Fundamental science and the mechanism to evidence around new drugs

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Outline

- **SGLT-2 inhibitors**
  - Mechanism of action
  - Outcome trials
- **GLP-1 receptor agonists**
  - Mechanism of action
  - Outcome trials

Where it all started

FDA NEWS RELEASE

FOR IMMEDIATE RELEASE
December 17, 2008

Media Inquiries:
Karen Riley, 301-796-4674
Consumer Inquiries:
888-INFO-FDA

FDA Announces New Recommendations on Evaluating Cardiovascular Risk in Drugs Intended to Treat Type 2 Diabetes

The U.S. Food and Drug Administration recommended today that manufacturers developing new drugs and biologics for type 2 diabetes provide evidence that the therapy will not increase the risk of such cardiovascular events as a heart attack. The recommendation is part of a new guidance for industry that applies to all diabetes drugs currently under development.

"We need to better understand the safety of new antidiabetic drugs. Therefore, companies should conduct a more thorough examination of their drugs' cardiovascular risks during the product's development stage," said Mary Parks, M.D., director, Division of Metabolism and Endocrinology Products, Center for Drug Evaluation and Research (CDER), FDA. "FDA's guidance outlines the agency's recommendations for doing such an assessment."

"…sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk."

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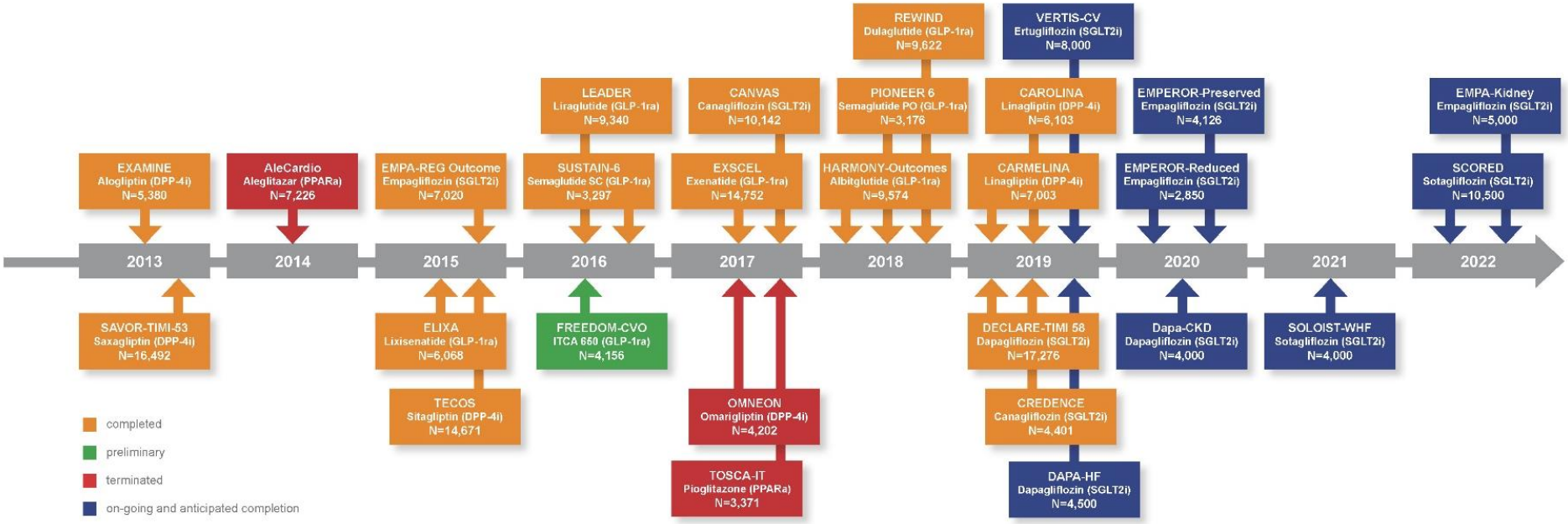
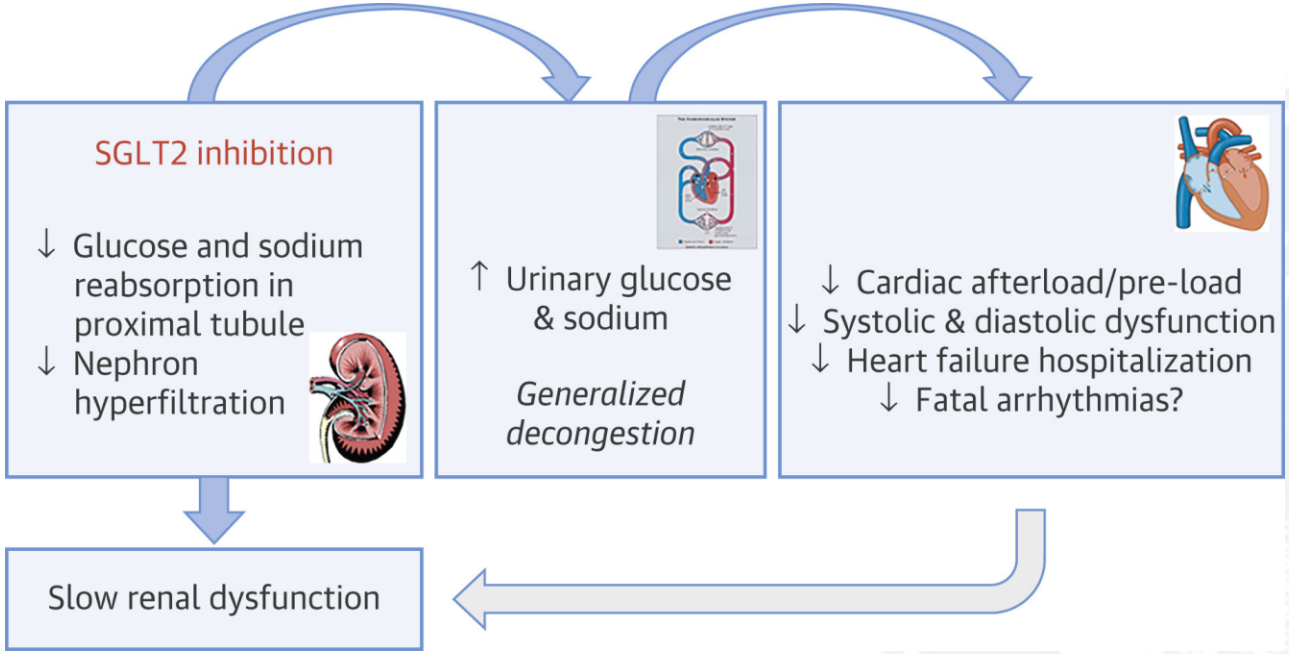
Timeline


