BẢO VỆ THẬN SỚM CHO BỆNH NHÂN ĐÁI THÁO ĐƯỜNG TÍP 2 CAO TUỔI TỪ GÓC NHÌN LÂM SÀNG

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Khoa Nội tiết, Bệnh viện Thống Nhất

NỘI DUNG

1. Gánh nặng bệnh thận mạn ở BN đái tháo đường cao tuổi
2. Chẩn đoán sớm bệnh thận đái tháo đường
3. Tiếp cận điều trị bệnh thận đái tháo đường ở người cao tuổi

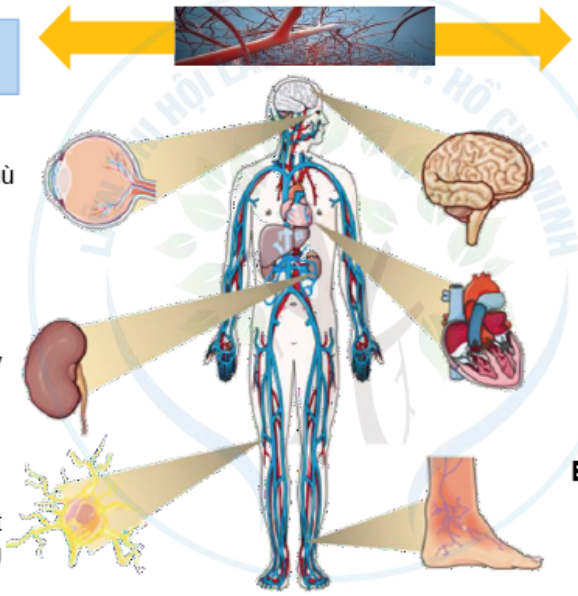
Biến chứng của bệnh nhân đái tháo đường

BIẾN CHỨNG MẠCH MÁU NHỎ

Bệnh mắt ĐTĐ
Dẫn đầu nguyên nhân gây mù ở người lớn [1,2]

Bệnh thận ĐTĐ
Dẫn đầu nguyên nhân gây bệnh thận giai đoạn cuối [3,4]

Bệnh thần kinh ĐTĐ
Dẫn đầu nguyên nhân cắt cụt chi xa không do chấn thương [7,8]



BIẾN CHỨNG MẠCH MÁU LỚN

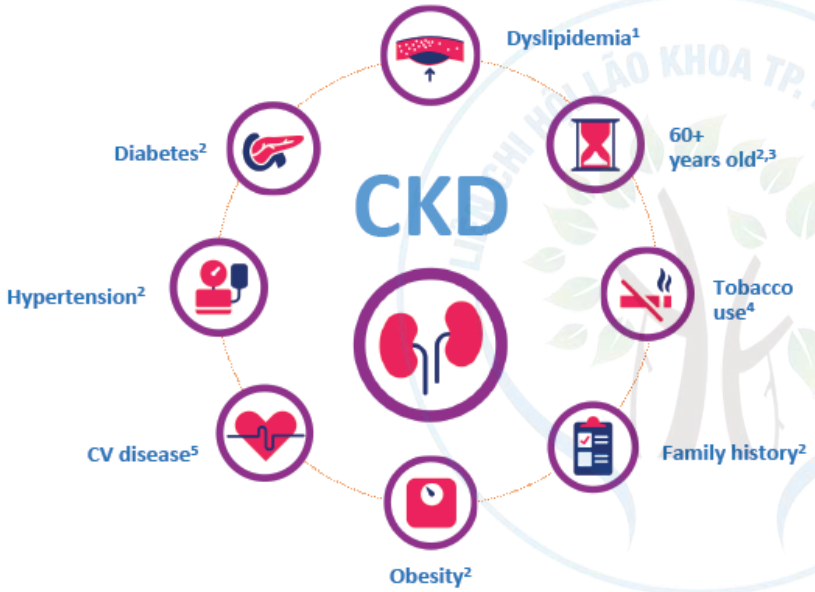
Đột quỵ
Tăng 2 – 4 lần nguy cơ TV tim mạch và đột quỵ [5]

Bệnh tim mạch
8/10 BN ĐTĐ tử vong do biến cố tim mạch [6]

Bệnh động mạch ngoại biên

[1]UK Prospective Diabetes Study Group. *Diabetes Res* 1990; 13:1–11. ; [2]Fong DS, *et al. Diabetes Care* 2003; 26 (Suppl. 1):S99–S102.; [3]The Hypertension in Diabetes Study Group. *J Hypertens* 1993; 11:309–317. ; [4]Molitch ME, *et al. Diabetes Care* 2003; 26 (Suppl. 1):S94–S98, [5]Kannel WB, *et al. Am Heart J* 1990; 120:672–676; [6]Gray RP & Yudkin JS. Cardiovascular disease in diabetes mellitus. In *Textbook of Diabetes* 2nd Edition, 1997. Blackwell Science; [7]King's Fund. *Counting the cost.* The real impact of non-insulin dependent diabetes. London: British Diabetic Association, 1996; [8]Mayfield JA, *et al. Diabetes Care* 2003; 26 (Suppl. 1):S78–S79.

