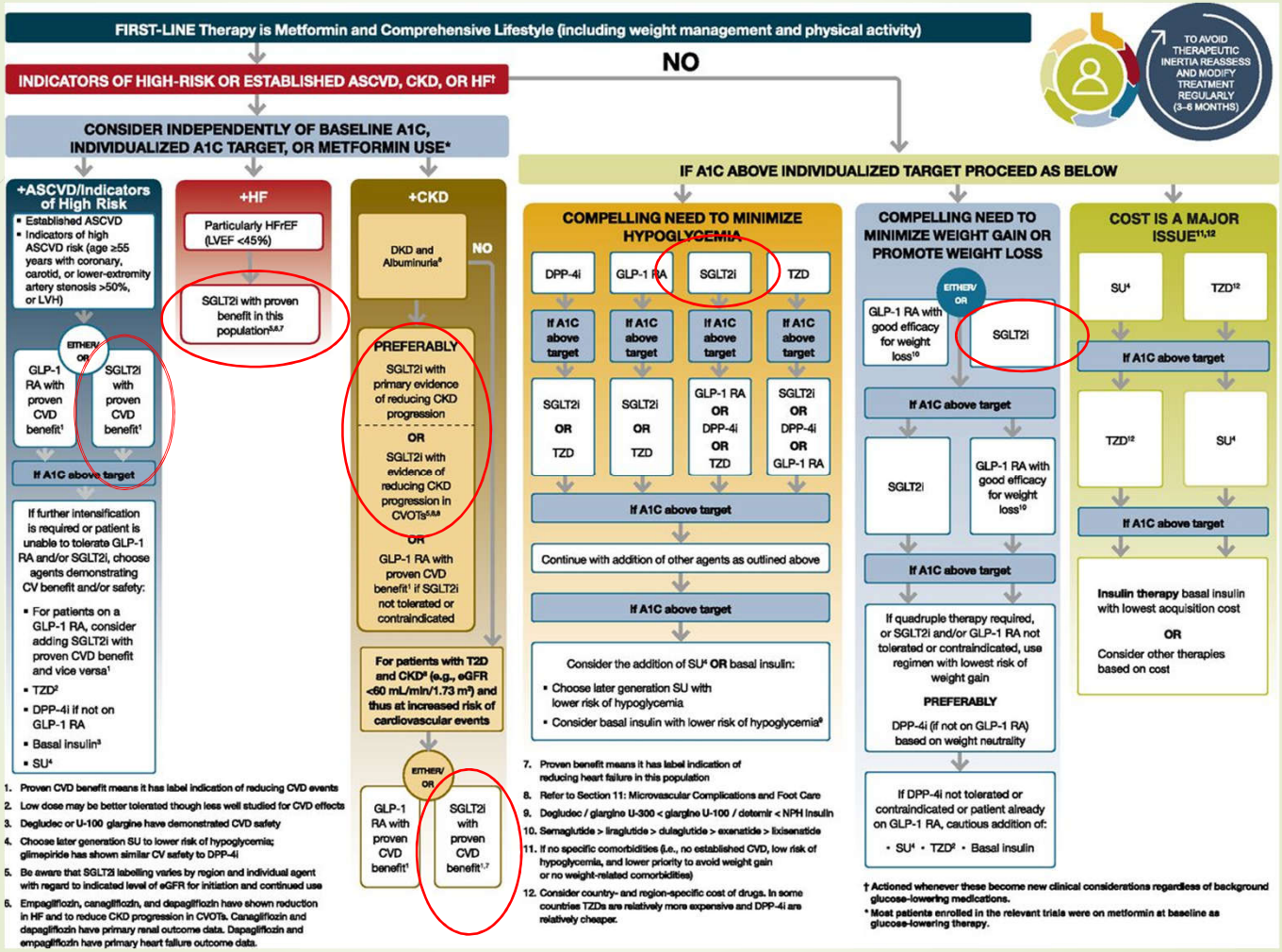
SGLT2-i

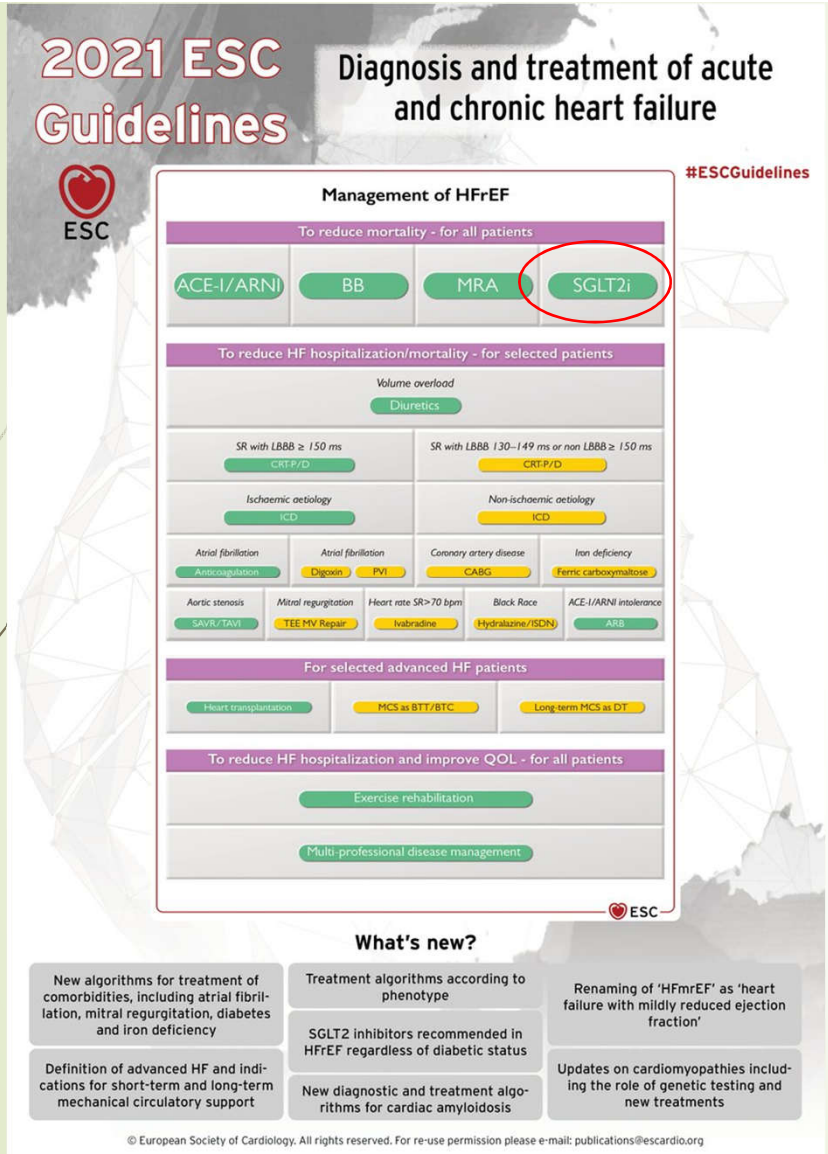
Bs Trương Đoàn Chí Trung
PK Thận nội
Khu Dịch vụ ban ngày - DS3

Vậy SGLT2-i là gì?

