SGLT2 Inhibitors and Heart Failure: What Do We Know and Where Are We Going?

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Presenter Disclosure

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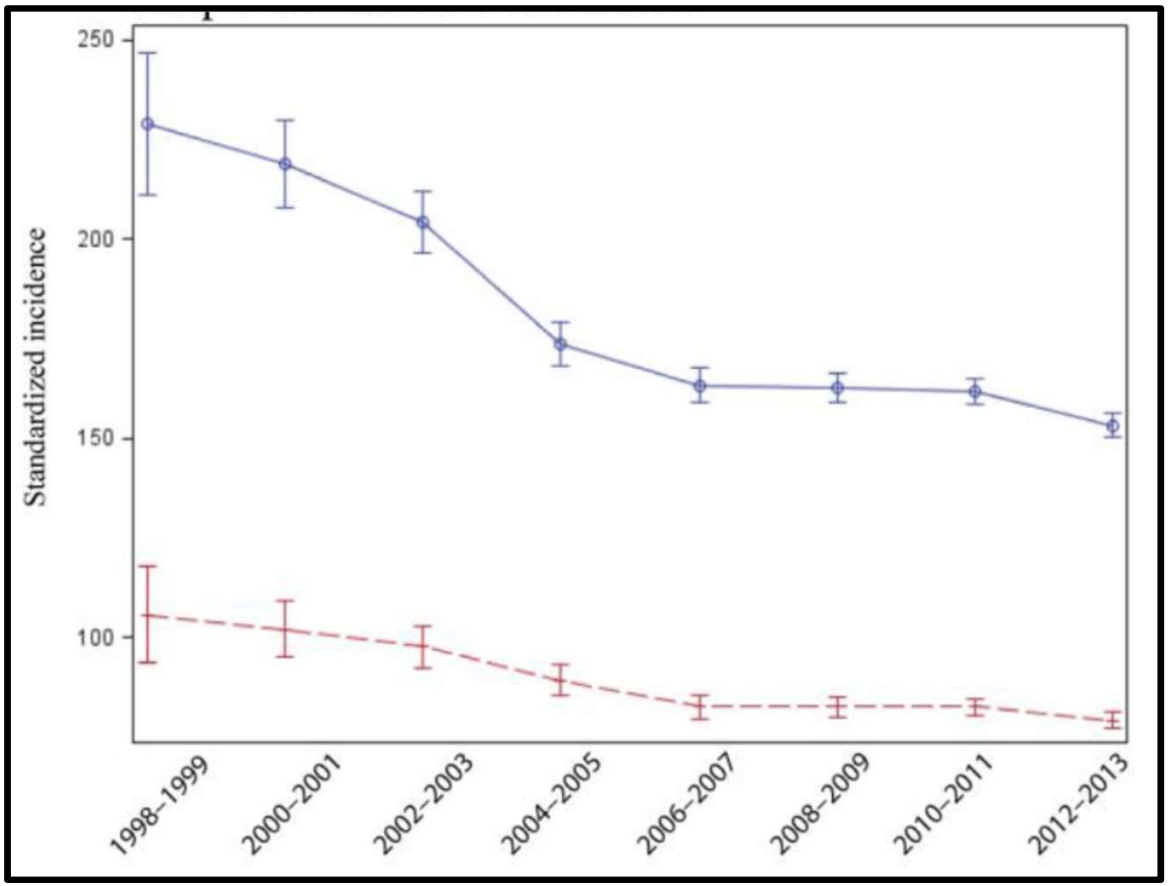
Clinical Trials Leadership

- Merck
- Pfizer
- AstraZeneca
- Janssen
- Lilly USA
- Boehringer Ingelheim
- Novo Nordisk
- Lexicon
- Eisai
- GlaxoSmithKline
- Sanofi Aventis

Consultancy

- Novo Nordisk
- Sanofi Aventis
- Boehringer Ingelheim
- Lilly USA
- Merck
- Metavant
- Applied Therapeutics
- Afimmune

HF Hospitalization Risk Associated with T2DM: Swedish National Registry Data 1998-2013



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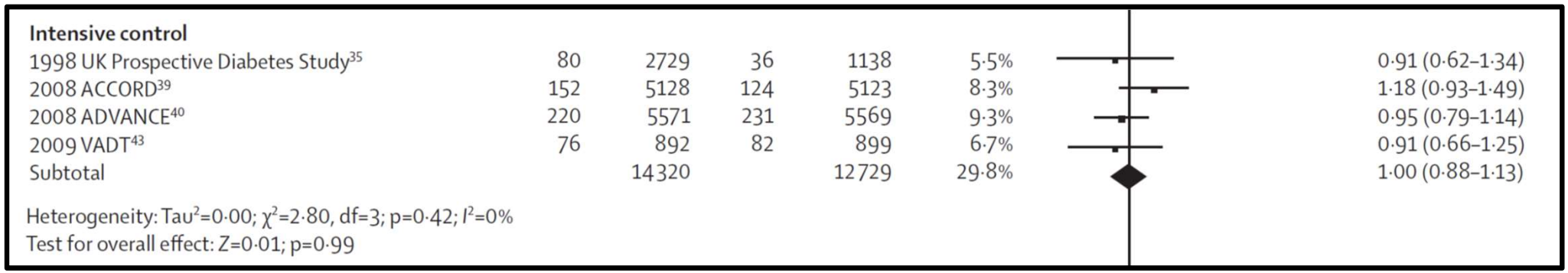
Rawshani, A., et al. N Engl J Med 2017; 376: 1407-1418.

