CARDIAC AND RENAL PROTECTIVE EFFECTS OF SGLT-2 INHIBITORS: BENEFITS BEYOND GLYCEMIC CONTROL

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OCTOBER 7, 2016

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OBJECTIVES

- Understand the role of the sodium-glucose co-transporter (SGLT) in glucose homeostasis in normoglycemic and hyperglycemic states
- Discuss pleiotropic effects observed with the use of SGLT-2 inhibitors and explore proposed pathophysiology
- Review clinical data studying renal and cardio protective endpoints related to SGLT2 inhibition
- Analyze the cardio and renal outcomes drawn from the EMPA-REG outcomes trial

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ABBREVIATIONS

- A1c/HbA1c: hemoglobin A1c
- ACE-I= Ace inhibitor
- ADA=American Diabetes Association
- ARB=angiotensin receptor blocker
- ARF=acute renal failure
- CKD=chronic kidney disease
- CV=cardiovascular
- CVD=cardiovascular disease
- DCCT=diabetes control and complications trial
- DKA=diabetic ketoacidosis
- DKD=diabetic kidney disease
- DM= diabetes mellitus
- DN=diabetic nephropathy
- EDIC=epidemiology of diabetes interventions and complications
- ESRD=end stage renal disease
- mAlb/Cr=microalbumin to creatinine ratio
- MI=myocardial infarction
- PAD=peripheral artery disease
- RAAS=renin-angiotensin-aldosterone system
- SGLT=sodium glucose co-transporter
- T1DM/T2DM: Type 1/Type 2 DM
- TGF=tubuloglomerular feedback
- UA=unstable angina
- UKPDS=United Kingdom Prospective Diabetes Study
- UTI=urinary tract infection

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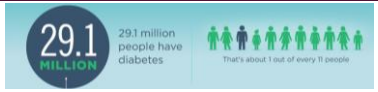
DM: A MAJOR CAUSE FOR CONCERN



- Hallmark: progressive insulin resistance or complete lack of insulin leading to hyperglycemia
- Goal: Achieve glycemic targets to reduce the risk of macrovascular and microvascular complications

Centers for Disease Control and Prevention. Updated 2014.
DCCT research group. *NEJM*. 1993;329(14):977-986.
King P. *Br J Clin Pharmacol*. 1999;48(5):643-648.

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DIABETES RELATED COMPLICATIONS

- Macrovascular
  - CVD, PAD, sudden cardiac death
- Microvascular
  - Diabetic neuropathy
  - Gastrointestinal/genitourinary dysfunction
  - **Diabetic nephropathy (DN)**
    - Leading cause of mortality and end stage renal disease
    - Early predictors: enlarged kidney, hyperfiltration, microalbuminuria
- **Every 5 minutes: 2 people die due to these complications**

Centers for Disease Control and Prevention. Updated 2014.
DCCT research group. *NEJM*. 1993;329(14):977-986. King P. *Br J Clin Pharmacol*. 1999;48(5):643-648.

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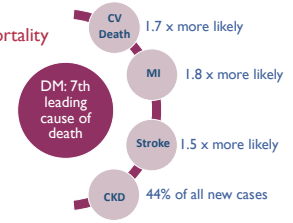
Major Causes of Mortality



Centers for Disease Control and Prevention. Updated 2014.

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ADA RECOMMENDATIONS

- Control blood pressure
- Control blood glucose
  - UKPDS and DCCT: Demonstrated microvascular benefit
  - EDIC: Demonstrated macrovascular benefit
- Screen for development of complications
  - mAlb/Cr
  - Dilated eye exam
  - Monofilament foot exam
  - Dental exam

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DCCT research group. *NEJM.* 1993;329(14):977-986.
King P. *Br J Clin Pharmacol.* 1999;48(5):643-648. ADA guidelines. *Diabetes Care.* 2016;39(1).