- SGLT2 : Sodium glucose co-transforter channel .
- SGLT2-i : nhóm thuốc ức chế kênh SGLT2
- Tại sao tìm hiểu nó?

Guideline : ADA 2021





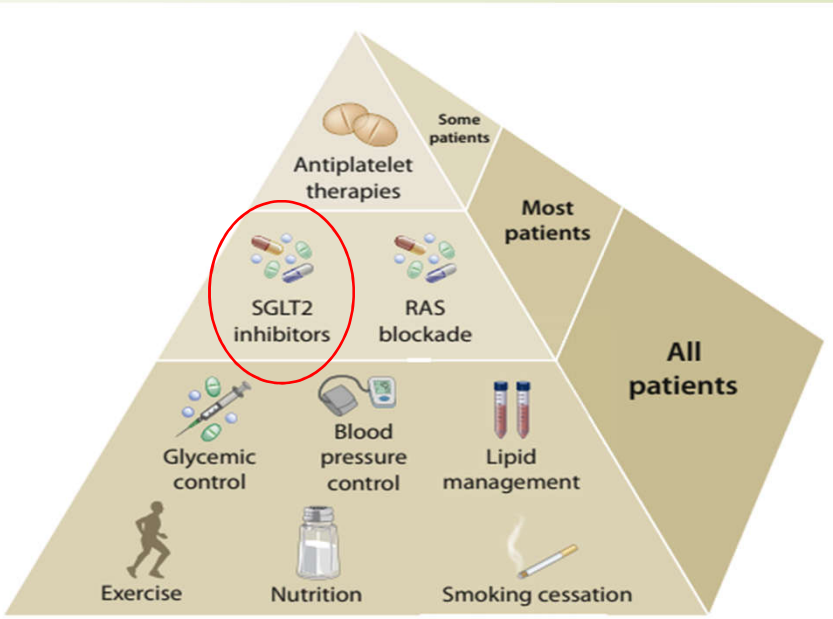
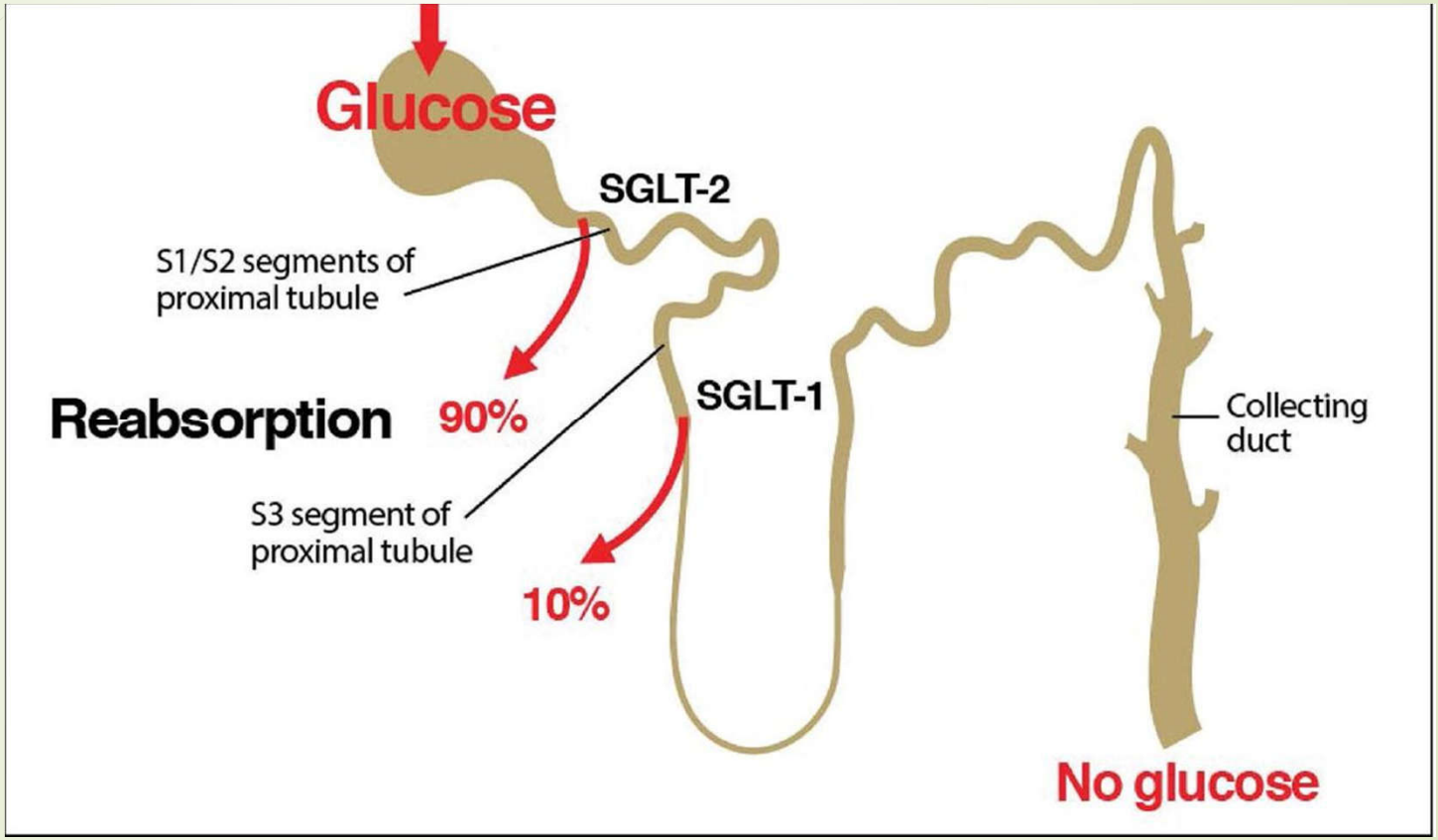


