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Review Article

Corroborating Packer's Posit regarding Advantageous actions of SGLT2 hampering agents on Advantageous Cardiovascular Outcome: with Nutrient Deprivation Signaling/ Autophagic flux Posit in the Absence of SGLT2 Receptors in Heart: A Narrative Review

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Abstract

SGLT2- hampering agents generate an inimitable fashion of advantageous evolution/properties of propagating cardiomyopathy /nephropathy, having features of diminished oxidative /endoplasmic reticulum (ER) stress, mitochondrial health replacement, escalated mitochondrial biogeneration, decreased proinflammatory /profibrotic pathways, and conservation of cellular/organ intactness/ viability. Considerable validation points that this canonical fashion of reactions might be explained by SGLT2- hampering agents actions in facilitating cellular housekeeping by escalating autophagic flux, which might be associated with actions of such agents for generating concomitant upregulation of nutrient deprivation signaling(NDS) and downregulation of nutrient surplus(NS) signaling, the way presenting by escalated expression /activity of AMP-activated protein kinase(AMPK), Sirtuins (SIRT1), SIRT3, SIRT6, Peroxisome Proliferator Activated Receptor γCoactivator -1α(PGC-1α) and diminished mammalian target of rapamycin (mTOR) activation .The unique cardioprotective / renoprotective SGLT2- hampering agents actions got ameliorated by particular hampering /knockdown of autophagy, AMPK and sirtuins. Proteomic evaluation of blood clinically, acquired during randomized controlled triasls this design of differentially escalated proteins is paralleled with these findings. Clinical studies further illustrated; SGLT2- hampering agents facilitate gluconeogenesis, ketogenesis, erythrocytosis and diminished uricemia, the emblem of NDS and the key statistical modulator of capacity of SGLT2- hampering agents for diminishing risk of HF and robust renal processes. SGLT2- hampering agents effects of exaggerating autophagic flux is found in secluded cells/tissue not expressing SGLT2; thereby not exposed to altered glucose/ketones in their milieu and probably associated with these agents capacity of directly binding sirtuins /mTOR. Altered renal/cardiovascular physiology/metabolism can't be explained by the advantageous SGLT2- hampering agents actions in clinical scenario /experimental ones. The direct molecular SGLT2- hampering agents actions in secluded cells are paralleled with the belief that SGLT2 works as NS sensor, thereby its hampering causes NDS with its associated cytoprotective actions which can be attenuated by hampering/ knockdown of autophagy, AMPK and sirtuins. This corroborated Packers posit given in 2020, thus explaining the cardioprotective actions of them with lack of SGLT2R.

Key Words: *SGLT2- hampering agents; nutrient deprivation signaling (NDS); autophagic flux. cardiorenal advantages*

Introduction

Sodium –glucose cotransporter 2(SGLT2) hampering agents result in reduction of propagation of heart failure (HF)on its delivery to high-risk patients without any symptoms or to the symptomatic patients over a wide spectrum of ejection fractions. In case of12 large scale randomized controlled trials (RCTs) inclusive of over 70,000 patients having long term SGLT2 hampering generated an agreeable 20-25% decline in the risk of cardiovascular mortality or hospitalization for HF **[**1**]**. SGLT2 hampering agents are currently believed to be 1outof the 4 elemental agents with regards to the management of HF in patients with a reduced ejection fraction(HFrEF).Earlier we have reviewed the aetiopathogenesis of adipocyte impairment in heart failure, Pathophysiology of Diabetic Cardiomyopathy highlighting Epigenetics Modifications and treatment besides Cardiovascular Outcome Trials (CVOT's) of SGLT2 hampering agents, molecular modes Implicated in Diastolic Impairment in Early Diabetic Cardiomyopathy. Here we have attempted to explain how SGLT2) hampering agents possess advantageous roles in HF despite no SGLT2 receptors in heart **[**2-10**]**.

Methods

Here we conducted a narrative review utilizing search engine pubmed, google scholar ;web of science ; embase; Cochrane review library utilizing the MeSH terms like DKD; Epigenetics; SGLT2 hampering agents; Nephroprotective effects; renal sympathetic activity ; glomerular hypertension abrogation; cardioprotective effects; NHE- exchanger; energy Substrates; ketone bodies; erythrocytosis; Histone post-translational modifications; Histone acetylation ; -β-hydroxy butyryl ate; Apelin;; from 2000 to 2023 till date in September 2023.

Results

We found a total of 2500 articles out of which we selected 143 articles for this review. No meta-analysis was done.

Probable Effects of SGLT2 Hampering Agents in Causing Nephrocentric Neurohormonal Antagonization along with Osmotic Diuretics

Other elemental agents for HF- angiotensin receptor neprilysin hampering agents (ARNi),β blockers as well as mineralocorticoid receptors(MR) antagonists disrupted the neurohormonal molecular modes whose activation results in inimical sequelae on the myocardium(for instance angiotensin II, catecholamines ,aldosterone along with neprilysin). Nevertheless, significant neurohormonal modes which is not completely antagonized by the present elemental agents is the considerable escalation of sympathetic nerve traffic towards the kidneys. Renal sympathetic tone is substantially escalated in experimental along with clinical HF in addition to deleteriously impact the prognosis **[**12**]**. An escalation in renal sympathetic nerve traffick inimically influences the heart by escalating the liberation of angiotensin II, in addition to neprilysin from the kidneys, both working in facilitating deleterious cardiac remodeling as well as fibrosis in addition to sodium getting retained along with volume expansion **[**13**]**. Escalated renal sympathetic nerve traffick has further been observed to be responsible for the propagation of Chronic Kidney Disease (CKD), partially correlated with the stimulation of intrarenal angiotensin II along with partially correlated with the activation of α2-adreno receptors which might possess a part in the pathogenesis of renal interstitial inflammation as well as fibrosis **[**14**]**. Renal denervation generates an attractive action in experimental HF along with renal disease as well as escalates cardiac working in a clinical scenario **[**13-15**]**. Noticeably, despite in general they have the properties of being hampering agents of the sympathetic nervous system (SNS) , however β blockers are not efficacious in resulting in diminished renal sympathetic nerve traffick **[**16**]**.

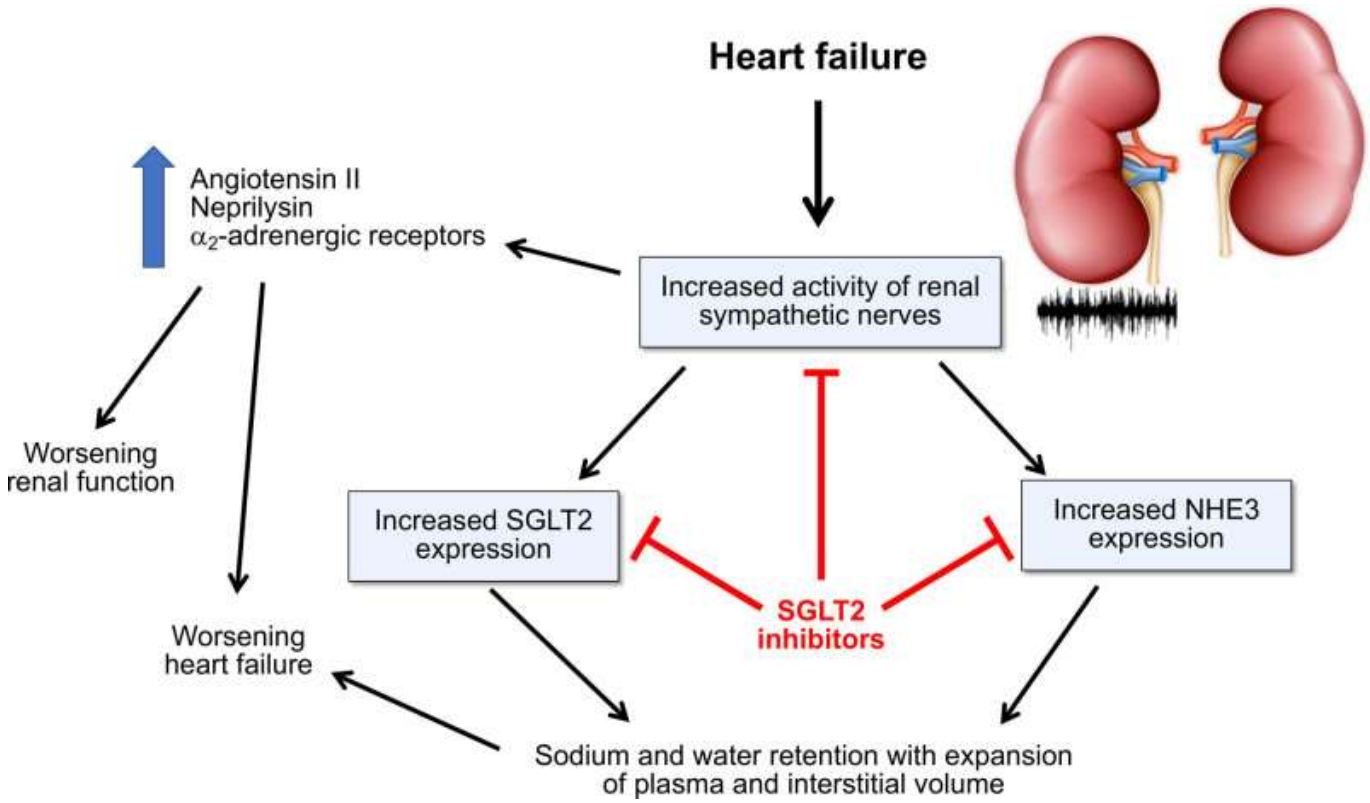
Probability of Hampering of Renal sympathetic activity by SGLT2 Hampering Agents

