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SOCIETY FOR HEART FAILURE AND TRANSPLANTATION'S

THE REVIVAL

Promoting Academics to Improve Clinical Outcomes.

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EDITOR'S NOTE

Dr. Manoj Durairaj

Heart Transplant Surgeon, MS, MCh. (AIIMS, New Delhi), FACC.

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Program Director, Department of Heart and Lung Transplantation, Sahyadri Hospitals, Pune.

Dear Colleagues,

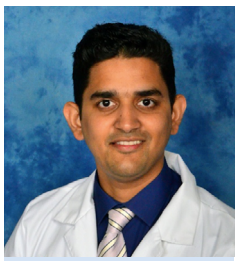
Greetings from the Editorial desk. The November 2021 issue of 'The Revival' carries a comprehensive article on the trials of SGLT inhibitors in Heart Failure. We are honoured to have as our guest author, Dr V K Chopra, Senior Director, Clinical Cardiology and Heart Failure, Max Hospital, Saket, New Delhi. Dr Chopra is the Founder President of the Heart Failure Association of India and is the national lead investigator in various high impact trials in heart failure including the Emperor-Reduced, Emperor-Preserved and PARADIGM trials.

SGLT2i has established its role as one of the 4 pillars of heart failure treatment. Along with ARNI, MRA and Beta blockers, this molecule has reduced the CV events, mortality, and heart failure hospitalisations in Diabetic and Non-Diabetic populations and demonstrated a salutary effect on renal outcomes evidenced by reducing the decline of the eGFR slope. The pump (cardiac) and pipe (arterial) beneficial effects of SGLTi have been demonstrated in various trials. Direct mechanistic effects on the cardiomyocyte via inhibition of sodium-hydrogen exchange (NHE) have been recently published and various mechanisms of the observed cardiovascular benefits of SGLTi will be answered by ongoing research.

I thank Dr Chopra for this brilliant article, and I wish our dear readers "Happy Reading".

- Dr Manoj Durairaj
Editor "The Revival"

SUB EDITOR



Dr. Talha Meeran

MBBS, MD, FACC, Consultant Cardiologist, Dept of Advanced Cardiac Sciences and Cardiac Transplant, Sir HN Reliance Foundation Hospital, Mumbai.

Dear Colleagues,

"This edition of REVIVAL brings to you a masterclass in SGLT2i presented by Dr VK Chopra. Dr Chopra has been the national PI for several international landmark CVD trials and he brings together all his research and clinical expertise together here for this brilliant and exhaustive review. The article delineates the evidence base for each SGLT2i molecule in all disease subsets including ASCVD with or without diabetes, heart failure with or without diabetes and CKD."

Sincerely,
Dr Talha Meeran
Sub Editor "The Revival"

PRESIDENTIAL MESSAGE

Prof. (Dr) V. Nandakumar

Director & Chief, Division of Cardio Vascular/Thoracic Surgery & Cardiac Transplantation, Metromed International Cardiac Centre, Calicut, Kerala.

Dear Colleagues,

Greetings from the Society for Heart Failure and Transplantation.

November issue of 'The Revival' has a very informative and exhaustive article by Dr V.K.Chopra on SGLT2 inhibitors in Cardiovascular Diseases. In this article Dr Chopra substantiates the significant benefits in cardiovascular and renal outcomes with SGLT 2 inhibitors by showing the results of various trials. For a wide range of patients with heart failure and preserved or reduced ejection fraction and with renal impairment ,this group of drugs might prove to be big boon.

- Prof. (Dr) V. Nandakumar
President

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Special thanks to Dr V.K. Chopra for authoring this month's article.

Designed by Maithili Kulkarni

SGLT2 INHIBITORS IN CARDIOVASCULAR DISEASES

Dr V.K. Chopra
DM, FACC, FESC, FHFA, FCSI

Dr V K Chopra
DM, FACC, FESC, FHFA, FCSI
Senior Director – Clinical Cardiology, Heart Failure & Research, Max Super - Speciality Hospital, Saket, New Delhi

- Founder President – Heart Failure Association of India 2013
- 75 papers publications in National and International Journals

Clinical Trials:
National Lead Investigator in TIMI-51, ELIXA, Red-HF, ROCKET-AF, PARAGON, FOURIER, Odyssey East, SCORED, DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DARE-19, FINE-ARTS, EMPACT-MI, PARADIGM and several others.

Recent years have witnessed exciting new treatment modalities in the management of patients with HF. After ARBs, there was a long period of hiatus in the pharmacological management of heart failure leading many cardiologists to wonder if we had reached the end of neurohormonal modulation. All this changed with the publication of the results of PARADIGM1, which demonstrated remarkable benefits in HFrEF when given over and above the currently available therapies. There has been a major shift in therapies; while till now all the benefits were seen in therapies which modulated neurohormonal systems, newer therapies have emerged dealing with completely different metabolic pathways. Among the new entrants, undoubtedly SGLT-2 I have come to occupy the number one position. Serendipity is to be credited for many advances in medicine and the story of SGLT-2 I is no different, as the results of the first CV outcomes trial namely EMPA-Reg2 were largely unexpected. After some of the anti-diabetic drugs demonstrated CV harm, the subsequent trials were required to demonstrate CV safety. However, it came as a pleasant surprise for the researchers, when EMPA-Reg trial demonstrated a remarkable benefit in pre- specified end points driven mainly by the reduction in HF hospitalizations in patients with Diabetes and established cardiovascular disease and started a lot of research with different drugs in this class.