RAAS INHIBITION

- Slows progression to diabetic kidney disease
- ADA recommendations
  - Initiate ACE-I or ARB in patients with macroalbuminuria (mAlb/Cr > 300 mg/gm)
  - Initiate ACE-I or ARB in patients with microalbuminuria (mAlb/Cr 30-300 mg/gm)
    - Weak evidence: small trials in normotensive patients with microalbuminuria

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ADA guidelines. *Diabetes Care.* 2016;39(1).

INTRODUCING THE CONCEPT

SODIUM GLUCOSE CO-TRANSPORTERS (SGLT)

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INTRODUCING SGLT

	Expression	Description
SGLT-1	Distal segment of the proximal tubule, intestine	High affinity, low capacity glucose transport ~10% of renal glucose reabsorption
SGLT-2	**Early convoluted segment of proximal tubules**, pancreatic α cells	Low affinity, high capacity glucose transport **80-90% of renal glucose reabsorption**

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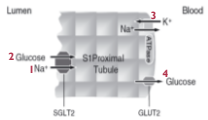
DeFronzo RA, et al. *Diab, Obesity, Metab.* 2012;14(1):5-15.

INTRODUCING SGLT



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DeFronzo RA, et al. *Diab, Obesity, Metab.* 2012;14(1):5-15.

ROLE IN GLUCOSE HOMEOSTASIS

- Purpose: maintain consistent fasting glucose level
- Threshold for reabsorption: BG 180-200 mg/dl
- BG>200 mg/dl: glycosuria
- Prolonged hyperglycemia→ maladaptive mechanism

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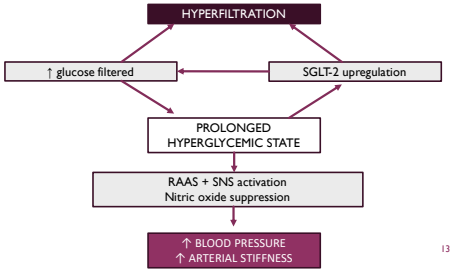
De Nicola L. *Am J Kidney Dis.* 2014;64(1):16-24.
DeFronzo RA, et al. *Diabetes, Obesity, Metab.* 2012;14(1):5-15.



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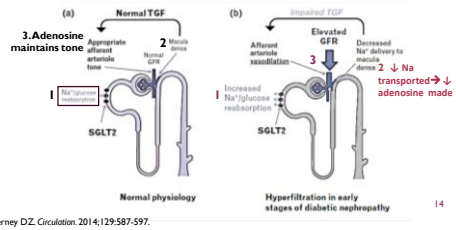
TUBULOGLOMERULAR FEEDBACK



Cherney DZ. *Circulation.* 2014;129:587-597.

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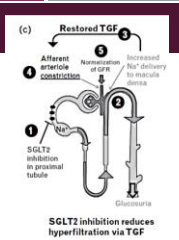
SGLT-2 INHIBITION

- Normalizes threshold for glycosuria
  - Excess glucose excreted in urine
- SGLT1 upregulated
  - Only 50% glucose reabsorbed
- Result
  - Decreases blood glucose
  - Decreased gluconeogenesis and increased insulin sensitivity
  - Restored TGF



Cherney DZ. *Circulation.* 2014;129:587-597.

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SGLT2 INHIBITORS: AT A GLANCE

Brand	Generic	Available dosing (mg)	Efficacy (A1c lowering)	ADEs
Invokana ®	canagliflozin	100-300	-0.7% -0.42% if CrCl 30-59 ml/min	• DKA, ketosis • Genital mycotic infections • UTI • Slight ↑ LDL • Bone fracture • Bladder cancer
Farxiga ®	dapagliflozin	5-10		
Jardiance ®	empagliflozin	10-25		
Suglat ®	ipragliflozin	25-100		

Invokana [package insert]. Princeton, NJ: Bristol-Myers Squibb Company.; 2013.
Farxiga [package insert]. Wilmington, DE: Astra Zeneca Pharmaceuticals LP.; 2014.
Jardiance [package insert]. Ridgefield, CT: Boehringer-Ingelheim Pharmaceuticals, Inc.: 2014.
Nainggolan L. Available at: http://www.medscape.com/viewarticle/819447. Updated January 20, 2014.

