Vai trò của SGLT2i: từ kiểm soát đường huyết đến bảo vệ cơ quan đích cho BN ĐTĐ T2

GS TS BS VÕ THÀNH NHÂN
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Supported by AstraZeneca for medical educational purpose

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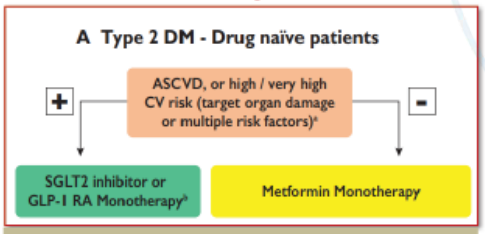
Diễn tiến bệnh lý tim mạch
Tử vong/Suy cơ quan đích...bắt đầu từ các YTNC

Circulation Volume 114, Issue 25, 19 December 2006, Pages 2850-2870

2

Vai trò của SGLT-2i ngày càng được khẳng định trong các khuyến cáo điều trị mới

ESC 08/2019



SGLT2i first line
T2D + high CV risk (naïve MET)

AHA/ACC 03/2022[2]

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

SGLT2i for HFrEF: IA
SGLT2i for HFmrEF, HFpEF: IIA

ADA EASD 09/2022

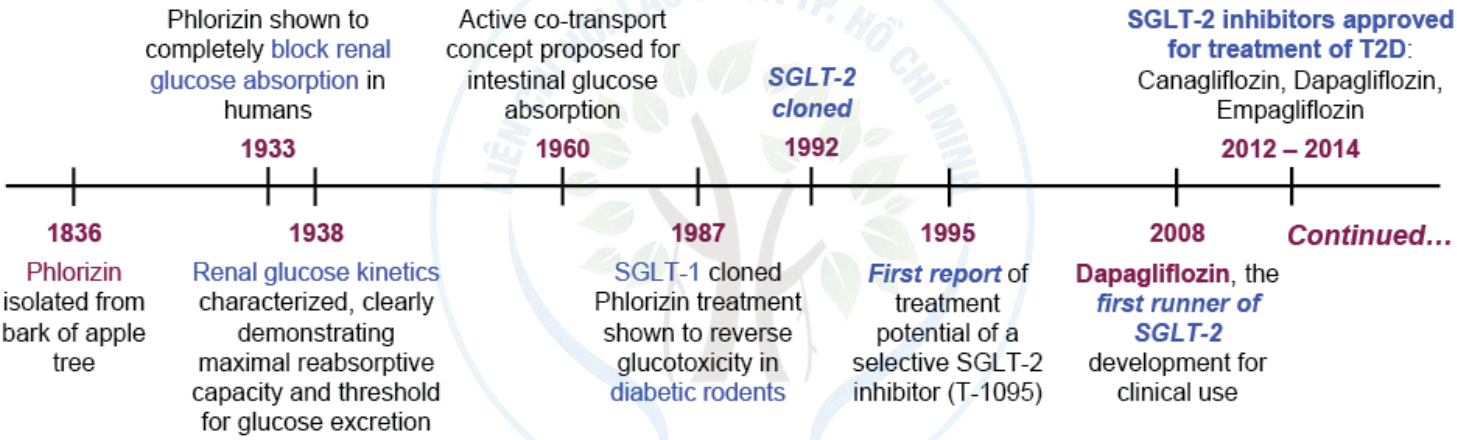
Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

SGLT2i first-line
T2D + high CV risk/HF/CKD

1. European Heart Journal (2020) 41, 255323. DOI:10.1093/eurheartj/ehz486
2. Circulation. 2022;145:e895–e1032. DOI: 10.1161/CIR.0000000000001063
3. Diabetes Care, https://doi.org/10.2337/dci22-0034

3

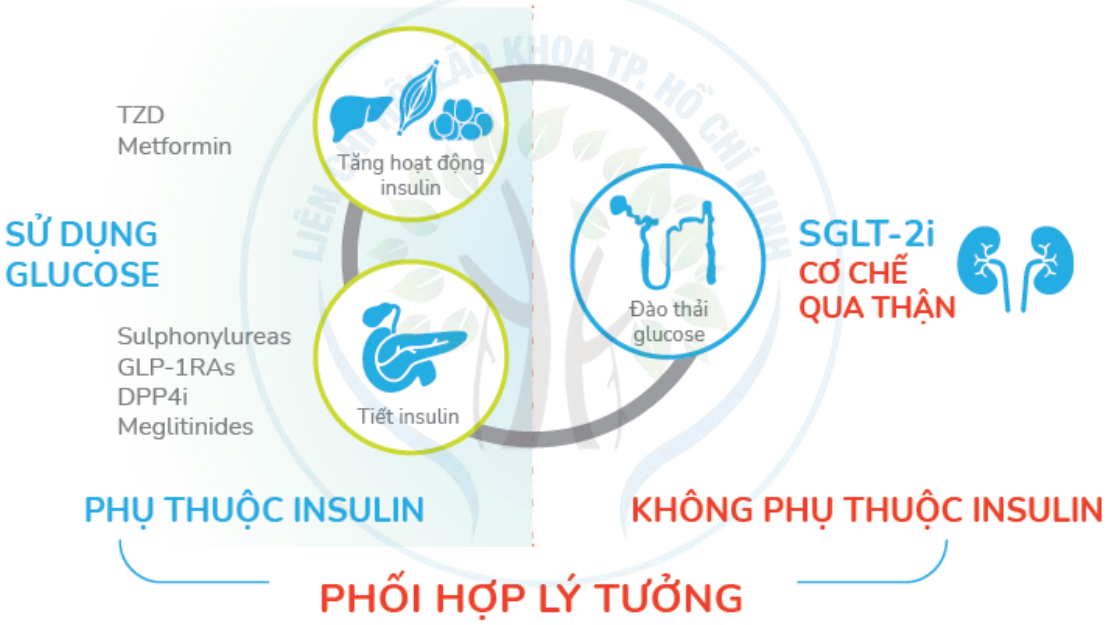
Sự ra đời và phát triển của nhóm thuốc SGLT2i



1. Mudaliar S, Polidori D, Zambrowicz B, Henry RR. Diabetes Care 2015;38:2344–2353 | DOI: 10.2337/dc15-0642. 2. Isaji M. Kidney Int 2011; 79 (Suppl 120): S14–S19.

4

Từ một thuốc kiểm soát đường huyết với cơ chế thải đường qua thận



1. Clark A, et al. Diabetes Res. 1988; 9: 151-159.
2. UKPDS 16. Diabetes. 1995; 44(11): 1249-1258.
3. Bruno RA, et al. J Clin Pract. October 2015, 69, 10 1071–1087

