# The Scientific Times

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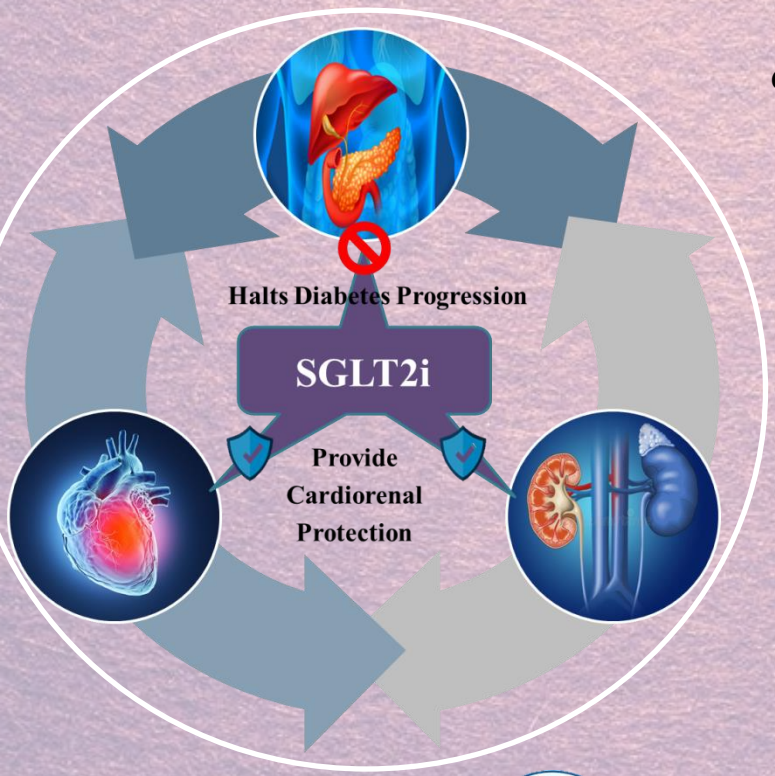
## The Immediate Impact of the 2022 Guidelines on Prescribing SGLT2 inhibitors

New trials with SGLT2 inhibitors has set a new stage in a paradigm change in the management of diabetes. It also set a new perspective for the management of Heart Failure (HF) and Chronic Kidney Disease (CKD) regardless of the diabetes.




Latest editions of 2022 AHA/ACC/HFSA GUIDELINE FOR THE MANAGEMENT OF HEART FAILURE and KDIGO 2022 CLINICAL PRACTICE GUIDELINE FOR DIABETES MANAGEMENT IN CHRONIC KIDNEY DISEASE have many new practice changing twists in the management of these conditions.

This volume of 'The Scientific Times' focuses on the new recommendations on the usage of SGLT2 inhibitors in patients with HF and CKD regardless of the presence or absence of diabetes.

American Heart Association.

HFSA HEART FAILURE SOCIETY OF AMERICA

KDIGO

ACC-American College of Cardiology, AHA-American Heart Association, CKD-Chronic Kidney Disease, HF-Heart Failure, HFSA-Heart Failure Society of America, KDIGO-Kidney Disease Improving Global Outcomes, SGLT-Sodium-glucose co-transporters

# SGLT2 inhibitors

## The Game Changers

*Sodium-glucose co-transporter 2 inhibitors (SGLT2i), also known as a glifozins, constitute a class of medication that was initially approved as an antidiabetic agent because the mechanism of action consisted of lowering blood glucose levels by promoting excretion of glucose through the kidneys via renal tubules.*

### *Effect on Cardio-renal Axis*

*As the medication was further studied, it was found to have positive cardioprotective and renoprotective effects in multiple recent large-scale randomized clinical trials (RCTs), not limited to the patients with type 2 diabetes.*

### *New Recommendations Pave the Way*

*The new recommendations was the addition of SGLT2i as a primary option for patients at varying stages or severity of HF and CKD, regardless of diabetes status.*

### *Changing the Game*

*Experts celebrated the new guidelines as game-changing clinical developments in the assessment of the SGLT2i proved their potential in mitigating the impact of HF and CKD.*

# 2022 Guideline for the Management of HF

**"2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure"**

*"HF remains a leading cause of morbidity and mortality globally."*

The 2022 HF guideline provides recommendations based on contemporary evidence for the treatment of HF patients.