Figure 2 | Kidney–heart risk factor management. Glycemic control is based on insulin for type 1 diabetes and a combination of metformin and SGLT2 inhibitors (SGLT2i) for type 2 diabetes, when eGFR is ≥30 ml/min per 1.73 m^2. SGLT2i are recommended for patients with type 2 diabetes and chronic kidney disease (CKD). Renin–angiotensin system (RAS) inhibition is recommended for patients with albuminuria and hypertension. Aspirin generally should be used lifelong for secondary prevention among those with established cardiovascular disease and may be considered for primary prevention among high-risk individuals, with dual antiplatelet therapy used in patients after acute coronary syndrome or percutaneous coronary intervention. RAS, renin-angiotensin system; SGLT2, sodium–glucose cotransporter-2.

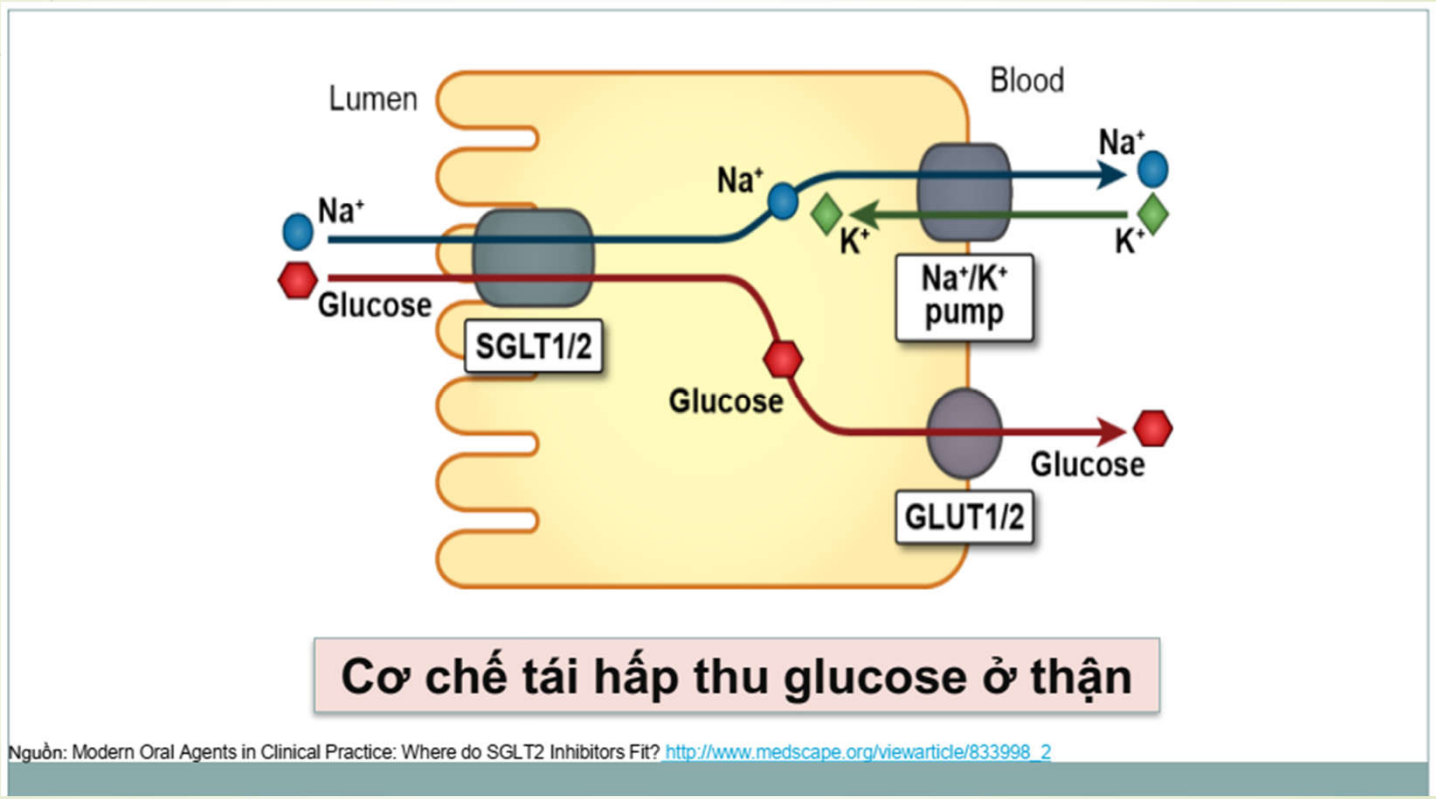
KDIGO -2020

Vị trí kênh SGLT1 và SGLT2 :



