Cardiovascular Diabetology

COMMENT

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CVOT Summit Report 2025: advances along the cardiovascular–kidney–metabolic disease continuum

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Abstract

The 11th Cardiovascular Outcome Trial (CVOT) Summit: Congress on Cardiovascular, Kidney, and Metabolic Outcomes was held virtually on November 20–21, 2025. The Summit provided a multidisciplinary forum to review and discuss recent outcome trials investigating emerging pharmacological therapies targeting diseases of the cardiovascular–kidney–metabolic (CKM) continuum. This report highlights the unique developments of 2025 discussed during the Summit, including the first head-to-head CVOT (SURPASS-CVOT), the growing evidence base for combination therapies across the disease spectrum, new insights into the inflammatory component of the CKM syndrome, and relevant policy developments. The first part of this report summarizes pioneering clinical trials addressing combination therapy with finerenone and empagliflozin (CONFIDENCE), the oral glucagon-like peptide-1 (GLP-1) receptor agonists orforglipron (ATTAIN-1), and the aldosterone synthase inhibitor (ASI) baxdrostat (BaxHTN). The second part presents recent guideline and policy developments discussed by experts in endocrinology, diabetology, cardiology, nephrology, hepatology, and general practice. In addition, advances in medical technology, particularly in continuous glucose and ketone monitoring, are highlighted, as well as emerging therapies for diseases of the CKM continuum. These include pharmacological agents for a broad spectrum of metabolic disorders such as metabolic liver disease and type 1 Diabetes (T1D) alongside emphasis

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on the importance of early detection and innovative treatment strategies. The 12th Cardiovascular Outcome Trial Summit will be held virtually on 19–20 November 2026 (http://www.cvot.org).

Keywords Diabetes, CGM, Heart failure, MASLD, Obesity, SGLT2 inhibitor, Incretin mimetics, Aldosterone synthase inhibitors, Soluble guanylate cyclase stimulators, Nonsteroidal mineralcorticoid receptor antagonists

Background

The annual CVOT Summit, held virtually from Munich, Germany, aims to highlight and disseminate the latest scientific advances in the management of cardiovascular, kidney, and metabolic diseases. The focus lies on emerging therapies and the practical implementation of recently published clinical guidelines. The latest CVOT Summit, held in November 2025, addressed novel pharmacological approaches and innovative medical devices, alongside early detection and prevention strategies.

Since 2008, cardiovascular outcome trials (CVOTs) have been a mandatory regulatory requirement for all new therapies targeting Type 2 Diabetes (T2D), as stipulated by the U.S. Food and Drug Administration (FDA) [1]. Subsequent CVOTs not only demonstrated the safety of the investigated drug, but even discovered cardioprotective effects in high-risk patients, e.g., for certain sodium–glucose transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) [2]. In recent years, CVOTs have increasingly incorporated additional endpoints, especially renal outcomes, which represent common complications associated with cardiovascular risk factors [3, 4]. This increasingly holistic cardio–renal–metabolic approach reflects the intrinsic interconnectedness of these systems—a perspective reinforced by the American Heart Association (AHA) through the introduction of the term cardiovascular–kidney–metabolic (CKM) syndrome in 2023 [5]. Adopting a syndromic perspective has significant therapeutic implications, extending the focus of T2D management beyond glycemic control to encompass cardiorenal risk reduction as well. Moreover, drugs initially approved for T2D, such as the SGLT2 inhibitor dapagliflozin, are now also indicated for heart failure (HF) and chronic kidney disease (CKD) [6–8]. These advances have the potential to benefit a vast population, including not only the 589 million adults worldwide affected by T2D [9], but also over 700 million suffering from CKD [10], and an estimated 598 million afflicted by cardiovascular disease (CVD) [11].

A notable recent development in CVOTs is the shift beyond placebo-controlled designs toward active-comparator, head-to-head studies, exemplified by the SURPASS-CVOT [12]. This trial evaluated cardiovascular and renal outcomes in patients with T2D treated with tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP)/glucagon-like peptide-1 (GLP-1) receptor agonist (RA), compared with dulaglutide, a GLP-1 RA [12].

The 11th CVOT Summit also highlighted the most relevant intervention studies published in 2025, which explored pharmacological approaches to managing the CKM syndrome. These include, among others, the CONFIDENCE [13], SURMOUNT-5 [14], and the ATTAIN trials [15, 16], the BaxHTN [17], and VICTOR [18] studies. Further discussions underscore advances in medical technology: Continuous Glucose Monitoring (CGM) systems improve glycemic control and reduce cardiometabolic risk in diabetes management [19, 20], while Continuous Ketone Monitoring devices facilitate early detection and management of ketoacidosis, a potentially life-threatening complication, particularly in patients with Type 1 Diabetes (T1D) [21].

Following the practice of previous years [22–31], we present and summarize key aspects discussed at the 11th CVOT Summit: Congress on Cardiovascular, Kidney, and Metabolic Outcomes held virtually on November 20–21, 2025. The Summit was an interdisciplinary platform organized in collaboration with six study groups: Primary Care Diabetes Europe (PCDE, www.pcdeurope.org), Diabetes and Cardiovascular Disease Study Group (DCVD, www.dcvd.org), Forschergruppe Diabetes e.V., Munich, Germany, the Working Group "Diabetes and the Heart" of the German Diabetes Society (DDG) (www.ddg.info), br1dge (www.bridget1d.com), and the European Association for the Study of the Liver (EASL, www.easl.eu). The Summit was endorsed by four scientific societies: European Association for the Study of Obesity (EASO, www.easo.org), European Renal Association (ERA, www.era-online.org), China CardioMetabolic Association, and Diabetes India (www.diabetesindia.com).

Updates on clinical outcome trials

The most relevant studies discussed during the CVOT Summit 2025 are presented in Table 1. A summary of the characteristics and results of kidney, cardiovascular, and metabolic outcome trials with dual GIP/GLP-1 RAs, GLP-1 RAs, nonsteroidal mineralocorticoid receptor antagonists (nsMRAs), SGLT2 inhibitors, aldosterone synthase inhibitors (ASIs), and soluble guanylate cyclase (sGC) stimulators published in 2025 is listed in Tables 2, 3, 4, 5, 6, and 7.

Incretin mimetics and amylin analogues

GLP-1–based therapies address core drivers of CKM disease by producing substantial reductions in body weight and glycemic burden, with accumulating evidence for

Table 1 Key trials discussed during the CVOT Summit 2025

Trial	Drug class	Study drug
SURPASS-CVOT	GIP/GLP-1 RAs	tirzepatide vs dulaglutide
SURMOUNT-5	GIP/GLP-1 RAs	tirzepatide vs semaglutide
ATTAIN-1	GLP-1 RA	orforglipron vs placebo
SOUL	GLP-1 RA	oral semaglutide vs placebo
REDEFINE-1	GLP-1 RA	semaglutide + cagrilintide vs monotherapy vs placebo
REDEFINE-2	GLP-1 RA + amylin analogue	semaglutide + cagrilintide vs placebo
FINE-ONE	nsMRA	finerenone vs placebo
CONFIDENCE	nsMRA + SGLT2i	finerenone + empagliflozin vs monotherapy
MIRO-CKD	nsMRA + SGLT2i	balcinrenone + dapagliflozin vs dapagliflozin
BaxHTN	ASI	baxdrostat vs placebo
VICTOR	sGC stimulator	vericiguat vs placebo

GIP, glucose-dependent insulinotropic polypeptide; *GLP-1*, glucagon-like peptide-1; *RAs*, receptor agonists; *vs*, versus; *nsMRA*, nonsteroidal mineralocorticoid receptor antagonist; *SGLT2i*, sodium–glucose transporter 2 inhibitor; *ASI*, aldosterone synthase inhibitor; *sGC*, soluble guanylate cyclase

cardiovascular and renal risk reduction beyond glucose lowering [32].

SURPASS-CVOT

The SURPASS-CVOT trial was a randomized, double-blind CVOT study assessing the cardiovascular safety of the GIP/GLP-1 RAs tirzepatide compared with the GLP-1 RA dulaglutide over a median follow-up of four years [12]. This was the first head-to-head CVOT study including an active comparator. Eligible participants were ≥ 40 years of age with T2D, glycated hemoglobin levels of 7.0–10.5%, a body-mass index (BMI) ≥ 25 kg/m^2, and documented atherosclerotic cardiovascular disease (ASCVD) involving at least one major vascular territory [12]. Participants were randomized 1:1 to once-weekly subcutaneous tirzepatide (up to 15 mg) or dulaglutide (1.5 mg), with stratification by country and baseline SGLT2 inhibitor use [12]. Time-to-event outcomes were analyzed using Cox proportional-hazards models stratified by baseline SGLT2 inhibitor use, with Kaplan–Meier estimates and sensitivity analyses accounting for competing risks. Changes in estimated glomerular filtration rate (eGFR), glycated hemoglobin, and body weight over 36 months were assessed using covariate-adjusted models with multiple imputations for missing data [12]. The primary composite endpoint of cardiovascular death, myocardial infarction, or stroke (Major Adverse Cardiovascular Event (MACE)-3) occurred in 12.2% of patients receiving tirzepatide and 13.1% receiving dulaglutide [12]. Compared with dulaglutide, tirzepatide was associated with greater reductions in glycated hemoglobin (– 1.66 percentage points (pp) vs. – 0.88 pp) and body weight (– 11.6% vs. – 4.8%) and a 16% lower risk of all-cause mortality (hazard ratio (HR) 0.84; 95% confidence interval (CI), 0.75 to 0.94) [12]. Further endpoints are described in Table 2. The divergence between tirzepatide's robust metabolic effects and the absence of demonstrated superiority for MACE compared with dulaglutide warrants further analysis. Possibly, cardiovascular benefit is driven by mechanisms beyond glycemic control. Importantly, tirzepatide was compared with dulaglutide, which is itself associated with reduced cardiovascular risk; therefore, using it as an active comparator likely attenuated the observable treatment difference, which might have been larger against placebo. Exploratory analyses suggested a potential reduction in all-cause mortality and non-cardiovascular mortality with tirzepatide versus dulaglutide, however, these findings require further investigation. Adverse and serious adverse event rates were comparable between groups (Table 2) [12]. Overall, tirzepatide demonstrated non-inferiority to dulaglutide for the primary cardiovascular endpoint, confirming its cardiovascular safety in patients with T2D and established ASCVD.

