New Horizons in Type 2 Diabetes Management and Associated Cardiorenal Risk Reduction:

A Pharmacotherapeutic Update

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Introduction

- Comprehensive diabetes assessment and management are essential to reduce the risks of complications related to cardiovascular, renal, hepatic, vision, and foot health. Prolonged duration within the hyperglycemic range or elevated blood glucose can increase the risks for heart diseases.
- Atherosclerotic cardiovascular disease (ASCVD) is one of the leading causes of morbidity and mortality for those living with diabetes. Those living with diabetes are also more prone to develop heart failure.
- Kidney disease often does not exhibit symptoms at earlier stages and is considered the 9th leading cause of death in the United States.[1] According to the CDC, about 1 in 3 adults with diabetes are estimated to develop chronic kidney disease.[1]
- According to the American Diabetes Association (ADA)[2] and American Association of Clinical Endocrinologists (AACE)[3] guidelines, sodium cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RA) are becoming the new approaches not only for diabetes management but also for reducing and slowing the progression of cardiorenal risks.
- New data have emerged around the safety and effectiveness of weekly insulin vs. daily insulin [5-11] with means to reduce injection and daily medication burden. High incidences of hypoglycemia may occur with the use of insulin, sulfonylureas and/or meglitinides. Traditionally used as syringe and vials, glucagon is now available subcutaneously via pre-filled syringes and nasally.

Weekly Basal Insulin Safety & Efficacy

Key Features of Insulin Icodec[4]

- Stability and prevention of enzymatic degradation: 3 amino acid substitutions
- Albumin binding: C20 fatty acid
- Half-life of 196 hours: continuous and gradual release from albumin-bound depot
- Steady state: expected around 3 to 4 weekly doses

Table 1. Summary of insulin icodec vs. standard insulin treatment (ONWARDS Trials).[5-11] As of June 2022, ONWARDS 1 and 6 trials achieved non-inferiority at Week 52 compared to insulin glargine and insulin degludec, respectively.[27] As of July 2022, ONWARDS 3 and 4 trials achieved non-inferiority in HbA1c reduction compared to insulin degludec and insulin glargine, respectively, at Week 26.[28]

Study	N	Study Population & Study duration	Base-line A1c	Intervention (weekly) vs. standard (daily)	Estimated mean time-in-range statistics	Severe or clinically significant hypoglycemia (events per patient-years)	Primary Outcomes	
							HbA1c reduction intervention vs. standard	Estimated treatment difference
ONWARDS -1[6]	984	Insulin-naïve w/ T2DM[†]; 78 weeks	8.5%	Insulin icodec vs. insulin glargine U-100, with non-insulin treatment		0.3 vs. 0.16	-1.55% vs. -1.35%	-0.19%
ONWARDS -2[7]	526	T2DM[†] switching from once-daily insulin; 26 weeks	8.3%	Insulin icodec vs. insulin degludec	At weeks 15 &16: Icodec LD* (n=54): 72.9% Icodec NLD** (n=50): 66.0% IGlar U-100 (n=50): 65% LD vs. Iglar: 7.9% [95% CI, 1.8-13.9]	0.73 vs. 0.27	-0.93% vs. -0.71%	-0.22%
ONWARDS -3[8]	588	Insulin-naive w/ T2DM[†]; 26 weeks	8.5%	Insulin icodec vs. insulin degludec		Rate higher in icodec, but no statistical significance	-1.57% vs. -1.36%	-1.43%
ONWARDS -4[9]	582	T2DM[†] on basal plus bolus; 26 weeks	8.3%	Insulin icodec vs. insulin degludec; combined with mealtime insulin		No statistical significance	-1.16% vs. -1.18%	-0.02%
ONWARDS -5[10]	1,085	Insulin-naive w/ T2DM[†]; 52 weeks	n/a	Insulin icodec vs. basal insulin		pending		
ONWARDS -6[11]	83	T1DM[ᶜ]; 52 weeks with 26-week extension	7.6%	Insulin icodec vs. insulin degludec; combined with 3 mealtime doses		19.93 vs. 10.37	-0.47% vs. -0.51%	0.05%

*LD = loading dose | **NLD = non-loading dose | [†] type 2 diabetes mellitus | [ᶜ] type 1 diabetes mellitus

Guidelines Updated to Reflect CVOT Trial Outcomes

Figure 1. AACE 2020 Guideline.[3]

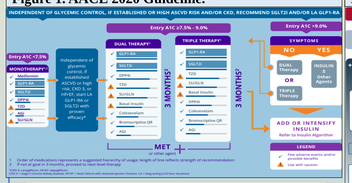
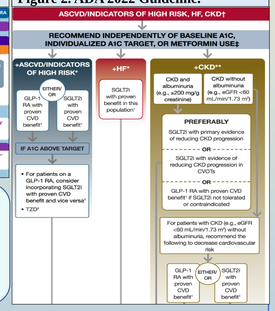


Figure 2. ADA 2022 Guideline.[2]



Both the ADA and AACE guidelines recommend the use of GLP-1 RAs and/or SGLT2-inhibitors independent of baseline A1c for those who have established or high cardiovascular and renal risks.

