Clinical Impact of Shortages: Role of GLP-1 RAs in the Management of Diabetes

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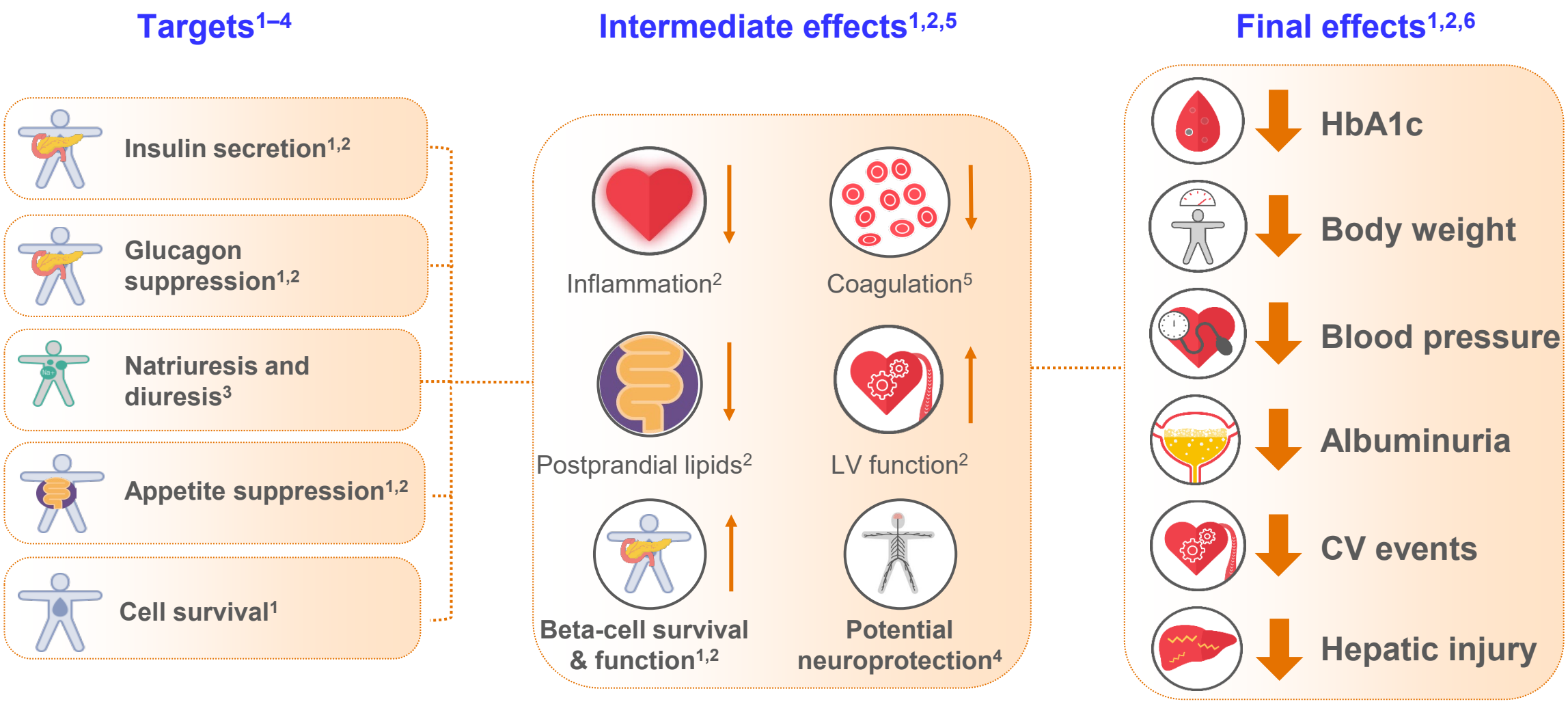
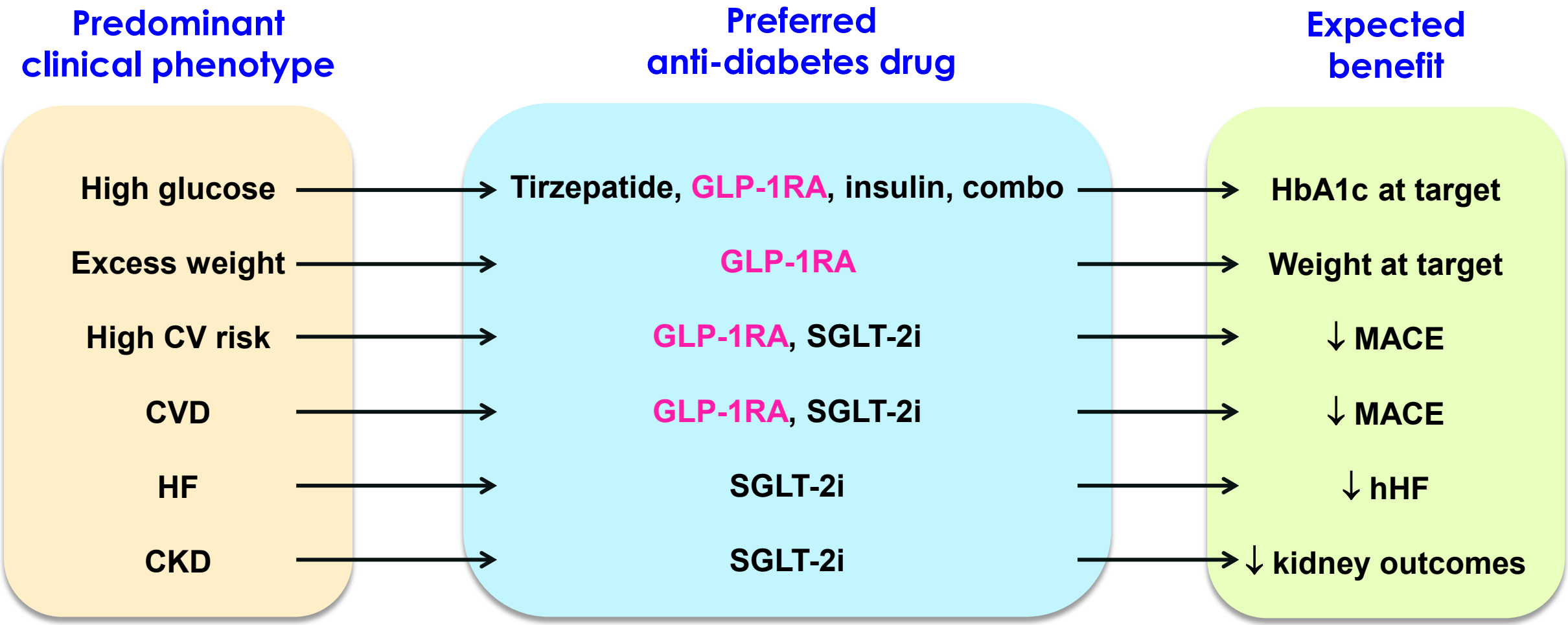
GLP-1 RAs Have Shown Multiple Favorable Effects in T2D



CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; LV, left ventricular; T2D, type 2 diabetes. Adapted from Drucker[1] and Rizzo.[2]

1. Drucker DJ. *Cell Metab.* 2018;27(4):740–756; 2. Rizzo M, et al. *Biochim Biophys Acta Mol Basis Dis.* 2018;1864(9 Pt B):2814–2821; 3. Greco EV, et al. *Medicina (Kaunas).* 2019;55(6):233; 4. Athauda D, et al. *JAMA Neurol.* 2019;76(4):420–429; 5. Cameron-Vendrig A, et al. *Diabetes.* 2016;65(6):1714–1723; 6. Zelniker TA, et al. *Circulation.* 2019;139(17):2022–2231.

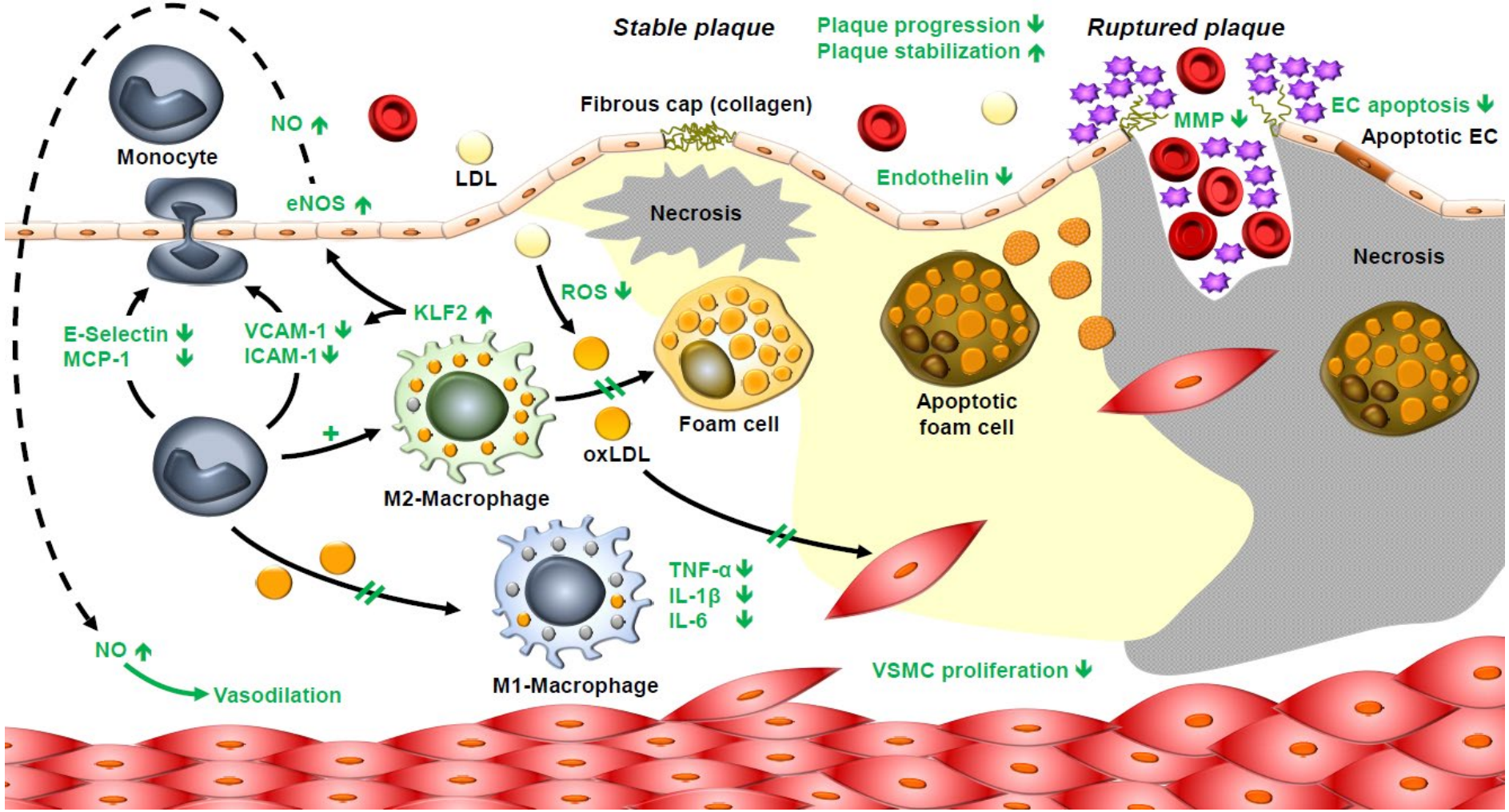
Management of Hyperglycaemia in Type 2 Diabetes
The logic behind ADA-EASD Consensus 2022



This slide reflects the speaker's point of view.

CKD, chronic kidney disease; CV, cardiovascular; GLP-1RA, glucagon-like peptide-1 receptor agonists; HbA1c, glycated hemoglobin; HF, heart failure; hHF, hospitalization for HF; MACE, major adverse cardiovascular events; SGLT-2i, sodium-glucose transporter 2 inhibitors.