SURMOUNT-5

The phase 3b, open-label, randomized SURMOUNT-5 trial compared the efficacy and safety of tirzepatide versus semaglutide in adults with obesity without T2D [14]. Eligible participants (≥ 18 years) had a BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with at least one obesity-related complication and a prior unsuccessful dietary weight-loss attempt [14]. Participants were randomized 1:1, stratified by BMI (< 35 vs. ≥ 35 kg/m^2), sex, and prediabetes status, and received once-weekly subcutaneous treatment for 72 weeks alongside lifestyle counseling [14]. Tirzepatide was titrated from 2.5 to 10 mg or 15 mg, and semaglutide from 0.25 to 2.4 mg. Continuous and categorical outcomes were analyzed using covariate-adjusted analysis-of-covariance and logistic-regression models, respectively [14]. At week 72, the least-squares mean (LSM) body-weight reduction was – 20.2% with tirzepatide versus – 13.7% with semaglutide, yielding a between-group difference of – 6.5 percentage points (95% CI, – 8.1 to – 4.9; $P < 0.001$) (Table 3) [14]. Waist circumference decreased by – 18.4 cm with tirzepatide and – 13.0 cm with semaglutide (difference – 5.4 cm; CI, – 7.1 to – 3.6; $P < 0.001$) (Table 3) [14], a clinically meaningful finding given the established association between increased waist circumference and mortality [33]. Both treatments improved cardiometabolic risk markers, including blood pressure, glycemic indices, and lipid profiles [14]. Further secondary endpoints as well as adverse events are reported in Table 3. Overall, tirzepatide produced greater reductions in body weight and central adiposity than semaglutide, consistent with the enhanced efficacy from dual GIP and GLP-1 receptor agonism.

Table 2 Key information of the SURPASS-CVOT trial [12]

SURPASS-CVOT (12)[†]			
Class & metabolic outcomes	**Tirzepatide (n = 6586)**	**Dulaglutide (n = 6579)**	**Hazard Ratio (95% CI)**
Primary endpoint			
Death from MACE-3*, no. of patients with event (%)	801 (12.2)	862 (13.1)	0.92 (0.83 to 1.01)[#]
Key secondary endpoints			
Death from cardiovascular causes, no. (%)	367 (5.6)	408 (6.2)	0.89 (0.77 to 1.02)
Myocardial infarction, no. (%)	311 (4.7)	357 (5.4)	0.86 (0.74 to 1.00)
Stroke, no. (%)	229 (3.5)	249 (3.8)	0.91 (0.76 to 1.09)
Death from any cause, no. (%)	566 (8.6)	669 (10.2)	0.84 (0.75 to 0.94)
	Tirzepatide (n = 6586)	**Dulaglutide (n = 6579)**	**Difference (95% CI)**
Change in eGFR at 36 mo, mL/min/1.73m^2[‡]	− 5.72 ± 0.44	− 8.90 ± 0.39	3.17 (2.09 to 4.26)
Change in triglycerides at 24 mo (95% CI), %	− 24.2 (− 25.1; − 23.3)	− 10.2 (− 11.2; − 9.1)	− 15.6 (− 16.9; − 14.3)[§]
Change in SBP at 36 mo (95% CI), mmHg	− 6.2 (− 6.6; − 5.8)	− 4.1 (− 4.6; − 3.7)	− 2.1 (− 2.6; − 1.5)
Safety assessments	**Tirzepatide (n = 6647) Number of patients (%)**		**Dulaglutide (n = 6647) Number of patients (%)**
Adverse events (AE)	5956 (89.6)		5894 (88.7)
Serious adverse event[$]	2117 (31.8)		2121 (31.9)
Discontinuation of treatment due to AE	878 (13.2)		672 (10.1)
Severe hypoglycemia	49 (0.7)		48 (0.7)
Gastrointestinal AE	2827 (42.5)		2387 (35.9)
Severe gastrointestinal AE	171 (2.6)		118 (1.8)
Pancreatitis[¶]	41 (0.6)		39 (0.6)
Acute kidney injury	226 (3.4)		178 (2.7)
Chronic kidney disease	147 (2.2)		170 (2.6)

MACE major adverse cardiovascular events, *no.* number, *CI* confidence interval, *eGFR* estimated Glomerular Filtration Rate, *mo* months, *SBP* systolic blood pressure, *AE* adverse events, *uACR* urinary albumin-to-creatinine ratio

[†]Confidence intervals were not multiplicity-adjusted and should not be interpreted as substitutes for formal hypothesis testing. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) (version 28.0)

*MACE-3: cardiovascular causes, myocardial infarction, or stroke

[#]After adjustment for interim analysis, the primary endpoint used a 95.3% CI (two-sided α = 0.047); noninferiority was met ($P = 0.003$), but superiority was not ($P = 0.09$)

[‡]Data are presented for patients with high/very-high–risk CKD (defined by the Kidney Disease: Improving Global Outcomes 2024 guideline): tirzepatide n = 1520, dulaglutide n = 1403, defined at baseline by eGFR ≥ 60 mL/min/1.73 m^2 with uACR > 300, eGFR 45– < 60 ml/min/1.73 m^2 with uACR > 30, or eGFR < 45 ml/min/1.73 m^2

[§]difference in percentage points

[$]Reported data exclude cardiovascular endpoint events adjudicated by an independent clinical endpoint committee, and adverse event severity was assessed by the study investigators

[¶]Pancreatitis events were adjudicated by a clinical endpoint committee

ATTAIN-1

Several Phase 3 studies were designed to evaluate the safety and efficacy of orforglipron, a small-molecule, nonpeptide GLP-1 RA, in managing obesity and T2D. Compared with peptide-based GLP-1 RA, orforglipron offers greater physicochemical stability, facilitating storage and distribution, as well as oral administration, which may enhance treatment adherence [15]. Initial results published in 2025 include ATTAIN-1 [15] and ATTAIN-2 [16], which evaluated weight management in individuals with overweight or obesity without and with T2D, respectively, and ACHIEVE-1 [35], which assessed glycemic control in T2D.

ATTAIN-1 was a phase 3, randomized, double-blind trial in adults with obesity or overweight comparing once-daily orforglipron (6, 12, or 36 mg) with placebo over 72 weeks, alongside lifestyle intervention [15]. Included were adults ≥ 18 years of age with a BMI ≥ 30 kg/m^2 or 27 kg/m^2 to 30 kg/m^2 with at least one obesity-related complication, and at least one unsuccessful attempt at losing weight [15]. Participants were randomized in a 3:3:3:4 ratio and stratified by country, sex, and prediabetes status. Continuous efficacy outcomes were analyzed using an analysis-of-covariance model, and binary outcomes were assessed employing logistic regression [15]. A graphical testing procedure was used to correct for multiple comparisons of the primary and multiplicity-adjusted secondary endpoints [15]. Mean body-weight reductions at week 72 were − 7.5%, − 8.4%, and − 11.2% with orforglipron 6 mg, 12 mg, 36 mg, respectively, versus − 2.1% with placebo (Table 4) [15]. Orforglipron improved key secondary endpoints, i.e., cardiometabolic risk factors, including waist circumference, systolic blood pressure, non-High-Density Lipoprotein

Table 3 Key information of the SURMOUNT-5 trial (14)