REWIND
Dulaglutide (GLP-1ra)
N=9,622
VERTIS-CV
Ertugliflozin (SGLT2i)
N=8,000
LEADER
Liraglutide (GLP-1ra)
N=9,340
CANVAS
Canagliflozin (SGLT2i)
N=10,142
PIONEER 6
Semaglutide PO (GLP-1ra)
N=3,176
CAROLINA
Linagliptin (DPP-4i)
N=6,103
EMPEROR-Preserved
Empagliflozin (SGLT2i)
N=4,126
EMPA-Kidney
Empagliflozin (SGLT2i)
N=5,000
EXAMINE
Alogliptin (DPP-4i)
N=5,380
AleCardio
Aleglitazar (PPARa)
N=7,226
EMPA-REG Outcome
Empagliflozin (SGLT2i)
N=7,020
SUSTAIN-6
Semaglutide SC (GLP-1ra)
N=3,297
EXSCEL
Exenatide (GLP-1ra)
N=14,752
HARMONY-Outcomes
Albiglutide (GLP-1ra)
N=9,574
CARMELINA
Linagliptin (DPP-4i)
N=7,003
EMPEROR-Reduced
Empagliflozin (SGLT2i)
N=2,850
SCORED
Sotagliflozin (SGLT2i)
N=10,500
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022
SAVOR-TIMI-53
Saxagliptin (DPP-4i)
N=16,492
ELIXA
Lixisenatide (GLP-1ra)
N=6,068
FREEDOM-CVO
ITCA 650 (GLP-1ra)
N=4,156
DECLARE-TIMI 58
Dapagliflozin (SGLT2i)
N=17,276
Dapa-CKD
Dapagliflozin (SGLT2i)
N=4,000
SOLOIST-WHF
Sotagliflozin (SGLT2i)
N=4,000
TECOS
Sitagliptin (DPP-4i)
N=14,671
OMNEON
Omarigliptin (DPP-4i)
N=4,202
CREDENCE
Canagliflozin (SGLT2i)
N=4,401
TOSCA-IT
Pioglitazone (PPARa)
N=3,371
DAPA-HF
Dapagliflozin (SGLT2i)
N=4,500
completed
preliminary
terminated
on-going and anticipated completion

SGLT2i: Mechanisms of action

- SGLT-2 expressed in proximal tubule
  - Reabsorb ~ 90% of filtered glucose load but inhibitors only reduce ~ 50% = ↓70-90g/day = 300kcal/d. Upregulation of SGLT-1?
- Glucose lowering effects dependent on GFR
  - Thus, ↓ GFR = less effect on HbA1c (FDA label)
  - **BUT** CV/renal benefit is preserved!
- Glucose lowering is independent of insulin/beta cell function
  - **RARELY** causes hypoglycemia in absence of other therapies that would
    - Insulin, sulfonylureas

SGLT2i: Mechanisms of benefit



Sattar, N. *J Am Coll Cardiol. 2017*

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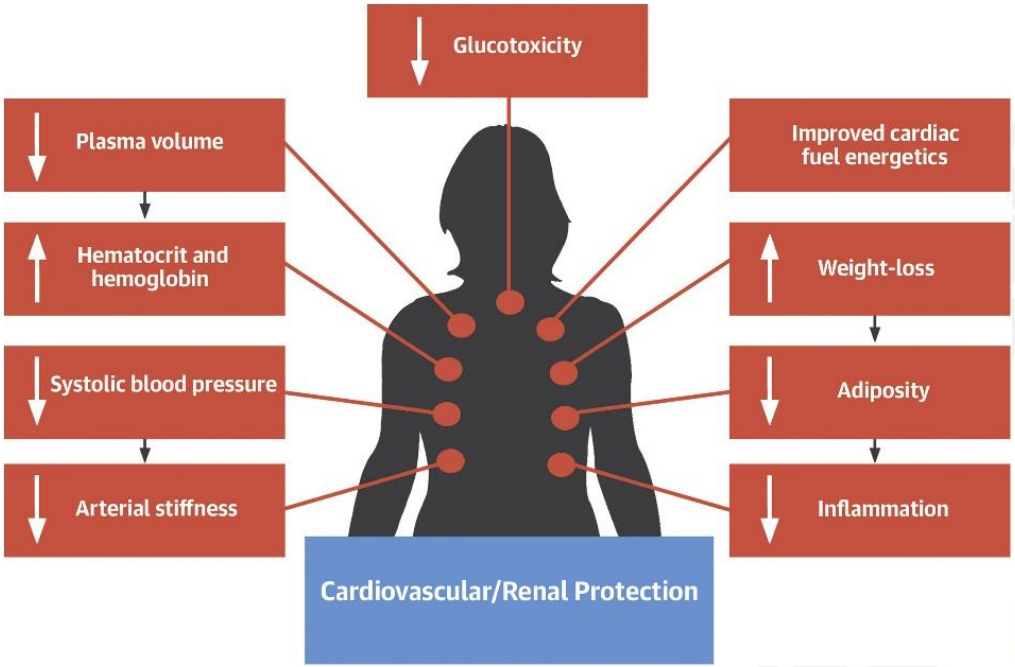
SGLT2i: Mechanisms of benefit



