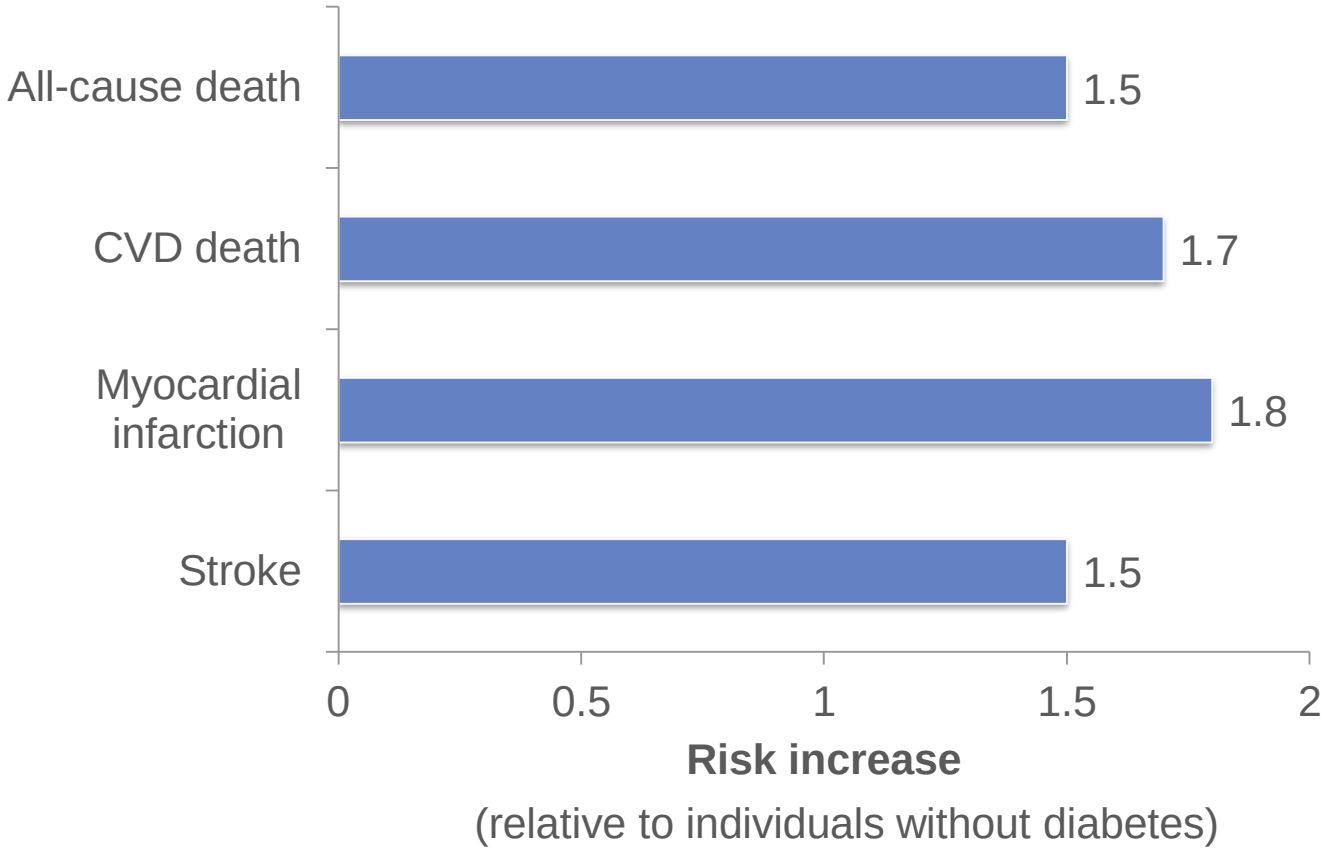
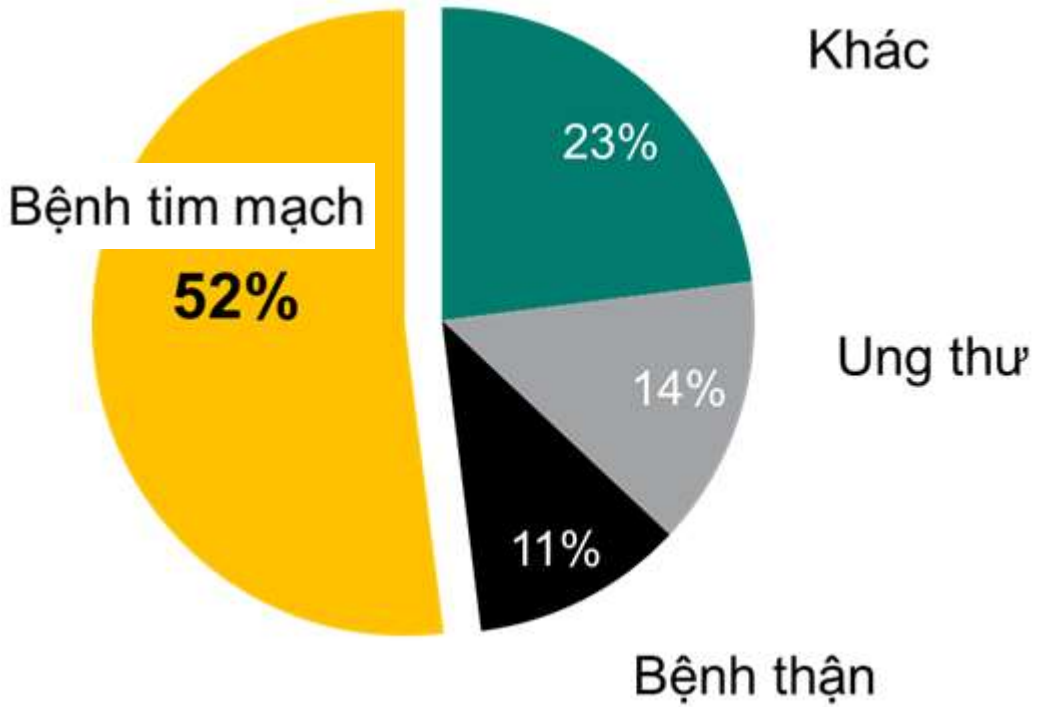
Quản lý ĐTĐ type 2:
Từ thử nghiệm lâm sàng đến kết quả điều trị

GIỚI THIỆU

1. Vai trò của KSĐH với gánh nặng bệnh tim mạch và tử vong ở BN ĐTĐ
2. Tác động trên BC tim mạch – thận của các thuốc hạ ĐH
3. Vị trí các thuốc hạ ĐH mới trong khuyến cáo cập nhật

ĐTĐ làm gia tăng nguy cơ BC tim mạch và tử vong

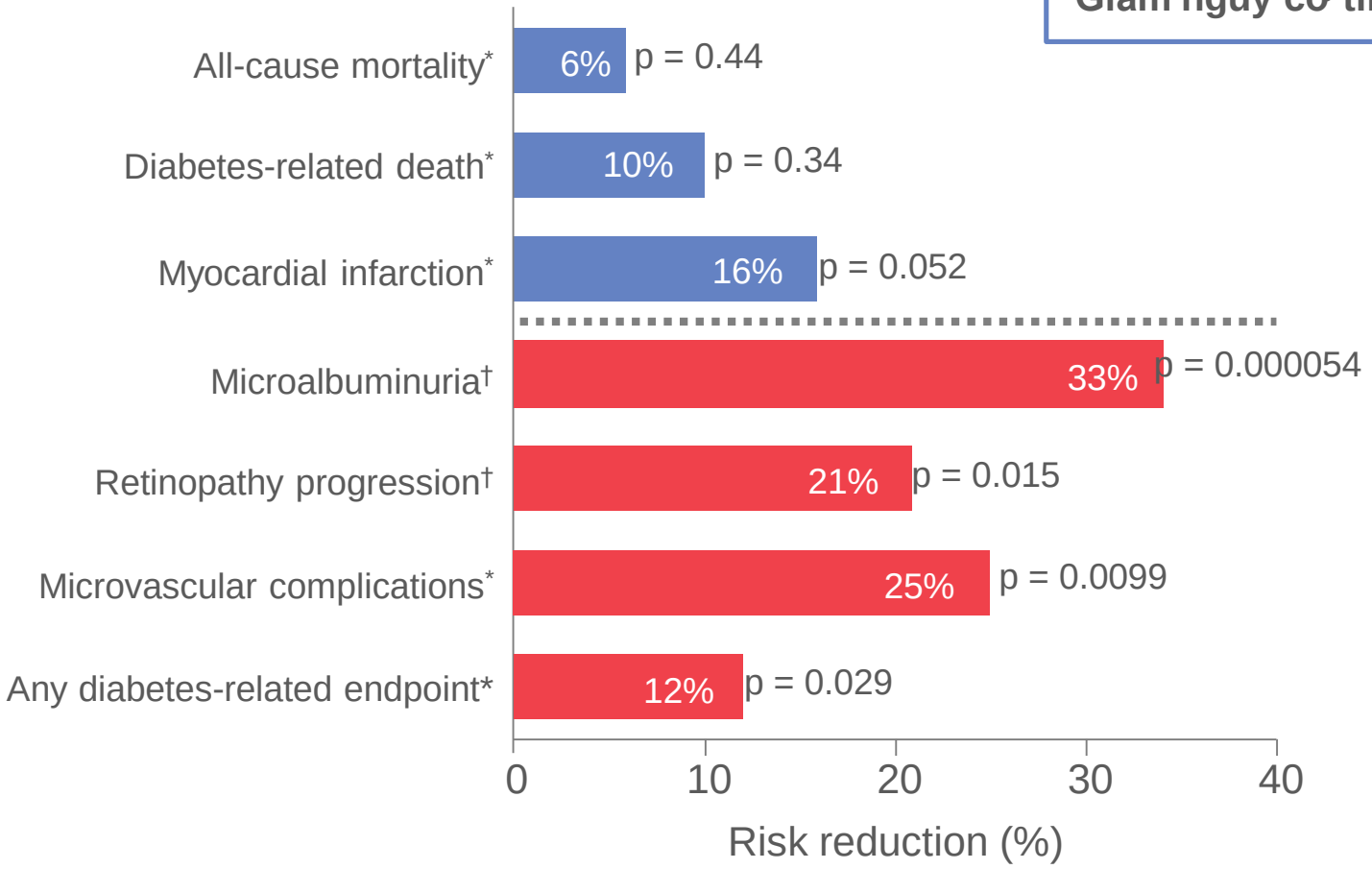




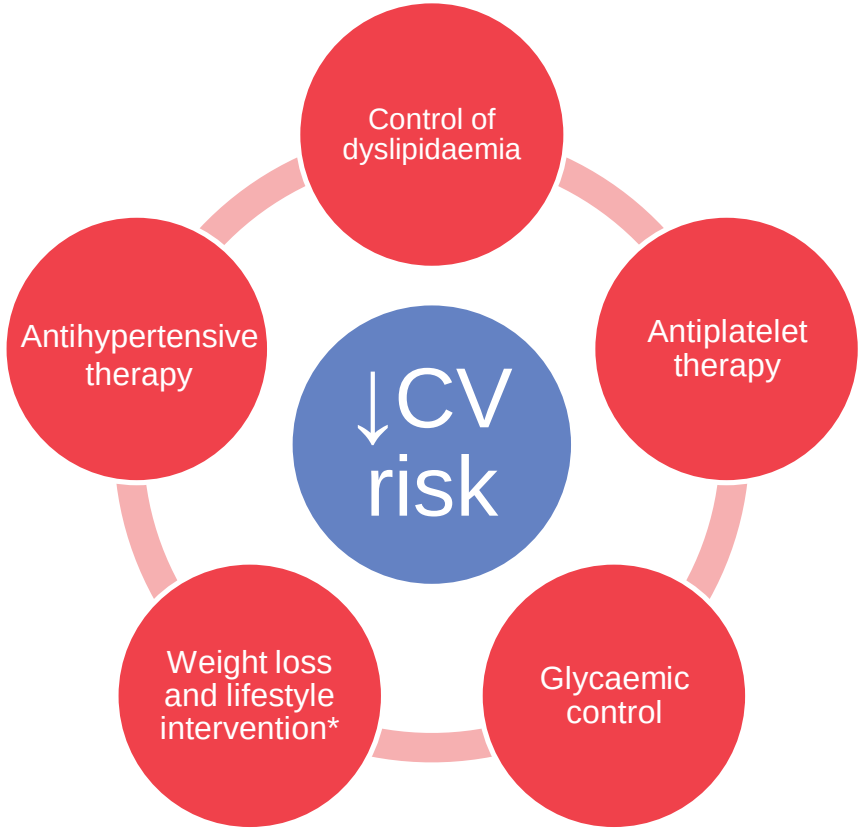
Bệnh tim mạch
Nguyên nhân gây tử vong hàng đầu ở bệnh nhân ĐTĐ

CDC. National diabetes statistics report, 2014. http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf

UKPDS: KSĐH tích cực giúp giảm BC mạch máu nhỏ nhưng không làm giảm BC mạch máu lớn



Giảm nguy cơ tim mạch ở BN ĐTĐ typ 2 đòi hỏi tiếp cận đa yếu tố

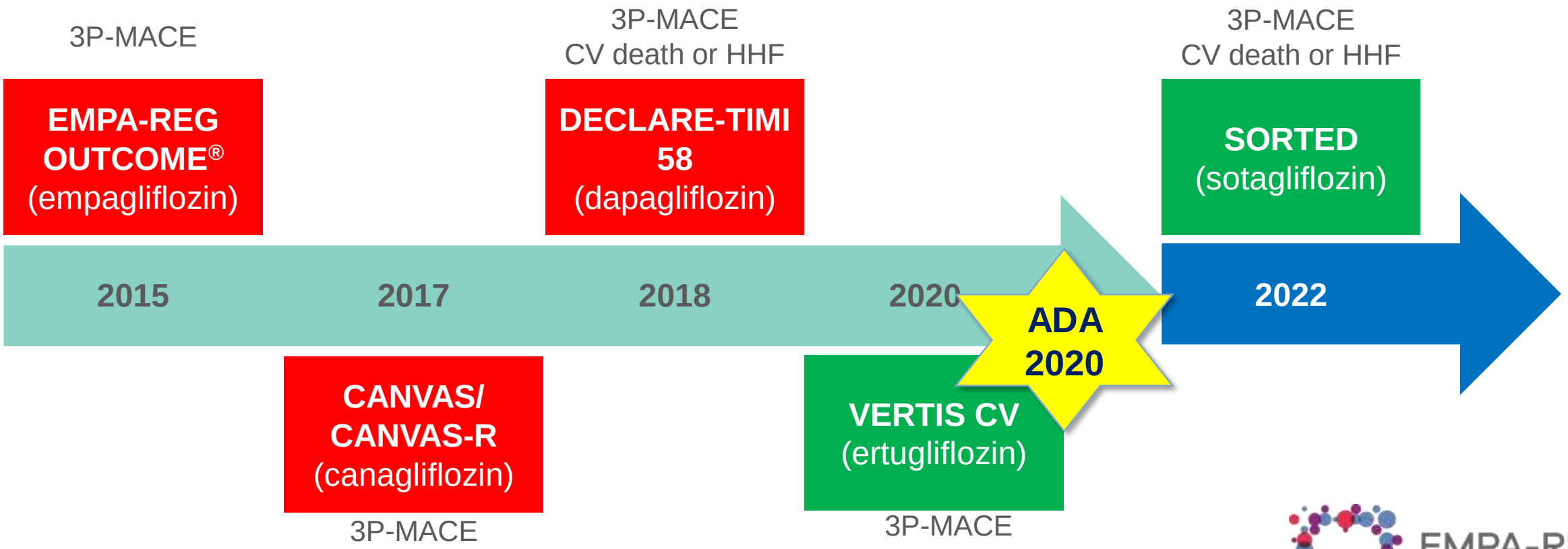


*Median follow-up, 10 years; †assessed as surrogate endpoints; follow-up, 12 years.
UKPDS 33. Lancet 1998;352:837–53.

*Includes smoking cessation.
Anonymous. Eur Heart J 2013;34:3035–87.

Thời gian các thử nghiệm CVOTs của SGLT2i

CVOTs are RCTs that are **primarily designed to assess CV outcomes**, typically with a composite primary outcome, such as 3P-MACE (CV death, non-fatal stroke or non-fatal myocardial infarction).



3P-MACE, 3-point major adverse CV event; CV, cardiovascular; CVOT, CV outcomes trial; HHF, hospitalisation for heart failure; SGLT2, sodium–glucose cotransporter 2.

1. Zinman et al. N Engl J Med 2015;373:2117–28. 2. Neal et al. N Engl J Med 2017;377:644–57. 3. Wiviott et al. N Engl J Med 2018;doi:10.1056/NEJMoa1812389. 4. NCT01986881. 5. NCT03315143.