Có nhiều nguyên nhân dẫn đến bệnh thận mạn



Có đến 50% bệnh nhân ĐTĐ có bệnh thận mạn trên toàn cầu[6]

ĐTĐ và cao tuổi (>60 tuổi) là những lý do dẫn đến bệnh thận mạn. Trong đó, ĐTĐ là lý do phổ biến nhất dẫn đến suy thận[8,9]

CKD, chronic kidney disease; T2D, type 2 diabetes; CV, cardiovascular.

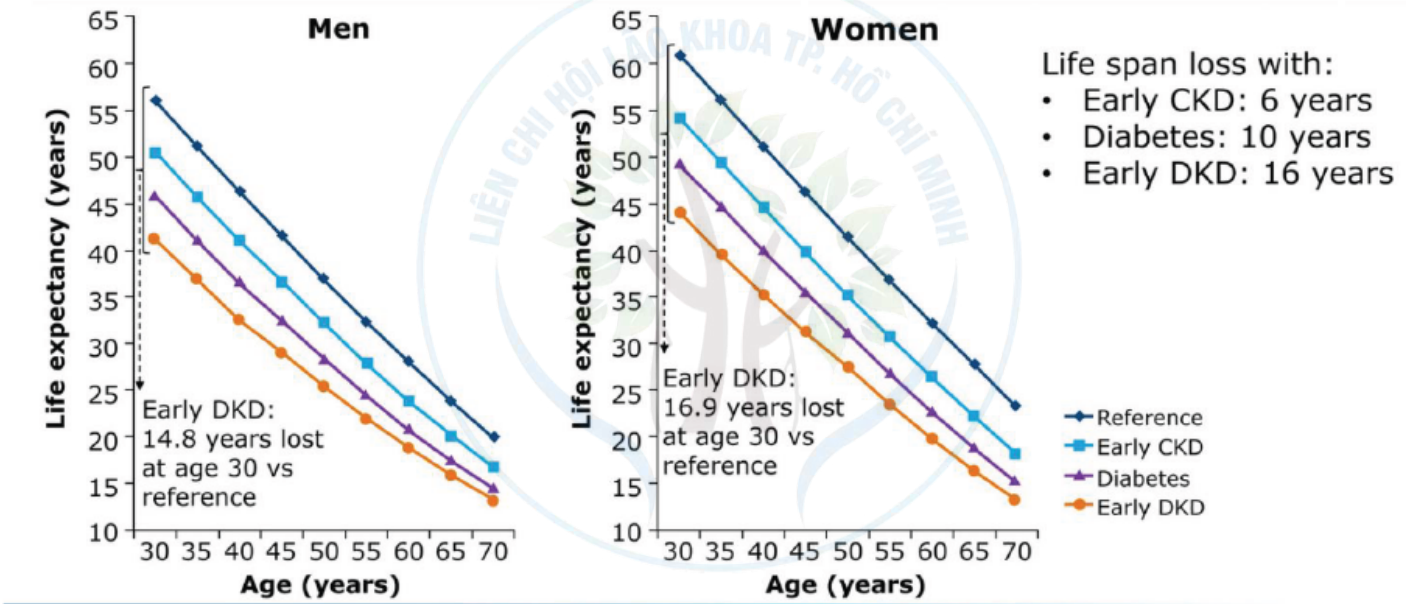
1. Trevisan R, *et al. J Am Soc Nephrol.* 2006;17:145–147. 2. Kazancioğlu R. *Kidney Int Suppl.* 2013;3(4):368–371. 3. National Kidney Foundation. Aging and Kidney Disease. Available at: https://www.kidney.org/news/monthly/wkd_aging. Accessed December 2021. 4. Jo W, *et al. PLoS One.* 2020;15:e0238111. 5. Menon V, *et al. Kidney International.* 2005;68:1413–1418. 6. Thomas M *et al. Nat Rev Nephrol.* 2016;12(2):73-81. 7. Jha V, *et al. Lancet.* 2013;382(9888):260–272. 8. Toth-Manikowski S & Atta MG. *J Diabetes Res.* 2015;697010. 9. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl.* 2013;3(1):1–150.

Sự hiện diện của BTM thường liên quan đến sự phát triển của các bệnh lý tim mạch gây tử vong ở BN cao tuổi

Bệnh nhân cao tuổi* có bệnh thận mạn có nguy cơ tử vong vì bệnh tim mạch **cao gấp 6 lần** so với nguy cơ tử vong do sự tiến triển đến bệnh thận giai đoạn cuối hoặc điều trị thay thế thận†

*≥65 years of age; †During 9.7 years of median follow-up
CKD, chronic kidney disease; CV, cardiovascular; ESKD, end-stage kidney disease; RRT, renal replacement therapy
Dalrymple L *et al. J Gen Intern Med* 2011;26:379

BN bệnh thận ĐTĐ giảm tuổi thọ trung bình 16 năm



Wen CP, et al. *Kidney Int.* 2017;92(2):388-396.

