CANVAS Program
Independent commentary

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Disclosures and disclaimers

Clifford J Bailey

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CANVAS Program. Independent commentary

Overview

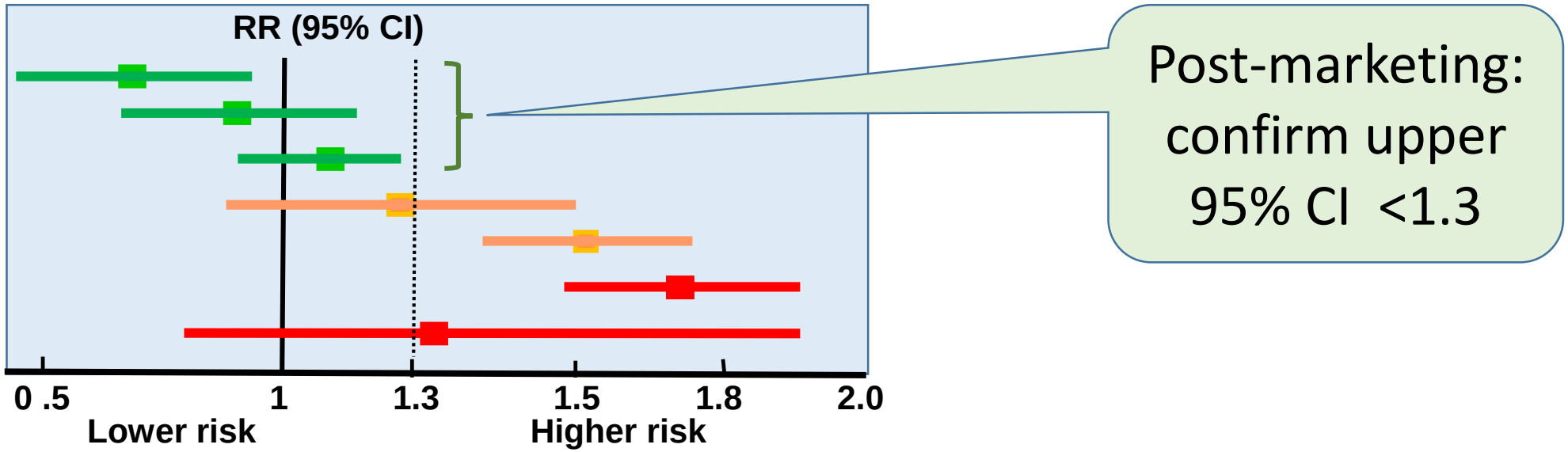
- Background
- Design
- Statistical analysis
- Conduct
- Interpretation
- Limitations
- Implications for clinical practice

CANVAS Program. Background

FDA, Guidance for Industry, 2008

Include type 2 diabetes patients at higher risk of CV events

- **Pre-specified analysis of CV events in phase 2/3 studies**
  - adjudicated CV mortality, MI, stroke, and can include hospitalization for ACS, urgent revascularization and possibly other endpoints.
- **Post-marketing trial**
  - to definitely show upper 95% is <1.3



FDA, Food and Drug Administration; CV, cardiovascular; ACS, acute coronary syndrome; CI, confidence interval; MI, myocardial infarction; RR, risk ratio.

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER),, December 2008

CANVAS and CANVAS-R. Design

Both Randomized, Double-Blind, Placebo-Controlled in T2DM. Canagliflozin 100 or 300 mg/d. Time to event

	CANVAS (start 2009)	**CANVAS-R** (start 2014)
1º end point	3 pt MACE (CV death, NF MI, NF stroke)	Progression of albuminuria*
2º end point	Fasting insulin secretion, Progression of albuminuria Effectiveness of lowering blood glucose (in sub-studies with other diabetes agents)	Composite of CV death or hospitalization for heart failure Death from CV Causes
Other endpoint		3 pt MACE (CV death, NF MI, NF stroke)
Inclusion	N=4,330, T2DM, HbA1c 7 -10.5%	N=5,812, T2DM, HbA1c 7-10.5%
CV status	≥30 yrs, history of CV disease, or ≥50 yrs, ≥2 risk factors for CV disease**	≥30 yrs, history of CV disease, or ≥50 yrs, ≥2 risk factors for CV disease**
Amended	**CANVAS was originally designed for up to 9 years. As per FDA post-marketing requirements for canagliflozin, the study's last subject last visit will now occur when enough MACE events (ie, CV death, nonfatal myocardial infarction, nonfatal stroke) are accumulated between the CANVAS and CANVAS-R studies.**	

* number who develop micro- or macro-albuminuria if baseline normoalbuminuria ***OR*** number who develop macro-albuminuria if baseline micro-albuminuria, with urinary albumin/creatinine ratio (ACR) increase ≥ 30% from baseline.

** diabetes ≥10 yrs, SBP >140 mmHg while on ≥1 antihypertensive agents, current smoker, micro- or macroalbuminuria, HDL-C <1 mmol/L.