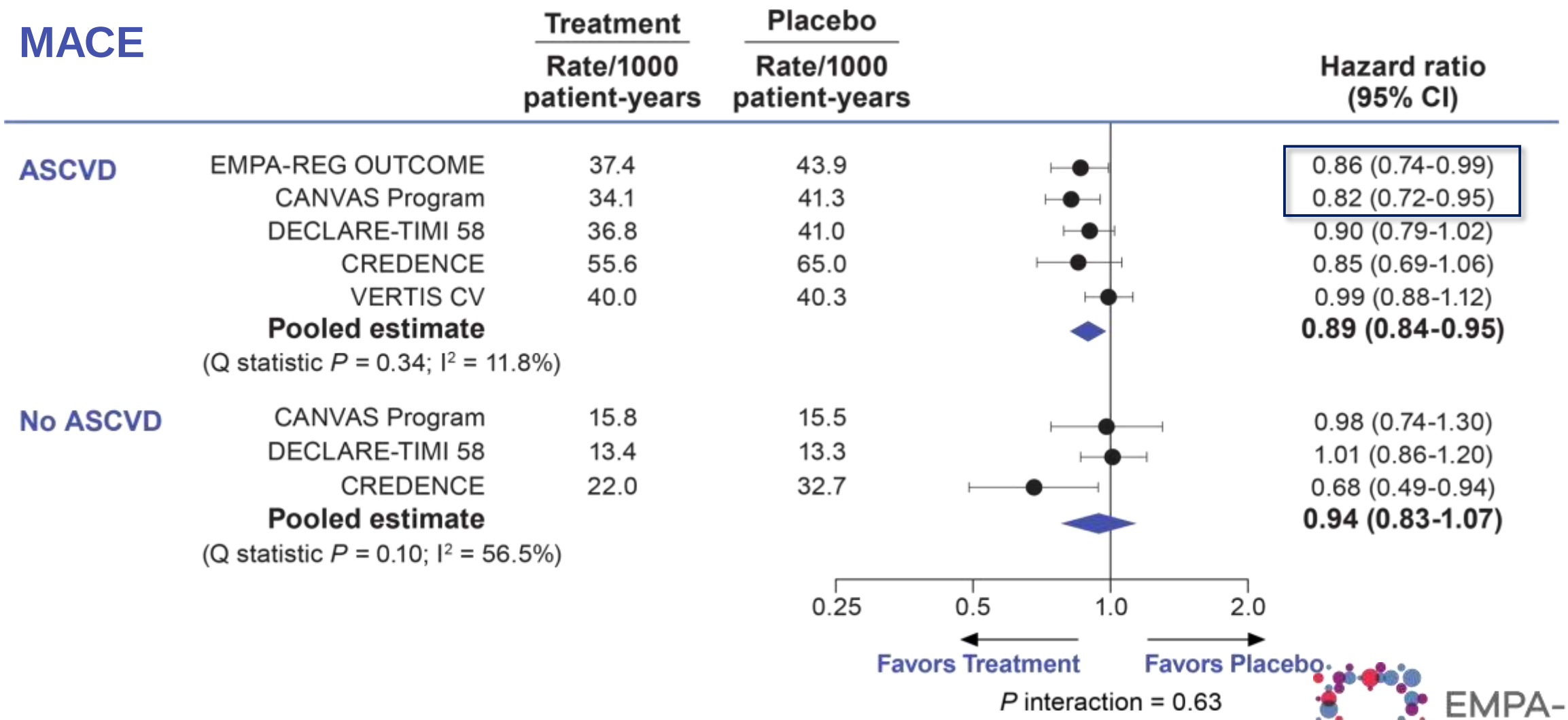
Nghiên cứu đánh giá an toàn tim mạch ở BN ĐTĐ

	EMPA-REG OUTCOME[1]	CANVAS Program[2]	DECLARE-TIMI 58[3]	CREDENCE[4]	VERTIS CV
SGLT2 inhibitor	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	Ertugliflozin
N	7020	10,142	17,160	4401	8246
Duration of follow-up, median, years	3.1	2.4	4.2	2.6	3.0
Age, mean ± SD, years	63.1 ± 8.6	63.3 ± 8.3	63.9 ± 6.8	63.0 ± 9.2	64.4 ± 8.1
Female, %	28.5	35.8	37.4	33.9	30.0
HbA1c, mean ± SD, %	8.1 ± 0.8	8.2 ± 0.9	8.3 ± 1.2	8.3 ± 1.3	8.2 ± 1.0
Diabetes duration, mean ± SD, years	NA	13.5 ± 7.8	11.8 ± 7.8	15.8 ± 8.6	13.0 ± 8.3
Established CV disease, %	100	65.6	40.6	50.4	100
History of HF, %	10.1	14.4	10.0	14.8	23.7
Reduced kidney function (eGFR <60 mL/min/1.73 m^2), %	25.9	20.1	7.4	59.8	21.9

CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HF, heart failure; NA, not available; SD, standard deviation.

1. Zinman B et al. *N Engl J Med* 2015;373:2117-2128. 2. Neal B et al. *N Engl J Med* 2017;377:644-657. 3. Wiviott SD et al. *N Engl J Med* 2019;380:347-357.
4. Perkovic V et al. *N Engl J Med* 2019; 380:2295-306.

Time to first MACE – subgroup analysis by ASCVD



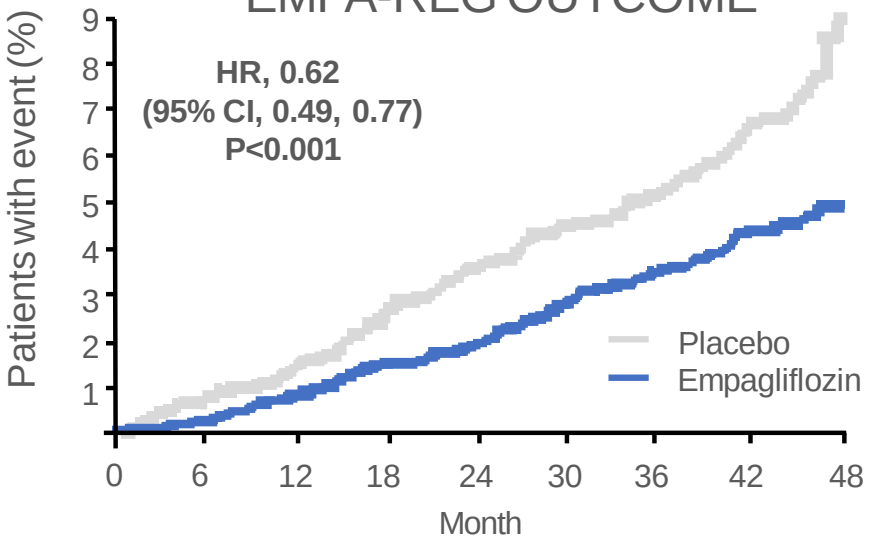
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; MACE, major adverse cardiovascular events.

EMPA-REG OUTCOME®

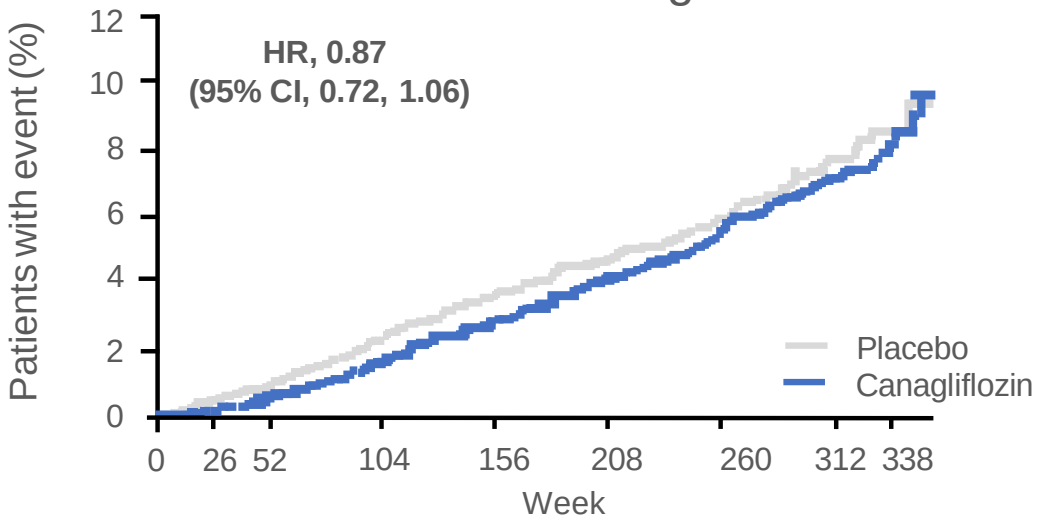
SGLT2i CVOTs: Kết quả giảm tử vong tim mạch

CV death endpoint in SGLT2 inhibitor in CV outcomes trials

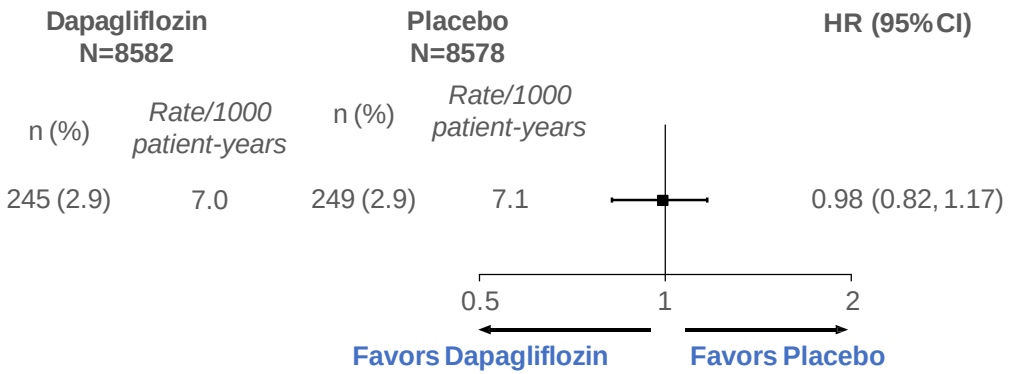
EMPA-REG OUTCOME[1]



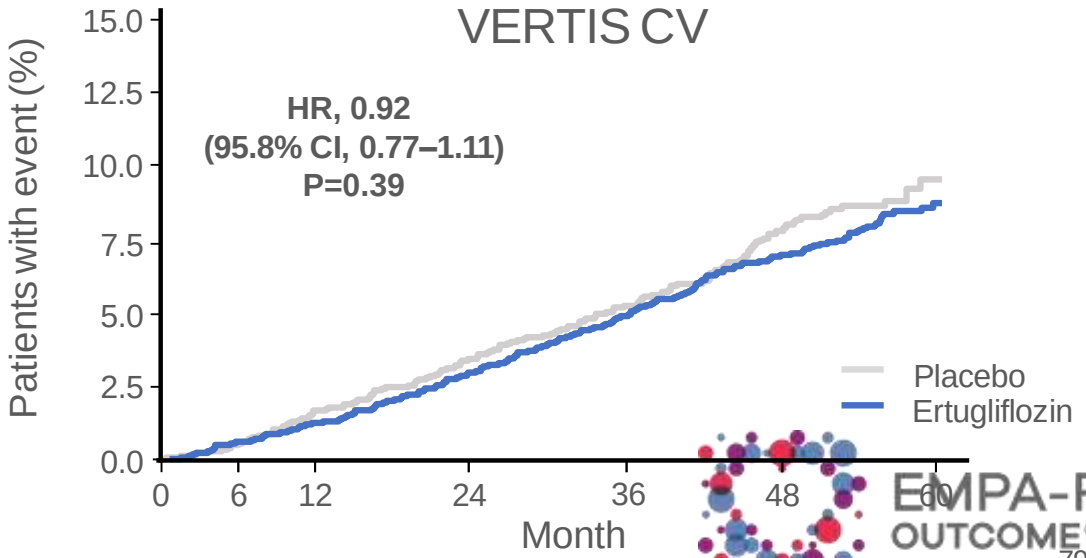
CANVAS Program[2]



DECLARE-TIMI 58[3]



VERTIS CV

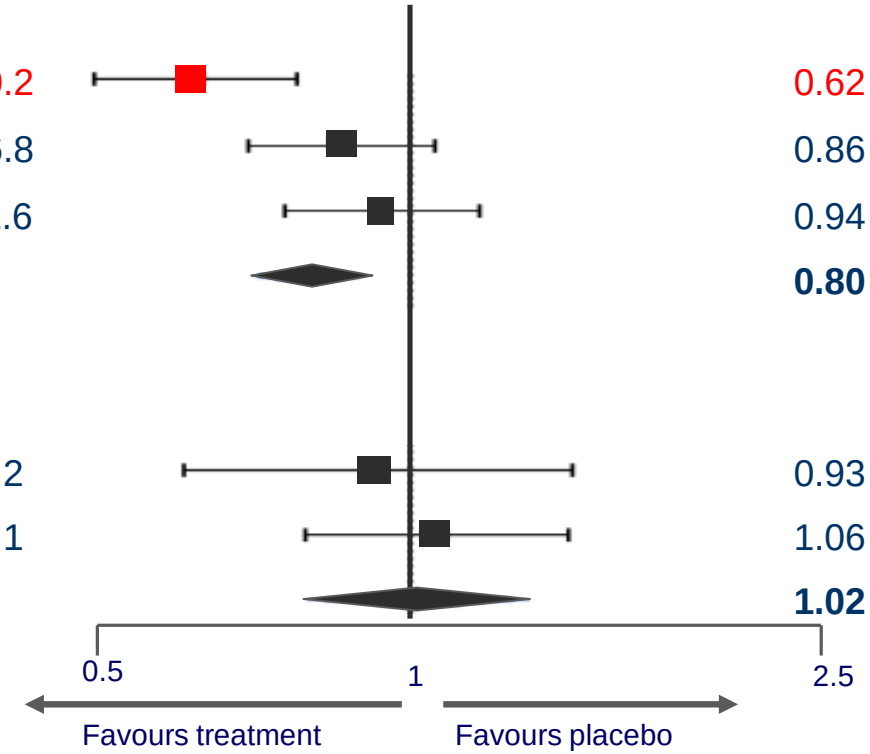


CI confidence interval; CV, cardiovascular; HR, hazard ratio

1. Zinman B et al. *N Engl J Med* 2015;373:2117-2128; 2. Neal B et al. *N Engl J Med* 2017;377:644-657;
3. Wiviott SD et al. *N Engl J Med* 2019;380:347-357.

Meta-analysis: Lợi ích giảm nguy cơ Tử vong tim mạch chỉ thấy với empagliflozin, không thấy với các SGLT-2i khác[1,4]

Study name	Events per 1,000 PY: SGLT2 inhibitor	Events per 1,000 PY: Placebo	CV death HR (95% CI)	*P*-value
Patients with ASCVD				
EMPA-REG OUTCOME®[1,4]	12.4	20.2	0.62 (0.49, 0.77)	
CANVAS Program[2,4]	14.8	16.8	0.86 (0.70, 1.06)	
DECLARE-TIMI 58[3,4]	10.9	11.6	0.94 (0.76, 1.18)	
Pooled analysis (all SGLT2 inhibitors)			**0.80 (0.71, 0.91)**	**0.0005**
Patients with multiple risk factors				
CANVAS Program[2,4]	6.5	6.2	0.93 (0.60, 1.43)	
DECLARE-TIMI 58[3,4]	4.4	4.1	1.06 (0.79, 1.42)	
Pooled analysis (all SGLT2 inhibitors)			**1.02 (0.80, 1.30)**	**0.89**



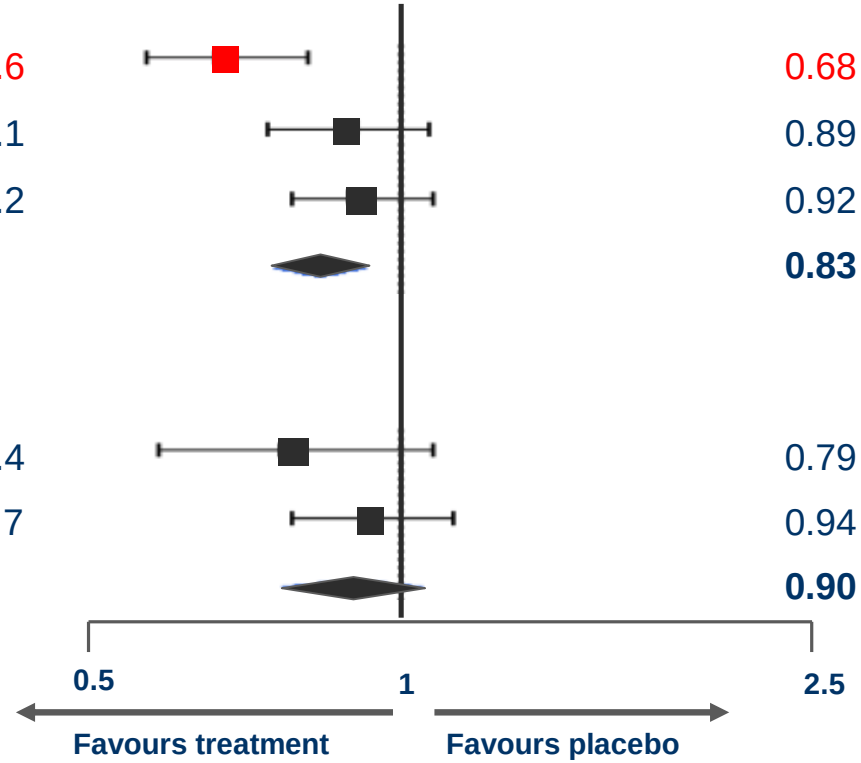
P-value for subgroup difference: 0.31

ASCVD: Q statistic = 7·42, p=0·0245, I^2= 73·0%; MRF: Q statistic = 0·24, p=0·62, I^2= 0%. P-value for subgroup differences: 0·31

1. Zinman et al. N Engl J Med 2015;373:2117–28. 2. Neal et al. N Engl J Med. 2017;377:644–57. 3. Wiviott et al. N Engl J Med 2018;doi:10.1056/NEJMoa1812389. 4. Zelniker et al. Lancet 2018;doi:10.1016/S0140-6736(18)32590-X.