5

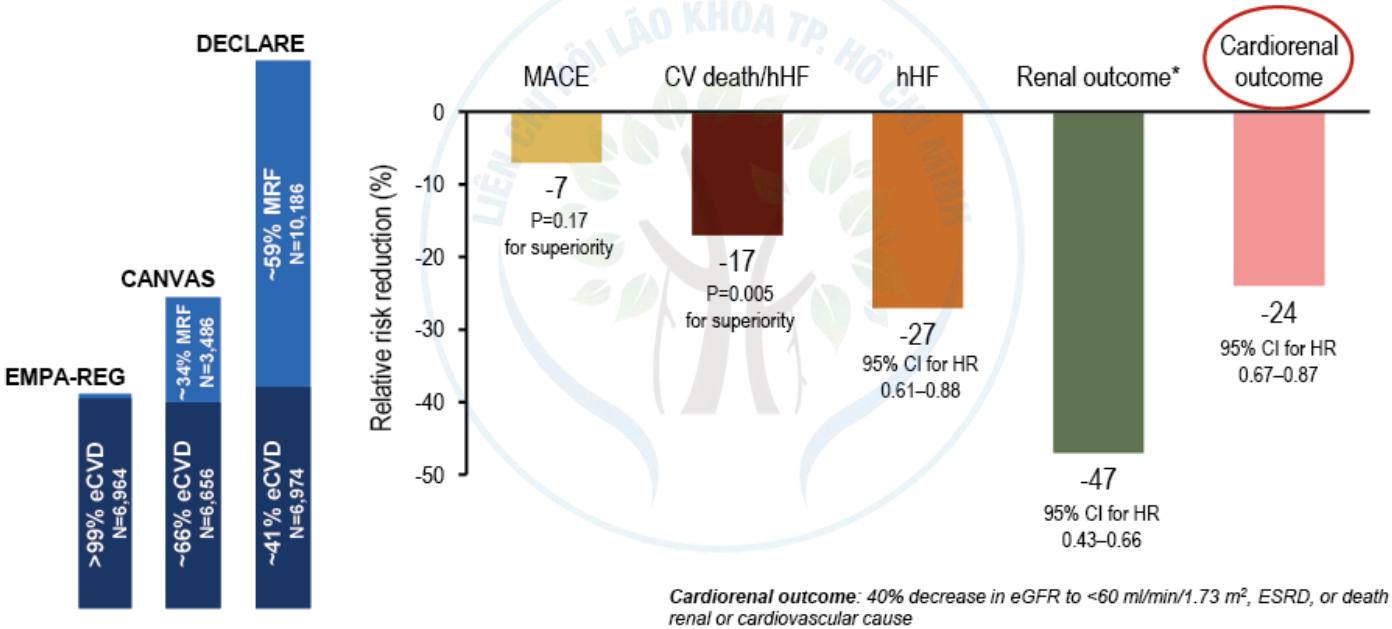
Lợi ích bảo vệ tim thận được phát hiện từ các thử nghiệm CVOT trên người bệnh đái tháo đường

	EMPA-REG[1]	CANVAS[2]	DECLARE TIMI 58[3]
Hospitalization for Heart failure	↓35%	↓33%	↓27%
Renal outcome	↓46%	↓34%	↓47%

1. N Engl J Med 2016;375:323-34, 2. N Engl J Med 2017;377:644-57 3. N Engl J Med 2019;380:347-57

6

Giảm biến cố tim-thận trên toàn thể dân số ĐTĐ típ 2 từ nguy cơ cao đến nguy cơ thấp hơn qua DECLARE-TIMI 58



***Cardiorenal outcome**: 40% decrease in eGFR to <60 ml/min/1.73 m², ESRD, or death from renal or cardiovascular cause*
** **Renal outcome** without death from cardiovascular cause*

Wiviott SD et al. Online ahead of print. *N Engl J Med.* 2018. DOI: 10.1056/NEJMoa1812389

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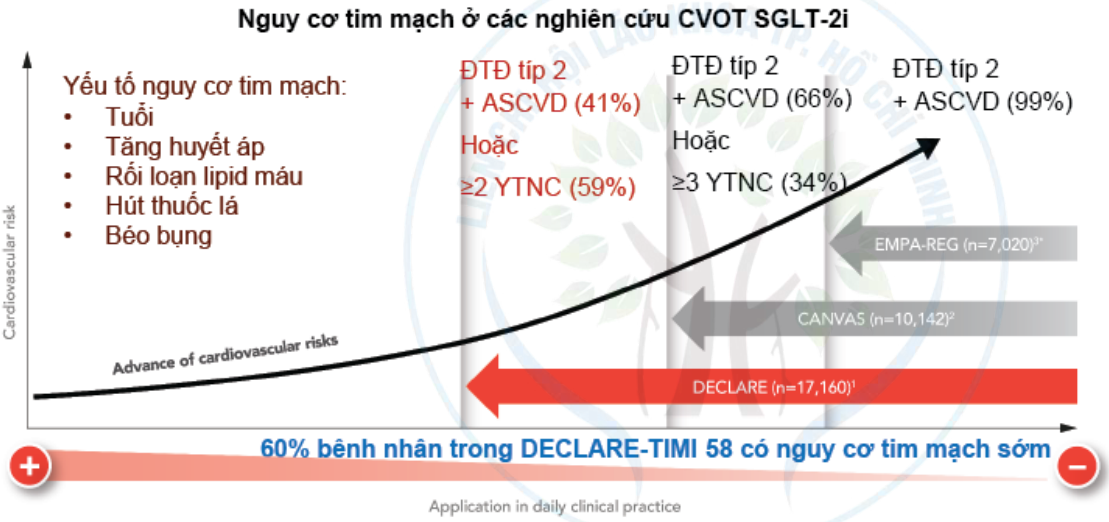
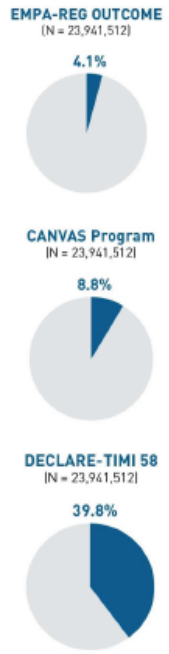
Lợi ích trên quần thể bệnh nhân ĐTĐ típ 2 trên thực tế có nhu cầu bảo vệ tim mạch sớm từ DECLARE-TIMI 58





1. Wiviott SD, et al. Am Heart J 2018;200:83–89; 2. Neal B, et al. N Engl J Med 2017;377:644–657; 3. Zinman B, et al. N Engl J Med 2015;373:2117–2128; 4. Einarson TR, et al. *Cardiovasc Diabetol* 2018;17:83; 5. McGurnaghan S, et al. Diabet. Med. 2019;36:718–725; 6. Raz I, et al. *Diabetes Obes Metab* 2018;20:1102–1110; 7. Wittbrodt ET, et al *Am J Manag Care*. 2018;24:S138-S145.

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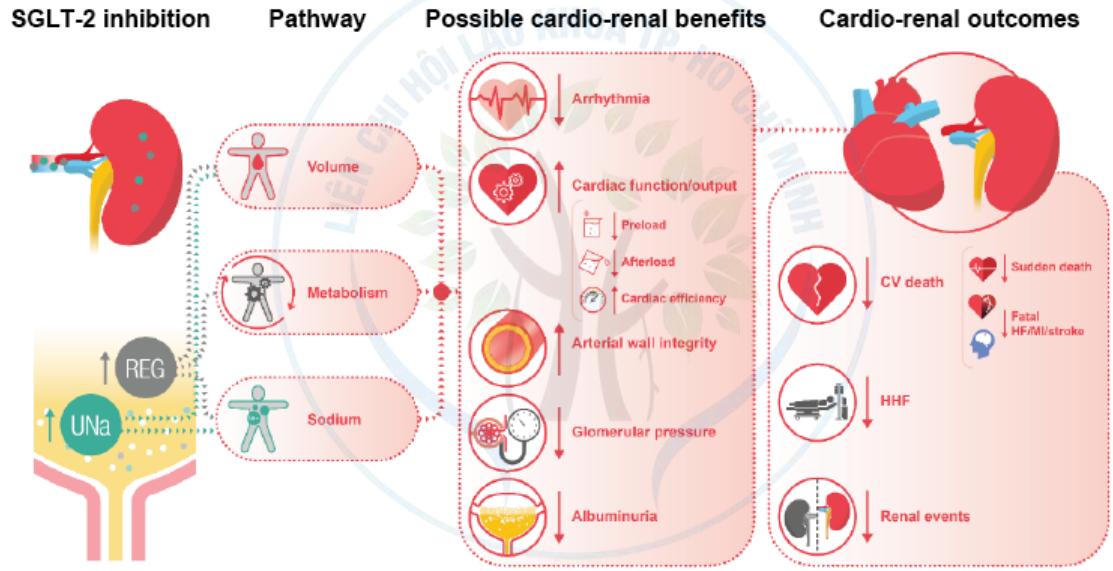
Các cơ chế ngoài đường huyết - Bảo vệ tim thận của SGLT2i



REG, removal of excess glucose; Una, urinary sodium

Butler J, et al. *Eur J Heart Fail.* 2017;19(11):1390-1400.