Escalated renal sympathetic nerve traffick would be anticipated to facilitate sodium getting retained by the kidney, This antinatriuretic action of renal sympathetic nerve activation is specifically prominent in the proximal renal tubule **[**17**]**, in addition to proximal renal tubular sodium hyper reabsorption gets ameliorated by renal denervation**[**18**]**.The crosstalk of Na+ /H+ exchanger(NHE-3) as well as SGLT2 possesses a crucial part in the sodium reabsorption in the proximal renal tubule along with escalated renal sympathetic nerve traffick accelerates the expression of NHE-3 as well as SGLT2**[**19**]**, which is implicated in their escalated action in case of HF**[**19-21**]**.

Maximum diuretics do not take care of the sodium reabsorption in the proximal renal tubule. Thereby it is noticeable that SGLT2 hampering agents disrupt expression of NHE-3 as well as SGLT2 in the proximal renal tubule **[**21**]**, along with this effect leads to short term enhancement of fractional excretion of sodium**[**22**]**. HF accelerates the natriuretic actions of hampering SGLT2 (the way it would be anticipated by upregulation of NHE-3 as well as SGLT2 in this condition) **[**19,21**]**, in addition to hampering of renal NHE-3 by SGLT2 hampering agents, they facilitate euvolumia in nondiabetic rats with HF**[**21**]**. Additionally, SGLT2 hampering abrogates renal sympathetic activity along with quantities of renal norepinephrine in situations of escalated nutrients **[**23**]**. Renal denervation mitigates the degree of reactions to SGLT2 hampering in the kidney in animals with (however not without) HF**[**14**]**.Overall these findings place SGLT2 hampering agents in the form of the functional antagonists of renal sympathetic hyperactivity in HF . Nevertheless, any of these sympatholytic effect has the probability of being substantially selective for the renal nerves, in view of SGLT2 hampering does not decrease cardiac sympathetic activity**[**24**]**, as well as has not been illustrated to diminish central sympathetic outflow.

Probable Advantages of SGLT2 Hampering in the form of Osmotic Diuretics

The Probability that SGLT2 hampering agents might possess the capacity of treating HF by functioning in the form of antagonists of renal sympathetic nerve hyperactivity or by abrogating sodium getting retained is attractive(Figure1)**[**rev in ref 24**]**.



Legend for Figure 1.

Courtesy ref no-24-Proposed framework by which SGLT2 (sodium-glucose cotransporter 2) inhibitors might exert cardioprotective and nephroprotective effects by acting to mute renal sympathetic nerve activity and promote natriuresis and osmotic diuresis.

NHE3 indicates sodium-hydrogen exchanger isoform 3.

Nevertheless, it has been tough to illustrate that the SGLT2 hampering agents impact significant natriuretic actions in patients with HF .In this scenario SGLT2 hampering influence a short term osmotic diuretic action with minimum escalation of urinary sodium excretion**[**25**]**, pointing that any enhanced urine volume is correlated with enhanced glucose excretion (along with not sodium) excretion. Nevertheless, sustenance of early escalation of urinary water excretion does not take place in view of activation of adaptive modes which diminishes free water clearance **[**26**]**, reasoning why long term SGLT2 hampering does not result in altered sodium quantities**[**27**]**.

Greater availability of proofs evokes further queries regarding sustenance of diuretic actions might be

implicated for the advantages observed behind SGLT2 hampering agents in the HF having volume overload in contrast to the ones who are euvolumic**[**27**]**. Despite, the formation of modest weight reduction of body weight, apparently this action is correlated with the urinary caloric depletion in addition to fat depots shrinking instead of alterations in fluid status **[**28**]**; alterations in body weight possess a minimal association with alterations in natriuretic peptides**[**30**]**. The escalated haematocrit observed in clinical trial is a postponed action which is correlated with erythrocytosis instead of hemoconcentration **[**29**]**. Despite, SGLT2 hampering agents possess the capacity of decreasing plasma volume, this portrays a compensatory mode which gets stimulated by the escalated red blood cell (RBC) mass**[**30**]**;once there was no reduction in plasma volume, erythrocytosis would results in hypervolemia which might not get tolerated .

It has been posited, that the osmotic diuretics action of SGLT2 hampering agents possess primary reduction in interstitial volume (instead of plasma volume),this posit has been made taking into account remodeling instead of direct determination**[**31**]**. Actually, during the time period when maximum diuretic action of SGLT2 hampering agents are evident(at the time of 1st week of treatment), alterations in cardiac filling pressure in addition to natriuretic peptides are substantially small **[**32**]**.Transitory diuresis does not possess the capacity of reasoning out the alterations in cardiac geometry with any meaning**[**33**]**,or the considerable decrease in the risk of main renal inimical sequelae observed in patients with heart failure , with a reduced ejection**[**34**]**. Any sort of enhancement resulting from the osmotic diuretic action of such agents would be anticipated to be accelerated in case of cases with type2 Diabetes mellitus (T2DM) (who illustrate maximum of glycosuria) however patients with HF do not have the probability of reacting to SGLT2 hampering agents in case of T2DM**[**34,35**]**. On the other hand, presence of previous renal dysfunction would be anticipated to ameliorate the glycosuric in addition to osmotic diuretics action of SGLT2 hampering agents; nevertheless, CKD does not reduce the actions of SGLT2 hampering agents of diminished hospitalization for HF**[**28,36**]**.

Excitement regarding SGLT2 hampering agents working in the form of nephrocentric neurohormonal antagonists primarily or in the form of osmotic diuretics has been posited with the thought that the effectiveness of these agents might be associated with their effects in the kidney in view of the expression of the SGLT2 basically in the proximal renal tubules. A diuretic action of SGLT2 hampering agents might be as the short term advantages of these agents in addition to the escalated delivery of sodium distally might further facilitate the exchanging of sodium for potassium thereby escalating kaliuresis as well as ameliorating the risk of hyperkalemia **[**37**]**.

Apart from these effects renal sympatholysis or escalated urine volume apparently do not aid in the long

term capacity of SGLT2 hampering agents in the reduction of the risk of HF or renal processes.

Probable Significance of Abrogation of Glomerular Hypertension by SGLT2 Hampering Agents