Tử vong do mọi nguyên nhân: Lợi ích cũng chỉ thấy khi điều trị empagliflozin

Study name	Events per 1,000 PY: SGLT2 inhibitor	Events per 1,000 PY: Placebo	All-cause mortality HR (95% CI)	*P*-value
Patients with ASCVD				
EMPA-REG OUTCOME®[1,2]	19.4	28.6	0.68 (0.57, 0.82)	
CANVAS Program[2,3]	21.1	23.1	0.89 (0.75, 1.07)	
DECLARE-TIMI 53[2,4]	21.3	23.2	0.92 (0.79, 1.08)	
Pooled analysis (all SGLT2 inhibitors)			**0.83 (0.75, 0.92)**	**0.0003**
Patients with multiple risk factors				
CANVAS Program[2,3]	11.2	13.4	0.79 (0.58, 1.07)	
DECLARE-TIMI 53[2,4]	11.0	11.7	0.94 (0.78, 1.12)	
Pooled analysis (all SGLT2 inhibitors)			**0.90 (0.77, 1.05)**	**0.18**



ASCVD: Q statistic = 6·87, p=0·0322, I^2= 70·9%; MRF: Q statistic = 0·92, p=0·34, I^2= 0%. P-value for subgroup differences: 0·69

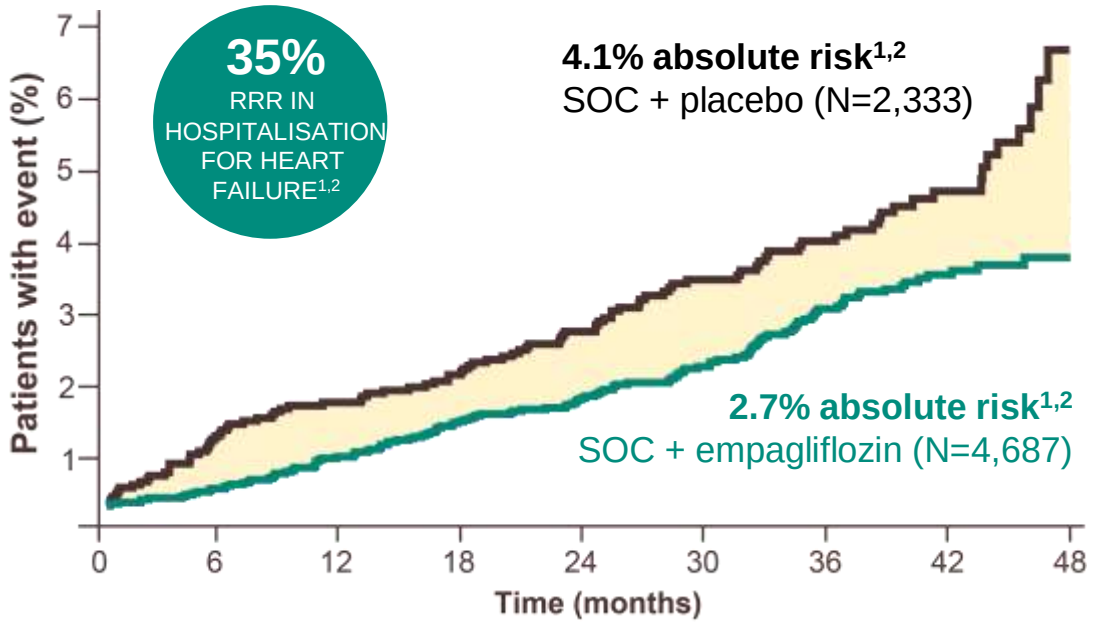
ASCVD, atherosclerotic cardiovascular disease, CI, confidence interval; HR, hazard ratio; PY, patient-year; SGLT2, sodium–glucose transporter 2.

1. Inzucchi et al. Diabetes Care 2018; 41:e4–5. 2. Zelniker et al. Lancet 2018;doi:10.1016/S0140-6736(18)32590-X. 3. Neal et al. N Engl J Med. 2017;377:644–57. 4. Wiviott et al. N Engl J Med 2018;doi:10.1056/NEJMoa1812389.

EMPA-REG OUTCOME: risk reduction in CV death and hHF with empagliflozin was early, sustained, and independent of baseline HbA1c and change in HbA1c

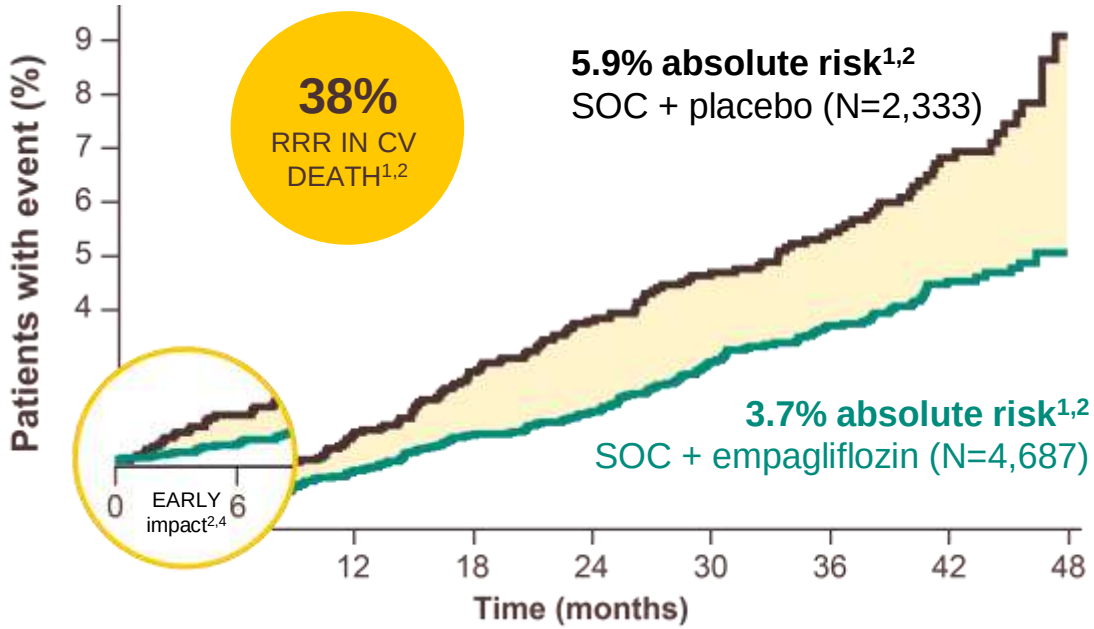
In patients with CV disease and T2D on top of standard of care

HOSPITALISATION DUE TO HF



Secondary endpoint: HR=0.62; 95% CI: 0.49, 0.77; p<0.001

CARDIOVASCULAR DEATH



Part of 3-P-MACE composite primary endpoint: HR=0.65; 95% CI: 0.50, 0.85; p=0.002

Empagliflozin is not indicated for the treatment of HF. Cumulative incidence function. SOC: statins, ACEis/ARBs, beta blockers, antiplatelets, glucose-lowering medications.

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; CV, cardiovascular; HF, heart failure; hHF, hospitalisation for heart failure; HR, hazard ratio; RRR, relative risk reduction; SOC, standard of care, T2D, type 2 diabetes mellitus

1. JARDIANCE (Summary product characteristics). Ingelheim am Rhein, Germany: Boehringer Ingelheim GmbH; February 2019.
2. Zinman B et al. *N Engl J Med* 2015;373:2117-2128.
3. Inzucchi SE et al. *Circulation* 2018;138:1904-1907.
4. Fitchett D et al. *J Am Coll Cardiol* 2018;23:71:364-367.

Kiểm soát biến chứng ở BN ĐTĐ typ 2

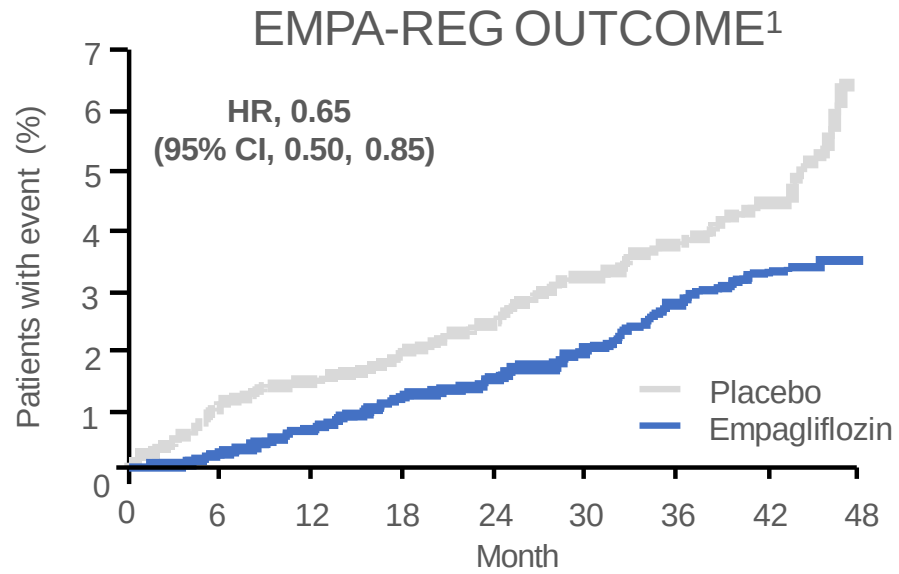
Ngừa BC
MẠCH MÁU NHỎ

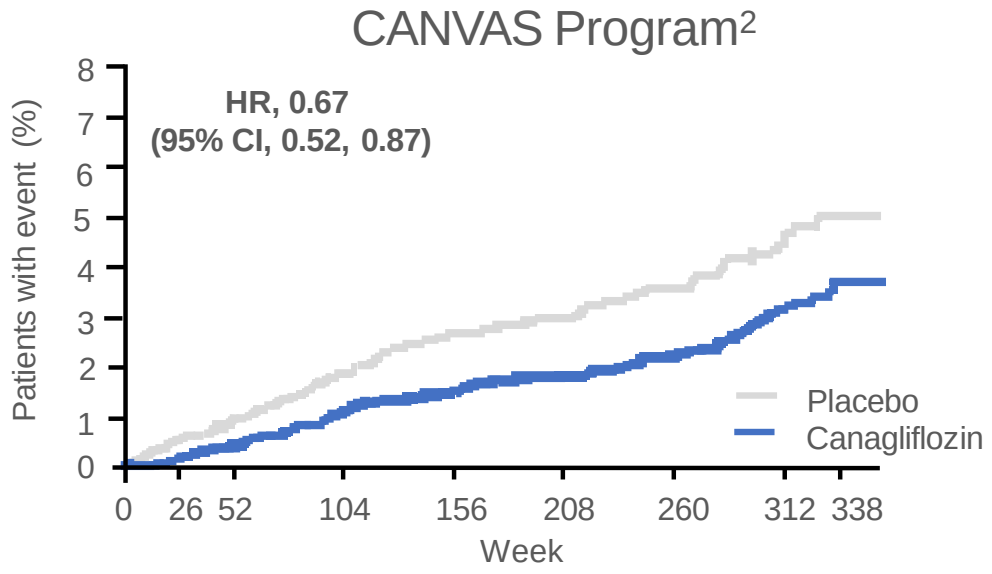
Quyết định bởi
KSĐH (A1C) bất kể
liệu pháp điều trị

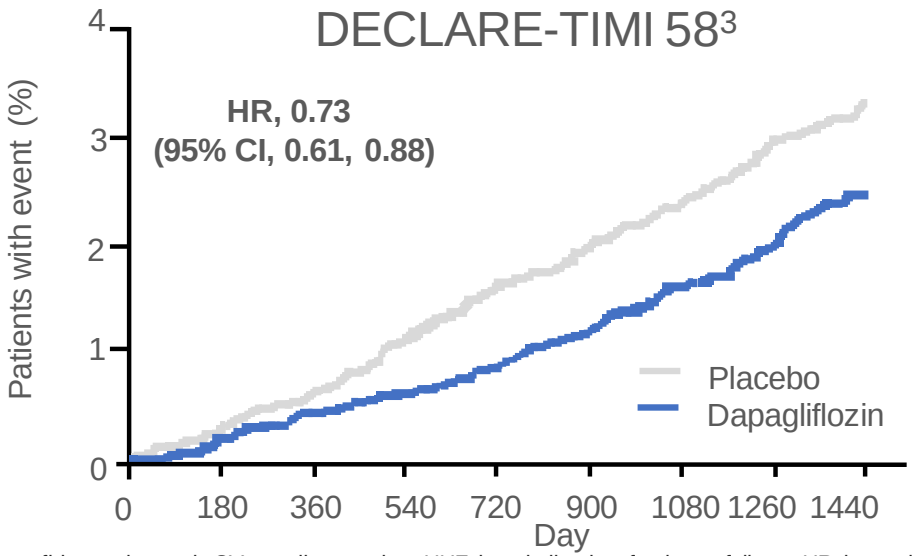
Ngừa BC
MẠCH MÁU LỚN
(MACE) & TỬ VONG

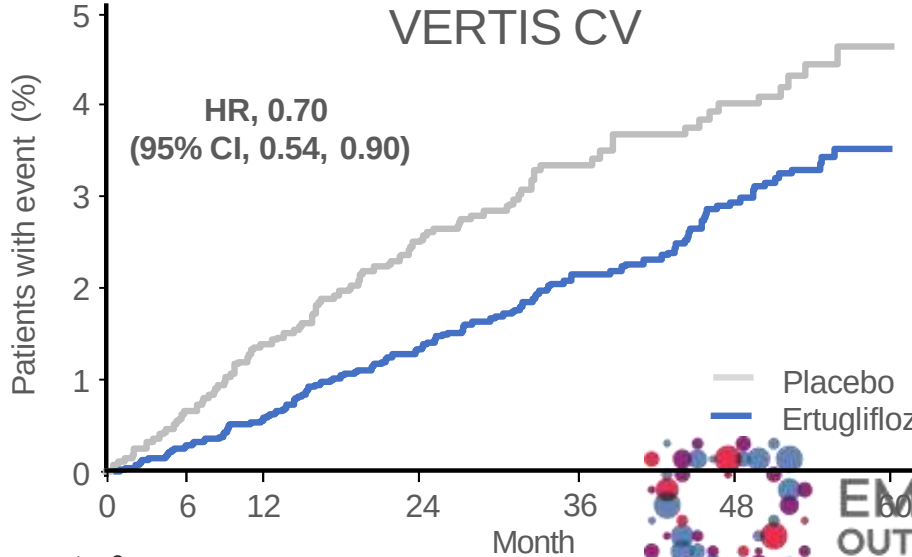
Quyết định bởi
liệu pháp điều trị hơn
KSĐH

HHF outcomes in SGLT2 inhibitor CV outcomes trials







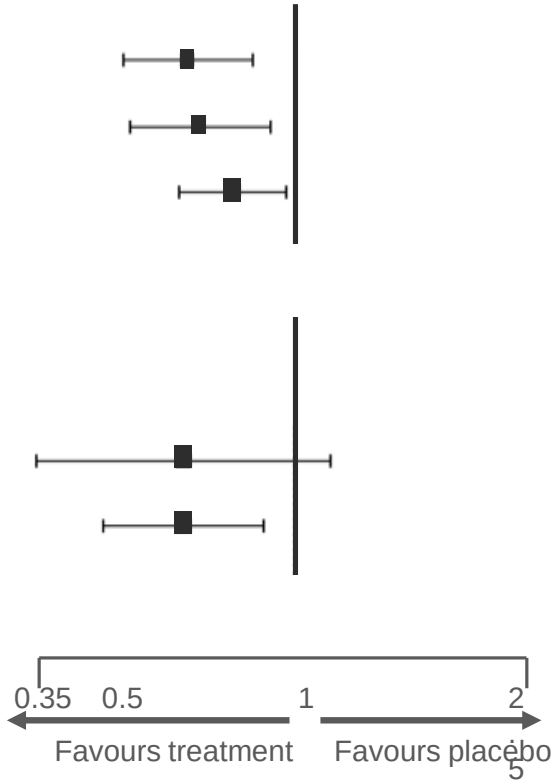


CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; SGLT2, sodium-glucose cotransporter 2.

1. Zinman B et al. *N Engl J Med* 2015;373:2117-2128. 2. Neal B et al. *N Engl J Med* 2017;377:644-657.
3. Wiviott SD et al. *N Engl J Med* 2019;380:347-357 (figure provided by D.K. McGuire with permission).

SGLT2i giảm nguy cơ Nhập viện do suy tim bất kể phân nhóm BN có/không BTM[1–4]

Study name	Events per 1,000 PY: SGLT2 inhibitor	Events per 1,000 PY: Placebo	HHF HR (95% CI)	*P*-value
Patients with ASCVD				
EMPA-REG OUTCOME®[1,4]	9.4	14.5	0.65 (0.50, 0.85)	
CANVAS Program[2,4]	7.3	11.3	0.68 (0.51, 0.90)	
DECLARE-TIMI 58[3,4]	11.1	14.1	0.78 (0.63, 0.97)	
Patients with multiple risk factors				
CANVAS Program[2,4]	2.6	4.2	0.64 (0.35, 1.15)	
DECLARE-TIMI 58[3,4]	3.0	4.6	0.64 (0.46, 0.88)	



ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; HHF, hospitalisation for heart failure; HR, hazard ratio; PY, patient-year; SGLT2, sodium–glucose transporter 2.

1. Zinman et al. N Engl J Med 2015;373:2117–28. 2. Neal et al. N Engl J Med. 2017;377:644–57. 3. Wiviott et al. N Engl J Med 2018;doi:10.1056/NEJMoa1812389.
4. Zelniker et al. Lancet 2018;doi:10.1016/S0140-6736(18)32590-X.

