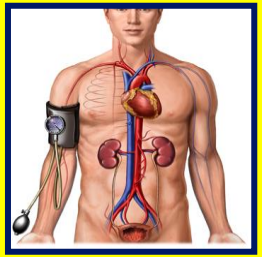
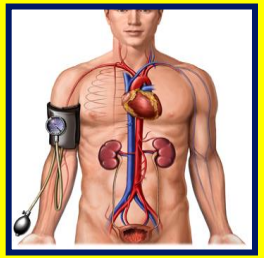


Reducing CV Mortality and Morbidity Beyond Glycemic Lowering in Type 2 Diabetes



Dr. Julie A. Lovshin, MD, PhD, FRCP (C)
Staff Endocrinologist and Clinician Investigator,
Assistant Professor of Medicine, Division of Endocrinology and Metabolism
University of Toronto, Ontario, CANADA

35th Annual SMJ Cardiology Day for the Practioner – May 4, 2024

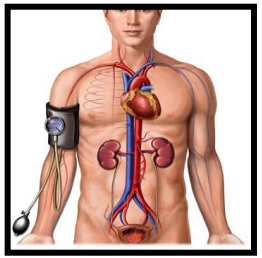
Twitter: @JulieALovshin, Email: Julie.lovshin@sunnybrook.ca

Presenter Disclosures:

In the past 24 months, I have served in the following roles with the pharmaceutical industry:

Advisory Board:	**Eli Lilly, Novo Nordisk**
Board Member:	**None**
Consultant/ Honoraria:	**BI, CHRC, Eli Lilly Alliance, Novo Nordisk**
Research Support:	**Merck Canada, Sanofi Canada, Novo Nordisk**
Speaker's Bureau:	**None**
Stock/Shareholder:	**None**

Reducing CV Mortality and Morbidity Beyond Glycemic Lowering in T2DM



Objectives:

At the end of this session, the attendee will be able to

1. Understand glucose-independent CV event reduction with glucose-lowering drugs (GLDs)

-GLP-1RA (glucagon-like-1 peptide receptors agonists)

-SGLT-2i (sodium glucose co-transporter-2 inhibitors)

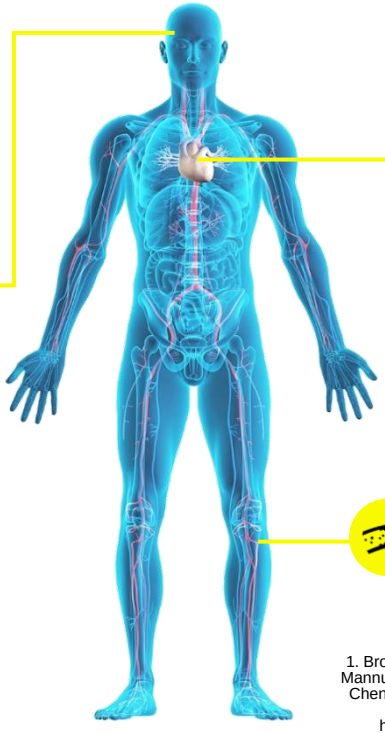
Hyperglycaemia causes vascular complications
Macrovascular disease

People with microvascular complications due to T2D are more likely to have a major CV event[1]

Chronic hyperglycaemia is associated with low-grade inflammation and accelerated atherosclerosis[3]

Brain
4x
higher risk of coronary artery disease and stroke[4]

For every 1% increase in **HbA_{1c}**, the risk of stroke is increased by up to
30%[5]



PAD
1/3
of T2D patients over 50 years of age, have PAD. This increases the risk of heart attack and stroke[9]

Heart
2/3
of deaths in T2D are attributable to CVD[6]

2–6x higher risk of mortality from CV events[7]

2.5x
Higher risk of developing congestive heart failure[8]

CV, cardiovascular; CVD, cardiovascular disease; PAD, peripheral artery disease

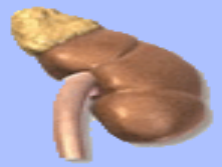
1. Brownrigg JR et al. *Lancet Diabetes Endocrinol* 2016;4:588–597; 2. Ross S et al. *Eur Heart J* 2015;36:1454–1462; 3. Mannucci E et al. *Diabetes Care* 2013;36(Suppl 2):S259–S263; 4. Lüscher TF et al. *Circulation* 2003;108:1655–1661; 5. Chen Y et al. *PLoS One* 2015;10:1–12; 6. Low Wang CC et al. *Circulation* 2016;133:2459–2502; 7. Fihn SD et al. *J Am Coll Cardiol* 2012;60:e44–e164; 8. Nichols GA et al. *Diabetes Care* 2004;27:1879–1884; 9. Diabetes UK website: https://www.diabetes.co.uk/diabetes-complications/peripheral-arterial-disease.html (accessed 26 September 2018)