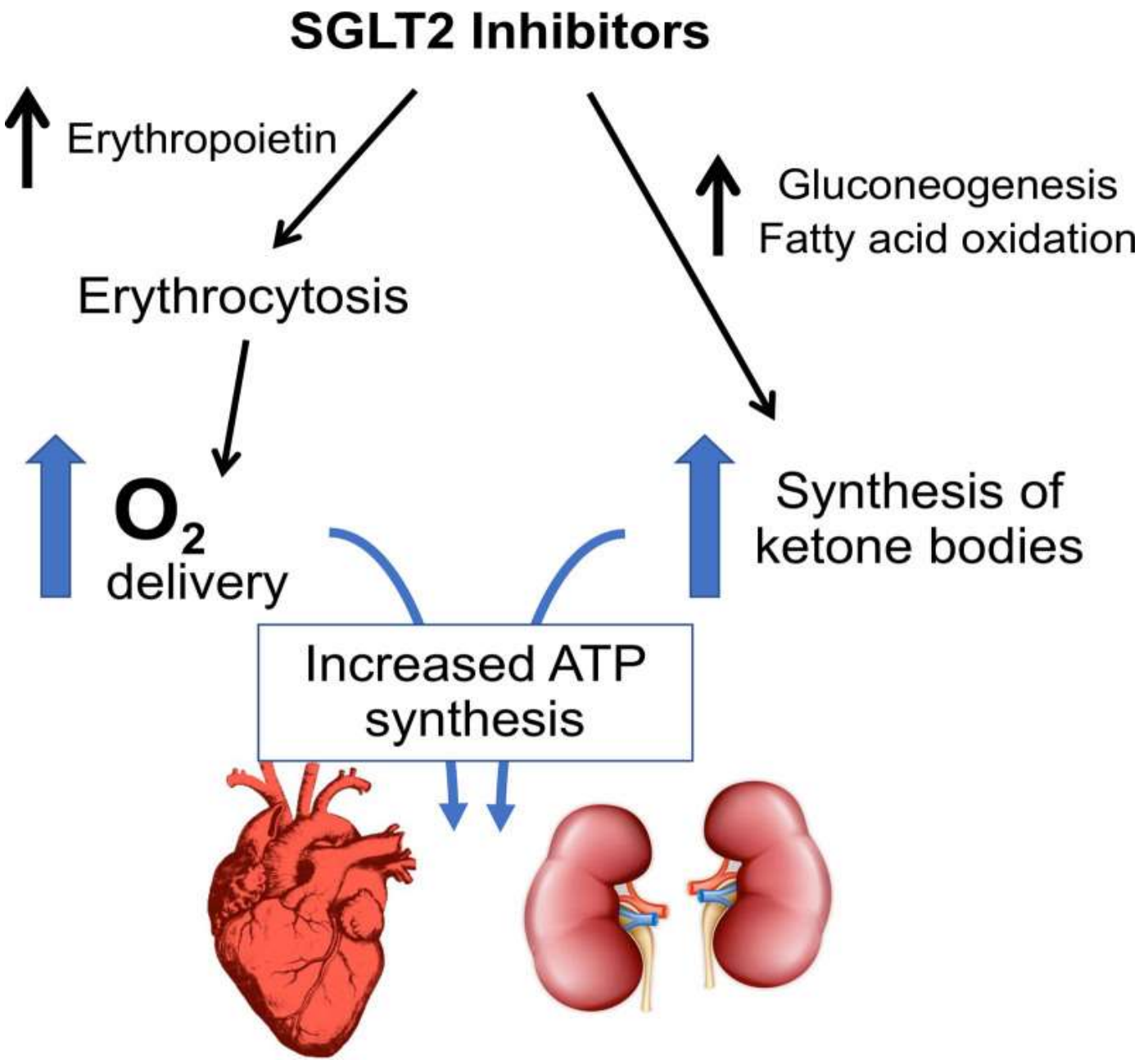
Glomerular hyperfiltration has been considered for long to be the mode behind the propagation of kidney disease in patients with type2 Diabetes. The advantages of angiotensin receptor blockers along with mineralocorticoid receptors antagonists on the evolution of Diabetic Nephropathy have been accounted by the actions of reduced intraglomerular pressures. Nevertheless, the part of glomerular hyperfiltration in the propagation of kidney disease in case of HF has been queried. Angiotensin converting enzyme (ACE2) hampering agents as well as mineralocorticoid receptors antagonists do not illustrate the depletion of nephrons in patients with HF**[**38**]**. Moreover, hampering of neprilysin, decreases the risk of main renal processes in patients with HF, despite the afferent arteriolar vasodilatation generated by cyclic guanosine monophosphate(cGMP) signaling escalates intraglomerular pressures along with albuminuria**[**39**]**.

Uncertainties with regards to the part of glomerular hyperfiltration in the propagation of renal disease in subjects of HF have inserted blocks in attaining insight regarding nephroprotective actions of SGLT2 hampering agents in this condition. Hampering the sodium hyperreabsorption in proximal tubules by SGLT2 hampering agents possess the capacity of escalating intraglomerular pressures, despite this might not be correlated with escalated tubuloglomerular feed back**[**4**]**. Hampering of SGLT2generates a rapid reduction of glomerular filtration rate(GFR) in patients with HF**[**34**]**.The degree of the early decreased glomerular filtration gets abrogated, in patients with renal dysfunction**[**41**]**, nevertheless, the capacity of SGLT2 hampering agents of diminishing the propagation of renal disease is not reduced**[**36**]** . Thereby, it is noticeable that experimental knockout of SGLT2 is enough to mitigate glomerular hyperfiltration, or fibrosis in experimental DM or ischaemia **[**44,5**]**. Any effects of SGLT2 hampering agents of diminishing intraglomerular pressures might not be germane regarding their renoprotective actions in HF.

Probable Effects of SGLT2 Hampering Agents in Facilitating Administration of Energy Substrates

With the elimination of nephrocentric reasoning for the advantages of SGLT2 hampering agents; evaluating researchers have been concentrating on the 2 significant properties of these agents: ketogenesis in addition to erythrocytosis. Ketonemia as well as escalated RBC mass might accelerate the effectiveness of fuels along with oxygen, both might be having a promising action on energy status of heart as well as kidneys

undergoing stress (Figure2).



Legend for Figure 2.

Courtesy ref no-24-Proposed framework by which SGLT2 (sodiumglucosecotransporter 2) inhibitors might act to increase delivery of substrates that could lead to enhanced synthesis of ATP (adenosine triphosphate).

Probable Part of Ketone bodies (KB) Working in the form of Fuel for Heart along with Kidneys

SGLT2 hampering agents by facilitating glycosuria stimulate the generation of a status simulating starvation having the properties of KB formation specifically β-hydroxy butyrate in the liver**[**43**]**. Despite, the infusion of large quantities of β-hydroxy butyrate evokes a positive inotropic along with chronotropic actions, SGLT2 hampering does not generate these haemodynamic actions in patients or in isolated cardiomyocytes**[**32,33,45**]**. Moreover, circulating KBs are escalated in patients with HF**[**46**]**, as well as heart which is undergoing failure are utilizing these KB even previously in the form of a fuel for which they possess preference**[**47**]**, in patients without diabetes, the extent of ketonemia is subdued**[**35,48**]**, however not the advantages in HF**[**34**]**.

Moreover, in case of experimental situations, SGLT2 hampering agents have not escalated with consistency the KBs utilization by the myocardium**[**49**]**, as well as escalated adenosine triphosphate(ATP) generation observed subsequent to SGLT2 hampering agents are not associated with escalated KBs metabolism**[**49**]**. Acceleration of oxidation of KBs is not observed to be advantageous in experimental HF**[**50**]**, in addition to clinically ketogenesis following SGLT2 hampering does not produce escalated myocardial ATPs**[**51**]**. Akin to that nephroprotective actions of SGLT2 hampering agents can not be directly correlated with ketogenesis associated escalation in ATPs**[**52**]**.

Probable part of Erythrocytosis for Escalating Delivery of Tissue Oxygen.

It has been proposed that the escalated tubular workload associated with enhanced delivery of sodium distally subsequent to SGLT2 hampering might generate renal medullary hypoxia**[**53**]**, thereby stimulating the generation of erythropoietin in addition to haemoglobin. Nevertheless, magnetic resonance imaging(MRI) has not been able to pick up the amelioration of renal hypoxia in patients treated with SGLT2 hampering agents**[**54**]**, pointing to enhanced erythropoietin has the probability of being correlated with an action on Hypoxia inducible factor 1(HIF 1)**[**55**]**.

Does the probability exist with regards to escalation of RBC mass result in improvement of tissue oxygen quantities as well as thus decrease HF or renal processes? Canonically hearts which are haemodynamically stressed do not possess reduction of oxygen utilization, however there might be significance of oxygen getting delivered in patients with coronary artery disease(CAD). Nevertheless, the advantages of SGLT2

hampering agents in HF are not escalated in the presence of ischaemic heart disease[35]. Moreover, once there is escalation of RBC mass secondary to erythropoietin-mimetic agents in large scale trials, the risk of the main HF processes or of propagation of renal disease is not decreased despite the presence of anaemia at the time of treatment initiation[56]. Thereby, in toto it has not been validated by all the proofs that the cardio protective/ renoprotective actions of SGLT2 hampering agents might be reasoned by escalated delivery of energy substrates.