Many recommendations from the earlier HF guidelines have been updated with new evidence, and new recommendations have been created when supported by published data.

## *Recommendations for Stage A and Stage B*

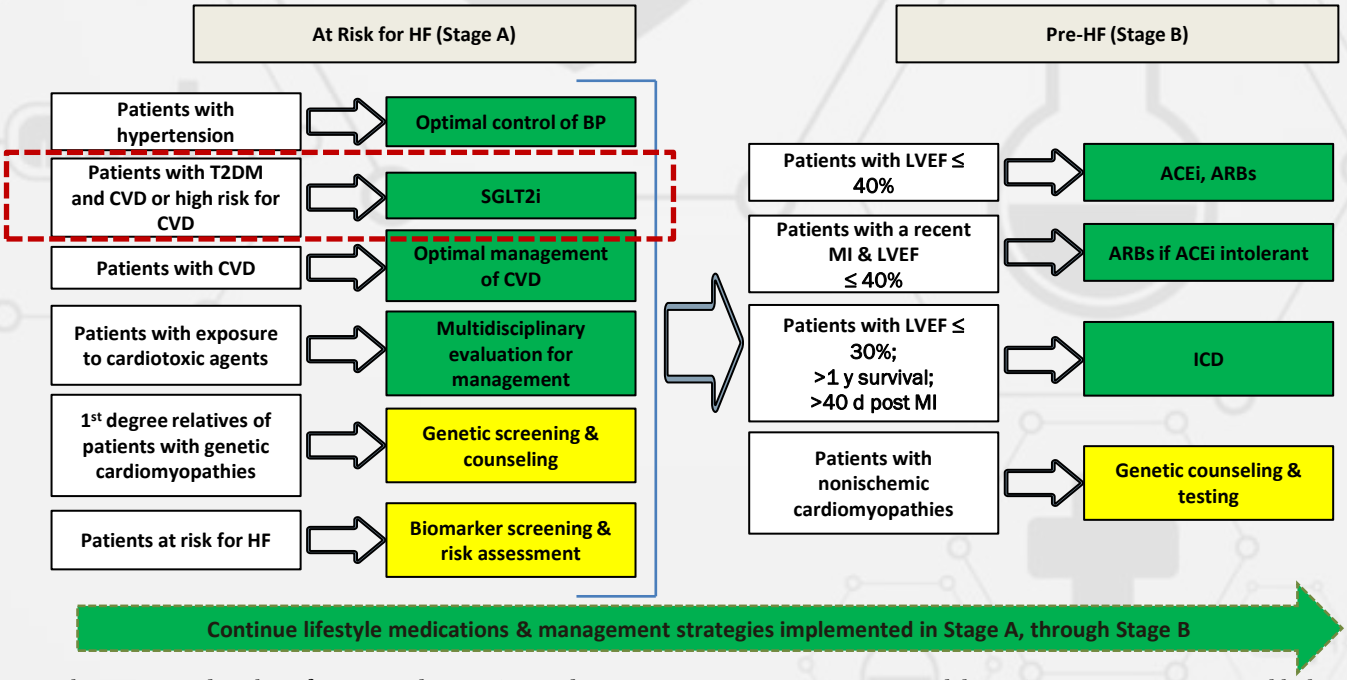
To stress the significance of primary prevention in HF patients, the guideline has proposed new terminology for the phases of HF:

- "at-risk for HF" for stage A and
- "pre-HF" for stage B.