Effects of GLP-1 RAs on the Progression of Atherogenesis and the Development of Its Complications

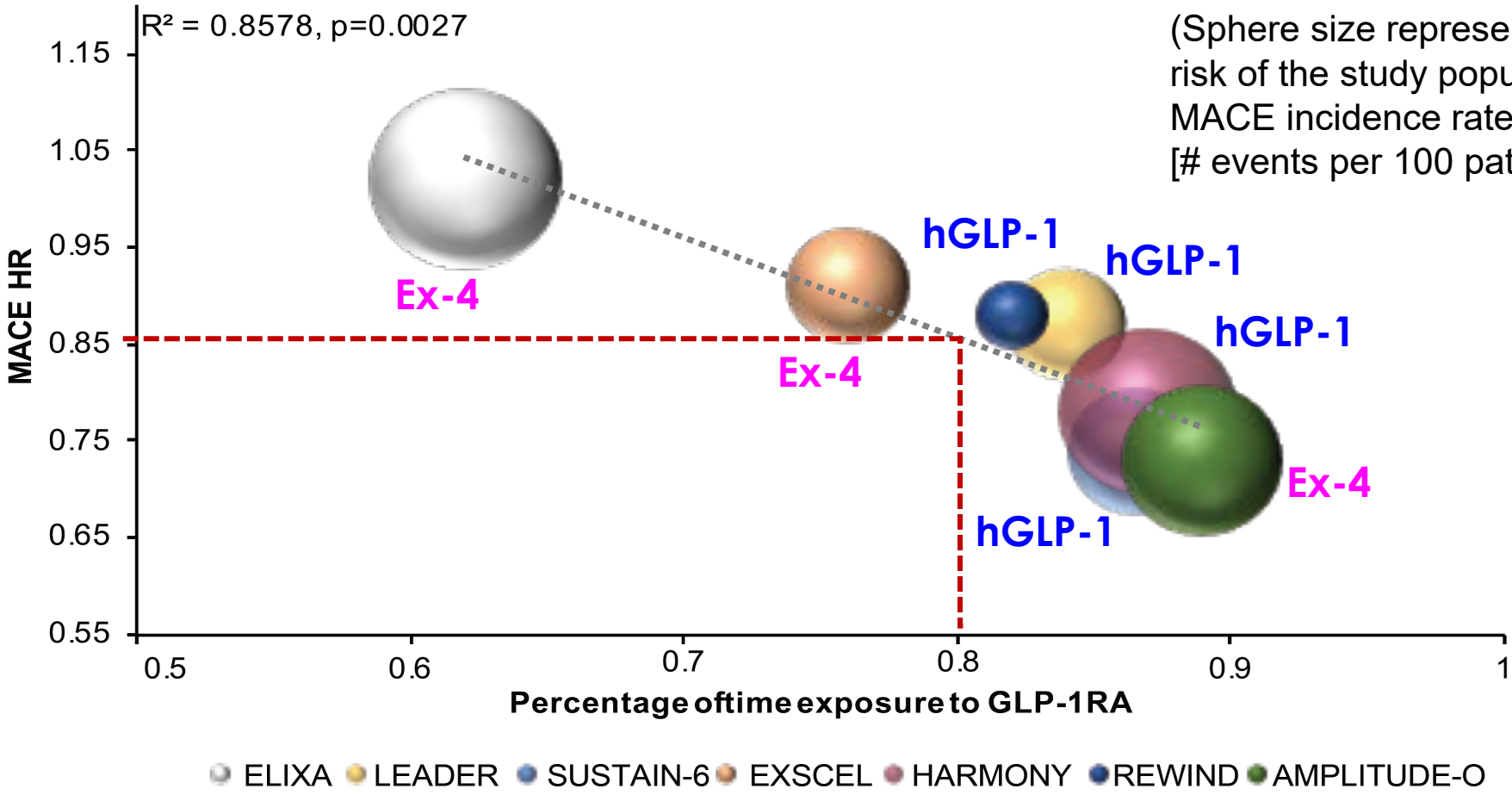


EC, endothelial cell; eNOS, endothelial nitrous oxide synthase; GLP-1RA, glucagon-like peptide 1 receptor agonists; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; KLF-2, Krüppel-like factor-2; LDL, low-density lipoprotein; MCP-1, monocyte chemoattractant protein-1; NO, nitrous oxide; oxLDL, oxidized low-density lipoprotein; ROS, reactive oxygen species; TNF-α, tumor necrosis factor; VCAM-1, vascular cell adhesion protein 1; VSMC, vascular smooth muscle cell.

Nauck MA, et al. *Mol Metab.* 2021;46:101102.