EMPRISE

EMPAGLIFLOZIN REAL-WORLD EFFECTIVENESS

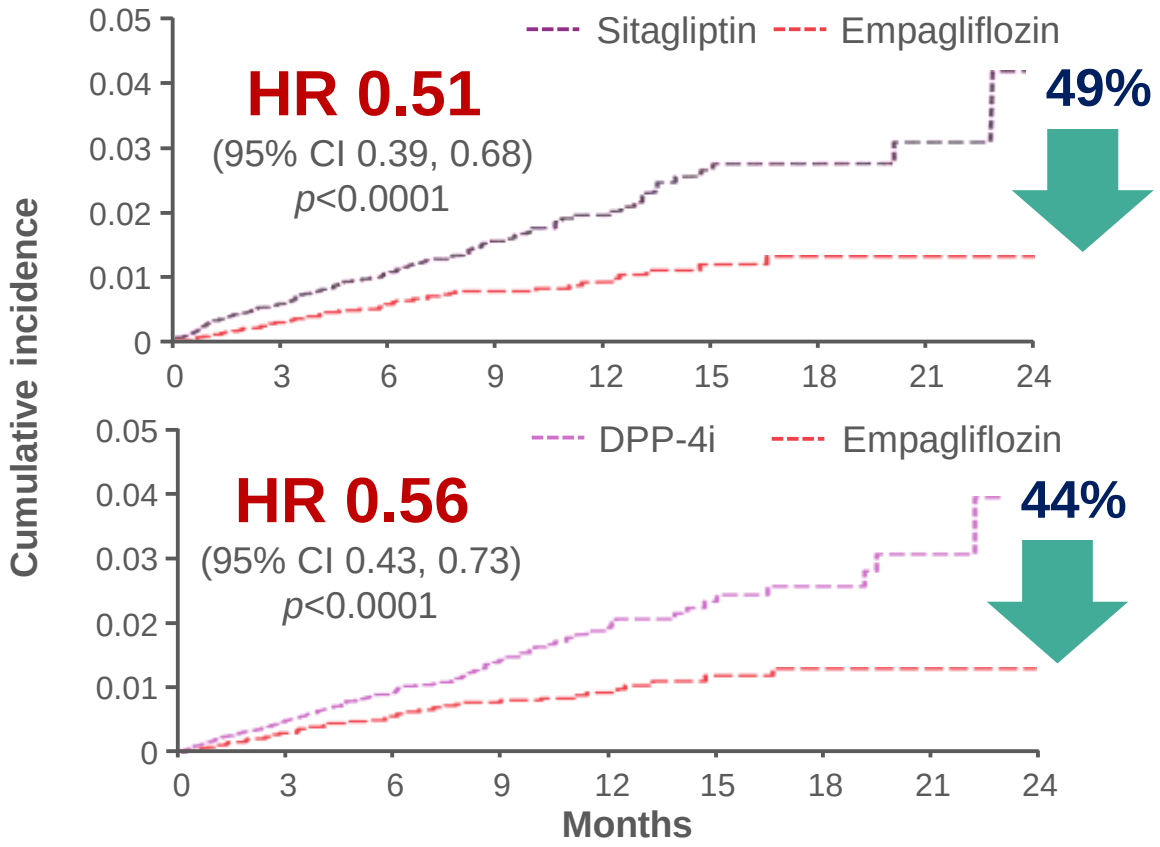
Empagliflozin and the risk of HHF in routine clinical care

A first analysis from the EMPRISE study

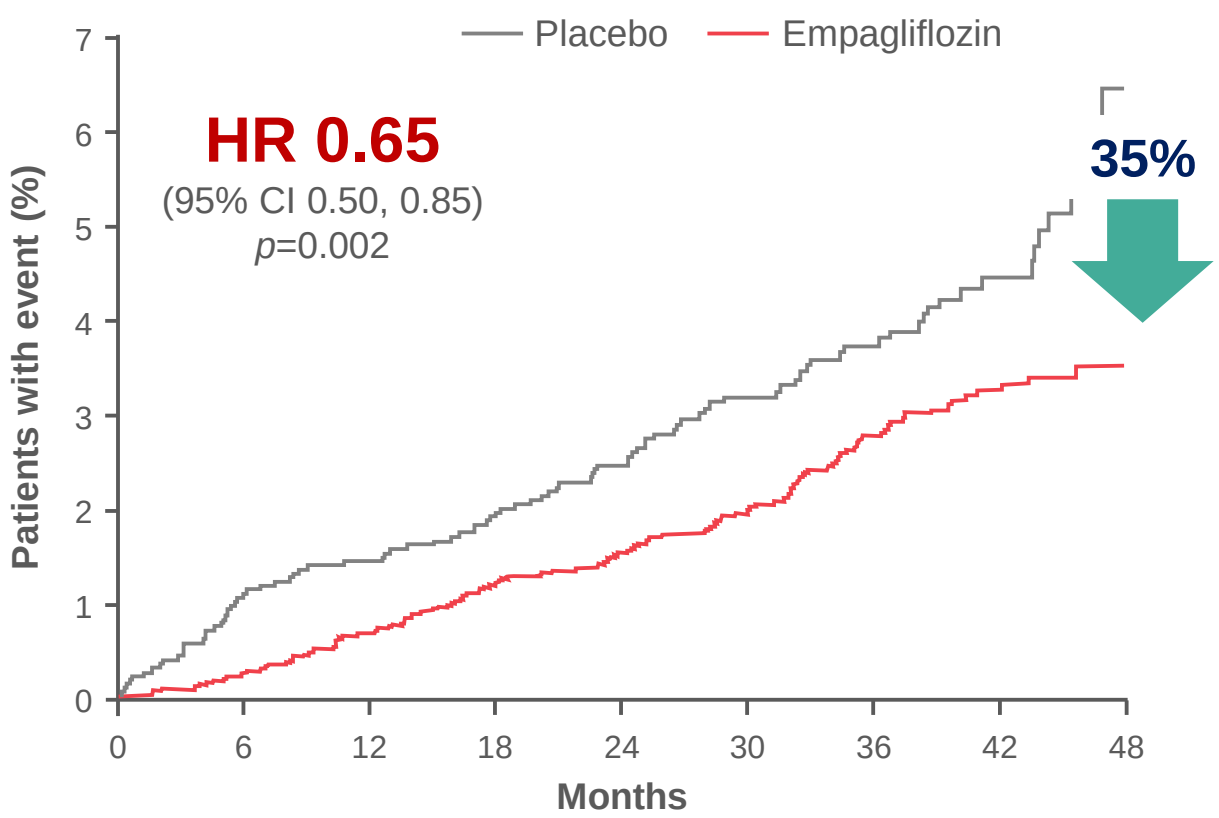
Patorno *et al. Circulation* 2019

Empagliflozin **giảm nhập viện do suy tim** ở cả BN có và không có bệnh tim mạch EMPRISE nhất quán với KQ của EMPAREG OUTCOME

EMPRISE*[1]



EMPA-REG OUTCOME®[2]

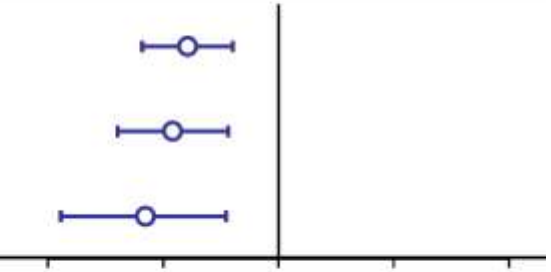


Comparison of studies should be interpreted with caution due to differences in study design, populations and methodology
Definitions of HHF vary between studies; *Broad HHF definition
DPP-4i, dipeptidyl peptidase-4 inhibitor; HHF, hospitalisation for heart failure; RCT, randomised controlled trial
1. Patorno E *et al. Circulation* 2019 (submitted); 2. Zinman B *et al. N Engl J Med* 2015;373:2117

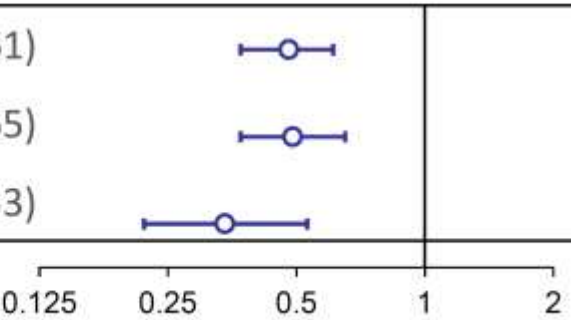
Empagliflozin **giảm nhập viện lần đầu và tái nhập viện do suy tim** ở cả BN có và không có suy tim ban đầu

Risk of HF-related hospitalizations in empagliflozin vs. DPP4i*

First event	Empagliflozin	DPP4i	HR (95% CI)
	n events/N analysed (IR/1000 PY)		
First HF-related hospitalization	82/17,549 (10.4)	141/17,549 (18.9)	0.58 (0.44, 0.76)
Patients with baseline HF†	54/2050 (61.9)	103/2050 (120.9)	0.53 (0.38, 0.74)
Patients without baseline HF†	23/15,428 (3.3)	54/15,428 (8.1)	0.45 (0.27, 0.73)



Recurrent events	Empagliflozin	DPP4i	Incident rate ratio (95% CI)
	PMPY		
Number of HF-related hospitalizations	0.01	0.03	0.48 (0.37, 0.61)
Patients with baseline HF†	0.08	0.16	0.49 (0.37, 0.65)
Patients without baseline HF†	0.003	0.01	0.34 (0.22, 0.53)



*Discharge diagnosis of HF in any position; †Defined as history of HF or use of loop diuretics. PMPY, per member per year

ESC 2019

Empagliflozin giúp **giảm nhập viện vì suy tim và tử vong do mọi nguyên nhân** so với DPP4i

EMPA vs DPP-4i

	DPP-4i* (n=17,551)		Empagliflozin (n=17,551)		HR (95% CI)
	n events	Rate/1000 PY	n events	Rate/1000 PY	
Gộp nhập viện vì suy tim có trong chẩn đoán và tử vong do mọi nguyên nhân	164	21.99	96	12.08	**0.58 (0.45, 0.74)**
Nhập viện vì suy tim có trong chẩn đoán†	146	20.0	82	10.3	0.56 (0.43, 0.73)
Gộp nhập viện vì suy tim trong chẩn đoán chính và tử vong do mọi nguyên nhân	63	8.42	33	4.14	0.61 (0.40, 0.95)
Nhập viện vì suy tim trong chẩn đoán chính‡	42	5.61	16	2.01	0.49 (0.27, 0.89)
Tử vong do mọi nguyên nhân§	22	2.9	17	2.1	0.78 (0.41, 1.48)

*Comprised of alogliptin=3.1%, linagliptin=19.1%, sitagliptin=66.5%, and saxagliptin=11.3%; †Defined as a discharge diagnosis of heart failure in any position (positive predictive value = 79–96%); ‡Defined as a discharge diagnosis of heart failure in the primary position (positive predictive value = 84–100%); §Available for a subset of patients

DPP-4i, dipeptidyl peptidase-4 inhibitor; EMPA, empagliflozin; HHF, hospitalisation for heart failure; PY, patient-years

Patorno E *et al. ACC* 2019; poster 19-A-15797-ACC

Empagliflozin giúp rút ngắn thời gian nằm viện so với DPP4i.

Số lần vào khoa cấp cứu, nhập viện do mọi nguyên nhân và số lần thăm khám ngoại trú ít hơn có ý nghĩa so với DPP4i

EMPA vs DPP-4i

	DPP-4i (n=17,549)		Empagliflozin (n=17,549)		HR (95% CI)
	n events	Rate/1000 PY	n events	Rate/1000 PY	
Nguy cơ nhập viện đầu tiên do mọi nguyên nhân	876	121.8	765	99.1	**0.84 (0.76, 0.92)**
Nguy cơ vào cấp cứu đầu tiên	502	68.6	428	54.7	**0.83 (0.73, 0.94)**
	Per member per year		**Per member per year**		**Difference (95% CI)**
Thời gian nằm viện (ngày) ở bệnh nhân có ≥1 lần nhập viện	9.77		8.41		**-1.36 (-3.23, 0.57)**
Ngày nằm viện	0.75		0.52		**-0.23 (-0.38, -0.08)**
	Per member per year		**Per member per year**		**Incidence rate ratio (95% CI)**
Số lần nhập viện do mọi nguyên nhân	0.15		0.11		**0.78 (0.72, 0.86)**
Số lần vào cấp cứu	0.09		0.07		**0.80 (0.71, 0.89)**
Số lần khám ngoại trú	8.39		8.03		**0.96 (0.95, 0.98)**

DPP-4i, dipeptidyl peptidase-4 inhibitor; ED, emergency department; EMPA, empagliflozin; PY, patient-years

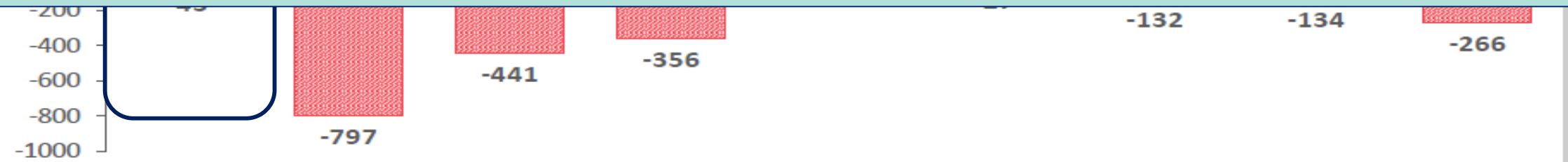
Najafzadeh M *et al. AMCP* 2019; poster 600446

Empagliflozin giúp **giảm tổng chi phí điều trị** so với DPP4i

EMPA vs DPP-4i

	Empagliflozin, PMPY	DPP-4i, PMPY	Incidence rate ratio (95% CI)
Number of distinct medication prescriptions	17.5	18.1	0.97 (0.96; 0.98)

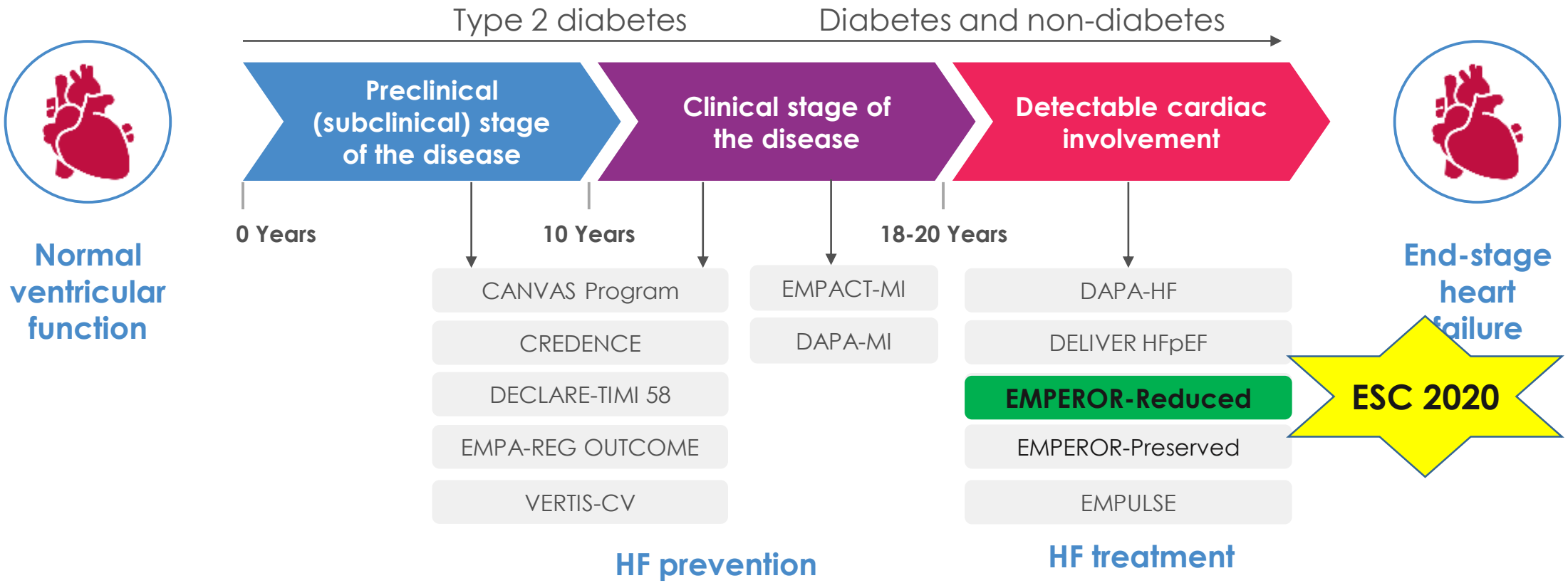
Trong thời gian theo dõi 5.4 tháng, phân tích từ NC EMPRISE trong thực tế lâm sàng cho thấy điều trị với empagliflozin giúp giảm tổng chi phí y tế chăm sóc của BN sv DPP4i do làm giảm tổng chi phí điều trị nội viện và ngoại viện (cũng như chi phí liên quan tới bệnh tim mạch)



95% CI:	-1,380; 1,295	-1,920; 380	-1,089; 253	-1,069; 365	149; 1,325	-67; 11	-462; 225	-556; 287	-867; 322
Per Member Per Year (PMPY) in $									
EMPA	17,771	8,932	2,418	6,514	8,772	67	624	2,321	2,945
DPP4i	17,814	9,729	2,859	6,870	7,990	94	756	2,455	3,211

ADA 2019

Story of SGLT2 inhibition in heart failure



SGLT2, sodium-glucose co-transporter-2
Adapted from Bhatt DL *et al. Cell Metab*. 2019;30:847

