

Review of Recent SGLT2 Inhibitor Data

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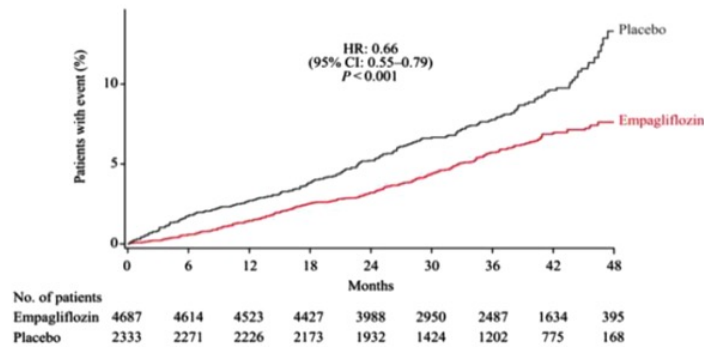
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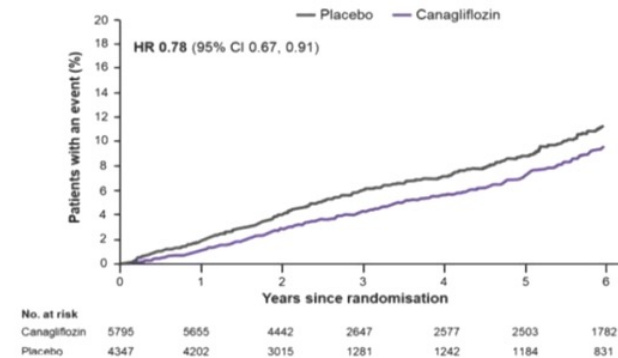
Radcliffe
Medical Education