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WEIGHT LOSS AND URIC ACID

- Weight loss of 1-4.5 kg
  - Loss of calories from glycosuria and osmotic diuresis
  - Contributes to reduced insulin requirements
  - Maintained past initial time period
- Uric acid
  - 10-15% reduction in plasma uric acid
  - Increased levels associated with HTN, CVD and renal disease
  - Unclear on clinical relevance

Heerspink HJ, et al. *Circulation.* 2016. Epub ahead of print.
Ghosh RK, et al. *Int J Cardio.* 2016;212:29-36.

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CARDIOVASCULAR EFFECTS

- Decrease in blood pressure without increase in orthostasis
  - SBP -4 mmHg
  - DBP -2 mmHg
- Decrease even in non-dippers
- Maintained in CKD patients

Baker WL, et al. *J Am Soc Hypertens.* 2014;8(4):262-275.
Ghosh RK, et al. *Int J Cardio.* 2016;212:29-36.
Heerspink JJ, et al. *Circulation.* 2016. Epub ahead of print.

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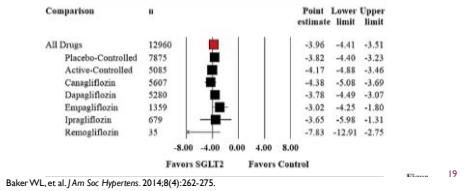
SBP REDUCTION



Baker WL, et al. *J Am Soc Hypertens.* 2014;8(4):262-275.

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ARTERIAL STIFFNESS

- Well established marker for CVD
- Improvements observed in studies for T1DM and T2DM
- Cherney and colleagues: 8 week open label prospective trial in T1DM
  - ↓ carotid-radial pulse wave velocity
- T2DM studies
  - ↓ pulse pressure and myocardial oxygen consumption

Cherney DZ, et al. *Cardiovascular Diabetology.* 2014;13:28.
Heerspink HJ, et al. *Circulation.* 2016. Epub ahead of print.

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PROPOSED PATHOPHYSIOLOGY

- **Volume contraction**
- **↓ Arterial stiffness**
- Weight loss
- Neurohormonal changes
  - Differences observed in trials not as expected
  - ↑ vasoconstrictors
  - **↑ urinary ACE2 (vasodilator)**

Baker WL, et al. *J Am Soc Hypertens.* 2014;8(4):262-275.
Ghosh RK, et al. *Int J Cardio.* 2016;212:29-36.
Heerspink JJ, et al. *Circulation.* 2016. Epub ahead of print.

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RENAL EFFECTS

- Decreased kidney weight and glomerular size
- Early decrease in eGFR
- Decreased occurrence of albuminuria
- Maintained in CKD independent of A1c reduction

Wanner C, et al. *N Engl J Med.* 2016;375:323-334.
De Nicola L, et al. *Am J Kidney Dis.* 2014;64(1):16-24.
Heerspink HJ, et al. *Circulation.* 2016. Epub ahead of print.
Cherney DZ, et al. *Circulation.* 2014;129(5):587-597.

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EARLY STUDIES

Trial	2013 Cefalu and colleagues	2014 ATIRMA trial
Subject type (n)	T2DM (n=1450)	T1DM (n=40)
Intervention	Canagliflozin 100 mg, 300 mg or glimepiride for 52 weeks	Empagliflozin 25 mg for 8 weeks
Endpoint	Primary: A1c reduction, eGFR as a safety measure	Change in eGFR in patients with normofiltration (N) vs hyperfiltration (H)
eGFR	• Week 4: greater ↓ in treatment group • Week 52: stabilized in Canagliflozin group vs steady decline in glimepiride group	Euglycemic conditions: -9 N vs -33 H Hyperglycemic conditions: -2 N vs -44 H

Cherney DZ, et al. *Circulation.* 2014;129(5):587-597.
Cefalu WT, et al. *Lancet.* 2013;382:941-950.

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CAN SGLT-2 INHIBITORS PROTECT PATIENTS WITH TYPE 2 DIABETES FROM RENAL AND CARDIOVASCULAR COMPLICATIONS?