Probable Effects of SGLT2 Hampering Agents in Hampering Na+ /H+ Exchange

The working of and sodium –glucose cotransporters in addition to Na+ /H+ exchangers are intricately associated in various organs. The effects of Sodium –glucose specific cotransporter 1(SGLT1) as well as NHE3 are correlated in the intestinal mucosa[57] , in addition to that SGLT1 as well as NHE3 are coplaced in the renal proximal tubule[58],so that hampering of SGLT2 further results in dysfunctional effects of NHE3[21].Thereby there is probability that SGLT2 hampering agents might disrupt other Na+ /H+ exchangers (for instance NHE1[Sodium-hydrogen exchanger 1]. Experimental activation of NHE1 in the heart possesses the capacity of facilitating hypertrophy, cell demise, along with generation of HF[59], which makes us consider them in the form of promising therapeutic targets.

Baartscheer's group[60], posited ,for the 1st time that SGLT2 hampering agents might work as NHE1 antagonists in the heart, theirposit was that these agents possess the capacity of impacting direct advantages over cardiomyocytes ,independent of renal glycosuria or any crosstalk with SGLT2 in view of no SGLT2 expression in myocardium .Rat cardiomyocytes which were incubated with SGLT2 hampering agents, illustrated postponement of pH recovery subsequent to an ammonium ion(NH4+)pulse along with decreased intracellular sodium quantities ,effects which were in agreement with NHE1 hampering , as well as Baartscheer's group[60], displayed a docking area for SGLT2 hampering agents on the NHE1 protein. The actions on the cardiomyocytes were ameliorated by cariporide, a classical NHE1 antagonist.

Although, with these findings, a part for NHE1 hampering in modulating cardiovascular advantages of SGLT2 hampering agents continue to be controversial. Chung, etal.[62], revealed no actions of SGLT2 hampering agents with regards to postponement of pH recovery subsequent to an ammonium ion(NH4+)pulse or in reduction of intracellular sodium quantities, thereby querying the observations of Baartscheer's group[60].On evaluating the variation amongst the 2 studies it was illustrated that study by Chung, etal.[62], got obtained from a substantially larger sample size[61,62]. Osaka etal.[63], reported that

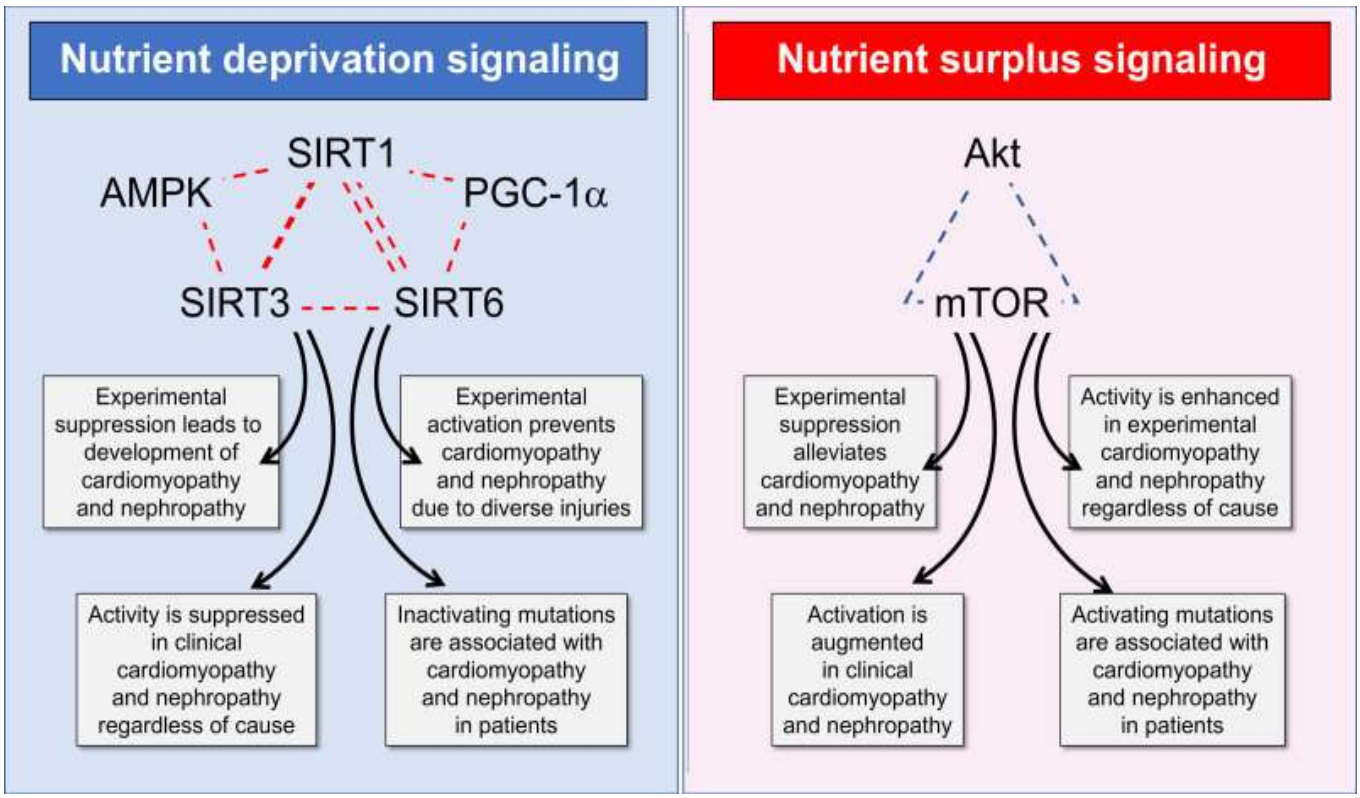
hampering SGLT2 hampered NHE1, however the actions were considerable lesser in contrast to that observed with cariporide. Nevertheless, Li etal.**[**45**]**, could not demonstrate any significant docking of empagliflozin to NHE1 in addition to revealed that cariporide failed to simulate the effects of SGLT2 hampering agents on isolated cardiomyocytes. Thereby, if any actions of SGLT2 hampering agents in blunting the escalated intracellular sodium quantities, it might be occurring in view of their actions on decreasing cellular stress or in view of an actions on the late sodium current**[**55,64**]**.

Effects of SGLT2 Hampering Agents in Facilitating Nutrient Deprivation Signaling& Autophagy for Decreasing Cellular Stress & Facilitate Survival

The crucial biomarkers of the effects of SGLT2 hampering agents-namely ketogenesis in addition to erythrocytosis- portray the canonical reactions to nutrient as well as oxygen deprivation **[**55**]**. SGLT2 hampering agents further diminish serum uric acid (a biomarker for oxidative stress(OS)**]** in patients with HF**[**65**]**.What is the manner which correlates these 3 biomarkers? escalated deprivation signaling of nutrient as well as oxygen possess the capacity of facilitating erythropoietin development as well as diminishes OS in case of cardiomyocytes along with renal parenchymal cells**[**55**]**. Thereby, it is noticeable that mediation evaluation of large scale outcome trials in patients of T2DM have constantly identified escalated haemoglobin as well as diminished serum uric acid in the form of statistical estimators of the capacity of SGLT2 hampering agents in decreasing hospitalization in addition to main renal inimical processes **[**66.67**]**.Overall considering these findings with extensive outcomes available from experimental studies have resulted in the posit that the cardiorenal advantages of SGLT2 hampering agents are associated with nutrient deprivation signaling with its correlated actions of facilitating autophagy in addition to mitochondrial health, reduction of formation of Reactive oxygen species(ROS), blunt inflammation along with fibrosis as well as escalate the viability of cardiomyocytes along with renal parenchymal cells**[**55**]** . Despite, this reaction might get stimulated by an effect of SGLT2 hampering agents resulting in a state of simulating starvation in view of urinary depletion of calories**[**68**]**,multiple studies released in the past 2 yrs have illustrated that the adaptive cellular reprogramming formed by these agents is observed in isolated cell cultures pointing that SGLT2 hampering agents possess direct glycosuria independent effects for decreasing cellular stress in addition to facilitate cellular survival .

Nutrient Sensors along with cellular Signaling in the Heart along with Kidneys During Health &Disease

SGLT2protein works in the form of a sensor of energy, finding an escalated nutrient state at the time of enhancement of glucose in the proximal renal tubules along with alteration in SGLT2 are consistent with alteration in other sensors of energy in reactions to alterations in nutrients milieu**[**69**]**. On being challenged with alteration in extracellular glucose along with amino acids, crosstalk of various master switches ensure adaptation of cells for facilitating growth as well as survival. These are inclusive of mammalian target of rapamycin (mTOR); Sirtuins (SIRT1), SIRT3 as well as SIRT6; AMP-activated protein kinase(AMPK).see Figure 3.



Legend for Figure 6.

Courtesy ref no-24- Effect of nutrient deprivation and nutrient surplus signaling on the evolution and progression of cardiomyopathy and nephropathy in experimental and clinical settings.