Hypoglycemia Management

Several systematic reviews and cohort studies revealed that severe hypoglycemia is associated with increased cardiovascular risks and mortality in patients with diabetes.[12,13]

- Glucagon is the first-line therapy for severe hypoglycemia associated with severe cognitive impairment, unresponsiveness, and/or unable to swallow.
- The ADA and AACE guidelines recommend glucagon for all individuals who may be at an increased risk for level 2 (glucose <54mg/dL) or level 3 hypoglycemia (altered mental status, physical functioning changes).[2, 3]

Table 2. Summary of available glucagon products for severe hypoglycemia management.

Types of Glucagon	Baqsimi[14,15] (nasal powder)	Glucagon Emergency Kits[16]	Gvoke HypoPen[17]	Zegalogue[18, 19, 20] (dasiglucagon)
Dose	3mg per dose/fixed	1mg	0.5mg/1 ml (2-11 years old); 1mg/0.2ml (≥12 years or ≥100 lbs)	0.6mg/0.6mL
Reconstitution	No	Yes	No	No
Administration Site	Nasal	Subcutaneous injection to thigh, buttock, upper arm	Subcutaneous injection (outer thigh, outer upper arm, lower abdomen)	Subcutaneous injection (outer thigh, outer upper arm, lower abdomen, buttocks)
Age	≥4 years	All ages	≥2 years	≥6 years
Age (years): mean time to treatment success[a] or time to plasma glucose recovery (minutes)	4 to <8: 10.8 8 to <12: 11.3 12 to <17: 14.2 >18: 11.6	30	13.8	Median time Adults A: 10 vs. 40 (p<0.001) Adults B: 10 vs. 35 Pediatrics: 10 vs. 30

[a] Treatment success: plasma glucose increase of ≥20mg/dL or increase to ≥70mg/dL from time of glucagon administration within 30 minutes, without rescue glucose.

Newest Pre-Filled Glucagon Auto-Injector

Dasiglucagon, a glucagon receptor agonist, received FDA approval in March 2021 for the treatment of severe hypoglycemia in both pediatric and adults with diabetes.

Mechanism: Reverses insulin-induced hypoglycemia within 10 minutes through activation of glucagon receptors in the liver.

Safety: Commonly reported adverse reactions include nausea, vomiting, and headache.

- Avoid use if patients have the following medical conditions: adrenal insufficiency, insulinoma, pheochromocytoma, chronic hypoglycemia and/or prolonged fasting/starvation.

Efficacy: Mean plasma glucose (PG) increased from baseline at 10, 15, 20, and 30 mins post-dasiglucagon administration (p<0.001).[19, 20] After 30 mins, mean PG increased by 98.2 (dasiglucagon) vs. 17.3mg/dL (placebo) from baseline in pediatrics.[19] In adults, mean PG increased by 90.9 (dasiglucagon) vs. 19.1mg/dL (placebo) from baseline.[20]

Cardiovascular Risk Reduction Agents

Table 3. Clinical trial data on cardiovascular effects.

Study	N	Mean Baseline HbA1c	CAD or CVD at Baseline*	Intervention Arm	Mean HbA1c Change at Follow-Up	MACE (events per 100 person-years)		Primary or Secondary Composite Outcome		
						Intervention	Placebo	Hazard Ratio	95% CI	P-value
AMPLITUDE-O[21]	4,076	8.9% ± 1.5	89.6%	4mg or 6mg efpeglenatide vs. placebo (1:1:1)	-1.24% (95% CI, 1.17 to 1.32)	3.9^	5.3^	0.73^	0.58 to 0.92	0.007 (superiority); <0.001 (non-inferiority)
SURPASS-4[ᴳ, 22, 23]	2,002	8.52% ± 0.88	87%	tirzepatide 5, 10, or 15mg vs. glargine (1:1:1:3)	-2.2% (5mg; p=0.053)[#] -2.43% (10mg; p=0.053)[#] -2.58% (15mg; p=0.053)[#] **vs.** -1.4% (p=0.03)[#]	2.97[ᵉ]	3.99[ᵉ]	0.74[ᵉ]	0.51 to 1.08[ᵉ]	>0.05
EMPEROR-Preserved[9, 24]	5,988	7.3% ± 1.5[ᵃ]	Stratified below[ᵇ]	empagliflozin 10mg daily vs. placebo (1:1)	-0.16% ± 0.02 **vs.** 0.03% ± 0.02	6.9[ᶜ]	8.7[ᶜ]	0.79[ᶜ]	0.69 to 0.90	<0.001
FIDELIO-DKD[9, 25]	5,674	7.7% ± 1.3	45.9%	finerenone 10 or 20mg vs. placebo (1:1)	n/a	5.11[ᵉ]	5.92[ᵉ]	0.86[ᵉ]	0.75 to 0.99	0.034
FIGARO-DKD[23, 26]	7,437	7.7% ± 1.4	45.3%	finerenone 10 or 20mg vs. placebo (1:1)	-0.25% vs. -0.11%	3.87[ʰ]	4.45[ʰ]	0.87[ʰ]	0.76 to 0.98	0.026