Prevention of Heart Failure in Patients with Diabetes

Treating Hyperglycemia

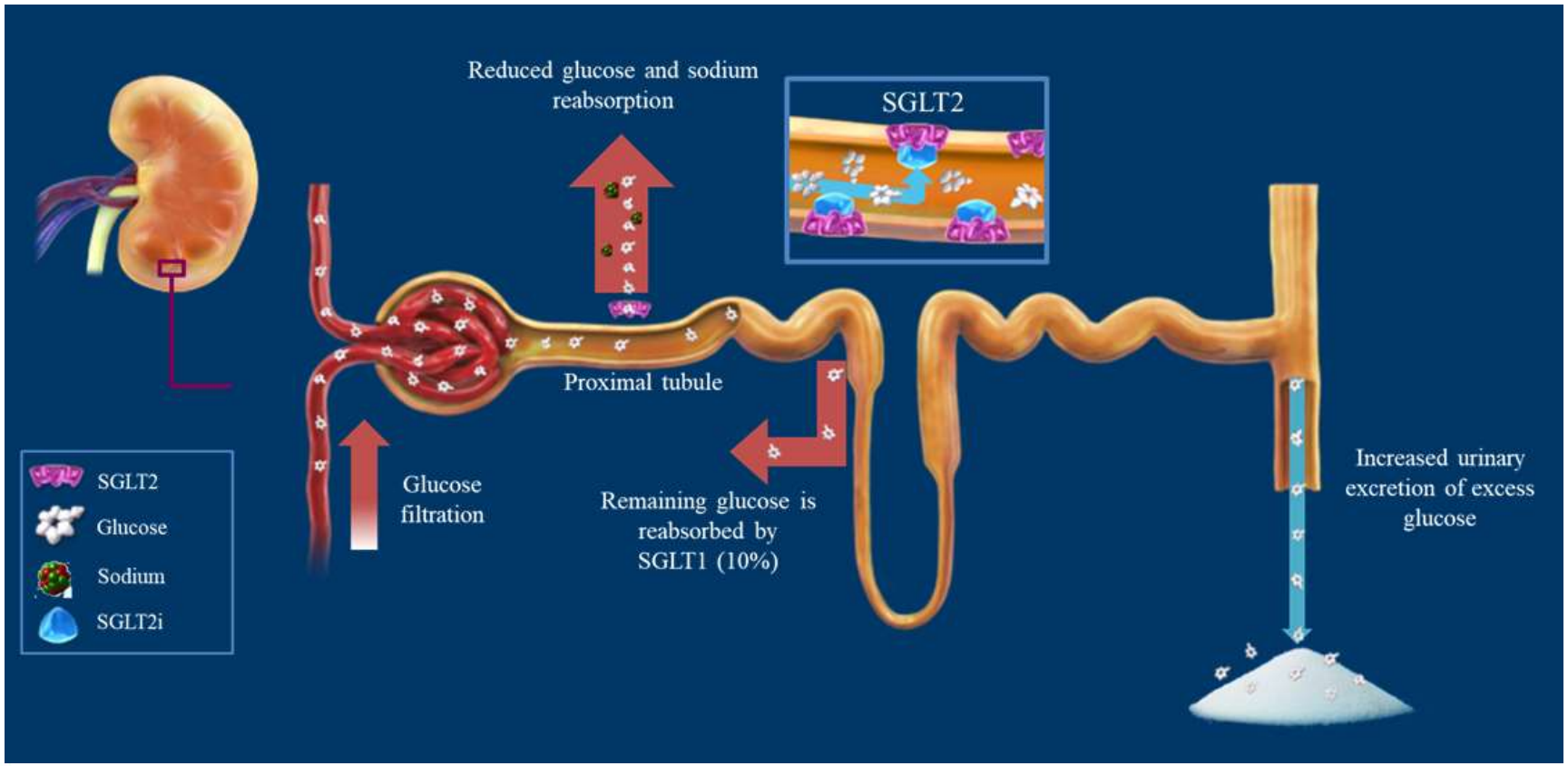


Intensive control						
1998 UK Prospective Diabetes Study[35]	80	2729	36	1138	5·5%	0·91 (0·62–1·34)
2008 ACCORD[39]	152	5128	124	5123	8·3%	1·18 (0·93–1·49)
2008 ADVANCE[40]	220	5571	231	5569	9·3%	0·95 (0·79–1·14)
2009 VADT[43]	76	892	82	899	6·7%	0·91 (0·66–1·25)
Subtotal		14320		12729	29·8%	1·00 (0·88–1·13)

Heterogeneity: Tau^2=0·00; χ^2=2·80, df=3; p=0·42; I^2=0%
Test for overall effect: Z=0·01; p=0·99

Udell JA et al. Lancet Diab Endocrinol 2015; 3: 356-366.

Sodium–glucose Cotransporter-2 Inhibitors (SGLT2i)



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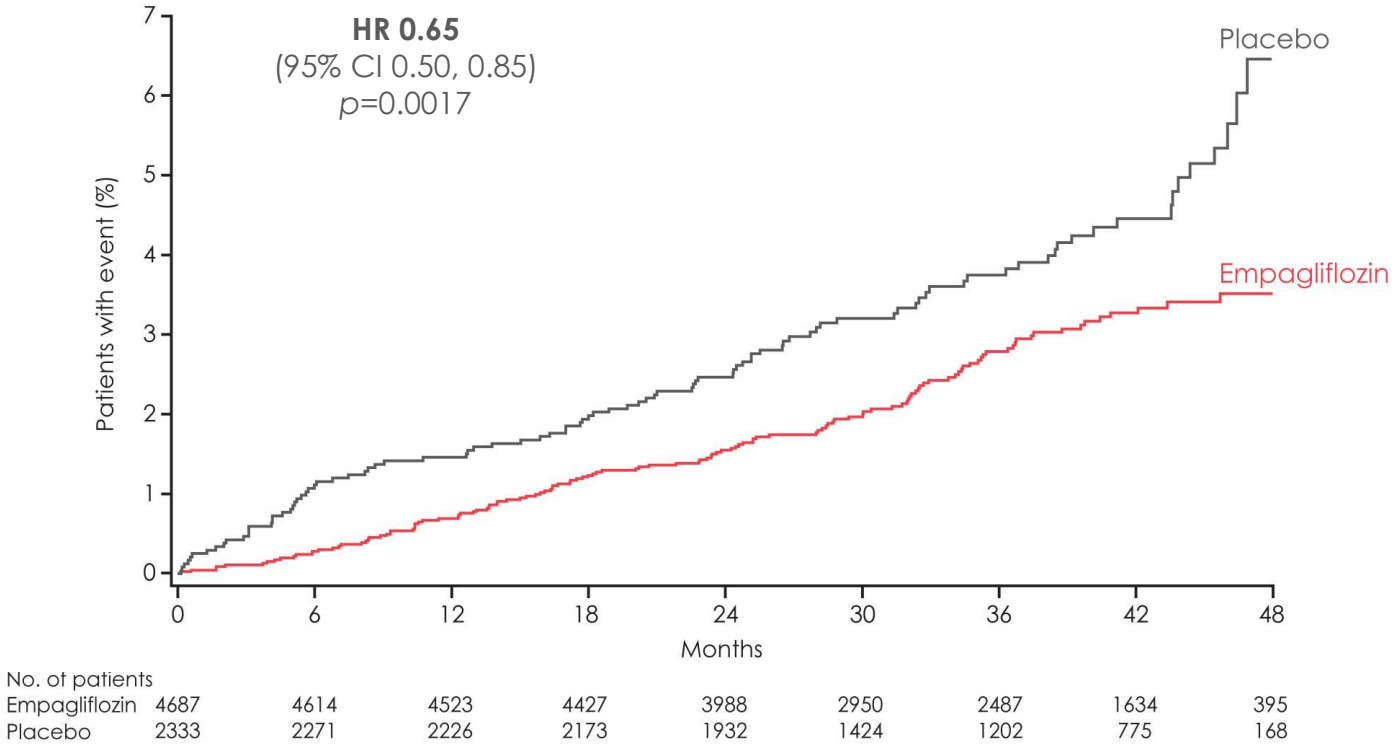
Heerspink HJ, et al. Circulation 2016: 134: 752-772.