https://clinical.diabetesjournals.org/content/32/1/4

Chức năng kênh SGLT1/2

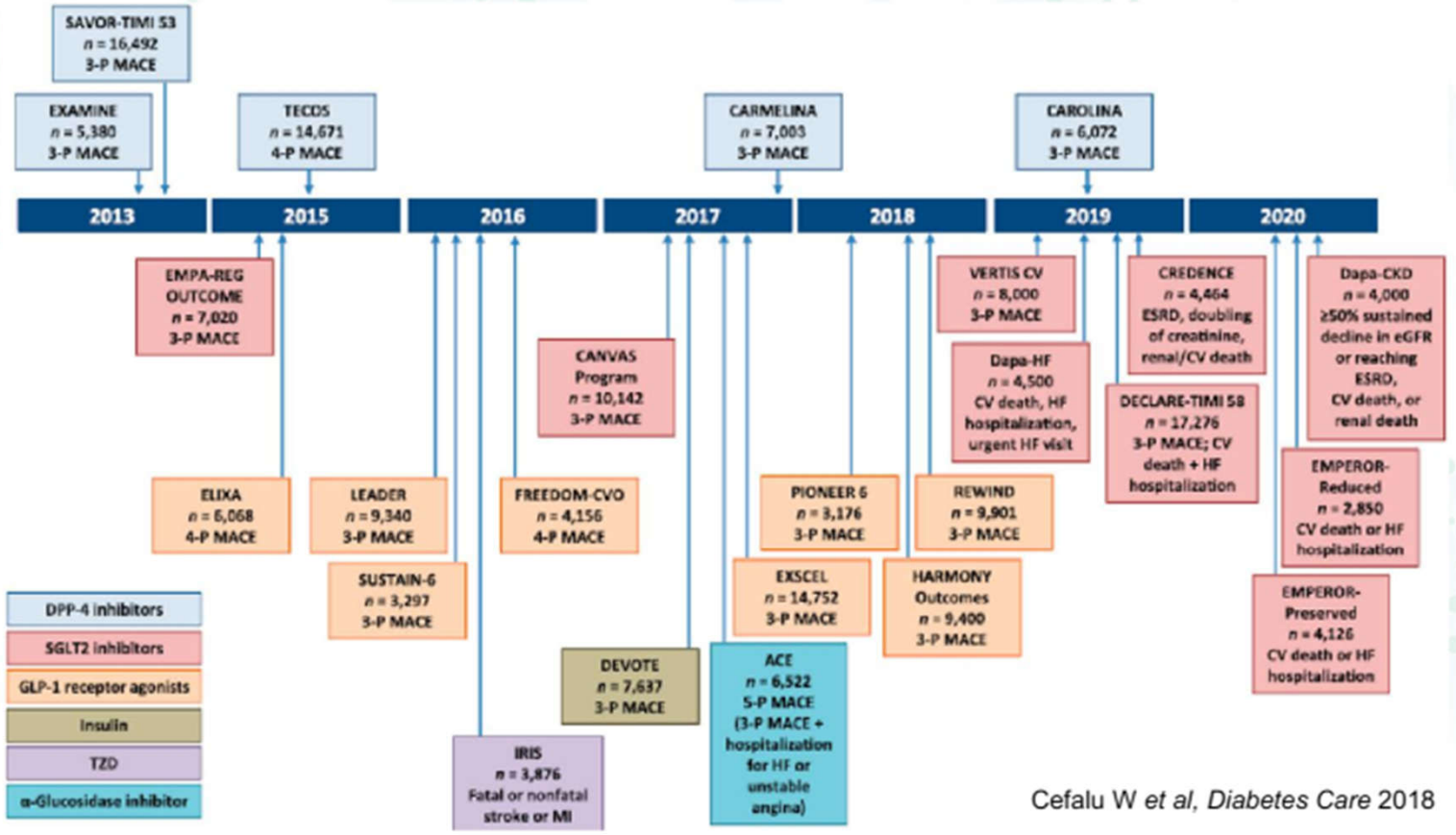


Từ Phlorizin đến nhóm thuốc SGLT2-i

- 1835 : Phlorizin được tìm thấy vỏ rễ cây táo.
- 1886: dùng Phlorizin bài tiết glucose đường niệu.
- 1950s: Phlorizin ức chế tái hấp thu glucose ống thận
- 1999: điều chế các analogue
- 2012 : SGLT2-i Dapagliflozin chấp thuận dùng trên người.

- *Ghi chú : 2008 FDA có CVOTs (cardiovascular outcome trials)- không tăng nguy cơ MI, stroke , CV death*