Therapeutic interventions in each stage aim to modify risk factors (stage A), treat risk and structural heart disease to prevent HF (stage B), and reduce symptoms, morbidity, and mortality (stages C and D).

**SGLT2i has been strongly recommended in patients with T2DM and CVD or high risk for CVD (HF Stage A)**

## Recommendations for Patients at Risk of HF (Stage A) and Those With Pre-HF (Stage B).



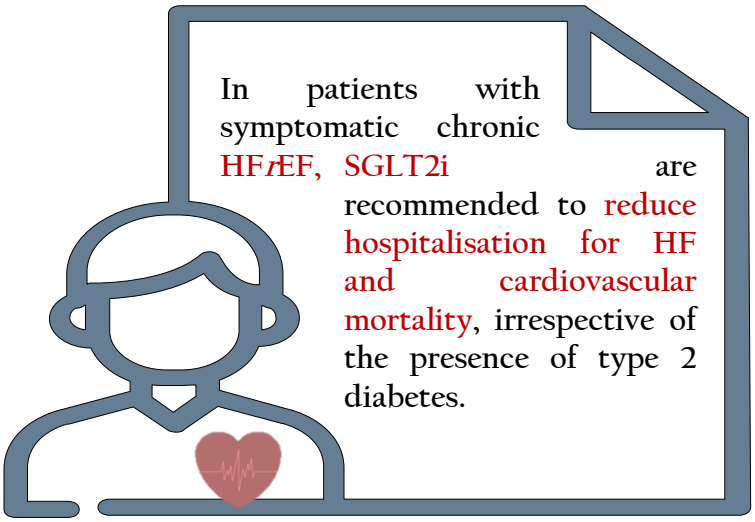

Colors correspond to class of recommendations. ACEi indicates angiotensin converting enzyme inhibitor; ARB- angiotensin receptor blocker; BP-blood pressure; CVD-cardiovascular disease; HF-heart failure; ICD-implantable cardioverter-defibrillator; LVEF-left ventricular ejection fraction; MI-myocardial infarction; and SGLT2i-sodium glucose cotransporter 2 inhibitor.