Zelniker, T.A. *J Am Coll Cardiol. 2020*

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SGLT2i: Mechanisms of benefit

Mechanism	Physiology
Glycosuria (SGLT-2)	• Osmotic diuresis → ↓ intravascular volume depletion → ↓ preload → ↓ oxygen demand • Altered insulin:glucagon ratio → ↑ ketones → ↓ weight → ↓ inflammation • ↓ glucotoxicity → ↑ insulin sensitivity
Natriuresis	• ↓ blood pressure ± ↑ ventricular function ± ↓ AF • ?improve arterial stiffness • ↑ Tubuloglomerular feedback → afferent art. vasoconstriction (cf ACE inhibitors) → ↓ intraglomerular pressure →↓ GFR (~5ml/min) and ↓ albuminuria
Inhibition of NH3	In myocardium: improved mitochondrial ATP In kidney: ↑ antioxidants
Uricosuria (GLUT9)	Reduction in plasma uric acid → improved gout

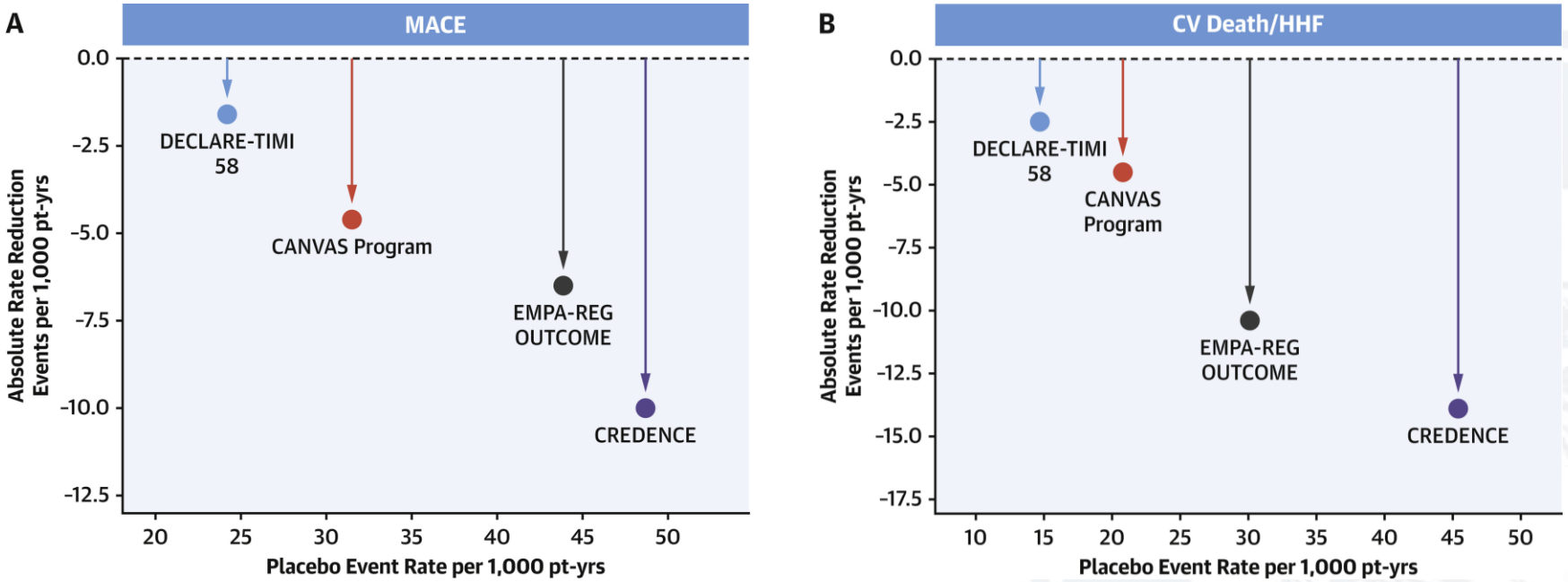
SGLT2i: Mechanisms of AE

Mechanism	Physiology
↑ Phosphate	Activation of FGF23-1,25$(OH)_2$-PTH axis → **bone turnover/fracture**
Glycosuria (SGLT-2)	• → Favorable growth media for **mycotic infections** • ↓ serum glucose → ↓ insulin dosage or production and ↑ glucagon → ↓ anti-lipolytic activity → increased FFA production → ketone bodies → **ketosis** (with less elevation in serum glucose e.g. <200mg/dL) • Unclear if the milieu of amplified urogenital flora (from glycosuria), together with a degree of neuropathy/microvascular disease may predispose to **Fournier's gangrene**
???	**Amputation** (toe/metatarsal) signal in CANVAS. Not well understood. Initially considered to be related to hypoperfusion but no associated signal for AKI/dehydration. Not seen in EMPA-REG (not systematically collected), DECLARE or CREDENCE (formal wound care plans)