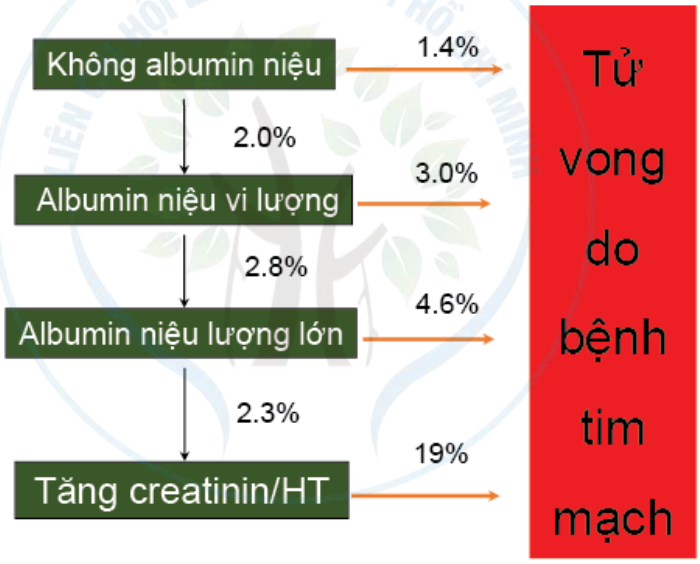
Diễn tiến tự nhiên bệnh thận ĐTĐ

Hyperfiltration	• Glomerular hyperfiltration and hypertrophy • Normoalbuminuria (<30 mg/g) • GFR increased
Silent	• Mild GBM thickening and focal mesangial sclerosis • Normoalbuminuria (<30 mg/g) • GFR normal
Incipient	• Mild to moderate GBM thickening and variable mesangial sclerosis • Moderately increased albuminuria (30–300 mg/g) • GFR normal or mildly decreased
Overt	• Marked GBM thickening and diffuse mesangial sclerosis (with or without nodules) • Severely increased albuminuria (>300 mg/g) • GFR decreased • Hypertension
ESRD	• Diffuse global glomerulosclerosis • Decreasing albuminuria • GFR < 15 ml/min • Hypertension

GBM: glomerular basement membrane
Kidney International (2016) 90, 24–26

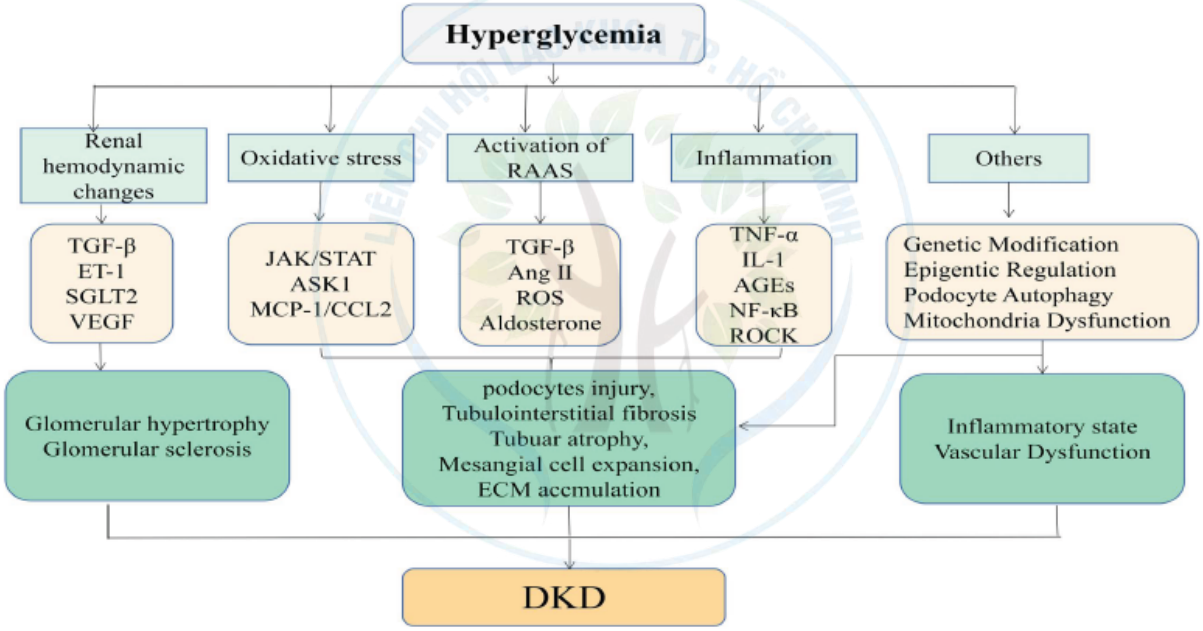
Bệnh nhân ĐTĐ có tiểu albumin có nhiều khả năng chết do bệnh tim mạch trước khi đến ESRD

Nghiên cứu UKPDS (United Kingdom Prospective Diabetes Study)
 # 5000 bệnh nhân ĐTĐ típ 2 mới chẩn đoán



Adler et al. *Kid Int*, 2003

Cơ chế bệnh sinh bệnh thận đái tháo đường



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Tầm soát bệnh thận mạn/BN đái tháo đường

Who and when to screen?

- **T1D** Yearly starting 5 years after diagnosis
- **T2D** Yearly starting at diagnosis

How to screen?

Spot urine ACR

and

eGFR

What to do with a positive result?