LITERATURE REVIEW

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EFFICACY AND SAFETY OF EMPAGLIFLOZIN FOR TYPE 2 DIABETES: A SYSTEMATIC REVIEW AND META-ANALYSIS

LIAKOS A, KARAGIANNIS T, ATHANASIADOU E, ET AL. *DIABETES, OBESITY AND METAB.* 2014;16(10):984-993.

25

METHODS

- Objective: To utilize available studies to assess the safety and efficacy of empagliflozin compared with placebo or other antidiabetic agents in patients with type 2 diabetes
- Searched studies through publication date December 19, 2013 and abstracts presented at Endocrinology meetings between 2009 and 2013
- Inclusion:
  - RCTs comparing empagliflozin to placebo or other antidiabetics
  - T2DM
  - Duration ≥ 12 weeks

Liakos A, et al. *Diabetes, Obesity and Metab.* 2014;16(10):984-993.

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OUTCOMES

- Primary: Absolute change in HbA1c
- Secondary: Absolute change in weight, SBP, DBP, % patients achieving target A1c<7%
- Safety: hypoglycemia, change in eGFR, incidence of UTI/genital tract infections, volume depletion

Liakos A, et al. *Diabetes, Obesity and Metab.* 2014;16(10):984-993.

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BIAS AND DATA ANALYSIS

- Bias assessments: key domains
  - Random sequence generation, allocation concealment and incomplete outcome data
  - Meta-regression analysis to adjust for publication type (abstract vs full text)
- Analysis
  - Type of comparator, dosage, intention to treat analysis
  - Continuous outcomes: weighted mean differences with inverse variance weighted random effects model
  - Dichotomous outcomes: odds ratio via Mantel-Haenzel formula assuming random effects
  - Heterogeneity: Cochran's Q test ($p<0.10$ and $I^2>50$ = high)

Liakos A, et al. *Diabetes, Obesity and Metab.* 2014;16(10):984-993.

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RESULTS

- 10 studies with 6203 patients
  - 8 with high bias: use of LOCF
- Duration 12-90 weeks
- Baseline A1c: 7.8% to 8.3%
- Background therapy:
  - 4 studies: none
  - 3 studies: metformin
  - 1: metformin + SU
  - 1: basal insulin
  - 1: any oral antidiabetic drug
  - 1: metformin + pioglitazone

Liakos A, et al. *Diabetes, Obesity and Metab.* 2014;16(10):984-993.

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Measure (change in)	Empagliflozin v placebo	Empagliflozin v active agent	I^2 (%)
Weight, kg (10 mg)	-1.85 (-2.09, -1.6)	-2.15 (-3.03, -1.27)	43/56
Weight, kg (25 mg)	-1.84 (-2.30, -1.38)	-2.56 (-3.57, -1.55)	85/66*/66
SBP mmHg (10 mg)	-3.49 (-4.32, -2.67)	-3.53 (-5.37, -1.69)	0/0
SBP mmHg (25 mg)	-4.19 (-5.17, -3.20)	-4.24 (-6.08, -2.41)	32/0
eGFR (10 mg)**	-0.09 (-1.14, 0.96)	--	0
eGFR (25 mg)**	-0.84 (-2.29, 0.62)	--	59

Values represented are mean changes and 95% confidence interval. Dose is representative of empagliflozin dosing. I^2 represented by Empagliflozin v placebo/empagliflozin v active agent. *Heterogeneity was reduced by removing studies including CKD patients; **ml/min/1.73m^2

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Liakos A, et al. *Diabetes, Obesity and Metab.* 2014;16(10):984-993.

RESULTS

- All cause mortality: 7 trials reported
- Empagliflozin 5 deaths (n=2874)
- Control 5 deaths (n=1704)
- None reported on hard cardiovascular outcomes

- Author's conclusion: Both doses of empagliflozin are effects at lowering blood glucose while providing benefits of weight loss and blood pressure reduction.

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Liakos A, et al. *Diabetes, Obesity and Metab.* 2014;16(10):984-993.