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Các thử nghiệm của SGLT2i về suy tim (HF)

Estimated completion	September 2019	September 2019	October 2019	October 2019	February 2020	February 2020	June 2020	2021	2021
	Outcome	Biomarker	Symptoms		Symptoms		Outcome	Outcome	Outcome
Study	DAPA-HF[1]	DEFINE-HF[2]	EMPERIAL REDUCED[3]	EMPERIAL PRESERVED[4]	DETERMINE REDUCED[5]	DETERMINE PRESERVED[6]	EMPEROR-Reduced[7]	DELIVER[9]	EMPEROR-Preserved[8]
Population	NYHA class II-IV, LVEF ≤40%, elevated NT-proBNP eGFR ≥30 mL/min/1.73 m²	NYHA class II or III, LVEF ≤40%, BNP ≥100 pg/mL and/or NTproBNP ≥ 400 pg/mL	NYHA class II–IV, LVEF ≤40%, elevated NT-proBNP	NYHA class II–IV, LVEF ≤40%, elevated NT-proBNP	NYHA class II-IV, LVEF≤40%, Elevated NT-proBNP	NYHA class II-IV, LVEF>40%, Elevated NT-proBNP	NYHA class II–IV, LVEF ≤40%, elevated NT-proBNP	NYHA class II–IV, LVEF ≥40%, elevated NT-proBNP	NYHA class II–IV, LVEF ≥40%, elevated NT-proBNP
Primary endpoint	Composite of CV death, hHF, or urgent hHF visit	1. Mean NT-proBNP at 6 and 12 weeks, 2. % patients ≥5-point increase on the KCCQ overall summary score or ≥30% decrease in NT-proBNP at 12 weeks	Change from baseline in 6-min walk test distance at week 12	Change from baseline in 6-min walk test distance at week 12	Change from baseline in 6-minute walking distance at Week16	Change from baseline in 6-minute walking distance at Week16	Composite of CV death or hHF	Composite of CV death, hHF, or urgent hHF visit	Composite of CV death or hHF
ey secondary endpoints	Renal composite: ≥50% sustained decline in eGFR, reaching ESRD, or renal death	Proportion of patients with ≥ 5pts increase in KCCQ	Change from baseline in KCCQ total symptom score and CHQ-SAS dyspnoea score at week 12	Change from baseline in KCCQ total symptom score and CHQ-SAS dyspnoea score at week 12	Change from baseline in the KCCQ Total symptom score (TSS) at Week16	Change from baseline in the KCCQ Total symptom score (TSS) at Week16	Time to hHF; eGFR slope change; time to dialysis, renal transplant, or ≥40% sustained decline in eGFR	Total number of CV death and hHF events	Time to hHF; eGFR slope change; time to dialysis, renal transplant, or ≥40% sustained decline in eGFR
Glycemic status	With/without T2D	With/without T2D	With/without T2D	With/without T2D	With/without T2D	With/without T2D	With/without T2D	With/without T2D	With/without T2D

', cardiovascular; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hHF, hospitalized heart failure; LVEF, left ntricular ejection fraction; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SGLT2, sodium–glucose co-transporter 2; T2D, Type 2 diabetes; KCCQ, Kansas City Cardiomyopathy Questionnaire Clinicaltrials.gov/ct2/show/NCT03036124; 2. https://clinicaltrials.gov/ct2/show/NCT02653482; 3. https://clinicaltrials.gov/ct2/show/NCT03448419; 4. https://clinicaltrials.gov/ct2/show/NCT03448406; 5. https://clinicaltrials.gov/ct2/show/NCT03877237; 6. ps://clinicaltrials.gov/ct2/show/NCT03877224; 7. https://clinicaltrials.gov/ct2/show/NCT03057977; 8. https://clinicaltrials.gov/ct2/show/NCT03057951; 9. https://clinicaltrials.gov/ct2/show/NCT03619213

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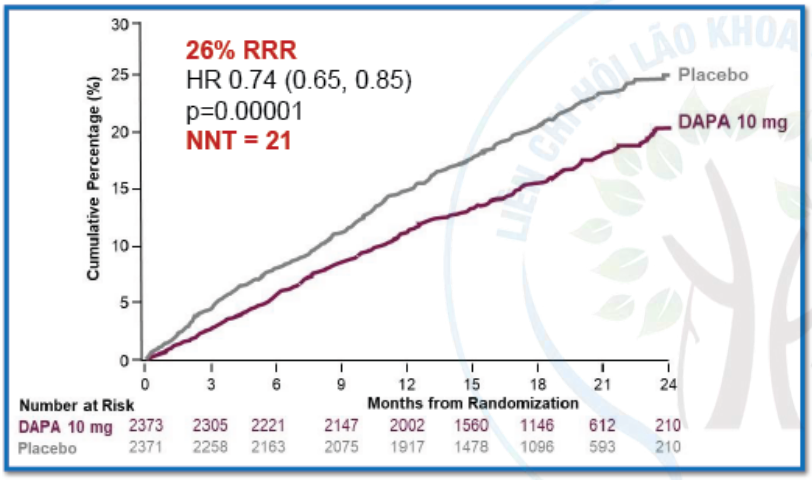
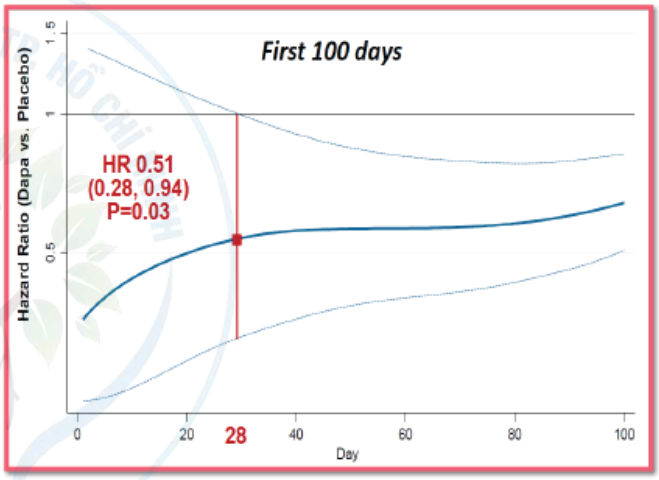
Lợi ích sớm trên suy tim HFrEF từ DAPA-HF, ngoài ĐTĐ

Tiêu chí gộp: tử vong do tim mạch, nhập viện do suy tim, khám suy tim cấp cứu





No Diabetes (n=2605)	HR 0.73 (0.60, 0.88), p=0.002. NNT = 22
History of Diabetes (n=2139)	HR 0.75 (0.63, 0.90), p=0.002. NNT = 18