Repeat and confirm:
- Evaluate possible temporary or spurious causes
- Consider using cystatin C and creatinine to more precisely estimate GFR
- Only persistent abnormalities define CKD

Initiate evidence-based treatments

What defines CKD diagnosis?

Persistent urine ACR ≥30 mg/g

and/or

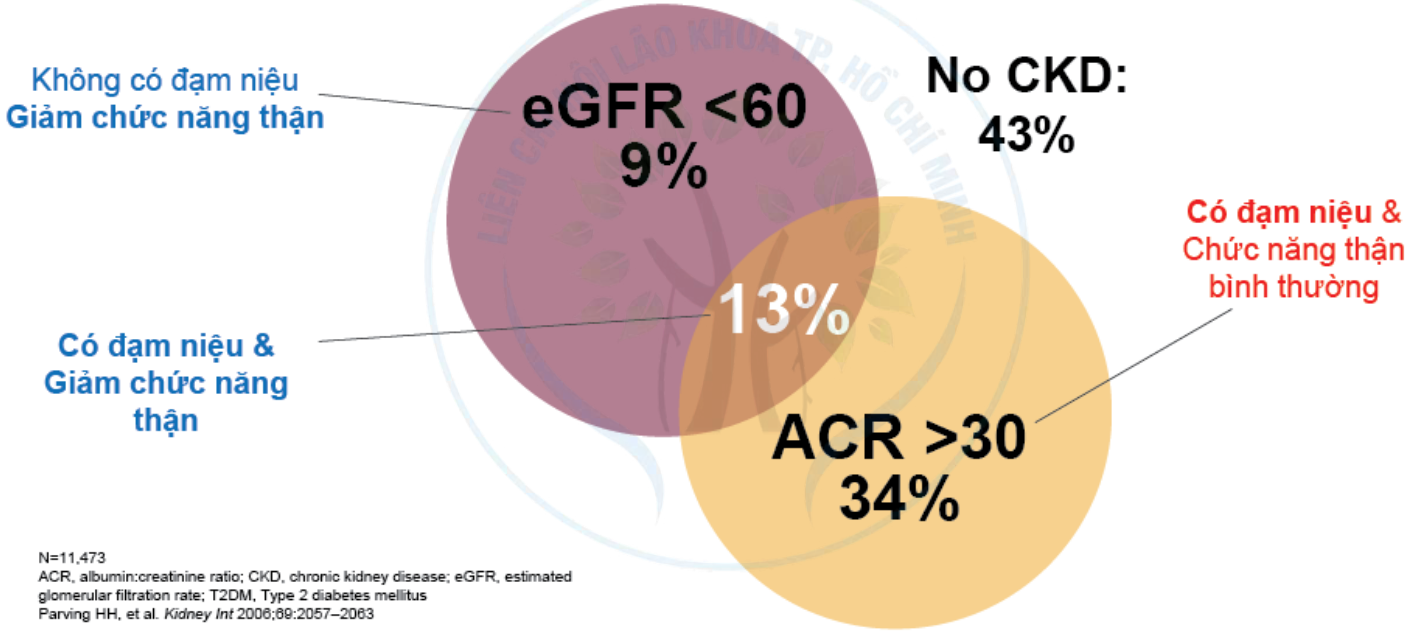
Persistent eGFR <60 mL/min/1.73 m^2

and/or

Other evidence of kidney damage

A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care. 2022 Oct 3:dci220027.

34% BN Đái tháo đường có đạm niệu mặc dù chức năng thận bình thường



N=11,473
ACR, albumin:creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; T2DM, Type 2 diabetes mellitus
Parving HH, et al. *Kidney Int* 2006;69:2057–2063

Nguy cơ diễn tiến bệnh thận mạn

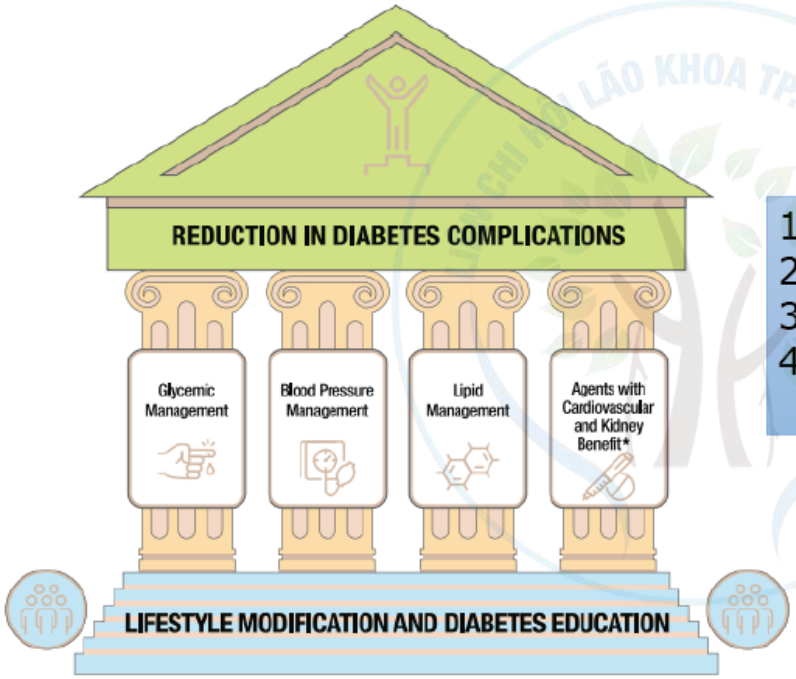
CKD is classified based on:
- **Cause (C)**
- **GFR (G)**
- **Albuminuria (A)**

GFR categories (mL/min/1.73 m²) Description and range				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat and refer 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15–29	Treat and refer* 3	Treat and refer* 3	Treat and refer 4+
	G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

- Low risk (if no other markers of kidney disease, no CKD)
- Moderately increased risk
- High risk
- Very high risk

A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care. 2022 Oct 3:dci220027.