DISCUSSION

Strengths	Weaknesses
• Meta-analysis with a large number of patients • Relatively low occurrence of heterogeneity • Appropriate statistics and methods used to reduce bias	• No data for empagliflozin 10 mg in CKD stage 3 and 4 • Limited number of trials against active controls • Assessed surrogate endpoints

- Valuable summation of results from early trials of patients with T2DM and treated with empagliflozin.
- Introduces a potential treatment option in patients with moderate renal impairment

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Liakos A, et al. *Diabetes, Obesity and Metab.* 2014;16(10):984-993.

DAPAGLIFLOZIN'S EFFECTS ON GLYCAEMIA AND CARDIOVASCULAR RISK FACTORS IN HIGH RISK PATIENTS WITH TYPE 2 DIABETES: A 24-WEEK, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

CEFALU WT, LEITER LA, DE BRUIN TW, ET AL. *DIABETES CARE.* 2015;38(7):1218-1227.

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METHODS

- Objective: To determine the efficacy of dapagliflozin in lowering HbA1c, body weight and SBP in patients determined to be at high risk for CVD events.
- Design:
  - 24-week multicenter, randomized, double blind, placebo-controlled international phase 3 study with a 28 week extension period
  - Funding: NIH grant and support from Bristol-Myers Squibb and AstraZeneca

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Cefalu WT, et al. *Diabetes Care.* 2015;38(7):1218-1227.

	Inclusion	Exclusion
Study Population	• Men ≥ 45 or women ≥ 50 years old • T2DM with CVD* and HTN • Stable antihyperglycemic therapy for 4 weeks • HbA1c 7.2% to ≤ 10.5%	• T1DM • On >3 oral antidiabetic medications • FPG>270 mg/dl at screening • h/o DKA • CV event within 2 months • SBP ≥ 165 mmHg, DBP ≥ 100 mmHg • CHF NYHA class IV or unstable CHF • Severe hepatic insufficiency
	*CVD= prior documented CHD (h/o MI, revascularization, coronary artery stenosis>50%) or documented stroke/TIA or PAD treated with revascularization	
Intervention	• Randomized 1:1 to Dapagliflozin 10 mg or placebo + existing stable background therapy • If on insulin: ↓ insulin dose by 25%	

Cefalu WT, et al. *Diabetes Care.* 2015;38(7):1218-1227.

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End Points	• Primary: Mean change in HbA1c and percent achieving 3 item composite (absolute ↓A1c of ≥0.5%, relative ≥3% ↓ weight, absolute ↓≥ 3 mmHg SBP) • Secondary: mean change in SBP, mean % weight change, proportion of patients with BMI ≥ 27 kg/m2 with ≥ 5% weight loss, A1c reduction in those with baseline A1c ≥ 8% and ≥ 9% and individual components of composite outcome • Safety: change in CV events, lab values, EKG results, vital signs, hypoglycemia, eGFR	
Statistical Analysis	Measure	Test
	Composite outcome	Cochran-Mantel-Haenzel method
	Continuous data at 52 weeks	Repeated measures model
	Primary endpoints: 2 sided α<0.025 No statistical testing on exploratory 52 week end points	

Cefalu WT, et al. *Diabetes Care.* 2015;38(7):1218-1227.

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	Characteristic		Placebo (n=459)	Dapagliflozin (n=455)
Baseline characteristics	Age (years ±SD)		63 ± 7.7	62.8 ± 7.0
	Female (%)		31.4	32.1
	White (%)		85.2	82.6
	CV event (%)	CHD	76.0	74.3
		CVA/TIA	19.4	22.0
		PAD	3.9	3.3
	HbA1c ±SD		8.08 ± 0.8	8.18± 0.84
	ACEI/ARB		98.3	98.9
	Lipid lowering medications		88.5	84.1

Cefalu WT, et al. *Diabetes Care*. 2015;38(7):1218-1227.

