AACE
Orlando
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EMPA-REG Results: Implications for CVD Prevention in Type 2 Diabetes Therapy

Robert H. Eckel, MD
Professor of Medicine
University of Colorado Anschutz Medical Campus
Aurora, CO

Metabolic Basis of Increased Atherosclerosis: Diabetes & Beyond

- Metabolic substrates
  - Glucose
  - Fatty acids
  - Lipoproteins
- ↑ Inflammation
- ↑ Oxidation/Glycoxidation
- ↑ Endothelial dysfunction
- Pro-thrombotic state
  - ↑ thrombosis
  - ↓ fibrinolysis

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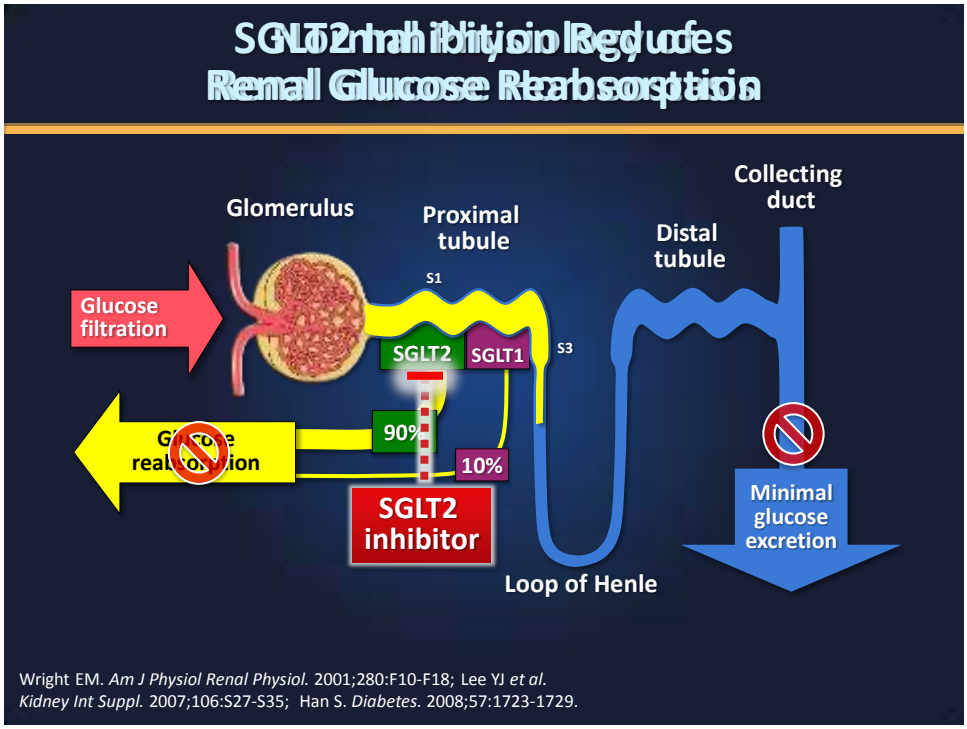
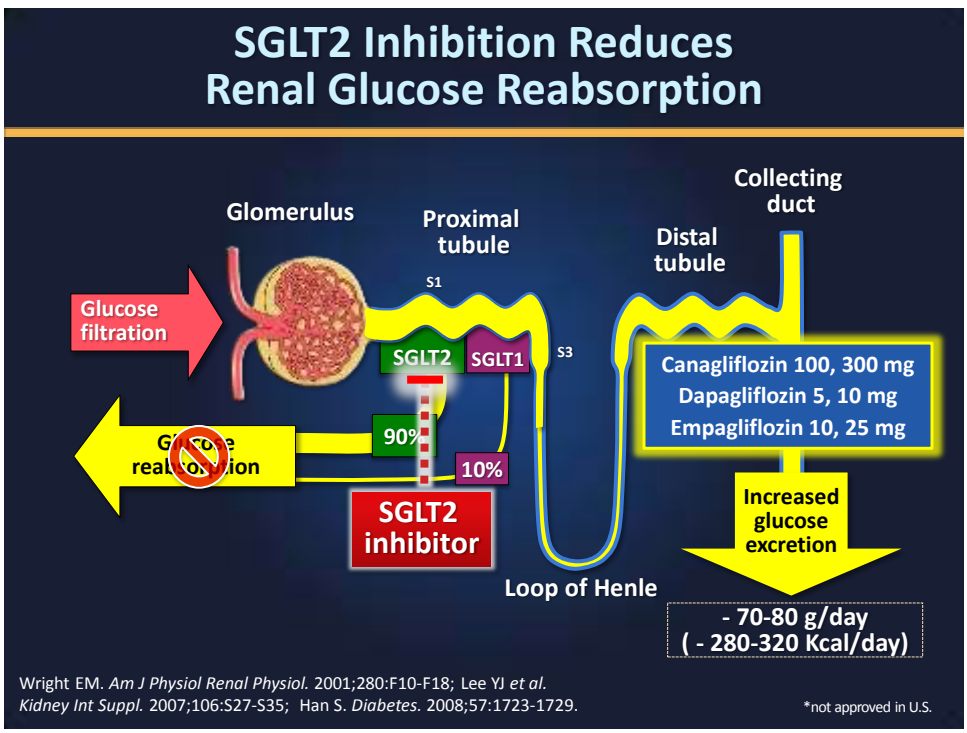
Learning Objectives