EMPA-REG OUTCOME:
Hospitalization for heart failure



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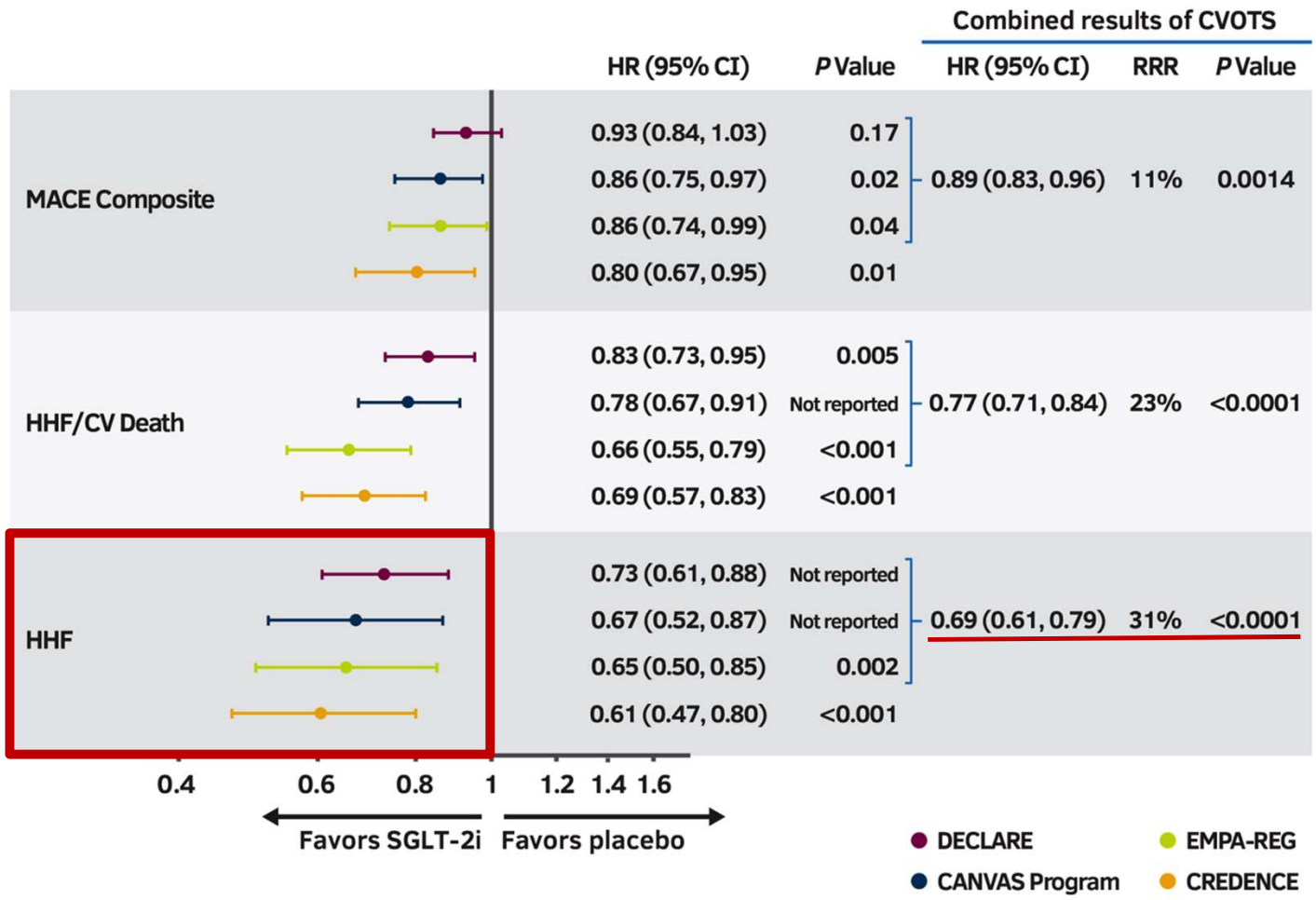
Zinman B et al. N Engl J Med 2015; 373: 2117-28

SGLT2i and CV Outcomes

- Three CVOTs and one renal outcome trial – all in patients with T2D at high ASCVD/HF risk – showed benefits on MACE and HF-related outcomes
- Empagliflozin and canagliflozin have CV indications independent of glucose
  - For T2DM with ASCVD



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ACC Clinical Decision Pathway

TABLE 11 **Patient and Clinician Preferences and Priorities for Considering SGLT2 Inhibitors with Demonstrated CV Benefit Versus GLP-1RAs With Demonstrated CV Benefit**

Consider Using an SGLT2 Inhibitor First When Patient and Clinician Priorities Include:	Consider Using a GLP-1RA First When Patient and Clinician Priorities Include:
Reducing MACE and CV death	Reducing MACE and CV death
Preventing heart failure hospitalization	Substantial weight loss
Reducing blood pressure	Once weekly (subcutaneous) dosing
Orally administered therapies	Therapy when eGFR consistently <45 ml/min/1.73 m^2*

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Das SR et al, J Am Coll Cardiol 2018; 72: 3200-3223

2019 ACC/AHA
CV Disease Primary Prevention Guideline

"Three RCTs have shown a significant reduction in ASCVD events ***and HF*** *with the use of an* ***SGLT2 inhibitor****. Although most patients studied had established ASCVD at baseline, the* ***reduction in HF*** *has been shown to* ***extend to primary prevention*** *populations."*

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Arnett DK et al. Circulation 2019; 140: e596-e646

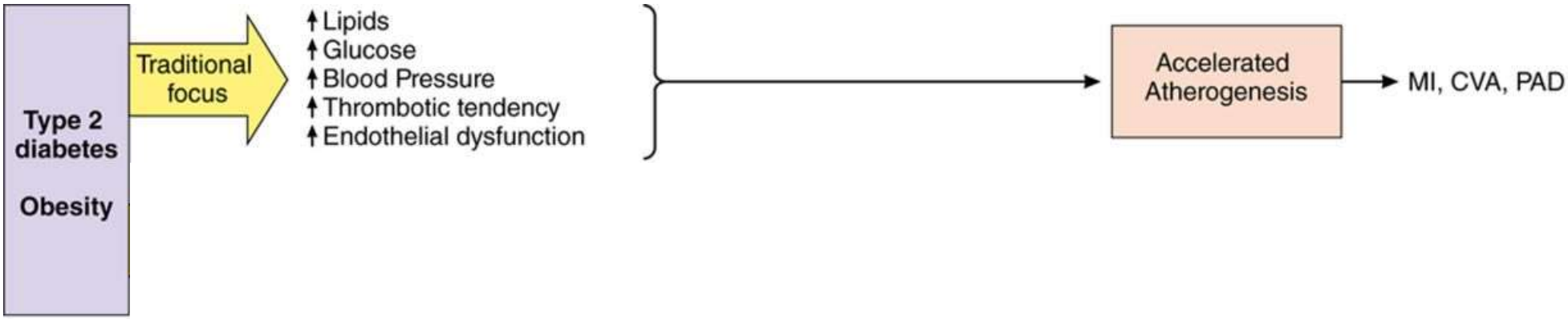
2019 ESC Guidelines for the Treatment of Type 2 Diabetes