OUTCOMES

End point		Placebo (n=459)	Dapagliflozin (n=455)
Change in HbA1c (95% CI)		0.08 (0.01, 0.16)	-0.38 (-0.46, 0.30)
3 item composite % (95% CI)		0.9 (0.0, 1.8)	11.7 (8.7, 14.7)
Weight loss (%)	Week 24 (kg)	-0.30	-2.56
	BMI ≥ 27 and ≥ 5% weight loss	4	16.5
Change in SBP, mmHg (95% CI)		-1.03 (-2.39, 0.32)	-2.99 (-4.36, -1.61)
Decreased eGFR at 52 weeks (%)		0.6	0.4
Renal failure*		0.6	1.3
Deaths (%)**		0.4	1.5

*resolved without discontinuation; **Deaths deemed to be unrelated to treatment. Dapagliflozin: (3) sudden death, (1) multi-organ failure, (2) MI, (1) cardiogenic shock) vs placebo: (1) CVA, (1) pulmonary embolism

Cefalu WT, et al. *Diabetes Care*. 2015;38(7):1218-1227.

CONCLUSIONS

- Author's Conclusion: Dapagliflozin was found to be superior to placebo in reducing A1c and achieving a 3 item composite representing reduction in cardiovascular risk in a population with documented CVD.

Strengths	Weaknesses
• Study design • Large % of patients on standard therapy • Long follow up period	• Dual primary endpoint • Use of surrogate markers • Lipid lowering tx unclear • Limited information on CHF patients • Vague safety endpoints

- Demonstrates the durability of efficacy of dapagliflozin in patients with cardiovascular disease. However, these endpoints are only surrogate markers and may hint at cardiovascular benefits.

Cefalu WT, et al. *Diabetes Care*. 2015;38(7):1218-1227.

EMPA-REG OUTCOMES TRIAL

ZINMAN B, WANNER C, LACHIN JM, ET AL. *N ENGL J MED*. 2015;373:2117-2128.
WANNER C, INZUCCHI SE, LACHIN JM, ET AL. *N ENGL J MED*. 2016;375:323-334.

METHODS

- Objective: To determine the cardiovascular related outcomes of adjunctive empagliflozin therapy when added to standard of care in patients with T2DM and high cardiovascular risk
- Study design:
  - Randomized, double-blind, placebo controlled, multinational and multicenter trial
  - 7028 patients randomized from September 2010-April 2013
  - Median treatment duration 2.6 years
  - Funding/oversight: Boehringer Ingelheim, Eli Lilly

Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.
Wanner C, et al. *N Engl J Med*. 2016;375:323-334.

Inclusion	Exclusion
• ≥ 18 years old • Uncontrolled T2DM[a] • BMI ≤ 45kg/m^2 • eGFR ≥ 30 ml/min/1.73m^2 • High risk for cardiovascular events[b] • On diet or exercise regimen and drug naïve or pre-treated with stable therapy for 12 weeks prior to randomization	• Fasting blood sugar (>240 mg/dl) • Active liver disease • Planned cardiac surgery/angioplasty within 3 months • eGFR <30 ml/min/1.73m^2 • Acute coronary syndrome, TIA or stroke within 2 months • Cancer treatment within 5 years

a) HbA1c between 7-9% if treatment naïve or 7-10% if on drug treatment; b) MI>2 months prior to study enrollment, multi-vessel CAD, single-vessel CAD with positive stress test or recent hospitalization for UA, history of stroke >2 months prior to consent, PAD

Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.
Wanner C, et al. *N Engl J Med*. 2016;375:323-334.

INTERVENTION

- 2 week open label placebo run in
  - Stable antihyperglycemic background therapy
- Randomized 1:1:1 to empagliflozin 10 mg, 25 mg or placebo for up to 204 weeks
  - 1st 12 weeks→ no changes to background therapy unless FPG >240 mg/dl
  - After 12 weeks→ free to adjust background therapy
  - Free to adjust other therapies to meet standard of care

Zinman B, et al. *N Engl J Med.* 2015;373:2117-2128.
Wanner C, et al. *N Engl J Med.* 2016;375:323-334.