CVOTs with SGLT2i in Patients with Diabetes

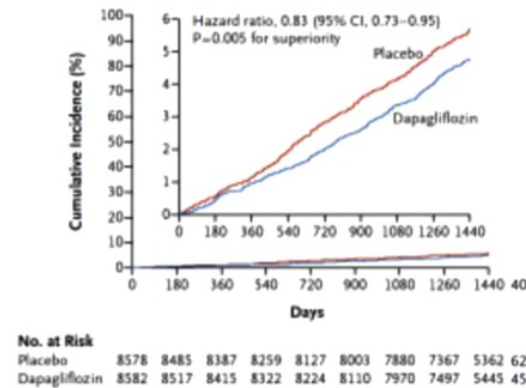
EMPA-REG Outcome¹



CANVAS Program²

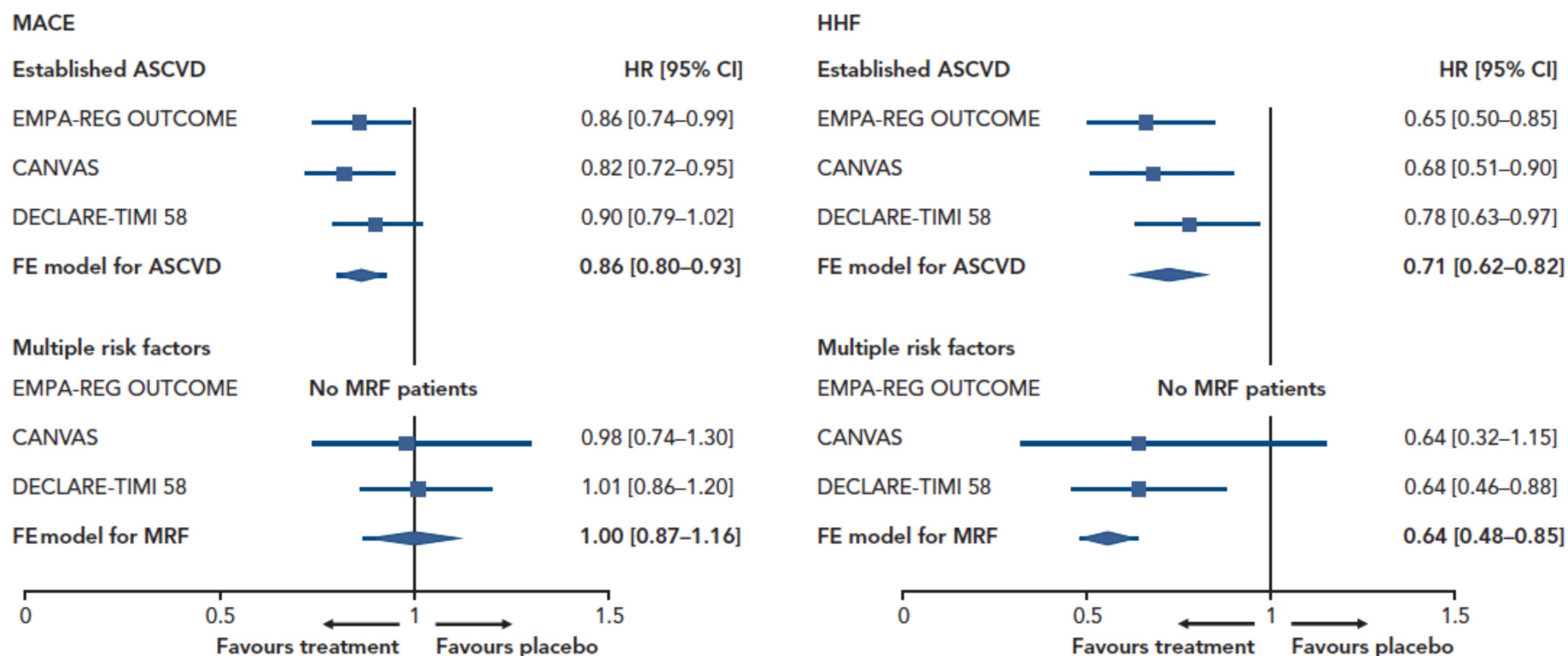


DECLARE³



1. Zinman B et al. *N Engl J Med*. 2015; 2. Neal B et al. *N Engl J Med* 2017; 3. Wiviott SD et al. *N Engl J Med* 2018

SGLT2 Inhibitors on CVD End-points in T2D Patients



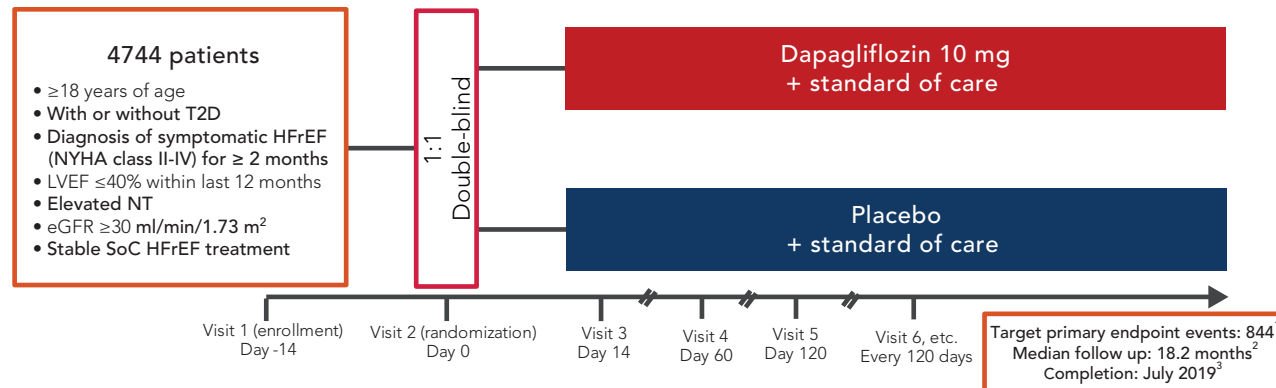
ASCVD = atherosclerotic CV disease; CV = cardiovascular; FE = fixed effects; hHF = hospitalized for heart failure;
 HR = hazard ratio; MACE = major cardiovascular adverse event; MRF = multiple risk factors;
 SGLT2 = sodium glucose co-transporter 2; T2D = type 2 diabetes; 1. Zelniker TA et al. Article and supplementary appendix.
Lancet. 2019;393:31-39; 2. Einarson et al. *Cardiovasc Diabetol*. 2018;17:83.

SGLT2i for the Prevention of HF in Diabetic Patients

Canagliflozin, dapagliflozin empagliflozin, or ertugliflozin have consistently demonstrated to be effective for the prevention of HF hospitalization in patients with type 2 diabetes mellitus & established cardiovascular disease or at high cardiovascular risk. The specifically listed agents are recommended.

DAPA – HF

Dapagliflozin in Patients with Chronic HFrEF With or Without T2D



CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease; HbA1c = glycated hemoglobin; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; hHF = hospitalization for heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; NT-proBNP = **N-terminal pro B-type natriuretic peptide**; NYHA = New York Heart Association; SoC = standard of care; T2D = type 2 diabetes.

1. McMurray JJV et al. Article and supplementary appendix.

al. N Engl J Med. 2019. <https://doi.org/10.1056/NEJMoa1911303>. Accessed September 19, 2019. 3. Study NCT03036124. ClinicalTrials.gov website. Accessed August 19, 2019. 4. McMurray JJV et al. Eur J Heart Fail. 2019;doi: 10.1002/ejhf.1548. Accessed July 16, 2019.