CLINICAL TRIALS OF NEW DIABETES DRUGS



Cefalu W *et al*, *Diabetes Care* 2018

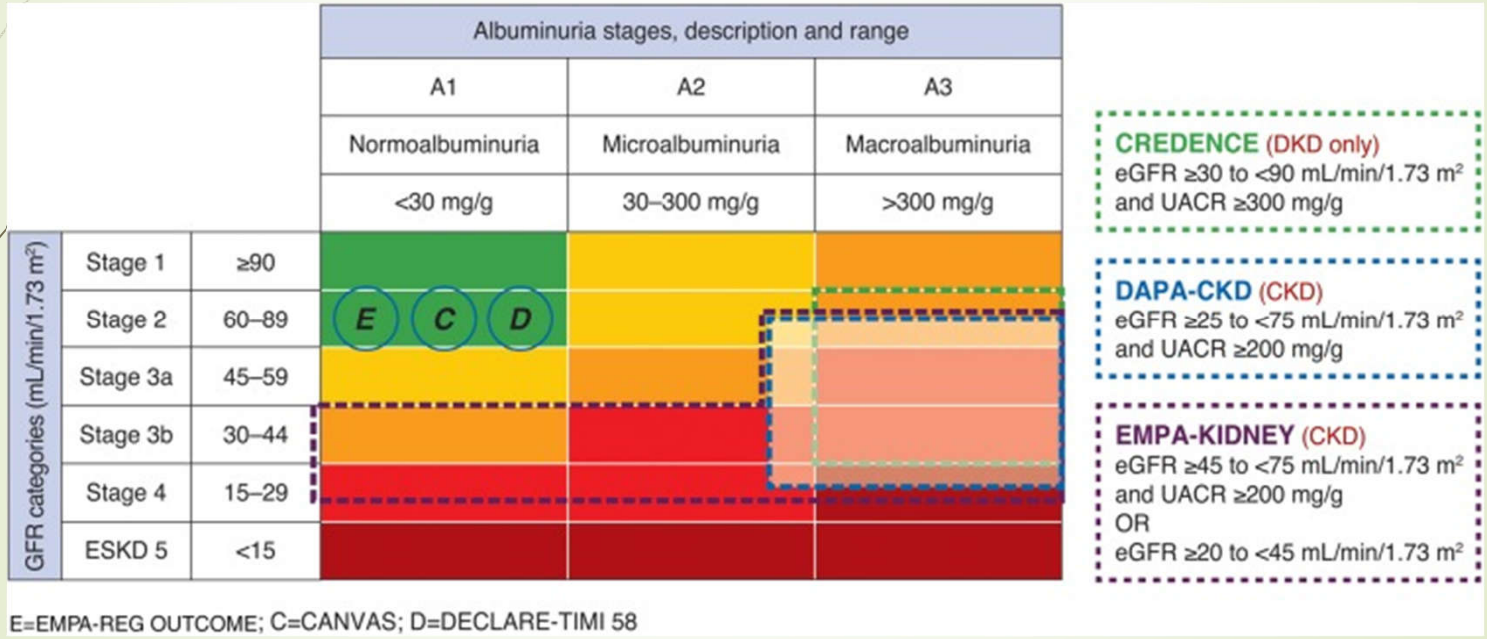
Thử nghiệm và khuyến cáo lợi ích SGLT2

Tên thử nghiệm	Cở mẫu	Đối tượng	Thời gian	Kết luận
EMPA-REG OUTCOME (Empagliflozin) (3-P MACE)	N=7020	-ĐTĐ (A1C=7-9%) -all CVD -Chức năng thận bình thường	Bắt đầu 2010 Báo cáo 09/2015	- AN TOÀN TIM MẠCH - Giảm tỉ lệ tử vong chung : 32% - Giảm ti lệ tử vong tim mạch : 38% -Giảm nguy cơ nhập viện vì suy tim : 35%
DECLARE-TIMI 58 (Dapagliflozin) (3-P MACE CV DEATH HF hospitalization)	N=17.276	-ĐTĐ -41% CVD -chức năng thận bình thường	Bắt đầu 2013 Báo cáo 11/2018 *Báo cáo 2019*	An toàn tim mạch -Giảm ti lệ tử vong tim mạch -Giảm nguy cơ nhập viện vì suy tim -Không giảm tỉ lệ MACE
CANVAS program (Canagliflozin) (3-P MACE)	N=10.142	-ĐTĐ -66% CVD -chức năng thận bình thường .	Bắt đầu : 2009 Báo cáo 06/2017	-An toàn tim mạch -giảm nguy cơ tử vong tim mạch ,nhồi máu cơ tim , đột quị không tử vong -giảm nguy cơ nhập viện vì suy tim . - Tăng nguy cơ đoan cắt cụt chi

Thử nghiệm lợi ích suy tim - SGLT2

TÊN THỬ NGHIỆM	CỠ MẪU	THỜI GIAN	Đối tượng	Kết luận
EMPEROR-reduced (Empaglifozin) Cv death HF hospitalization	N=2850	08/2020	Bn suy tim PSTM giảm (PSTM ≤40%), Có hay không đtđ	Empagliflozin significaly reduced the primary endpoint (CV death and HHF)
EMPAROR-Preserved (Empagliflozin)	N=5988	08/ 2021	LV-EF >40%, NYHA II-IV CÓ HAY KHÔNG DTD	Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes.
DAPA-HF (Dapagliflozin)	N=4500	11/2019	Bn suy tim PSTM≤40%,NYHA II-IV 58% không đtđ	Dapagliflozin reduced the primary endpoint (CV death and HHF)

Trong các nghiên cứu có bệnh lý thận



E=EMPA-REG OUTCOME; C=CANVAS; D=DECLARE-TIMI 58

CREDENCE: Canagliflozin and renal outcomes in type 2 diabetes and nephropathy

The George Institute for Global Health

Study design and participants

4401 patients with T2DM & UACR >300 mg/g

62 years

eGFR 57

UACR 927 mg/g

Intervention

Stable on maximum dose tolerated ACEi or ARB for 4 weeks

Canagliflozin **Placebo**

Outcomes

Primary outcome
(Doubling of serum creatinine, ESKD, death due to cardiovascular or kidney disease)

HR 0.70
(95% CI 0.59-0.82)

NNT 21

End-stage kidney disease

HR 0.68
(95% CI 0.54-0.86)

NNT 42

No increased risk of:

Amputations

HR 1.10
(95% CI 0.79-1.56)

Fractures

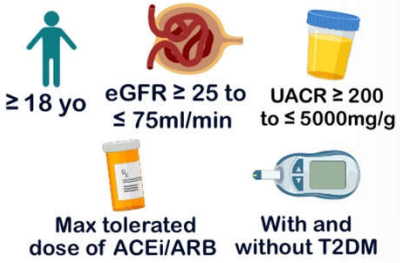
HR 0.98
(95% CI 0.70-1.37)

Conclusion

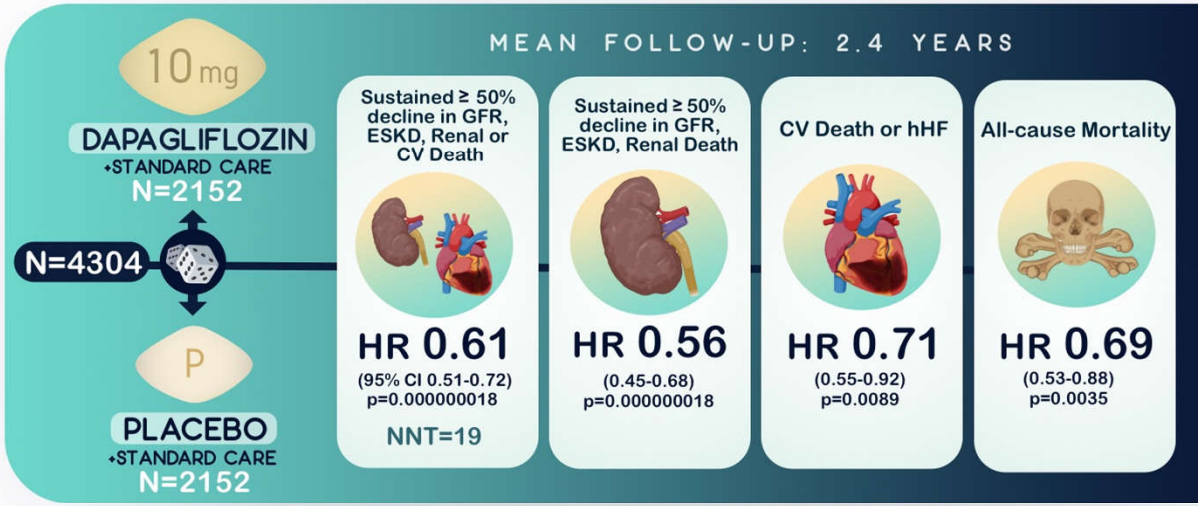
In patients with type 2 diabetes and kidney disease, canagliflozin reduces the risk of kidney failure and cardiovascular events

Does Dapagliflozin compared to placebo reduce the risk of kidney failure and CV events in CKD patients with and without T2DM?