SGLT2 Inhibitors had been in use as anti-diabetic drugs for some time. They primarily act by inhibiting the SGLT-2, which is present in the proximal convoluted tubules of the kidney and is responsible for re-absorption of glucose and sodium. This results in loss of glucose and sodium in urine accompanied by osmotic diuresis. There is also an accompanying weight loss of 3-4 Kg and a drop of 3-4 mm Hg.in most people (Fig.1). Due to their unique mechanism of action, which is preventing the re-absorption of only filtered glucose, they do not result in hypoglycemia even in non-diabetic patients, unless being administrated with some of the other anti-diabetic drugs that are known to cause hypoglycemia. Though these mechanisms were initially thought be responsible for their benefits, it is now evident that these are not the primary reasons of their benefits.

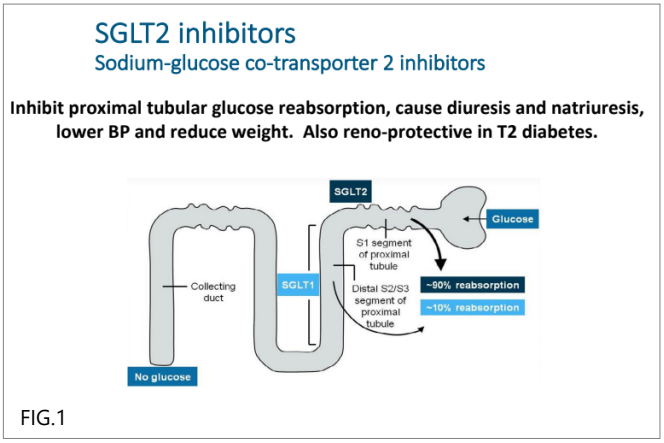

FIG.1

Major SGLT2 trials in prevention of cardiovascular events and what have they shown:

Several trials were launched after EMPA-Reg to explore the role of these drugs in CV and renal outcomes in diabetic patients, but with different characteristics. They explored the role of SGLT2 inhibitors in reduction of cardiovascular

endpoints in patients with Diabetes, either with established heart disease or the presence of multiple CV risk factors. This is important as several patients with CVD have renal dysfunction which plays a critical role in their disease progression and prognosis. These trials demonstrated a remarkable homogeneity in their results which reinforces the role of this group of drugs in the management of diabetic patients with established CAD or the presence of multiple risk factors. At present, we have data for cardiovascular outcomes for 4 major drugs in this class, namely, Empagliflozin, Dapagliflozin, Canagliflozin and Ertugliflozin, of which the first 3 are available in India. There is another drug in this class, Remogliflozin, which though available in India, does not have robust data on CV outcomes, but is much cheaper.

A) Empagliflozin:

Empa-Reg outcomes trial [2]

This was the first trial to show a significant benefit in CV outcomes with SGLT2 inhibitors. The goal of the trial was to assess the cardiovascular (CV) safety of empagliflozin, a sodium–glucose cotransporter 2 (SGLT-2) inhibitor, in patients with type 2 diabetes mellitus (DM2) and established CV disease

The results were: (Fig.2)

- All-cause mortality reduced (3.8% vs. 5.1%), p < 0.01
- Congestive heart failure (CHF) hospitalization reduced similarly in patients with or without CHF at baseline (2.7% vs. 4.1%, p = 0.002)
- CHF hospitalization or CV death reduced (: 5.7% vs. 8.5%), p < 0.001

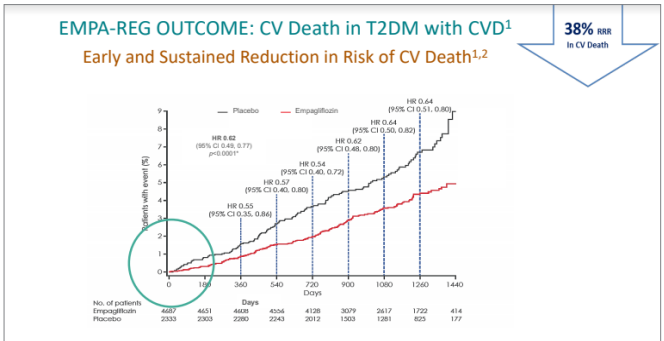

FIG. 2

This trial showed the superiority of empagliflozin in reducing CV events, mortality and HHF in patients with DM2 and established CVD and also a significant benefit on renal outcomes both in patients with and without HF at baseline., it demonstrated a salutary effect on renal outcomes too, including the need to initiate renal replacement therapy.