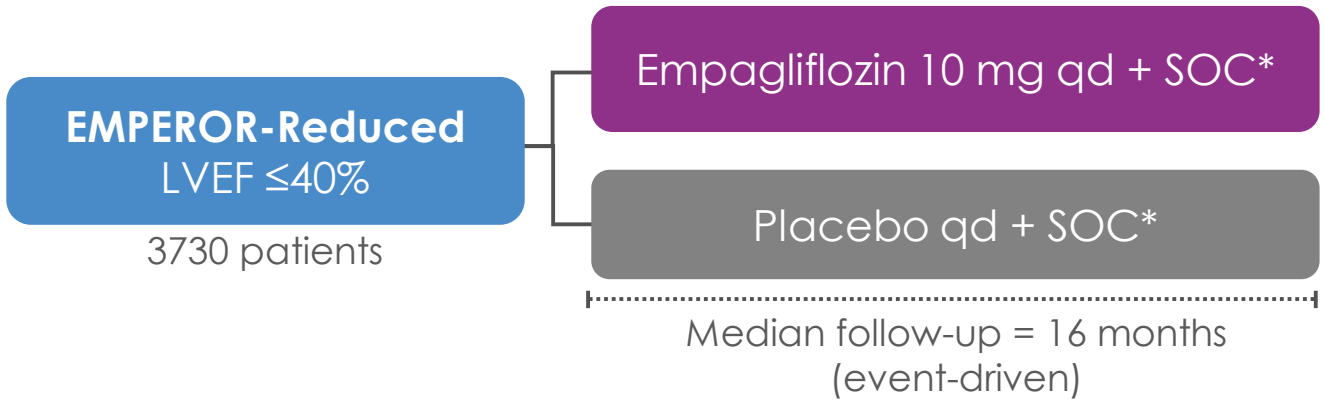
EMPEROR-Reduced

Phase III randomised double-blind placebo-controlled trial

Aim: To investigate the safety and efficacy of empagliflozin versus placebo on top of guideline-directed medical therapy in patients with HF with **reduced ejection fraction**

Population: T2D and non-T2D, aged ≥18 years, chronic HF (NYHA class II–IV)

Study design[1-3]



Confirmatory endpoints[1,2]

COMPOSITE PRIMARY ENDPOINT

Time to first event of adjudicated CV death or adjudicated HHF

SECONDARY ENDPOINTS

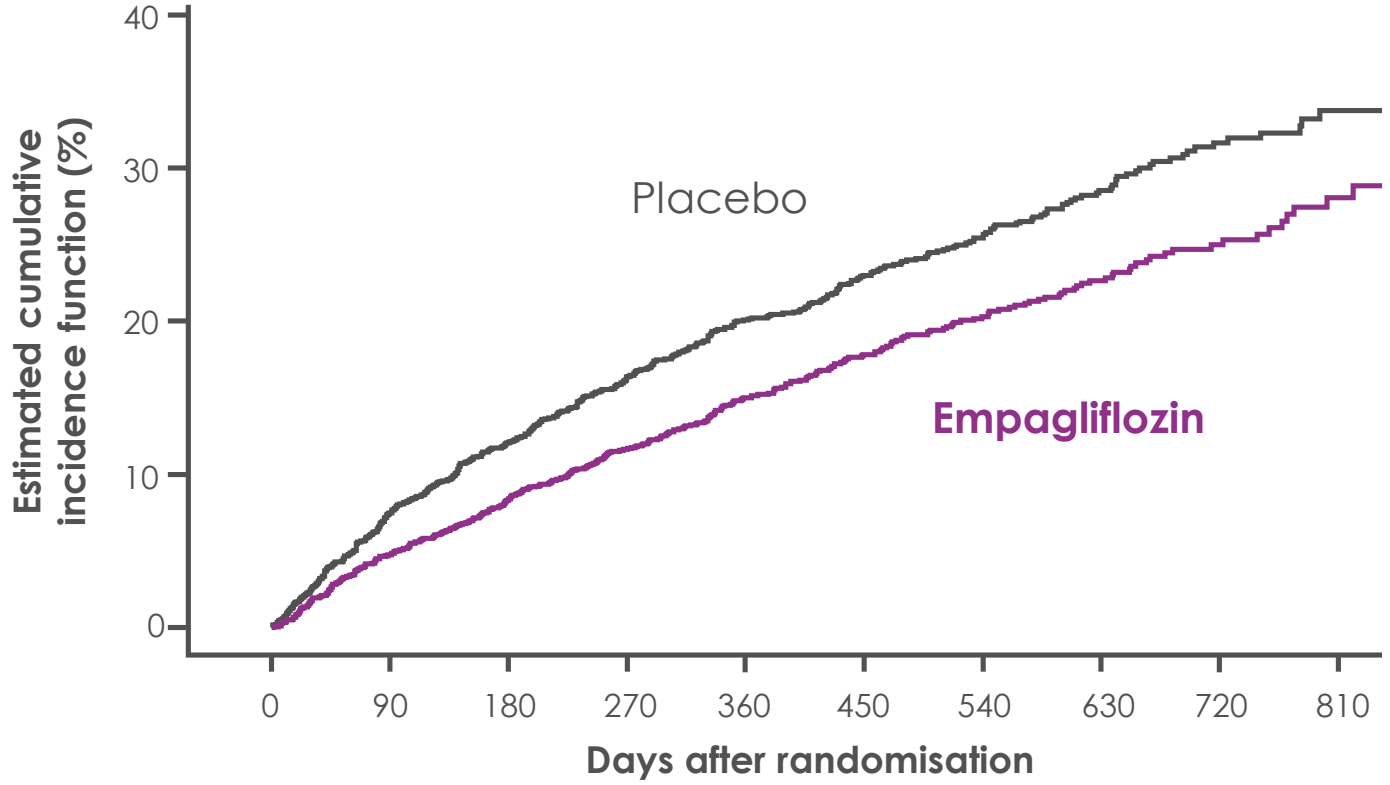
- **First and recurrent adjudicated HHF events**
- **Slope of change in eGFR (CKD-EPI) from baseline**

*Guideline-directed medical therapy

CV, cardiovascular; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalisation for heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; qd, once daily; SOC, standard of care; T2D, type 2 diabetes

1. ClinicalTrials.gov. NCT03057977 (accessed Aug 2020); 2. Packer M *et al. Eur J Heart Fail* 2019;21:1270–8; Data on file

Primary endpoint: First adjudicated CV death or hospitalisation for heart failure



Patients at risk

Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

RRR 25%

ARR 5.2%

NNT = 19

HR 0.75
(95% CI 0.65, 0.86)
p<0.001

Empagliflozin:
361 patients with event
Rate: 15.8/100 patient-years
Placebo:
462 patients with event
Rate: 21.0/100 patient-years

Empagliflozin is not indicated for the treatment of HF

Cox regression model including covariates age, baseline eGFR, geographic region, baseline diabetes status, sex, LVEF and treatment

CV, cardiovascular; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; ARR, absolute risk reduction; RRR, relative risk reduction. NNT: Number needed to treat

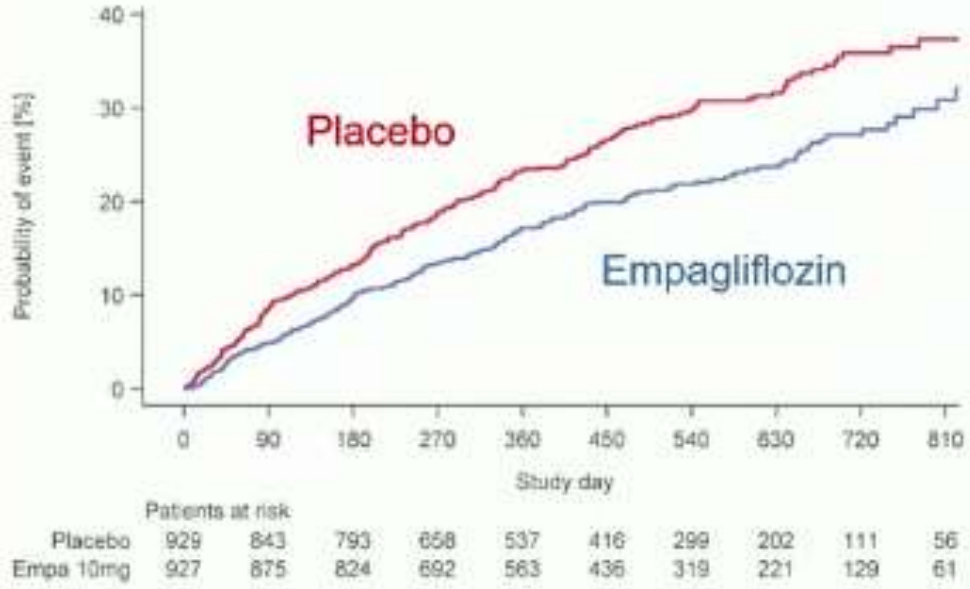
Data on file

Empagliflozin reduces time to first hospitalisation for HF or CV death similarly in patients with or without diabetes

With diabetes

HR 0.72 (0.60, 0.87)
p=0.0006

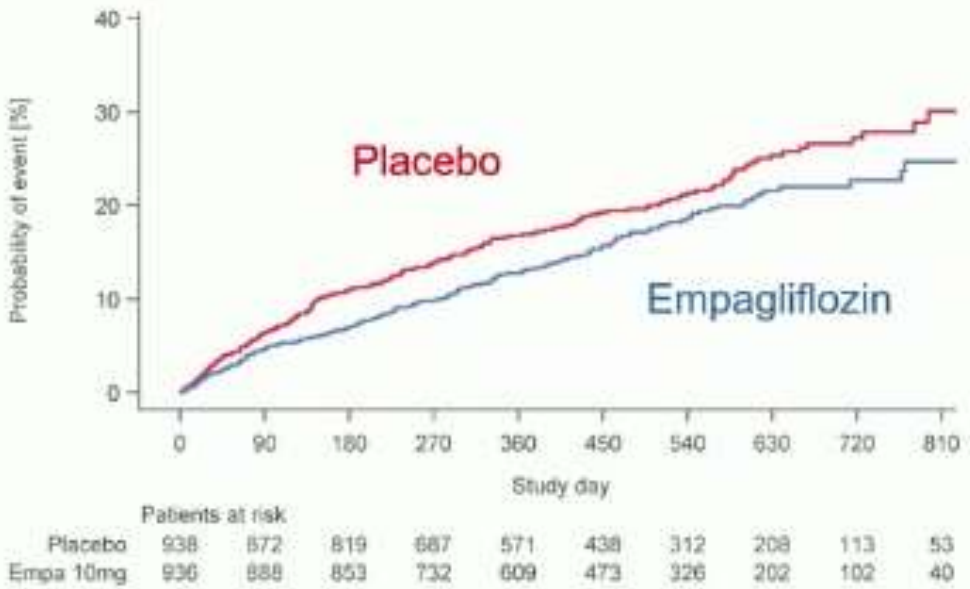
Interaction p=0.57



In diabetics:
Event rate in the empagliflozin group:
17.7/100 patient years

Without diabetes

HR 0.78 (0.64, 0.97)
p=0.0225



In non-diabetics:
Event rate in the placebo group:
17.6/100 patient years

Empagliflozin is not indicated for the treatment of HF

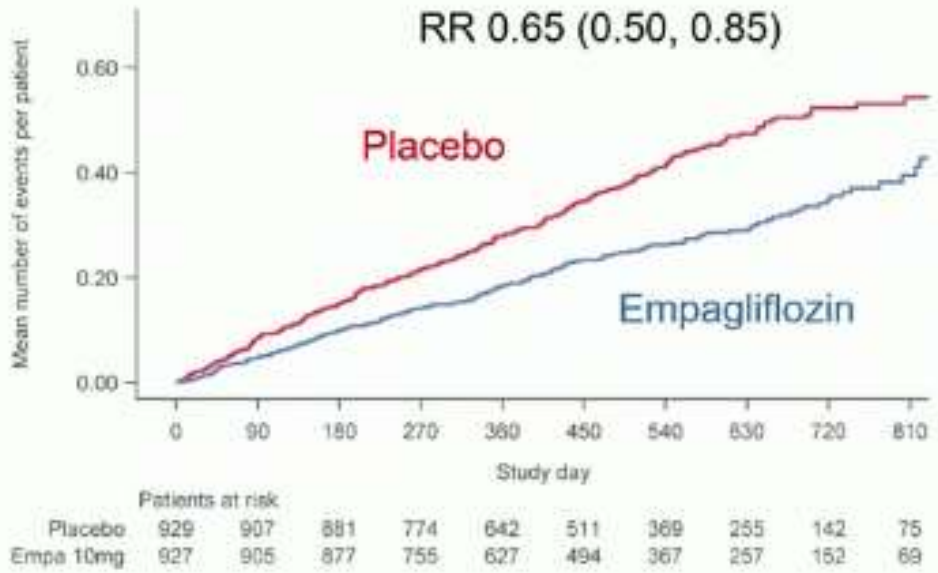
Anker S, EASD 2020

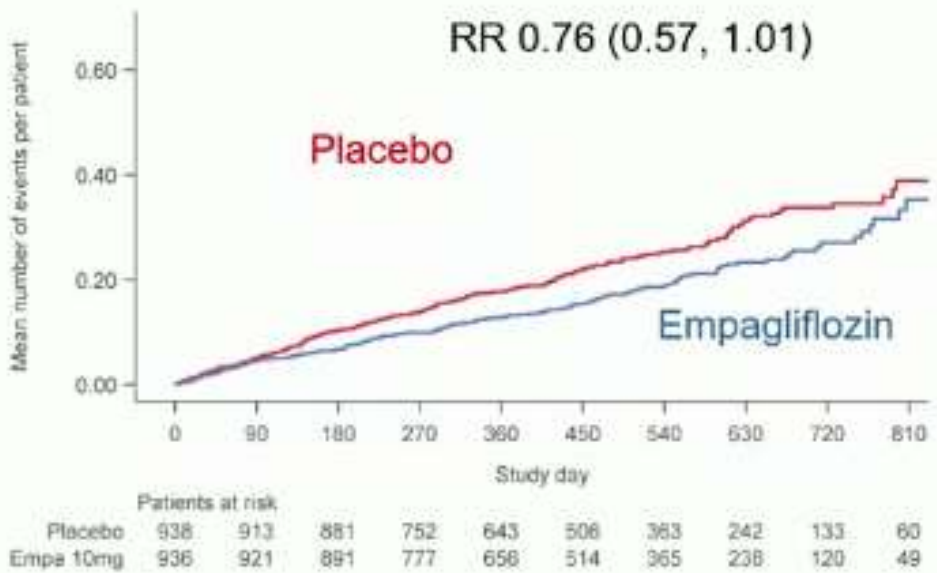
Key secondary outcome: total (first plus recurrent) hospitalisation for HF similarly reduced in patients with and without diabetes

With diabetes

Interaction p=0.44

Without diabetes





Empagliflozin is not indicated for the treatment of HF

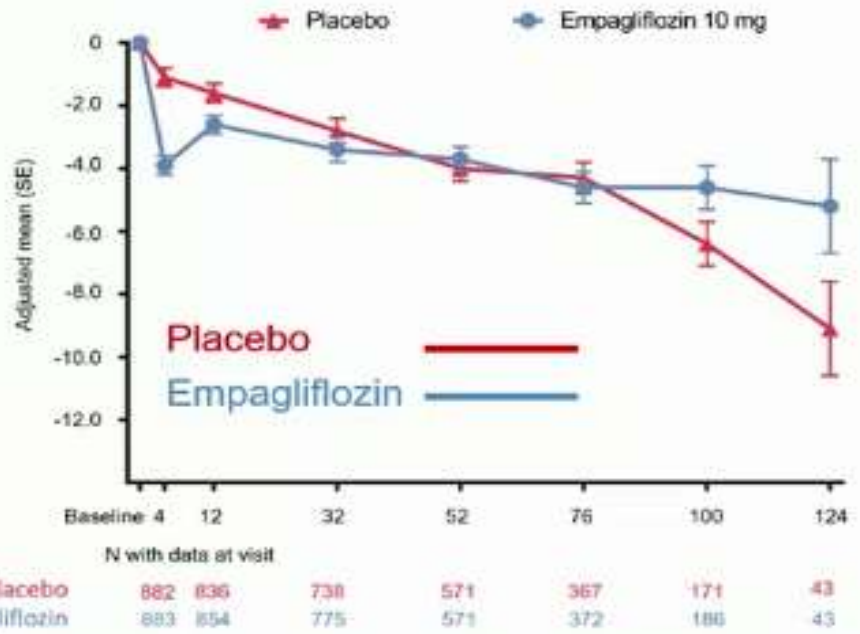
Anker S, EASD 2020

Empagliflozin slowed the rate of decline in eGFR similarly in patients with or without diabetes