Akt indicates protein kinase B; AMPK, adenosine monophosphate–activated protein kinase; mTOR, mammalian target of rapamycin; PGC-1α, peroxisome proliferator–activated receptor γ coactivator 1-α;

SIRT1, sirtuin 1; SIRT3, sirtuin 3; and SIRT6, sirtuin 6.

Mammalian target of rapamycin(mTOR)

mTOR represents a serine /threonine protein kinase which gets activated by abundance of amino acids milieu as well as facilitates cellular growth along with proliferation . Presence of mTOR takes place in the form of 2 complexes; mTOR complex1(mTORC1) as well as mTOR complex2(mTORC2) of which mTORC1 get potentiated by Akt(protein kinase B),that is hampered by rapamycin . Akt / mTORC1 signaling impacts numerous downstream effectors for facilitating anabolic pathway -i)guiding the mitochondrial generation of ROS for promoting cellular reproduction,ii) proinflammatory pathways, iii)innate immunity in addition to iv) escalating the expression of Senescence- associated secretory phenotype(SASP) which is imperative for cellular depletion that is the requirement for efficacious growth of organs**[**70**]**.The effects of mTOR actions in facilitating the anabolic pathway is needed for cardiomyocytes proliferation at the time of fetal generation along with adaptive hypertrophy at the time of considerable pressure overload **[**71**]**, however it results in maladaptive cardiac remodeling on activation in hearts damaged during adulthood. In case of experimental model, cardiac-particular over activation of Akt / mTOR pathway results in induction of HF **[**72**]**, while repression of Akt or mTOR signaling abrogates generation of cardiomyopathy **[**73**]**. Akin to that Akt / mTOR signaling gets hyperactivated in the Kidney in case of abundance of nutrient state; thereby stimulating proinflammatory pathway, thus facilitating renal damage **[**74**]**, while hampering of mTOR abrogates fibrosis as well as generation of CKD **[**75**]**.

In this clinical scenario patients presenting with dilated cardiomyopathy illustrate abnormal mTORC1 activation, the degree of which is associated with robustness of cardiac fibrosis as well as poor prognosis **[**76**]**. Akt activation in the human myocardium possess the properties of transitioning from a good compensated left ventricular hypertrophy to decompensated HF **[**77**]**. Variation amongst mTOR activating sequences might result in clinical cardiomyopathy as well as kidney tubulopathy **[**78**]**, along with renal mTORC1 activation is correlated with disease as well as prognosis in patients with non-diabetic kidney disease**[**79**]**.

SIRT1 along with other Sirtuins

Sirtuins, (or silent information regulator 2 family- SIRT family) Sirtuins, reflects a family of NAD+/

nicotinamide adenine dinucleotide (NAD+)-based protein deacetylases along with ADP ribosyl transferases have been revealed tobe key controllers of genome sustenance, ageing in addition to chromosomal intactness of oocyte**[**80**]**. Escalating proof has validated that interplay amongst ROS as well as Sirtuins family possesses crucial part in controlling the cellular ageing events. Sirtuins, further have been illustrated to confer protection from OS **[**81**]**. They represent Class III histone deacetylases(HDACs) that are comprised of 7 subtypes(SIRT1-SIRT7) with various subcellular placements as well as functions. These proteins might be probable markers regarding ovarian ageing along with SIRT1, SIRT3, as well as SIRT6 are acknowledged to be target molecule for postponement of organs ageing**[**82**]**.They catalyze post-translational modifications of numerous proteins implicated in metabolism in addition to sustenance of cellular homeostasis. They work in the form of a redox rheostat(rheostat is a variable resistor utilized for controlling current. Furthermore they possess the capacity of varying resistance in case of a circuit without any break)as well as portrays the primary cellular reactions to glucose deprivation. Akin working gets shared amongst, SIRT1 SIRT3, as well as SIRT6 . SIRT 1 along with SIRT 2 exist in nucleus as well as cytoplasm. SIRT 3 is basically placed in mitochondria along with nucleus**[4]**. SIRT 4 ,SIRT5 along with SIRT 6, represent mitochondrial sirtuins, whereas SIRT 6, SIRT 7are located in nucleus. Cardiac particular depletion or repression of SIRT1 SIRT3, as well as SIRT6 accelerates generation of ROS, escalated endoplasmic reticulum (ER) stress in addition to results in sensitization of heart to damage resulting in cardiomyopathy**[**83**]**. On the other hand, SIRT1, SIRT3, as well as SIRT6 abundance or activation ameliorates OS or ER stress, removes impaired mitochondria as well as facilitates mitochondrial biogeneration, attenuates cell senescence, as well as demise, attenuates fibrosis along with remodeling conserves cardiac working**[**84**]**. SIRT1, SIRT3, as well as SIRT6 deficiencies lead to aggravation of glomerular damage as well as glomerulosclerosis subsequent to renal stress**[**85**]**. In addition to that activation of SIRT1 SIRT3, as well as SIRT6 is correlated with decreased OS, tubulointerstitial inflammation along with fibrosis, mitigation of glomerular as well as tubular damage; sustenance of renal function**[**86**]**.The adaptive actions of sirtuins on health of organelles along with cellular stress which gets aggravated by the downstream effector Peroxisome Proliferator Activated Receptor γCoactivator -1α(PGC-1α) that possesses a crucial part in the mitochondrial biogeneration as well as PGC-1α has been held responsible in the pathogenesis of experimental cardiomyopathy along with nephropathy**[**87**]**.

At the time of clinical scenario patients with cardiomyopathy illustrate repression of the expression of SIRT1, SIRT3, as well as PGC-1α**[**88**]**, along with point sequence differences in the genes for SIRT3, as well as PGC-1α**[**89.**]**.

Loss of function polymorphisms in the SIRT1 gene escalates the risk of CKD in the patients with T2DM [90]. There is repression of glomerular expression of SIRT6 in the subjects having Diabetes [85]; reduction of serum SIRT1 quantities along with a fall concurrently with the generation of albuminuria[91]. Apart from that an inverse association exists amongst the expression of SIRT1 along with SIRT 2 in the human diabetic kidney [69].

AMP-activated protein kinase(AMPK)

AMPK portrays a serine /threonine kinase which detects the balance amongst cytosolic quantities of ATP along with adenosine mono phosphate(AMP). Activation of AMPK takes place at the time of low ATP: AMP ratio which phosphorylates downstream proteins which facilitate escalated catabolism as well as reduced anabolism, thus escalating ATP generation[199] . Knockout or repression of AMPK decreases the capacity of heart to react to stress, facilitates cardiac aging as well as results in cardiomyopathy [93]. AMPK activation abrogates OS, mitochondrial impairment, proinflammatory pathways, fibrosis, apoptosis along with conserves ventricular working at the time of cellular stress generated by ischaemia, diabetes, pressure overload, or substances that are cardiotoxic[94]. Dysfunctional AMPK activity which is present in diabetic kidney aids in the generation of nephropathy[95]. Moreover, AMPK activation facilitates glomerular health as well as podocyte survival in addition to decreases tubular damage stimulated by metabolic stresses, ischaemia along with substances that are nephrotoxic [96].

At the time of clinical scenario patients with sequence differences in the PPKAG2 gene (that encodes AMPK subunit) generates cardiomyopathy with atrial as well as ventricular fibrillation [97]. Sequence variants of PPKAG2 gene are further correlated with augmented reduction in the glomerular filtration rate (GFR) along with generation of kidney disease in general population along with patients with diabetes[98].

All these 3 master controllers mTOR, sirtuins as well as AMPK modulates alterations in cellular biology which aid the organism with regards to adaptation to the opportunities along with problems correlated with environment. In the case of abundance of nutrients organisms give a priority to utilization of fuels for expansion of cell mass along with mTOR signaling, being central to this event .In comparison to that at the time of nutrients depletion taking place, anabolic pathways are blocked by the organism as well as utilization of biological situations that prove to be working in the conservation of structural along with functional intactness of the cells that are present; Sirtuins, PGC-1α as well as AMPK, are key for this reaction. The set

point for the crosstalk of these master controllers gets estimated by the quantities of nutrients along with redox status[99].

Noticeably, considerable intercommunication exists at the molecular level amongst SIRT1 / PGC-1α as well as Akt/ mTOR pathway. SIRT1 in addition to PGC-1α possess the capacity of negatively controlling the transcription of Akt as well as directly disrupt the effects of Akt along with mTOR [100]. On the other hand, Akt upregulation results in repression of PGC-1α, while hampering of mTOR by rapamycin or downregulation of Akt results in activation of SIRT1 in addition to PGC-1α [101]. The actions of AMPK in facilitating NAD+ results in SIRT1 activation [102], besides AMPK possess the capacity of activating PGC-1α by phosphorylation [103]. On the other hand, AMPK has the capacity of hampering mTOR by an effect on Akt in addition to directly acting on the mTORC1complex [104].