1. McMurray JJV et al. Online. *N Engl J Med*. 2019;381:1995-2008 DOI: 10.1056/NEJMoa1911303. 2. Patrie MC et al. *JAMA*. doi:10.1001/jama.2020.1906

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Kết quả các nghiên cứu lớn trên suy tim nhìn từ mục tiêu điều trị

	Tiêu chí	DAPA-HF (Dapagliflozin)	EMPEROR-Reduced (Empagliflozin)	PARADIGM (sacubitril/ valsartan)	SHIFT (ivabradine)	EMPHASIS-HF (eplerenone)
Giảm tỉ lệ tử vong	Tử vong tim mạch	18% p=0.029	Not significant	20% P<0.001	Not significant	23% P<0.001
	Tử vong do mọi nguyên nhân	17% p=0.022	Not significant	16% P<0.001	Not significant	22% P<0.001
Giảm tần suất nhập viện	Nhập viện (lần đầu & tái nhập viện)	30% p=0.00003	30% p=0.003	21% P<0.001	26% P<0.001	39% P<0.001
Cải thiện triệu chứng cơ năng/ CLCS	Thay đổi KCCQ	+2.8 (8 tháng) P<0.001	+1.7 (12 tháng) p: not applicable	+1.6 (8 tháng)	+1.8 (12 tháng)	

Dữ liệu từ các nghiên cứu riêng biệt, không nhằm mục đích so sánh trực tiếp

1. Volume 133, Issue 25, 21 June 2016, Pages 2671-2686; 2. N Engl J Med 2011; 364:11-2; 3. N Engl J Med 2014; 371:993-1004
4. https://doi.org/10.1161/CIRCULATIONAHA.116.023518; 5. doi.org/10.1016/S0140-6736(10)61198-1

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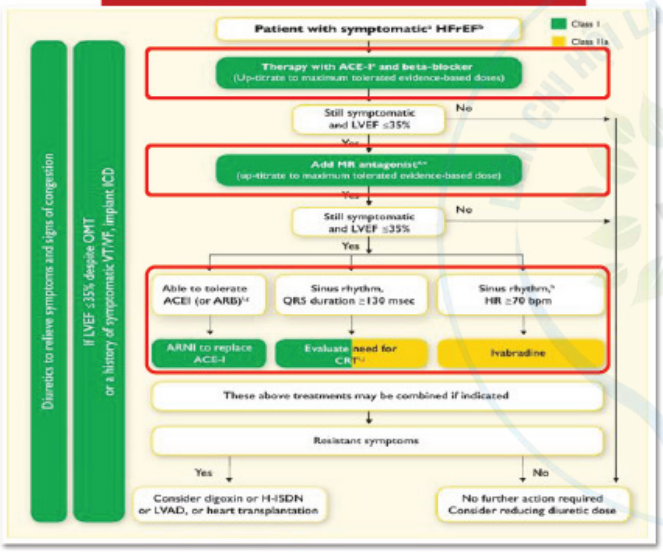
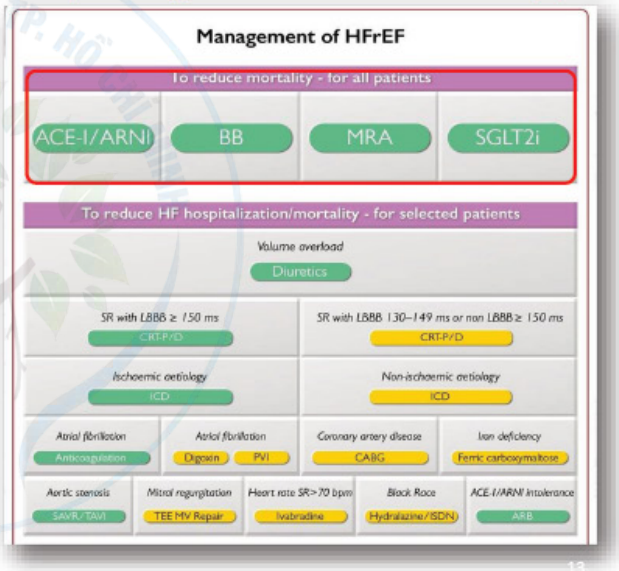
Từ nhu cầu điều trị đến bước tiến của khuyến cáo điều trị HFrEF
ESC 2021 - SGLT2i được khuyến cáo ngay từ bước khởi đầu

ESC 2016 - Điều trị từng bước



ESC 2021
Phối hợp SỚM 4 nhóm thuốc nền tảng



1. Eur J Heart Fail. 2016 Aug;18(8):891-975. doi: 10.1002/ejhf.592
2. ESC/HFA guideline on management of heart failure 2021

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ĐIỀU TRỊ HFrEF vs HFpEF

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

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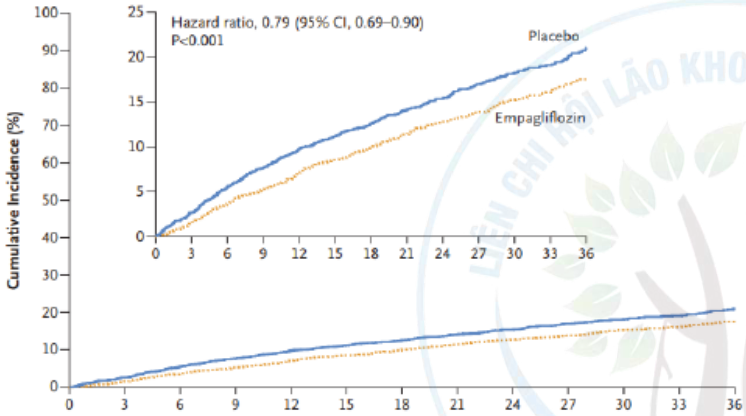
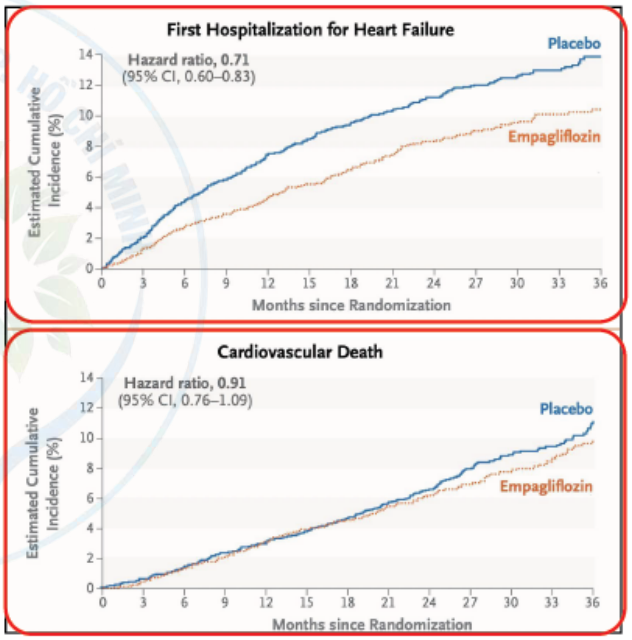
ESC 2021 - NGHIÊN CỨU EMPEROR-PRESERVED



Subgroup	Empagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
Overall	415/2997	511/2991	0.79 (0.69–0.90)
Diabetes at baseline			
Yes	239/1466	291/1472	0.79 (0.67–0.94)
No	176/1531	220/1519	0.78 (0.64–0.95)
LVEF at baseline			
<50%	145/995	193/988	0.71 (0.57–0.88)
≥50% to <60%	138/1028	173/1030	0.80 (0.64–0.99)
≥60%	132/974	145/973	0.87 (0.69–1.10)