DAPA-CKD



Mean Age 62y, 67% ♂
eGFR 43ml/min
UACR 950mg/g
ACEi/ARB 97%
With T2DM 68%



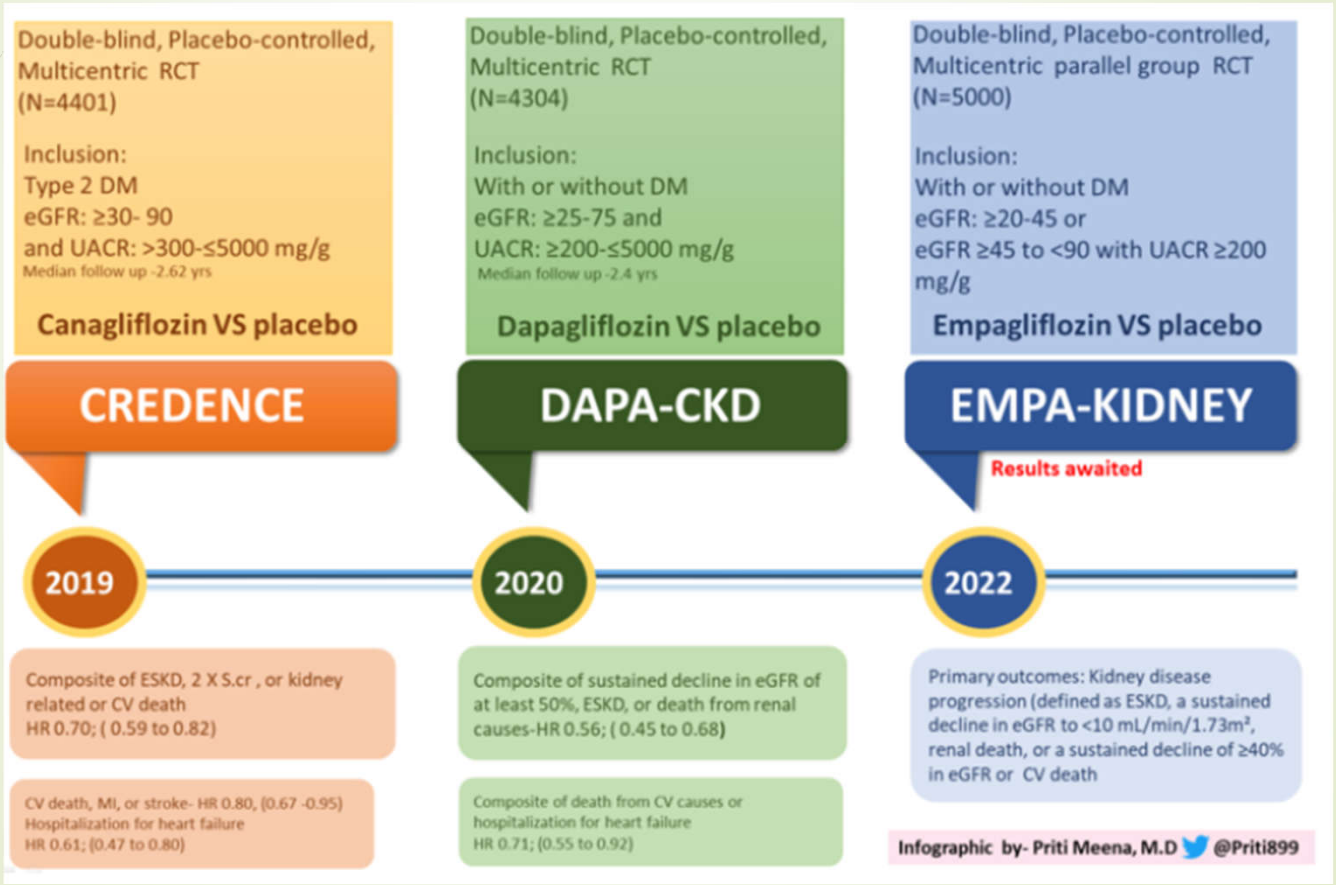
Results are consistent with patients with and without T2DM
% of patients who discontinued the drug or who experienced SAE was similar in both groups
DKA, 2 in placebo group vs none in Dapagliflozin group
No DKA or severe hypoglycemia in patients without T2DM

CONCLUSION: Dapagliflozin significantly reduces the risk of kidney failure, CV death or hospitalization for HF and all-cause mortality in patients with CKD with and without T2DM compared to placebo. Dapagliflozin was well-tolerated, in keeping with its established safety profile.

DAPA-CKD
presented by Professor Heerspink at the ESC Congress
August 30, 2020

Visual Abstract by: Ana Naidas, MD

Nghiên cứu ích lợi trên thận SGLT2-i

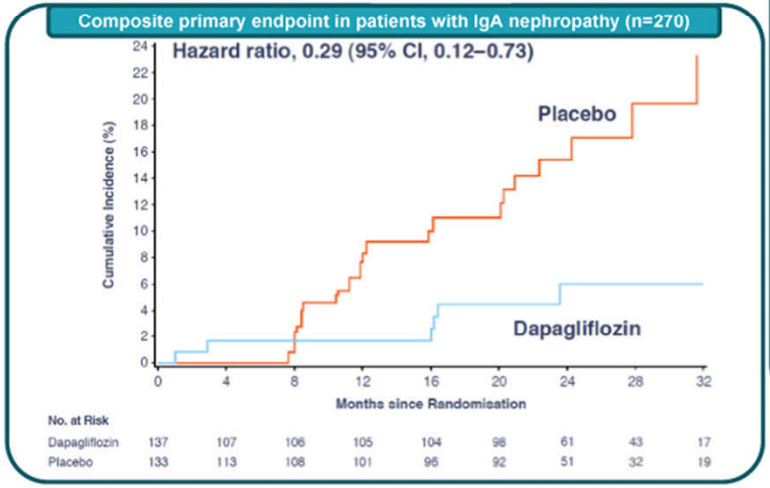


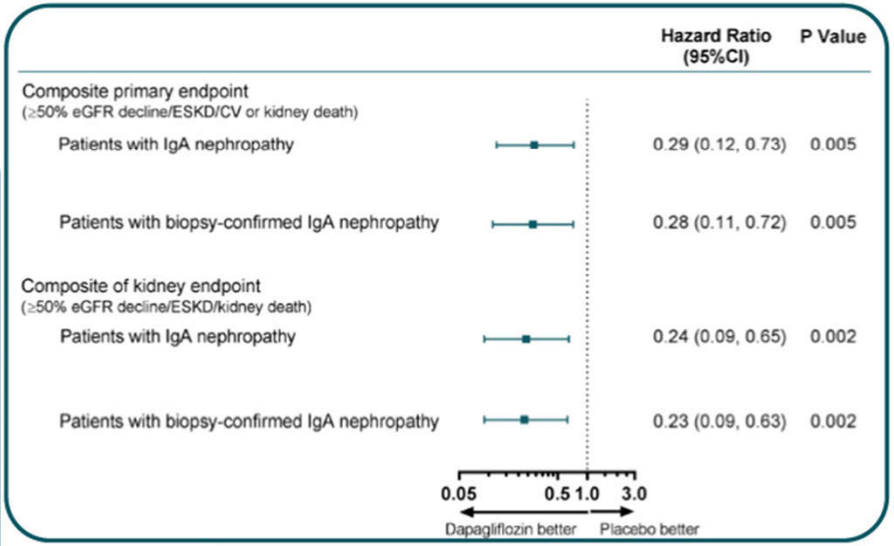
A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy.