Primary Endpoint

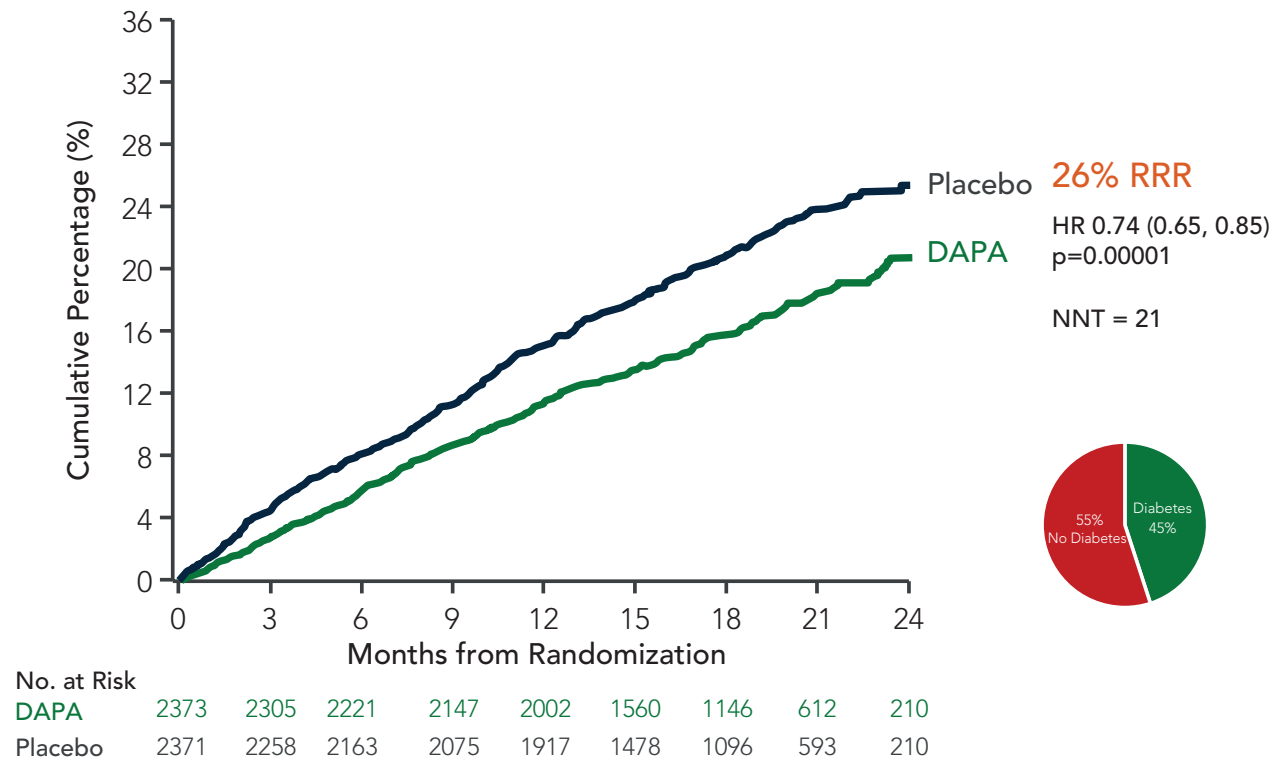
- Time to first occurrence of any of the components of the composite: CV death or hHF or an urgent HF visit

Secondary Endpoints

- Time to first occurrence of either of the components of the composite: CV death or hHF
- Total number of (first and recurrent) hHF and CV death
- Change from baseline measured at 8 months in the total symptom score of the KCCQ
- Time to first occurrence of any of the components of the composite: ≥50% sustained decline in eGFR or reaching ESRD or renal death
- Time to death from any cause