AMPLITUDE-O Trial[21]
[ᵛ] Median time to follow-up was 1.81 years. 21.8% participants have cardiovascular disease (CVD) and low eGFR at baseline.
^ Primary composite outcome was first major adverse CV event [MACE] (nonfatal stroke, nonfatal myocardial infarction (MI), death due to CV or undetermined causes), and secondary composite outcome was MACE, coronary revascularization, or hospitalization for unstable angina.

SURPASS-4 Trial[ᴳ, 22, 23] met noninferiority and superiority for improved glycemic management compared to daily glargine.
[ᵃ] Median time to follow-up was 85 weeks, with a 52-week treatment period.
[ᵉ] Adjudicated MACE-4 composite outcome included MI, stroke, hospitalization for unstable angina, and cardiovascular death
- Tirzepatide initiation dose was at 2.5mg once weekly, increased by 2.5mg every 4 weeks until randomly assigned dose reached. Study population included those at increased risk of CV events, >50 years old with history of CKD (eGFR <60 ml/min/1.73m^2), or NYHF Class II/III heart failure.
- Other key findings: reduction in body weight and HbA1c with lower incidence of hypoglycemia [glucose of <54mg/dL in 6-9% (tirzepatide) vs. 19% (glargine)]. Commonly reported adverse events were similar to previous trials and expected in the GLP-1 RA class, e.g., nausea, vomiting, diarrhea, and reduced appetite.

EMPEROR-Preserved[24]
[ᶜ] Median time to follow-up was 26.2 months.
[ᵃ] Participants with type 2 diabetes
[ᵇ] History of atrial fibrillation/flutter (57%); coronary artery disease (46%); myocardial infarction (31%); prior heart failure (HF) hospitalization within 12 months before first visit (26%); malignancy (23%); stroke (10%)
Baseline mean left ventricular ejection fraction (both empagliflozin and placebo): 54.3±8.8%
[ᶜ] Primary composite outcome was CV death or HF hospitalization regardless of type 2 diabetes.

FIDELIO-DKD[25]
[ᵠ] Median time to follow-up was 2.6 years.
[ᵉ] Secondary composite outcome was time to first occurrence of CV death, nonfatal MI, nonfatal stroke, or hospitalization for HF.

FIGARO-DKD[26]
[ᵻ] Median time to follow-up was 3.4 years.
[ʰ] Primary composite outcome was time to first occurrence of CV death, non-fatal MI, non-fatal stroke, or hospitalization for HF.

Key Takeaways: CV Effects & More

- GLP-1 RAs have been shown to reduce MACEs in adults with type 2 diabetes.
- The exendin-based GLP-1 receptor agonist, efpeglenatide – a once-weekly subcutaneous injectable – has also been shown to reduce glucose levels with minimal hypoglycemia and CV event risks in people with type 2 diabetes regardless of renal disease status.
- A dual GLP-1 RA and glucose-dependent insulinotropic polypeptide (GIP), tirzepatide, has been shown to reduce CV risk, sustain weight loss, and delay eGFR decline when given in addition to SGLT-2 inhibitors and/or renin-angiotensin-aldosterone system inhibition agents (FDA approved in May 2022 for treatment of type 2 diabetes).

References

Available Upon Request.

Renal Risk Reduction Agents

Table 4. Clinical trial data on renal effects.