Correlation between Percentage of Time Exposure to GLP-1 RA and MACE HR in GLP-1RA CVOT

- **Baseline CV risk level not apparently related to MACE HR.**
(Sphere size represents the baseline CV risk of the study population, expressed as MACE incidence rate in the control arm [# events per 100 patient-year])



The percentage of time exposure to study drug is expressed as median in ELIXA, HARMONY Outcomes, REWIND and AMPLITUDE-O, and as mean in LEADER, SUSTAIN–6 and EXSCEL. Actual exposure to lixisenatide in ELIXA is estimated to be approximately 55%.

CVOT, cardiovascular outcome trials; Ex-4, exendin-4; GLP-1 RA, glucagon-like peptide-1 receptor agonists; hGLP-1, human GLP-1; HR, hazard ratio; MACE, major adverse cardiovascular event. **Adapted from *Caruso I, et al. Diabetes Care.* 2022;45(2):e30–e31.**

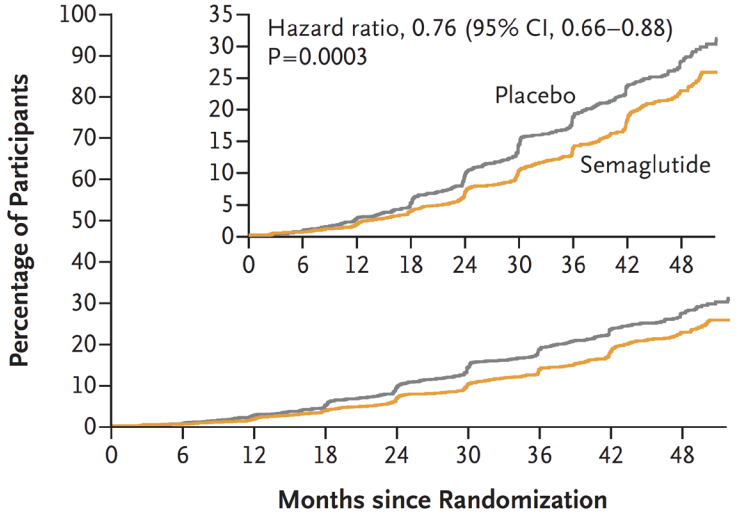
Effects of Semaglutide 1.0 mg on CKD in Patients with T2D

eGFR 50-75 ml/min/m^2 and UACR >300 -<5000
eGFR 25-50 ml/min/m^2 and UACR >100 -<5000

Major kidney disease events, a composite of the onset of kidney failure (dialysis, transplantation, or an eGFR of <15 ml/min/m^2), at least a 50% reduction in the eGFR from baseline, or death from kidney-related or cardiovascular causes

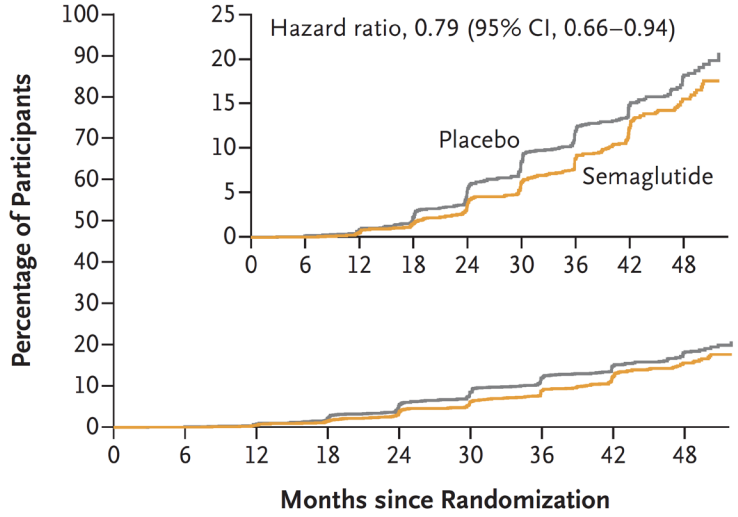
Perkovic V et al,
***N Engl J Med* 2024**