Changes in Estimated Glomerular Filtration Rate During Double-Blind Treatment

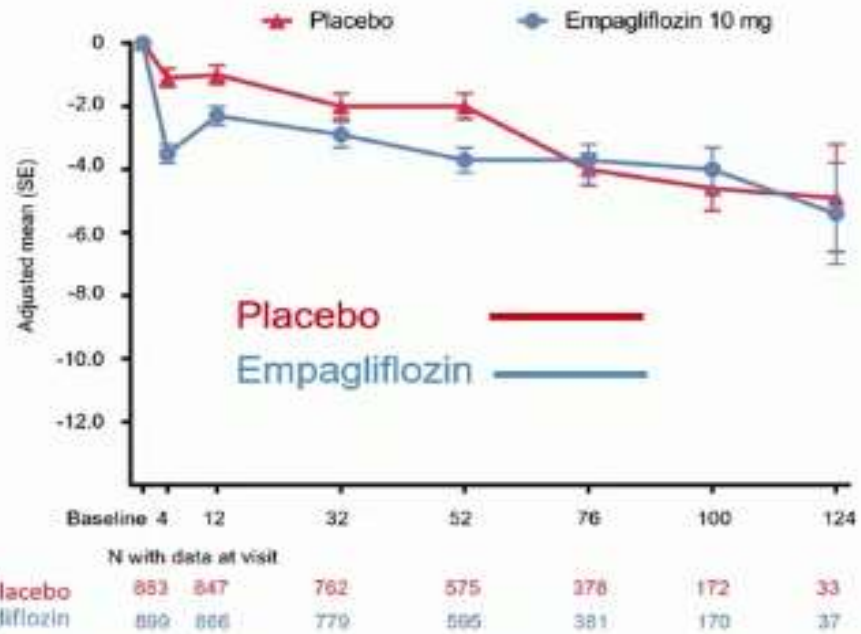
With diabetes

+2.21* ml/min/1.73 m²/year in favor of empagliflozin



Without diabetes

+1.27* ml/min/1.73 m²/year in favor of empagliflozin



* Data from eGFR slope analyses

Interaction p-value: 0.15*

Empagliflozin is not indicated for the treatment of HF

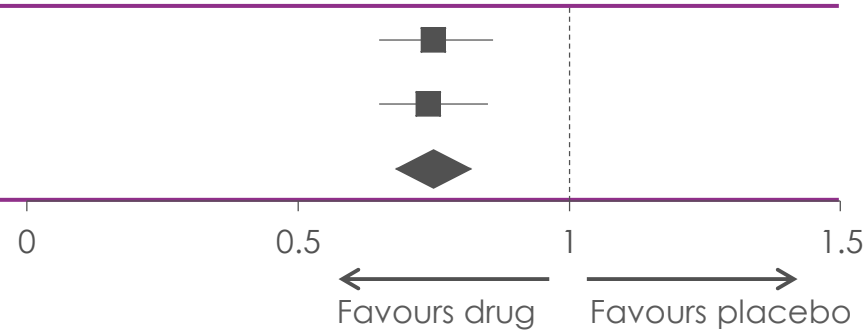
Anker S, EASD 2020

Meta-analysis of DAPA-HF and EMPEROR-Reduced

First hospitalisation for HF or CV death

Trial	SGLT2i, n/N (%)	Placebo, n/N (%)	HR (95% CI)
EMPEROR-Reduced	361/1863 (19.4)	462/1867 (24.7)	0.75 (0.65, 0.86)
DAPA-HF	386/2373 (16.3)	502/2371 (21.2)	0.74 (0.65, 0.85)
Total			0.74 (0.68, 0.82)

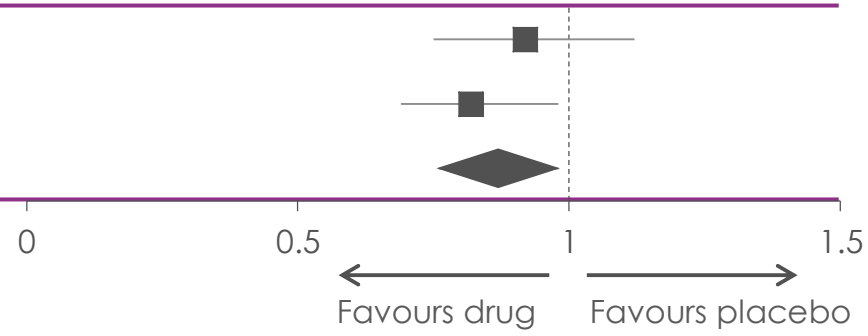
Test for overall treatment effect, $p<0.0001$
Test for heterogeneity of effect, $p=0.89$



CV death

Trial	SGLT2i, n/N (%)	Placebo, n/N (%)	HR (95% CI)
EMPEROR-Reduced	187/1863 (10.0)	202/1867 (10.8)	0.92 (0.75, 1.12)
DAPA-HF	227/2373 (9.6)	273/2371 (11.5)	0.82 (0.69, 0.98)
Total			0.86 (0.76, 0.98)

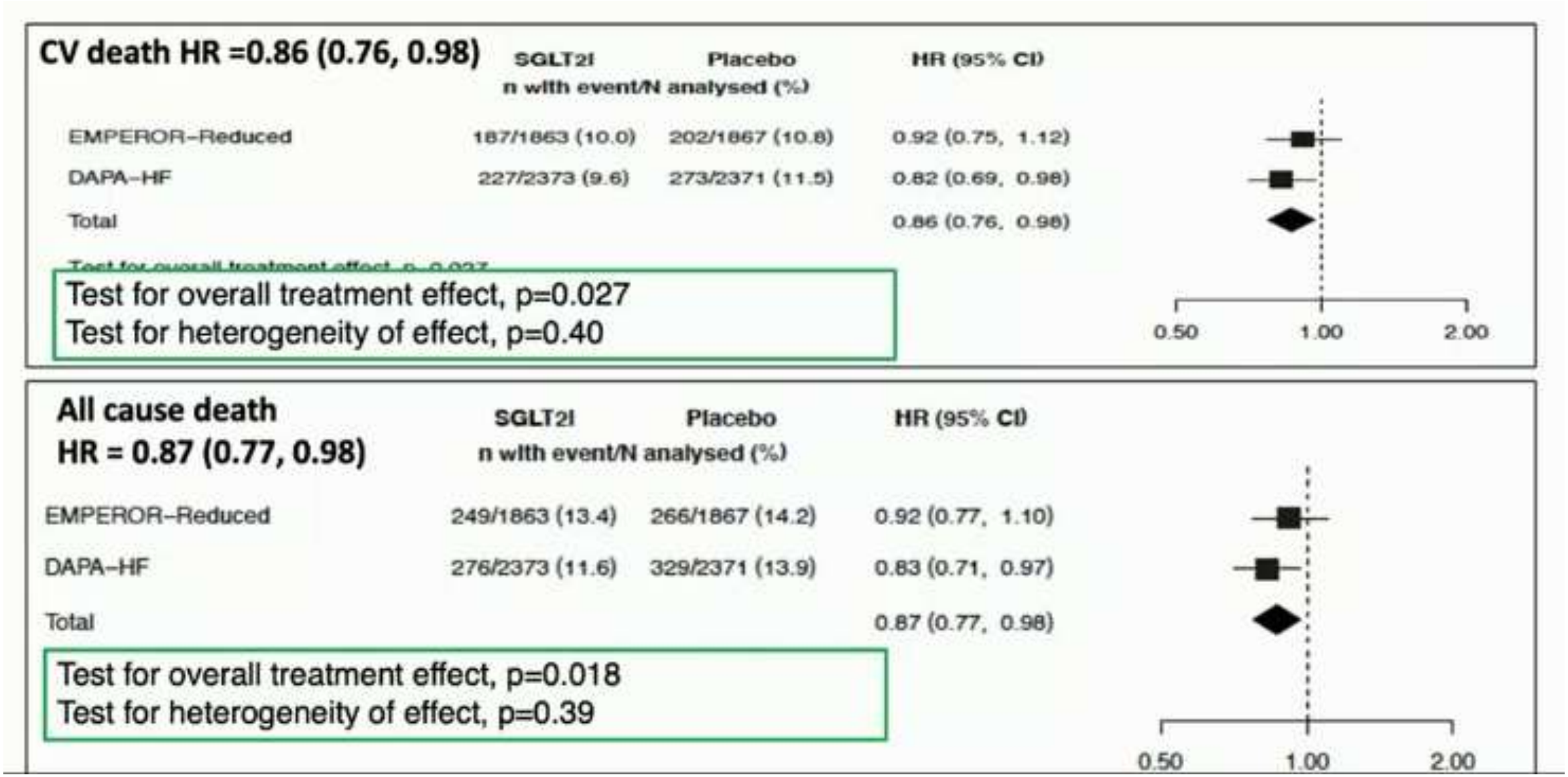
Test for overall treatment effect, $p=0.027$
Test for heterogeneity of effect, $p=0.40$



HF, heart failure; SGLT2i, sodium-glucose co-transporter-2 inhibitor

The LANCET, Published online August 30, 2020 https://doi.org/10.1016/S0140-6736(20)31824-9

Meta-analysis of DAPA-HF and EMPEROR-Reduced



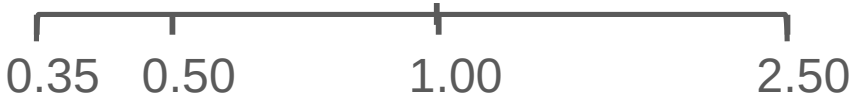
HF, heart failure; SGLT2i, sodium-glucose co-transporter-2 inhibitor

The LANCET, Published online August 30, 2020 https://doi.org/10.1016/S0140-6736(20)31824-9

SGLT2i giảm tổ hợp biến cố thận thống nhất trên các phân nhóm BN

Renal composite: worsening of kidney disease, ESRD, or death due to renal disease*

Study name	SGLT2 inhibitor	Placebo	Renal composite HR (95% CI)	*P*-value
Patients with ASCVD				
EMPA-REG OUTCOME®[1,2]	6.3	11.5	0.54 (0.40, 0.75)	
CANVAS Program[2–4]	6.4	10.5	0.59 (0.44, 0.79)	
DECLARE-TIMI 58[2,5]	4.7	8.6	0.55 (0.41, 0.75)	
Patients with multiple risk factors				
CANVAS Program[2–4]	4.1	6.6	0.63 (0.39, 1.02)	
DECLARE-TIMI 58[2,5]	3.0	5.9	0.51 (0.37, 0.69)	



*Definitions differ between studies

ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; ESRD, end-stage renal disease; HR, hazard ratio; PY, patient-year; SGLT2, sodium–glucose transporter 2.

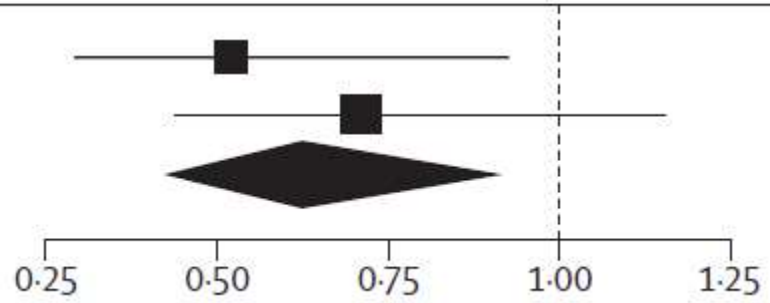
1. Wanner et al. N Engl J Med 2016;375:323–4. 2. Zelniker et al. Lancet 2018;doi:10.1016/S0140-6736(18)32590-X. 3. Neal et al. N Engl J Med. 2017;377:644–57. 4. Perkovic et al. Lancet Diabetes Endocrinol 2018;6:691–704..5. Wiviott et al. N Engl J Med 2019;doi:10.1056/NEJMoa1812389

Composite kidney outcomes: end stage renal disease, sustained and profound decrease in eGFR

E First kidney outcome composite

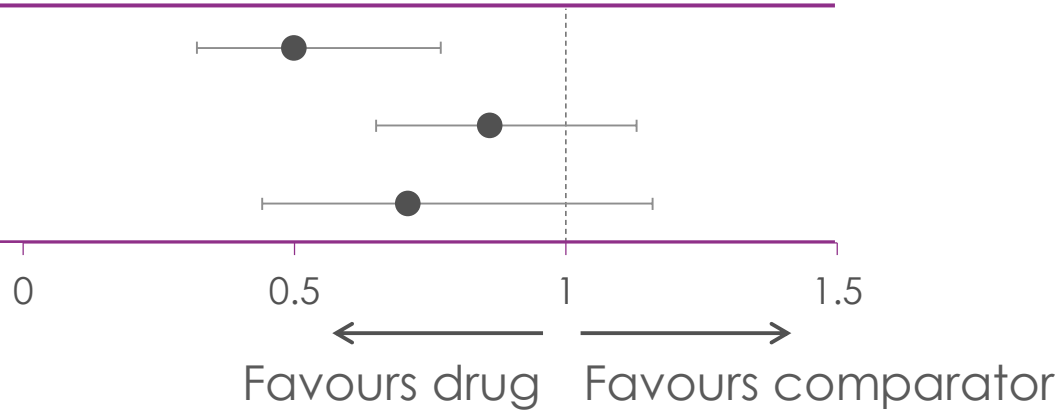
	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
EMPEROR-Reduced	18/1863 (1·0%)	33/1867 (1·8%)	0·52 (0·29–0·92)
DAPA-HF	28/2373 (1·2%)	39/2371 (1·6%)	0·71 (0·44–1·16)
Total			0·62 (0·43–0·90)

Test for overall treatment effect p=0·013
Test for heterogeneity of effect p=0·42



Trial	HR	95% CI
EMPEROR-Reduced[1]	0.50	(0.32, 0.77)
PARADIGM-HF[2]	0.86	(0.65, 1.13)
DAPA-HF[3]	0.71	(0.44, 1.16)

HR (95% CI)



Comparison of studies should be interpreted with caution due to differences in study design, populations and methodology

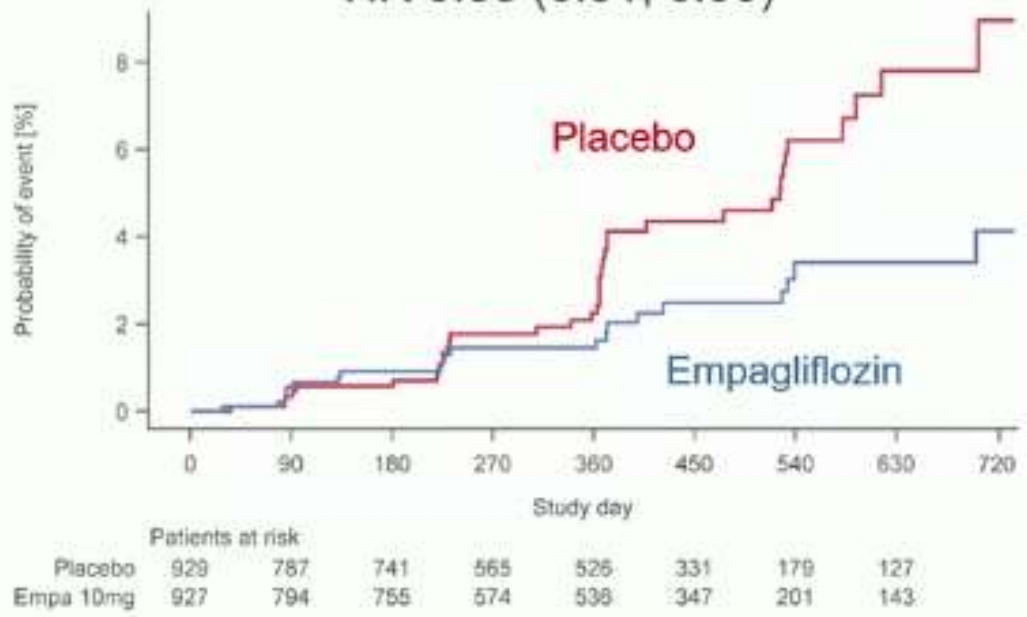
eGFR, estimated glomerular filtration rate

1. Packer et al. NEJM 2020. DOI: 10.1056/NEJMoa2022190.; 2. McMurray JJV, et al. *N Engl J Med*. 2014;371:993–3; McMurray JJV, et al. *N Engl J Med* . 2019;381:1995

Composite renal outcome (end-stage kidney disease or sustained profound decrease in eGFR)

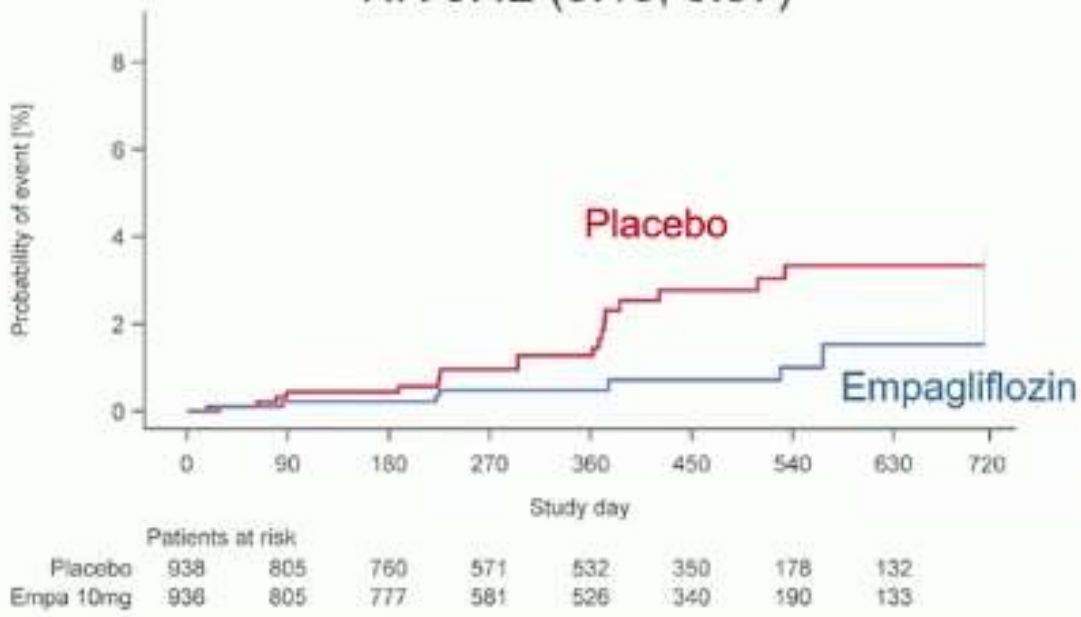
With diabetes

HR 0.53 (0.31, 0.90)

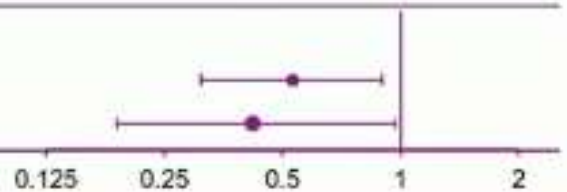


Without diabetes

HR 0.42 (0.19, 0.97)