OUTCOMES

Cardiovascular

- **Primary:** MACE (CV death, non-fatal MI, non-fatal stroke)
- **Key secondary outcome:** Composite of MACE + hospitalization for UA
- **Safety:** Confirmed hypoglycemic events, UTI, genital infection, volume depletion, ARF, bone fracture, DKA, thromboembolic events

Renal

- Incident or worsening nephropathy
- Composite of incident or worsening nephropathy or death cardiovascular causes
- Individual components of the composites
- Incident albuminuria if previously normal baseline urinary albumin
- Safety: AKI, hyperkalemia, mycotic infections, diabetic ketoacidosis

Zinman B, et al. *N Engl J Med.* 2015;373:2117-2128.
Wanner C, et al. *N Engl J Med.* 2016;375:323-334.

STATISTICAL ANALYSIS

- Primary outcome: Cox proportional hazards model
  - Non-inferiority analysis followed by a 4 step hierarchical testing for superiority
  - Power analysis: 691 events needed for 90% power with assumed hazard ratio of 1.0
- Between group differences and risk of an outcomes: Cox-proportional hazards model
- Change in weight, HbA1c, waist circumference, heart rate, LDL, HDL, uric acid, eGFR from baseline: repeated measures mixed model

Zinman B, et al. *N Engl J Med.* 2015;373:2117-2128.
Wanner C, et al. *N Engl J Med.* 2016;375:323-334.

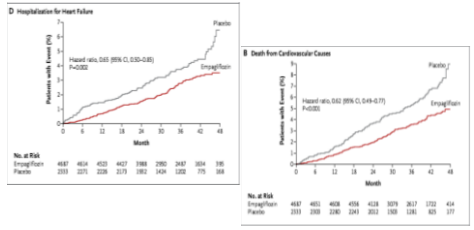
	Characteristic		Placebo (n=2333)	Pooled empagliflozin (n=4687)
Baseline Characteristics	Age (years ±SD)		63.2 ± 8.8	63.1 ± 8.6
	Male (%)		72	71.2
	White race (%)		71.9	72.6
	BMI (kg/m² ±SD)		30.7 ±5.2	30.6 ± 5.3
	A1c (%±SD)		8.08 ± 0.84	8.07 ± 0.85
	CAD (%)		75.6	75.6
	Heart failure (%)		10.5	9.9
	SBP (mmHg ±SD)		135.8 ± 17.2	135.3 ± 16.9
	eGFR (%)	≥ 90	20.9	22.4
		60 to <90	53.1	51.7
		<60	26.0	25.9
	Urine albumin: Cr >300mg/g (%)		11.1	10.9
	Antihypertensive therapy	ACE-I/ ARB	80.1	81.0
		B blockers	64.2	65.2
	Statin		76.0	77.4

Zinman B, et al. *N Engl J Med.* 2015;373:2117-2128
Wanner C, et al. *N Engl J Med.* 2016;375:323-334.

Cardiovascular Outcomes (n%)	Placebo (n=2333)	Empagliflozin (n=4687)	Hazard ratio (95% CI)	P value
Primary outcome	282 (12.1)	490 (10.5)	0.86 (0.74-0.99)	0.04*
Key secondary outcome	333 (14.3)	599 (12.8)	0.89 (0.78-1.01)	0.08**
Death from any cause	194 (8.3)	269 (5.7)	0.68 (0.57-0.82)	<0.001
Death from CV causes	137 (5.9)	172 (3.7)	0.62 (0.49-0.77)	<0.001
Hospitalization for HF	95 (4.1)	126 (2.7)	0.65 (0.50-0.85)	0.002
Nonfatal stroke	60 (2.6)	150 (3.2)	1.24 (0.92-1.67)	0.16
Fatal or nonfatal stroke	69 (3.0)	164 (3.5)	1.18 (0.89-1.56)	0.26

*for superiority, Noninferiority, P<0.001; **0.08 for superiority, Noninferiority <0.001