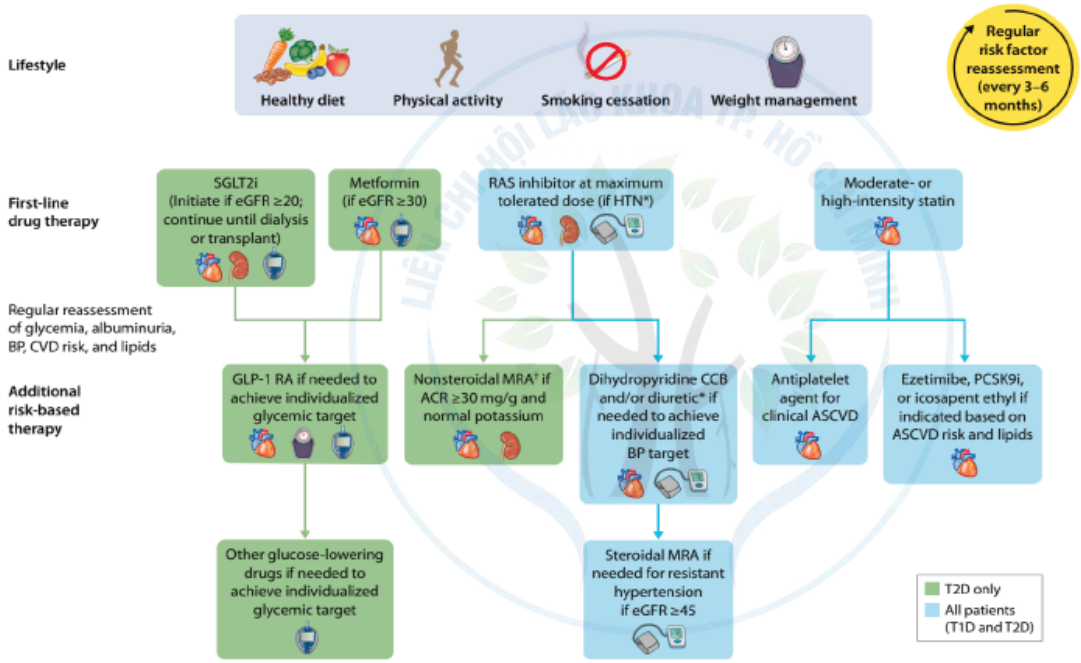
4 yếu tố chính giúp giảm biến chứng đái tháo đường



1. Kiểm soát **đường huyết**
2. Kiểm soát **huyết áp**
3. Kiểm soát **lipid máu**
4. Các **thuốc** có bằng chứng **lợi ích tim mạch và thận**

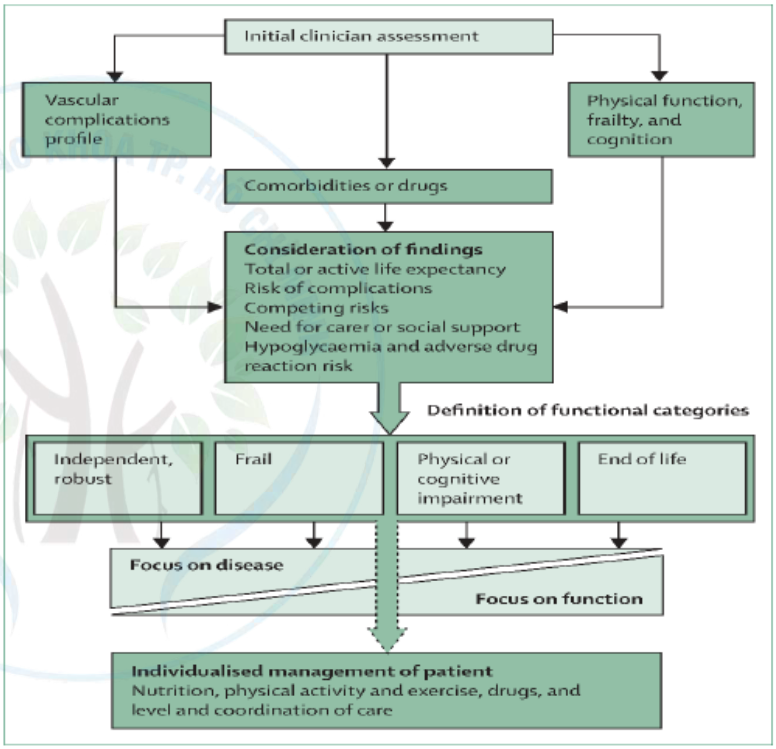
ADA. Diabetes Care 2022

Tiếp cận điều trị bệnh thận đái tháo đường



A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care. 2022 Oct 3:dci220027.