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ESC 2022 – NGHIÊN CỨU DELIVER

Eligibility Criteria

- Age ≥ 40 years
- NYHA class II-IV
- LVEF > 40% (including prior LVEF ≤ 40%)
- Structural Heart Disease (LVH or LA Enlargement)
- Elevated Natriuretic Peptides (> 300 pg/ml or 600 pg/ml in AFF)
- Either Ambulatory or Hospitalized for Heart Failure

Double-blind Treatment period

Dapagliflozin 10mg once daily

Event Driven (1117 estimated events)

Placebo

N Engl J Med 2022; 387:1089-1098

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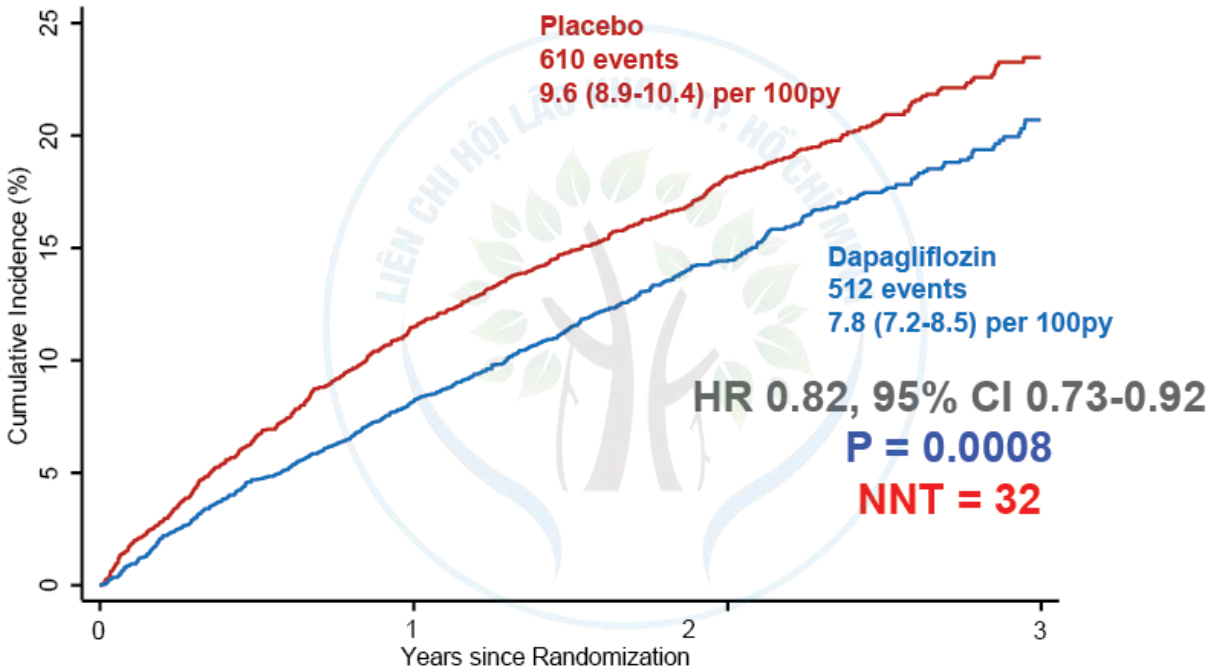
Tiêu chí chính: Tử vong tim mạch/Suy tim nặng lên



N Engl J Med 2022; 387:1089-1098

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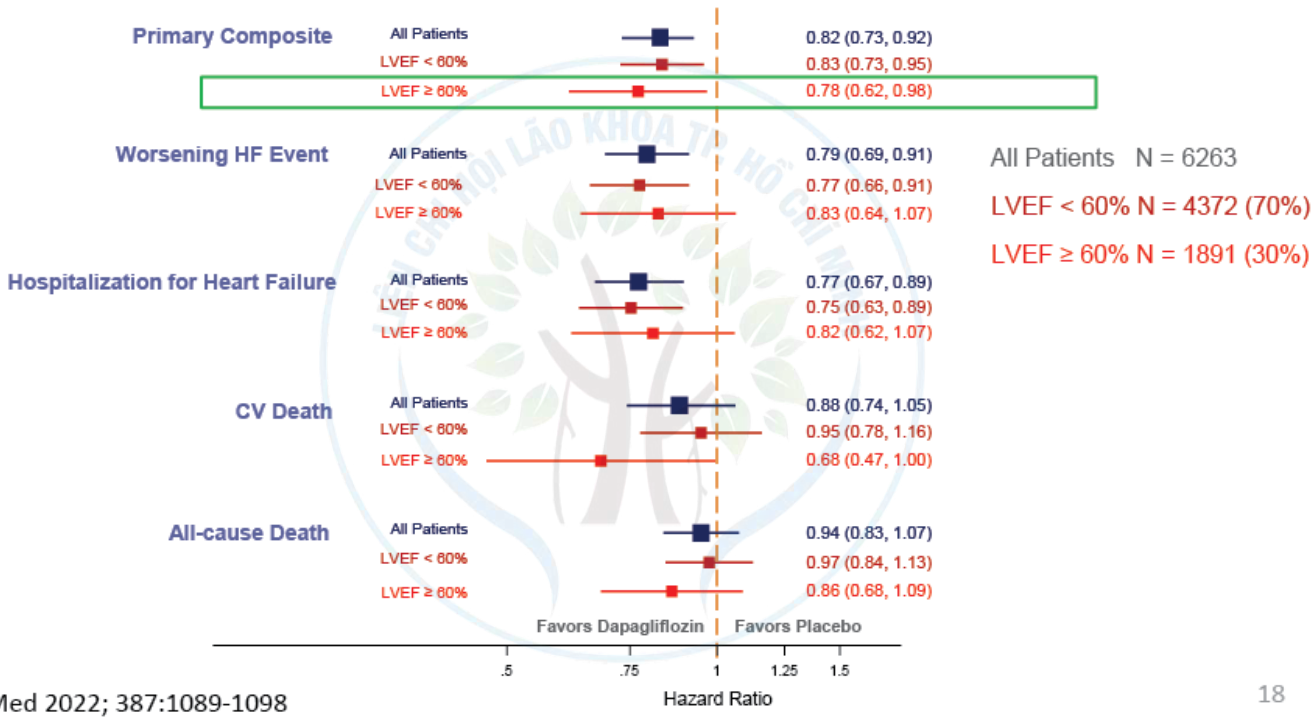
Kết quả có ý nghĩa trên BN có EF ≥ 60%



N Engl J Med 2022; 387:1089-1098

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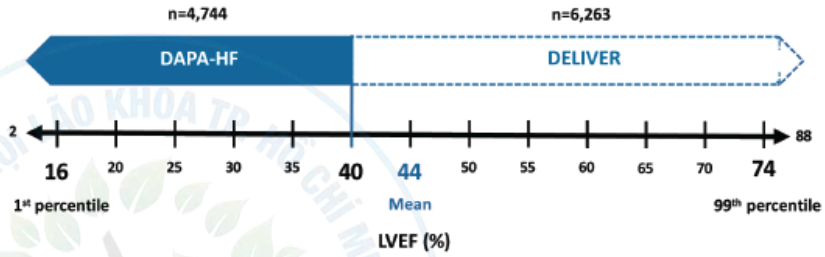
Phân tích gộp DAPA-HF DELIVER (n=11,007)