Good News !!
GLDs Coordinate Many Actions Beyond Glucose Lowering

SGLT-2i
GLP-1R agonists

↓

Renal Effects

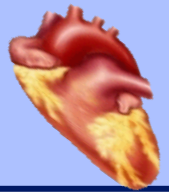


- ↓ Nephropathy
- ↓ Albuminuria

SGLT-2i
GLP-1R agonists

↓

CV Effects

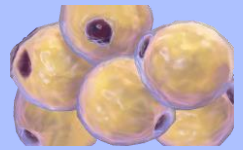


- ↓ Cardiac Death
- ↓ Myocardial Infarction
- ↓ Stroke

SGLT-2i
GLP-1R agonists

↓

Weight Loss



- ↓ Body Weight

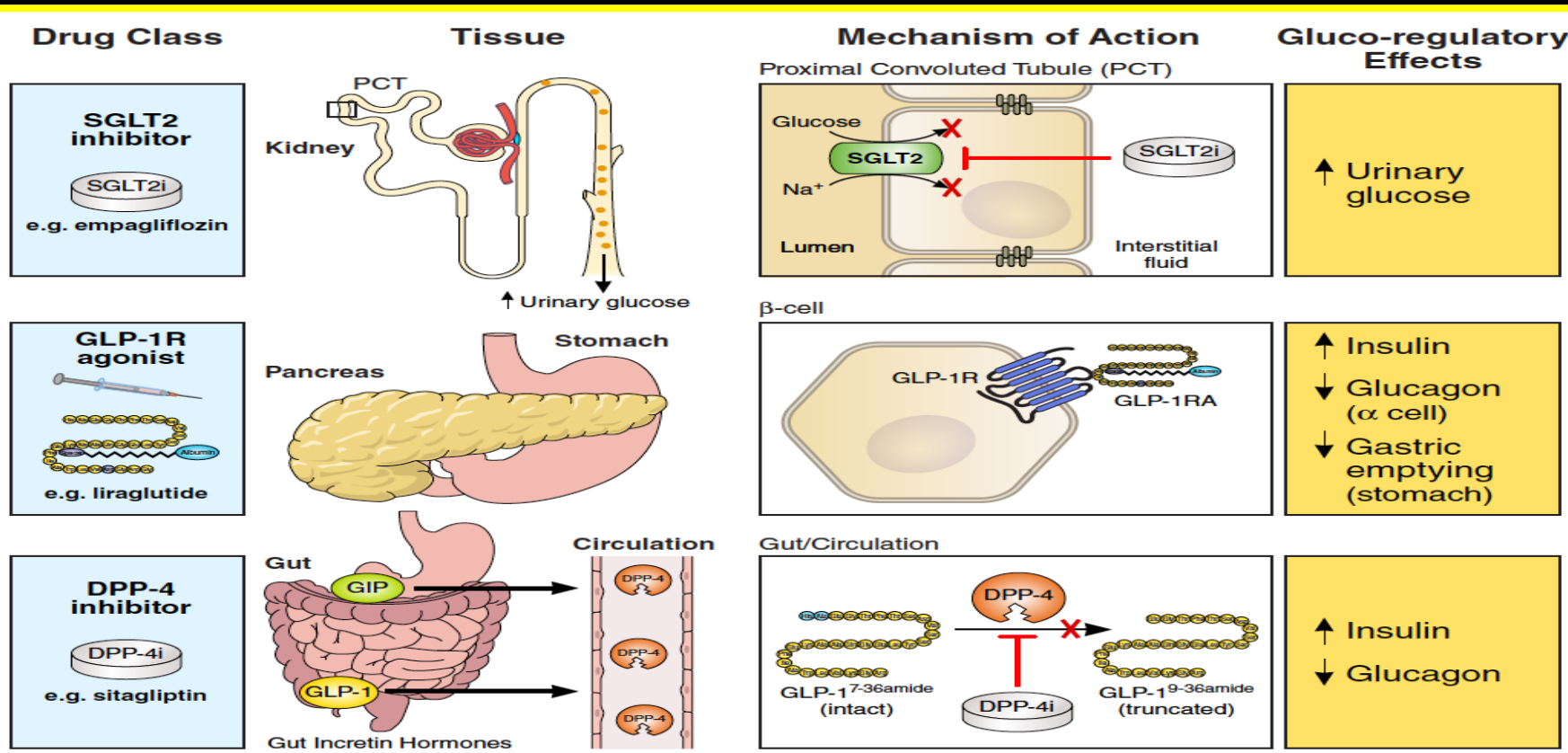
SGLT-2i
GLP-1R agonists

↓

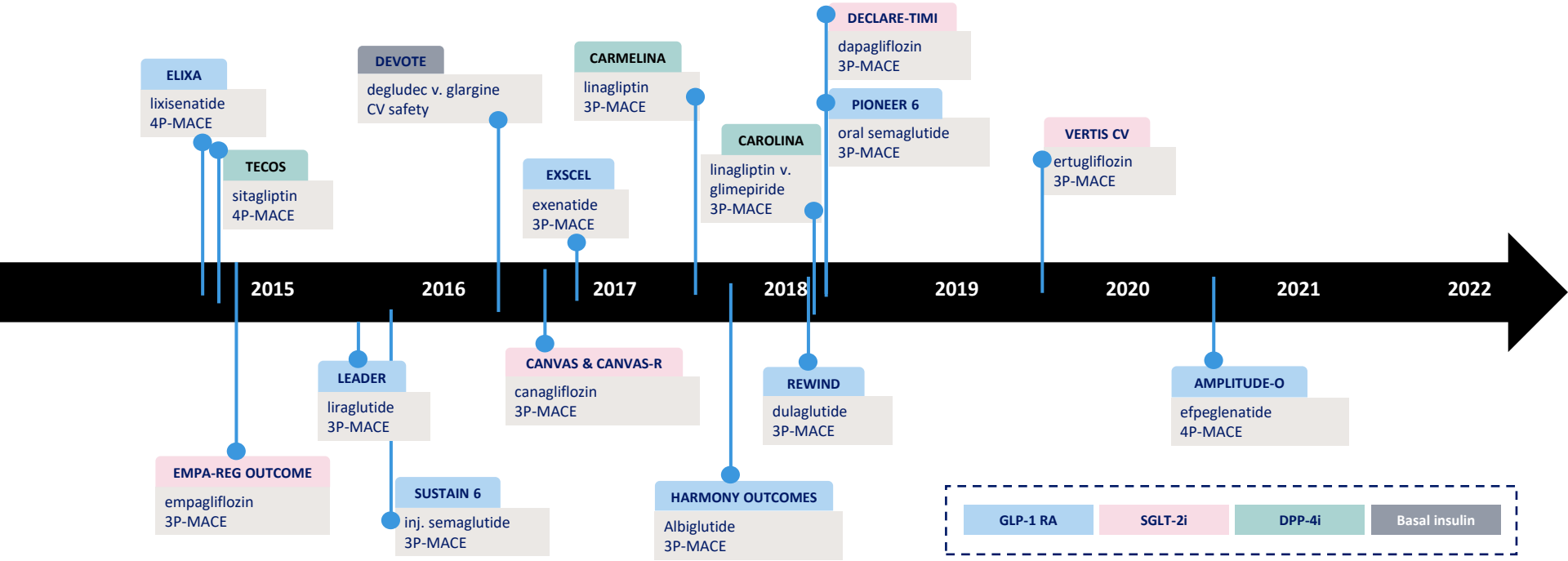
Metabolic

- ↓ BP/Lipids
- ↓ Inflammation
- ↓ steatosis (NAFLD)