B) Dapagliflozin:

1-DECLARE TIMI -58 [3]

Declare TIMI-58 enrolled a different population of patients with Diabetes and either established CVD (40.6%) or multiple risk factors for ASCVD (59.4%).The majority of patients did not have a history of HF. The primary endpoint of MACE and mortality was similar in both groups but there was a significantly lower rate of CV death or HHF along with reduction in adverse renal events in those with and without ASCVD, HF or CKD at baseline. (Fig.3, 4)

Primary endpoints

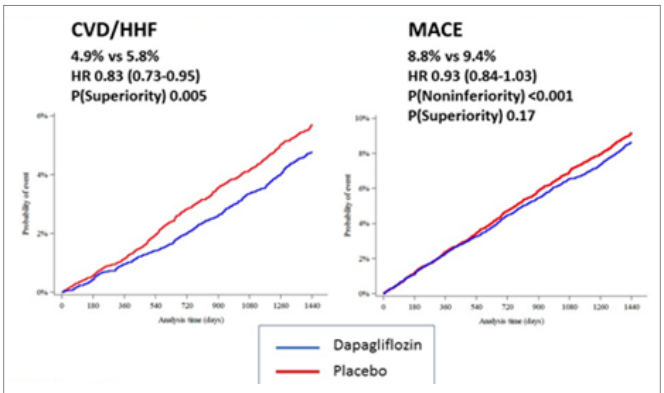

FIG. 3

Secondary endpoints

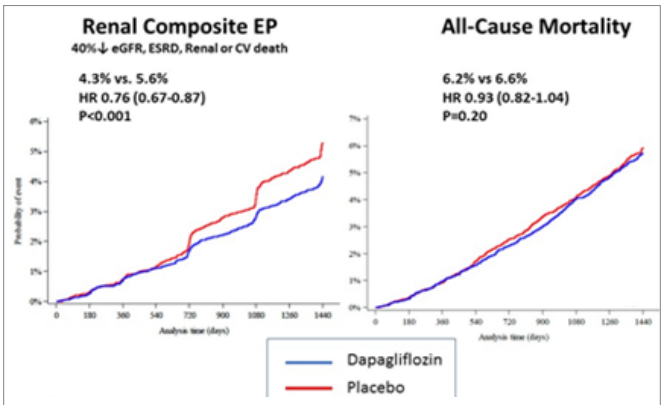

FIG. 4

C) Canagliflozin: (Fig 5)

1-CANVAS [4]

The CANVAS Program combined data from two trials comparing Canagliflozin and placebo involving a total of 10,142 participants with type 2 diabetes and high cardiovascular risk. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Patients treated with canagliflozin had a lower risk of cardiovascular events than those who received placebo but a greater risk of amputation, primarily at the level of the toe or metatarsal. This risk was

never replicated in any other trial, raising the question whether it was a chance occurrence.

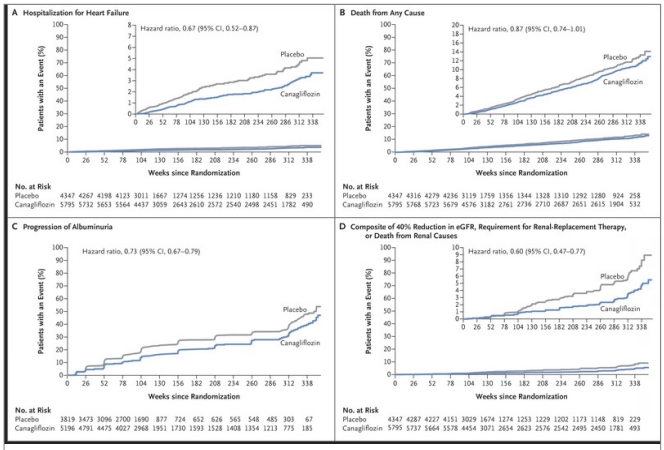

FIG. 5

D) Ertugliflozin:

VERTIS CV Trial [5]

This trial investigated the role of Ertugliflozin in patients with T2DM and established ASCVD involving the coronary, cerebrovascular, and/or peripheral arterial systems (Fig 6,7). The results were somewhat different from the other SGLT-2 inhibitor trials. Ertugliflozin added to guideline-directed secondary prevention therapies was non-inferior versus placebo for MACE. The key secondary composite endpoint of CV death or HHF did not differ between groups, nor did CV death, but there was a 30% lower risk of HHF. The overall pattern of the effects on endpoints of HHF and renal outcomes was in line with those seen in other large trials of SGLT2 inhibitors. The effects of ertugliflozin on the primary end points were less than those demonstrated in other major trials with Dapagliflozin and Empagliflozin. It is unclear if this represents a difference in patient populations between the trials, or a true biological difference in the drug efficacy. (Fig. 6,7)