DAPA – HF

Primary Endpoint: CV Death or hHF or an Urgent HF Visit

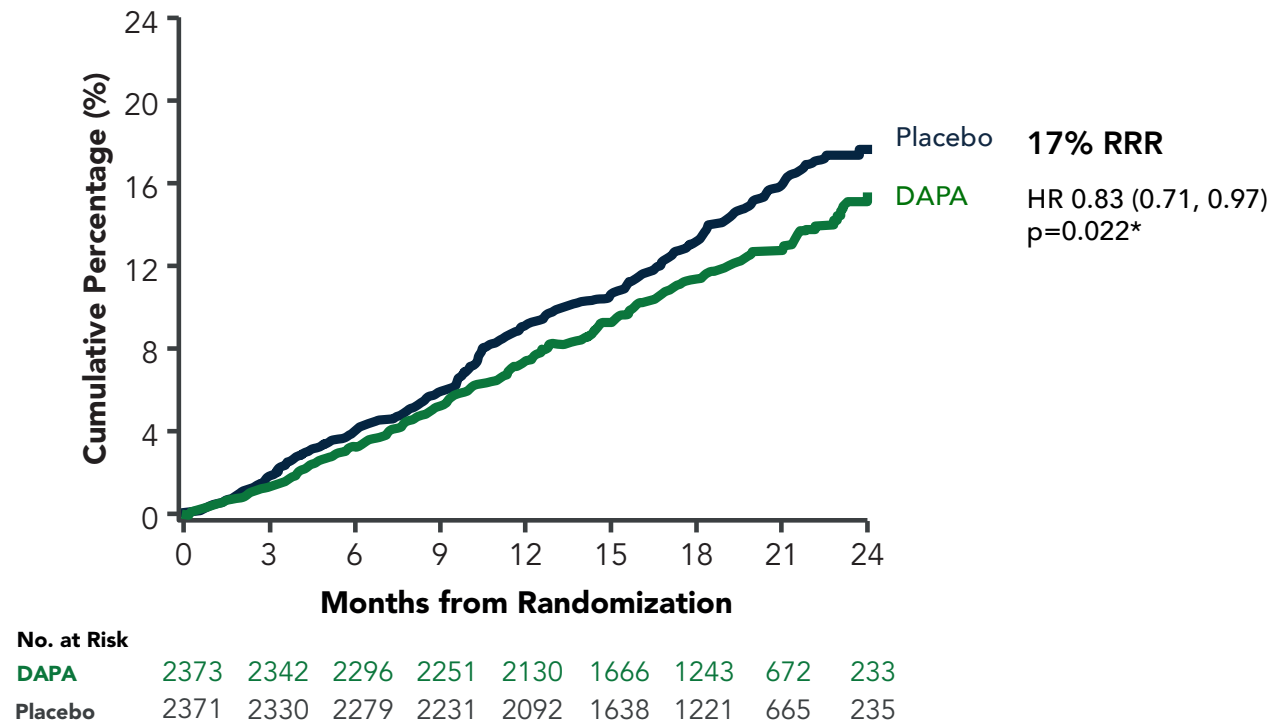


DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio;
NNT = number needed to treat; RRR = relative risk reduction

1. McMurray JJV et al. *N Engl J Med*. 2019. <https://doi.org/10.1056/NEJMoa1911303>. Accessed September 19, 2019.

DAPA – HF

Effect of Dapagliflozin on All-cause Death

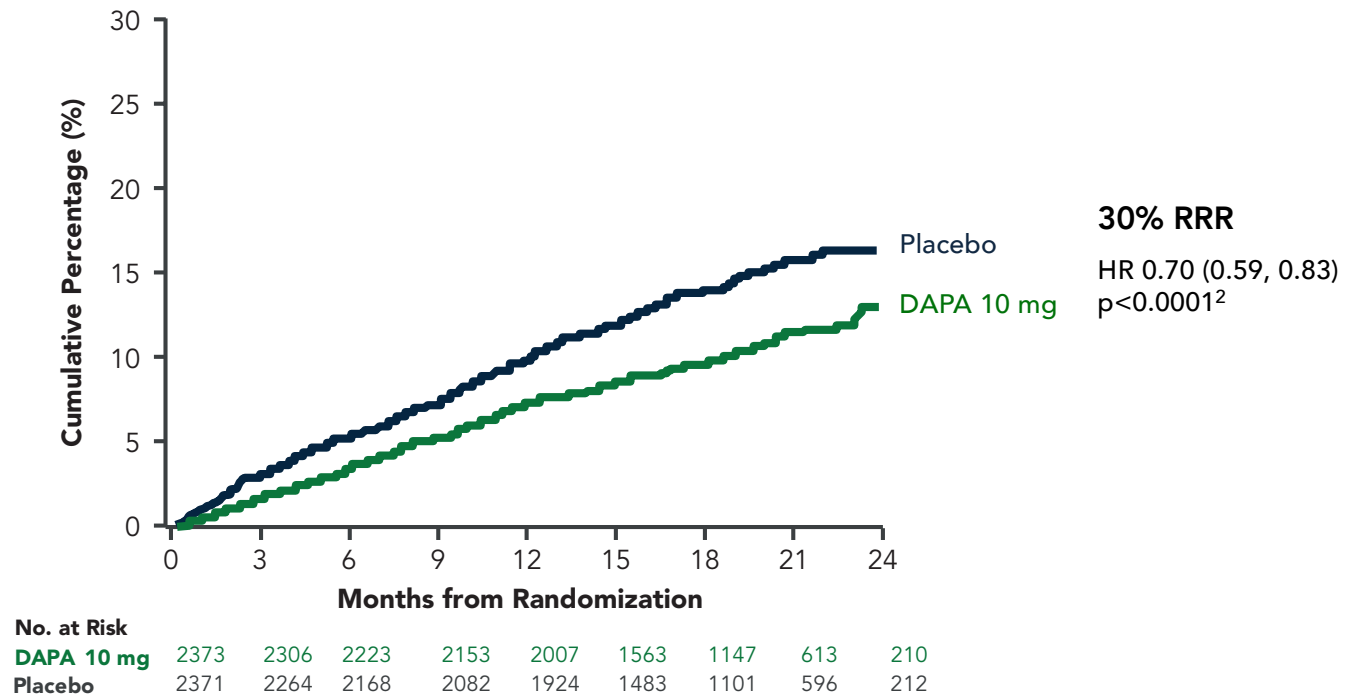


* Nominal p-value.
DAPA = Dapagliflozin; HR = Hazard ratio.

1. McMurray JJV et al. *N Engl J Med*. 2019. <https://doi.org/10.1056/NEJMoa1911303>. Accessed September 19, 2019.. 2. McMurray J.