At the conclusion of this activity, the participant will be able to:

1. **Describe the mechanism of action of the SGLT2 inhibitors.**
2. **Review the main findings of the EMPA-REG OUTCOME trial.**
3. **Discuss the implicatons that the EMPA-REG OUTCOME trial has for CVD risk reduction in diabetes treatment.**



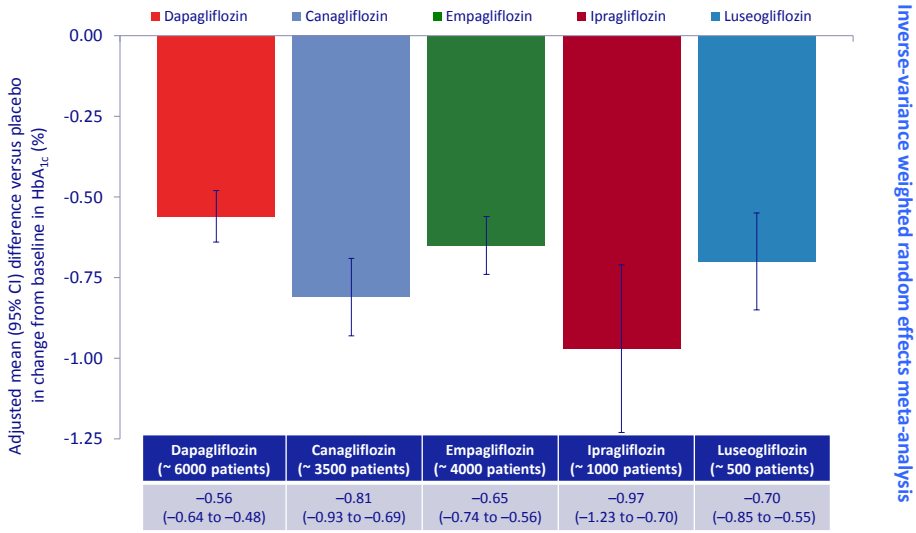
Wright EM. *Am J Physiol Renal Physiol.* 2001;280:F10-F18; Lee YJ *et al.* *Kidney Int Suppl.* 2007;106:S27-S35; Han S. *Diabetes.* 2008;57:1723-1729.



Wright EM. *Am J Physiol Renal Physiol.* 2001;280:F10-F18; Lee YJ *et al.* *Kidney Int Suppl.* 2007;106:S27-S35; Han S. *Diabetes.* 2008;57:1723-1729.

*not approved in U.S.

Placebo-corrected change from baseline in HbA1c

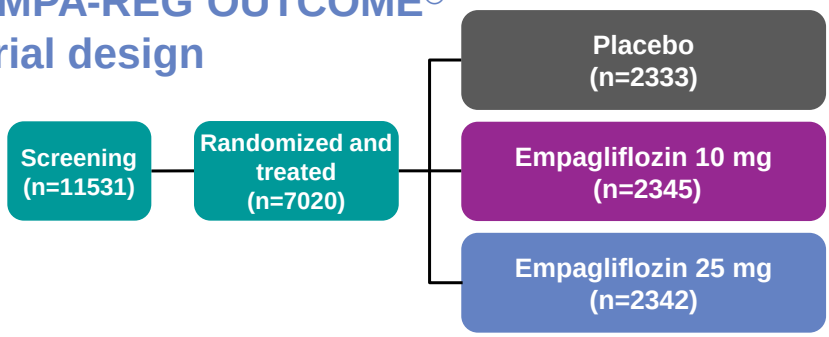


Pooled results for 22 dapagliflozin, 11 empagliflozin, 9 canagliflozin, 7 ipragliflozin and 3 luseogliflozin studies with ≥ 12 weeks duration from published and gray literature sources through June 30, 2014 [search strategy adapted from *Vasilakou et al. Ann Intern Med. 2013;159(4):262-274*]. Results are presented for the group allocated to the highest, most common dose across studies. SGLT2: sodium glucose cotransporter 2, CI: confidence interval, HbA_{1c}: haemoglobin A_{1c}.