SGLT2i: Clinical outcomes

HbA1c reduction	↓ 0.5 - 1%
Blood pressure	↓ 4 / 1mmHg
Body weight	↓ 2 - 3 kg

SGLT2i: CVOTs



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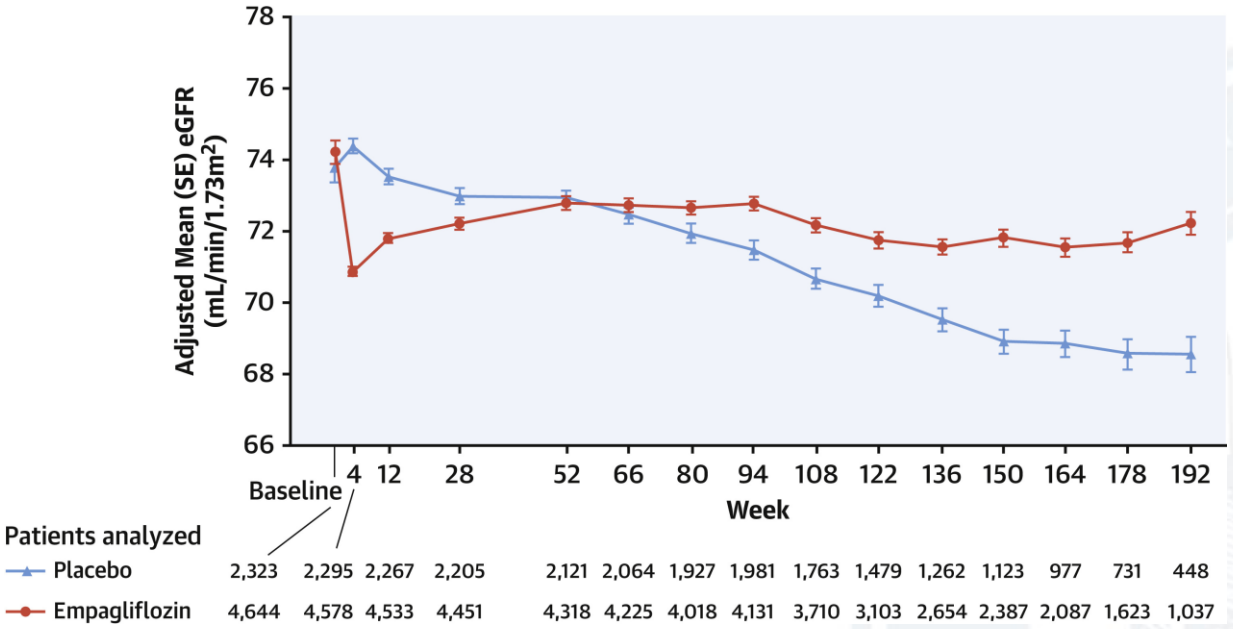
SGLT2i: Renal effects



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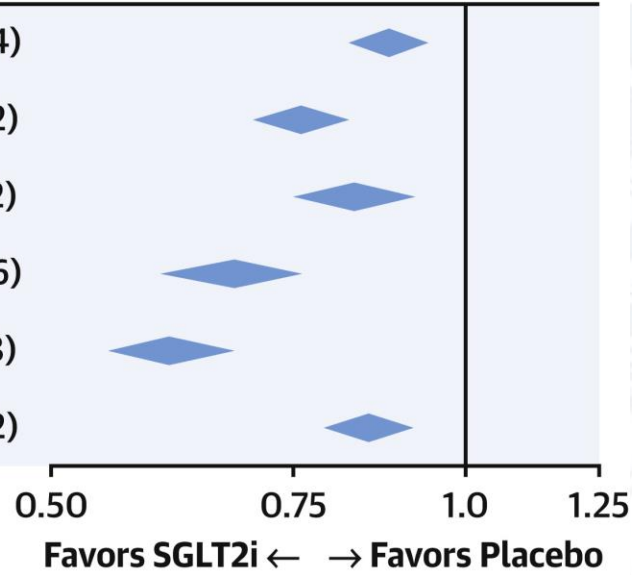
SGLT2i: Meta-analysis

Outcome	# Events	HR (95% CI)
MACE	3,828	0.88 (0.82-0.94)
CV death/HHF	2,460	0.76 (0.70-0.82)
CV death	1,506	0.83 (0.75-0.92)
HHF	1,192	0.68 (0.60-0.76)
Composite Renal Endpoint	1,351	0.61 (0.55-0.68)
All-cause Mortality	2,493	0.85 (0.79-0.92)