Dapagliflozin 10mg once daily vs placebo

Median follow-up = 22 (IQR 17-30) months

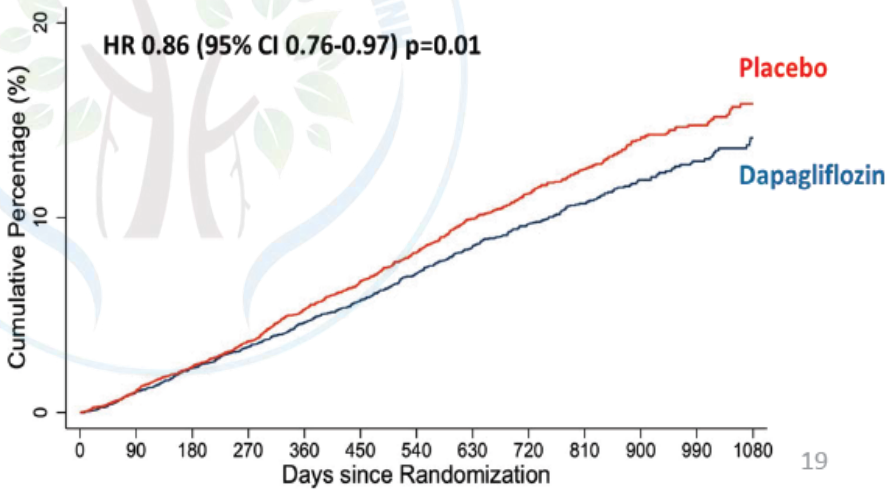


nature medicine ANALYSIS

OPEN

Dapagliflozin across the range of ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER

Pardeep S. Jhund[1], Toru Kondo[1], Jawad H. Butt[1], Kieran F. Docherty[1], Brian L. Claggett[2], Akshay S. Desai[2], Muthiah Vaduganathan[2], Samvel B. Gasparyan[3], Olof Bengtsson[3], Daniel Lindholm[3], Magnus Petersson[3], Anna Maria Langkilde[3], Rudolf A. de Boer[4], David DeMets[5], Adrian F. Hernandez[6], Silvio E. Inzucchi[7], Mikhail N. Kosiborod[8], Lars Køber[9], Carolyn S. P. Lam[10], Felipe A. Martinez[11], Marc S. Sabatine[12], Sanjiv J. Shah[13], Scott D. Solomon[2] and John J. V. McMurray[1]



McMurray JJV et al Eur J Heart Fail. 2019;21:665-675
Solomon SD et al Eur J Heart Fail 2021;23:1217-1225

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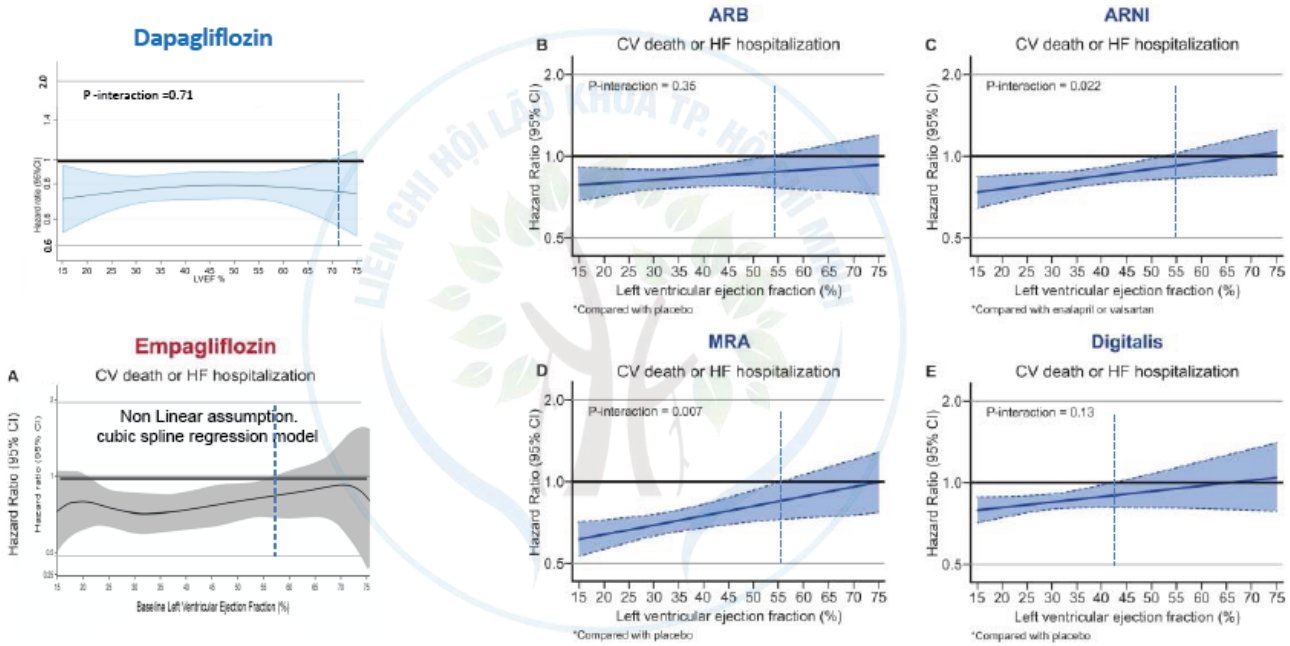
Nhìn lại hiệu quả của các nhóm thuốc theo PSTM (EF)



Kondo T & McMurray JVV Eur Heart J 2021 Interaction between the effect of: (*A*) the sodium–glucose co-transporter 2 (SGLT2) empagliflozin; from Butler *et al.*;[6] and of (*B*) the angiotensin receptor blocker (ARB) candesartan; (*C*) the angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril valsartan; (*D*) the mineralocorticoid receptor antagonists (MRAs) spironolactone and eplerenone; and (*E*) the digitalis glycoside digoxin according to baseline LVEF in the trials reported by Dewan *et al.*[3] and the Digitalis Investigation Group[12].

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Các thử nghiệm của SGLT2i về bệnh thận mạn (CKD)

Completion	Study	Population	Primary endpoint	Key secondary endpoints	Glycemic status	Approval
2020	DAPA CKD[1]	eGFR 25-75ml/min/1.73m² and UACR ≥200mg/g but ≤5000mg/g* • ≤10% have eGFR >60ml/min/1.73m² • ≥30% do not have T2D	Composite of: (>50% decline in eGFR, ESRD, or renal death), or CV death	1. Composite of >50% decline in eGFR, ESRD, or renal death 2. Time to hHF/CV death 3. Time to death from any cause	With without T2D	FDA (30/04/2021) Euro (09/08/2021)
2022	EMPA KIDNEY[2]	eGFR ≥20 to <45 mL/min/1.73m² or eGFR ≥45 to <90 mL/min/1.73m² with UACR ≥200 mg/g (or protein:creatinine ratio ≥300 mg/g)	Time to first occurrence of (i) ESKD, a sustained decline in eGFR to <10 mL/min/1.73m², renal death, or a sustained decline of ≥40% in eGFR from randomization) or (ii) CV death	1. Time to first hHF or CV death 2. Occurrences of all-cause hospitalization 3. Time to death from any cause 4. Time to first occurrence of kidney disease progression	With without T2D	Estimate 2023