SURMOUNT-5 (14)			
Class & metabolic outcomes	**Tirzepatide (n = 374)**	**Semaglutide (n = 376)**	**Treatment difference or RR (95% CI)[†]**
Primary endpoint			
LSM change, body weight, % (95% CI)	− 20.2 (− 21.4; − 19.1)	− 13.7 (− 14.9; − 12.6)	− 6.5 (− 8.1; − 4.9)
Key secondary endpoints			
LSM change, waist circumference, cm	− 18.4 (− 19.6; − 17.2)	− 13.0 (− 14.3; − 11.7)	− 5.4 (− 7.1; − 3.6)
Weight reduction of ≥ 10%, no. (%)*	304 (81.6)	227 (60.5)	1.3 (1.2; 1.5)
Weight reduction of ≥ 15%, no. (%)*	241 (64.6)	151 (40.1)	1.6 (1.4; 1.9)
Weight reduction of ≥ 20%, no. (%)*	181 (48.4)	103 (27.3)	1.8 (1.5; 2.2)
Weight reduction of ≥ 25%, no. (%)*	118 (31.6)	60 (16.1)	2.0 (1.5; 2.6)
Safety Assessments[#]	**Number (%)**	**Number (%)**	**Total, Number (%)**
Adverse events (AE)	287 (76.7)	297 (79.0)	584 (77.9)
Serious adverse event	18 (4.8)	13 (3.5)	31 (4.1)
Adverse events leading to death	0	0	0
Discontinuation of trial due to AE	6 (1.6)	6 (1.6)	12 (1.6)
Discontinuation of treatment due to AE	23 (6.1)	30 (8.0)	53 (7.1)
Discontinuation of treatment due to gastrointestinal AE	10 (2.7)	21 (5.6)	31 (4.1)

LSM least-squares mean, *CI* confidence interval, *RR* Relative Risk, *no.* number, *AE* adverse events

[†]Results are reported as percentage-point differences between groups, except for ≥ 10–30% weight-loss categories, which are shown as relative risks (calculated from logistic regression using G-computation [34]). All primary and key secondary endpoints were significant ($P < 0.001$)

[*]Numbers and percentages are based on imputed data. The number is the rounded average of participants who achieved the target weight reduction, while the percentage is the pooled estimate using Rubin's rule

[#]Safety endpoints were assessed using data from all participants, regardless of treatment adherence, use of other anti-obesity medications, or bariatric surgery

Table 4 Key information of the ATTAIN-1 trial (15)

ATTAIN-1 (15)				
	Orforglipron, 6 mg (n = 723)	**Orforglipron, 12 mg (n = 725)**	**Orforglipron, 36 mg (n = 730)**	**Placebo (n = 949)**
Class & cardiovascular outcomes[†]				
Primary endpoints				
Percent change in body weight (95% CI)*	−7.5 (−8.2; −6.8)	−8.4 (−9.1; −7.7)	−11.2 (−12.0; −10.4)	−2.1 (−2.8; −1.4)
Difference to placebo (95% CI), pp	−5.5 (−6.5; −4.5)	−6.3 (−7.3; −5.4)	−9.1 (−10.1; −8.1)	–
Key secondary endpoints				
Category of weight reduction, % of patients (95% CI)[#]				
≥ 5%	60.6 (56.5; 64.6)	63.5 (59.8; 67.2)	71.8 (68.1; 75.4)	26.8 (23.3; 30.2)
≥ 10%	33.3 (29.7; 36.9)	40.0 (36.4; 43.7)	54.6 (50.7; 58.4)	12.9 (10.3; 15.6)
≥ 15%	15.1 (12.4; 17.8)	20.3 (17.3; 23.3)	36.0 (32.4; 39.5)	5.9 (4.0; 7.8)
≥ 20%	6.4 (4.6; 8.3)[§]	9.0 (6.9; 11.1)	18.4 (15.5; 21.3)	2.8 (1.6; 4.0)
Change in waist circumference (95% CI), cm*	−7.1 (−7.7; −6.5)	−8.2 (−8.9; −7.5)	−10.0 (−10.7; −9.3)	−3.1 (−3.7; −2.4)
Adverse events	**Number (%)**	**Number (%)**	**Number (%)**	**Number (%)**
Any adverse event during treatment	603 (83.4)	627 (86.6)	620 (85.2)	763 (80.5)
Serious adverse event	40 (5.5)	39 (5.4)	28 (3.8)	46 (4.9)
Death[$]	1 (0.1)	1 (0.1)	0	1 (0.1)
Events leading to discontinuation of orforglipron or placebo	38 (5.3)	57 (7.9)	75 (10.3)	26 (2.7)
Gastrointestinal disorder	25 (3.5)	38 (5.2)	51 (7.0)	4 (0.4)
Adjudication-confirmed pancreatitis	1 (0.1)	2 (0.3)	2 (0.3)	0
Hypotension or syncope[¶]	0	0	1 (0.1)	1 (0.1)
Adjudication-confirmed MACE	7 (1.0)	0	4 (0.5)	4 (0.4)
Acute renal event[¶]	0	0	0	1 (0.1)

CI, Confidence interval; *pp*, percentage points; *MACE*, major adverse cardiovascular events

[†]The primary and key secondary endpoints were analyzed using a multiplicity-controlled procedure, with all comparisons to placebo reaching $P < 0.001$

*Data are model-based estimates with 95% confidence intervals from an ANCOVA using the treatment-regimen estimand. Confidence intervals were not adjusted for multiplicity and are not for hypothesis testing. All changes are from baseline to week 72

[#]Data are shown as model-based estimates with 95% confidence intervals derived from logistic regression using the treatment-regimen estimand. Percentages were calculated by pooling patients who met the target in imputed datasets with the use of Rubin's rule

[§]Not controlled for multiplicity

[$]Deaths occurred due to undetermined causes (6 mg group), metastatic ovarian cancer (12 mg group), and pulmonary embolism (placebo). All were classified as serious adverse events and resulted in trial regimen discontinuation

[¶]Includes only events that were classified as severe or serious adverse events

(HDL) cholesterol, and triglycerides [15]. Adverse events are reported in Table 4. In ATTAIN-2, orforglipron also induced clinically meaningful weight loss in patients with T2D (−5.1% to −9.6% across doses) compared with placebo (−2.5%) [16]. In ACHIEVE-1, conducted in patients with T2D not receiving glucose-lowering therapy, orforglipron reduced glycated hemoglobin by up to −1.47 and −1.48 pp with 12 mg and 36 mg orforglipron, respectively, at week 40, compared with −0.41 pp with placebo [35]. Collectively, these data demonstrate that orforglipron effectively improves weight and glycemic outcomes while offering the advantages of oral administration and enhanced stability [15]. Additional ACHIEVE trials are further evaluating orforglipron in head-to-head comparisons to dapagliflozin (ACHIEVE-2: NCT06192108), semaglutide (ACHIEVE-3: NCT06045221), and insulin glargine (ACHIEVE-4: NCT05803421) as well as in long-term trials of 104 weeks (ACHIEVE-4).

SOUL

This double-blind, placebo-controlled superiority trial demonstrated an association between the daily use of oral semaglutide (n = 4825) and a significantly reduced risk of MACEs compared to placebo (n = 4825) in participants with T2D and ASCVD or CKD, or both [36]. The primary outcome specified as MACEs (three-point composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) occurred in 12% of participants in the semaglutide group and in 13.8% of participants in the placebo group (HR, 0.86; 95% CI, 0.77 to 0.96; $P = 0.006$) after 49.5 months (interquartile range, 44.0 to 54.9) [36]. After three years, the difference in risk between the oral semaglutide group and the placebo group was 2.0 percentage points [36]. Serious adverse events were reported for 47.9% participants in the semaglutide group and 50.3% in the placebo group, with cardiac disorders and infections or infestations being the most frequent ones [36]. Overall, oral semaglutide

Table 5 Key information of the CONFIDENCE trial [13]

CONFIDENCE (13)			
	Combination Therapy	**Finerenone**	**Empagliflozin**
Class & kidney outcomes	**LSMR (95% CI)**	**LSMR (95% CI)**	**LSMR (95% CI)**
Change in urinary albumin-to-creatinine ratio			
Primary endpoint[†]			
From baseline to day 180	0.48 (0.44–0.54)	0.68 (0.61–0.76)	0.71 (0.64–0.79)
Key secondary endpoints*			
From baseline to 210 days	0.82 (0.73–0.91)	0.85 (0.76–0.96)	0.90 (0.80–1.00)
From 180 to 210 days	1.63 (1.49–1.78)	1.45 (1.32–1.59)	1.44 (1.32–1.58)
Adverse Events[#,‡]	**Number (%)**	**Number (%)**	**Number (%)**
Any adverse event	144 (53.7)	136 (51.5)	135 (50.8)
Any serious adverse event	19 (7.1)	16 (6.1)	17 (6.4)
Death	3 (1.1)	0	3 (1.1)
Hyperkalemia[§]	25 (9.3)	30 (11.4)	10 (3.8)
Safety Assessment[#]			
> 30% decline in eGFR from baseline to 30 days[$]	17 (6.3)	10 (3.8)	3 (1.1)
Serum potassium level—no./total no. (%)[¶]			
> 5.5 mmol/L	40/262 (15.3)	48/258 (18.6)	25/257 (9.7)
> 5.5 to ≤ 6.0 mmol/L	34/262 (13.0)	43/258 (16.7)	21/257 (8.2)
> 6.0 mmol/L	12/263 (4.6)	12/262 (4.6)	7/262 (2.7)

LSMR, least-squares mean ratio; *CI*, confidence interval; *eGFR*, estimated glomerular filtration rate; *no*, number

[†]number of participants per group: combination therapy = 240, finerenone = 236, empagliflozin = 238

[*]95% CI widths for non-primary outcomes are unadjusted for multiplicity and should be excluded for efficacy testing. Number of participants per group for baseline to 210 days: combination therapy = 238, finerenone = 227, empagliflozin = 232. Number of participants per group for 180 to 210 days: combination therapy = 239, finerenone = 234, empagliflozin = 238

[#]Safety analysis population included all randomized participants who received at least one dose of the study treatment. Combination therapy group = 268, Finerenone group = 264, Empagliflozin group = 266

[‡]Participants included had at least one dose and experienced an adverse event during treatment or within 3 days of stopping it

[§]Hyperkalemia was identified using the terms "hyperkalemia" and "blood potassium increased" from MedDRA version 27.1

[$]Calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration equation with modifications for Japanese participants[47]

[¶]Denominator: participants with baseline and postbaseline lab values (postbaseline measured after first dose to 3 days post-treatment interruption) and baseline not above the threshold. Numerator: those participants with ≥ 1 postbaseline lab result meeting the criterion

demonstrated cardiovascular benefits comparable to injectable semaglutide and other GLP-1 RAs [36].