Study	N	eGFR <60 (ml/min/1.73^2) at baseline	Albuminuria[†] at baseline	SGLT2-inhibitor at baseline	Intervention Arm(s) vs. placebo (1:1:1)	Composite renal event (events per 100 person-years)		Primary or Secondary Composite Outcome		
						Intervention	Placebo	Hazard Ratio	95% CI	P-value
AMPLITUDE-O[21]	4,076	31.6%	48.5%	15.2%	4mg or 6mg efpeglenatide	7.7[ᵍ]	11.6[ᵍ]	0.68[ᵍ]	0.57 to 0.79	<0.001
SURPASS-4[ᴳ, 22, 23]	2,002	17%	36%	26%	tirzepatide 5, 10, or 15mg vs. glargine	64	105	0.59	0.43 to 0.8	<0.05
EMPEROR-Preserved[24]	5,988	50.2	n/a	n/a	empagliflozin 10mg daily vs. placebo	2.1[ᵈ]	2.2[ᵈ]	0.95[ᵈ]	0.73 to 1.24	>0.05
FIDELIO-DKD[25]	5,674	88.4%	99.6%	4.6%	finerenone 10 or 20mg vs. placebo	7.59[ᶠ]	9.08[ᶠ]	0.82[ᶠ]	0.73 to 0.93	0.0014
FIGARO-DKD[23, 26]	7,437	38.3%	97.1%	8.4%	finerenone 10 or 20mg vs. placebo	3.04[ᵍ]	3.49[ᵍ]	0.88[ᵍ]	0.76 to 1.01	>0.05

AMPLITUDE-O Trial[21]
[ᵍ] Secondary composite outcome: macroalbuminuria [urinary-albumin-to-creatinine-ratio (UACR) of >300 mg/g], UACR increase ≥30% from baseline, sustained eGFR decline of ≥40% for ≥30 days, sustained eGFR <15ml/min/1.73^2 for ≥30 days, renal replacement therapy for ≥90 days.
† Albuminuria: UACR at least 30mg/g or 3.39 mg/mmol

SURPASS-4 Trial[ᴳ, 22, 23]
New-onset macroalbuminuria (all studied population) – HR 0.41 [95% CI, 0.26-0.66]
Composite renal outcome (new onset of macroalbuminuria, eGFR decline ≥40% from baseline, renal death, ESRD progression) in participants non-SGLT2-inhibitors – HR 0.57 [95% CI, 0.40-0.81]

EMPEROR-Preserved[24]
Rate of eGFR decline empagliflozin vs. placebo: -1.25 vs. -2.62 ml/min/1.73^2 (p<0.001)
[ᵈ] Composite renal outcome included time to first occurrence of chronic dialysis, renal transplantation, sustained reduction of ≥40% in eGFR or sustained eGFR <15 (if baseline ≥30) or sustained eGFR <10 (if baseline eGFR <30).

FIDELIO-DKD[25]
[ᶠ] Primary composite outcome included time to first onset of renal failure (e.g., chronic dialysis for >90 days, kidney transplant or eGFR <15 confirmed after ≥4 weeks), death from renal causes, or sustained reduction of ≥40% in eGFR from baseline.

FIGARO-DKD[26]
[ᵍ] Secondary composite outcome was end-stage kidney disease or sustained eGFR decrease of <15ml/min/1.73^2, sustained eGFR decrease of ≥40% from baseline or death from renal causes.

Key Takeaways: Renal Effects & More

- SGLT-2 inhibitors – dapagliflozin, canagliflozin, empagliflozin – are indicated to reduce risks of CV death, hospitalization for heart failure in adults with type 2 diabetes, or nephropathy with albuminuria, depending on the agent used. Empagliflozin is the only agent in its class indicated for treatment of heart failure regardless of left ventricular ejection fraction (FDA approved in February 2022).
- New trials showed reduction in HF hospitalization and CKD progression with the use of finerenone, a non-steroidal, selective mineralocorticoid receptor antagonist (FDA approved in July 2021 to treat CKD in people with type 2 diabetes).
- With emerging data, the guidelines have shifted its recommendation to initiate a GLP-1 RA and/or SGLT2-inhibitor for individuals with established or high ASCVD risk or renal progression regardless of glycemic levels.
- Once-weekly insulin icodec offers a potential option for patients who have injection burden and fatigue. Evidence is needed to show its safety in specific populations, such as those with existing renal impairment, high risk for hypoglycemia, undergoing elective or major surgical procedures.
- Emergency glucagon has been around to rescue those who experience severe hypoglycemic episodes and are unable to swallow, unresponsive/unconscious or convulsing. With new data, dasiglucagon provides another option to correct severe hypoglycemic state. This product is only indicated for individuals 6 years and older. The traditional glucagon that requires reconstitution is approved for all ages, whereas the nasal and pre-filled formulations are approved for specific age groups.