	Empagliflozin (N=1863) N with event /N analysed	Placebo (N=1867) N with event /N analysed	HR (95% CI)
Composite renal outcome			
With diabetes	22/927	39/929	0.53 (0.31, 0.90)
Without diabetes	8/936	19/938	0.42 (0.19, 0.97)



Empagliflozin is not indicated for the treatment of HF

Anker S, EASD 2020

Tổng quan các nghiên cứu CVOTs

	Study	MACE*	CV death	MI	Stroke	Any Death	HHF	Renal Outcome
DPP-4i	**SAVOR-TIMI** (Saxagliptin)	↔	↔	↔	↔	↔	↑	↔
	EXAMINE (Alogliptin)	↔	↔	↔	↔	↔	↔	–
	TECOS (Sitagliptin)	↔	↔	↔	↔	↔	↔	–
SGLT2i	**EMPA-REG OUTCOME** (Empagliflozin)	↓	↓	↔	↔	↓	↓	↓
	CANVAS (Canagliflozin)	↓	↔	↔	↔	↔	↓	↓
	DECLARE (Dapagliflozin)	↔	↔	↔	↔	↔	↓	↓
GLP-1	**ELIXA** (Lixisenatide)	↔	↔	↔	↔	↔	↔	–
	LEADER (Liraglutide)	↓	↓	↔	↔	↓	↔	↓
	SUSTAIN-6 (Semaglutide)	↔	↔	↔	↓	↔	↔	↓
	EXSCEL (Exenatide)	↔	↔	↔	↔	↓	↔	–

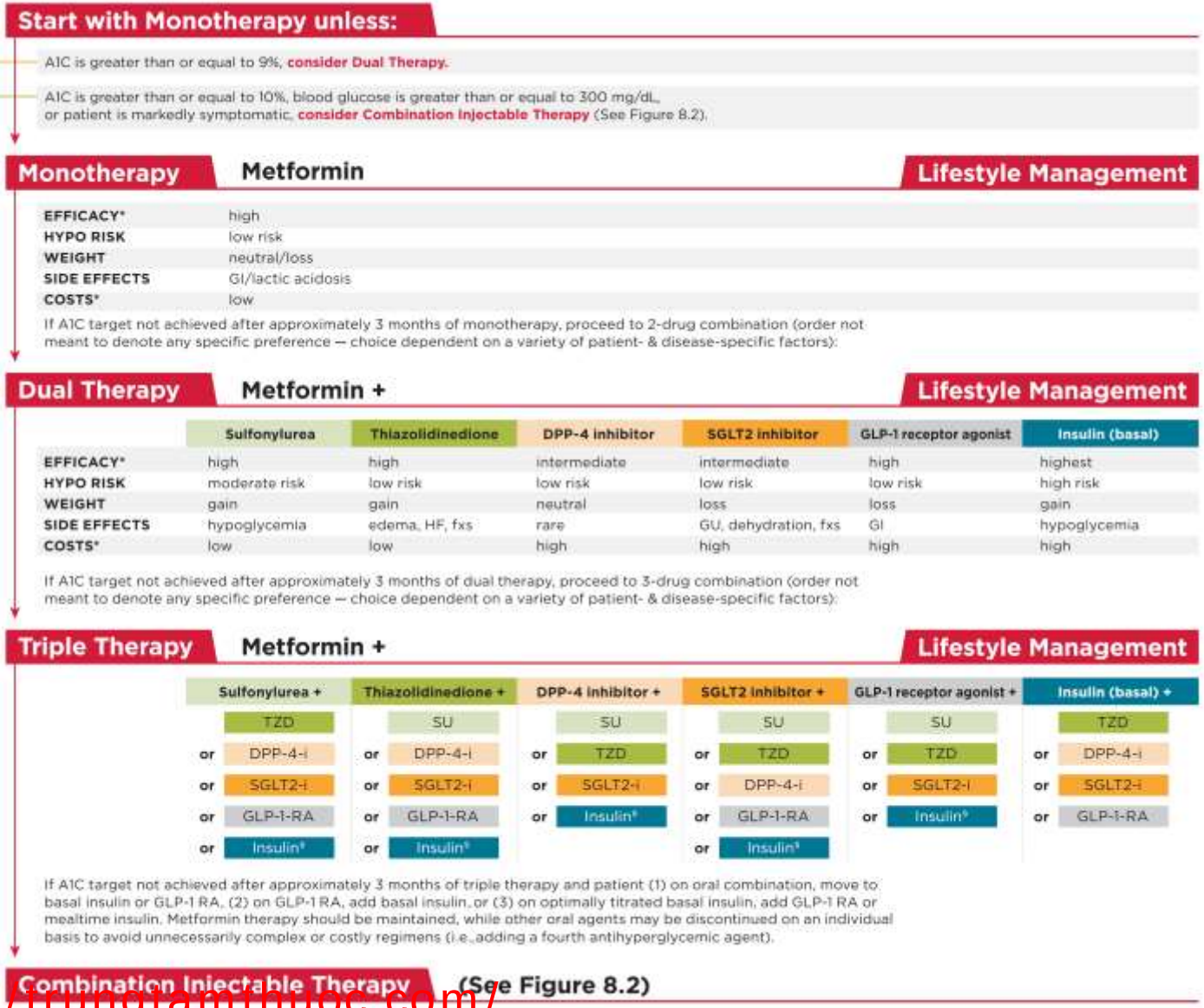
* All studies use 3P-MACE (CV death, MI, stroke) except TECOS and ELIXA which adds hospitalization for unstable angina

** p>0.05 for individual components of fatal, nonfatal and silent MI, p=0.046 for composite of fatal, nonfatal and silent MI

Khuyến cáo ADA trước 2017:

Tiếp cận tập trung KSĐH

Không có sự ưu tiên rõ rệt giữa các thuốc hạ ĐH



Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy Metformin **Lifestyle Management**

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy Metformin + **Lifestyle Management**

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy Metformin + **Lifestyle Management**

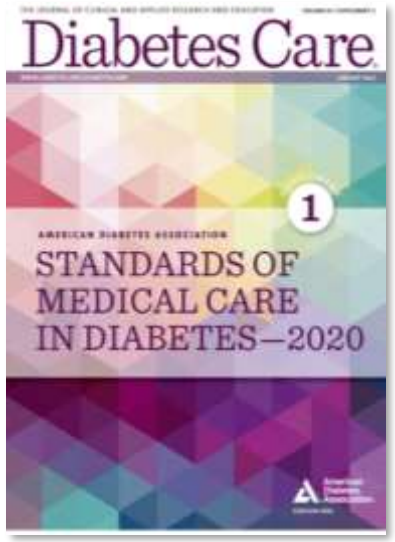
Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin[§]	or GLP-1-RA	or Insulin[§]	or GLP-1-RA
or Insulin[§]	or Insulin[§]		or Insulin[§]		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy **(See Figure 8.2)**

Guidelines hiện nay nói gì về

VAI TRÒ CỦA CÁC THUỐC HẠ ĐH TRONG CAN THIỆP SỚM TRÊN BN ĐTĐ?

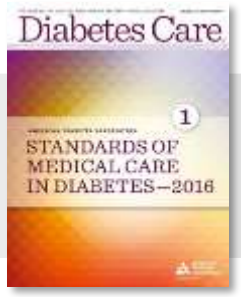


ADA Standards of Medical Care In Diabetes - 2020

Evolution of the ADA Standards of Medical Care in Diabetes, 2016–2020

A shift in focus from glucose control towards CVD risk management

Jan 2016



Glucose lowering

"SGLT2 inhibitors provide insulin-independent glucose lowering…
These agents provide modest weight loss and blood pressure reduction"[1]

Jan 2017

Consider SGLT2i or GLP-1 RA to reduce mortality (Level B)

In patients with long-standing suboptimally controlled T2D and established CVD, **an SGLT2 inhibitor or GLP-1 RA should be considered as they have been shown to reduce CV and all-cause mortality** when added to standard care"[2]

Jan 2018

Incorporate an agent proven to reduce CV events and mortality (Level A)

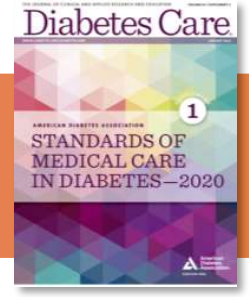
incorporate an agent proven to reduce major adverse CV events and CV mortality)"[3]

Jan 2019

SGLT2 inhibitors or GLP-1 RAs with demonstrated CVD benefit are recommended (Level A)

"Among patients with **ASCVD at high risk of heart failure or in whom heart failure coexists, SGLT2 inhibitors are preferred.** For patients with **T2D and CKD**, consider use of an **SGLT2 inhibitor or GLP-1 RA** shown to reduce risk of CKD progression, CV events, or both"[4]

Jan 2020

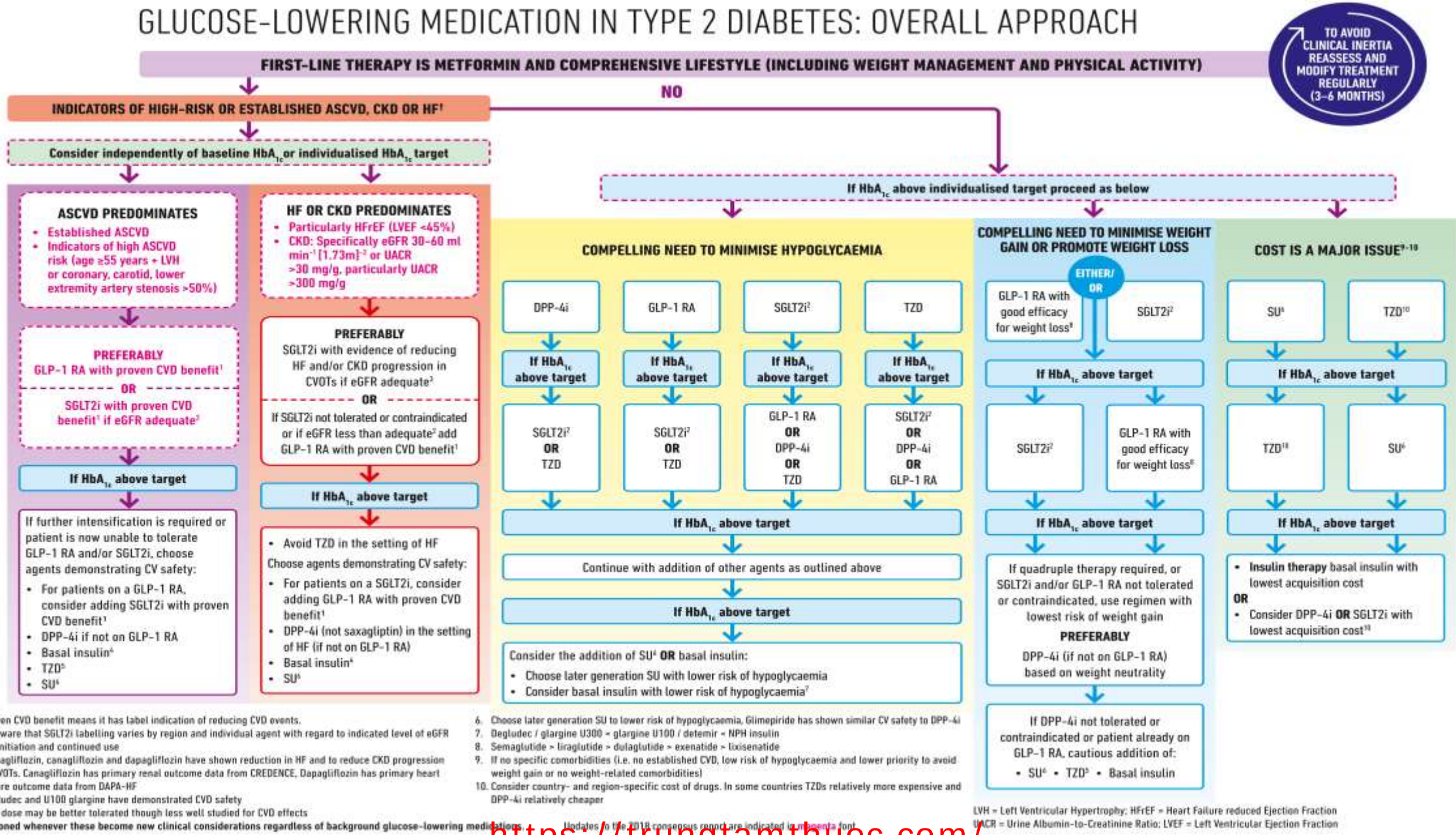


SGLT2 inhibitors or GLP-1 RAs with demonstrated CVD benefit are recommended independent of HbA1c (Level A)

"In patients with **T2D and established HF**, an **SGLT2 inhibitor may be considered** to reduce risk of HHF. For patients with **T2D and DKD**, consider use of an **SGLT2 inhibitor** to reduce risk of CKD progression, CV events or both. In patients **with CKD** who are at increased risk for CV events, use of a **GLP-1 RA** may reduce risk of progression of albuminuria,
CV events or both"[5]

American Diabetes Association. Diabetes Care 2016;39:S1;American Diabetes Association. Diabetes Care 2017;40:S1;American Diabetes Association. Diabetes Care 2018;41:S1
American Diabetes Association. Diabetes Care 2019;42:S1; American Diabetes Association. Diabetes Care 2020;43:S1

ADA/EASD 2019- Pharmacologic approaches to Glycemic Treatment



1. Proven CVD benefit means it has label indication of reducing CVD events.
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE, Dapagliflozin has primary heart failure outcome data from DAPA-HF
4. Degludec and U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications

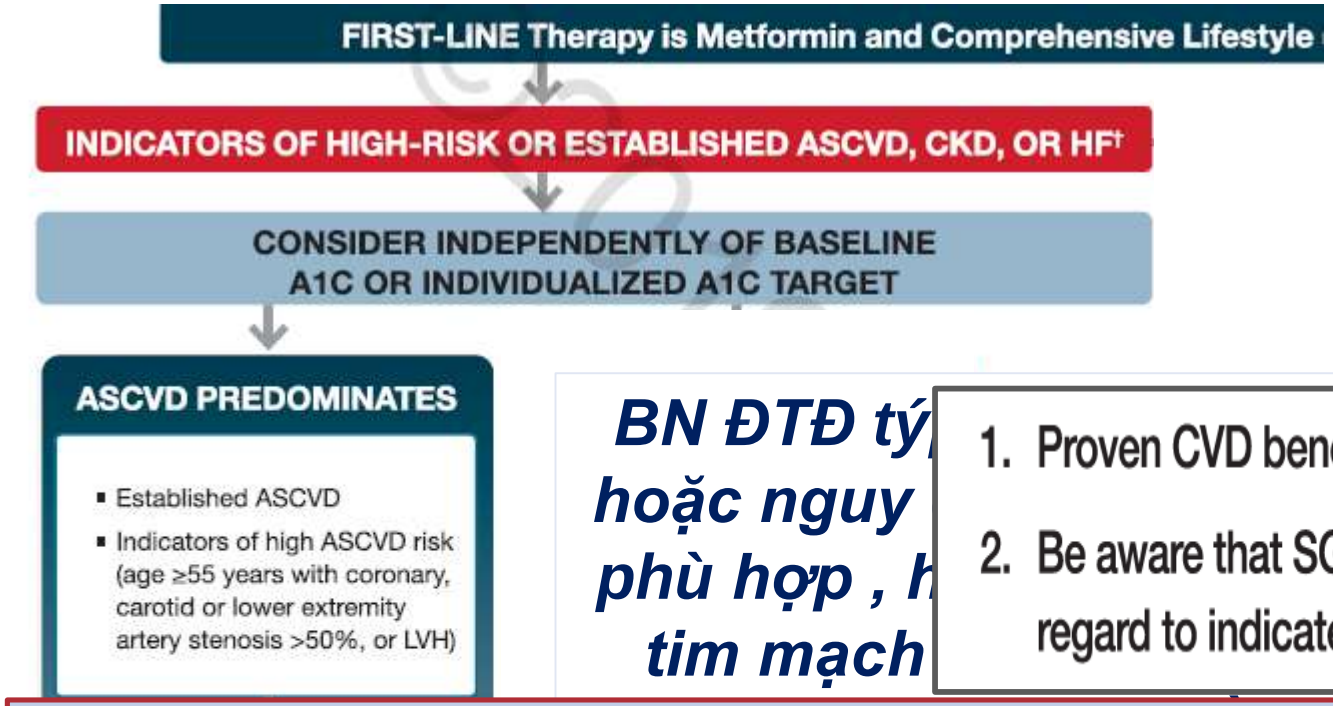
6. Choose later generation SU to lower risk of hypoglycaemia, Glimepiride has shown similar CV safety to DPP-4i
7. Degludec / glargine U300 = glargine U100 / detemir = NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

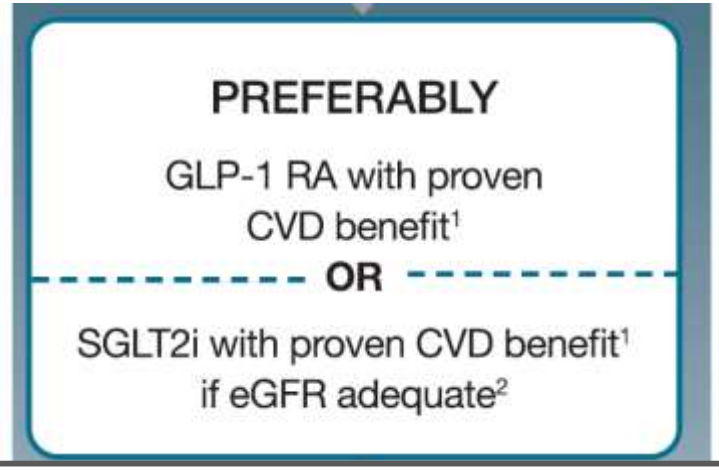
Updates to the 2018 consensus report are indicated in magenta font