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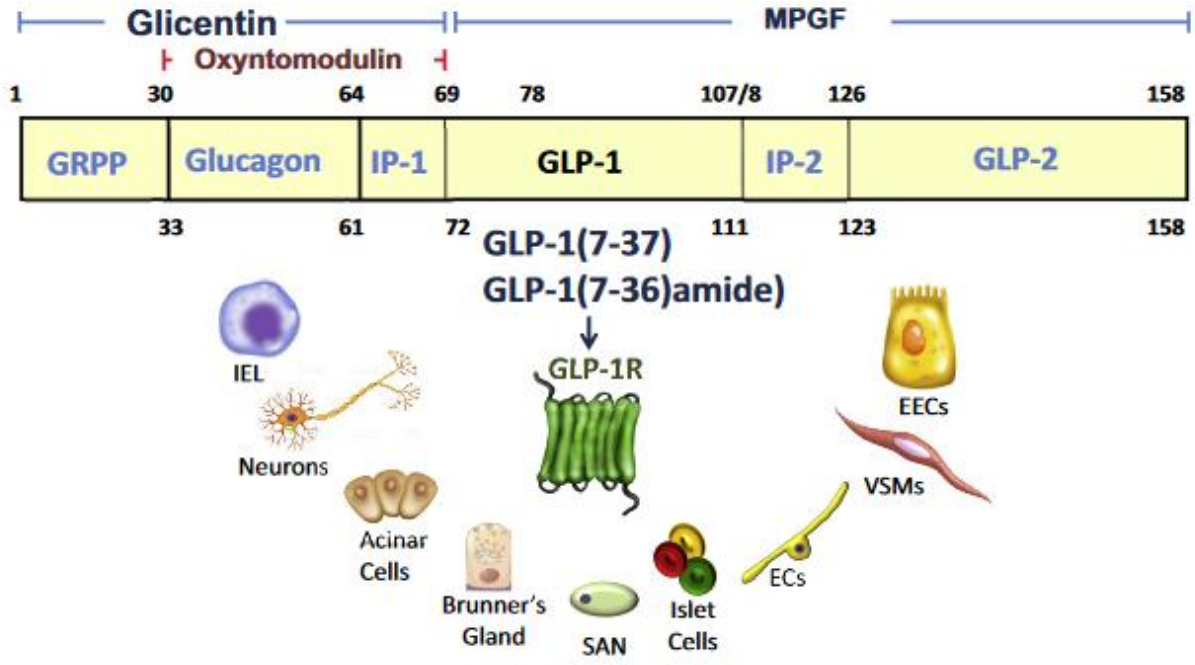
Structure of proglucagon and proglucagon-derived peptides, and principal cell types that express the canonical GLP-1 receptor



Drucker DJ, *Cell Metab* 27:740, 2018

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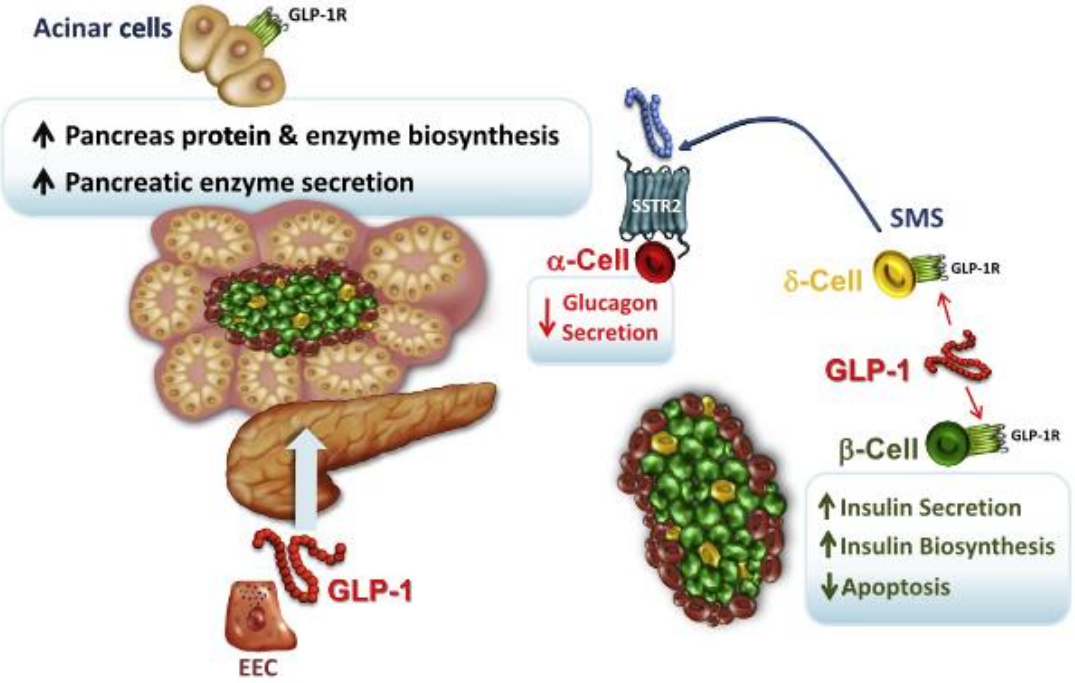
Pancreatic endocrine and exocrine actions of GLP-1 on islet and acinar cells



Drucker DJ, *Cell Metab* 27:740, 2018

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GLP-1RA: Mechanisms of benefit

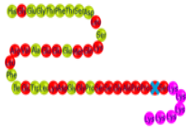
Mechanism	Physiology
Endothelial cell (EC) GLP1	Downstream eNOS signaling → vasodilatation • Improved insulin/nutrient delivery • Improved tissue oxygenation and glucose utilization Reduced EC apoptosis
Gastric GLP1	• Slowing of gastric emptying → satiety (? short term) → reduce post prandial glycemic spikes
CNS GLP1	• Sensation of satiety → weight loss
Renal GLP1	• Increases diuretic and natriuretic rate (?inconsistent) • Reduced expression of pro-apoptotic caspase-3/Bax/Bcl-2 • Increased anti-oxidant heme oxygenase-1
Adipocyte GLP1	• Stimulation of brown adipose thermogenesis via PPARγ
Hepatic GLP1	• Unknown mechanism, reduce liver fat and fibrosis ?exendin-4//mTOR

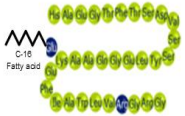
GLP-1RA: Clinical outcomes

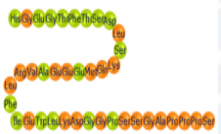
HbA1c reduction	↓ 0.6 – 1.5%
Blood pressure	↓ 3 / (1)mmHg
Body weight	↓ 2 - 3 kg

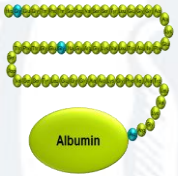
GLP-1RA benefits: homology?