# SGLT2i Pave The Way Through All Stages Of HF

## *Recommendations for HFrEF*

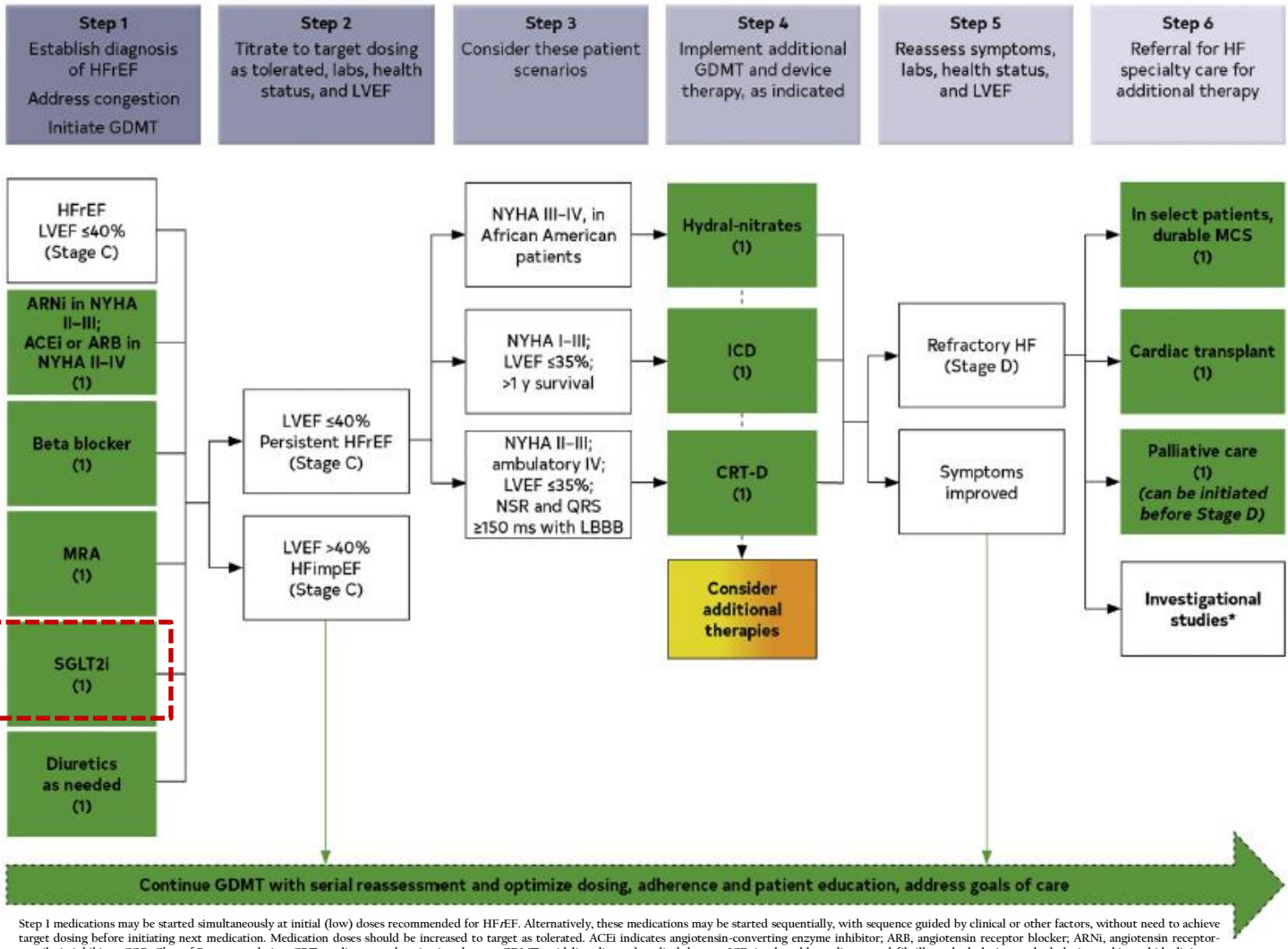
Guideline-directed medical therapy (GDMT) for HF with reduced ejection fraction (HF*r*EF) now includes 4 medication classes that include sodium-glucose cotransporter-2 inhibitors (SGLT2i). The 4 groups are:

1. Renin-angiotensin system inhibition, with angiotensin receptor-neprilysin inhibitors (ARNi, sacubitril/valsartan), angiotensin-converting enzyme inhibitors (ACEi, Enalapril), or angiotensin (II) receptor blockers (ARB, Telmisartan) alone;
2. Beta blockers (BB, Bisoprolol);
3. Mineralocorticoid receptor antagonists (MRAs, Spironolactone/Eplerenone); and
4. SGLT2i (Dapagliflozin, Empagliflozin).



In patients with symptomatic chronic HF*r*EF, SGLT2i are recommended to reduce hospitalisation for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes.

## Recommendations for Treatment of HF*r*EF Stages C and D.




Step 1 medications may be started simultaneously at initial (low) doses recommended for HF*r*EF. Alternatively, these medications may be started sequentially, with sequence guided by clinical or other factors, without need to achieve target dosing before initiating next medication. Medication doses should be increased to target as tolerated. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; COR, Class of Recommendation; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; ICD, implantable cardioverter-defibrillator; hydral-nitrates, hydralazine and isosorbide dinitrate; HFrEF, heart failure with reduced ejection fraction; LBBB, left bundle branch block; MCS, mechanical circulatory support; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NSR, normal sinus rhythm; NYHA, New York Heart Association; and SGLT2i, sodium-glucose cotransporter 2 inhibitor. *Participation in investigational studies is appropriate for stage C, NYHA class II and III HF.