Quản lý ĐTĐ ở người cao tuổi cần đánh giá toàn diện và cá thể hóa điều trị

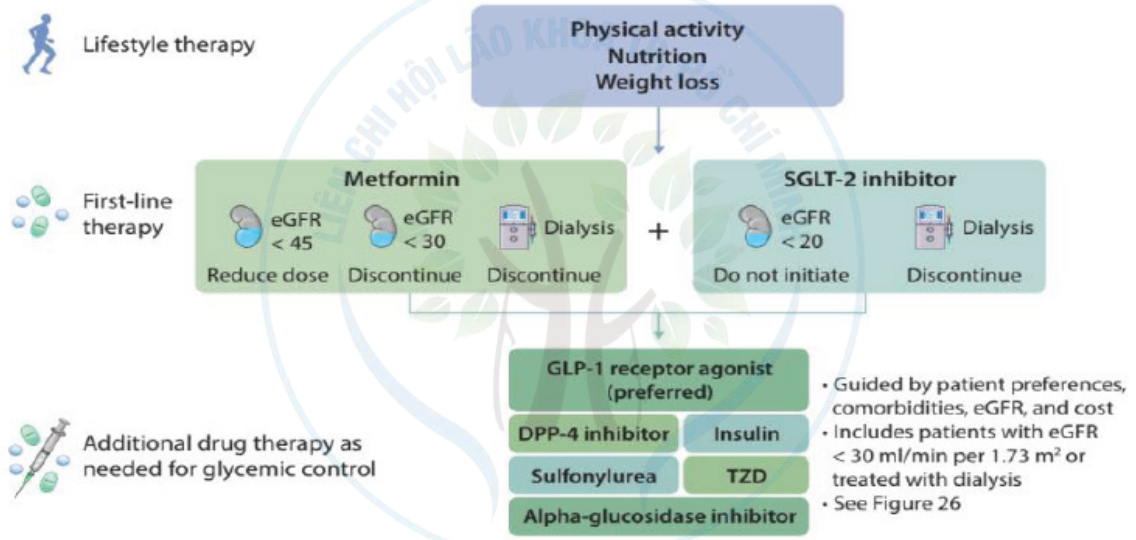


Lancet Diabetes Endocrinol 2015; 3: 275–85

ADA 2023: cá thể hóa mục tiêu điều trị đái tháo đường

Patient characteristics/ health status	Rationale	Reasonable A1C goal‡	Fasting or preprandial glucose	Bedtime glucose	Blood pressure	Lipids
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	<7.0–7.5% (53–58 mmol/mol)	80–130 mg/dL (4.4–7.2 mmol/L)	80–180 mg/dL (4.4–10.0 mmol/L)	<130/80 mmHg	Statin, unless contraindicated or not tolerated
Complex/intermediate (multiple coexisting chronic illnesses* or two or more instrumental ADL impairments or mild-to-moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	<8.0% (64 mmol/mol)	90–150 mg/dL (5.0–8.3 mmol/L)	100–180 mg/dL (5.6–10.0 mmol/L)	<130/80 mmHg	Statin, unless contraindicated or not tolerated
Very complex/poor health (LTC or end-stage chronic illnesses** or moderate-to-severe cognitive impairment or two or more ADL impairments)	Limited remaining life expectancy makes benefit uncertain	Avoid reliance on A1C; glucose control decisions should be based on avoiding hypoglycemia and symptomatic hyperglycemia	100–180 mg/dL (5.6–10.0 mmol/L)	110–200 mg/dL (6.1–11.1 mmol/L)	<140/90 mmHg	Consider likelihood of benefit with statin

Kiểm soát đường huyết / bệnh thận đái tháo đường



Kidney icon indicates estimated glomerular filtration rate (eGFR; ml/min per 1.73 m²); dialysis machine icon indicates dialysis. CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium–glucose cotransporter-2; T2D, type 2 diabetes; TZD, thiazolidinedione

KDIGO 2022

Lựa chọn thuốc điều trị ĐTĐ/bệnh thận mạn

	Progression of CKD	ASCVD	Heart failure	Glucose-lowering efficacy	Hypoglycemia risk	Weight effects	Cost
Metformin	Neutral	Potential benefit	Potential benefit	High	Low	Neutral	Low
SGLT2 inhibitors	Benefit[a]	Benefit[c]	Benefit	Intermediate	Low	Loss	High
GLP-1 receptor agonists	Benefit[b]	Benefit[c]	Potential benefit	High	Low	Loss	High
DPP-4 inhibitors	Neutral	Neutral	Potential risk[d] (saxagliptin)	Intermediate	Low	Neutral	High
Insulin	Neutral	Neutral	Neutral	Highest	High	Gain	High (analogs) Low (human)
Sulfonylureas	Neutral	Neutral	Neutral	High	High	Gain	Low
Thiazolidinediones	Neutral	Potential benefit (pioglitazone)	Increased risk	High	Low	Gain	Low
α-Glucosidase inhibitors	Neutral	Neutral	Neutral	Intermediate	Low	Neutral	Low

Neutral
Potential benefit or intermediate glucose-lowering efficacy
Benefit (organ protection, high efficacy, low hypoglycemia risk, weight loss, or low cost)
Potential risk or high cost to patient
Increased risk for adverse effects

A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care. 2022 Oct 3:dci220027.