ESC
European Society of Cardiology

DM treatment to reduce HF risk
SGLT2 inhibitor (empagliflozin, canagliflozin, and dapagliflozin) to lower risk of HF hospitalization if eGFR >30 mL/min/1.73 m^2
Metformin in patients with DM and HF if eGFR >30 mL/min/1.73 m^2
GLP1-RAs and DPP4 inhibitors sitagliptin and linagliptin have a neutral effect on risk of HF
Insulin treatment in HF
DPP4 inhibitor saxagliptin in HF is not recommended
Thiazolidinediones (pioglitazone, rosiglitazone) in HF is not recommended

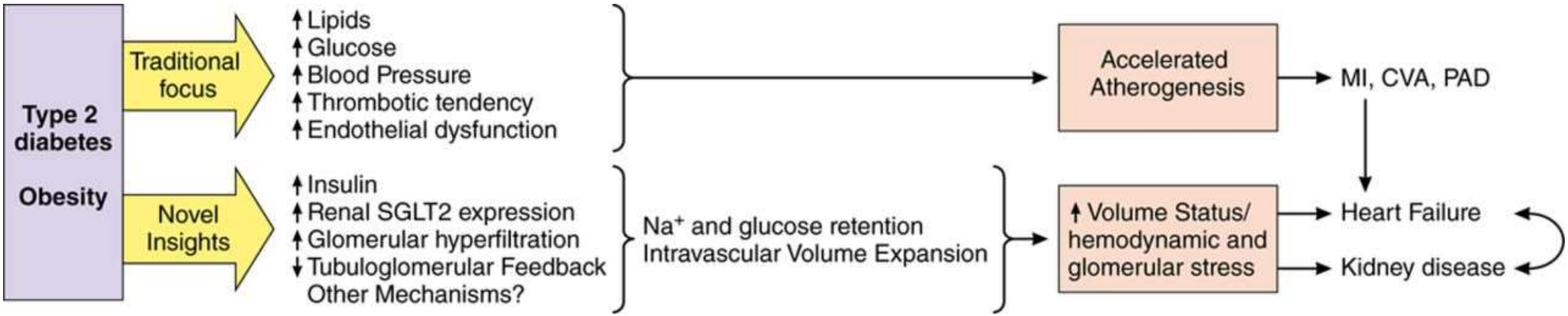
ESC Guidelines on Diabetes, pre-diabetes and cardiovascular diseases in collaboration with EASD (European Heart Journal 2019 - doi/10.1093/eurheartj/ehz486)

Redefining pathways to cardiorenal complications of type 2 diabetes mellitus.



Sattar N & McGuire DK. Circulation 2018; 138:7-9

Redefining pathways to cardiorenal complications of type 2 diabetes mellitus.



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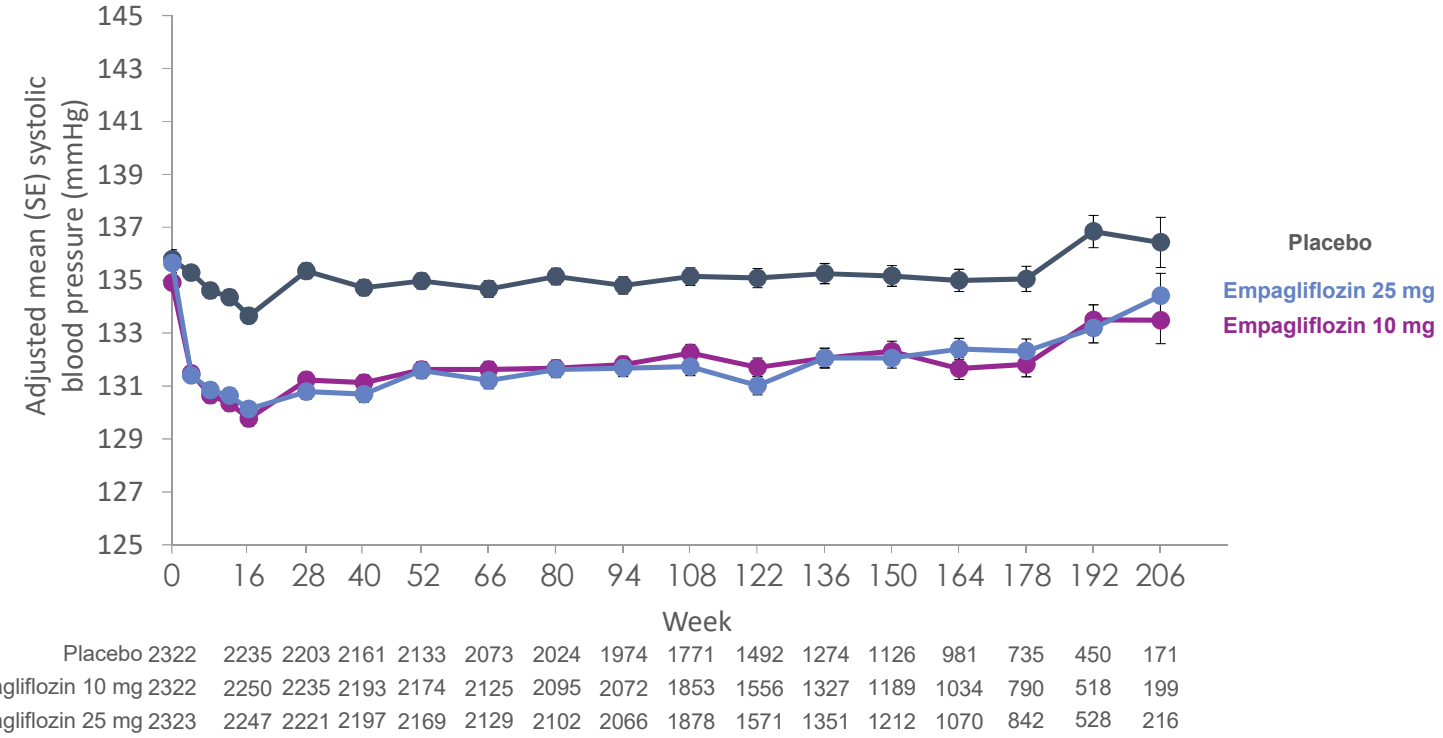
Sattar N & McGuire DK. Circulation 2018; 138:7-9