Gluco-Regulatory Effects of SGLT-2i and Therapies



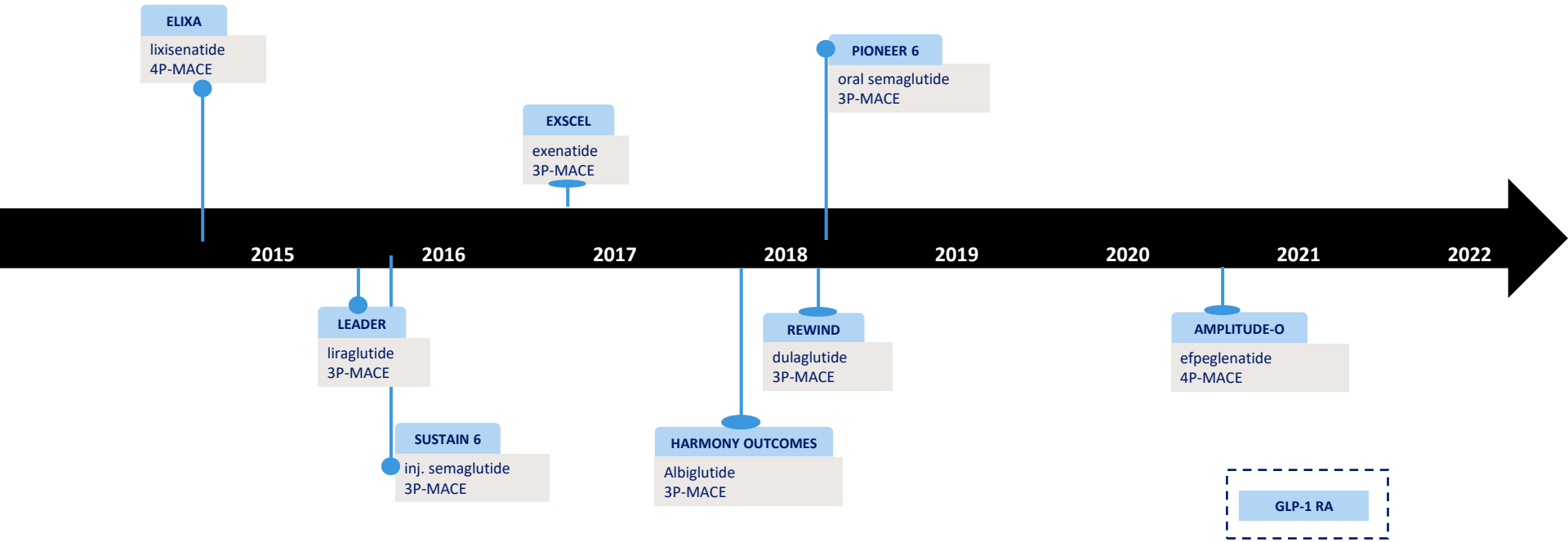
Recent Cardiovascular Outcomes Trials of Glucose-lowering Drugs (GLDs) in T2DM+ASCVD



CVOT, cardiovascular outcome trials; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium glucose cotransporter-2 inhibitor; MACE, major adverse cardiovascular events.

Davies M et al. Cardiovasc Diabetol 2022;21:1-20

Cardiovascular Outcomes of GLP-1RA in T2DM + ASCVD or ↑CV Risk



Albiglutide was withdrawn from the worldwide market in July 2018

CVOT, cardiovascular outcome trials; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium glucose cotransporter-2 inhibitor; MACE, major adverse cardiovascular events.

Davies M et al. Cardiovasc Diabetol 2022;21:1-20

GLP-1 receptor agonists reduce MACE by 14%

(HR 0·86 [95% CI 0·80–0·93]; p<0·0001)

without significant heterogeneity across GLP-1 receptor agonists

	GLP-1 Receptor agonist, n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	*p* value
Three-point MACE					
ELIXA *(Lixisenatide)*	400/3034 (13%)	392/3034 (13%)	1.02 (0.89-1.17)		0.78
LEADER *(Liraglutide)*	608 (4668 (13%)	694/4672 (15%)	0.87 (0.78-0.97)		0.01
SUSTAIN-6 *(OW-Semaglutide)*	108 (1648 (7%)	146/1649 (9%)	0.74 (0.58-0.95)		0.016
EXSCEL *(Exenatide)*	839/7356 (11%)	905/7396 (12%)	0.91 (0.83-1.00)		0.061
Harmony Outcomes *(albiglutide)*	338/4731 (7%)	428/4732 (9%)	0.78 (0.68-0.90)		0.0006
REWIND *(Dulaglutide)*	594/4949 (12%)	663/4952 (13%)	0.88 (0.79-0.99)		0.026
PIONEER 6 *(oral-semaglutide)*	61/1591 (4%)	76/1592 (5%)	0.79 (0.57-1.11)		0.17
AMPLITUDE-O *(efpeglenatide)*	189/2717 (7%)	125/1359 (9%)	0.73 (0.58-0.92)		0.0069
Subtotal (I^2=44.5%, *p*=0.082)			**0.86 (0.80-0.93)**	**65 (45-130)**	**<0.0001**

Favours GLP-1 receptor agonists Favours placebo

Weights are from random effect analysis. In addition to primary cardiovascular outcome results papers, data were extracted from additional sources. AMPLITUDE-O data were provided by the authors. Three-point MACE consisted of cardiovascular death, myocardial infarction, and stroke. NNTs were calculated over a weighted average median follow-up of 3.0 years. P values are for superiority

CI, confidence interval; CVOTs, cardiovascular outcome trails; GLP-1, glucagon-like peptide-1; GLP-1 RAs, GLP-1 receptor agonists; MACE, major adverse cardiovascular events; NNT, number needed-to-treat