First Major Kidney Disease Event



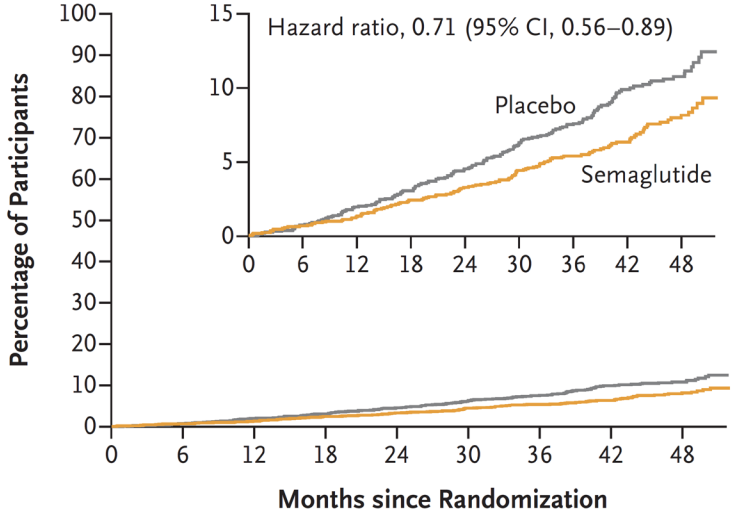
No. at Risk									
Placebo	1766	1736	1682	1605	1516	1408	1048	660	354
Semaglutide	1767	1738	1693	1640	1572	1489	1131	742	392

First Kidney-specific Component Event



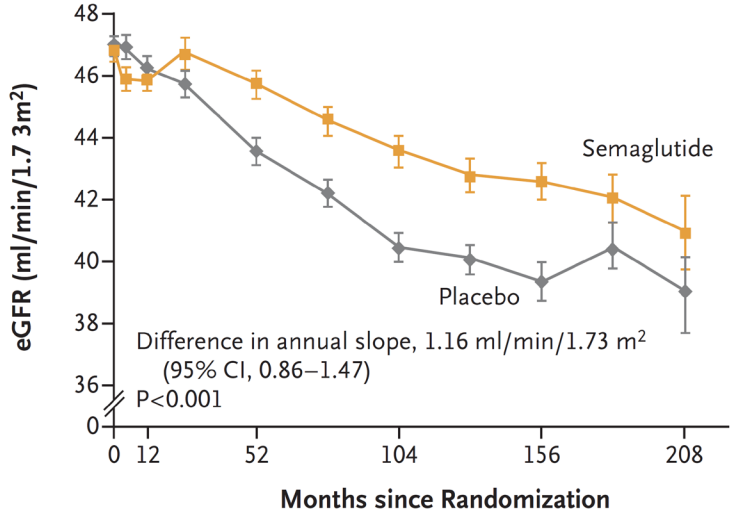
No. at Risk									
Placebo	1766	1736	1682	1605	1516	1408	1048	660	354
Semaglutide	1767	1738	1693	1640	1572	1489	1131	742	392

Death from Cardiovascular Causes



No. at Risk									
Placebo	1766	1737	1697	1641	1601	1544	1185	772	437
Semaglutide	1767	1739	1703	1665	1627	1583	1234	838	460