CV, cardiovascular; CKD, chronic kidney disease, eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; ESRD, end-stage renal disease; HF, heart failure; hHF, hospitalisation for heart failure; SGLT2, sodium–glucose co-transporter 2; T2D, Type 2 diabetes; UACR, urine albumin creatinine ratio
1. https://clinicaltrials.gov/ct2/show/NCT03036150; 2. https://clinicaltrials.gov/ct2/show/NCT03594110

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DAPA-CKD: Dapagliflozin ở BN có bệnh thận mạn Nghiên cứu dừng sớm vào tháng 03/2020

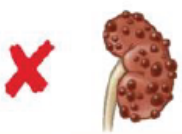
DAPACKD

RCT Protocol

Dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD)
Rationale and trial protocol

Multicentre ~ 400
Target n = 4300
Patients with and without type 2 diabetes

≥ 18 years
25–75 ml/min/1.73 m²
uACR ≥ 200 mg/g



Polycystic kidney disease
Lupus nephritis
ANCA vasculitis
Type I diabetes

Interventions

Dapagliflozin 10 mg

1:1

Placebo

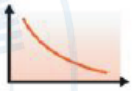
Follow-up

~ 45 months

Event-driven (681 events)

Primary outcome

Composite renal endpoint



≥ 50% decline in eGFR

End-stage kidney disease

Renal or cardiovascular death

ndt NEPHROLOGY DIALYSIS TRANSPLANTATION

Heerspink HJL et al. NDT (2019)
@NDTSocial

2

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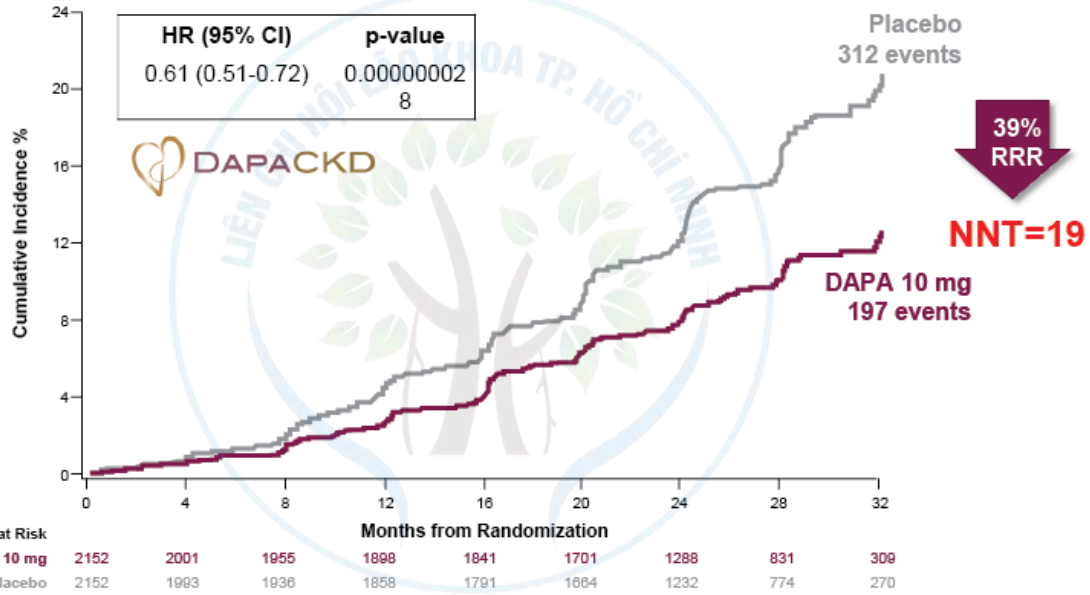
Tiêu chí chính: Giảm liên tục eGFR ≥50%, bệnh thận giai đoạn cuối, tử vong do TM hoặc thận



[a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m² for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.[2] CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; ; NNT = number needed to treat; RRR = relative risk reduction.

23 I. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020. 2. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282.

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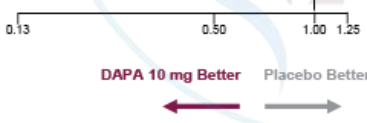
Tiêu chí chính của NC: Hiệu quả điều trị đồng nhất giữa các phân nhóm định trước, bất kể có hay không ĐTĐ

	Number of Events				
HR (95% CI)	DAPA 10 mg (N=2152)	Placebo (N=2152)	HR	95% CI	p-value Interaction
Composite of ≥50% eGFR Decline, ESKD, or Renal or CV Death					
All Patients	197	312	0.61	(0.51, 0.72)	
T2D at Baseline					0.24
Yes	152	229	0.64	(0.52, 0.79)	
No	45	83	0.50	(0.35, 0.72)	
UACR (mg/g) at Baseline					0.52
≤1000	44	84	0.54	(0.37, 0.77)	
>1000	153	228	0.62	(0.50, 0.76)	
eGFR (mL/min/1.73m²) at Baseline					0.22
<45	152	217	0.63	(0.51, 0.78)	
>45	45	95	0.49	(0.34, 0.69)	



CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.

24 Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020.

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DAPA-CKD: Giảm có ý nghĩa tất cả các tiêu chí phụ

Outcome	Dapagliflozin		Placebo		Hazard Ratio (95% CI)	P Value
	no./total no. (%)	*events/100 patient-yr*	*no./total no. (%)*	*events/100 patient-yr*		
Primary outcome						
Primary composite outcome	197/2152 (9.2)	4.6	312/2152 (14.5)	7.5	0.61 (0.51–0.72)	<0.001
Secondary outcomes						
Composite of decline in estimated GFR of ≥50%, end-stage kidney disease, or death from renal causes	142/2152 (6.6)	3.3	243/2152 (11.3)	5.8	0.56 (0.45–0.68)	<0.001
Composite of death from cardiovascular causes or hospitalization for heart failure	100/2152 (4.6)	2.2	138/2152 (6.4)	3.0	0.71 (0.55–0.92)	0.009
Death from any cause	101/2152 (4.7)	2.2	146/2152 (6.8)	3.1	0.69 (0.53–0.88)	0.004

N Engl J Med 2020;383:1436-46.
DOI: 10.1056/NEJMoa2024816
Vui lòng tham khảo thông tin kê toa Dapagliflozin tại Việt Nam

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Nghiên cứu EMPA-KIDNEY
Giảm 28% tiêu chí chính (diễn tiến bệnh thận/tử vong tim mạch)

Outcome	Empagliflozin (N=3304)		Placebo (N=3305)		Hazard Ratio (95% CI)*	P Value
	no. (%)	*no. of events/100 patient-yr*	*no. (%)*	*no. of events/100 patient-yr*		
Primary outcome: progression of kidney disease or death from cardiovascular causes	432 (13.1)	6.85	558 (16.9)	8.96	0.72 (0.64–0.82)	<0.001
Key secondary outcomes†						
Hospitalization for heart failure or death from cardiovascular causes	131 (4.0)	2.04	152 (4.6)	2.37	0.84 (0.67–1.07)	0.15
Hospitalization for any cause‡	—	24.8	—	29.2	0.86 (0.78–0.95)	0.003
Death from any cause	148 (4.5)	2.28	167 (5.1)	2.58	0.87 (0.70–1.08)	0.21