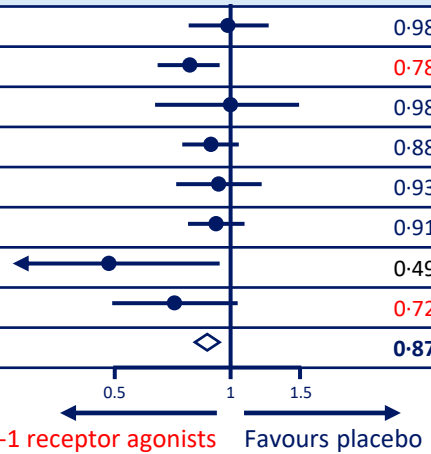
Sattar N et al. Lancet Diabetes Endocrinol. 2021; S2213-8587(21)00203-5., doi:10.1016/S2213-8587(21)00203-5

GLP-1 receptor agonists reduce CV death by 13%

(HR 0·87 [0·80–0·94]; p=0·0010),

without significant heterogeneity across GLP-1 receptor agonists

	GLP-1 Receptor agonist, n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	*p* value
Cardiovascular death					
ELIXA (Lixisenatide)	156/3034 (5%)	158/3034 (5%)	0·98 (0·78–1·22)		0·85
LEADER (Liraglutide)	219/4668 (5%)	278/4672 (6%)	0·78 (0·66–0·93)		0·007
SUSTAIN-6 (OW-Semaglutide)	44/1648 (3%)	46/1649 (3%)	0·98 (0·65–1·48)		0·92
EXSCEL (Exenatide)	340/7356 (5%)	383/7396 (5%)	0·88 (0·76–1·02)		0·096
Harmony Outcomes	122/4731 (3%)	130/4732 (3%)	0·93 (0·73–1·19)		0·58
REWIND (Dulaglutide)	317/4949 (6%)	346/4952 (7%)	0·91 (0·78–1·06)		0·21
PIONEER 6 (oral-semaglutide)	15/1591 (1%)	30/1592 (2%)	0·49 (0·27–0·92)		0·021
AMPLITUDE-O (efpeglenatide)	75/2717 (3%)	50/1359 (4%)	0·72 (0·50–1·03)		0·07
Subtotal (I^2=13·4%, *p*=0·33)			**0·87 (0·80–0·94)**	**163 (103–353)**	**0·0010**



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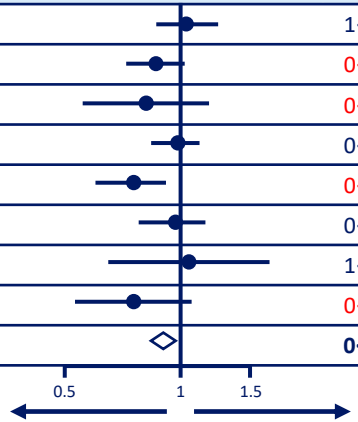
Sattar N et al. Lancet Diabetes Endocrinol. 2021; S2213-8587(21)00203-5., doi:10.1016/S2213-8587(21)00203-5

GLP-1 receptor agonists reduce risk of non-fatal MI by 10%

(0·90 [0·83–0·98]; p=0·020)

without significant heterogeneity across GLP-1 receptor agonists

	GLP-1 Receptor agonist, n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	*p* value
Fatal or non-fatal myocardial infarction					
ELIXA (Lixisenatide)	270/3034 (9%)	261/3034 (9%)	1·03 (0·87–1·22)		0·71
LEADER (Liraglutide)	292/4668 (6%)	339/4672 (7%)	0·86 (0·73–1·00)		0·046
SUSTAIN-6 (OW-Semaglutide)	54/1648 (3%)	67/1649 (4%)	0·81 (0·57–1·16)		0·26
EXSCEL (Exenatide)	483/7356 (7%)	493/7396 (7%)	0·97 (0·85–1·10)		0·62
Harmony Outcomes	181/4731 (4%)	240/4732 (5%)	0·75 (0·61–0·90)		0·003
REWIND (Dulaglutide)	223/4949 (5%)	231/4952 (5%)	0·96 (0·79–1·15)		0·63
PIONEER 6 (oral-semaglutide)	37/1591 (2%)	35/1592 (2%)	1·04 (0·66–1·66)		0·49
AMPLITUDE-O (efpeglenatide)	91/2717 (3%)	58/1359 (4%)	0·75 (0·54–1·05)		0·09
Subtotal (I^2=26·9%, *p*=0·21)			**0·90 (0·83–0·98)**	**175 (103–878)**	**0·020**



Favours GLP-1 receptor agonists Favours placebo

Weights are from random effect analysis. In addition to primary cardiovascular outcome results papers, data were extracted from additional sources. AMPLITUDE-O data were provided by the authors. Three-point MACE consisted of cardiovascular death, myocardial infarction, and stroke. NNTs were calculated over a weighted average median follow-up of 3.0 years. P values are for superiority
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Sattar N et al. Lancet Diabetes Endocrinol. 2021; S2213-8587(21)00203-5., doi:10.1016/S2213-8587(21)00203-5

GLP-1 receptor agonists reduced risk of non-fatal stroke by 17%

(0·83 [0·76–0·92; p=0·0002)

without significant heterogeneity across GLP-1 receptor agonists

ordisk®

	GLP-1 Receptor agonist, n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	*p* value
Fatal or non-fatal stroke					
ELIXA (Lixisenatide)	67/3034 (2%)	60/3034 (2%)	1·12 (0·79–1·58)		0·54
LEADER (Liraglutide)	173/4668 (4%)	199/4672 (4%)	0·86 (0·71–1·06)		0·16
SUSTAIN-6 (OW-Semaglutide)	30/1648 (2%)	46/1649 (3%)	0·65 (0·41–1·03)		0·066
EXSCEL (Exenatide)	187/7356 (3%)	218/7396 (3%)	0·85 (0·70–1·03)		0·095
Harmony Outcomes	94/4731 (2%)	108/4732 (2%)	0·86 (0·66–1·14)		0·30
REWIND (Dulaglutide)	158/4949 (3%)	205/4952 (4%)	0·76 (0·62–0·94)		0·010
PIONEER 6 (oral-semaglutide)	13/1591 (1%)	17/1592 (1%)	0·76 (0·37–1·56)		0·43
AMPLITUDE-O (efpeglenatide)	47/2717 (2%)	31/1359 (2%)	0·74 (0·47–1·17)		0·19
Subtotal (I^2=0·0%, *p*=0·64)			**0·83 (0·76–0·92)**	**198 (140–421)**	**0·0002**