Total eGFR Slope



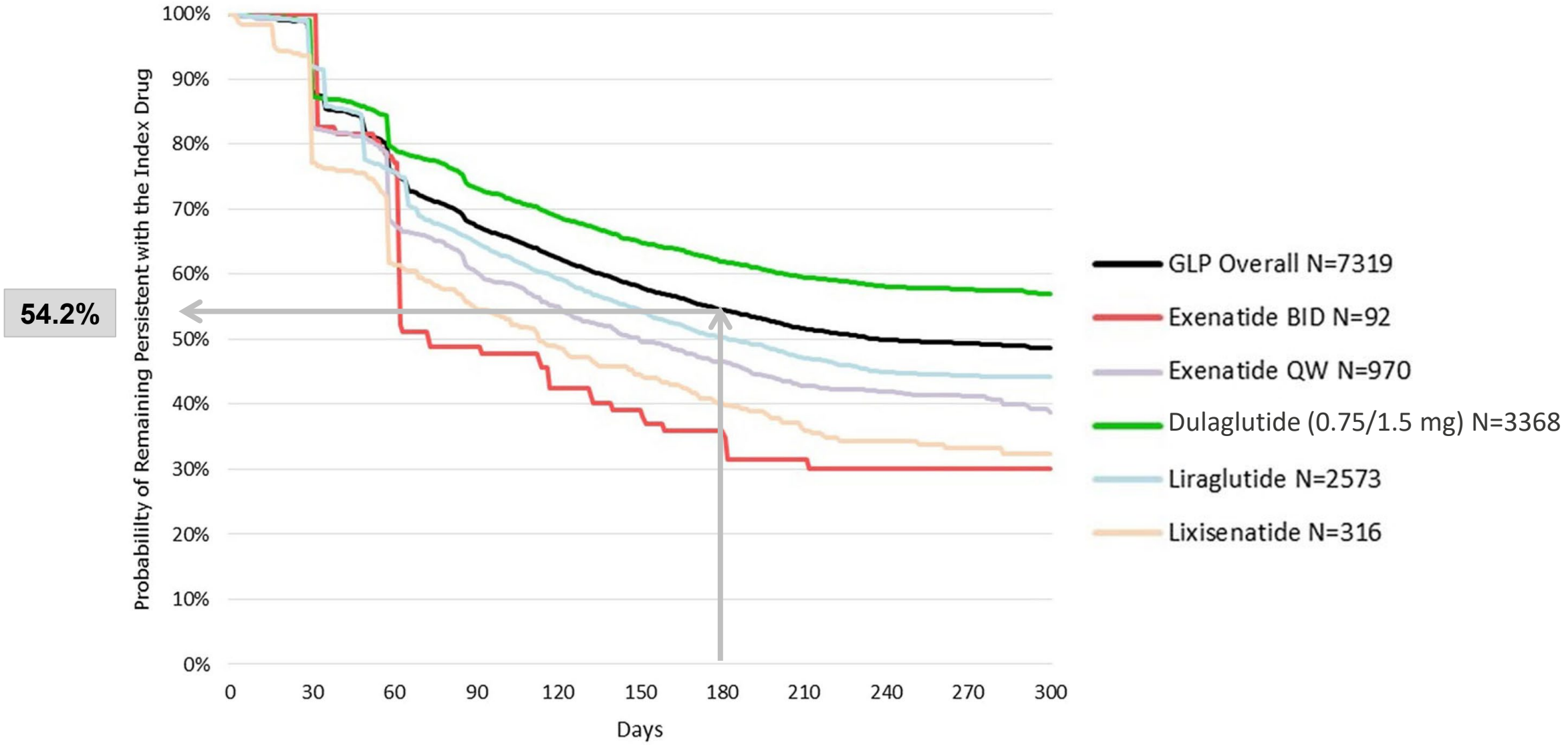
No. at Risk										
Placebo	1766	1663	1573	1609	1490	1441	1284	876	609	199
Semaglutide	1766	1665	1590	1606	1521	1468	1345	952	651	218

Insulin versus GLP-1RA in Achieving Diabetes Goals

Goals	GLP-1RA	Insulin
Control hyperglycemia	Yes (++)	Yes (+)
Reduce excess body weight	Yes	No
Avoid hypoglycemia	Yes	No
Reduce CV outcomes	Yes	No
Reduce mortality (CV and non-CV)	Yes	No
Prevent heart failure outcomes	Yes (±)	No
Prevent CKD progression	Yes (±)	No
Ameliorate NAFLD/NASH	Yes	No
Ameliorate cognitive impairment	Yes	No
Prevent diabetes progression	Yes (?)	No (?)
Improve patient's adherence/persistence	Yes (?)	No (?)

This slide reflects the speaker's point of view. CV, cardiovascular; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; GU, genitourinary; MI, myocardial infarction; QoL, quality of life; T2D, type 2 diabetes.

Kaplan-Meier Analyses over the Available Follow-up Durations: Probability of Remaining Persistent with the Index Therapy



BID, twice daily; GLP, glucagon-like peptide; QW; once weekly

Orsini Federici M, et al. *Diabetes Ther* 2018;9:789–801

Potential Consequences of Shortage of GLP-1RA Resulting in Therapy Interruption in T2D Patients

- Loss of glucose and weight control with rise in HbA1c and weight regain
- Reduction of protective effects on heart, vessels and kidney with loss of protection against adverse cardiovascular and renal events
- Switch to other therapies without cardiorenal protective effects and with high risk of hypoglycemia (e.g., insulin, sulphonylureas)
- Reduction of adherence to (and confidence in) GLP-1RA-based therapeutic regimens

GLP-1RA, glucagon-like peptide 1 receptor agonists; T2D, type 2 diabetes.