MACE, major adverse cardiac events; NF non-fatal, MI myocardial infarction

https://clinicaltrials.gov/ct2/show/NCT01032629 https://clinicaltrials.gov/ct2/show/NCT01989754

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CANVAS Program. Statistical analysis

Modified statistical analysis plan

with input by FDA

Purpose

- Maximise opportunity for new discoveries from the data

Actual changes

- Integrate datasets of CANVAS and CANVAS-R
- Include more efficacy and safety parameters
- Additional sequential testing (includes original)

Extra CV & renal outcomes
DKA, fractures, amputations

Avoid bias

- Worse case imputation of missing data
- Interim unblinded data (2012) are small proportion of total

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Interim analysis in 2012

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CANVAS Program. Conduct

Features of a well conducted clinical trial

Feature	Success
Population - appropriate	✓
Recruitment – any biases	✓
Power – event driven	✓
Retention	✓
Monitoring/documentation	✓
Adherence	✓
Adjudication of events	✓
Data handling	✓

Conduct categories based on World Health Organization WHO Technical Report Series, No. 850, 1995, Annex 3 Guidelines for good clinical practice (GCP) for trials on pharmaceutical products

CV outcome trials: different populations

Baseline characteristics of type 2 diabetes populations

	SGLT-2 inhibitors		GLP-1 receptor agonists			DPP-4 inhibitors		
Trial →	**EMPA-REG**	**CANVAS**	**ELIXA**	**LEADER**	**SUSTAIN**	**SAVOR**	**EXAMINE**	**TECOS**
Baseline	**Empagliflozin**	**Canagliflozin**	**Lixisenatide**	**Liraglutide**	**Semaglutide**	**Saxagliptin**	**Alogliptin**	**Sitagliptin**
n	7,020	10,142	6,068	9,340	3,297	16,492	5,400	14,671
Age (yr)	63	63.3	60	64.3	64.6	65	61	66
Diabetes (yr)	57%>10y	13.5	9.3	12.8	13.9	10	7.2	9.4
BMI (kg/m^2)	30.6	32.0	30.1	32.5	32.8	31	29	29
Insulin (%)	48	50	39	44	58	41	30	23
HbA1c (%)	8.1	8.2	7.7	8.7	8.7	8.0	8.0	7.3
Prior CV disease (%)	99	65	100	~81	~83	78	100	100
Types of prior CV disease	MI, CHD, CVD, PVD	MI, CHD, CVD, PVD	ACS <180 days	≥50y + CV disease* or CKD or ≥60y + ≥1 CV risk factor		≥40y + CV dis (CHD, CVD, PVD) or ≥55y + ≥1 CV risk factor	ACS <90 days	CHD, CVD, PVD
Hypertension (%)	94	89.9	76.4	92	92.8	81	83	86
Follow-up (yr)	3.1	3.6	2.1	3.8	2.1	2.1	1.5	2.8

Test agent or placebo given as add-on to usual care, aiming for glycaemic equipoise

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65% prior CV disease

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3pt MACE	**0.86*** 0,74, 0.99		**1.02** 0.89,1.17	**0.87*** 0.78. 0.97	**0.74*** 0.58, 0.95	**1.0** 0.89, 1.08	**0.96** Upper ≤1.16	**0.98^** 0.89, 1.08
CV death	**0.62*** 0.49, 0.77		**0.98** 0,78, 1.22	**0.78*** 0.66, 0.93	**0.98** 0.65. 1.48	**1.03** 0.87, 1.22	**0.79** 0.60, 1.04	**1.03** 0.89, 1.19
Non-fatal MI	**0.87** 0.70, 1.09		**1.03⁺** 0.87, 1.22	**0.88** 0.75, 1.03	**0.74** 0.51, 1.08	**0.95** 0.80, 1.12	**1.08** 0.88, 1.33	**0.95⁺** 0.81, 1.11
Non-fatal stroke	**1.24** 0.92, 1.67		**1.12⁺** 0.79, 1.58	**0.89** 0.72, 1.11	**0.61*** 0.38, 0.99	**1.11** 0.88, 1.39	**0.91** 0.55, 1.50	**0.97⁺** 0.89, 1.08
Hospitalized HF	**0.65*** 0.50, 0.85		**0.96** 0.75, 1.23	**0.87** 0.73, 1.05	**1.11** 0.77, 1.61	**1.27*** 1.07, 1.51	**1.07** 0.78, 1.15	**1.00** 0.83, 1.20
All cause death	**0.68*** 0.57, 0.82		**0.94** 0.78, 1.13	**0.85*** 0.74, 0.97	**1.05** 0.74, 1.50	**1.11** 0.96, 1.27	**0.88** 0.71, 1.09	**1.01** 0.90, 1.14

* statistically significant. ^ TECOS !º endpoint was a 4pt MACE of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina. + Fatal and non-fatal MI and stroke CVD, cerebrovascular disease; Scirica BM, et al. New Engl J Med 2013;369:1317-1326; White WB, et al. N Engl J Med 2013;369:1327-1335; Bethel et al. 2015; Zinman et al. Cardiovasc Diabetol 2014;13:102-110. Pfeffer et al, N Engl J Med 2015; 373:2247-2257. Marso et al, N Engl J Med 2016; 375: 311-322; Marso et al, N Engl J Med, 2016, 375: 1834-44.