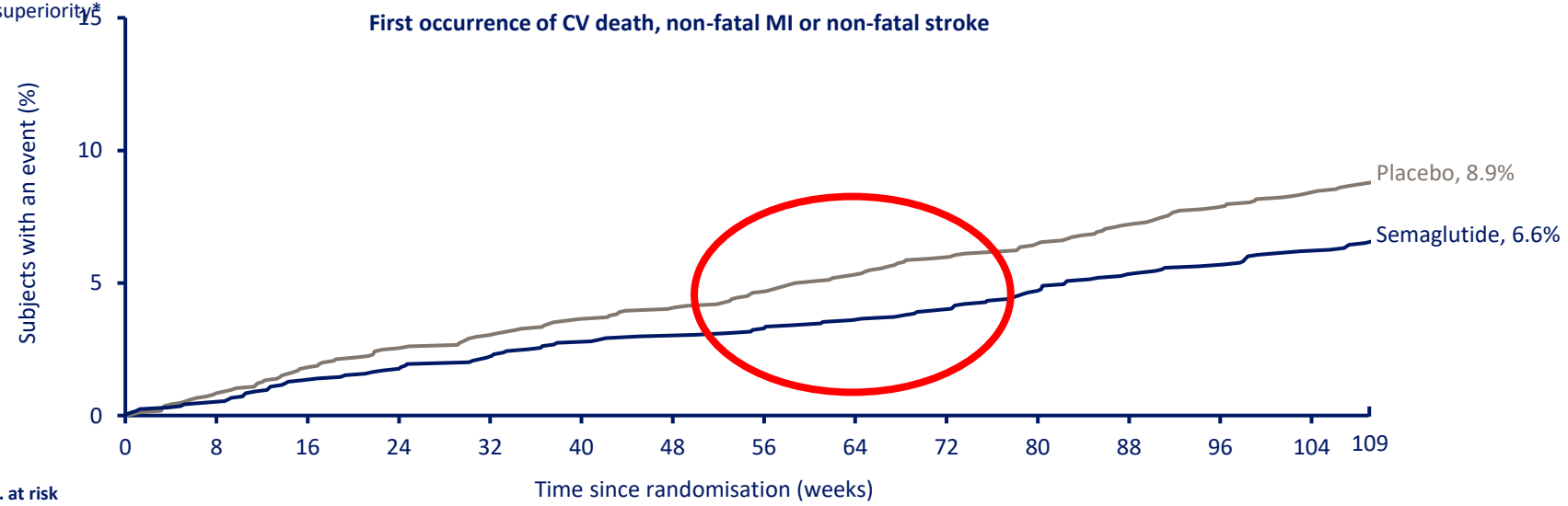
Favours GLP-1 receptor agonists Favours placebo

Weights are from random effect analysis. In addition to primary cardiovascular outcome results papers, data were extracted from additional sources. AMPLITUDE-O data were provided by the authors. Three-point MACE consisted of cardiovascular death, myocardial infarction, and stroke. NNTs were calculated over a weighted average median follow-up of 3.0 years. P values are for superiority
CI, confidence interval; CVOTs. cardiovascular outcome trials; GLP-1, glucagon-like peptide-1; GLP-1 RAs, GLP-1 receptor agonists; NNT, number needed-to-treat

Sattar N et al. Lancet Diabetes Endocrinol. 2021; S2213-8587(21)00203-5., doi:10.1016/S2213-8587(21)00203-5

Once Weekly semaglutide Reduced MACE by 26%, HR 0.74 [95% CI: 0.58;0.95]

HR 0.74 [95% CI: 0.58;0.95]
Events: 108 semaglutide; 146 placebo
p<0.001 for non-inferiority
p=0.02 for superiority*



No. at risk								
Semaglutide	1,648	1,619	1,601	1,584	1,568	1,543	1,524	1,513
Placebo	1,649	1,616	1,586	1,567	1,534	1,508	1,479	1,466

*Kaplan–Meier plot for first event adjudication committee-confirmed CV death, non-fatal MI and non-fatal stroke using 'in-trial' data from subjects in the full analysis set. *Not prespecified.*
CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.
Marso SP et al. N Engl J Med 2016;375:1834–44.

Completed and Future CV and Renal Clinical Studies with GLP-1RA

Cardiovascular effects

- **STRIDE** — Effects on peripheral arterial disease
- **CV MoA** — CV mechanism of action
- **SOUL** — oral semaglutide CVOT

Microvascular effects

- **FOCUS** — Effects on diabetic retinopathy
- **FLOW** — Renal effects
- **REMODEL** — Renal mechanism of action

Effects in patients without T2D

- **STEP HFpEF** — Sema 2.4 in pts w/heart failure
- **SELECT** — Sema 2.4 CVOT in pts w/Obesity
- **SELECT-LIFE** — Long-term follow-up of SELECT pts

Effectiveness in the real-world setting

- Other prospective studies
- Retrospective database studies

CV, cardiovascular; MoA, mechanism of action; RWE, real-word evidence.