Courtesy, A. Tsapas MD, Aristotle Univ, Thessaloniki, Greece

Vasilakou D, et al. Ann Intern Med. 2013;159:262-74.

EMPA-REG OUTCOME® Trial design



- **Study medication was given in addition to standard of care.**
- **Primary outcome: 3-point MACE**
- **Analysis: Placebo vs. pooled empagliflozin groups**
- **Key inclusion criteria:**
  - Adults with type 2 diabetes and established CVD
  - BMI ≤45 kg/m^2; HbA1c 7–10%; eGFR ≥30 mL/min/1.73m^2 (MDRD)

Zinman B *et al. N Engl J Med* 2015;373:2117-28

EMPA-REG OUTCOME

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Baseline characteristics

	Placebo (n=2333)	Empagliflozin 10 mg (n=2345)	Empagliflozin 25 mg (n=2342)
Age, years	63.2 (8.8)	63.0 (8.6)	63.2 (8.6)
Body mass index, kg/m^2	30.7 (5.2)	30.6 (5.2)	30.6 (5.3)
HbA1c, %	8.08 (0.84)	8.07 (0.86)	8.06 (0.84)
eGFR*, mL/min/1.73m^2	73.8 (21.1)	74.3 (21.8)	74.0 (21.4)
<60 mL/min/1.73m^2∞	607 (26.0%)	605 (25.8%)	607 (25.9%)
Glucose-lowering medication			
Metformin	1734 (74.3)	1729 (73.7)	1730 (73.9)
Sulphonylurea	992 (42.5)	985 (42.0)	1029 (43.9)
Thiazolidinedione	101 (4.3)	96 (4.1)	102 (4.4)
Insulin	1135 (48.6)	1132 (48.3)	1120 (47.8)

Data are n (%) or mean (SD) in patients treated with ≥1 dose of study drug

∞ According to approved EU label, empagliflozin should not be initiated in patients with eGFR < 60 ml/min/1.73m^2

* Based on MDRD, Modification of Diet in Renal Disease equation

EMPA-REG OUTCOME

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Baseline characteristics

	Placebo (n=2333)	Empagliflozin 10 mg (n=2345)	Empagliflozin 25 mg (n=2342)
Any CVD	2307 (98.9%)	2333 (99.5%)	2324 (99.2%)
Coronary artery disease	1763 (75.6%)	1782 (76.0%)	1763 (75.3%)
History of MI	1083 (46.4%)	1107 (47.2%)	1083 (46.2%)
History of stroke	553 (23.7%)	535 (22.8%)	549 (23.4%)
Anti-hypertensive therapy	2221 (95.2%)	2227 (95.0%)	2219 (94.7%)
ACE inhibitors/ARBs	1868 (80.1%)	1896 (80.9%)	1902 (81.2%)
Diuretics	988 (42.3%)	1036 (44.2%)	1011 (43.2%)
Lipid-lowering drugs	1864 (79.9%)	1926 (82.1%)	1894 (80.9%)
Statins	1773 (76.0%)	1827 (77.9%)	1803 (77.0%)
Anti-coagulants and anti-platelets	2090 (89.6%)	2098 (89.5%)	2064 (88.1%)
Acetylsalicylic acid	1927 (82.6%)	1939 (82.7%)	1937 (82.7%)

Data are n (%) in patients treated with ≥1 dose of study drug

*Based on narrow standardised MedDRA query "cardiac failure"