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CV death	**0.62*** 0.49, 0.77	**0.87** 0,72, 1.06	**0.98** 0,78, 1.22	**0.78*** 0.66, 0.93	**0.98** 0.65. 1.48	**1.03** 0.87, 1.22	**0.79** 0.60, 1.04	**1.03** 0.89, 1.19
Non-fatal MI	**0.87** 0.70, 1.09	**0.85** 0,69, 1.05	**1.03+** 0.87, 1.22	**0.88** 0.75, 1.03	**0.74** 0.51, 1.08	**0.95** 0.80, 1.12	**1.08** 0.88, 1.33	**0.95+** 0.81, 1.11
Non-fatal stroke	**1.24** 0.92, 1.67	**0.90** 0,71, 1.15	**1.12+** 0.79, 1.58	**0.89** 0.72, 1.11	**0.61*** 0.38, 0.99	**1.11** 0.88, 1.39	**0.91** 0.55, 1.50	**0.97+** 0.89, 1.08
Hospitalized HF	**0.65*** 0.50, 0.85	**0.67** 0,52, 0.87	**0.96** 0.75, 1.23	**0.87** 0.73, 1.05	**1.11** 0.77, 1.61	**1.27*** 1.07, 1.51	**1.07** 0.78, 1.15	**1.00** 0.83, 1.20
All cause death	**0.68*** 0.57, 0.82	**0.87** 0,74, 1.01	**0.94** 0.78, 1.13					**1.01** 0.90, 1.14

All cause death just missed statistical significance

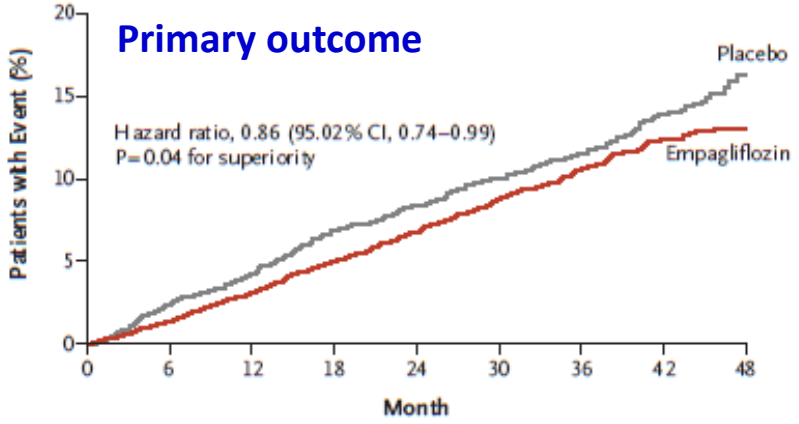
* statistically significant. ^ TECOS !º endpoint was a 4pt MACE of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina. + Fatal and non-fatal MI and stroke CVD, cerebrovascular disease; Scirica BM, et al. New Engl J Med 2013;369:1317-1326; White WB, et al. N Engl J Med 2013;369:1327-1335; Bethel et al. 2015; Zinman et al. Cardiovasc Diabetol 2014;13:102-110. Pfeffer et al, N Engl J Med 2015; 373:2247-2257. Marso et al, N Engl J Med 2016; 375: 311-322; Marso et al, N Engl J Med, 2016, 375: 1834-44.

EMPA-REG: Empagliflozin CV outcomes

N=7020, T2DM with CV disease, RDBPC design, Empa 10 or 25 mg/d added to standard care for median 3.1 yrs.

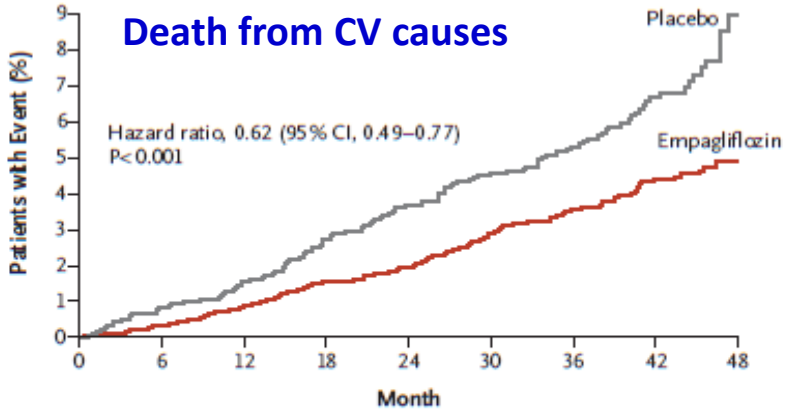
Age 63 yrs, Wt ~86 kg. 1º endpoint = 3pt MACE, composite of CV death, fatal and non-fatal MI and stroke

Primary outcome



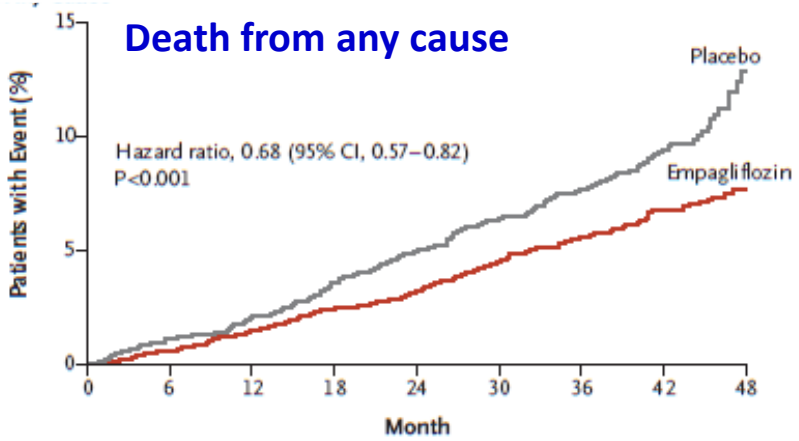
No. at Risk									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