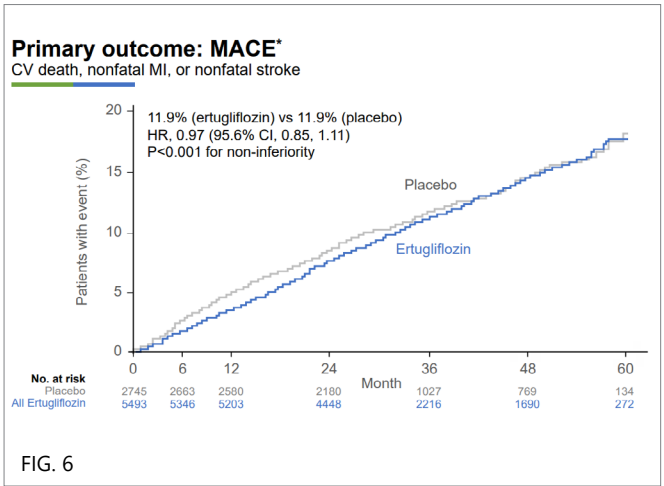

FIG. 6

HHF

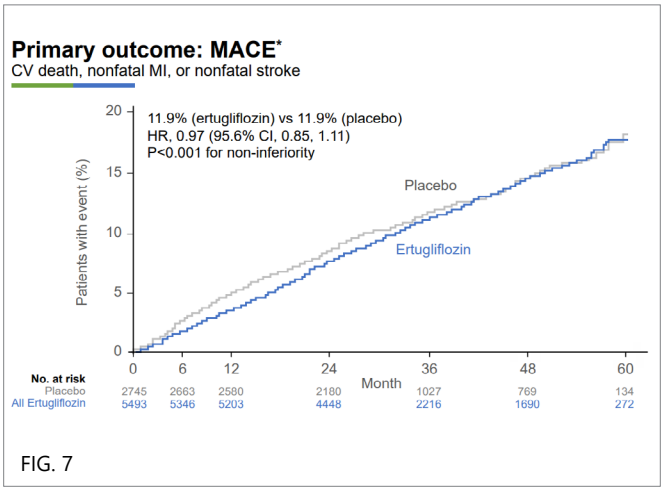

FIG. 7

E) Remogliflozin:

This is another drug in the same class. A few studies are available which demonstrate its efficacy in reduction of blood glucose comparable to the other SGLT2 inhibitors. However, no major CV outcome trials have been performed and therefore its effect on reduction of CV enter is not known. It is however much cheaper than the other SGLT2 inhibitors.

A brief summary of the effects of major CV outcome trials in prevention of CV outcomes is given below. Fig 8

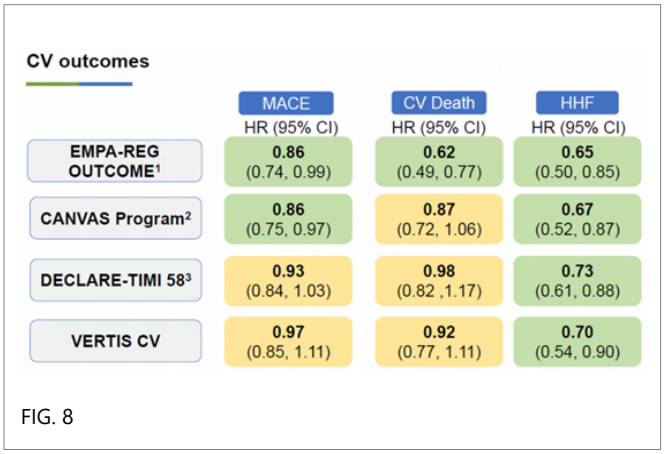

FIG. 8

As all these trials had different populations, one should not draw any comparative conclusions about their relative efficacy. It appears, however, that their primary benefit is a consistent reduction in HHF in patients with multiple risk factors or established cardiovascular disease. This benefit is seen in both diabetics and non-diabetics (Fig. 9), regardless of the baseline treatment with other disease modifying agents and other co-morbid conditions. Variability in mortality could be explained by inclusion of different patient populations and trial design.

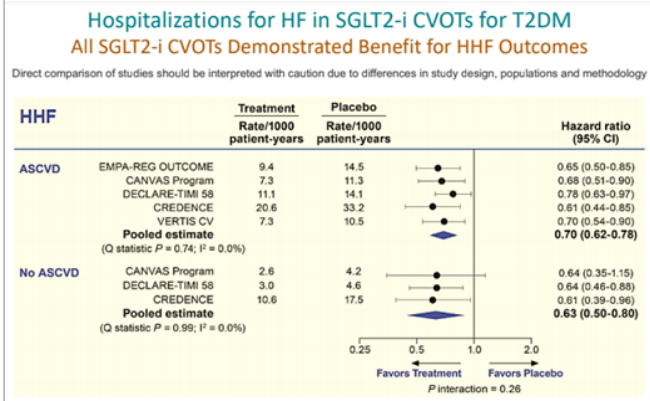

FIG. 9

SGLT2 Inhibitors as a treatment for patients with established HF :