EMPA-REG OUTCOME

Zinman B *et al. N Engl J Med* 2015;373:2117-28\

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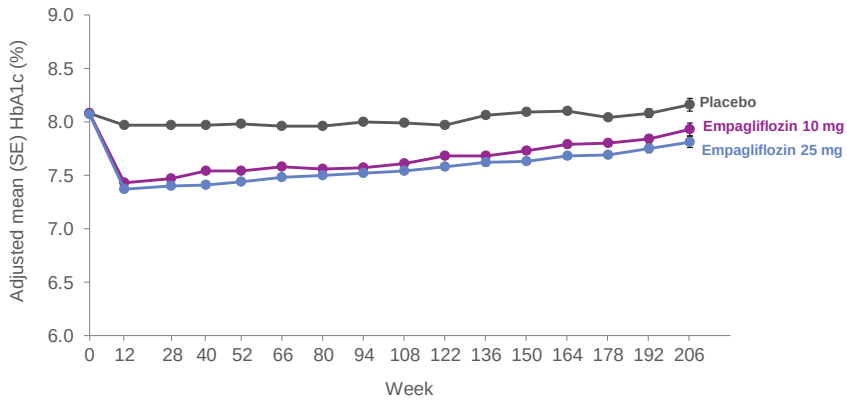
EMPA-REG: Treatment and Observation Times

	Placebo (n=2333)	Pooled Empagliflozin (n=4687)
Treatment: Median (interquartile range)	**2.6 (1.8-3.40) years**	**2.6 (2.0-3.4) years**
Observation: Median (interquartile range)	**3.1 (2.2-3.5) Years**	**3.2 (2.2-3.6) years**

Zinman B et al, *NEJM* 373:2117, 2015

HbA1c



Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozin 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
Empagliflozin 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat)X-axis: timepoints with reasonable amount of data available for pre-scheduled measurements

Zinman B *et al. N Engl J Med* 2015;373:2117-28

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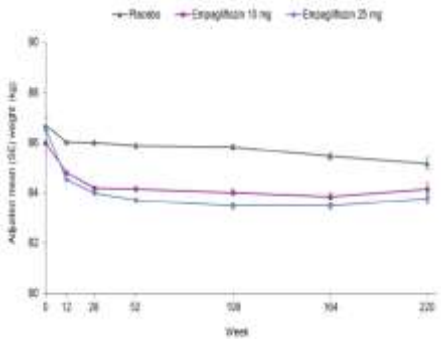
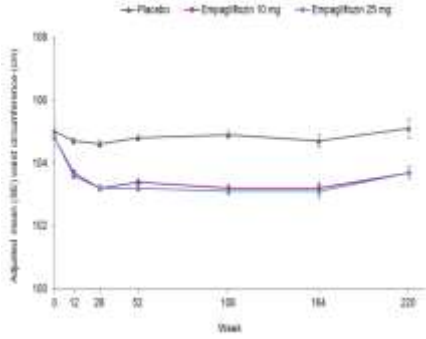
EMPA-REG: Weight and Waist Circumference

Weight



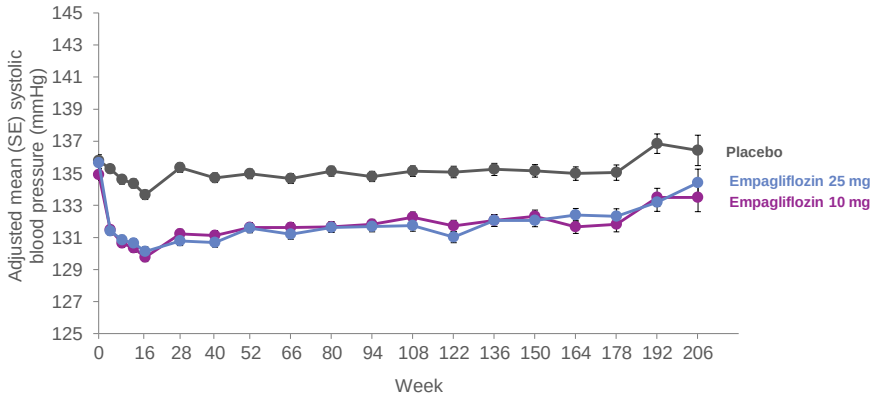
Waist Circumference



EMPA-REG OUTCOME®

Zinman B et al, *NEJM* 373:2117, 2015

Systolic blood pressure



Placebo	2322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
Empagliflozin 10 mg	2322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
Empagliflozin 25 mg	2323	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat)X-axis: timepoints with reasonable amount of data available for pre-scheduled measurements