REDEFINE-1 and REDEFINE-2

The phase 3 REDEFINE studies evaluated once-weekly combination therapy with semaglutide and cagrilintide, a long-acting amylin analogue, for weight management over 68 weeks in adults with overweight or obesity without T2D (REDEFINE-1 [37]) and with T2D (REDEFINE-2 [38]). In REDEFINE-1, combination therapy resulted in a mean body-weight reduction of − 20.4% (n = 2108), exceeding reductions observed with semaglutide alone (− 14.9%) (n = 302), cagrilintide alone (− 11.5%) (n = 302), or placebo (− 3.0%) (n = 705) [37]. In REDEFINE-2, combination therapy reduced body weight by − 13.7% and glycated hemoglobin by − 1.8% (n = 904), compared with − 3.4% and − 0.4%, respectively, with placebo (n = 302) [38]. Adverse events were common, but mostly transient and mild-to-moderate in severity [37, 38]. Overall, cagrilintide–semaglutide produced greater weight loss than monotherapy or placebo, likely due to complementary effects on appetite and satiety [37]. Weight reduction was larger in individuals without T2D, consistent with prior trials and potentially influenced by metabolic differences, weight-promoting antidiabetic therapies, older age, and obesogenic environments [39].

Nonsteroidal mineralocorticoid receptor antagonists

NsMRAs modulate mineralocorticoid receptor–driven inflammatory and fibrotic pathways in the heart and kidneys, contributing to cardio-renal protection in patients with CKM diseases [40].

FINE-ONE

The FINE-ONE trial was a phase 3, randomised, placebo-controlled, double-blind trial investigating the effects of the nsMRA finerenone on kidney outcomes in patients with T1D, following its approval for reducing the risk of kidney failure in patients with T2D and CKD [41].

Study participants had CKD with urinary Albumin-to-Creatinine Ratio (uACR) ≥ 200 to < 5000 mg/g and an eGFR ≥ 25 to < 90 mL/min/1.73 m^2 as well as T1D, Hemoglobin A1c (HbA1c) < 10%, and serum potassium ≤ 4.8 mmol/L. Patients with current or previous

Table 6 Key information of the BaxHTN trial [17]

BaxHTN (17)			
	Baxdrostat, 1 mg	**Baxdrostat, 2 mg**	**Placebo**
Class & cardiovascular outcomes			
Primary endpoint			
LSM Placebo-corrected difference in seated SBP from baseline to wk 12[†]	−8.7 (−11.5 to −5.8)*	−9.8 (−12.6 to −7.0)*	–
Number of patients	264	266	263
Secondary endpoints			
Change in seated SBP during randomized-withdrawal period from wk 24 to 32[#]	NA	−5.1 (−8.3 to −1.9)[§]	–
Number of patients	NA	172	85
Change in seated SBP from baseline to wk 12 in the resistant-hypertension subpopulation[$]	−9.1 (−12.6 to −5.7)*	−9.8 (−13.1 to −6.4)*	–
Number of patients	187	199	192
Change from baseline in seated DBP to wk 12[¶]	−3.3 (−5.2 to −1.4)[‡]	−3.9 (−5.7 to −2.0)*	–
Number of patients	264	266	263
Adverse events week 1–12	**Number (%) (N = 264)**	**Number (%) (N = 266)**	**Number (%) (N = 264)**
Any adverse event	125 (47.3)	119 (44.7)	109 (41.3)
Any serious adverse event	5 (1.9)	9 (3.4)	7 (2.7)
Death	0	0	1 (0.4)
Hyperkalemia	7 (2.7)	21 (7.9)	0
Hyponatremia	2 (0.8)	6 (2.3)	1 (0.4)
Hypotension	5 (1.9)	6 (2.3)	2 (0.8)
Serum potassium level—no./total no. (%)[ł]			
> 5.5 mmol/L	16/262 (6.1)	29/261 (11.1)	1/260 (0.4)
> 6.0 mmol/L	6/262 (2.3)	8/263 (3.0)	1/262 (0.4)
> 6.5 mmol/L	5/262 (1.9)	1/263 (0.4)	1/263 (0.4)

LSM, Least-squares mean; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *CI*, confidence interval; *wk*, week; *no.*, number; *NA*, not applicable

[†]Analysis was performed on the full analysis population. The analysis used ANCOVA with treatment and baseline hypertension status (uncontrolled or resistant) as factors, and baseline seated SBP as a covariate. Results are reported as least-squares mean placebo-corrected difference (95% CI) — mm Hg

[*]*P* value < 0.001

[#]Analysis was performed on the randomized-withdrawal population. The analysis compared 2-mg baxdrostat with placebo using ANCOVA, with treatment and baseline hypertension status (uncontrolled or resistant) as factors, and week-24 seated SBP as a covariate. Results are reported as least-squares mean placebo-corrected difference (95% CI)—mm Hg

[§]*P* value 0.002

[$]Analysis was performed on the full analysis population. The analysis in patients with resistant hypertension used ANCOVA with treatment as a factor and baseline seated SBP as a covariate. Results are reported as least-squares mean placebo-corrected difference (95% CI)—mm Hg

[¶]Analysis was performed on the full analysis population. The analysis used ANCOVA with treatment and baseline hypertension status (uncontrolled or resistant) as factors, and baseline seated DBP as a covariate. Results are reported as least-squares mean placebo-corrected difference (95% CI)—mm Hg

[‡]*P* value 0.001

[ł]Denominators include patients who did not already meet the criterion at baseline. If the baseline value was missing but postbaseline values were available, it was assumed the patient did not meet the criterion

(≤ 8 weeks prior) use of SGLT2/1 inhibitors or GLP-1 RAs were excluded [41, 42]. Overall, 242 individuals receiving renin-angiotensin system therapy were randomized 1:1 to finerenone (10 mg or 20 mg) or placebo [41]. Preliminary primary-endpoint data demonstrated a significant reduction in uACR over 6 months compared to placebo, with a safety profile largely consistent with prior outcomes of finerenone [42, 43]. Collectively, these results suggest finerenone represents a promising therapeutic option for CKD in patients with T1D. This is particularly notable given the lack of major CKD-directed therapeutic advances in T1D since the 1990s, and because newer agents such as SGLT2 inhibitors have been approved only for T2D, as their use in T1D is constrained by an increased risk of diabetic ketoacidosis (DKA) [44].

Combination therapy of nsMRAs and SGLT2 inhibitors

The combination of nsMRAs and SGLT2 inhibitors represents a complementary, mechanism-based approach to CKM diseases, simultaneously addressing hemodynamic stress, inflammation, and fibrosis, with the potential to amplify cardio-renal protection across disease stages [45].

Table 7 Key information of the VICTOR trial (18)

VICTOR (18)			
	Vericiguat (N = 3053)	**Placebo (N = 3052)**	**HR (95% CI)**
Class & cardiovascular outcomes	**Events (%)**	**Events (%)**	
Primary composite outcome[†] and components			
Time from randomization to CV death or HHF	549 (18.0%)	584 (19.1%)	0.93 (0.83–1.04)*
Cardiovascular death	201 (6.6%)	222 (7.3%)	
Hospitalization for heart failure	348 (11.4%)	362 (11.9%)	
Secondary endpoints			
Time from randomization to CV death	292 (9.6%)	346 (11.3%)	0.83 (0.71–0.97)
Time from randomization to first HHF	348 (11.4%)	362 (11.9%)	0.95 (0.82–1.10)
Total HHF events (first and recurrent)	549	597	0.90 (0.80–1.02)
Time from randomization to all-cause death	377 (12.3%)	440 (14.4%)	0.84 (0.74–0.97)
Adverse events[#]	**Number (%)**	**Number (%)**	
Any adverse event	1265 (41.5%)	1197 (39.3%)	
Any serious adverse event	717 (23.5%)	751 (24.6%)	
Adverse events leading to permanent treatment discontinuation	253 (8.3%)	219 (7.2%)	
Symptomatic hypotension	345 (11.3%)	281 (9.2%)	
Blood and lymphatic system disorders	234 (7.7%)	199 (6.5%)	
Anemia	233 (7.6%)	193 (6.3%)	
Hepatic injury	9 (0.3%)	12 (0.4%)	
Cardiac failure	124 (4.1%)	123 (4.0%)	
Renal and urinary disorders	98 (3.2%)	110 (3.6%)	
Acute kidney injury	33 (1.1%)	59 (1.9%)	