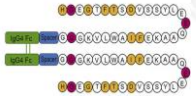
Drug	Lixisenatide od	Liraglutide od	Semaglutide qw	Exenatide XR qw	Albiglutide qw	Dulaglutide qw
Structure (sequence homology)	Exendin-4 (50%)	GLP-1 (97%)	GLP-1 (94%)	Exendin-4 (53%)	GLP-1 (97%)	GLP-1 (90%)
In vivo EC_{50} nmol/kg)*	0.02	0.5	NA	0.01	1.4	
t½	2–4 h	11.6–13 h	7 days	2 weeks	~ 5 days	~ 5 days
Dose	20 µg	0.6–1.8 mg	0.5, 1 mg	2 mg	30, 50 mg	0.75, 1.5 mg











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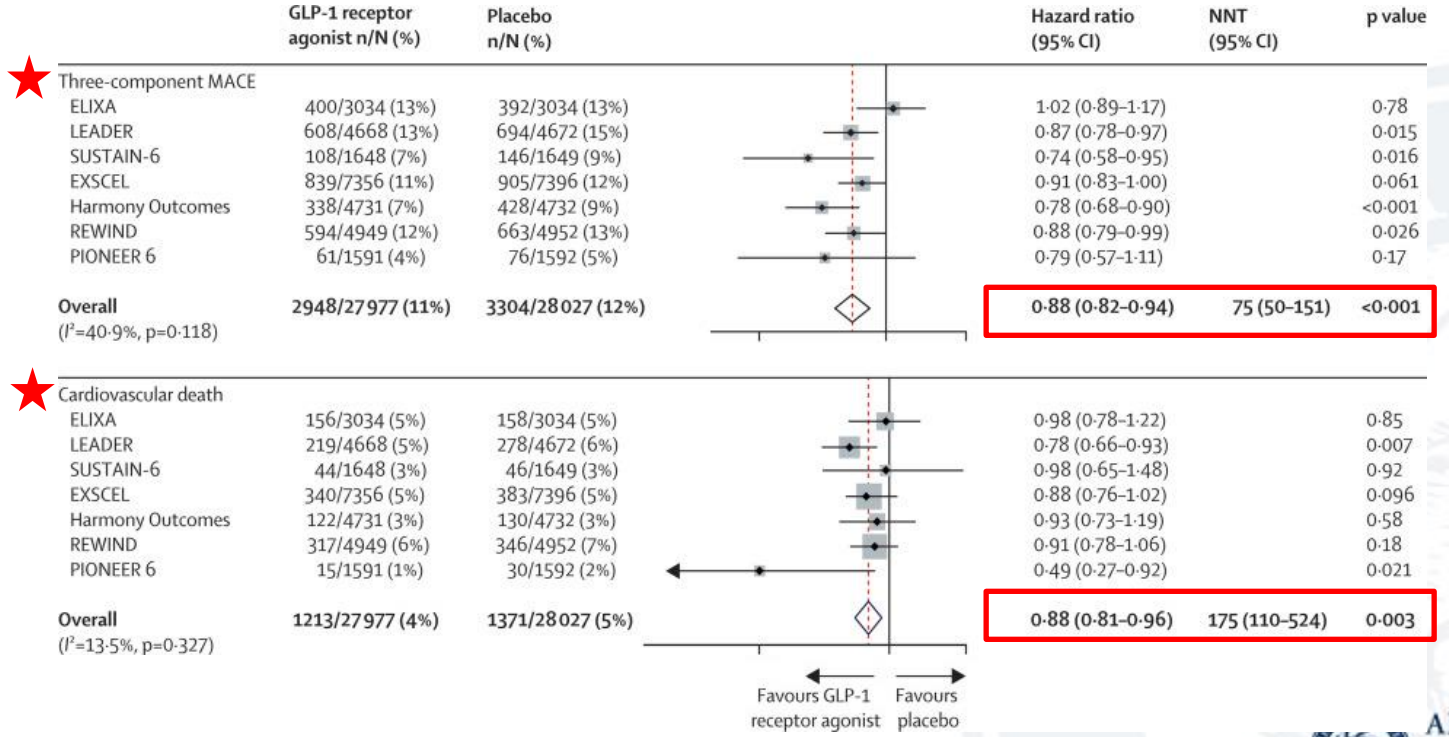
GLP-1RA: Meta-analysis