Having conclusively established the role of SGLT2 Inhibitors in reduction in HHF, mortality and in renal endpoints based on several trials, researchers moved on to investigate whether these agents could actually be used to treat patients with established HF, both HFrEF and HFpEF. As these drugs do not cause hypoglycemia, the trials also explored their benefit in non- diabetic patients. The concern about higher incidence of DKA was still present and was marked as an area of special interest in the subsequent trials. Two major trials for HFrEF that reported in quick succession are DAPA-HF and EMPEROR-Reduced. Their results are briefly summarized below:

1- DAPA-HF [6]

This trial conclusively proved that Dapagliflozin used on top of an excellent background standard of care therapy was safe and resulted in a statistically significant and clinically meaningful reduction in HF events and CV mortality. The drug was equally effective in patients with and without diabetes with no significant hypoglycemia in either group. Only a small number of patients were on ARNI as it had been launched shortly before the trial got under way, and the benefits observed in these patients were similar. There was a consistent benefit irrespective of baseline NT-ProBNP levels, SBP, BMI, GFR and background therapies. (Fig 10,11)

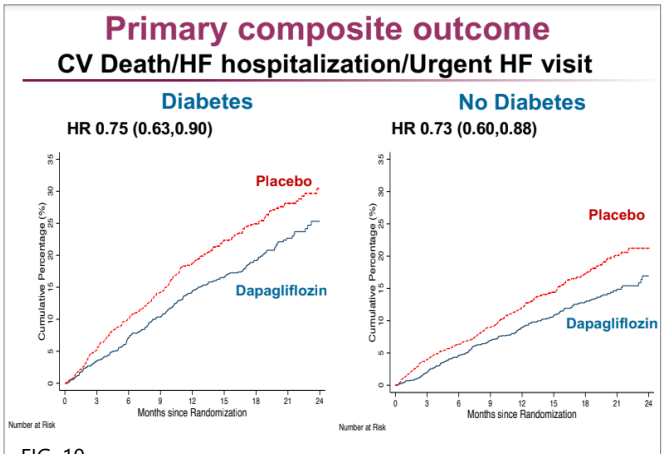

FIG. 10

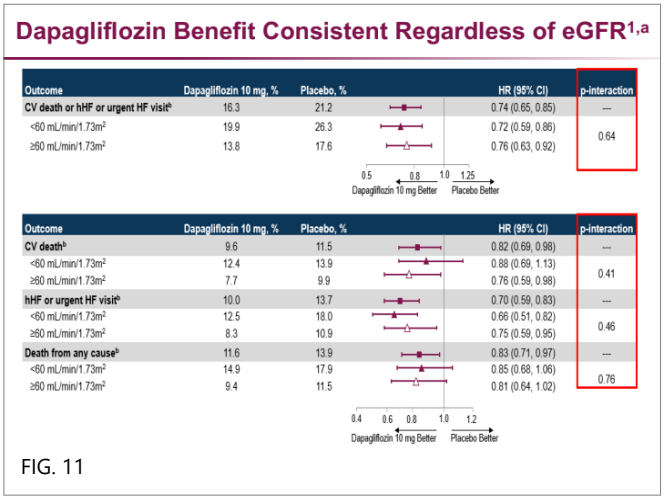

FIG. 11

2- EMPEROR-Reduced [7]

The results of this trial were presented in August 2020. This trial enrolled 3730 patients with HF and reduced ejection fraction and studied the effects of adding Empagliflozin to the standard of care in CV outcomes. Half the patients were non diabetic and on an average had more severe heart failure than those in DAPA-HF Trial. Mean ejection fraction was 27%, mean NT Pro BNP was 1907 and over 70% patients had LVEF 30% or less. There was an impressive reduction in HHF, both first and repeat, and the decline in renal functions was significantly less in the empagliflozin group. The benefits were seen equally in both diabetics and non-diabetics. The mortality reduction, however, was modest at 8%. (Fig 12,13,14)