CV, cardiovascular; *HHF*, hospitalization for heart failure; *HR*, Hazard Ratio; *CI*, Confidence Interval

[†]If both events contributing to the composite endpoint occurred on the same day, the event was classified as CV death. Analyses were performed on all randomized patients. 3053 patients in the vericiguat group and 3052 patients in the placebo group

[*]*p* value 0.22

[#]Analyses were performed on all patients who received at least one dose. 3049 patients in the vericiguat group and 3049 patients in the placebo group. Numbers and percentages refer to the number of participants with events

CONFIDENCE

The phase 2, double-blind, randomized, trial CONFIDENCE investigated whether combination therapy with finerenone and empagliflozin was superior to either agent alone in persons with CKD, albuminuria, and T2D [13]. Eligible participants had T2D, glycated hemoglobin < 11%, an eGFR of 30–90 mL/min/1.73 m^2, albuminuria defined by a uACR of 100–5000 mg/g, were receiving angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), and had avoided SGLT2 inhibitors and potassium binders for ≥ 8 weeks [13]. Participants were randomized 1:1:1, stratified by eGFR and uACR, to finerenone (10 or 20 mg) plus placebo, empagliflozin (10 mg) plus placebo, or combination therapy, administered daily for 180 days with a 30-day follow-up [13]. The primary endpoint, change in uACR at day 180, was analyzed using a mixed model for repeated measures; serum potassium and blood pressure were summarized descriptively, and changes in eGFR were assessed with a mixed model [13]. The LSM ratio of the change in uACR was 0.48 with combination therapy, compared with 0.68 with finerenone and 0.71 with empagliflozin alone (Table 5), corresponding to 29% and 32% greater reductions versus finerenone and empagliflozin, respectively (both $P < 0.001$) [13]. Secondary endpoints as well as adverse events are reported in Table 5. Within 30 days of initiation of the combination therapy, the frequency of eGFR declines > 30% was higher than with finerenone or empagliflozin monotherapy. Notably, eGFR subsequently plateaued after this early reduction and was largely reversible after treatment discontinuation. Acute kidney injury events were infrequent in the combination group (1.9%). Overall, combination therapy reduced uACR by 52%, reflecting the additive effects of finerenone and empagliflozin [13]. These can be explained by the underlying mechanisms of the two agents which are distinct yet complementary with the SGLT2 inhibitor lowering intraglomerular pressure by restoring tubuloglomerular feedback and finerenone blocking mineralocorticoid receptor–driven inflammation and fibrosis [46].

MIRO-CKD

Similar to the CONFIDENCE study, the MIRO-CKD trial investigated pharmacological agents relevant to the management of CKD. This randomised, double-blind, active-controlled phase 2b study demonstrated superiority of the combination therapy of the nsMRA balcinrenone and dapagliflozin over dapagliflozin alone in reducing uACR [48]. Patients with eGFR of 25 to < 60 mL/min/1.7 m^2, a uACR of > 100 to ≤ 5000 mg/g, and a serum potassium concentration 3.5 to 5.0 mmol/L received balcinrenone 15 mg plus dapagliflozin 10 mg (n = 108), balcinrenone 40 mg plus dapagliflozin 10 mg (n = 110), or dapagliflozin 10 mg plus placebo (n = 106) in addition to a renin–angiotensin system inhibitor [48]. After 12 weeks, the difference in uACR compared to the placebo group was significant, with – 22.8% (90% CI, – 33.3 to – 10.7; $p = 0.0038$) for balcinrenone 15 mg plus dapagliflozin 10 mg and – 32.8% (90% CI, – 42.0 to – 22.1; $p < 0.0001$) for balcinrenone 40 mg plus dapagliflozin 10 mg [48]. Adverse events were reported by 42% of patients on balcinrenone 15 mg plus dapagliflozin 10 mg, 45% on balcinrenone 40 mg plus dapagliflozin 10 mg, and 48% dapagliflozin 10 mg plus placebo [48]. The most frequently observed adverse events in the treatment groups with balcinrenone were hyperkalemia (max. 6%),

nasopharyngitis (max. 4%), and metabolic acidosis (max. 4%). In conclusion, in higher-risk patients with CKD, the combination of balcinrenone with dapagliflozin achieved a greater reduction in albuminuria than dapagliflozin monotherapy [48].

Aldosterone synthase inhibitors

ASIs reduce aldosterone production, a central mediator of hypertension and mineralocorticoid receptor activation that contributes to cardiovascular and renal dysfunction within the CKM syndrome [49].

BaxHTN

The phase 3, double-blind, randomized, placebo-controlled BaxHTN trial evaluated baxdrostat added to background antihypertensive therapy in patients with hard-to-control (uncontrolled or resistant) hypertension [17]. Hard-to-control hypertension was defined as a seated systolic blood pressure (SBP) of 140 to < 170 mmHg despite ≥ 4 weeks of maximally tolerated therapy with either two agents (uncontrolled hypertension) or ≥ 3 agents including a diuretic (resistant hypertension) [17]. Key inclusion criteria were age ≥ 18 years, hard-to-control hypertension, and prespecified requirements for eGFR, serum potassium, and morning cortisol levels [17]. Following a two-week, single-blind run-in phase with placebo alongside background antihypertensive therapy, adherent patients with a seated SBP ≥ 135 mmHg were randomized in a 1:1:1 ratio to once-daily 1 mg baxdrostat, 2 mg baxdrostat, or placebo, stratified by hypertension status (uncontrolled vs. resistant) and SBP (< 145 vs. ≥ 145 mmHg) [17]. The trial comprised four sequential parts: part 1 (weeks 1–12) and 3 (weeks 24–32) have been published, with part 1 establishing the primary efficacy endpoint and part 3 serving as a withdrawal phase for patients receiving 2 mg baxdrostat [17]. The primary endpoint, change in seated SBP at week 12, was analyzed using analysis of covariance, with baseline SBP as a covariate, and hierarchical testing [17]. LSM mean SBP reductions were – 14.5 mmHg with baxdrostat 1 mg, – 15.7 mmHg with baxdrostat 2 mg, and – 5.8 mmHg with placebo [17]. In the resistant-hypertension subgroup, the LSM estimated placebo-corrected SBP reductions were – 9.1 mmHg with 1 mg and – 9.8 mmHg with 2 mg baxdrostat (both $P < 0.001$; Table 6), supporting a role for aldosterone dysregulation in both uncontrolled and resistant hypertension [17]. Secondary endpoints and safety outcomes are summarized in Table 6. In patients with CKD and uncontrolled hypertension receiving background therapy with an ACEi or ARB, baxdrostat significantly reduced SBP at 26 weeks compared with placebo in the phase 2 FigHTN study [50]. The phase 3 Bax24 trial assessed the effect of 2 mg baxdrostat added to standard care on ambulatory 24-h mean SBP in patients with resistant hypertension following a 12-week placebo run-in period [51]. Preliminary results showed reductions in 24-h SBP, including during early morning hours, a time associated with increased risk of heart attack and stroke [52]. Overall, the blood pressure-lowering effects of baxdrostat in hard-to-control hypertension were comparable to those reported for other ASIs [53].

Soluble guanylate cyclase stimulators

sGC stimulators enhance nitric oxide(NO)-sGC-cyclic guanosine monophosphate (cGMP) signaling, a pathway commonly disrupted in cardiorenal disease, with downstream effects on vascular function and biological processes implicated in inflammation, fibrosis, and angiogenesis [54].

VICTOR

VICTOR was a phase 3, double-blind, placebo-controlled trial evaluating vericiguat in patients with HF with reduced ejection fraction (HFrEF) without recent HF worsening [18]. As a follow-up to VICTORIA [55], which supported approval of vericiguat for worsening HFrEF, VICTOR enrolled a clinically more stable population, excluding patients with prior heart failure worsening [18]. Eligible patients were ≥ 18 years old, had left ventricular ejection fraction ≤ 40%, New York Heart Association (NYHA) class II–IV symptoms despite optimally tolerated guideline-directed medical therapy, no hospitalization for heart failure (HFF) within six months, and no intravenous diuretics within three months [18]. Participants were randomized 1:1 to vericiguat or placebo, stratified by NYHA class, and received once-daily treatment titrated from 2.5 to 10 mg based on blood pressure and tolerability [18]. Time-to-first events were analyzed with stratified log-rank tests and stratified Cox proportional hazards models to estimate hazard ratios and 95% CI, with proportional hazards tested by the weighted Schoenfeld residuals test [18]. First and recurrent HHF were assessed using the Andersen–Gill Cox model with robust standard errors [18]. Formal hypothesis testing of secondary endpoints was predetermined to occur only if the primary endpoint reached statistical significance [18]. The primary endpoint, time to first cardiovascular death or HHF, occurred in 18.0% of patients receiving vericiguat and 19.1% receiving placebo (HR 0.93; 95% CI, 0.83 to 1.04; $p = 0.22$), with consistent effects across prespecified subgroups (Table 7) [18]. Cardiovascular death occurred in 9.6% of patients in the vericiguat group and 11.3% of patients in the placebo group (HR 0.83; 95% CI, 0.71 to 0.97) (Table 7); however, as the primary composite endpoint was not met, this should be interpreted with caution in line with the formal hypothesis testing strategy [18]. Further secondary endpoints and safety outcomes

are reported in Table 7 [18]. The failure to meet the primary endpoint likely reflects the enrollment of stable patients and a ceiling effect from high use of contemporary guideline-directed therapy: in the vericiguat group, 94.5% of patients received β-blockers, 77.2% MRAs, 69.8% loop diuretics, 59.4% SGLT2 inhibitors and 56.8% angiotensin receptor-neprilysin inhibitors (ARNIs) alongside other therapies [18]. In contrast, vericiguat reduced cardiovascular death or HHF in recently destabilized HFrEF patients in the VICTORIA trial [55] and in a prespecified pooled analysis of VICTOR/VICTORIA (n = 11,155) compared to placebo (HR 0.91; 95% CI, 0.85 to 0.98; $p = 0.0088$) [56]. As worsening HF is associated with heightened oxidative stress, inflammation and with attenuation of NO–sGC–cGMP signaling, sGC stimulation by vericiguat may be particularly advantageous in high-risk patients by directly targeting the underlying pathophysiological mechanism [57]. Accordingly, the available evidence supports positioning vericiguat within a tailored regimen for patients with worsening HFrEF at highest risk of cardiovascular death or HHF [56].