Death from CV causes



No. at Risk									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Death from any cause



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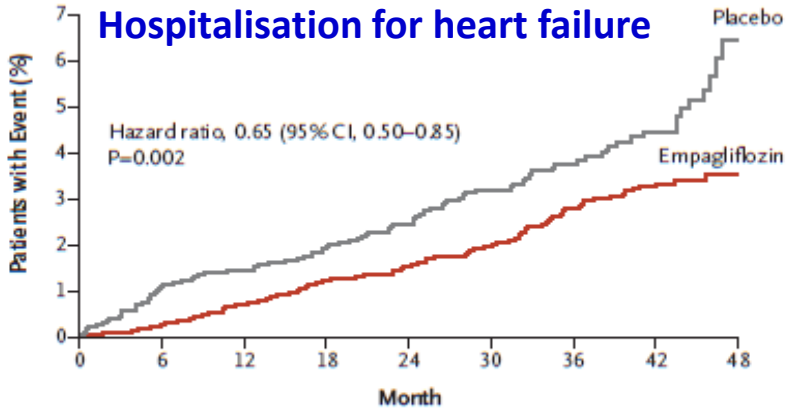
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Hospitalisation for heart failure



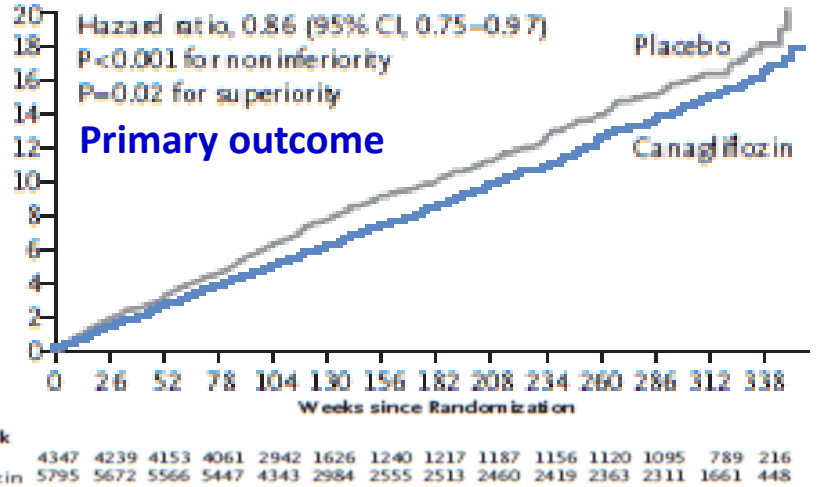
No. at Risk									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

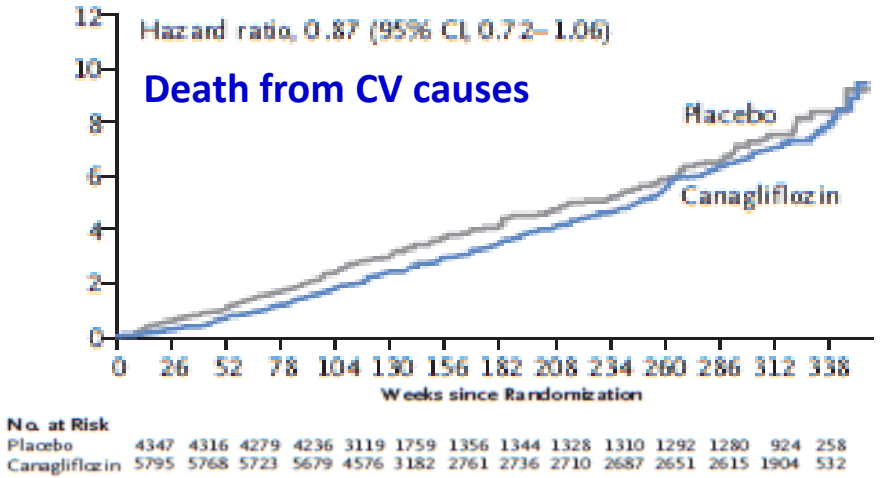
1º in 490/4687 (10.5%) in Empa gps vs 282/2333 (12.1%) in Pbo, HR 0.86; 95% CI 0.74 to 0.99; P = 0.04. N/S differences in MI or stroke, but Empa lowered rates of CV deaths (3.7%, vs. 5.9%; RRR 38%), hospitalization for HF (2.7% vs 4.1%, RRR 35%), and death from any cause (5.7% vs 8.3%, RRR 32%).