DAPA-CKD population:

- eGFR 25-75 mL/min/1.73m^2
- UACR 200-5000 mg/g
- Receiving a stable, maximally tolerable ACEi/ARB dose
- With and without type 2 diabetes

⇨ **270 participants with IgA nephropathy** ⇨ **254 participants with biopsy-confirmed IgA nephropathy**





IgA, immunoglobulin A; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; ESKD, end-stage kidney disease

kidney INTERNATIONAL ISN

Wheeler et al, 2021

CONCLUSION:

In patients with IgA nephropathy, when added to ACEi/ARB therapy, dapagliflozin significantly and substantially reduced the risk of CKD progression

Những lợi ích khác

- Cân nặng
- Hạ huyết áp
- Tăng HDL, giảm LDL và Triglyceride
- Fatty liver (NAFLD, NASH)

Theo nội tiết học căn bản – Ts Trần Quang Nam 2020; trang58-59

The impact of sodium glucose co-transporter 2 inhibitors on non-alcoholic fatty liver disease

Lampros Chrysavgis [1], Alkistis-Maria Papatheodoridi [1], Antonios Chatzigeorgiou [1 2], Evangelos Cholongitas [3]

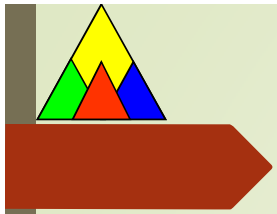
Affiliations + expand

PMID: 33439540 DOI: 10.1111/jgh.15202

Abstract

Affecting one fourth of the global population, non-alcoholic fatty liver disease (NAFLD) is the commonest chronic liver disorder. It encompasses the simple liver fat accumulation to more progressive steatosis, inflammation, and fibrosis characterized as non-alcoholic steatohepatitis (NASH) and in some cases cirrhosis and hepatocellular carcinoma. NAFLD regularly coexists with metabolic disorders, such as obesity and mostly type 2 diabetes mellitus (T2DM). A relatively new class of antidiabetic drugs, the sodium glucose co-transporter 2 (SGLT2) inhibitors exert their action by increasing the urinary glucose and calorie excretion leading to ameliorated plasma glucose levels and lower bodyweight. Recently, several animal studies and human clinical trial have emphasized the possible beneficial impact of SGLT2 inhibitors on NAFLD and its progression to NASH. In this present review, we summarize the current literature regarding the efficacy of the aforementioned category of drugs on anthropometric, laboratory, and histological features of patients with NAFLD. Conclusively, as SGLT2 inhibitors seem to be an appealing therapeutic opportunity for NAFLD management, we identify the open issues and questions to be addressed in order to clarify the impact in choosing antidiabetic medication to treat NAFLD patients associated with T2DM.

Keywords: hepatic steatosis; liver enzymes; non-alcoholic fatty liver disease; sodium glucose co-transporter 2 inhibitors; type 2 diabetes mellitus.



Meta-Analysis > Front Endocrinol (Lausanne). 2021 Feb 11;11:609135.
doi: 10.3389/fendo.2020.609135. eCollection 2020.

Sodium-Glucose Co-Transporter 2 Inhibitors for Non-Alcoholic Fatty Liver Disease in Asian Patients With Type 2 Diabetes: A Meta-Analysis

Chloe Wong [1], Clyve Yu Leon Yaow [1], Cheng Han Ng [1], Yip Han Chin [1], Yi Fen Low [1], Amanda Yuan Ling Lim [1 2], Mark Dhinesh Muthiah [1 2 3], Chin Meng Khoo [1 2]

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PMID: 33643221 PMCID: PMC7905212 DOI: 10.3389/fendo.2020.609135
Free PMC article

Abstract

Objective: Non-alcoholic fatty liver disease (NAFLD) is a very common disorder among patients with type 2 diabetes and may share causal relationship. Type 2 diabetes is a risk factor for progression and potential poor outcomes in NAFLD patients. This meta-analysis aimed to analyze the current evidence of sodium-glucose co-transporter-2 inhibitors (SGLT2i), a glucose-lowering drug to improve NAFLD in patients with Type 2 Diabetes.

Methods: Medline, Embase and Cochrane Central Register of Controlled Trials were searched for articles examining efficacy of SGLT2i on treatments of NAFLD in type 2 diabetes in July 2020, and articles were sieved. Continuous data were extracted in the form of mean and standard deviation and were pooled with standardized mean difference (SMD).

Results: 10 articles involving 555 patients from seven randomized controlled trials (RCTs) and three cohort studies, were included in this meta-analysis. Our analysis revealed significant improvements in hepatic fat content (after treatment: -0.789 (-1.404 to -0.175), p = 0.012; compared with control: -0.923 (-1.562 to -0.285), p = 0.005), AST (After Treatment: -0.539 (-0.720 to -0.357), p < 0.001; compared with control: -0.421 (-0.680 to -0.161), p = 0.001), ALT (after treatment: -0.633 (-0.892 to -0.373), p < 0.001; compared with Control: -0.468 (-0.685 to -0.251), p < 0.001), body composition (BMI: after treatment: -0.225 (-0.456 to 0.005), p = 0.055; compared with Control: -1.092 (-2.032 to -0.153), p = 0.023), glycemic control (HbA1c: After Treatment: -0.701 (-1.098 to -0.303), p = 0.001; compared with control: -0.210 (-0.603 to 0.183), p = 0.295), lipid parameters (Triglycerides: after treatment: -0.230 (-0.409 to -0.052), p = 0.011; compared with control: -0.336 (-0.597 to -0.076), p = 0.011), inflammatory markers (serum ferritin: after treatment: -0.409 (-0.694 to -0.124), p = 0.005; compared with control: -0.814 (-1.688 to 0.059), p = 0.068) after SGLT2i treatment, and when compared against controls. There was a trend in the improvement in fibrosis markers after SGLT2i treatment.