Adjusted mean 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

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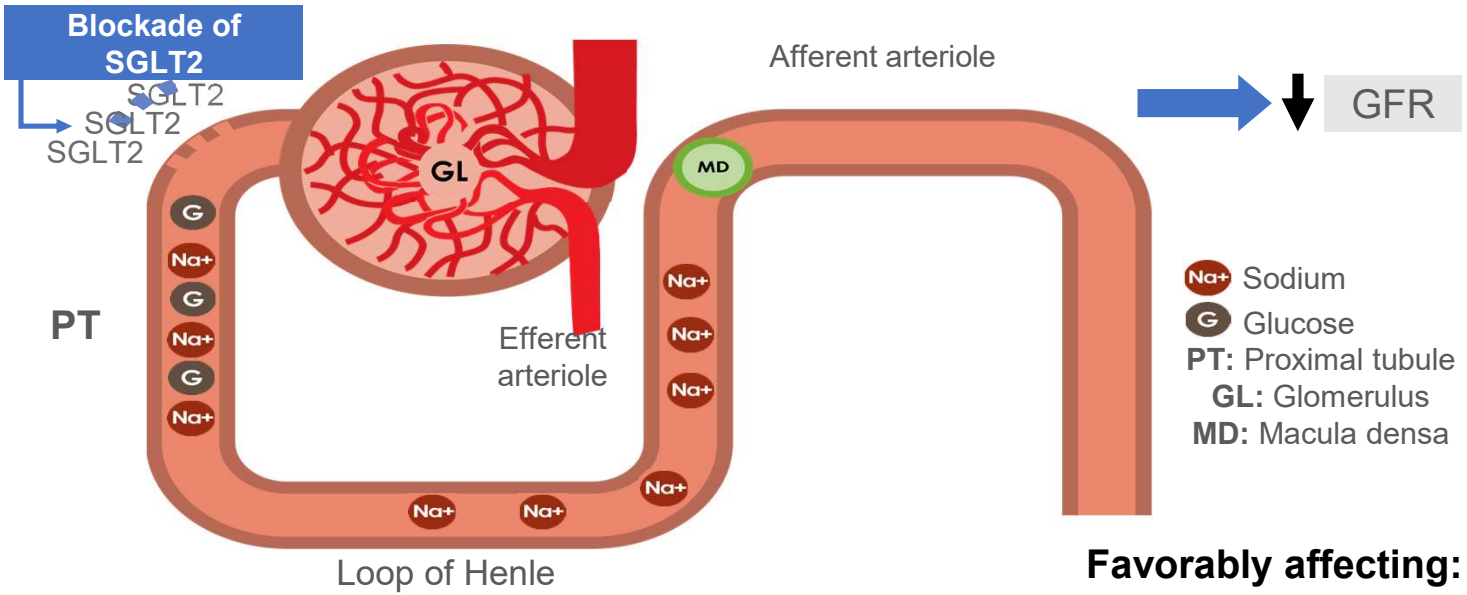
Zinman B et al. N Engl J Med 2015; 373: 2117-28

Effects of SGLTi on Glomerular Hemodynamics



Favorably affecting:
RAAS
Sympathetic tone

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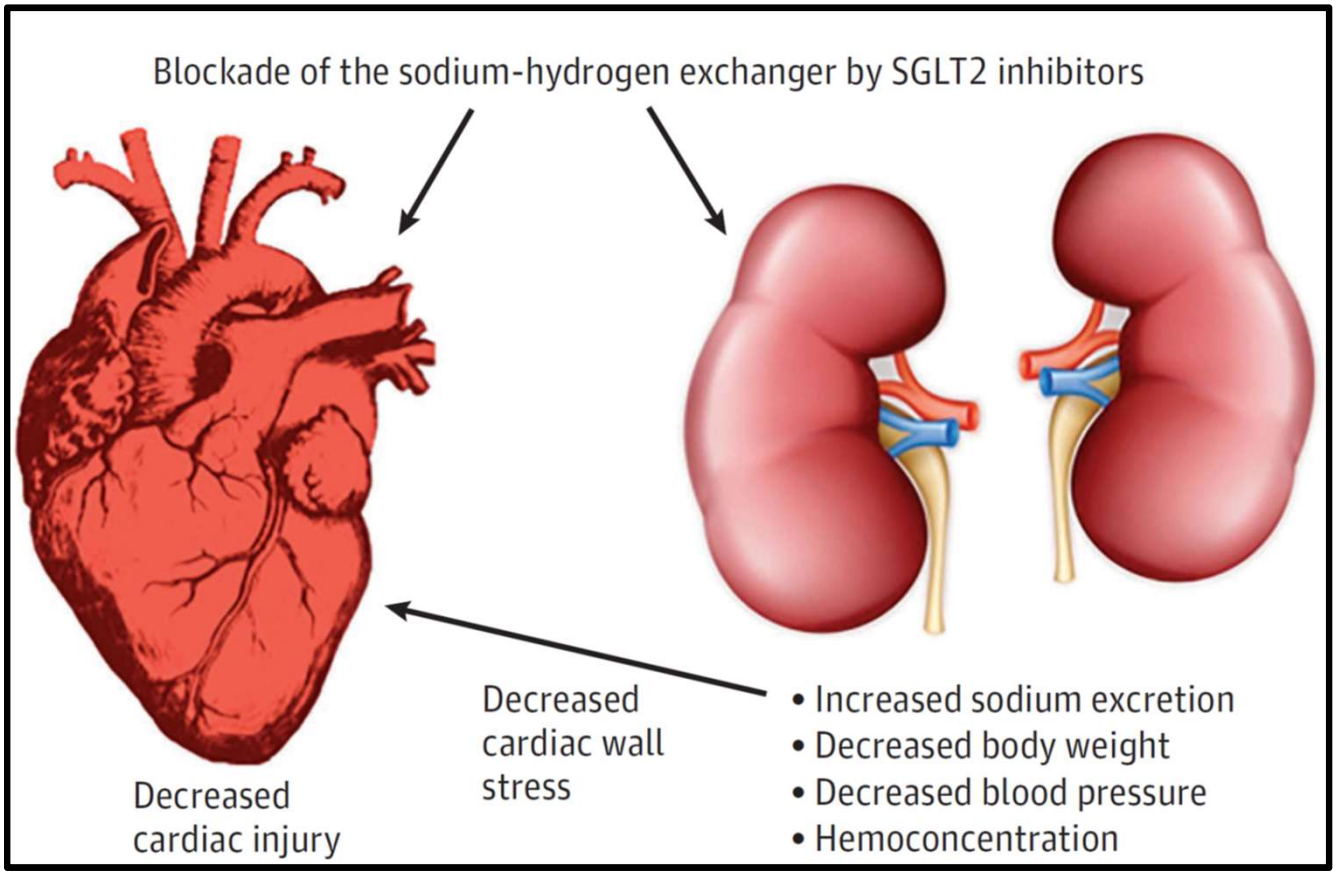
Adapted from: Cherney D et al. Circulation 2014;129:587
Heerspink HJ, et al. Circulation 2016; 134: 752.