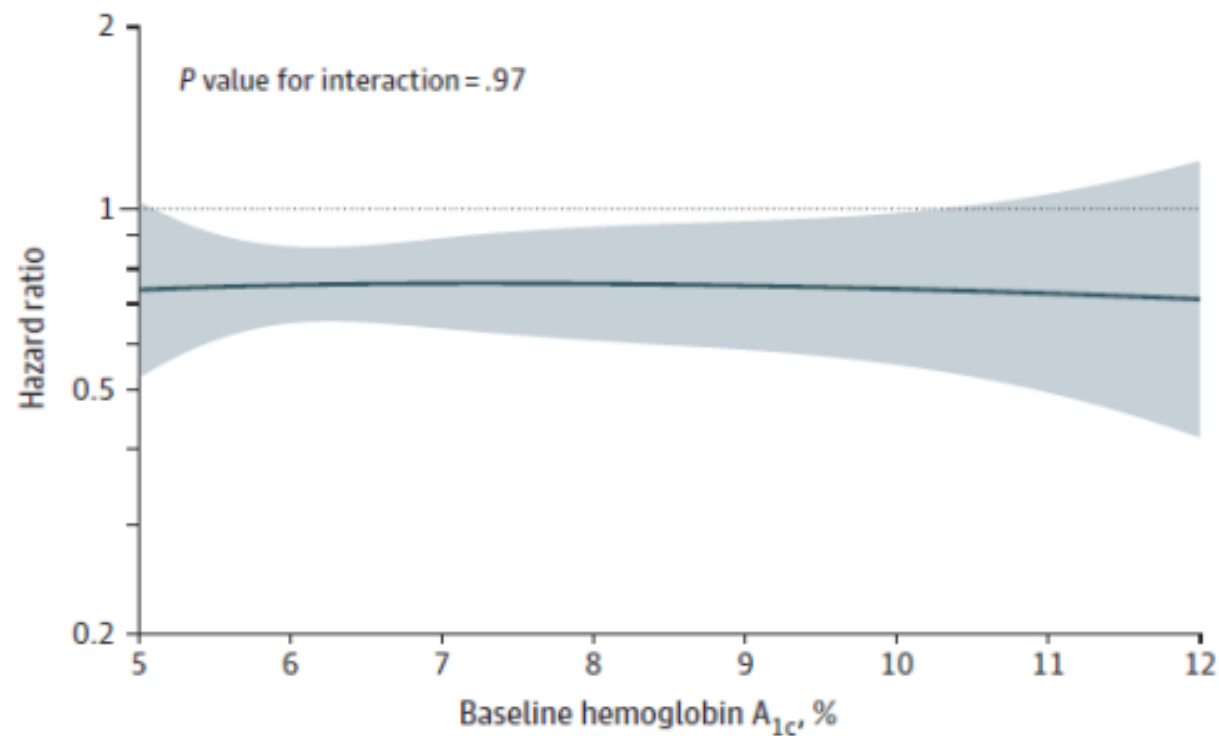
DAPA – HF

Hospitalization for Heart Failure (hHF)^{1,2}



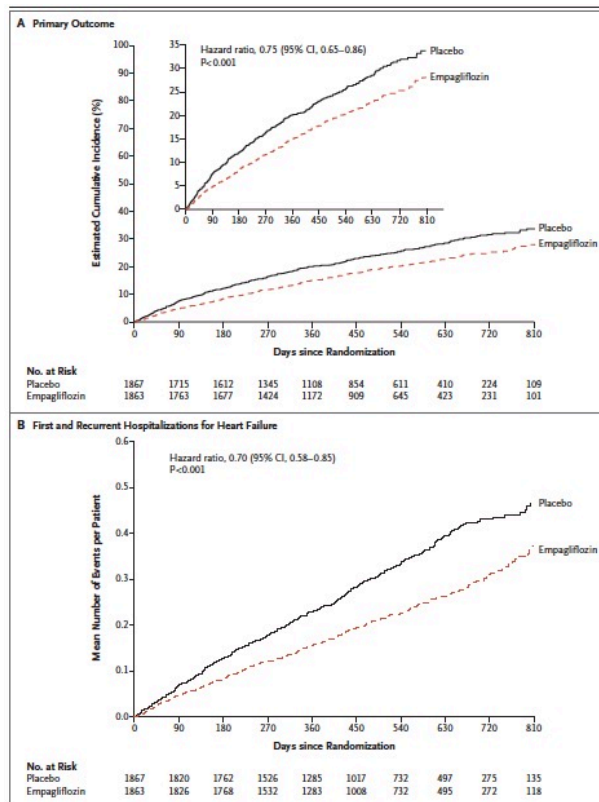
1. McMurray JJV et al. *N Engl J Med*. 2019. <https://doi.org/10.1056/NEJMoa1911303>.

Dapagliflozin Reduces the Primary End Point Regardless of Baseline HbA1c

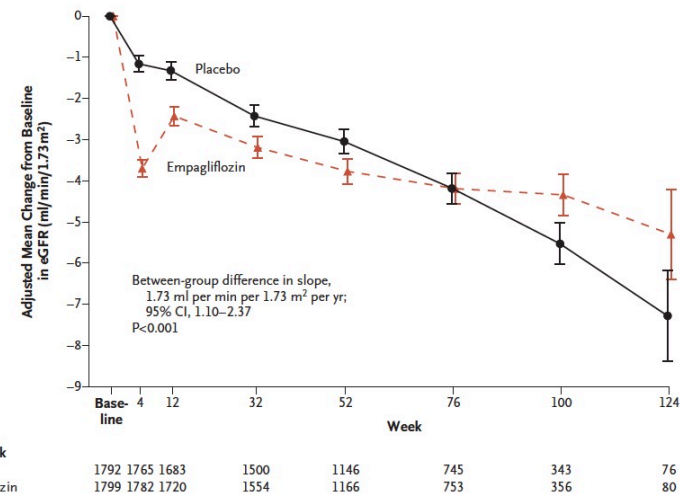


JAMA 2020;323:1353-1368

Emperor Reduced



No effect on mortality



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Summary of Heart Failure Outcomes in SGLT2 Inhibitor Clinical Studies