Key topics discussed during the 11th CVOT Summit

The evidence generated by recent cardiovascular outcome trials provides the scientific foundation for contemporary clinical decision-making. Translating these data into routine practice requires careful integration into guideline recommendations and health policy frameworks. The following updates focus on emerging evidence on pharmacological interventions and its implications for current CKM care strategies.

Advances in clinical practice guidelines

Translating evidence into real-world clinical practice

Clinical practice guidelines are developed from evolving estimates of benefit and harm derived from recent clinical trials. In T2D, the availability of multiple pharmacotherapies necessitates comparative effectiveness approaches to inform the development of such guidelines [58]. Conventional meta-analyses offer a static summary of different pharmacological approaches. In contrast, living network meta-analyses (NMA) allow dynamic integration of direct and indirect comparisons of multiple interventions through a common comparator, enabling juxtaposition of different treatment options even in the absence of direct head-to-head trials [58].

Although clinical practice guidelines are designed to support the translation of new evidence into routine care, their influence on clinician behavior remains limited in the absence of structured implementation strategies [59]. Implementation science identifies multilevel barriers to guideline uptake, including guideline complexity, inadequate reimbursement structures, constraints on time and other resources within care settings, gaps in clinician knowledge, and heterogeneity in patient preferences and values [59, 60]. Hypertension management exemplifies this guideline-to-practice gap: in high-income Western countries, only about 40% of individuals with hypertension achieve adequate blood pressure control [61], despite estimates from the European Society of Cardiology (ESC) suggesting that up to 95% of patients could reach target levels with dual or triple pharmacological therapy [62]. Clinician-related barriers may be mitigated through, e.g., targeted educational initiatives [63]. Patient-level factors, such as poor medication adherence, can be addressed through person-centered approaches that emphasize questioning, involvement, and shared decision-making [64], complemented by regular patient contact and educational interventions [65]. Meaningful shared decision-making requires that patients are provided with clear, understandable information on the benefits, risks, and long-term implications of available treatment options, enabling choices that align with individual values and life circumstances [66]. Patient organizations can further support these processes by strengthening health literacy, facilitating peer education, and contributing to the co-development of implementation strategies that reflect patient priorities and real-world constraints [67].

Guideline update on the management of obesity and dyslipidemia

In a guideline from late 2025, the World Health Organization (WHO) recommended long-term use of GLP-1–based therapies for adult obesity as an adjunct to lifestyle interventions, emphasizing the need for health-system preparedness, equitable and affordable access, and person-centered care [68].

The ESC and European Atherosclerosis Society (EAS) updated their dyslipidemia guidelines in August 2025 [69]. The revision introduces SCORE2 and SCORE2-OP as the primary instruments for cardiovascular risk estimation and expands individual risk profiling by incorporating modifiers such as ethnicity, comorbidities, family history, and biomarkers, including high-sensitivity C-reactive protein and lipoprotein(a) [Lp(a)]. Furthermore, risk categories are refined, and new recommendations are introduced for rapid lipid lowering in the context of acute coronary syndrome, emphasizing immediate initiation of high-intensity statin therapy, frequently in combination with ezetimibe. Particular emphasis is placed on elevated Lp(a) and on specific high-risk subgroups (e.g., people living with Human Immunodeficiency Virus (HIV) for > 40 years and high-risk patients receiving anthracyclines), with statin therapy recommended irrespective of baseline Low-Density Lipoprotein (LDL)-cholesterol levels. Collectively, these updates broaden the therapeutic framework and underscore the clinical importance of early initiation and sustained

intensity of lipid-lowering management [70]. However, translating these recommendations into population-level impact also depends on the surrounding healthcare system and policy environment.

European Union (EU) policies on transforming cardiometabolic health

CVD remains the leading cause of death in the EU, accounting for 1.7 million deaths in 2021 and an estimated annual economic burden of about €282 billion [71]. Despite reliable data on cardiovascular management and prevention, a substantial evidence-to-practice gap persists, reflected in late diagnosis, uneven implementation of clinical guidelines, and fragmented healthcare systems [59, 72, 73]. To address this, the EU's Council Conclusions on cardiovascular health and the Commission's forthcoming Cardiovascular Health Plan offer a political framework for EU Member States [74]. Translating this framework into personalized, patient-centered care will require targeted national initiatives. Priority actions include improving health literacy among the population, strengthening school nutrition programs, and scaling validated digital tools for prevention and self-management. Because metabolic disorders, CKD, and CVD share major risk factors and frequently coexist in the same patients, there is increasing advocacy for cardiovascular health policies that explicitly integrate metabolic and kidney health, addressing coordinated prevention, earlier detection, and synchronized care across all three domains [75]. A coordinated EU strategy that explicitly embeds kidney and metabolic health within CVD policy can help close the evidence-to-practice gap, reduce avoidable deaths, and alleviate the growing economic burden. Systematic involvement of patients and patient organizations in the design, implementation, and evaluation of national strategies can support the translation of policy initiatives into measurable benefits at the individual level [67].

Innovations shaping the future of cardiovascular, renal, and metabolic treatment

Modern pharmacological therapies increasingly aim to target multiple components of the CKM syndrome. For instance, incretin mimetics such as GLP-1 RAs not only lower body weight and HbA1c [76], but also reduce cardiovascular and kidney events as well as all-cause mortality, while maintaining a favorable safety profile regarding hypoglycemia, retinopathy, pancreatitis, and overall cancer risk [77]. Building on these benefits, dual (tirzepatide) and triple agonists (retatrutide) are developed to further enhance the effects of GLP-1 monoagonists across the CKM spectrum [78] These multi-receptor agonists target several receptors, including GLP-1, GIP, glucagon, amylin, oxyntomodulin, and peptide YY receptors [79]. While weight loss and HbA1c reduction are largely attributable to the impact of incretin mimetics on energy and glucose metabolism, their cardiorenal benefits may additionally reflect improvements in insulin resistance, dyslipidemia, endothelial function, inflammation, and inhibition of the renal renin–angiotensin–aldosterone system (RAAS) [80]. The latter pathway is of particular relevance, as RAAS plays a central role in the pathogenesis of hypertension and cardiorenal disease. Consequently, several established drug classes are already part of the current CVD guidelines, most notably ACEi and ARBs [49, 81]. Despite their effectiveness, chronic RAAS inhibition can lead to compensatory increases in aldosterone secretion, a phenomenon known as "aldosterone breakthrough" [49]. Steroidal MRAs are traditionally used to counteract the effects of aldosterone, yet newer nonsteroidal MRAs, such as finerenone, exhibit greater receptor selectivity and therefore a more favorable side-effect profile [49, 82]. In parallel, ASIs have emerged as an alternative strategy, particularly where selective aldosterone suppression is desired without interfering with other mineralocorticoid receptor ligands such as cortisol [49]. ASIs' development is challenging as aldosterone synthase shares 95% amino-acid sequence homology with cortisol synthase [49]; nonetheless, several candidates, including lorundrostat [83], baxdrostat [17], and vicadrostat [84], are in clinical development with promising early results. For instance, in participants with uncontrolled and treatment-resistant hypertension on two to five antihypertensive medications, lorundrostat reduced 4-h average blood pressure compared to placebo after 12 weeks in a phase 2 trial [83]. Building on successful phase 2 results, baxdrostat is under investigation in a phase 3 trial in combination with dapagliflozin in patients with CKD and hypertension (BaxDuo-Pacific: NCT06742723), whereas vicadrostat is being studied in a phase 3 trial in combination with empagliflozin in patients with CKD (EASi-KIDNEY: NCT06531824). Additional comparative studies of ASIs and nsMRAs are warranted to clarify the clinical settings in which each therapeutic strategy is most appropriate.