Proposed SGLT2i Effects on Cardiac Na/H Exchangers 1 (heart) & 3 (kidneys)



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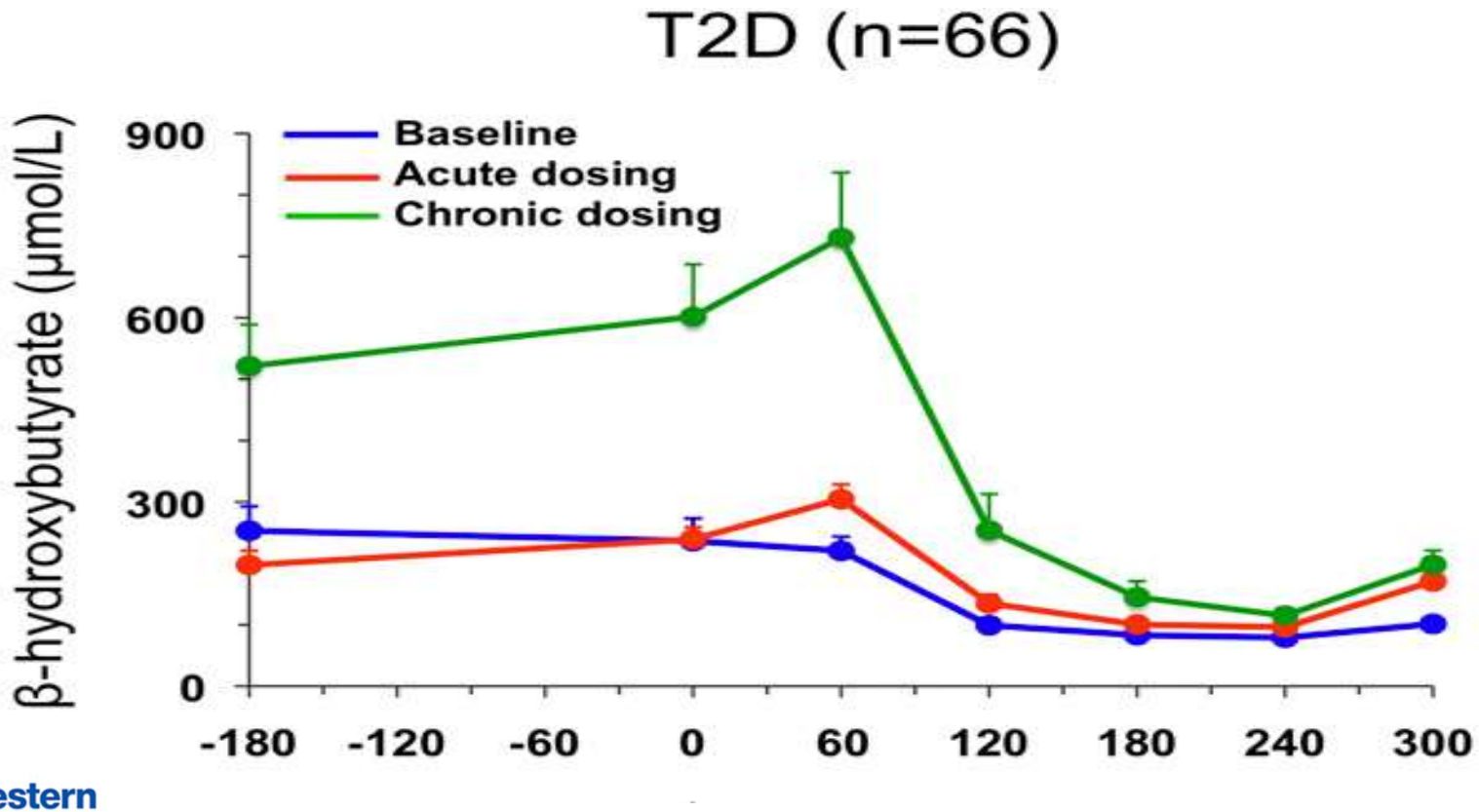
Packer M, et al. JAMA Cardiol 2017; 2: 1025-1029
Packer M. Circulation 2017; 136: 1548-1559

Empagliflozin elevates ketone bodies – especially in the fasted state



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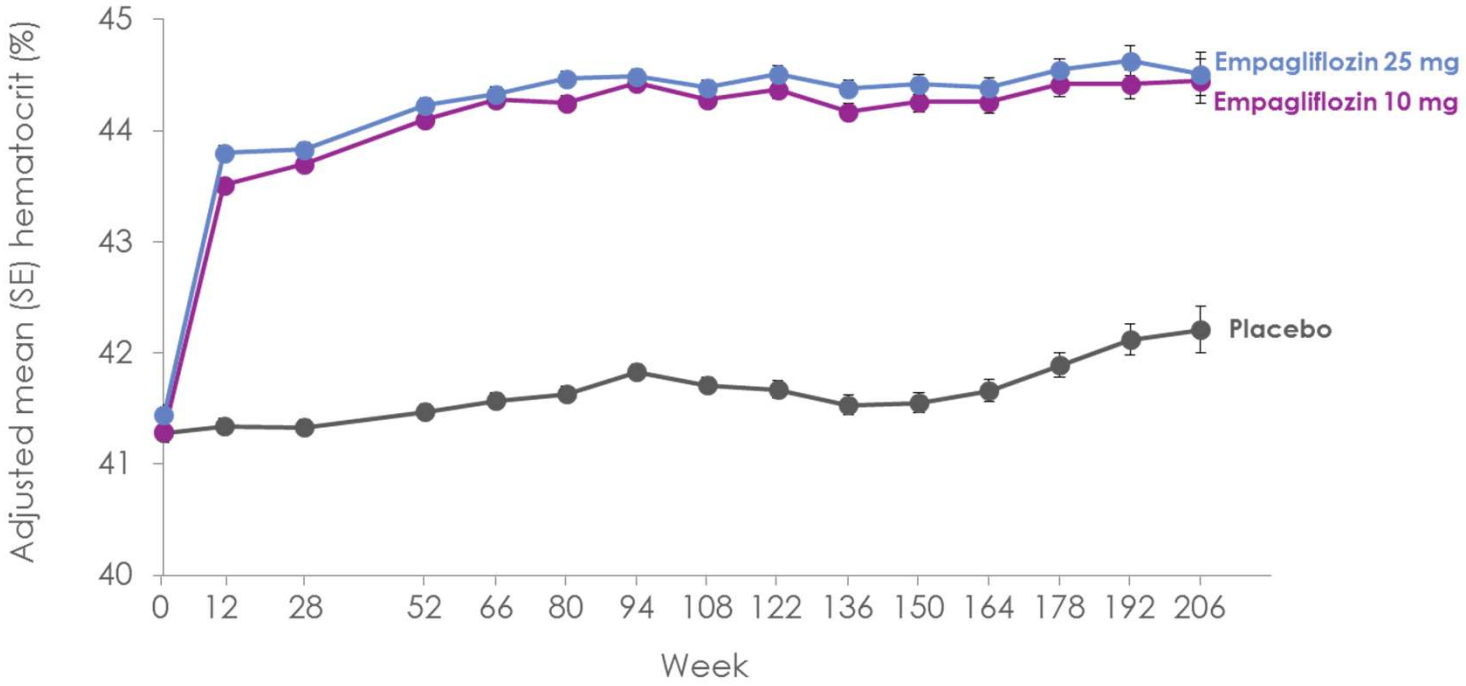
Ferrannini et al, Diabetes 2016;65:1190–1195

