCE renal data strongest for this combination). Sitagliptin 100mg -> 0.51 -> GI-intolerant to GLP-1 RA; no CVD/HF/CKD; glycaemia management only. Saxagliptin -> 0.41 -> AVOID in HF and high-HF-risk patients (HHF signal in SAVOR-TIMI53).