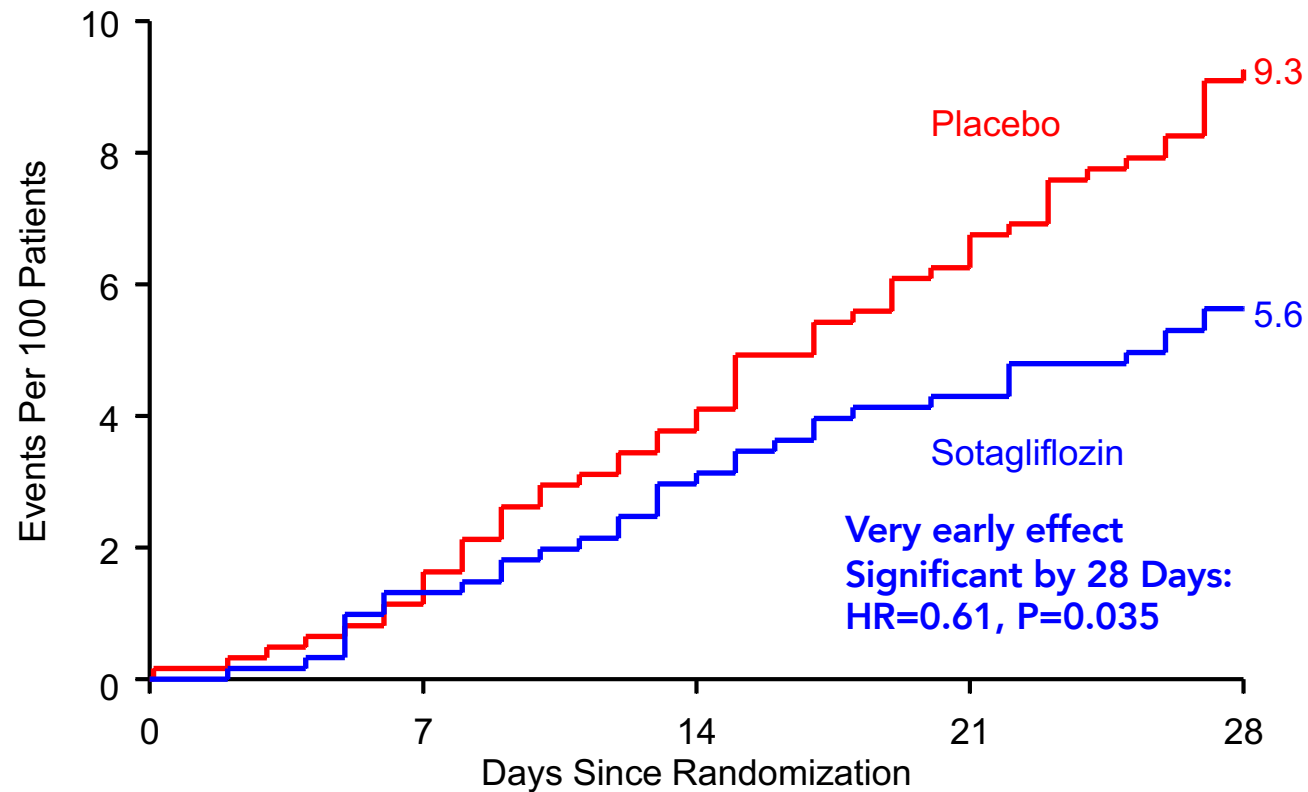
Outcome	Meta-analysis of SGLT2 Inhibitors in T2D CVOTs (Empagliflozin, Canagliflozin and Dapagliflozin) ¹⁷		DAPA-HF (Dapagliflozin) ⁸	EMPEROR-Reduced (Empagliflozin) ⁹
	Overall Population (n=38,723)	History of HF (n=4,543)	HFrEF (n=4,744)	HFrEF (n=3,700)
Relative risk reduction (%)				
HHF	32	31	30	30
HHF and CV death	24	27	26	25
HR				
HHF	0.68 (95% CI [0.60–0.76]; p<0.001)	0.69 (95% CI [0.57–0.83]; p<0.001)	0.70 (95% CI [0.59–0.83]; p<0.001)	0.70 (95% CI [0.58–0.85]; p<0.001)
HHF and CV death	0.76 (95% CI [0.63–0.84]; p<0.001)	0.73 (95% CI [0.63–0.84]; p<0.001)	0.74 (95% CI [0.65–0.85]; p<0.001)	0.75 (95% CI [0.65–0.86]; p<0.001)