## *Recommendations for HFmrEF*

SGLT2i have a class of recommendation (COR) 2a in heart failure with mildly reduced ejection fraction (HF*mr*EF). Weaker recommendations (COR 2b) are made for ARNi, ACEi, ARB, MRA, and beta blockers in this population.

*"In patients with HFmrEF, SGLT2i can be beneficial in decreasing HF hospitalisation and cardiovascular mortality."*

**Treatment of HF*mr*EF**

- Symptomatic HF with LVEF 41%-49%
  - Diuretics, as needed (1)
  - SGLT2i (2a)
  - ACEi, ARBs, ARNI (2b)
  - MRA (2b)
  - Evidence-based beta blockers for HF*r*EF (2b)

Among patients with current or previous symptomatic HF*mr*EF, (LVEF 41%-49%), (use of evidence-based beta blockers for current HF*r*EF), ARNi, ACEi, ARBs, and MRAs may be considered, to reduce the risk of HF hospitalisation and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum.

## *Recommendations for HFpEF*

New recommendations for heart failure with preserved ejection fraction (HF*p*EF) are made for SGLT2i (2a), MRAs (2b), and ARNi (2b).

**Treatment of HF*p*EF**

- Symptomatic HF with LVEF ≥50%
  - Diuretics, as needed (1)
  - SGLT2i (2a)
  - ARNI* (2b)
  - MRA* (2b)
  - ARB* (2b)

*"In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalisation and cardiovascular mortality."*

Until recently, clinical trials of standard agents used in HF*r*EF had been generally disappointing, with no benefit on mortality and marginal benefits on hospitalisation for heart failure (HHF) in patients with HF*p*EF.

EMPEROR-Preserved showed a significant benefit of the SGLT2i in HF*p*EF patients. The 21% reduction in primary composite endpoint & 29% reduction in HHF were observed.

SGLT2i are the only antidiabetic agents approved in management of HF patients. SGLT2i pave the way through all stages and types of HF from patients at risk for HF to advance stage and in HF*r*EF, HF*mr*EF as well HF*p*EF.

### *Forces Behind These Changes:*

| | | DAPA HF | EMPEROR-Reduced | EMPEROR-Preserved |
|---|---|---|---|---|
| Composite Primary Outcome | HHF, CV death | 26% ↓ | 25% ↓ | 21% ↓ |
| HHF | | 30% ↓ | 30% ↓ | 29% ↓ |
| CV Death | | 18% ↓ | NA | 9% ↓ |

HHF- hospitalisation for heart failure, CV- cardiovascular, DAPA-HF-Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure, EMPEROR-Reduced-EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction, EMPEROR-Preserved -Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction

# KDIGO 2022 CLINICAL PRACTICE GUIDELINE FOR DIABETES MANGEMENT IN CKD

*"Of all diabetes patients, more than 40% patients eventually develop CKD"*

The prevalence of diabetes around the world has reached epidemic proportions. The International Diabetes Federation estimated that 537 million people were living with diabetes in 2021.

Patients with T2DM and CKD are at increased risk of both cardiovascular events and progression to kidney failure. Thus, preventive treatment strategies that reduce both the risk of adverse kidney and cardiovascular outcomes are paramount.

**KDIGO recommends SGLT2i as first-line agent in patients with T2DM, CKD, and an eGFR ≥20 ml/min per 1.73 m².**

KDIGO 2022 guideline updated sections on SGLT2i which includes new data, additional discussion, modification of the SGLT2i recommendation to reflect new evidence of benefits and safety with eGFR ≥20 ml/min per 1.73 $m^2$ (from ≥30 ml/min per 1.73 $m^2$ previously) among people with type 2 diabetes, and revised or added practice points and research recommendations.