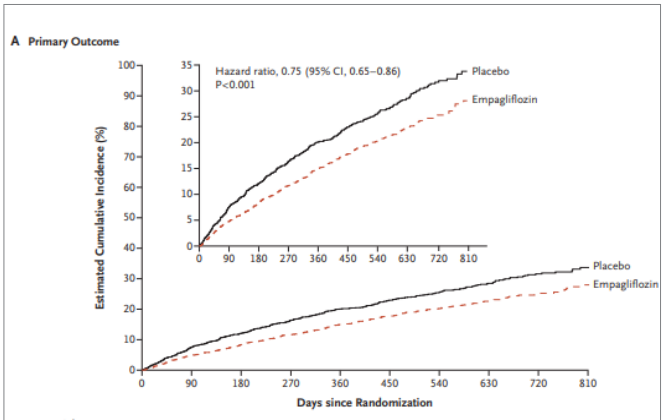

FIG. 12

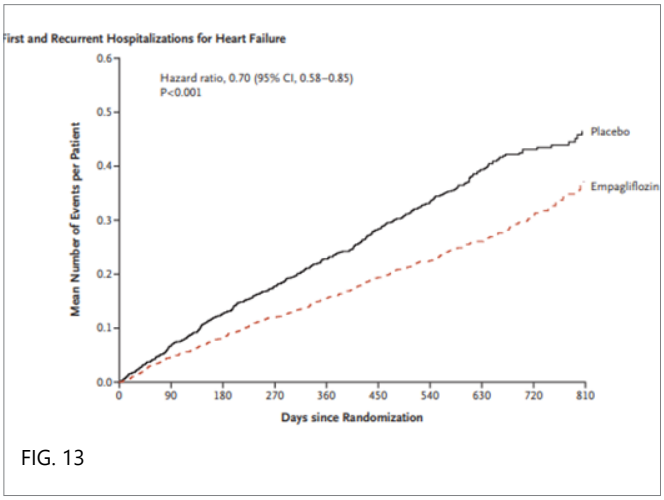

FIG. 13

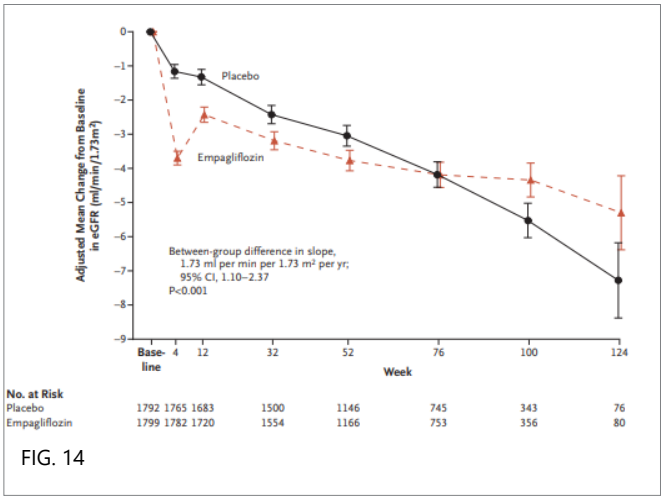

FIG. 14

Sotagliflozin:

This drug is different as it is an SGLT-1 and 2 inhibitor. SGLT-1 is present in the gut and its inhibition prevents absorption of glucose from the gut. Its side effects include GI disturbances. Two trials were done with this drug: SOLOIST8 and SCORED9. SOLOIST enrolled patients with hospitalization due to worsening HF and SCORED looked at endpoints in diabetic kidney disease. Both trials were stopped during COVID due to loss of funding, but they yielded important information.

SOLOIST:

This is the only trial so far with acute heart failure. Its results were in line with the other SGLT2-I trials. The drug was started before discharge from the hospital or soon after.

It showed a very significant 33% reduction in the primary end point of death, HHF and urgent HF visits. Fig.15

SOLOIST Result.

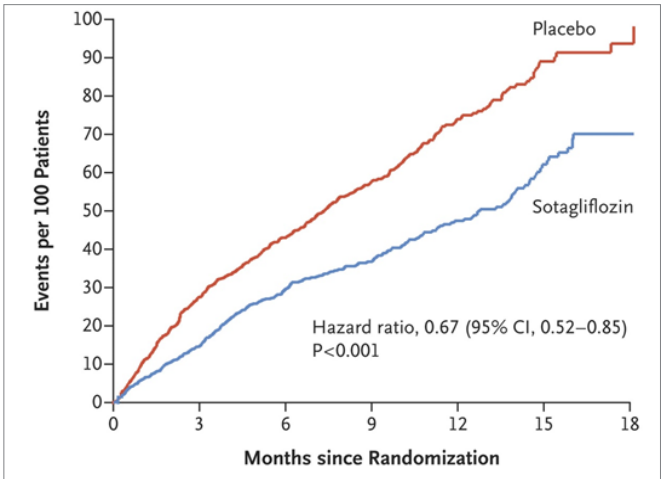

FIG. 15

SCORED:

In this trial, 10,584 patients with type 2 diabetes and CKD were randomized to receive either sotagliflozin or placebo.

Results showed the cohort of patients receiving sotagliflozin had a 26% reduction in the number of cardiovascular deaths, hospitalizations for HF or urgent visits for HF. Additionally, a 23% decrease in myocardial infarction and stroke was observed, which was likely to be due to the SGLT1 effect. (Fig.16)

SCORED Results.