CV = cardiovascular; CVOT = cardiovascular outcomes trial; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HHF = hospitalisation for heart failure; SGLT2 = sodium-glucose co-transporter 2; T2D = type 2 diabetes. Source: Arnett et al. 2020,¹⁷ McMurray et al. 2019⁸ and Packer et al. 2020.⁹

SGLT2 Inhibitors in Patients with HFrEF

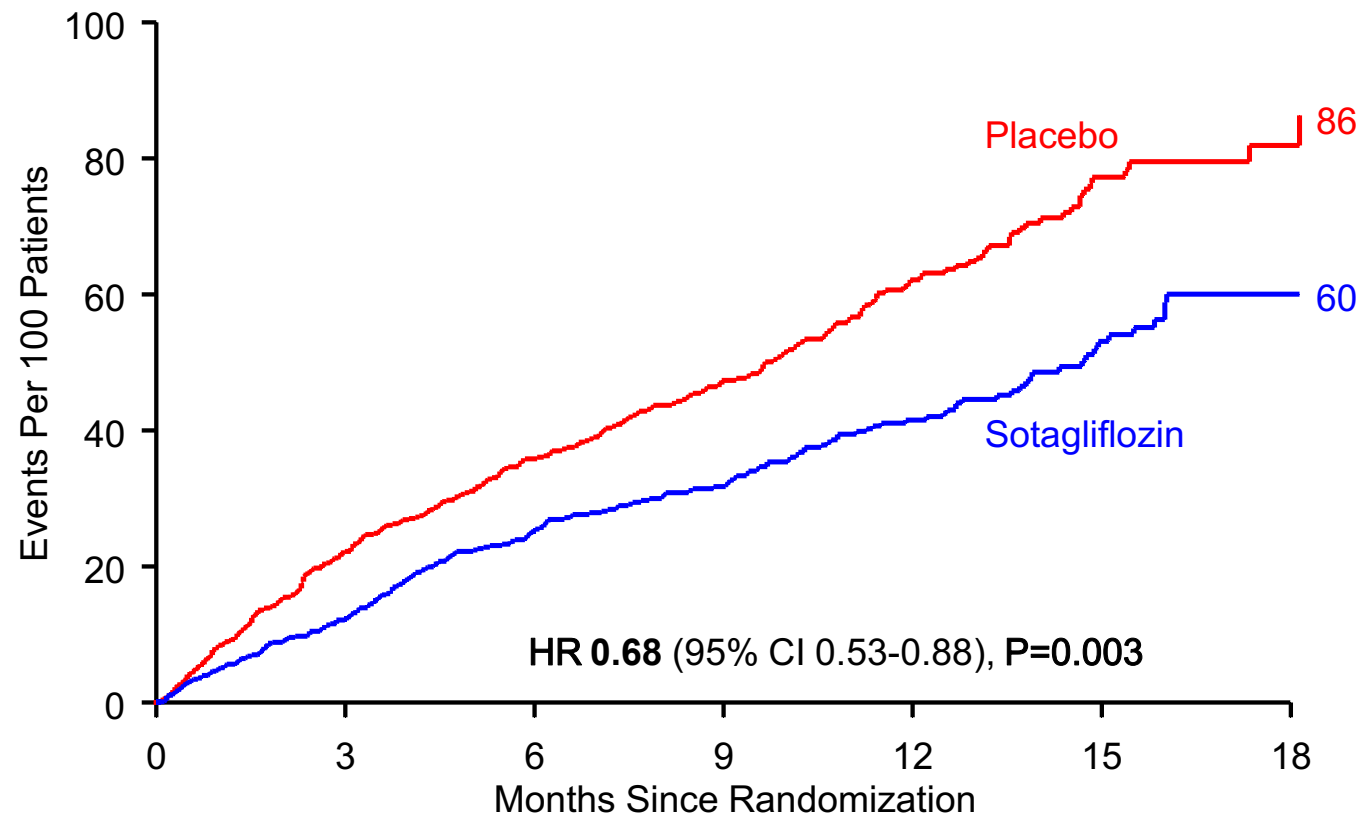
- SGLT2 inhibitors (dapagliflozin, empagliflozin) are recommended for the treatment of patients with heart failure