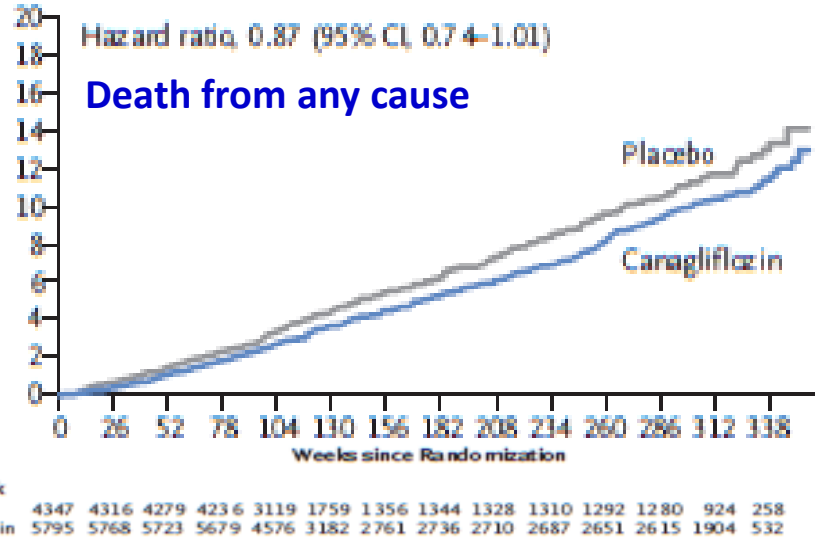
Zinman et al, N Engl J Med 2015; 373:2117-2128

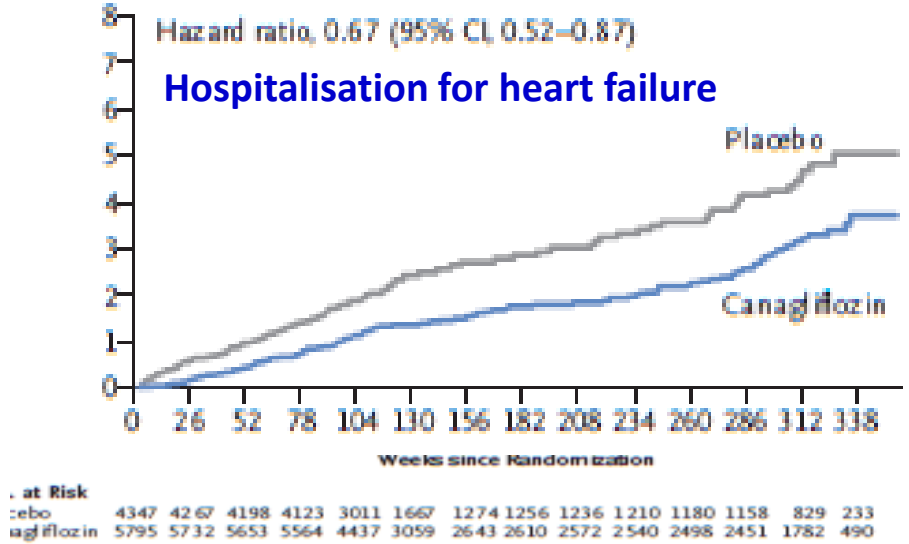
CANVAS Program. CV outcomes

N=10,142, T2DM, 65% with CV disease, RDBPC design, Cana 100 or 300 mg/d added to standard care for median 3.6 yrs.
Age 63 yrs, HbA1c 8.2%, BMI 32 kg/m^2. 1^o endpoint = 3pt MACE, composite of CV death, fatal and non-fatal MI and stroke









1^o in 490/4687 (10.5%) in Empa gps vs 282/2333 (12.1%) in Pbo, HR 0.86; 95% CI 0.75 to 0.97; P = 0.015. N/S differences in individual components of CV death, MI or stroke, while all cause death narrowly missed significance HR 0.87; 95% CI 0.74 to 1.01. decrease in hospitalization for HF 0.67; 95% CI 0.52 to 0.87.

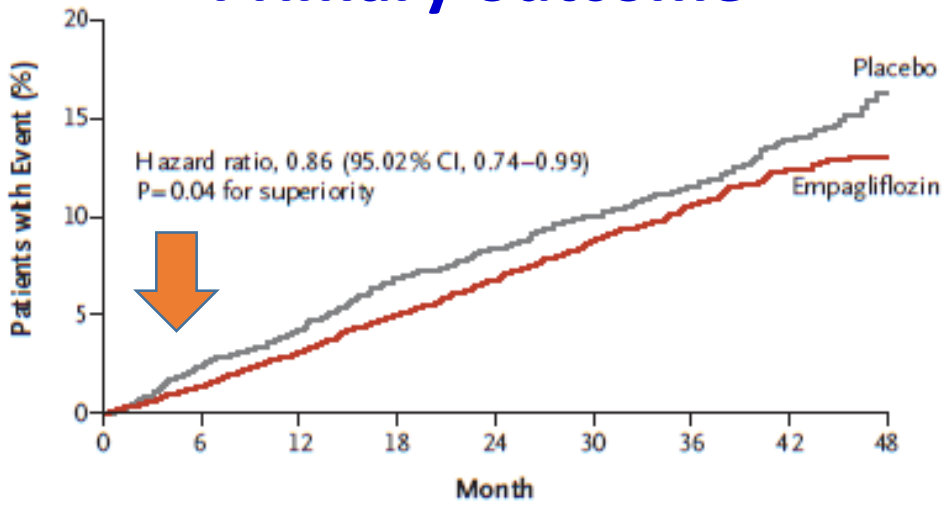
Neal et al, N Engl J Med 2017, DOI. 10.1056/NEJMoa1611925