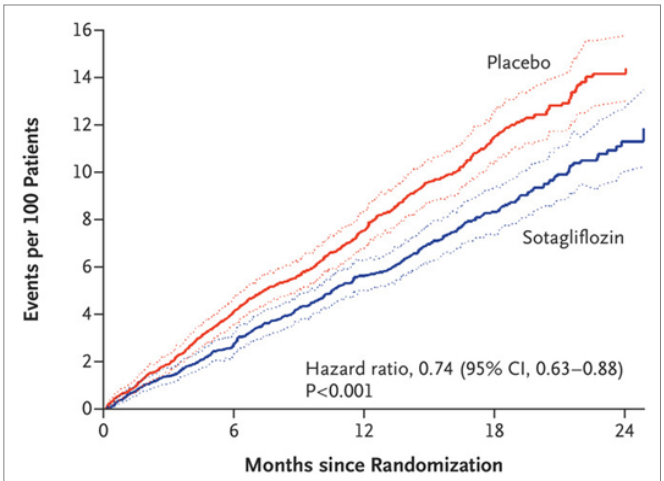

FIG. 16

EMPEROR-Preserved [10]

While there are a large number of effective disease modifying therapies available for HFrEF, there was no proven therapy for HFpEF except diuretics to reduce congestion. EMPEROR-Preserved was published in 2021 and established the role of Empagliflozin in significantly reducing the combined end point of HHF and CV mortality, driven mainly by a reduction

in HHF. This benefit was consistently seen across all pre-specified subgroups, both in patients with and without diabetes and across a broad range of renal functions. There was no effect on mortality and in renal end points, possibly due to the relatively shorter duration of the trial. (Fig.17).

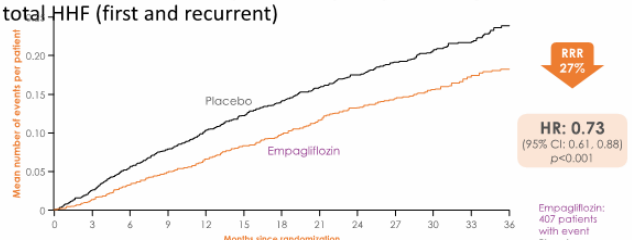

FIG. 17

RENAL OUTCOMES:

A significant number of patients with heart failure have renal dysfunction, either due to HF or due to concomitant renal disease. It worsens the prognosis and also creates difficulties in utilizing some of the disease modifying drugs, specially neurohormonal modulators. Exploratory endpoints from the EMPA-REG OUTCOME and CANVAS trial showed decreased albuminuria, while the CANVAS and DECLARE TIMI-58 trial also showed better renal outcomes of reduction in worsening of estimated glomerular filtration rate (eGFR), initiation of renal-replacement therapy, and CKD related death (7-9). However, these trials were not designed to address the possible reno-protective effects of the SGLT2 inhibitors because the participants enrolled were at a relatively low risk for progression to kidney failure.

CREDENCE Trial: [11]

The goal of the trial was to assess the effect of canagliflozin on renal outcomes among patients with type 2 diabetes mellitus (DM2) and chronic kidney disease (CKD). Patients with Type-2 DM, albuminuria and GFR between 30-60 and on stable doses of ACEI/ARB were enrolled. The trial was stopped early due to overwhelming benefit. Canagliflozin reduced the risk of the primary outcome of ESKD, doubling of serum creatinine, or renal or CV death by 30% ,P = 0.00001 (Fig18)

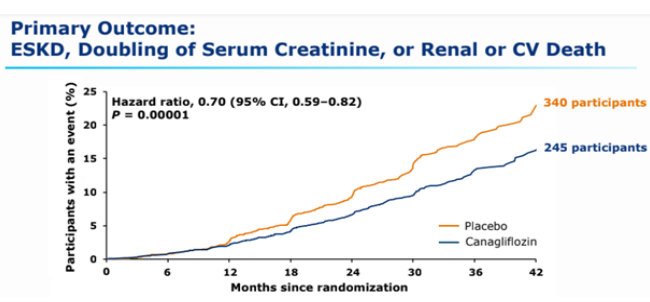

FIG. 18

DAPA-CKD Trial [12]

DAPA CKD Trial was presented in 2020. 4304 patients were enrolled with eGFR between ≥ 25 and ≤ 75 mL/min/1.73 m2; urinary albumin to creatinine ratio between ≥ 200 mg/g and ≤ 5000 mg/g; and were on a stable, maximum tolerated dose of ACE Inhibitor or ARB for at least 4 weeks. 2906 patients had Type II Diabetes.

Dapagliflozin was safe and well tolerated. Neither diabetic ketoacidosis nor severe hypoglycemia were observed in patients with Type II Diabetes.

DAPA-CKD showed that dapagliflozin significantly reduced the risk of worsening of kidney function or death from cardiovascular or kidney disease in patients with chronic kidney disease with and without Type II Diabetes (p =0.000000028). The results highlight the medicine's potential to benefit patients with chronic heart disease who are in need of improved treatment options.(Fig 19, 20).