Conclusions: SGLT2i is an effective treatment to improve NAFLD among patients with type 2 diabetes. Further studies are needed to understand the direct and indirect effects of SGLT2i on NAFLD and if SGLT2i could prevent the progression of NAFLD or NASH. SGLT2i could potentially be considered for patients with type 2 diabetes and NAFLD, if there are no contraindications.

Keywords: hepatic fat; meta-analysis; non-alcoholic fatty liver disease; sodium-glucose co-transporter-2 inhibitors; type 2 diabetes.

Nguy cơ khi dùng SGLT2-i

- Nhiễm trùng niệu –sinh dục ; hoại thư Founier
- Giảm thể tích tuần hoàn : hạ huyết áp tư thế , nguy cơ AKI
- Tăng nguy cơ gãy xương , đoạn chi (Canagliflozin)
- Nhiễm Ceton máu (có thể khi đường không cao) :
  - Nữ
  - Giảm liều hay ngưng insuline đột ngột
  - Ăn kém(ít tinh bột)

Chú ý :

Nếu phẫu thuật : Canagliflozin , Empagliflozin, Dapagliflozin ngưng trước 03 ngày;

Ertugliflozin ngưng trước 04 ngày

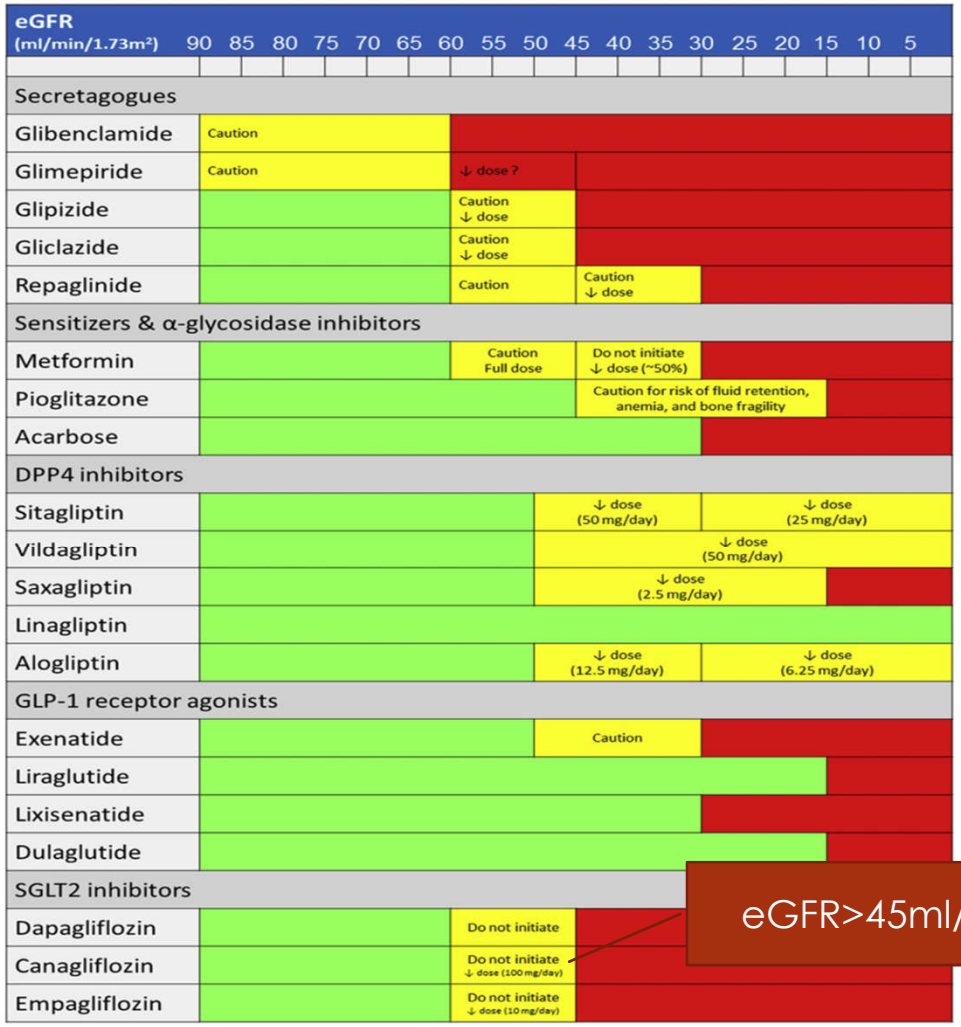
Ts Bs Trần Quang Nam , Nội tiết học lâm sàng , NXB y học , trang 72-74

Chú ý khi dùng các loại thuốc nguy cơ AKI

'SADMANS'

- **S** Sulfonylureas, e.g. gliclazide, glimepiride
- **A** ACE-inhibitors, e.g. ramipril, perindopril
- **D** Diuretics, e.g. furosemide, bendroflumethiazide
  Direct renin inhibitors, e.g. aliskerin
- **M** Metformin
- **A** ARBs, e.g. valsartan, losartan
- **N** NSAIDs, e.g. Ibuprofen, diclofenac
- **S** SGLT2 inhibitors, e.g. dapagliflozin, canagliflozin

Fig. 2 Recommended usage and dosage of currently available non-insulin drugs according to the level of eGFR. *eGFR* estimated glomerular filtration rate, *DPP-4* dipeptidyl peptidase 4, *GLP-1* glucagon-like peptide 1, *SGLT2* sodium-glucose cotransporter 2



Liều thông thường

- Empagliflozin : 10-25 mg /ngày uống sáng
- Dapagliflozin : 5-10 mg/ngày uống sáng
- Canagliflozin : 100-300mg/ngày uống sáng

Take home message- SGLT2-i :

- Thuốc đái tháo đường
- Tim mạch : an toàn , bảo vệ , điều trị (không phụ thuộc HbA1C)
- Thận : bảo vệ thận (nhóm bệnh nhân có DTD)
- Chuyển hóa : giảm cân, fatty liver (NAFLE ,NASH)

- Chú ý nguy cơ :
  - Nhiễm trùng niệu- dục
  - Tình trạng mất nước : AKI
  - nhiễm ceton máu

Xin cảm ơn sự lắng nghe
của quý đồng nghiệp !