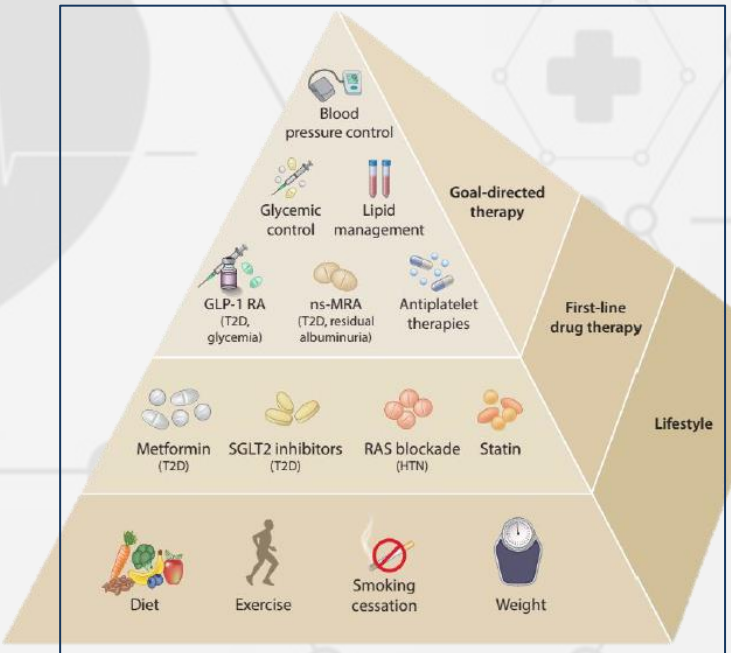
In addition, the SGLT2i section was moved from the glycemic control section to the comprehensive care section to reflect growing acknowledgement that these drugs are an essential component of CKD care irrespective of glycemic effects.

These changes were supported by multiple new large randomized controlled trials assessing the benefits and risks of SGLT2i.

## *Comprehensive diabetes and CKD management*

*"Patients with diabetes and CKD should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular diseases."*

For glycemic management in T2DM, most guidelines recommend starting with Metformin, while others suggest starting with SGLT2i or GLP-1 RA in patients with CKD or ASCVD, as their organ protective effects are better documented. The KDIGO guideline recommends that Metformin and an SGLT2i generally both be used as first-line treatment of patients with T2DM and CKD, when eGFR allows.




Kidney-heart risk factor management

The recommendation for SGLT2i is for kidney and cardiovascular protection and has been shown to have safety and benefit in CKD patients, even for those without T2DM. Thus, if patients are already being treated with other glucose-lowering agents, an SGLT2i can be added to current treatment regimen.

## *A mountain of evidence*

There are substantial evidence confirming that SGLT2i confer significant kidney and heart protective effects in CKD patients.

Three large RCTs reported efficacy for primary CV outcomes and secondary kidney outcomes: the EMPA-REG trial, CANVAS, and DECLARE-TIMI 58 trial.