Hematocrit increased with empagliflozin: hemoconcentration and/or RBC expansion



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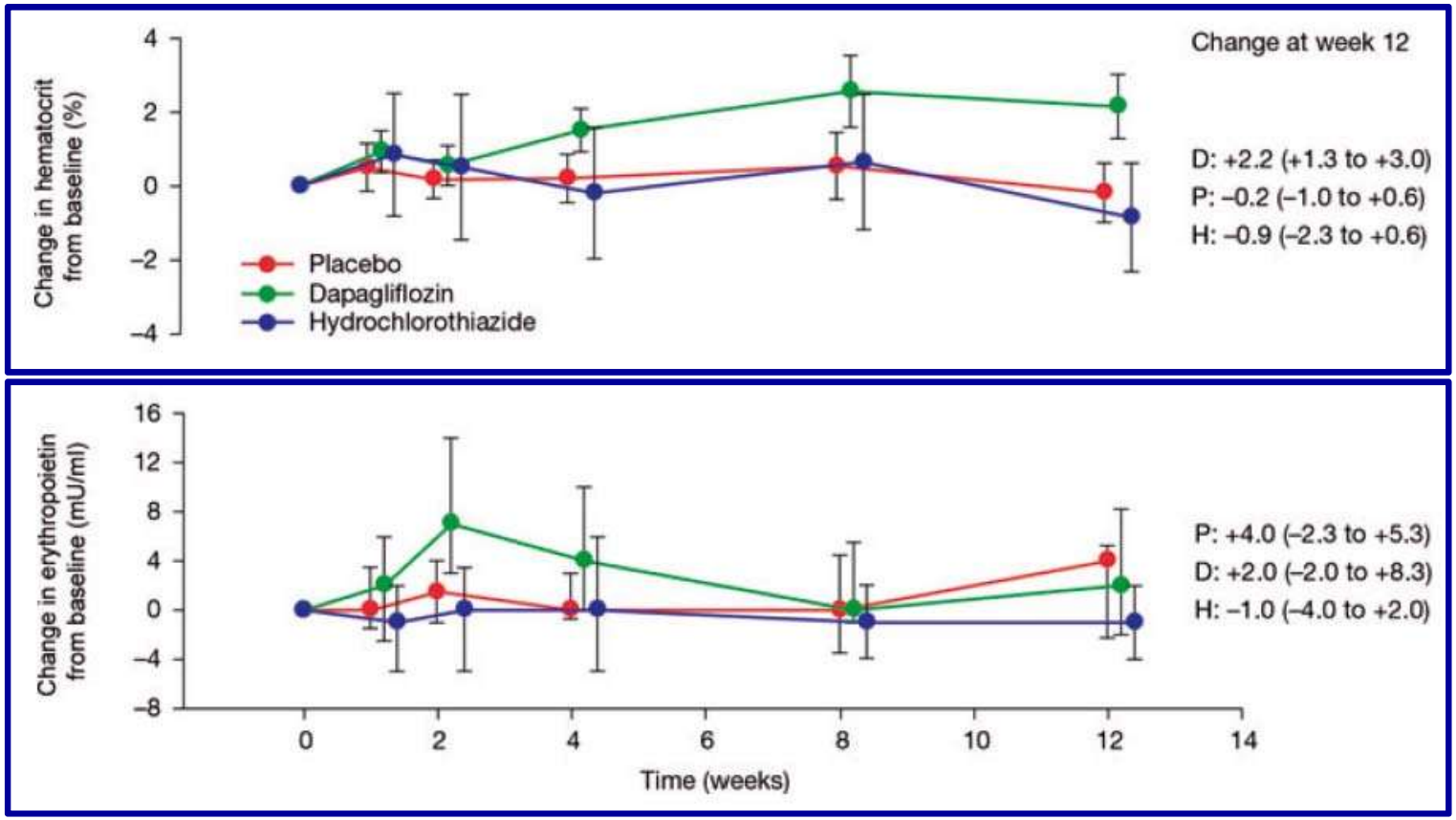
Zinman B et al. N Engl J Med. 2015;373:2117-28

Hematopoietic effects of dapagliflozin



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Lambers Heerspink, H. J., et al. Diabetes Obes Metab 2013 159: 853-862.

SGLT2i and HF: The Next Frontier

- SGLT2i's prevent HF in patients with T2DM at high-risk, but:
  - What is their effect on treating HF?
    - HFrEF, HFpEF (or both)?
    - T2DM versus all-comers?
    - If effective, will benefit wane with lower eGFR
  - What is safety profile in HFrEF patients?
    - Interactions with background therapies
    - Volume depletion/hypotension risks
  - Are there differences within the class?