	Stage 3b (eGFR 30–44 mL/min/1.73 m²)	Stage 4 (eGFR 15–29 mL/min/1.73 m²)	Stage 5 (eGFR <15 mL/min/1.73 m²)
Metformin	Reduce dose to 1000 mg/day	Contraindicated	
Insulin	Initiate and titrate conservatively to avoid hypoglycemia		
SGLT2 inhibitors*			
Canagliflozin	Maximum 100 mg daily	Initiation not recommended; may continue 100 mg daily if tolerated for kidney and CV benefit until dialysis	
Dapagliflozin	10 mg daily†	Initiation not recommended with eGFR <25 mL/min/1.73 m²; may continue if tolerated for kidney and CV benefit until dialysis	
Empagliflozin	10 mg daily‡		Initiation not recommended with eGFR <20 mL/min/1.73 m²; may continue if tolerated for kidney and CV benefit until dialysis
Ertugliflozin	Use not recommended with eGFR <45 mL/min/1.73 m²		
GLP-1 receptor agonists§			
Exenatide	Caution initiating or increasing dose; avoid once-weekly formulation	Use not recommended	
Dulaglutide	No dose adjustment required		
Liraglutide	No dose adjustment required		
Lixisenatide	No dose adjustment required		Use not recommended
Semaglutide	No dose adjustment required		

	Stage 3b (eGFR 30–44 mL/min/1.73 m²)	Stage 4 (eGFR 15–29 mL/min/1.73 m²)	Stage 5 (eGFR <15 mL/min/1.73 m²)
DPP-4 inhibitors			
Alogliptin	Maximum 12.5 mg daily	Maximum 6.25 mg daily	
Linagliptin	No dose adjustment required		
Saxagliptin	Maximum 2.5 mg daily		
Sitagliptin	Maximum 50 mg daily	Maximum 25 mg once daily	
Sulfonylureas (2nd generation)			
Glimepiride	Initiate conservatively at 1 mg daily and titrate slowly to avoid hypoglycemia		
Glipizide	Initiate conservatively (e.g., 2.5 mg once daily) and titrate slowly to avoid hypoglycemia		
Glyburide	Use not recommended		
Thiazolidinediones			
Pioglitazone	No dose adjustment required		
α-Glucosidase inhibitors			
Acarbose	No dose adjustment required	Use not recommended	
Miglitol	No dose adjustment required	Use not recommended	

A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving GlobalOu tcomes (KDIGO) 2022

Hiệu quả bảo vệ thận của ức chế SGLT2

SGLT-2 inhibitor	Study	State/disease	Main kidney outcomes	Ref.
Canagliflozin	CREDENCE	RCT (Phase 3) Diabetes Mellitus, Type 2 Diabetic Nephropathy	Compared with placebo, canagliflozin lowered UACR by 31% (95% confidence interval [95% CI], 27–36%) at week 26	NCT02065791 [82]
	CANVAS	RCT (Phase 3) Diabetes Mellitus, Type 2 Cardiovascular Diseases Risk Factors	The composite outcome of sustained doubling of serum creatinine, ESRD, and death from renal causes occurred less frequently in the canagliflozin group compared with the placebo group (1.5 per 1000 patient-years in the canagliflozin group vs 2.8 per 1000 patient-years in the placebo group; hazard ratio 0.53, 95% CI 0.33–0.84)	NCT01032629 NCT01989754 [73,81]
Empagliflozin	EMPA-REG OUTCOME	RCT (Phase 3) Diabetes Mellitus, Type 2	39% relative risk reduction for incident or worsening nephropathy; 38% relative risk reduction for progression to albuminuria; 44% relative risk reduction of doubling of serum creatinine	NCT01131676 [72,83]
	EMPA-KIDNEY	RCT (Phase 3) Chronic Kidney Disease	Results pending: Kidney disease progression (ESRD, sustained decline in eGFR to □10 mL/min/1.73 m^2, kidney death, or a sustained decline of ≥ 40% in eGFR from randomization)	NCT03594110 [85]
Dapagliflozin	DECLARE-TIMI 58	RCT (Phase 3) Diabetes Mellitus, Non-Insulin-Dependent High Risk for Cardiovascular Event	The renal-specific outcome was reduced with dapagliflozin versus placebo in the overall cohort (HR [95%CI] 0.53[0.43–0.66])	NCT01730534 [86]
	PADA-CKD	RCT (Phase 3) Chronic Kidney Disease	Mean rates of eGFR decline with dapagliflozin and placebo were −3.5 and −4.7 mL/min/1.73 m^2/year, respectively. Dapagliflozin reduced the urinary albumin-to-creatinine ratio by 26% relative to placebo.	NCT03036150 [87–89]

Abbreviation: SGLT-2, sodium-glucose cotransporter 2; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; CANVAS, Canagliflozin Cardiovascular Assessment Study; EMPA-REG OUTCOME, Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes; EMPA-KIDNEY, The Study of Heart and Kidney Protection With Empagliflozin; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58; PADA-CKD, A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease; RCT, randomized controlled trials.