Primary Efficacy: Total CV Death, HHF, and Urgent HF



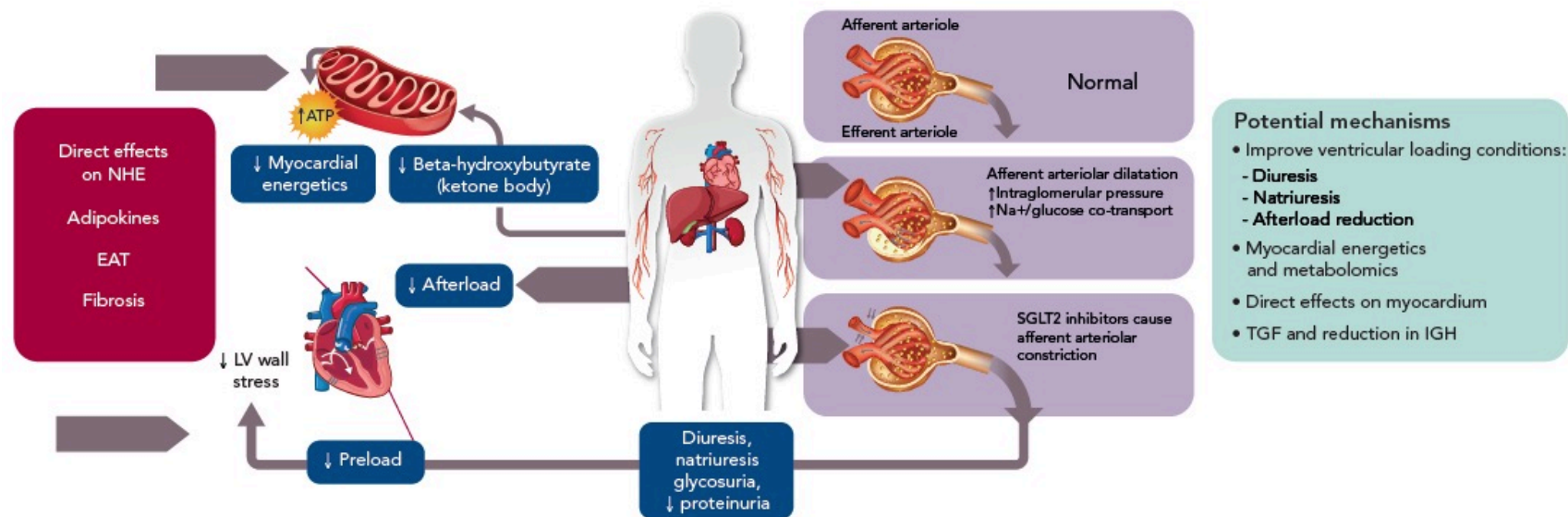
Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.

Total CV Death and HHF



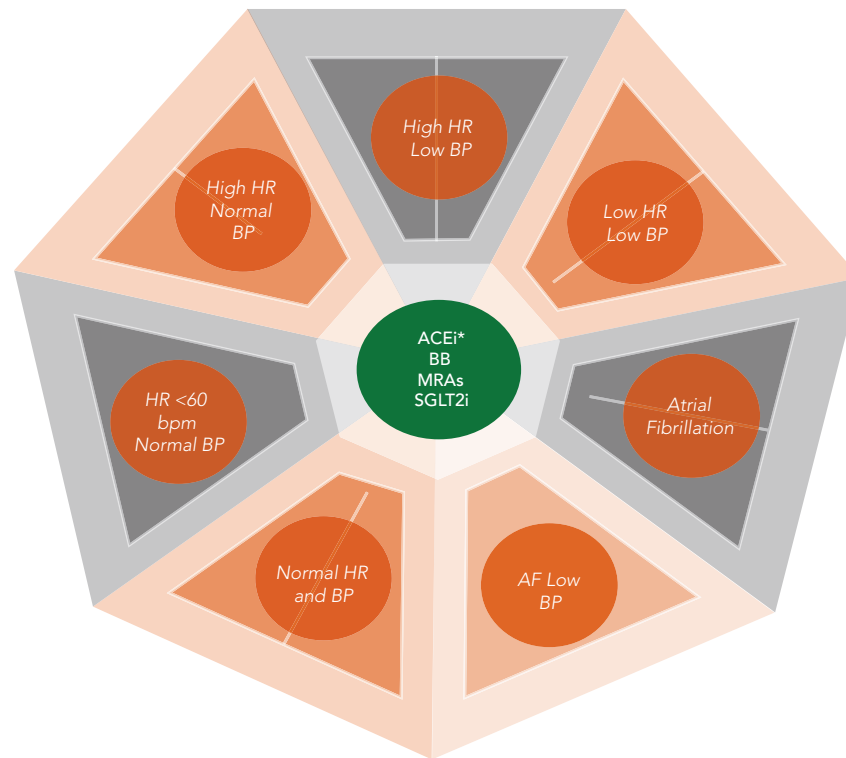
Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.

Proposed Mechanism of Cardiovascular Benefits of SGLT2 Inhibitors



ATP = adenosine triphosphate; BP = blood pressure; EAT = epicardial adipose tissue; eGFR = estimated glomerular filtration rate; IGH = intraglomerular hypertension; LV = left ventricular; NHE = sodium-hydrogen exchanger; SGLT2 = sodium-glucose co-transporter 2; TGF = tubuloglomerular feedback. Source: Verma et al. 2017.³⁷ Adapted with permission from the American Medical Association.

An Updated Algorithm for the Management of Heart Failure



* ARNI in patients with LVEF <35%, NT pro-BNP >600 pg/ml, Enalapril 10 mg bd and still symptomatic

Rosano G HFA workshop on phenotyping of HF patients 2020

Conclusion

- SGLT2i reduce CV events and the risk of heart failure in diabetic patients and reduce the risk of mortality and hospitalisations for heart failure in patients with heart failure with or without diabetes.
- SGLT2i should be considered in all diabetic patients for the prevention of HF and in all patients with HFrEF
- SGLT2i should be considered as the mainstay of treatment of heart failure as should be implemented as soon as possible in all HFrEF patients with and without diabetes