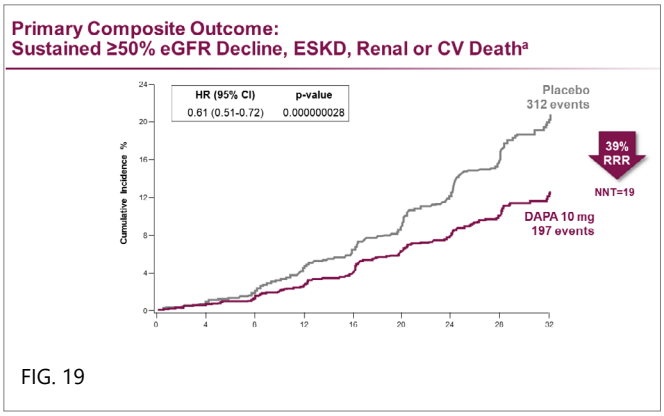

FIG. 19

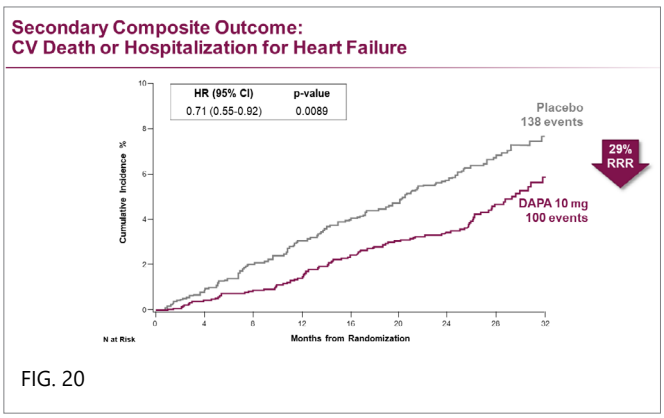

FIG. 20

Mechanism of action

SGLT-2 I have several well documented actions13 Suggested mechanisms include natriuresis and osmotic diuresis; reductions in inflammation, oxidative stress, and arterial stiffness; reductions in blood pressure and body weight; and possible reno protective effects. These effects could produce cardiovascular benefits through a range of cardiac effects, including reduction in left ventricular load, attenuation of cardiac fibrosis and inflammation, and improved myocardial

energy production. Other possible mechanisms include inhibition of sodium-hydrogen exchange, increases in erythropoietin levels, and reduction in myocardial ischemia or reperfusion injury. It is likely that a range of mechanisms underlie the observed cardiovascular benefits of SGLT2 inhibitors; further elucidation of these mechanisms will be answered by ongoing research. (Fig.21)

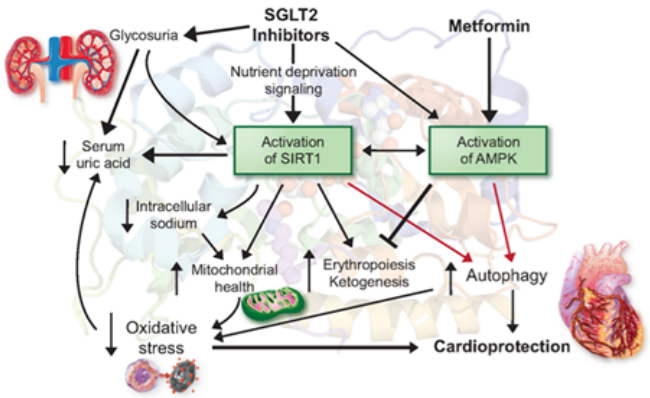

FIG. 21

Proposed framework to explain the mechanism of the cardioprotective effect of SGLT2 inhibitors.

Conclusions:

With such strong data from large well designed clinical trial appearing in rapid succession, it is safe to say that they have firmly established their place in prevention of HF and improving CV outcomes in carefully selected diabetic patients and have received strong recommendation in various guidelines. Additionally, as a class, SGLT2 inhibitors should be strongly considered in the majority of patients with acute decompensated HF and HF with either reduced or preserved ejection fraction; and with CKD across the full range of proteinuria.

Abbreviations :

ARB : Angiotensin II receptor blockers
CV : Cardiovascular
HFrEF : Heart Failure with reduced ejection fraction
SGLT2 : Sodium-glucose co-transporator-2
Empa-Reg : Empagliglozin Cardiovascular Outcome Event
CVD : Cardiovascular disease
ASCVD : Atherosclerotic cardiovascular disease
CKD : Chronic Kidney Disease
CV : Cardiovascular
T2DM : Type2 Diabetes Mellitus
EMPA-REG : Empagliglozin Cardiovascular Outcome Event
CANVAS : Canagliflozin Cardiovascular Assessment Study
HF : Heart Failure
MACE : Major adverse cardiovascular events
NTProBNP : N-terminal (NT) pro-Brain Natriuretic Peptide
SBP : Spontaneous bacterial peritonitis
BMI : Body mass index
eGFR : Estimated glomerular filtration rate
MI : Myocardial Infarction
LVEF : Left ventricular ejection fraction
COVID : Coronavirus disease
HFpEF : Heart Failure with Preserved Ejection Fraction

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