EMPA-REG OUTCOME®

Zinman B *et al. N Engl J Med* 2015;373:2117-28

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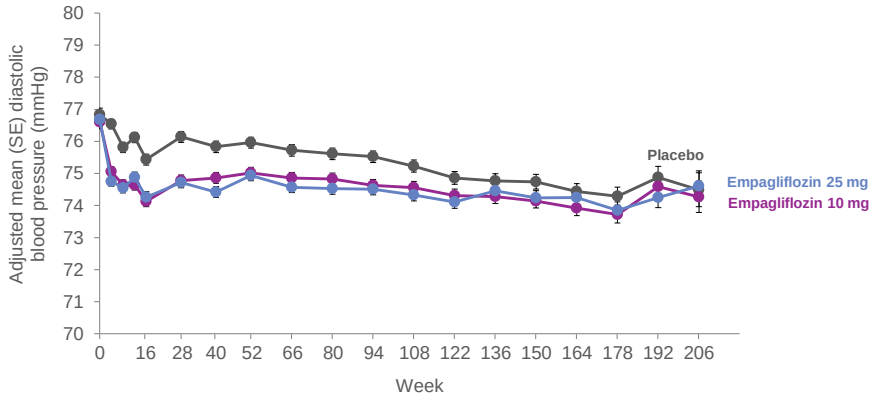
Diastolic blood pressure



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EMPA-REG OUTCOME

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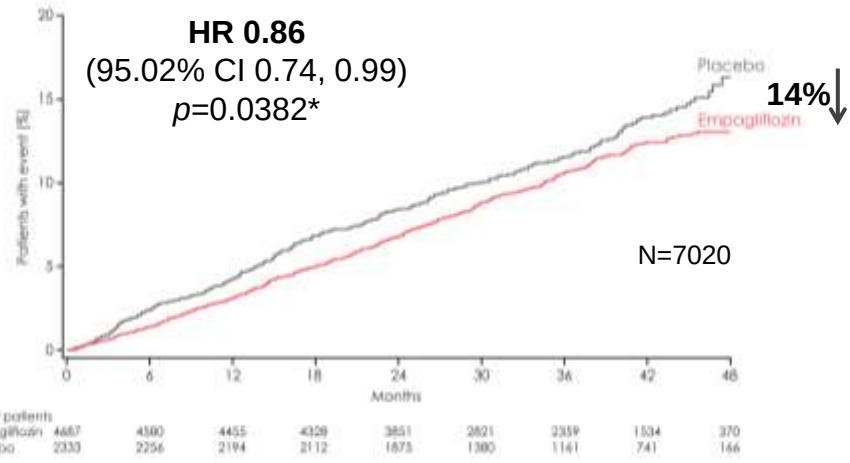
Primary outcome: 3-point MACE



Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.
* Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)

EMPA-REG OUTCOME

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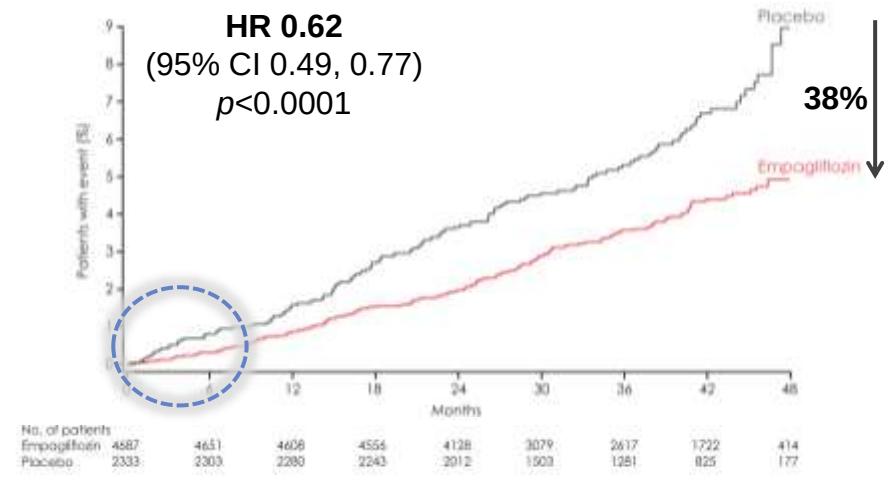
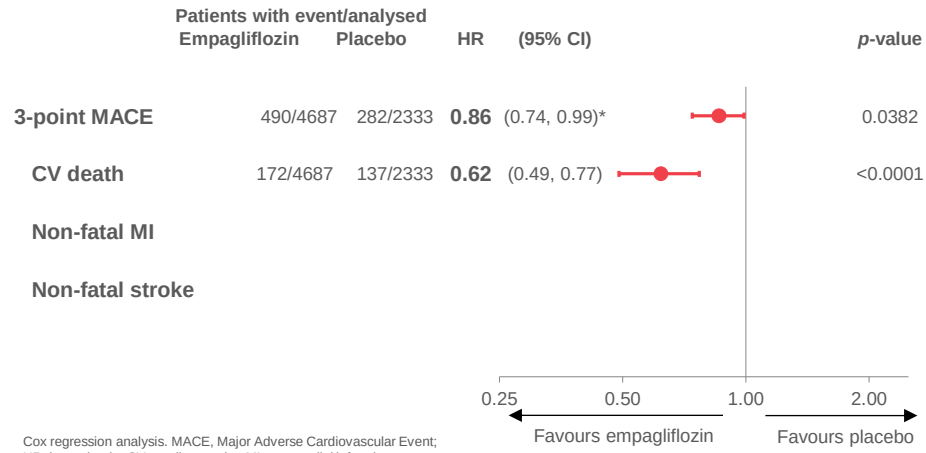
CV death