LVH = Left Ventricular Hypertrophy; HFrEF = Heart Failure reduced Ejection Fraction
UACR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction

Diabetes Care. 2020 Feb;43(2):487-493

ADA 2020: Chiến lược lựa chọn thuốc





BN ĐTĐ týp
hoặc nguy
phù hợp , h
tim mạch

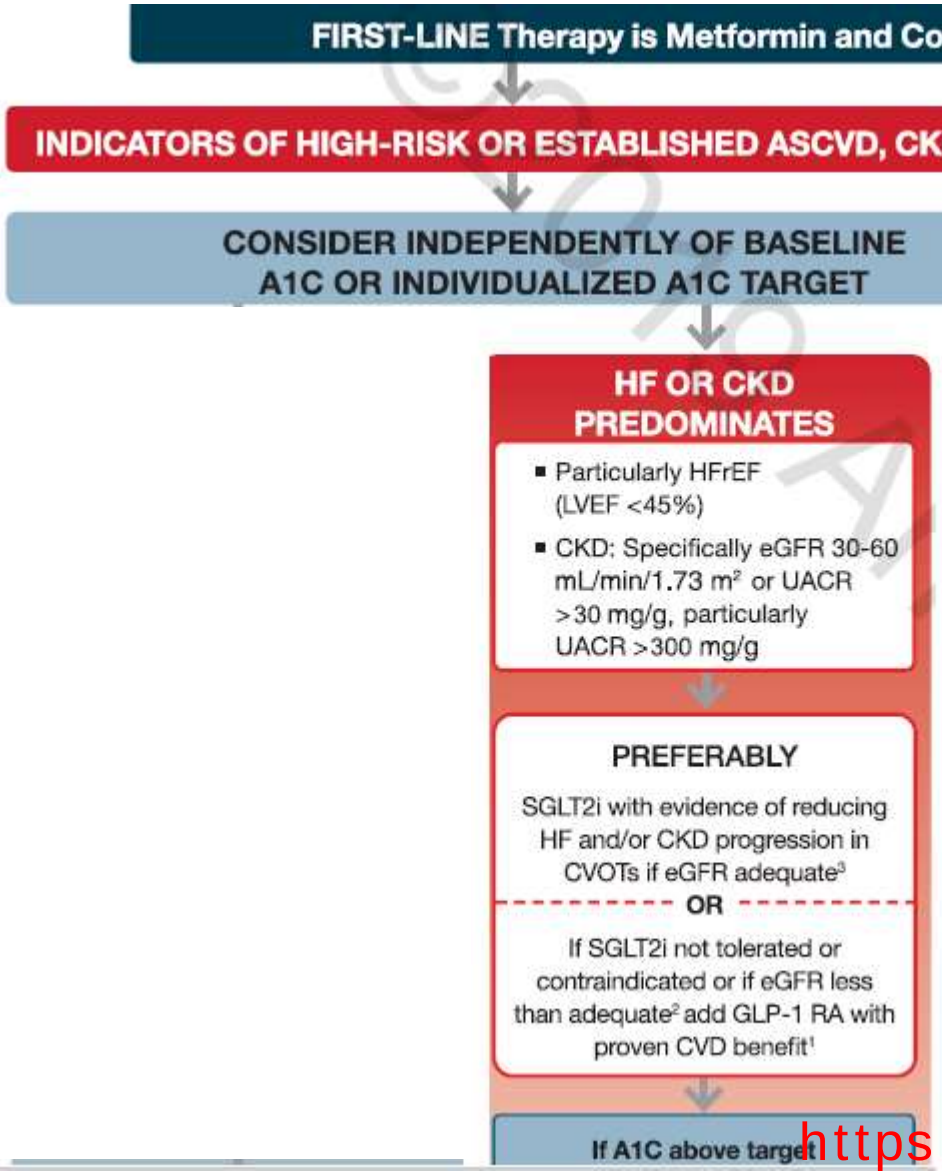
1. Proven CVD benefit means it has label indication of reducing CVD events
2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use

Lựa chọn thuốc GLP-1RA hoặc SGLT-2i với lợi ích tim mạch đã được chứng minh:

[1]Lợi ích tim mạch đã được chứng minh nghĩa là thuốc đã được chỉ định giảm biến cố tim mạch.

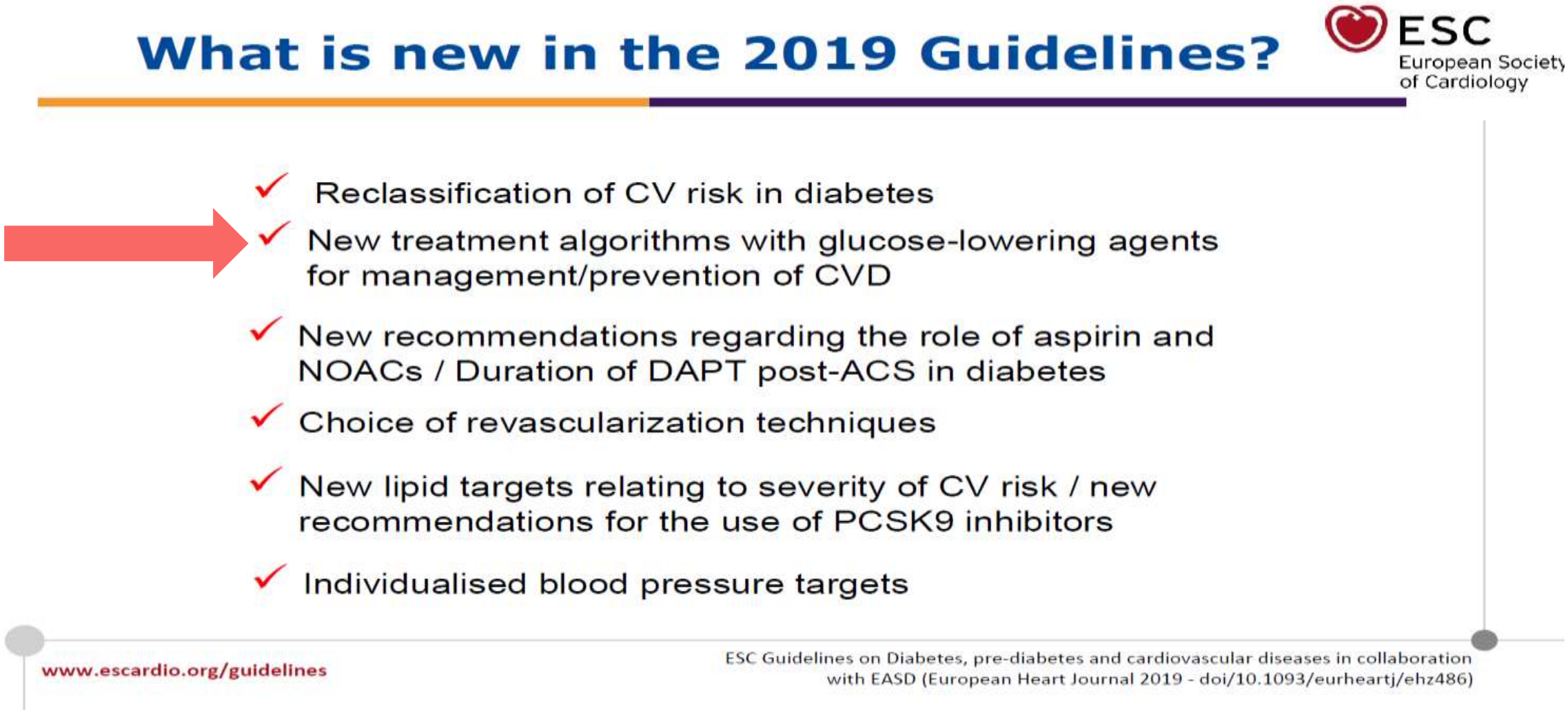
Tại Việt Nam, empagliflozin được chỉ định **làm giảm nguy cơ tử vong tim mạch ở bệnh nhân trưởng thành đái tháo đường typ 2 và có sẵn bệnh lý tim mạch**

ADA 2020: Chiến lược lựa chọn thuốc



- Đối tượng mắc kèm suy tim (đặc biệt HFrEF) hoặc bệnh thận mạn, cân nhắc dùng SGLT-2i để giảm nguy cơ nhập viện do suy tim và/hoặc tiến triển bệnh thận mạn. Nếu SGLT-2i không dung nạp hoặc chống chỉ định hoặc eGFR không phù hợp thì bổ sung GLP-1 RA đã được chứng minh lợi ích trên tim mạch
- Ở bệnh nhân ĐTĐ típ 2 kèm suy tim phân suất tống máu giảm, cân nhắc thuốc SGLT-2i với lợi ích đã được chứng minh để làm giảm nguy cơ suy tim nặng hơn và tử vong tim mạch.
- Ở bệnh nhân ĐTĐ típ 2 kèm bệnh thận mạn do đái tháo đường, cân nhắc sử dụng thuốc SGLT-2i ở bệnh nhân có eGFR ≥ 30ml/ph/1,73m^2 và có tỷ số A/C > 30mg/g, đặc biệt ở những bệnh nhân có tỷ lệ A/C > 300mg/g để làm giảm nguy cơ tiến triển bệnh thận, biến cố tim mạch, hoặc cả hai. Nếu có nguy cơ cao tim mạch kèm theo, đồng vận thụ thể GLP-1 có thể được xem xét để làm giảm diễn tiến albumin niệu, biến cố tim mạch, hoặc cả hai.

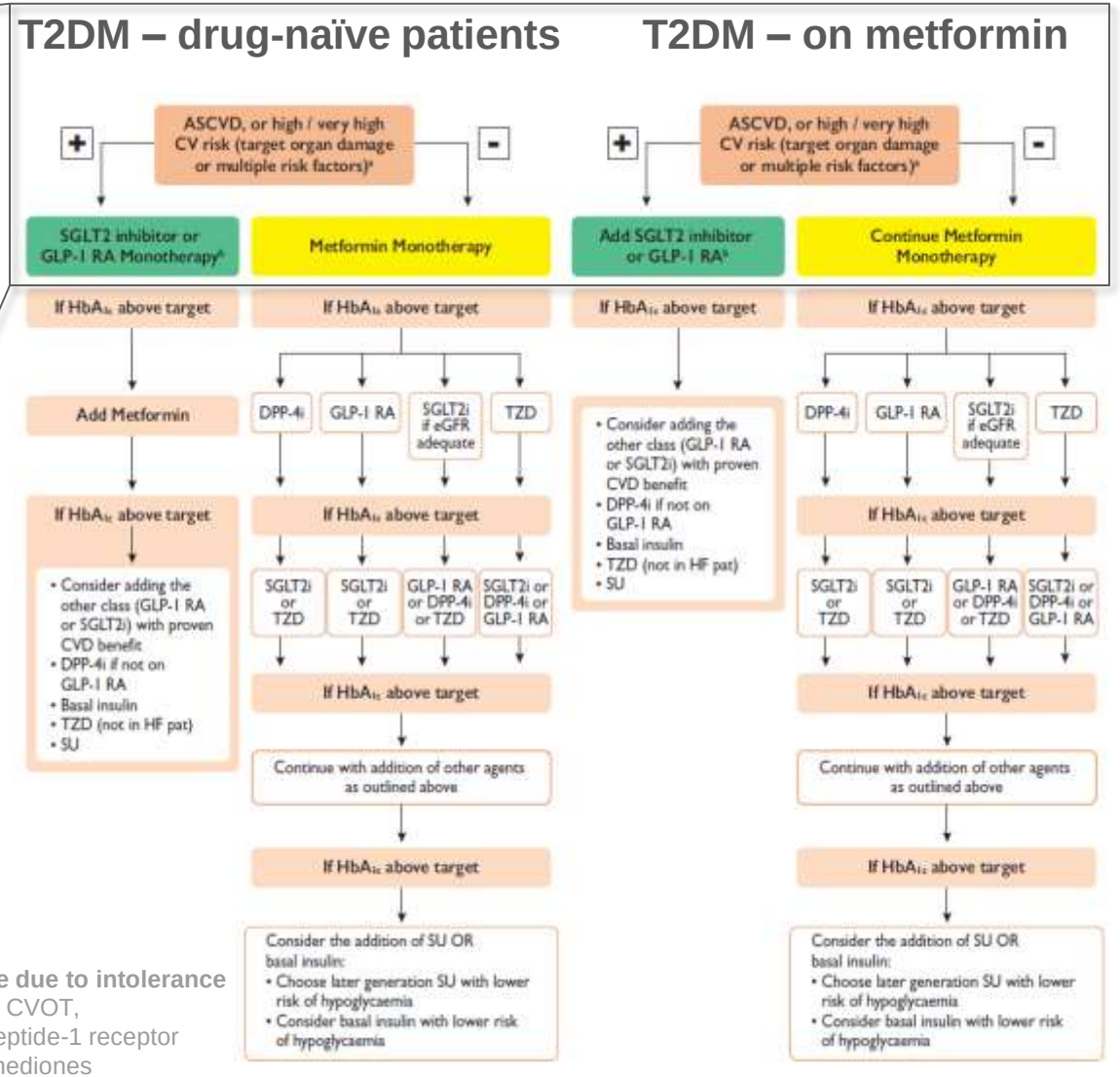
2019 ESC Guidelines on diabetes, pre-diabetes and cardiovascular disease



ESC Guidelines on diabetes, pre-diabetes and CV diseases

Treatment algorithm in patients with T2D and ASCVD or high/very high CV risk

- **Choice of drug** to reduce CV events in patients with T2DM **should be prioritised based on the presence of CV disease or CV risk**
- CVOT data strongly suggest that **SGLT2 inhibitors and GLP-1 RAs should be recommended** in patients with T2DM with prevalent CVD or very high/high CV risk, **whether treatment naïve or already on metformin**
- As **metformin was similarly present in the active and placebo** groups of recent CVOTs, **it is unlikely to explain the beneficial effects** of the newer drugs under test



SGLT2 inhibitors are indicated as monotherapy when metformin is considered inappropriate due to intolerance

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose co-transporter-2; T2DM, type 2 diabetes mellitus; TZD, thiazolidinediones

Cosentino F *et al. Eur Heart J* 2019; doi: 10.1093/eurheartj/ehz486

ESC Guidelines on diabetes, pre-diabetes and CV diseases

Recommendations for glucose-lowering treatment for patients with diabetes

Recommendation	Class of recommendation	Level of evidence
SGLT2 inhibitors		
Empagliflozin, canagliflozin, or dapagliflozin are **recommended in patients with T2DM and CVD, or at very high/high CV risk, to reduce CV events**	I	A
Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death	I	B
GLP-1 RAs		
Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or at very high/high CV risk, to reduce CV events	I	A
Liraglutide is recommended in patients with T2DM and CVD, or at very high/high CV risk, to reduce the risk of death	I	B
Biguanides		
Metformin should be considered in overweight patients with T2DM without CVD and at moderate CV risk	IIa	C
Insulin		
Insulin-based glycaemic control should be considered in patients with ACS with significant hyperglycaemia (>10 mmol/l or >180 mg/dl), with the target adapted according to comorbidities	IIa	C
Thiazolidinediones		
Thiazolidinediones are not recommended in patients with HF	III	A
DPP4 inhibitors		
Saxagliptin is not recommended in patients with T2DM and a high risk of HF	III	B

ACS, acute coronary syndrome; CV, cardiovascular; CVD, cardiovascular disease; DPP4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; SGLT2, sodium-glucose co-transporter-2

Cosentino F *et al. Eur Heart J* 2019; doi: 10.1093/eurheartj/ehz486

Chiến lược điều trị mới trong quản lý BN ĐTĐ

TIẾP CẬN TẬP TRUNG ĐH "GLUCOCENTRIC"

→

GIẢM BIẾN CỐ TIM MẠCH VÀ TỬ VONG

CAN THIỆP ĐA YẾU TỐ
(BLOOD PRESSURE CONTROL, STATINS, WEIGHT REDUCTION)
+
THUỐC GIẢM BIẾN CỐ TIM MẠCH
(SLGT-2 i / GLP-1 Agonist)
+
GIẢM HbA1c
(TO REDUCE MICROVASCULAR COMPLICATIONS)

Kết luận

1. Mục tiêu điều trị cốt lõi với BN ĐTĐ là ngăn ngừa BC, Tuy nhiên, KSĐH tích cực chỉ có thể làm giảm BC mạch máu nhỏ mà không giúp làm giảm biến chứng tim mạch và tử vong ở BN ĐTĐ.

2. Kết quả từ các CVOTs của các thuốc hạ ĐH mới cho thấy tác động khác nhau trên tim mạch:
   - Thuốc ức chế DPP-4: An toàn tim mạch (Linagliptin có bằng chứng an toàn trên phổ rộng chức năng thận)
   - Thuốc ức chế SGLT2: Tác động khác nhau trên tim mạch, cụ thể:
     - Empagliflozin: Giảm biến chứng tim mạch và tử vong, giảm nhập viện do suy tim và ngừa tiến triển bệnh thận
     - Dapagliflozin: Giảm nhập viện do suy tim & ngừa tiến triển bệnh thận

3. Tiếp cận điều trị ĐTĐ đã thay đổi từ tập trung mục tiêu ĐH sang quản lý toàn diện nguy cơ tim mạch – thận. Trong đó, đánh giá đặc điểm lâm sàng của BN là quan trọng và thuốc được chứng minh giảm biến cố & tử vong tim mạch, ngừa diễn tiến bệnh thận ở BN được đưa vào là 1 phần của chiến lược điều trị, bất kể đã/ chưa đạt mục tiêu ĐH. Các thuốc hạ ĐH khác có thể được thêm vào sau đó nhằm quản lý ĐH của BN đạt mục tiêu.