EMPA-REG vs CANVAS: CV outcomes

Onset of primary CV composite endpoint

EMPA-REG

Primary outcome



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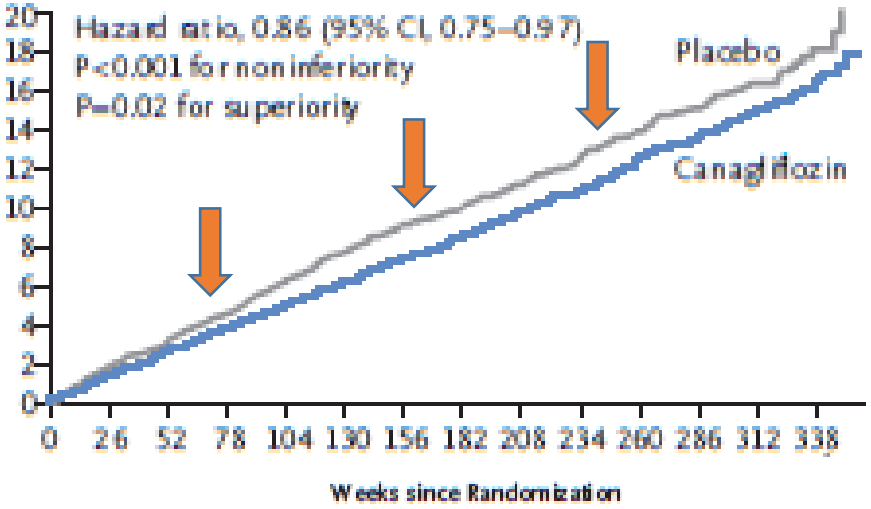
CANVAS

Primary outcome



No. at Risk															
Placebo	4347	4239	4153	4061	2942	1626	1240	1217	1187	1156	1120	1095	789	216
Canagliflozin	5795	5672	5566	5447	4343	2984	2555	2513	2460	2419	2363	2311	1661	448

Different rates of onset of primary CV composite endpoint

- Differences in prior CVD 99% vs 65% ?
- Agent specific differences ?
- Differences in placebo arm ?

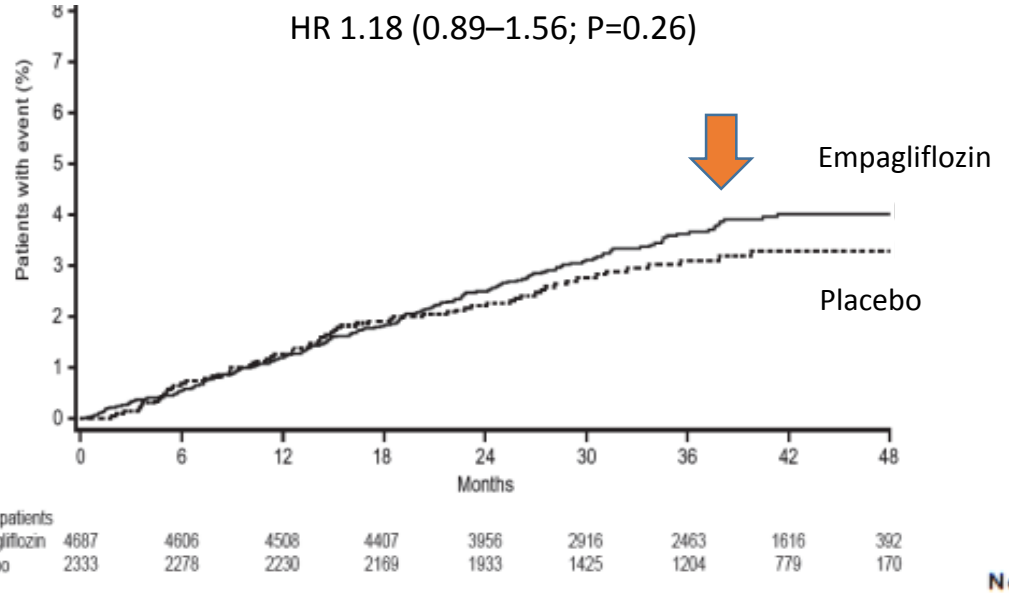
Zinman et al, N Engl J Med 2015; 373:2117-2128 Neal et al, N Engl J Med 2017, on-line. DOI. 10.1056/NEJMoa1611925