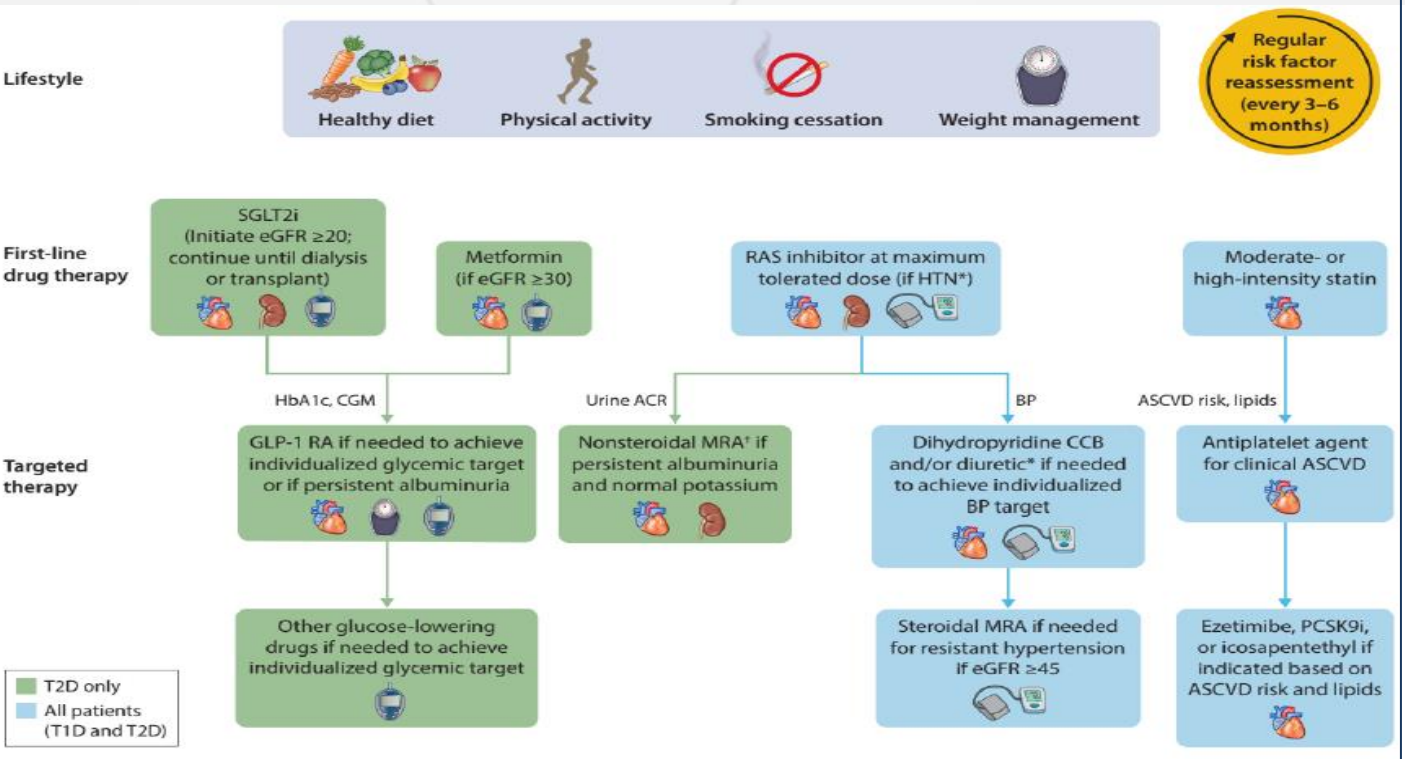
Subsequently, VERTIS-CV was an additional RCT of patients with T2DM and ASCVD which found non-inferiority for CV outcomes with an SGLT2i.

## *Setting the new levels*

The DAPA-CKD and SCORED trials enrolled CKD patients with an eGFR down to as low as 25 ml/min per 1.73 $m^2$. The EMPEROR-Reduced and EMPEROR-Preserved trials, although not an exclusive CKD population, did allow enrolment of patients with an eGFR as low as 20 ml/min per 1.73 $m^2$.

In DAPA-CKD trial, Dapagliflozin reduced the primary kidney outcome by 39%. Findings were similar among patients with and without T2DM.

Holistic approach for improving outcomes in patients with T2DM and CKD.




*ACEi or ARB should be first-line therapy for hypertension when albuminuria is present, otherwise dihydropyridine CCB or diuretic can also be considered; all three classes often needed to attain BP targets.