November 4, 2022
DOI: 10.1056/NEJMoa2204233

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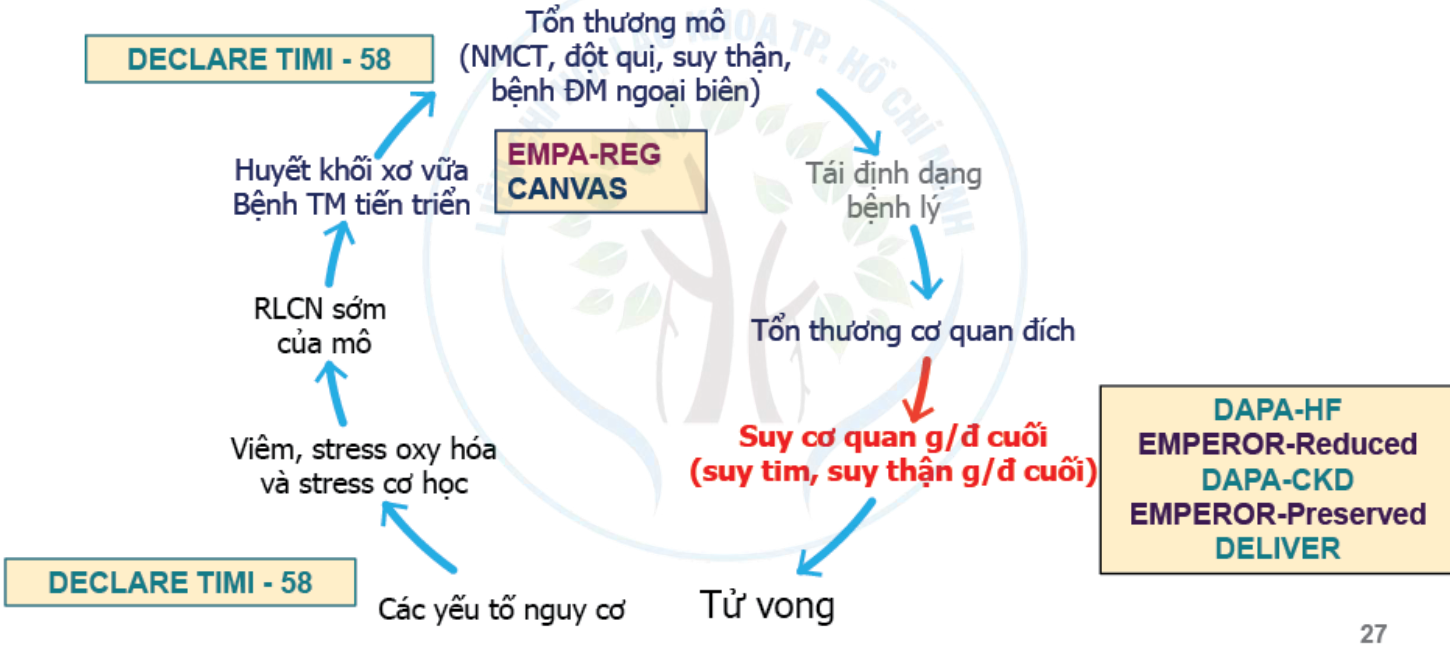
Các nghiên cứu về SGLT2i:
Từ BN ĐTĐ týp 2 kèm yếu tố nguy cơ đến BN suy tim-suy thận



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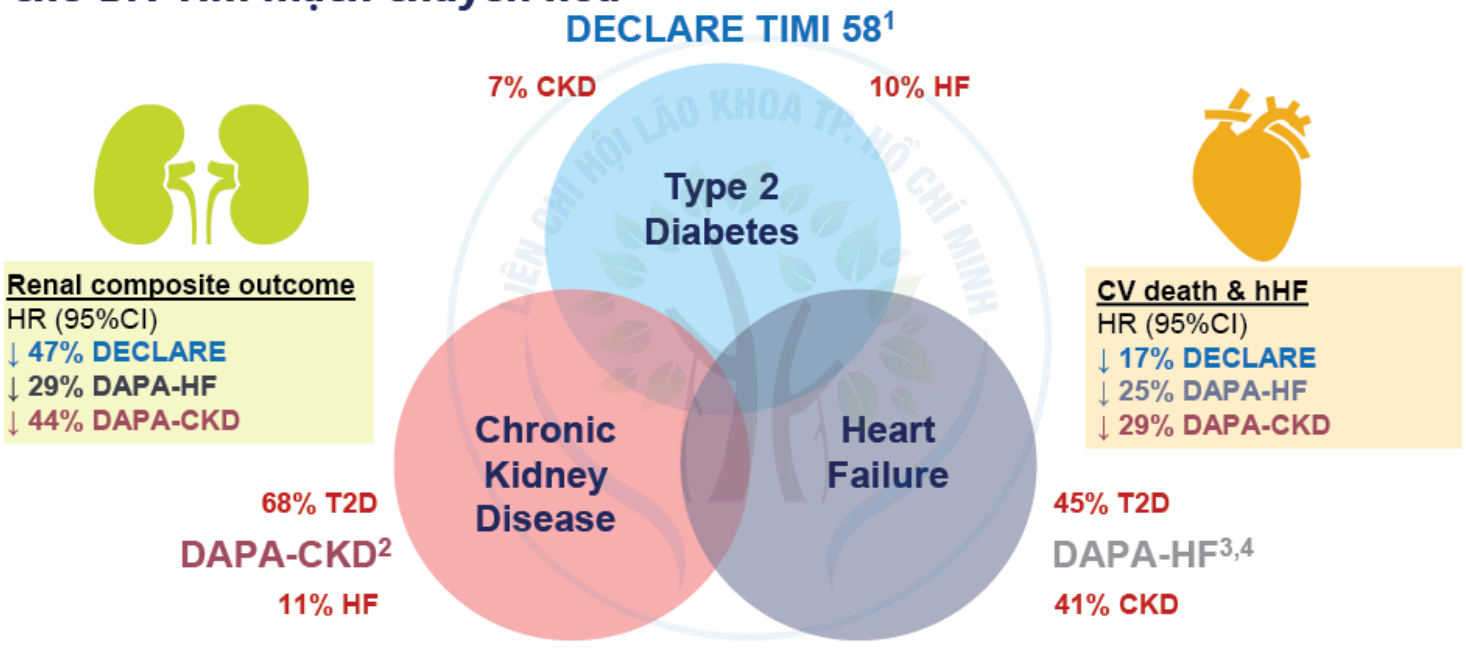
Circulation. Volume 114. Issue 25. 19 December 2006. Pages 2850-2870

Dapagliflozin trong bảo vệ cơ quan đích
cho BN Tim mạch chuyển hóa



1. Wiviott SD et al. N Endl J Med, 2019;380:347-357; 2. Heerspink HJL. Et al. N Engl J Med 2020; 383: 1436-1446;
3. McMurray JJV et al. N Engl J Med 2019;381;1995-2008; 4. Petrie et al. JAMA 2020;323; 1353-1386

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Kết luận

- SGLT2i giúp điều trị kiểm soát đường huyết ở bệnh nhân ĐTĐ típ 2 bằng cơ chế độc lập với insulin, ở cả đơn trị và phối hợp với các thuốc hiện có.
- Giá trị về lợi ích lâm sàng của SGLT-2i không còn nằm ở dự hậu tim mạch thông qua MACE mà là lợi ích kép bảo vệ tim-thận chứng minh từ DECLARE-TIMI 58 trên dân số rộng có bệnh tim mạch và/hoặc yếu tố nguy cơ.
- SGLT2i (Dapagliflozin) qua nghiên cứu DAPA-HF, DELIVER trên BN suy tim và DAPA-CKD trên BN suy thận cũng đồng thời mở rộng lợi ích bảo vệ tim thận của SGLT2i cho cả bệnh nhân suy tim, suy thận không ĐTĐ.

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