Completed and Future CV and Renal Clinical Studies with GLP-1RA

Cardiovascular effects

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Effectiveness in the real-world setting

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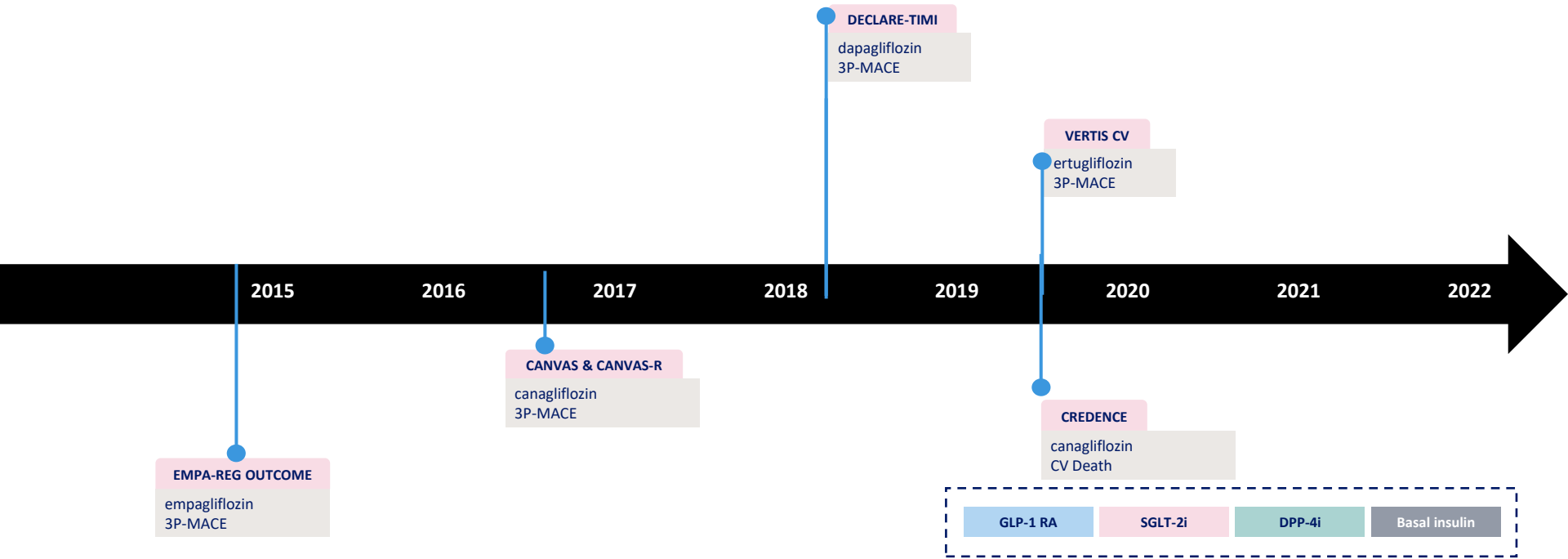
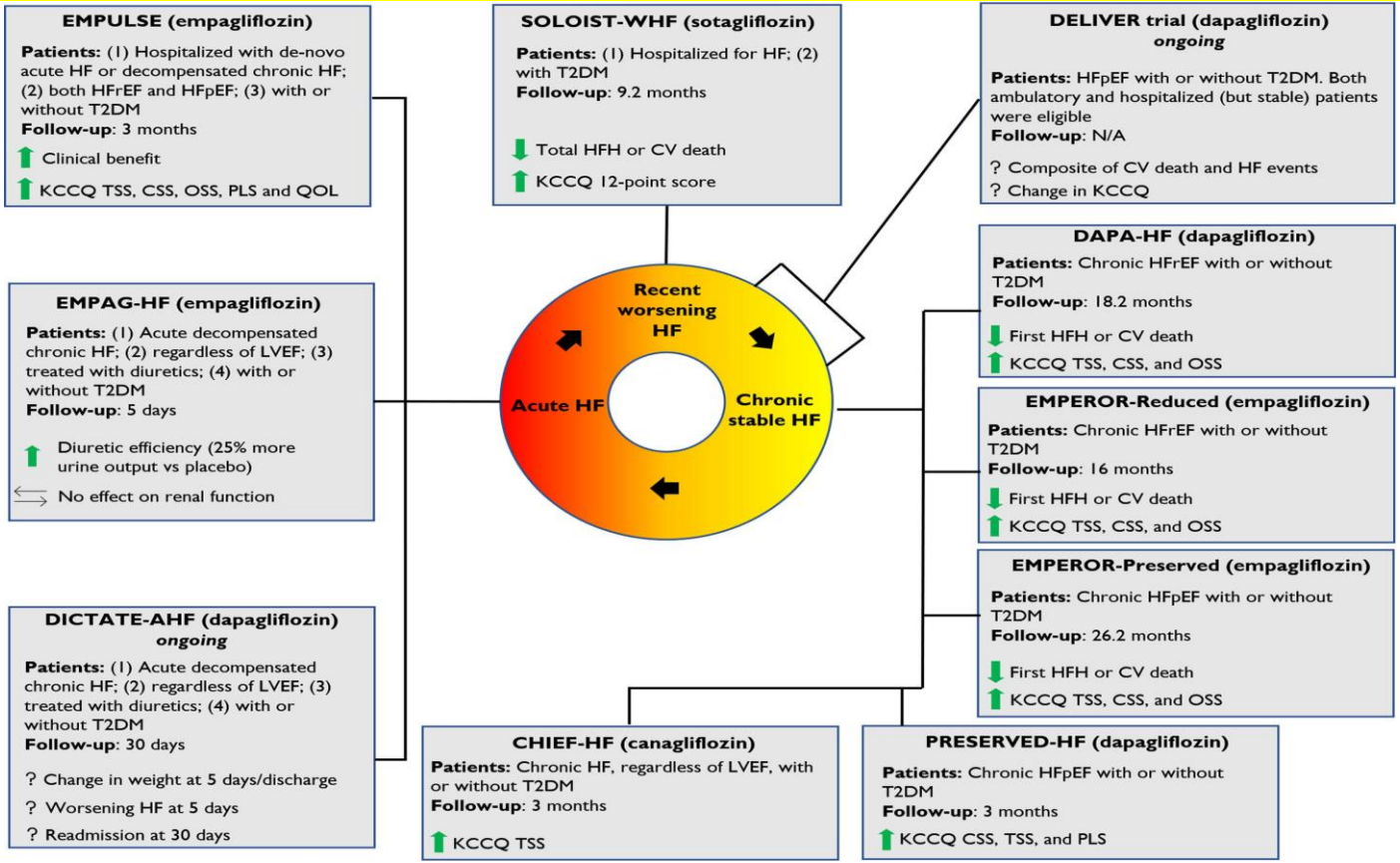
Recent Cardiovascular Outcomes of Glucose-lowering Drugs (GLDs) in T2DM+ASCVD or ↑CV Risk – SGLT-2i



CVOT, cardiovascular outcome trials; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT-2i, sodium glucose cotransporter-2 inhibitor; MACE, major adverse cardiovascular events.