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Hiệu quả bảo vệ thận của GLP-1a

Molecular targets	Drug	Situation	Recent clinical trials	Effect on renal outcomes	Ref.
Enhancing GLP-1 expression	Liraglutide	FDA:2010	LEADER	Lower rates of progression and development of DKD	[94,95]
	Lixisenatide	FDA:2016	ELIXA	Slow down the progression of UACR and reduced albuminuria	[NCT01147250], [97,98]
	Dulaglutide	FDA:2014	REWIND	Reduced albuminuria and the decline of eGFR	[99]
Inhibiting DPP-4	Linagliptin	FDA:2011	MARLINA-T2D™	Improved blood glucose control and reduced albuminuria	[111–113]
	Saxagliptin	FDA:2009	SAVOR-TIMI 53	Improved UACR	[114]
	Sitagliptin	FDA:2006	TECOS	Reduced albuminuria	[115,116]

Abbreviation: GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; FDA, food and drug administration; LEADER, Liraglutide Effect and Action in Diabetes; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; REWIND, Dulaglutide and cardiovascular outcomes in type 2 diabetes; MARLINA-T2D™, Modification of Albuminuria in Type 2 Diabetes Subjects with Renal Disease with Linagliptin; SAVOR-TIMI 53, saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; DKD, diabetic kidney disease; UACR, urinary albumin/creatinine ratio; eGFR, estimated glomerular filtration rate.

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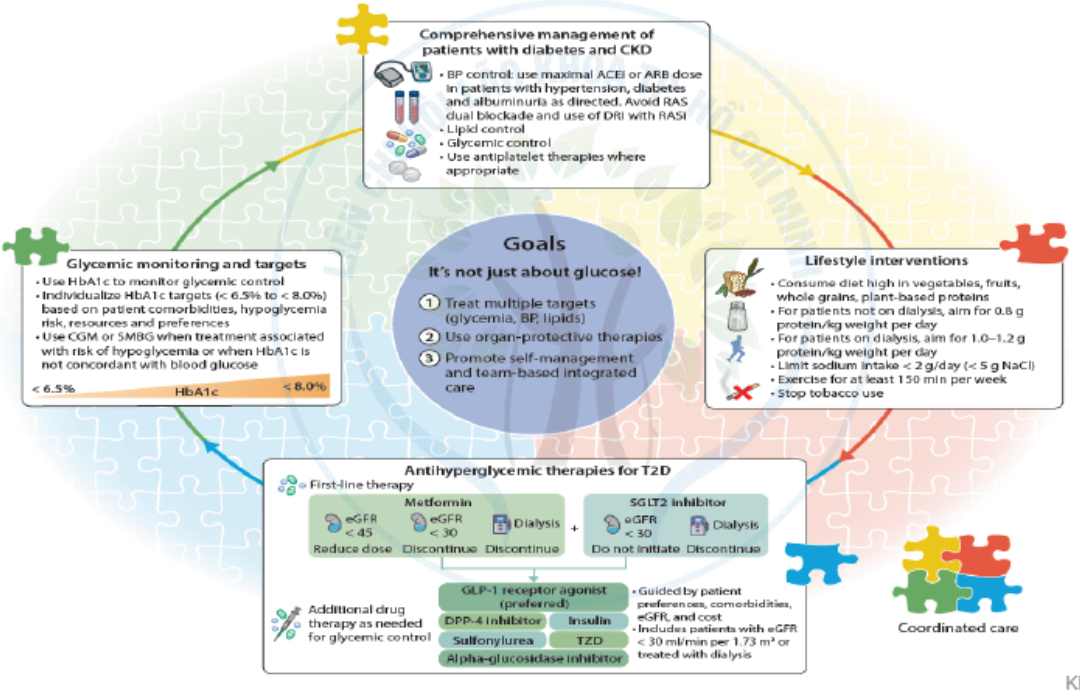
Chiến lược điều trị bệnh thận đái tháo đường



KẾT LUẬN

- ĐTĐ là nguyên nhân hàng đầu của bệnh thận mạn. Bệnh thận ĐTĐ là nguyên nhân chính gây ESRD, làm tăng nguy cơ bệnh lý TM và tử vong.
- Đánh giá toàn diện và cá thể hóa điều trị ở BN ĐTĐ cao tuổi.
- **Albumin niệu** là chỉ dấu để phát hiện sớm và chính xác biến chứng thận, cần được theo dõi định kỳ trên tất cả BN ĐTĐ.
- Điều trị bệnh thận mạn/ĐTĐ kinh điển: phối hợp đa chuyên khoa, thay đổi lối sống, can thiệp đa yếu tố, sử dụng thuốc ức chế RAAS.
- Điều trị bệnh thận mạn/ĐTĐ có nhiều cập nhật mới với vai trò bảo vệ thận của các nhóm thuốc mới SGLT2i, GLP-1a.


THANK YOU
FOR YOUR ATTENTION