Cumulative incidence function. HR, hazard ratio

Zinman B *et al. N Engl J Med* 2015;373:2117-28

CV death, MI and stroke

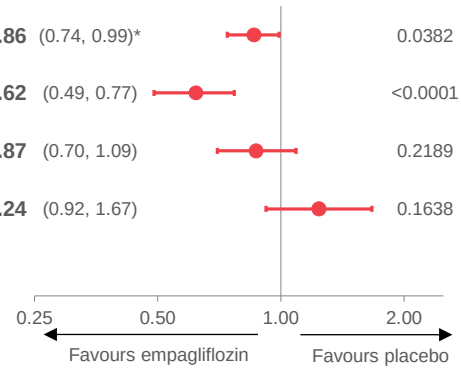


Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction
*95.02% CI

Zinman B *et al. N Engl J Med* 2015;373:2117-28

CV death, MI and stroke

	Patients with event/analysed Empagliflozin	Placebo	HR	(95% CI)	*p*-value
3-point MACE	490/4687	282/2333	**0.86**	(0.74, 0.99)*	0.0382
CV death	172/4687	137/2333	**0.62**	(0.49, 0.77)	<0.0001
Non-fatal MI	213/4687	121/2333	**0.87**	(0.70, 1.09)	0.2189
Non-fatal stroke	150/4687	60/2333	**1.24**	(0.92, 1.67)	0.1638



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EMPA-REG OUTCOME

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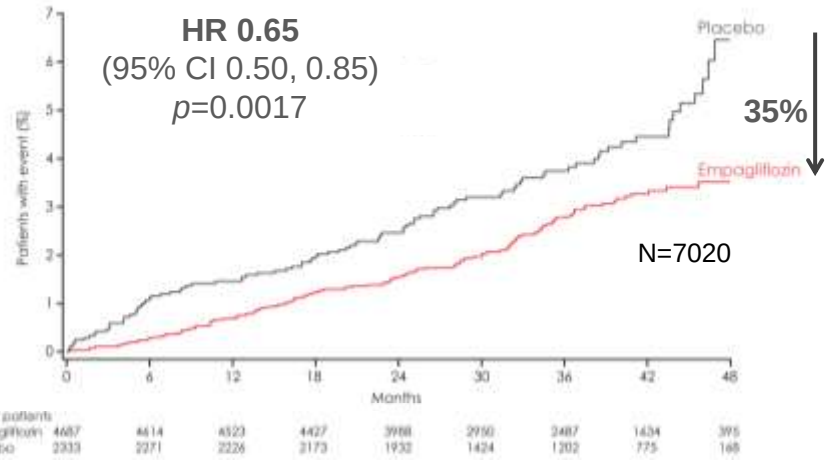
Hospitalization for heart failure