Davies M et al. Cardiovasc Diabetol 2022;21:1-20

Recent Cardiovascular Outcomes of Glucose-lowering Drugs (GLDs) in T2DM – SGLT-2i - HF



Stefan D. Anker. Circulation. SGLT2 Inhibitors: From Antihyperglycemic Agents to All-Around Heart Failure Therapy, Volume: 146, Issue: 4, Pages: 299-302, DOI: (10.1161/CIRCULATIONAHA.122.060348)

Recent Trials Cardiovascular Outcomes of Glucose-lowering Drugs (GLDs) in T2DM – SGLT-2i

Table 2. Clinical trial results regarding the impact of SGLT2 inhibitors on HF and other cardiovascular outcomes

Relevant clinical trial	Number of patients	Hospitalization for HF Only, HR (95% CI)	Hospitalization for HF and cardiovascular death, HR (95% CI)	Major adverse cardiac events, HR (95% CI)	Cardiovascular death, HR (95% CI)
Type 2 diabetes and multiple risk factors (no known cardiovascular disease)					
EMPA-REG OUTCOME, CANVAS-R, DECLARE-TIMI 58	13,672	0.64 (0.48-0.85)	0.84 (0.69-1.01)	1.00 (0.87-1.16)	1.02 (0.80-1.30)
Type 2 diabetes and known cardiovascular disease					
EMPA-REG OUTCOME, CANVAS-R, DECLARE-TIMI 58	20,650	0.71 (0.62-0.82)	0.76 (0.69-0.84)	0.86 (0.80-0.93)	0.80 (0.71-0.91)
Type 2 diabetes and albuminuric chronic kidney disease					
CREDENCE	4401	0.69 (0.57-0.83)	0.61 (0.47-0.80)	0.80 (0.67-0.95)	0.78 (0.61-1.00; $P = 0.0502$)
Stable heart failure and reduced left ventricular ejection fraction irrespective of diabetes					
DAPA-HF	4744	0.70 (0.59-0.83)	0.75 (0.65-0.85)	N/A	0.82 (0.69-0.98)

CANVAS-R, **CAN**agliflozin cardio**V**ascular **A**ssessment **S**tudy—**R**enal; CI, confidence interval; CREEDENCE, **C**anagliflozin and **R**enal **E**vents in **D**iabetes With **E**stablished **N**ephropathy **C**linical **E**valuation; DAPA-HF, **Dapa**gliflozin on Incidence of Worsening **H**eart **F**ailure or Cardiovascular Death in Patients with CHF; DECLARE-TIMI 58, **D**apagliflozin **E**ffect on **C**ardiovascu**l**ar **E**vents -**T**hrombolysis **i**n **M**yocardial **I**nfarction 58; EMPA-REG OUTCOME, **Empa**gliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients - **R**emoving **E**xcess **Gl**ucose; HF, heart failure; HR, heart rate; N/A, not available.

Recent Trials Cardiovascular Outcomes of Glucose-lowering Drugs (GLDs) in T2DM – SGLT-2i

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CREDENCE	4401	0.69 (0.57-0.83)	0.61 (0.47-0.80)	0.80 (0.67-0.95)	0.78 (0.61-1.00; $P = 0.0502$)
Stable heart failure and reduced left ventricular ejection fraction irrespective of diabetes					
DAPA-HF	4744	0.70 (0.59-0.83)	0.75 (0.65-0.85)	N/A	0.82 (0.69-0.98)

CANVAS-R, **CAN**agliflozin cardio**V**ascular **A**ssessment **S**tudy—**R**enal; CI, confidence interval; CREEDENCE, **C**anagliflozin and **R**enal **E**vents in **D**iabetes With **E**stablished **N**ephropathy **C**linical **E**valuation; DAPA-HF, **Dapa**gliflozin on Incidence of Worsening **H**eart **F**ailure or Cardiovascular Death in Patients with CHF; DECLARE-TIMI 58, **D**apagliflozin **E**ffect on **C**ardiovascu**l**ar **E**vents -**T**hrombolysis **i**n **M**yocardial **I**nfarction 58; EMPA-REG OUTCOME, **Empa**gliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients - **R**emoving **E**xcess **Gl**ucose; HF, heart failure; HR, heart rate; N/A, not available.

Recent Trials Cardiovascular Outcomes of Glucose-lowering Drugs (GLDs) in T2DM – SGLT-2i

Table 2. Clinical trial results regarding the impact of SGLT2 inhibitors on HF and other cardiovascular outcomes