Kristensen, S.L. *Lancet Diabetes Endocrinol. 2019*

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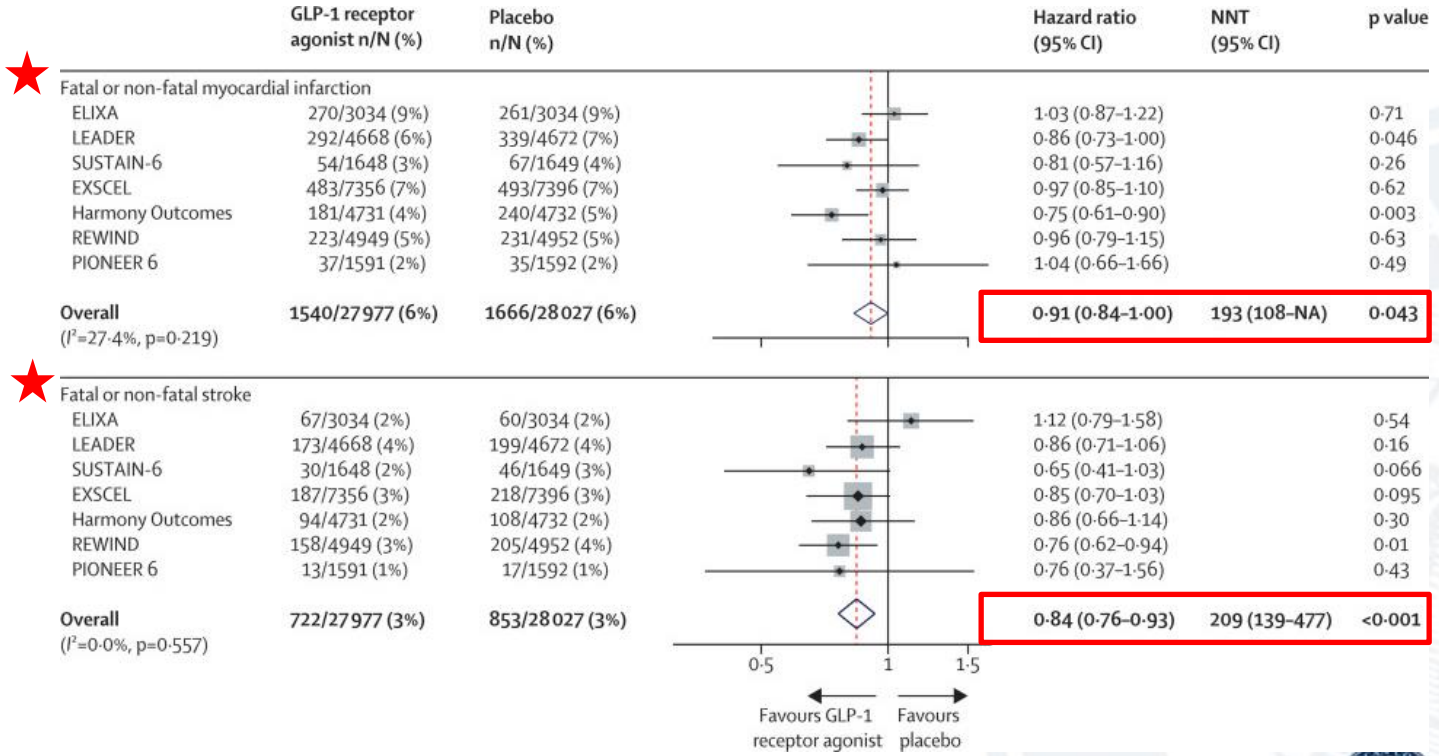
GLP-1RA: Meta-analysis



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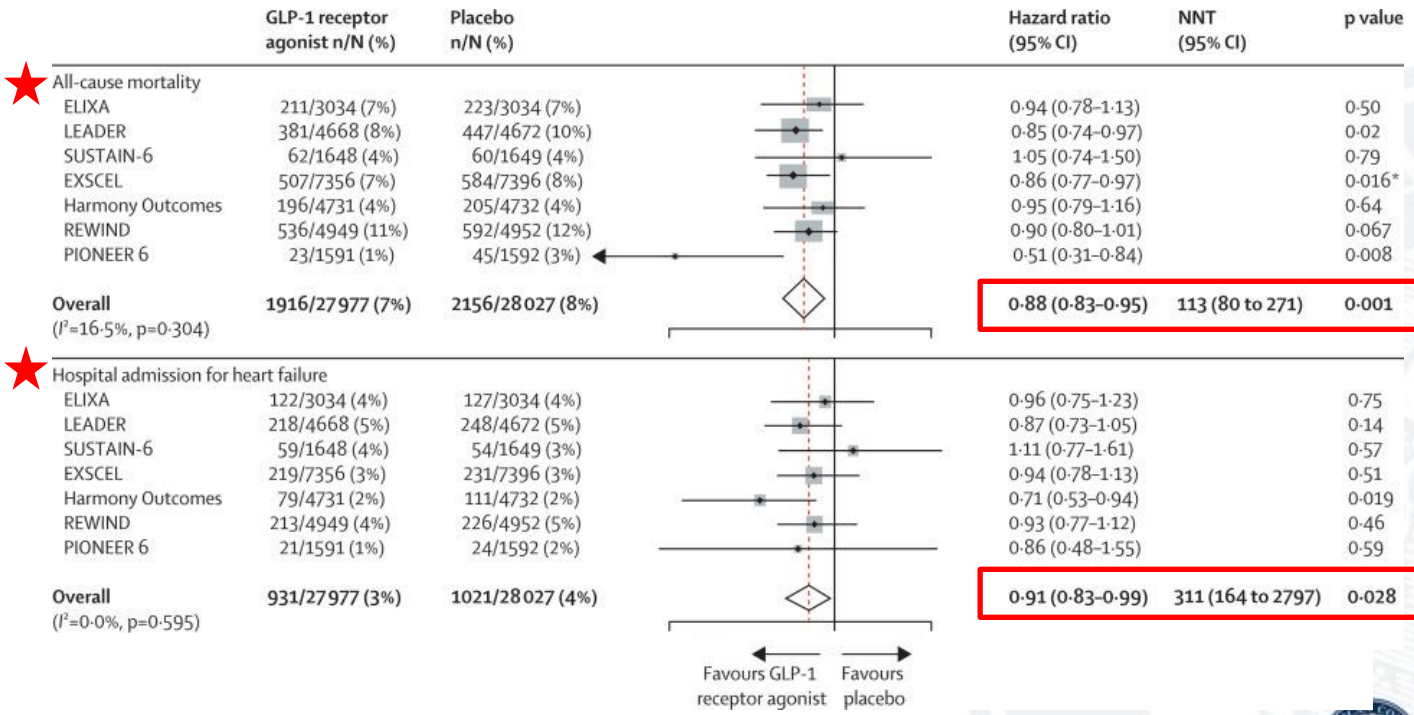