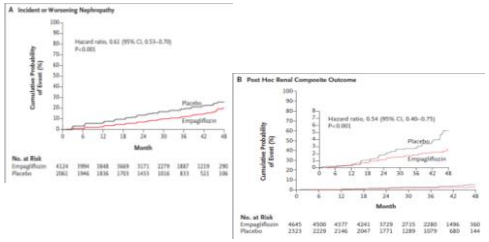
Zinman B, et al. *N Engl J Med.* 2015;373:2117-2128



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

Renal Outcomes (%)	Empagliflozin (n=4124)	Placebo (n=2061)	Hazard Ratio (95% CI)
Incident or worsening nephropathy or death from cardiovascular causes	16.2	23.6	0.61 (0.55-0.69)
Incident or worsening nephropathy	12.7	18.8	0.61 (0.53-0.70)
Progression to macroalbuminuria	11.2	16.2	0.62 (0.54-0.72)
Doubling of SCr	1.5	2.6	0.56 (0.39-0.79)
Initiation of renal replacement therapy	0.3	0.6	0.45 (0.21-0.97)
Incident albuminuria	51.5	51.2	0.95 (0.87-1.04)

Wanner C, et al. *N Engl J Med.* 2016;375:323-334.



Wanner C, et al. *N Engl J Med.* 2016;375:323-334.

CONCLUSIONS

- Author's Conclusions: Patients with type 2 diabetes with high cardiovascular risk had significantly lower rates of cardiovascular related deaths and were noted to have a slower progression of kidney disease while on standard treatment.

Strengths	Weaknesses
• Large sample population • Well-designed outcomes study • Large number of patients on standard of care • Good distribution of baseline renal function • Funding source	• Cannot be extrapolated to patients a low CV risk • Baseline BP and A1c near goal • Renal outcomes as a secondary endpoint • Funding source

Zinman B, et al. *N Engl J Med.* 2015;373:2117-2128.
Wanner C, et al. *N Engl J Med.* 2016;375:323-334.

FUTURE STUDIES

Drug Name	Study Name	Description
Canagliflozin (Invokana®)	*CANVAS*	T2DM with inadequate DM control and CVD • Primary: composite CV death, nonfatal MI, nonfatal stroke
	CANVAS-R	Studying renal endpoints over 78-156 weeks To be completed April 2017
	CREDENCE	T2DM with diabetic nephropathy • Primary: ESRD, doubling of SCr, renal or cardiovascular death
Dapagliflozin (Farxiga®)	*DECLARE-TIMI 58*	Primary: MI, ischemic stroke, CV related death To be completed April 2019

Ghosh RK, et al. *J AM Soc Hypertens.* 2014;8(4):262-275.

SUMMARY

- SGLT's role in glucose homeostasis presents an interesting target for not only glucose homeostasis, but for renal and cardiac protection.
- Pathophysiology is unclear, but appears to be multifactorial and related to reduction in arterial stiffness and renal damage.
- Benefits appear to be independent of SGLT-2 dose or renal function and indicate class-wide modification of early endpoints of renal and cardiovascular disease.
- The EMPA-REG study demonstrated cardio protective and renal protective effects in diabetic patients with high cardiovascular risk factors.

CONCLUSIONS

- In this group of patients with type 2 diabetes who are at high risk for cardiovascular events on standard of treatment, empagliflozin appears to be beneficial in secondary prevention of cardiovascular events and progression of renal damage.
- It remains to be seen if empagliflozin may be beneficial for primary prevention in a population initiated on therapy earlier in disease progression.
- Further studies are warranted to fully assess mechanisms behind these improvements, to clearly elucidate effects in patients without cardiovascular disease and establish benefit as a class-wide effect.

ACKNOWLEDGEMENTS

- Review Committee
  - Aida Garza, Pharm.D., BCACP, CDE
  - Jason Jokerst, Pharm.D., BCPS
  - Michelle Nguyen, Pharm.D., BCACP
- Evaluator
  - Nile Barnes, Pharm.D., BCPS

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CARDIAC AND RENAL PROTECTIVE EFFECTS OF SGLT-2 INHIBITORS: BENEFITS BEYOND GLYCEMIC CONTROL

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OCTOBER 7, 2016

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