Relevant clinical trial	Number of patients	Hospitalization for HF Only, HR (95% CI)	Hospitalization for HF and cardiovascular death, HR (95% CI)	Major adverse cardiac events, HR (95% CI)	Cardiovascular death, HR (95% CI)
Type 2 diabetes and multiple risk factors (no known cardiovascular disease)					
EMPA-REG OUTCOME, CANVAS-R, DECLARE-TIMI 58	13,672	0.64 (0.48-0.85)	0.84 (0.69-1.01)	1.00 (0.87-1.16)	1.02 (0.80-1.30)
Type 2 diabetes and known cardiovascular disease					
EMPA-REG OUTCOME, CANVAS-R, DECLARE-TIMI 58	20,650	0.71 (0.62-0.82)	0.76 (0.69-0.84)	0.86 (0.80-0.93)	0.80 (0.71-0.91)
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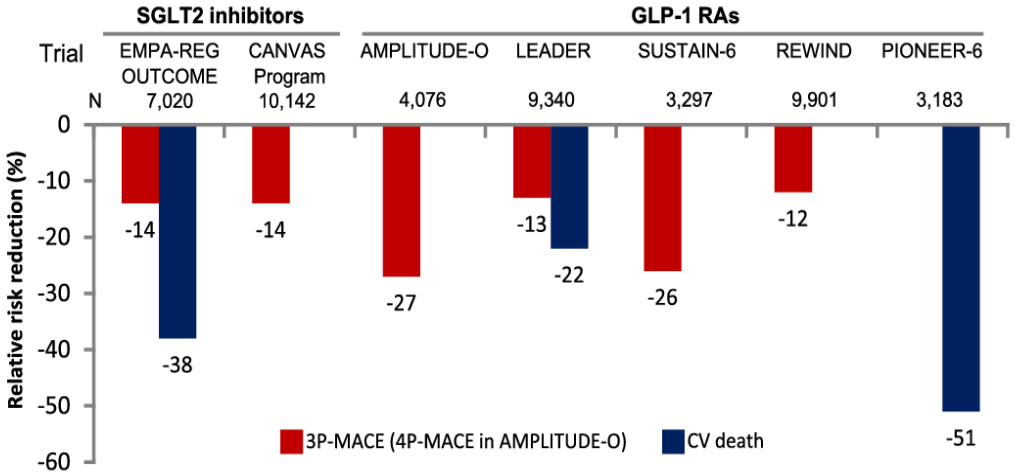
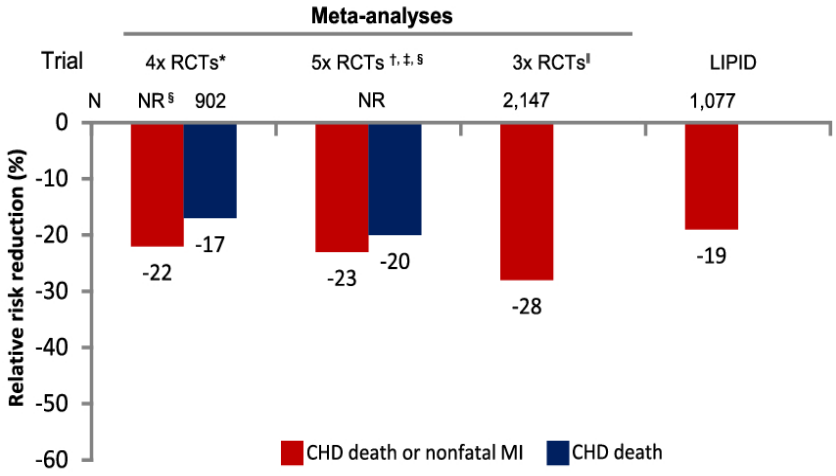
CV Event Risk Reduction - GLP-1RA, SGLT-2i, Statins, Cardiorenal Therapies

A

Relative risk reduction in **3P-MACE** and **CV death** with **GLDs**



Secondary prevention with **statins** in patients with diabetes



Reductions only shown for diabetes CVOTs with statistically significant benefit

B

NNT with **GLDs**

Empagliflozin EMPA-REG OUTCOME	**Liraglutide** LEADER	**Semaglutide** SUSTAIN-6	**Empagliflozin** EMPA-REG OUTCOME
63 NNT	53 NNT	44 NNT	39 NNT
in **3.1 years** to prevent one **3P-MACE**	in **3.8 years** to prevent one **3P-MACE**	in **2 years** to prevent one **3P-MACE**	in **3.1 years** to prevent one **death**

NNT with **cardiorenal therapies**

Aspirin in prior MI or stroke	**Statins** in known CAD or stroke	**Antihypertensive therapy**
50 NNT	83 NNT	125 NNT
in **2 years** to prevent one **3P-MACE**	in **5 years** to prevent one **death**	in **5 years** to prevent one **death**

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

CV Event Risk Reduction - DPP-4i, GLP-1RA, SGLT-2i

Interpretation of Risk Ratios (Relative Reduction in Percentage) and Absolute Risk Differences (per 1000 Treated)								
	All-Cause Mortality	MACE	MI	Stroke	CHF Hospitalization	CKD Stage ≥3	SAEs*	Severe Hypoglycemia
Compared with usual care or placebo								
DPP-4 inhibitors	No difference	No difference	No difference	No difference	No difference	No difference	No difference	No difference
GLP-1 agonists	*Reduce all-cause mortality by 12% or 10 fewer events*	*Reduce MACE by 9% or 11 fewer events*	No difference	*Reduce stroke by 14% or 5 fewer events*	No difference	No data	No difference	Probably no difference
Long-acting insulins	May be no difference	May be no difference	No data	No data	May be no difference	No data	Probably no difference	Insufficient evidence
SGLT-2 inhibitors	*Reduce all-cause mortality by 14% or 9 fewer events*	*Probably reduce MACE by 10% or 12 fewer events*	No difference	No difference	*Reduce hospitalization due to CHF by 36% or 19 fewer events*	*Reduce progression of CKD by 34% or 12 fewer events*	*Reduce SAEs by 7% or 23 fewer events*	*Reduce severe hypoglycemia by 15% or 3 fewer events*
Tirzepatide	May be no difference	Insufficient evidence	No data	No data	No data	No data	No difference	Probably no difference

Newer Pharmacologic Treatments in Adults With Type 2 Diabetes:
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FLOW TRIAL

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SURPASS CVOT

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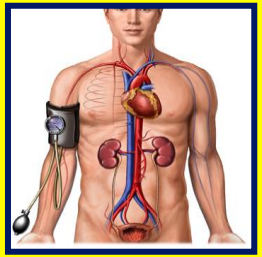
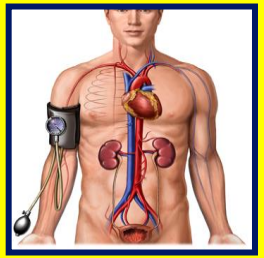


Reducing CV Mortality and Morbidity Beyond Glycemic Lowering in Type 2 Diabetes



Dr. Julie A. Lovshin, MD, PhD, FRCP (C)
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35th Annual SMJ Cardiology Day for the Practioner – May 4, 2024

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