EMPA-REG vs CANVAS: Stroke

Differences in stroke during and after SGLT2 inhibitor

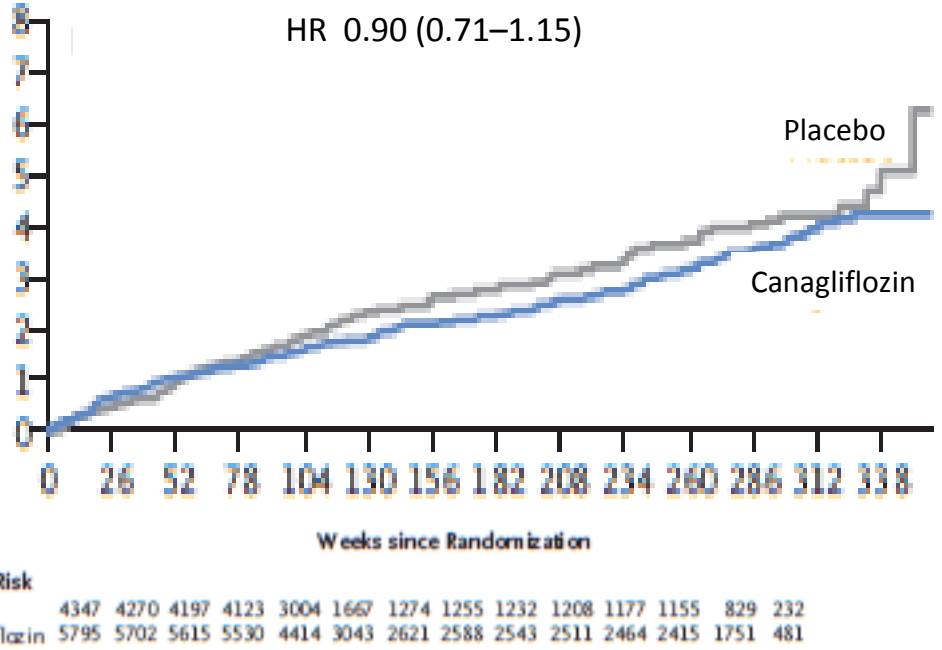
EMPA-REG. Stroke

HR 1.18 (0.89–1.56; P=0.26)



CANVAS. Stroke

HR 0.90 (0.71–1.15)



18 patients in empagliflozin group had stroke >90 days after last intake of drug (versus 3 on placebo).
Analysis during treatment or ≤90 days after last dose
HR 1.08 (0.81–1.45; P=0.60).
Patients with the largest increases in hematocrit or largest decreases in systolic blood pressure did **not** have an increased risk of stroke

Zinman et al, Stroke. 2017;48:online. DOI: 10.1161/STROKEAHA.116.015756.

Neal et al, N Engl J Med 2017, on-line. DOI. 10.1056/NEJMoa1611925

CV outcome trials: renal outcome data

	Trial →	EMPA-REG	CANVAS
Baseline	eGFR ml/min/1.73m^2	**74**	**76**
	Microalbuminuria (%)	**29**	**22.7**
	Macroalbuminuria (%)	**11**	**7.6**
Completion	New or worse nephropathy	**0.61*** 0.53, 0.70	**0.73** 0.67, 0.79
	Progression to macroalbuminuria	**0.62*** 0.54, 0.72	
	Renal composite 40% ↓ eGFR, dialysis/transplant, renal death		**0.60** 0.47, 0.77
	Regression of albuminuria		**1.70** 1.51, 1.91
	UTI	18.0 vs 18.1 %	40 vs 37 per 1000 pt yrs
	Follow-up (yr)	3.1	3.6

Renal protection
especially in CANVAS-R

Microalbuminuria: albumin 30-300 mg/day; 30-300 ug albumin/mg creatinine; albumin/creatinine ratio (ACR) >2.5-25 mg/mmol (M), >3.5-35 mg/mmol (F).
Renal composite was 40% reduction in eGFR, need for renal-replacement therapy, or renal death. Progression of albuminuria was defined as more than a 30% increase in albuminuria and a change from either normoalbuminuria to microalbuminuria or macroalbuminuria or from microalbuminuria to macroalbuminuria.. UTI, urinary tract infection, Empa 18.0% vs Pbo 18.1, Cana 40 vs Pbo 37 per 1000 patient yrs. Follow up Empa median, Canvas mean. Wanner et al, N Engl J Med 2016, 375:323-334; Neal et al, N Engl J Med 2017, on-line. DOI. 10.1056/NEJMoa1611925

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Renal protection
especially in CANVAS-R

Reversing renal decline

Microalbuminuria: albumin 30-300 mg/day; 30-300 ug albumin/mg creatinine; albumin/creatinine ratio (ACR) >2.5-25 mg/mmol (M), >3.5-35 mg/mmol (F).
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CV outcome trials: adverse events

	CANVAS		
	Canagliflozin	**Placebo**	**HR (95% CI)**
	Events per 1000 patient yrs		
Female genital mycotic l infection	68.8	17.5	4.37 (2.78-6.88)
Volume depletion	26.0	18.5	1.44 (1.09-1.90)
DKA (adjudicated) (n = 18/10,134)	0.6*	0.3	2.33 (0.76-7.17)
Bone fractures	15.4	11.9	1.26 (1.04–1.52)
- Fractures in CANVAS - Fractures in CANVAS-R			1.55 (1.21–1.97) 0.86 (0.62–1.19)
Amputations	6.3	3.4	1.97 (1.41-2.75)

Some type 1 diabetes patients?

*5 patients reporting diabetic ketoacidosis (all on canagliflozin) identified as having autoimmune diabetes (positive GADA and mIAA or a reported history of T1DM

Neal et al, N Engl J Med 2017, on-line. DOI. 10.1056/NEJMoa1611925

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Bone fractures heterogeneity

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71% toe & metatarsal

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71% toe & metatarsal

Mainly if
- Prior amputation
- Peripheral vasc dis

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CANVAS Program. Limitations

Limitations: standard for these types of studies

as noted by authors

- Moderate number of events for some outcomes
  — eg for end-stage kidney disease
- Limited number of participants with established kidney disease
- Interim analysis data of CANVAS included
- Integration of two separate populations
- Changes in glycaemic control between groups
- Variable use of other glucose-lowering agents in placebo group

Neal et al, N Engl J Med 2017, on-line. DOI. 10.1056/NEJMoa1611925

CANVAS Program. Unanswerable questions

Even large prospective randomised double-blinded placebo-controlled studies are difficult to interpret

How much is

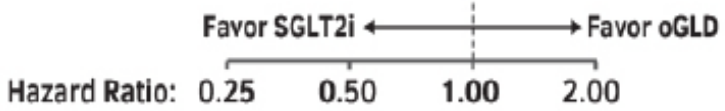
- a class effect ?
- specific to the agent ?
- population heterogeneity ?
- noise in the data ?