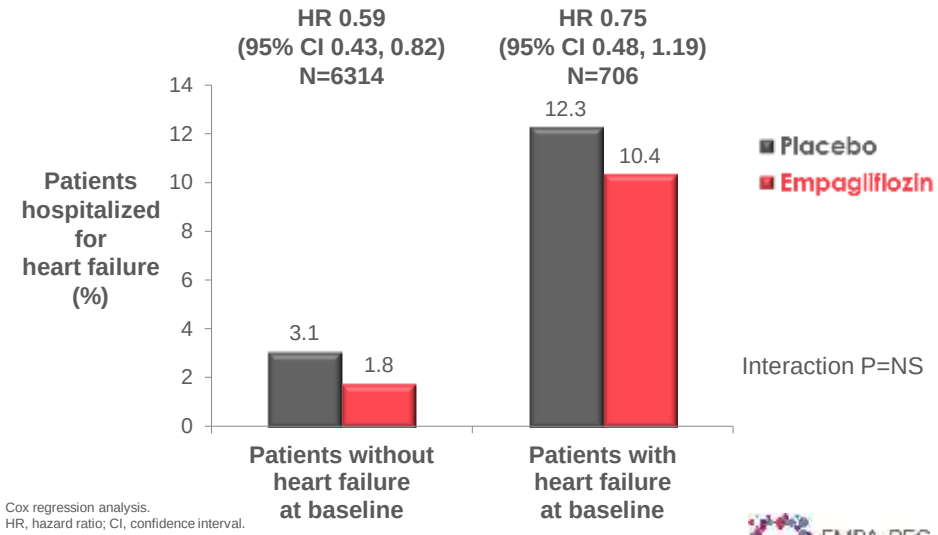


Cumulative incidence function. HR, hazard ratio

EMPA-REG OUTCOME

Zinman B *et al. N Engl J Med* 2015;373:2117-28

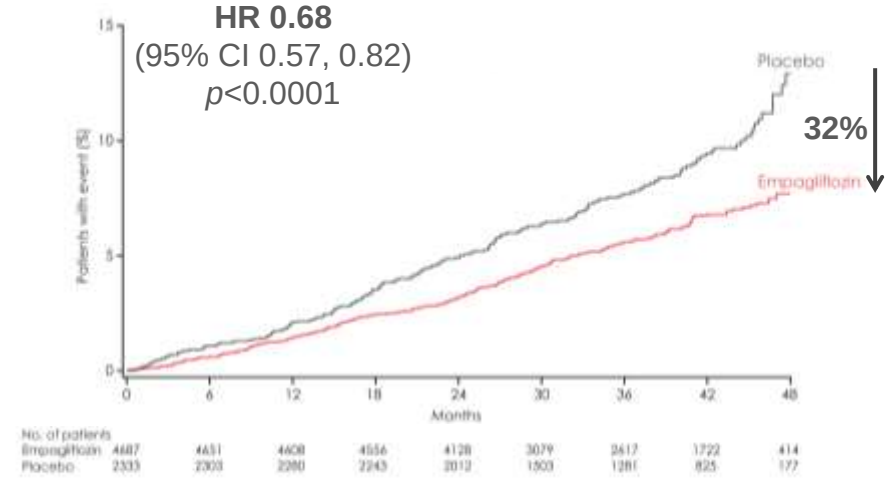
Hospitalization for heart failure in patients with *vs.* without heart failure at baseline



Cox regression analysis.
HR, hazard ratio; CI, confidence interval.

Fitchett D *et al. Eur Heart J* 2016 Jan 26. pii: ehv728

All-cause mortality



Kaplan-Meier estimate. HR, hazard ratio

Zinman B *et al. N Engl J Med* 2015;373:2117-28

Predefined AEs of special interest

	Placebo (n=2333)		Empagliflozin 10 mg (n=2345)		Empagliflozin 25 mg (n=2342)	
	n (%)	Rate/ 100 pt-years	n (%)	Rate/ 100 pt-years	n (%)	Rate/ 100 pt-years
Diabetic ketoacidosis	1 (<0.1)	0.02	3 (0.1)	0.05	1 (<0.1)	0.02
Urinary tract infection	423 (18.1)	8.21	426 (18.2)	8.02	416 (17.8)	7.75
Complicated UTI	41 (1.8)	0.71	34 (1.4)	0.57	48 (2.0)	0.80
Genital infection	**42 (1.8)**	**0.73**	**153 (6.5)**	**2.66**	**148 (6.3)**	**2.55**
Confirmed hypoglycemia AEs[1]	650 (27.9)	–	656 (28.0)	–	647 (27.6)	–
Hepatic injury	108 (4.6)	1.91	80 (3.4)	1.35	88 (3.8)	1.48
Decreased renal function (including AKI)	155 (6.6)	2.77	121 (5.2)	2.07	125 (5.3)	2.12
Volume depletion	115 (4.9)	2.04	115 (4.9)	1.97	124 (5.3)	2.11
Hypersensitivity	197 (8.4)	3.59	158 (6.7)	2.75	181 (7.7)	3.14
Bone fractures	91 (3.9)	1.61	92 (3.9)	1.57	87 (3.7)	1.46
Venous thrombotic events	20 (0.9)	0.35	9 (0.4)	0.15	21 (0.9)	0.35