DAPA-HF Objective

- To test the safety and efficacy of the SGLT2i dapagliflozin, 10 mg once daily versus placebo, added to standard HFrEF therapy, in patients with HFrEF both ***with and without T2D***

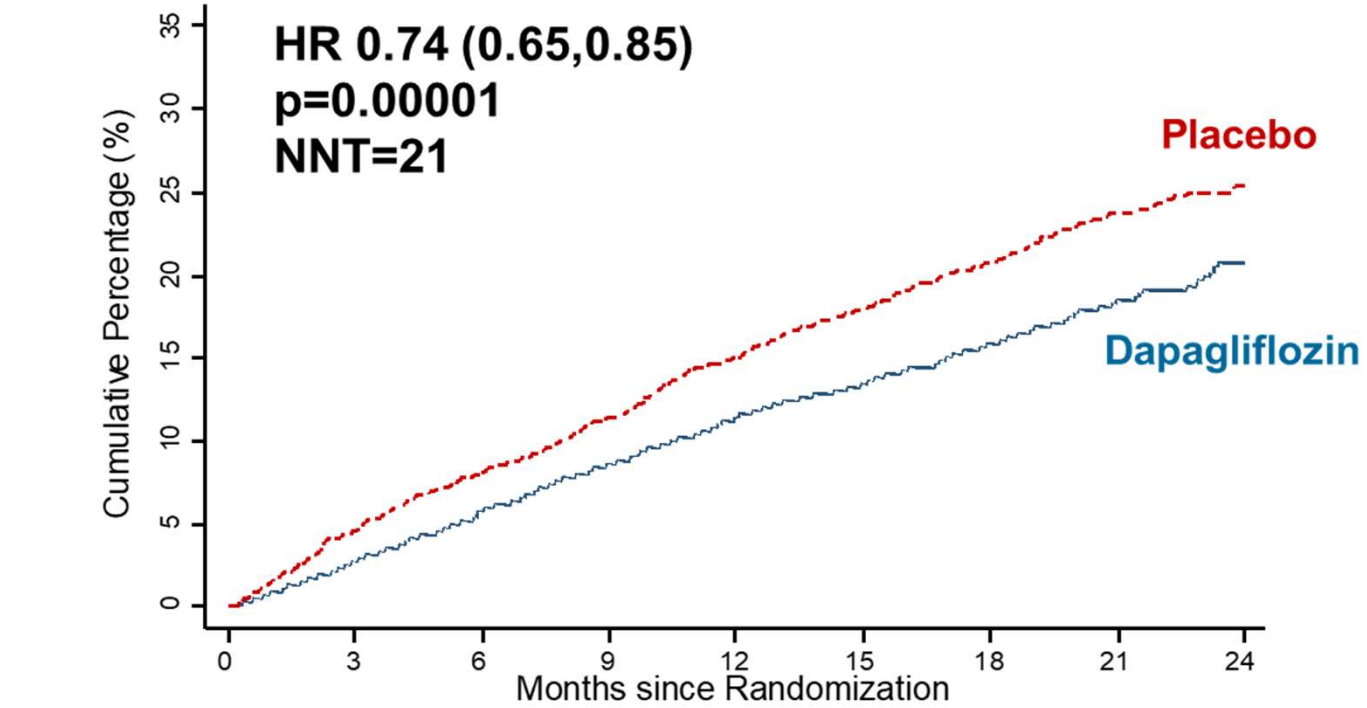
McMurray JJV, et al. N Engl J Med 2019 doi: 10.1056/NEJMoa1911303

Trial Design

- **Key inclusion criteria:**
  - Symptomatic HF with EF ≤40%;
  - NT-proBNP ≥600 pg/ml (if HHF in past year, ≥400 pg/mL; if AF/Flutter ≥900 pg/mL)
- **Key exclusion criteria:**
  - eGFR <30 ml/min/1.73 m^2
  - SBP <95 mmHg
  - type 1 diabetes
- **Primary outcome:**
  - Time for first: CV death/HF hosp/urgent HF visit requiring IV therapy)

McMurray JJV et al Eur J Heart Fail. 2019;21:665-675

Dapagliflozin reduces CV death and heart failure admissions/visits compared to placebo



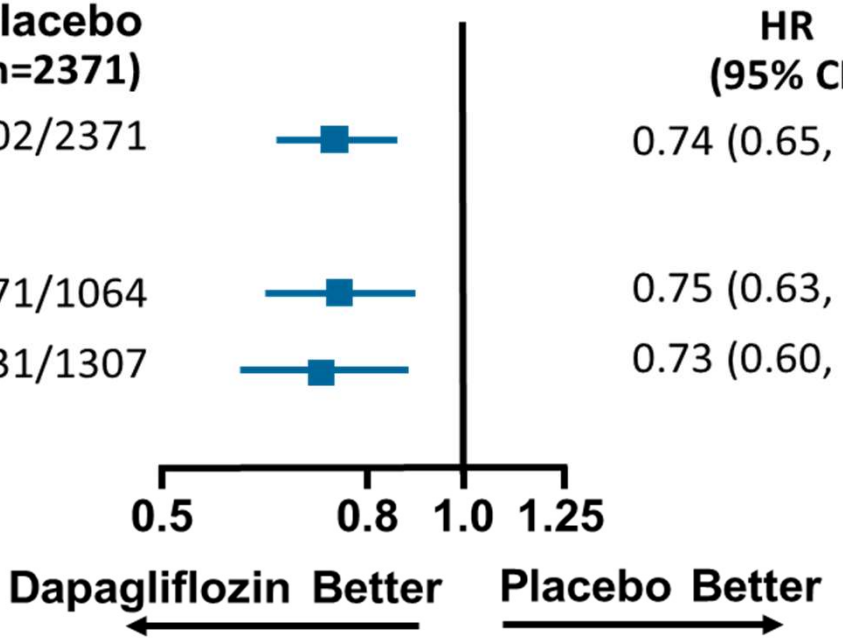
Number at Risk									
Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

386 vs 502 events

McMurray JJV, et al. N Engl J Med 2019

No diabetes/diabetes subgroup: Primary endpoint

	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
Type 2 diabetes at baseline*			
Yes	215/1075	271/1064	0.75 (0.63, 0.90)
No	171/1298	231/1307	0.73 (0.60, 0.88)



*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrollment and randomization visits.

McMurray JJV, et al. N Engl J Med 2019 doi: 10.1056/NEJMoa1911303

PERSPECTIVE

Use of Sodium Glucose Cotransporter 2 Inhibitors in the Hands of Cardiologists

With Great Power Comes Great Responsibility

FRAME OF REFERENCE

- Consider altering background blood pressure medications if intensively controlled
- Consider stopping/reducing background diuretics
- If on insulin and/or sulfonylurea, consider dose reducing each of those

- Counsel re: urinary hygiene
- “Sick Day” medication concept-hold on days with reduced PO intake

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Cherney DZ and Udell JA. Circulation 2016; 134: 1915-1917

Conclusions

- SGLT2 Inhibitors prevent HF in patients with T2DM with ASCVD risk or disease
  - Consistent “IA” recommendations across Guidelines/Consensus recommendations
  - These must become part of routine cardiology care
- Dapagliflozin is a safe and effective treatment for HFrEF, added to existing evidence-based therapies
  - Independent of diabetes status
  - These findings should immediately impact practice
  - Insurance coverage may be an obstacle ahead of FDA indication
- Uncertainties remain
  - Class effect or dapagliflozin effect; empagliflozin and sotagliflozin trials ongoing?
  - Unique to HFrEF or will this also impact HFpEF outcomes?
  - Mechanism(s) of benefit remain unknown