Effects of Nutrient Sensors on Impacting Cellular Stress by Modulating Autophagy

The crosstalk of the effects of mTOR, sirtuins along with AMPK, master controllers for decreasing cellular stress in addition to facilitating cellular survival might be basically modulated by their effects of impacting cellular house keeping event of autophagy. Autophagy represents necessary controlled along with conserved catabolic events which modulate recycling along with breakdown of various cytoplasmic constituents of the eukaryotic cell[105]. Macroautophagy ,the maximum functional along with properties of kinds of autophagy implicated in the generation of double membranevesicle alias autophagosome that result in elimination of injured organelles or undesired cellular constitutents by administration to lysosomes for fusion for aiding breakdown enzymes to degrade the vesicular contents [106].The basic stimulus for autophagy is nutrient deprivation, along with on non selective activation, autophagy aids in recycling of the cellular components that produce ATP for cells which are starved of energy[107]. Nevertheless, autophagic flux might further get selectively activated in reaction to a wide variety of cellular stresses inclusive of OS as well as ERstress. The maximum significant stimuli for OS would be impaired mitochondria, as well as peroxisomes in addition to labelling of this clearance is known as mitophagy, along with peroxophagy. ERstress canonically takes place in view of accrual of misfolded proteins or glucose or fatty acid intermediates for which variable cellular damages might be implicated. Clearance by autophagy of such injured cellular components substantially decreases cellular stress along with autophagic flux further directly works to attenuate proinflammatory in addition to profibrotic reactions[108].The total actions of escalated autophagic flux is for conservation of cellular intactness along with avoidance of cell demise, thereby sustenance in addition

to restored organ structure as well as function.

Guidance of autophagic flux takes place by the crosstalk of nutrient deprivation along with sensors for the abundance of nutrients. The initiation of generation of autophagosome takes place by the concurrent crosstalk of ULK1(Unc-51 like kinase 1) complex with the Beclin1- PI3KC3 (Class III phosphatidyl inositol 3 - kinase) complex[107,108]. ULK1 gets activated by AMPK; however phosphorylation of ULK1 by mTORC1 avoidsits activation. Activation of Beclin1 takes place subsequent to deacetylation by SIRT1[109], in addition to toll like receptor 9 (TLR9) crosstalk with Beclin1 for controlling the PI3KC3 complex in getting assembled[110].Attempting explanation of multiple impacts of mTOR, Sirtuins along with AMPK over the constitutents of the autophagic machine is not feasible here.

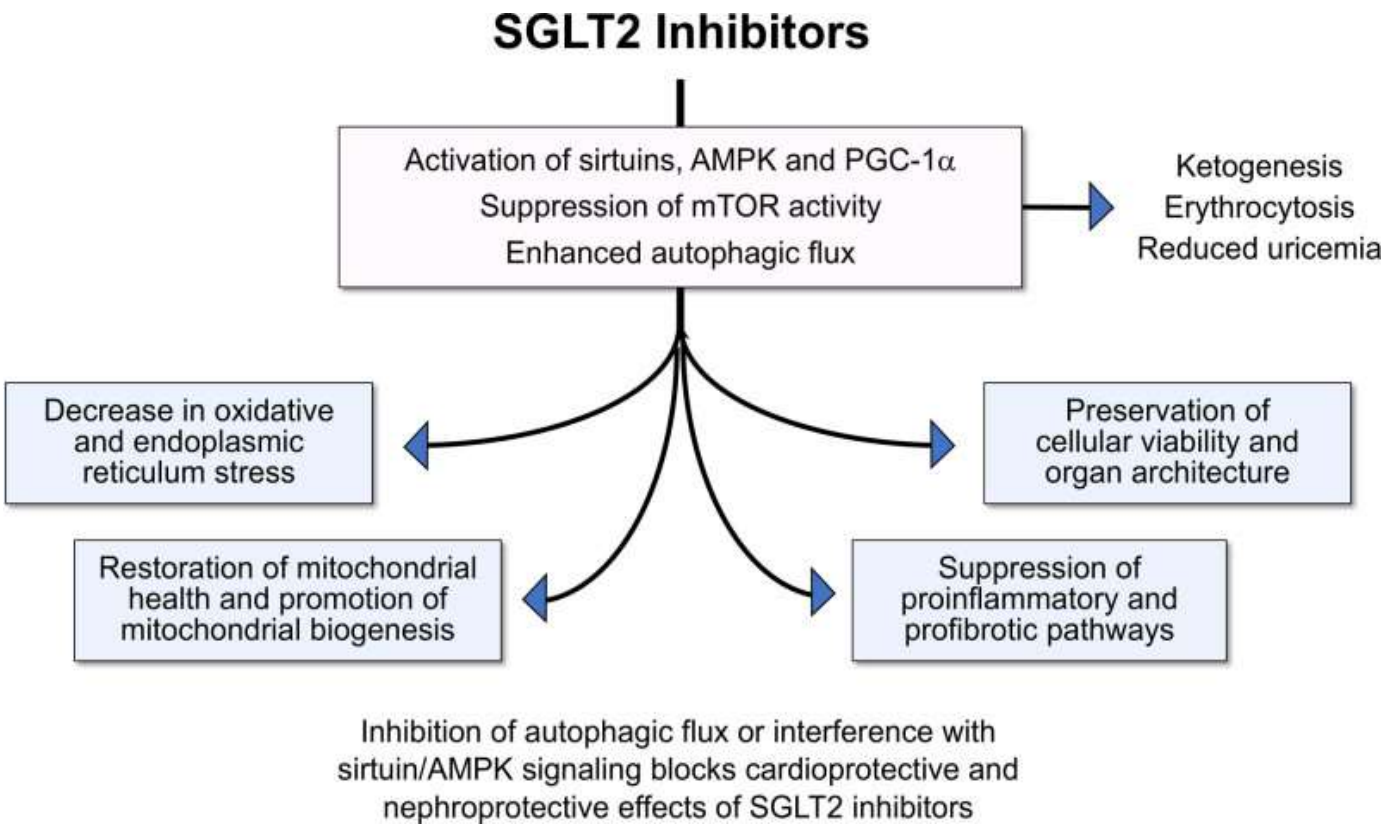
The adaptive effects of autophagy are specifically significant with regards to heart as well as kidney. Heart as well as kidney, both possess abundance of mitochondria, as well as peroxisomes in view of which they have the escalated capacity of utilization of oxygen, thus forming ROS. Abrogation of OS along with ER stress specifically is significant in cardiomyocytes in view of non proliferative cells do not have the capacity of replacement of cells which have undergone demise. Chronic HF as well as CKD possess the properties of accrual of intracellular debris in addition to inimical metabolic intermediates, considerable enhancement of OS as well as activation of proinflammatory as well as profibrotic signaling[60]. Autophagic flux mirrors a main adaptation along with restoration reaction; dysfunctional autophagy drastically escalates the probability of an injurious process would be resulting in generation of cardiomyopathy along with nephropathy[111]. Despite, escalated stimulation of autophagy might have an inimical impact on the heart(specifically subsequent to acutely presented substantial stress in case of lack of HF)[112] estimated aggravation of selective autophagy confers protection on the heart against pressure overload, hypoxia as well as damage generated by cardiotoxic substances[113] along with protect podocytes as well as renal tubular cells from injury which take place from diabetes, ischaemia along with substances that are nephrotoxic[114].

Escalated autophagic vacuoles in case of patients who illustrate reverse cardiac remodeling or get mechanical unloading[115], while continued dysfunction in autophagic flux in the human heart undergoing failure, represents a poor sign for prognosis[116]. Akin to that, autophagic working is subdued in renal tubular cells in case of patients having Diabetic nephropathy[117], in addition to elimination of autophagosome is an emblem of chronic graft dysfunction in case of patients having had a renal transplant[118].In comparison, enhanced autophagosome in podocytes portrays a warning with regards to

an imminent conservation of glomerular working along with a decreased risk of propagation in patients having kidney Disease**[**119**]**.

Actions of SGLT2 Hampering Agents on Nutrient Deprivation Signaling,Autophagic flux, cellular stress in Experimental Cardiomyopathy& Nephropathy

SGLT2 hampering agents generate a substantially unique design of promising actions on the evolution along with propagation of cardiomyopathy as well as nephropathy in experimental animals(Figure4).