Beyond their potential use in hypertension and cardiorenal disease, ASIs may also have applications in CKD management. CKD remains substantially underdiagnosed, even among high-risk groups, e.g., an estimated 84.3% of stage 3 CKD cases in Germany are undetected [85]. Although therapeutic options have historically been limited, a growing number of novel agents are now in development. For instance, the aforementioned vicadrostat reduced uACR in patients with CKD on renin-angiotensin system inhibition therapy after 14 weeks in a phase 2 trial [86]. As GLP-1 RAs are now one of the four foundational pillars in the standard care of T2D and CKD [87], ongoing studies are further evaluating the efficacy of

incretin-based therapy in CKD independent of diabetes [88].

In parallel with these advances in metabolic, cardiovascular, and renal therapies, additional contributors to the CKM syndrome warrant targeted intervention. As metabolic and cardiovascular factors are closely linked to atherosclerosis [89], effective management of the CKM syndrome also requires targeted treatment of atherosclerotic disease. Therapeutic innovations in this area increasingly focus on vascular inflammation, with novel anti-inflammatory agents being developed to reduce atherosclerotic burden independently of lipid-lowering. These agents target key inflammatory pathways using, for example, anti-interleukin (IL)-1β [90], anti-IL-6 (e.g., ziltivekimab [91]), or anti-IL-1α therapies [92]. In addition, the impact of inflammasome-modulating approaches (such as colchicine [93] and emerging NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inhibitors [94]), and incretin-based therapies with documented anti-inflammatory effects (e.g., reductions in C-reactive protein and IL-6) [95], is being investigated. Although the central role of inflammation in atherosclerosis is well established, a major challenge is to attenuate inflammatory activity without compromising host defense mechanisms [96]. Determining the optimal strategies for incorporating such agents into multimodal, CKM-focused treatment regimens without increasing infection risk will be a key priority for future research.

Collectively, these developments underscore a shift from single–risk factor control towards integrated, mechanism-based therapies. Although mechanistically diverse, multi-receptor incretin agonists, nsMRAs, ASIs, sGC stimulators, and anti-inflammatory approaches address shared pathophysiological features of the CKM syndrome, including metabolic dysregulation, vascular and hemodynamic impairment, as well as inflammation. Furthermore, these advances have introduced effective therapies for CKM syndrome–related conditions that historically lacked robust treatment options.

A new therapeutic era in HFpEF

HF is currently classified according to left ventricular ejection fraction (LVEF) into HFrEF (LVEF ≤ 40%), mildly reduced ejection fraction (HFmrEF, LVEF 41–49%), and HF with preserved ejection fraction (HFpEF, LVEF ≥ 50%) [97]. While several traditional pharmacological therapies are well established for the treatment of HFrEF, therapeutic options for HFmrEF and HFpEF have historically been limited. Recent evidence has reshaped this landscape, as SGLT2 inhibitors have emerged as a foundational therapy across the entire HF spectrum [98]. Notably, these agents can also be safely initiated during hospitalization for acute HF and provide measurable clinical benefit within the first 90 days following treatment initiation [99]. Their therapeutic effects are believed to arise from a combination of hemodynamic [100], metabolic [101], and hematologic mechanisms [102].

Beyond SGLT2 inhibition, several additional pharmacological strategies are being explored for the management of HFpEF. In 2024, the FINEARTS-HF trial demonstrated that the nsMRA finerenone reduced total HF events and cardiovascular death in patients with HFpEF, expanding the range of pharmacological therapies that improve outcomes across the HF spectrum [103, 104]. Further research is ongoing with the steroidal MRA spironolactone in HFpEF patients [105], and the combination therapy of balcinrenone and dapagliflozin in patients with HF and CKD (BALANCED-HF trial: NCT06307652). In parallel, GLP-1 RA-based therapies are being tested in HFpEF management, with semaglutide and tirzepatide demonstrating reductions in HF-related symptoms and improvements in health status among patients with HFpEF and obesity [106, 107]. Together, these data suggest that HFpEF management is transitioning from a historically treatment-poor condition to one with multiple evidence-based pharmacological options. Furthermore, the described therapeutic advances once again highlight the interconnected nature of CKM syndrome-diseases, e.g., as therapies developed for obesity have demonstrated benefit in HFpEF. This underscores the rationale for a holistic perspective on the CKM syndrome and aligns with evolving conceptualizations of its individual components.

Obesity as a multisystem disease with organ-specific pathophysiology

Contemporary guidance defines obesity as an adiposity-based chronic disease (ABCD) staged by complications rather than BMI alone. The 2025 American Association of Clinical Endocrinology (AACE) algorithm and the updated European Association for the Study of Obesity (EASO) framework characterize obesity as a chronic, progressive, and relapsing condition, recommending staging based on medical, mental, and functional impairment rather than body weight per se [108, 109]. This paradigm aligns obesity management with other chronic diseases and shifts therapeutic goals from weight loss alone toward preservation of organ function and functional outcomes [108]. Within this framework, pharmacological agents are increasingly selected for their pleiotropic benefits across obesity-related cardiometabolic comorbidities in addition to inducing weight loss [108]. Yet, the therapeutic landscape is anchored by established incretin-based therapies such as semaglutide and tirzepatide, with novel agents including the amylin receptor agonist eloralintide and the triple GIP/GLP-1/glucagon receptor agonist retatrutide, both of which

demonstrated clinically meaningful weight loss in phase 2 trials [78, 110].

The rapid expansion of obesity pharmacotherapy has raised concerns regarding fat-free mass loss; however, available evidence indicates that lean mass reductions with incretin-based therapies generally fall within ranges observed with other weight-loss strategies and are not associated with impaired muscle strength or function. Preventive strategies to mitigate lean mass loss include adequate protein intake and regular exercise [111, 112]. Notably, agents that preferentially reduce fat mass while preserving or increasing lean mass are in development. Bimagrumab, for instance, reduced fat mass, increased lean mass, and improved metabolic parameters in individuals with obesity and T2D in a phase 2 trial [113].

Obesity is increasingly recognized as a multisystem disorder in which adipose tissue functions as a dysregulated endocrine–immune organ, promoting insulin resistance, chronic inflammation, and ectopic fat deposition in organs such as the liver, pancreas, muscle, and heart [114]. Ectopic fat accumulation contributes to cardiometabolic disease, including metabolic dysfunction–associated steatotic liver disease (MASLD) and its progressive form, metabolic dysfunction–associated steatohepatitis (MASH), which affects approximately 34% of individuals with obesity and 37% of people with T2D [115–118]. Current guidelines recommend non-invasive diagnostic and monitoring approaches, including FIB-4, transient elastography, the enhanced liver fibrosis (ELF™) test, and magnetic resonance elastography, reserving liver biopsy for selected cases [119]. Several pharmacotherapies are emerging in this field, including resmetirom, semaglutide, survodutide, tirzepatide and pemvidutide. While long-term outcome data for liver-related and cardiometabolic complications are pending, pharmaceutical options for MASH and liver fibrosis have received FDA approval, including semaglutide [120] and remetirom (also approved in the EU), a liver-directed thyroid hormone receptor-β agonist [121, 122]. Further promising results are available from phase 2 trials: the dual glucagon/GLP-1 RA survodutide reduced liver fat and improved MASH and fibrosis [123], while tirzepatide was superior to placebo for MASH resolution and fibrosis improvement in the SYNERGY-NASH trial [124]. Lastly, the dual GLP-1/glucagon receptor agonist pemvidutide improved MASH resolution without fibrosis benefit at 24 weeks [125].

These developments reflect a shift toward organ-protective, multisystem approaches in obesity management enabled by rapidly advancing pharmacotherapies. This move toward mechanism-targeted intervention extends beyond obesity, with emerging disease-modifying strategies now reshaping the field of T1D.

Disease-modifying strategies in T1D

T1D results from immune-mediated destruction of pancreatic β-cells. A consensus staging system (stages 1–2) distinguishes presymptomatic stages defined by islet autoantibodies and dysglycemia from clinical T1D (stage 3), providing a framework for interventions that aim not only to delay disease progression but to approximate an earlier, β–cell–preserved stage [126]. Residual endogenous insulin secretion can be assessed by C-peptide levels, which are released in equimolar amounts with insulin from pro-insulin [127]. Beyond serving as a biomarker, C-peptide exerts physiological effects by itself, including enhancement of microvascular blood flow and anti-inflammatory actions on the vascular endothelium [128, 129]. Administration of C-peptide has been shown to improve renal hemodynamics and reduce albuminuria in T1D [130]. C-peptide preservation is widely used as a clinically meaningful endpoint in trials of β-cell–preserving therapies. For instance, Teplizumab, an anti-CD3 antibody and the first approved disease-modifying therapy in T1D, delayed the onset of stage 3 disease by about two years and preserved C-peptide in high-risk relatives with stage 2 T1D [131]. In new-onset stage 3 T1D, several agents, including golimumab (anti-Tumor Necrosis Factor [TNF]) [132], the Janus Kinase 1/2 (JAK1/2) inhibitor baricitinib [133], low-dose anti-thymocyte globulin [134], and the calcium-channel blocker verapamil [135], each reduced stimulated C-peptide decrease versus placebo. These findings support an emerging therapeutic strategy that combines glycemic management with β-cell–directed interventions.