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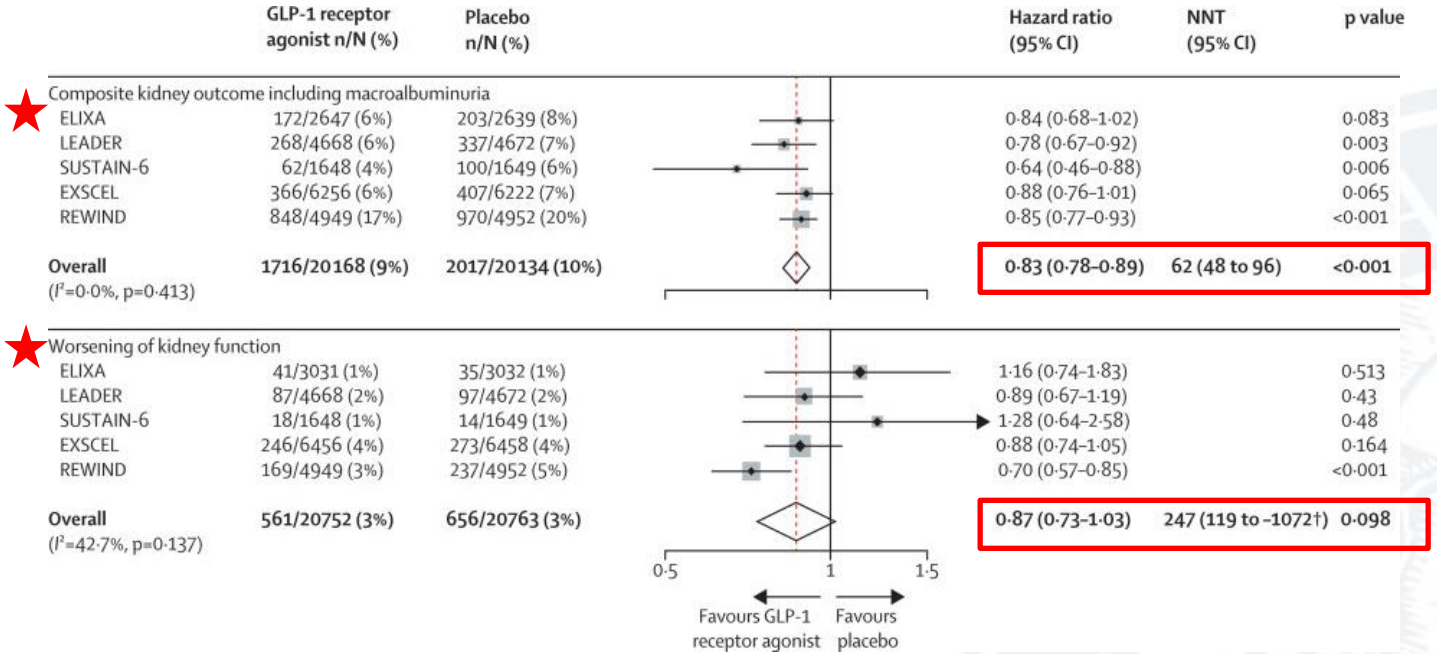

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Summary: MACE

	saxagliptin	alogliptin	sitagliptin	linagliptin		
DPP-4 inhibitor	= NEUTRAL	= NEUTRAL	= NEUTRAL	= NEUTRAL		
	liraglutide	lixisenatide	semaglutide	exenatide	albiglutide	dulaglutide
GLP-1 RA	✓ BENEFICIAL	= NEUTRAL	✓ BENEFICIAL	= NEUTRAL	✓ BENEFICIAL	✓ BENEFICIAL
	empagliflozin	canagliflozin	dapagliflozin	ertugliflozin		
SGLT2-Inhibitor	✓ BENEFICIAL	✓ BENEFICIAL	= NEUTRAL	**Q2 2020**		

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Summary: HF

	saxagliptin	alogliptin	sitagliptin	linagliptin		
DPP-4 inhibitor	✗ INCREASED RISK	= NEUTRAL	= NEUTRAL	= NEUTRAL		
	liraglutide	lixisenatide	semaglutide	exenatide	albiglutide	dulaglutide
GLP-1 agonist	= NEUTRAL	= NEUTRAL	= NEUTRAL	= NEUTRAL	= NEUTRAL	= NEUTRAL
	empagliflozin	canagliflozin	dapagliflozin	ertugliflozin		
SGLT2-Inhibitor	✓ BENEFICIAL	✓ BENEFICIAL	✓ BENEFICIAL	**Q2 2020**		

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