Courtesy ref no-24-- Proposed framework by which SGLT2 (sodium-glucose cotransporter 2) inhibitors can modulate nutrient deprivation signaling and thereby enhance autophagic flux and reduce cellular stress.

AMPK indicates adenosine monophosphate–activated protein kinase; mTOR, mammalian target of rapamycin; and PGC-1α, peroxisome proliferator–activated receptor γ coactivator 1-α.

1) Firstly SGLT2 hampering agents continuously escalate the autophagic flux(inclusive of mitophagy) in the heart along with kidney; the effects on acceleration of autophagy is observed in tissues procured from animals which chronically received treatment in addition to isolated cell cultures which had been perfused with pressure SGLT2 hampering agents.

2) Secondly SGLT2 hampering agents blunt the development of ROS, ii) escalate the antioxidant modes along with attenuate ER stress**[**120-123**]** .

3) Third SGLT2 hampering agents augmented the elimination of damage mitochondria, ii) resulted in restoration of healthy mitochondrial working, iii) facilitate mitochondrial bio generation**[**121,122**]**,iv) escalated mitochondrial mass is the property of these agents as evidenced by electron microscopy**[**124**]**.

4) Fourth SGLT2 hampering agents decrease fibrosis as well as inflammation by disturbing the activation of nuclear factor κB(NFκB) in addition to nucleotide-binding domain, leucine-rich-repeat containing family, pyrin domain-containing 3(NLRP3) inflammasome thereby decreasing the generation of proinflammatory cytokines ii) further these agents blunt the profibrotic pathways, fibroblast proliferation, collagen getting deposited **[**125**]**.

5) Fifth SGLT2 hampering agents conserve cellular functions as well as intactnes , avoidance of cellular depletion by apoptosis, in addition to senescence as well as they work for sustenance of normal architecture of tissues resulting in avoidance of inimical structural remodeling apart from restoration of working of organs**[**33,45,121,126**]**.This kind of typical pattern of cellular along with tissue reactions have been found with different SGLT2 hampering agents in in experimental cardiomyopathy along with nephropathy irrespective of the stimulating mode.

The unique fashion of cellular along with tissue of SGLT2 hampering agents in the heart along with kidney are constantly correlated with concurrent upregulation of nutrient deprivation signaling as well as downregulation of nutrient abundance signaling. The actions of SGLT2 hampering agents in decreasing OS, escalated mitochondrial intactness, blunt the inflammatory pathways in addition to conservation of cell viability take place concurrently with escalated expression of AMPK, SIRT1, SIRT3, SIRT6 as well as PGC-1α in addition to reduced activation of mTOR in variable tissues at the time of stress specifically in cardiomyopathy along with nephropathy which gets stimulated experimentally**[**33,43,68,69,75,89,121-122,123,125,126**]**.The escalated AMPK, in addition to autophagic flux further reasons out the escalated

generation of ATP which gets observed in heart along with kidneys, both subsequent to experimental as well as clinical observations following SGLT2 hampering agents[33,43,127].

At the time of the initial posit given by PackerM in 2020 regarding SGLT2 escalated nutrient deprivation signaling in addition to autophagic flux[55], there were just occasional reports which confirmed these observations. Nevertheless, in the last 2yrs,practically 60 more studies have been in the arena utilization of wide variety of experimental situations as well as strategies with all of them validating the posit hypothesized to start with. Alterations in nutrient deprivation signaling along with signaling regarding abundance generated by SGLT2 hampering agents have been observed in whole organs obtained or isolated cell cultures as well as have further been detected in tissues which express SGLT2(for instance renal tubular cells) in addition to tissues which do not (for instance heart).They have further been illustrated in endothelium, liver, adipose tissue(AT).Of maximum significance, in greater percentage of these publications, once the actions of SGLT2 hampering agents facilitated the activation of AMPK, SIRT1, SIRT3, as well as SIRT6 were abrogated by particular pharmacologic hampering or knockdown of nutrient deprivation signaling or once their capacity of facilitating autophagy had been genetically/ pharmacologically blocked the advantageous actions of SGLT2 hampering agents in blocking OS , facilitate healthy mitochondria, ameliorate fibrosis as well as inflammation, sustenance of cell viability in addition to intactness of organs got abrogated. These experimental findings in toto yielded remarkable proof regarding cardioprotective along with nephroprotective actions of SGLT2 hampering agents might be reasoned by their effects of modulation of nutrients as well as energy sensors along with their downstream actions for facilitating autophagy.

Now the other query arises are the nutrient deprivation signaling pathways activated at the time of utilization of SGLT2 hampering agents in the clinical scenario? AMPK, SIRT1, SIRT3, as well as PGC-1α portray the hallmark of the reactions of the body to starvation; as well as there production in the liver is escalated subsequent to remarkable depletion of calories(like following SGLT2 hampering agents utilized)[68].Once induction of glycosuria has taken place activation of SIRT3, as well as PGC-1α aids in blood glucose by facilitating gluconeogenesis[68,128]-an inimitable metabolic signatures of SGLT2 hampering agents(illustrated clinically), that restricts their antihyperglycemic reactions[129]. Fatty acids oxidation gets facilitated by activation of AMPK along with PGC-1α which further escalates generation of SIRT1, as well as SIRT3, followed by stimulation of 3 hydroxy,3 methyl glutaryl-coenzyme synthase, the rate restricting enzyme for generation of Ketone bodies(KB)[130].Thus resultantly AMPK, SIRT1, SIRT3, as well as PGC-

1α work concomitantly for facilitating ketogenesis in the liver along with clinical observation of ketogenesis at the time of starvation in addition to subsequent to SGLT2 hampering agents mirrors escalated nutrient deprivation signaling, as well as SIRT1 causes activation Hypoxia inducible factor 2α(HIF2α)**[**131**]**, the master controllers for the formation of erythropoietin along with stimulus for erythrocytosis. The effects of SIRT1 in decreasing OS can further aid in the reduction of the uric acid liberation found in patients having treatment with SGLT2 hampering agents**[**72**]** as well as SIRT1 possesses the capacity of directly stimulating uric acid liberation**[**132**]**.The concomitant observation of ketogenesis, erythrocytosis, as well as decreased uricaemia in the clinical trials with SGLT2 hampering agents indicate that nutrient deprivation signaling gets upregulated in patients having treatment with SGLT2 hampering agents. Escalated AMPK along with SIRT1 actions further directly escalate tubuloglomerular feed back **[**132**]**,thus associating alterations of these sensors of energy with the actions of SGLT2 hampering agents for decreasing GFR at a fast pace agents in the Clinical scenario**[**34**]**.Recently Proteomic assessment of blood samples obtained from greater than1100 patients having HF prior to as well as subsequent to treatment with placebo or empagliflozin isolated restricted levels of proteins whose serum contents quantities were significant altered secondary to SGLT2 hampering agents**[**133**]**.Out of the21 proteins that were enhanced differentially, with acknowledged actions on the heart in addition to kidney,6 were associated in facilitating of autophagy in heart , kidney, endothelium, in addition to 4 proteins; insulin like growth factor(IGF1) binding protein1(IGF1BP1), transferrin receptor protein1(TIR1), erythropoietin , adipocytes fatty acid binding protein(AFABP) are further acknowledged to be upregulated subsequent to SIRT1 signaling**[**131,132**]**. Ferraninietal.**[**133**]**, further noticed differential escalation of the latter proteins in a second Proteomic evaluation of blood samples obtained from patients having T2D.Neither of these 2 Proteomic evaluations conducted direct determination of SIRT1, SIRT3, as well as PGC-1α, or phosphorylated AMPK; however no clarification exists regarding alterations in blood quantities of these proteins possess the capability of representing significance of their intracellular effects with precision.

Modes behind cellular advantages of SGLT2 hampering agents in organs not expressing SGLT2

What is the mode by which SGLT2 hampering agents facilitate nutrient deprivation signaling in addition to autophagic flux with their associated advantageous actions on cellular stress, homeostasis in addition to cellular survival in tissues not expressing SGLT2?3 probabilities are feasible. I) glycosuric caloric

depletionii) ketogenesis stimulated autophagic flux iii) direct nutrient independent cellular actions.