CVD-REAL. Hospitalization for heart failure or death

Type 2 diabetes patients in countries using different SGLT2 inhibitors
N=154,523 starting an SGLT2 inhibitor vs 154, 523 propensity-matched starting another oral glucose-lowering agent

Hospitalization for heart failure or all-cause death

Database	N	# of events	HR (95% CI)
US	143,264	424	0.44 (0.36, 0.54)
Norway	25,050	622	0.58 (0.50, 0.69)
Denmark	18,468	477	0.57 (0.48, 0.67)
Sweden	18,378	364	0.50 (0.41, 0.63)
UK	10,462	96	0.66 (0.44, 1.00)
Total	215,622	1983	0.54 (0.48, 0.60)



P-value for SGLT2i vs oGLD: <0.001

SGLT, sodium-glucose co-transporter; oGLD, oral glucose-lowering drug

Kosiborod et al, American College of Cardiology 2017 and Circulation on-line

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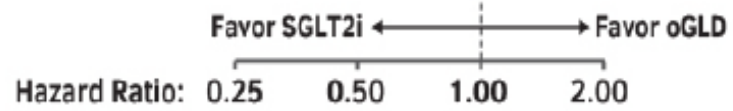
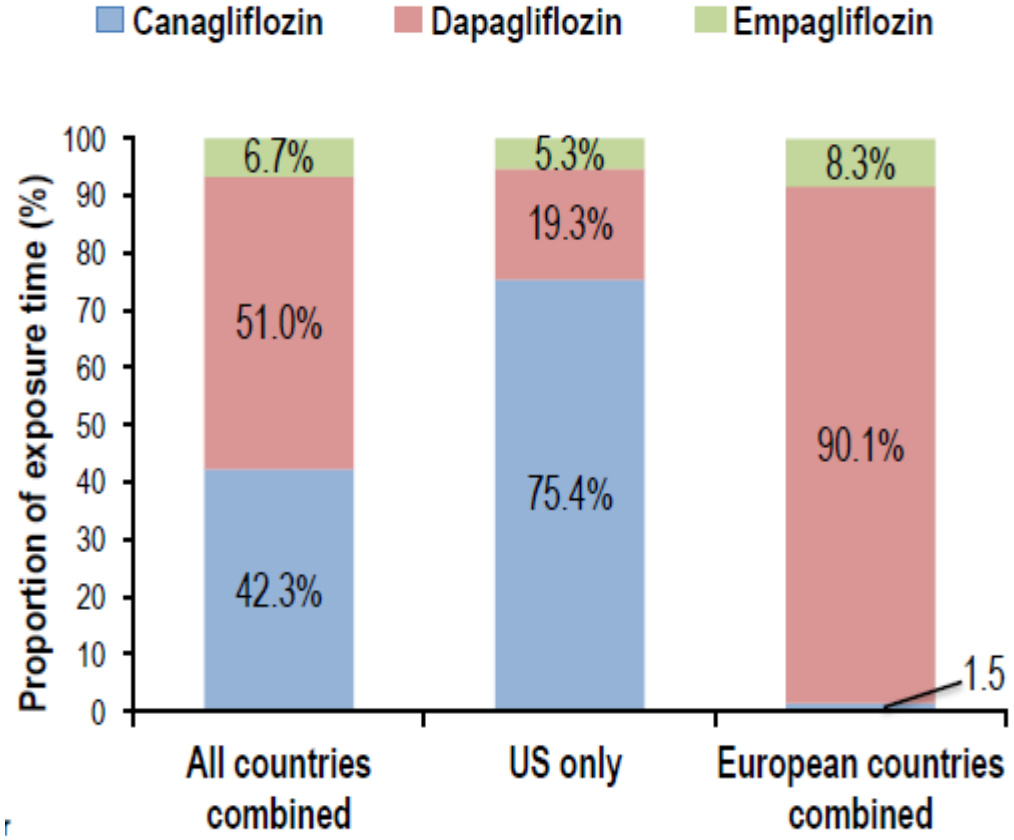


P-value for SGLT2i vs oGLD: <0.001



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Kosiborod et al, American College of Cardiology 2017 and Circulation on-line

CANVAS Program. Independent commentary

Summary

• FDA criteria	1º endpoint achieved
• MACE	Superiority
• Individual CV events	?↓ risk of CV death, MI, stroke, HHF
• Other benefits	Renal protection
• Risks	Amputation, fracture?
• Mechanisms	Rapid, several likely contributors
• Clinical practice	Probably CV/renal class benefits
	(1º prevention and 2º intervention benefits)

MACE, major adverse cardiac events: MI, myocardial infarction, stroke, HHF, hospitalization for heart failure.

Thank you