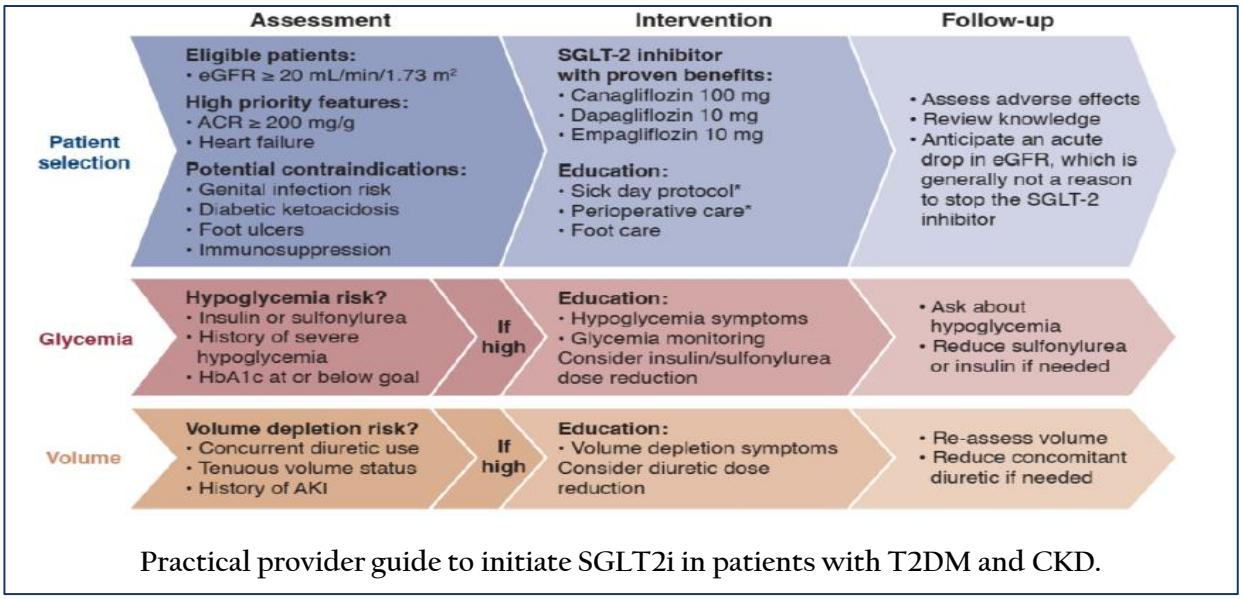
CREDENCE and DAPA-CKD trials were two RCTs which specifically enrolled a CKD population and was designed to evaluate primary kidney outcomes but also reporting on secondary cardiovascular outcomes.

DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved and SOLOIST-WHF are the RCTs that enrolled patients with heart failure evaluating primary cardiovascular outcomes, but also reported on secondary kidney outcomes.

The results of DAPA-CKD trials led to the approval of new indication of Dapagliflozin in CKD patients regardless the status of T2DM.

"Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 20 ml/min per 1.73 $m^2$, unless it is not tolerated or kidney replacement therapy is initiated."

# Practical approach to initiate SGLT2i in patients with T2DM & CKD




Practical provider guide to initiate SGLT2i in patients with T2DM and CKD.

The benefits of SGLT2i on kidney outcomes were seen across all eGFR subgroups, including those with an eGFR of 30–45 ml/min per 1.73m$^2$.

In real-world registry data, the initiation of SGLT2i was associated with a 51% reduced risk of composite kidney outcome of ›50% eGFR decline or kidney failure.

These recommendations based on new evidence places a high value on the kidney and heart protective effects of using an SGLT2i in patients with T2DM and CKD, and a lower value on the costs and adverse effects of this class of drug.

The recommendation is strong because in the judgment of the Work Group, all or nearly all well-informed patients would choose to receive treatment with an SGLT2i.

## Summary

Diabetes, CKD and HF are closely intertwined in pathophysiology and have a complex and multidirectional relationship and most of the time they coexists.

Newer evidence of SGLT2i have set new stage in paradigm change in the management of not only diabetes but also in the management of HF and CKD regardless of the diabetes.

SGLT2i now recommended in all stages & types of HF as an adjunct to standard of care in management of HF patients with or without diabetes.

Break-through trials of SGLT2i in CKD patients with or without diabetes conferred reduced decline in the eGFR, kidney failure, or death from kidney or cardiovascular causes.

Latest guidelines based on latest evidence of SGLT2i are changing the way of management of diabetes as well as HF and CKD with or with diabetes.

**For any scientific queries on the above topic**
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