Glycosuric Caloric Depletion

SGLT2 hampering agents generation remarkable elimination of calories in the urine along with the associated elimination of glucose possesses the capacity of stimulating system-wide upregulation of nutrient deprivation signaling in case of organs right through body ,a switch which can take place irrespective of the existence or lack of SGLT2 in a particular tissue**[**68**]**. In view of the effects of SGLT2 hampering agents in facilitating gluconeogenesis via SIRT1restricts the decrease in glucose, glycosuria works in the form of a switch for transferring the set point amongst the SIRT1 signaling as well as glycemia; thereby leading to upregulation of nutrient deprivation signaling can take place with SGLT2 hampering agents despite just moderate reduction of blood glucose**[**61**]**.This posit might reason out the revealed association of escalation of erythropoietin levels patients having treatment with SGLT2 hampering agent**[**136**]**. Nevertheless, this posit is tough to adapt with the acknowledged finding regarding CKD evokes a dysfunctional glycosuric reaction to SGLT2 hampering agents; however it does not decrease the capacity of these agents in decreasing HF in addition to main renal processes**[**28,36**]**.

Ketone bodies(KB) stimulated Nutrient Deprivation Signaling along with Autophagic Flux

Akin to starvation SGLT2 hampering agents simulate that situations having the properties of ketogenesis**[**46,51**]** along with administration of Ketone bodies(KB) to the organs have the capacity of directly escalating AMPK, in addition to decreasing mTOR phosphorylation for escalating the expression of PGC-1α along with facilitate the autophagic flux**[**52,137**]**. Probably working via these mediators ketonemia has been illustrated to decrease OS, block inflammation, conserve cardiac in addition to the renal function subsequent to different stresses**[**52,137**]**. Supplementation with KB hampers hypertrophy stimulated by phenylephrine at the time of experiments**[**137**]**, as well as disturbance of ketonemia observed subsequent to utilization of SGLT2 hampering agents might impact cardioprotective along with nephroprotective actions of SGLT2 hampering agents secondary to direct effects on stimulating nutrient deprivation signaling instead of in view of the capacity of working in the form of an efficacious fuel regarding ATP production . Nevertheless, in the existence of Diabetes there is mitigation of degree of ketonemia, however it does not impact the Cardiorenal advantages produced by SGLT2 hampering agents**[**34,35,48**]**. Moreover , SGLT2 hampering agents have direct advantageous actions on the heart as

well as kidney in isolated cell cultures/preparation, that are not getting exposed to variations in the KB content in the milieu.

Direct glucose along with in Ketone independent Cellular Actions

Furthermore, SGLT2 hampering agents possess the capacity of directly exerting cellular actions which are independent of alterations in glucose stimulated by elimination of glucose by the kidneys orgeneration of KB in the liver. Multiple studies have illustrated that SGLT2 hampering agents possess the capacity of enhancement of nutrient deprivation signaling, facilitate autophagy, sustenance of mitochondrial health, blunt cellular stresses, ameliorate proinflammatory as well as profibrotic pathways in isolated organs in addition to cell cultures-namely experimental situations, where the quantities of glucose / Ketones are maintained at same quantities. studies illustrating the direct actions of these agents over isolated cardiomyocytes ,podocytes, proximal renal tubular cells have further displayed regarding the cardioprotective along with nephroprotective advantages produced by SGLT2 hampering agents are not on alterations in cardiovascular physiology(alterations in BP or renal sympathetic tone); on alterations in proximal renal tubular working(glycosuria or natriuresis);or on alterations in the quantities of blood components (hemoglobin , glucose , uric acid Ketone).

Another query is the mode by which SGLT2 hampering agents have a action on cardiac in addition to the renal parenchymal cells for conservation of homeostasis along with survival ? numerous studies have been conducted in cells which express SGLT2, experimentally or Clinically. It is feasible that the utilization of quantities of SGLT2 hampering agents in some experiments might be disrupting other glucose transporters. Kondo et al.**[**138), pointed that the cardioprotective actions generated by canagliflozin was correlated with of hampering of SGLT1**[**139**]**, however empagliflozin(that does not hamper SGLT1) generates cardioprotective actions on isolated cardiomyocytes. Li et al.**[**48), have posited that empagliflozin might dock with glucose transporter1(GLUT1) in addition to GLUT4 receptors for hampering cellular glucose uptake, that might stimulate nutrient deprivation signaling as well as autophagy. This hampering actions of SGLT2 hampering agents on GLUT receptors has been posited by others as well**[**140**]**; however there is requirement of validating it. Probable actions of SGLT2 hampering agents on ion or reduced Calcium(Ca2+ / calmodulin dependent kinase**[**141**]** does not have the capacity of reasoning out their actions on nutrient deprivation signaling as well as autophagy**[**142**]**. in view of SGLT2 work with in the form sensors for nutrient abundance , it is noticeable that there is existence of an inverse association amongst SGLT2 in

addition to nutrient deprivation signaling in distinctive cells. This finding incites the probability that SGLT2 hampering agents might be directly binding to nutrient sensors for impacting their working. Sun et al.**[**143), displayed that canagliflozin binds to mTOR in the akin structural domain utilized by rapamycin. Ying et al.**[**144), illustrated that phloretin(a hamper or of SGLT1 along with SGLT2) attenuates cardiomyocytes damage by upregulation of SGLT1 along with displayed that phloretin docks directly with SIRT1 for generating a complex which is stable. WangCY et al.**[**89), hypothesized that empagliflozin works directly on SIRT3 to facilitate the generation of a complex comprised of SIRT3 , Beclin1 along with TLR 9, that results in escalation of autophagic flux. They performed an experimental knockout of either SIRT3 or TLR 9 and found they attenuated the capacity of SGLT2 hampering from conferring protection to the heart from damage in case of doxorubicin toxicity. WangCY et al. **[**89), further isolated 3 patients with dilated cardiomyopathy who had undergone myocardial biopsy prior to along with subsequent to empagliflozin treatment for 28 days. 2 patients not having SIRT3 variant illustrated the anticipated escalation of mitochondrial respiration in addition to expression of TLR 9 subsequent to empagliflozin treatment; nevertheless, these alterations were not observed in a patient having loss of function SIRT3 variant in the myocardium **[**89**]**.

Conclusions

SGLT2 hampering agents generate a unique fashion of advantageous actions on the evolution in addition to propagation of cardiomyopathy along with nephropathy having the properties of diminished Oxidative along with endoplasmic reticulum (ER) stress, restored mitochondrial working, escalated mitochondrial biogeneration, reduction in proinflammatory as well as profibrotic pathways, conservation of cellular intactness along with viability, sustenance of normal organ structure as well as working. A remarkable corroboration is present pointing to the canonical fashion of SGLT2 hampering agents in cellular housekeeping by escalating autophagic flux, an action which might be associated with the actions of such agents for generating concomitant upregulation of nutrient deprivation signaling in addition to downregulation of nutrient surplus signaling, the way presenting by an escalation in the expression along with activity of AMPK, SIRT1, SIRT3 in addition to SIRT6, as well as PGC-1α along with reduction in activation of mTOR .The unique fashion of cardioprotective in addition to renoprotective actions of SGLT2-hampering agents got ameliorated by particular hampering/knockdown of autophagy, AMPK as well as Sirtuins. In the clinical scenario, this design of differentially escalated proteins by proteomic evaluation of

the blood acquired at the time of randomized controlled triasl(RCT),is parallel with these observations. Clinical studies have further illustrated that SGLT2- hampering agents facilitate gluconeogenesis, ketogenesis in addition to erythrocytosis as well as diminished uricemia, the emblem of nutrient deprivation signaling in addition to the key statistical modulator the capacity of SGLT2- hampering agents for reduction of risk of HF as well as robust renal processes. The effects of SGLT2- hampering agents to exaggerate autophagic flux is found in secluded cells in addition to tissues which do not express SGLT2;thereby not exposed to alterations in glucose or ketones in their milieu along with might be associated with the capacity of these agents to directly bind to sirtuins or mTOR. Alterations in renal or cardiovascular physiology or metabolism can't be reasoned out by the advantageous actions of SGLT2- hampering agents in clinical scenario / experimental ones. The direct molecular actions of SGLT2- hampering agents in secluded cells are in agreement with the belief that SGLT2 works in the form of nutrient excess sensor , thereby its hampering results in nutrient deprivation signaling with its associated cytoprotective actions which can be abrogated by hampering/ knockdown of autophagy, AMPK as well as sirtuins. Having reviewed earlier with regards to how no treatment existed for diastolic dysfunction it was very tough to get insight on how these SGLT2- hampering agents were of advantage in Cardiovascular Outcome Trials (CVOT's) trials of SGLT2-hampering agents and further observed advantageous actions on the 1 of authors herself when none of SGLT2 receptors are present in the heart. Thus this nutrient deprivation signaling in the presence of nutrient excess downregulation in addition to autophagic flux explain this.

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