Treated set (patients randomised and treated with at least one dose of study drug)

EMPA-REG OUTCOME

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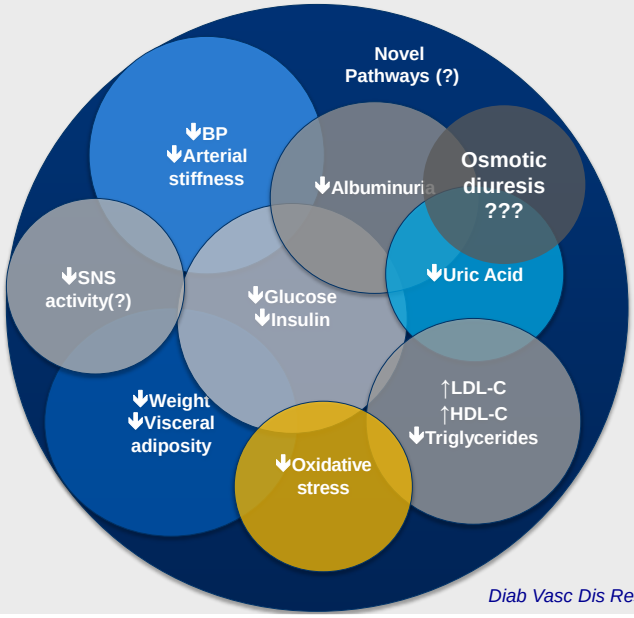
What was the underlying reason(s) for the dramatic benefit on CV outcomes observed in EMPA-REG?



Inzucchi SE *et al.*
Diab Vasc Dis Res 2015;12:90-100

SGLT2 Inhibitors: Risks & Benefits*

BENEFITS

- Insulin-independent glucose lowering effect (irrespective of DM duration)
- Low hypoglycemia rates
- Modest ↓ weight
- Modest ↓ BP
- ↓ uric acid
- ↓ Albuminuria
- Small ↓ TGs

RISKS

- **DKA**
- Genital mycotic infections
- ? UTIs
- Polyuria / Dehydration
- Reversible ↓ GFR
- Small ↑ Hgb/Hct
- Small ↑ LDL-C
- ? Fractures

* Prior to CV outcomes trial(s)

Kim Y et al. *Diabetes Metab Syndr Obes*. 2012;5:313-327.
Inzucchi SE et al. *Diabetes Care* 2015;38:140-159

*not approved for weight loss; BMI, WC, BP, TG, albuminuria reduction; or to increase HDL-C

Large CV Outcomes Trials in Diabetes (Non-Insulin)

Study	SAVOR	EXAMINE	TECOS	CAROLINA	CARMELINA
DPP4-i	saxagliptin	alogliptin	sitagliptin	linagliptin	linagliptin
Comparator	pl…	pl…	pl…	sulfonylurea	placebo
N	…,500	…,400	…,000	6,000	8,300
Results	2013	2013	2015	2017	2017

NEUTRAL

Study	LEADER	ELIXA	SUSTAIN 6	EXSCEL	REWIND
GLP1-RA	liraglutide	lixisenatide	semaglutide	exenatide LR	dulaglutide
Comparator	p…	pla…	…o	placebo	placebo
N	16,500	…,000	6,000	5,400	8,300
Results	2016	2015	2016	2018	2019

NEUTRAL

Study	EMPA-REG	CANVAS	DECLARE	NCT01986881
SGLT-2-i	empaglifozin	canagliflozin	dapagliflozin	ertugliflozin
Comparator	p…	placebo	placebo	placebo
N	7300	4300	22,200	3900
Results	2015	2017	2019	2020

EMPA-REG: Impact on Diabetes Therapy

SUMMARY

1. SGLT2-i's exert their glucose-lowering effect through the augmentation of urinary glucose excretion and are associated with modest weight loss and BP reduction.
2. Risks include DKA, GU infections, & polyuria/dehydration.
3. In the first SGLT2-i CV outcome trial (OT), empagliflozin ↓'d 3-pt MACE (CV death) & HF hospitalizations.
4. The drug also had a significant benefits on renal outcomes.
5. The mechanisms behind these effects are not clear.
6. Other CVOT's with other SGLT2-i's are currently underway.
7. Guidelines writers will need to consider these findings when developoing future T2DM treatment algorithms.