As β-cell destruction begins years before clinical presentation, initiatives such as INNODIA and EDENT1FI are establishing longitudinal cohorts and autoantibody screening to detect early-stage T1D and halt T1D progression [136, 137]. In parallel, contemporary management of T1D is evolving to systematically address common comorbidities such as CKD, as exemplified by the FINE-ONE trial [41]. Together, these developments mark a shift from pure insulin replacement towards integrated β-cell and organ-protective strategies aimed at arresting and slowing the course of T1D. Within this shift toward earlier and more comprehensive care, metabolic monitoring has emerged as an enabling strategy.

Integrated metabolic monitoring for prevention, safety, and management

Effective glycemic control is central to diabetes management, given the well-established deleterious effects of chronic hyperglycemia on macrovascular outcomes. Adverse cardiometabolic processes appear to begin long before the clinical diagnosis of T2D, with observational data showing an approximately two-fold higher incidence of cardiovascular events up to three decades prior

to diagnosis compared with non-diabetic controls [138]. Conversely, lower mean glucose exposure has been associated with a dose-dependent reduction in coronary heart disease risk in people without T2D [139]. In this context, CGM, particularly when combined with structured education, has emerged as a key strategy to improve glycemic outcomes and may also support broader risk-factor modification, including weight loss and LDL-cholesterol reduction [140]. Reflecting this evidence, the 2026 American Diabetes Association (ADA) Standards of Care place stronger emphasis on initiating CGM directly at the onset of diabetes [141].

CGM-derived metrics, notably time in range (TIR, 70 to 180 mg/dL) and time in tight range (TITR, 70 to 140 mg/dL), are increasingly recognized as clinically meaningful treatment targets. Reduced TITR has been associated with higher all-cause and cardiovascular mortality even in apparently well-controlled T2D [142]. In addition, lower TIR has been linked to cognitive decline and impairment [143, 144] as well as adverse kidney outcomes [145], supporting a shift toward tighter glycemic regulation. Emerging computational approaches further extend CGM utility, as illustrated by artificial intelligence (AI)-based models that accurately predicted microvascular complications using reconstructed CGM data [146].

Despite these advances, suboptimal glucose control continues to predispose patients to hypoglycemia, hyperglycemia, and DKA [147]. Individuals with diabetes, especially T1D, remain at substantial risk for DKA even when using automated insulin delivery systems [148]. Although CGM can reduce DKA incidence by stabilizing glucose levels [147], its accuracy diminishes during rapid metabolic shifts, prompting interest in continuous ketone monitoring [149]. Early human studies demonstrate the feasibility of real-time interstitial ketone sensing [21, 150], suggesting that future integrated glucose–ketone monitoring systems could enable early detection of dysglycemia and provide timely warnings of impending DKA [150]. Furthermore, ketone monitoring can enable safer, sustained therapy by providing insight into patients' responses to pharmacological treatment and the trajectory of DKA. It can also enhance safety during perioperative fasting and intra-operative care, particularly in acute and non-acute surgical procedures commonly performed in people with diabetes such as bariatric surgery (particularly associated with DKA) or orthopedic surgery [151]. Overall, ketone monitoring could improve treatment of patients with diseases of the CKM syndrome by providing metabolic surveillance and increased safety during therapy and peri- and intra-operative periods.

Collectively, these data support the use of CGM for early detection of dysglycemia and prioritization of high TIR/TITR as central therapeutic goals and highlight the potential of emerging continuous ketone monitoring technologies. While monitoring technologies optimize individual care, coordinated initiatives, including integrated, multidisciplinary strategies, are necessary to ensure effective disease management.

Global cardiometabolic alliance

Cardio-metabolic-renal diseases, largely driven by insulin resistance, constitute an increasing global health burden [73, 152]. Importantly, insulin resistance extends beyond cardiometabolic disease and is also linked to conditions such as dyslipidemia, MASLD, and even neurodegenerative disorders [3, 152, 153]. Given the broad spectrum of diseases linked by this shared pathophysiology, effective disease management requires a re-evaluation of current care models, moving away from fragmented approaches toward integrated, multidisciplinary strategies. The Global Cardiometabolic Alliance is an international clinical and research initiative established to address these challenges by promoting a holistic approach to prevention, diagnosis, and care. Its activities focus on translational research of shared disease mechanisms, complemented by dissemination strategies such as guideline-based protocols and training programs aimed at improving risk detection and therapeutic implementation in routine clinical practice [73].

Hellmut Mehnert Award

The Hellmut Mehnert Award Lecture 2025, "The discovery of multi-receptor drugs: The end of obesity and type 2 diabetes? ", given by Matthias Tschöp, expanded perfectly on the overarching topic of this year's CVOT Summit of looking at new horizons in cardiovascular, kidney, and metabolic care. The development of synthetic incretin-based "master molecules" by the awardee and Richard DiMarchi that act simultaneously through multiple specific receptors in the brain and the periphery, and thereby enhance metabolic outcome beyond what is possible with targeting any single receptor type alone, has led to unprecedented efficacy in reducing excessive body weight comparable with bariatric metabolic surgery [154, 155]. While GIP/GLP-1 co-agonists such as tirzepatide are already approved and supported by robust clinical evidence for the treatment of obesity and diabetes, triple agonists underway that activate the signaling pathways of the hormones GIP, GLP-1 and glucagon are expected to provide a new gold standard in reverting overt T2D to normoglycemia and thus preventing cardiovascular and other complications including cancer—making gut hormone polyagonists game changers for the treatment of obesity and T2D [154–156].

Conclusions

The 11th CVOT Summit: Congress on Cardiovascular, Kidney, and Metabolic Outcomes presented recent evidence that shapes cardiovascular, renal, and metabolic medicine. The central theme was the imperative to view the CKM syndrome as a multisystem disorder, potentially integrating hepatic and neurodegenerative dimensions as well. This system-level perspective is crucial not only for optimizing clinical management and guideline development, but also for shaping health policies, including European initiatives. A notable strength of this year's Summit was the engagement of both researchers and policy representatives, underscoring that meaningful translation of scientific evidence into patient care depends on coordinated efforts across sectors. Subsequently, the effective implementation of policies and guidelines requires mitigating barriers at the level of patients, clinicians, and health systems, such as improving patient-centered care and ensuring evidence-based education for healthcare professionals. Simultaneously, an expanding range of pharmacotherapies is enabling more individualized risk reduction with several options to target various aspects of multisystemic disorders. In conclusion, lasting improvements in population health will require continued scientific advances alongside robust policies and guidelines, as well as growing awareness across clinical disciplines. The latest advances will be discussed once more at the 12th Cardiovascular Outcome Trial Summit, to be held on 19–20 November 2026 (http://www.cvot.org).

Abbreviations

AACE	American Association of Clinical Endocrinology
ABCD	Adiposity-based chronic disease
ACEi	Angiotensin-converting-enzyme inhibitor
ADA	American Diabetes Association
AE	Adverse Events
AHA	American Heart Association
AI	Artificial intelligence
ARB	Angiotensin receptor blocker
ASCVD	Atherosclerotic cardiovascular disease
ASIs	Aldosterone synthase inhibitors
BMI	Body-mass index
CGM	Continuous glucose monitoring
cGMP	Cyclic guanosine monophosphate
CI	Confidence interval
CKD	Chronic kidney disease
CKM	Cardiovascular–kidney–metabolic
CV	Cardiovascular
CVD	Cardiovascular disease
CVOTs	Cardiovascular outcome trials
DBP	Diastolic blood pressure
DCVD	Diabetes and Cardiovascular Disease Study Group
DDG	German Diabetes Society
DKA	Ketoacidosis
EAS	European Atherosclerosis Society
EASL	European Association for the Study of the Liver
EASO	European Association for the Study of Obesity
eGFR	Estimated glomerular filtration rate
ELF	Enhanced liver fibrosis
EMA	European Medicines Agency
ERA	European Renal Association
ESC	European Society of Cardiology
EU	European Union
FDA	Food and Drug Administration
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1 RAs	Glucagon-like peptide-1 receptor agonists
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HF	Heart failure
HFF	Hospitalization for heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HFmrEF	Heart failure with mildly reduced ejection fraction
HIV	Human immunodeficiency virus
HR	Hazard ratio
IL	Interleukine
JAK1/2	Janus kinase 1/2
LDL	Low-density lipoprotein
Lp(a)	Lipoprotein(a)
LSM	Least-squares mean
LSMR	Least-squares mean ratio
MACE	Major Adverse Cardiovascular Event
MASH	Metabolic dysfunction–associated steatohepatitis
MASLD	Metabolic dysfunction–associated steatotic liver disease
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
NMA	Network meta-analyses
mo	Months
no.	Number
nsMRAs	Nonsteroidal mineralocorticoid receptor antagonists
NYHA	New York Heart Association
PCDE	Primary Care Diabetes Europe
pp	Percentage points
RAAS	Renin–angiotensin–aldosterone system
RR	Relative Risk
SBP	Systolic blood pressure
sGC	Soluble guanylate cyclase
SGLT2	Sodium–glucose transporter 2
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TIR	Time in range
TITR	Time in tight range
TNF	Tumor necrosis factor
uACR	Urinary albumin-to-creatinine ratio
WHO	World Health Organization
wk	Week

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