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DIABIZ (DAPAGLIFLOZIN) - PROTECTIVE EFFECTS OF SODIUM GLUCOSE COTRANSPORTER 2 INHIBITORS ON ATRIAL FIBRILLATION

Diabetes and Atrial Fibrillation:

According to a 10-year projection, the number of people with diabetes mellitus (DM) is expected to rise steadily to 580 million worldwide. DM is associated with a 40% higher risk of atrial fibrillation (AF) occurrence as compared with general population. Diabetes mellitus induces intra-cardiac processes such as left ventricular hypertrophy (LVH), endothelium dysfunction, interstitial fibrosis, inflammation and microvascular damage. Therefore, occurrence of AF is strongly connected with DM, and its manifestation leads to unfavourable cardiovascular (CV) outcomes such as increased risk of ischemic stroke, heart failure (HF), hospitalization, and mortality.

Conventional antiarrhythmic drugs, acting as ion blockers, are ineffective in about half of patients suffering from AF and are associated with severe cardiac and extra cardiac side effects. Hence, it is critical to modify AF risks and prevent its complications through some other available pharmacological options.

Promising role of Sodium glucose cotransporter-2 inhibitor:

Sodium glucose cotransporter 2 inhibitor (SGLT2i) one of the potent anti-diabetic drug class have shown a broad class effect in reducing HF hospitalizations in patients with or without cardiovascular disease (CVD), as well as a proven benefit in renal protection through some path breaking trials.

➡ Mechanisms of SGLT2i induced AF prevention

SGLT2i benefit in AF prevention and reduction include plasma volume reduction, cardiac remodelling and enhanced cardiac energy status by increased ketone oxidation and cardio-myocyte Na–H exchange.

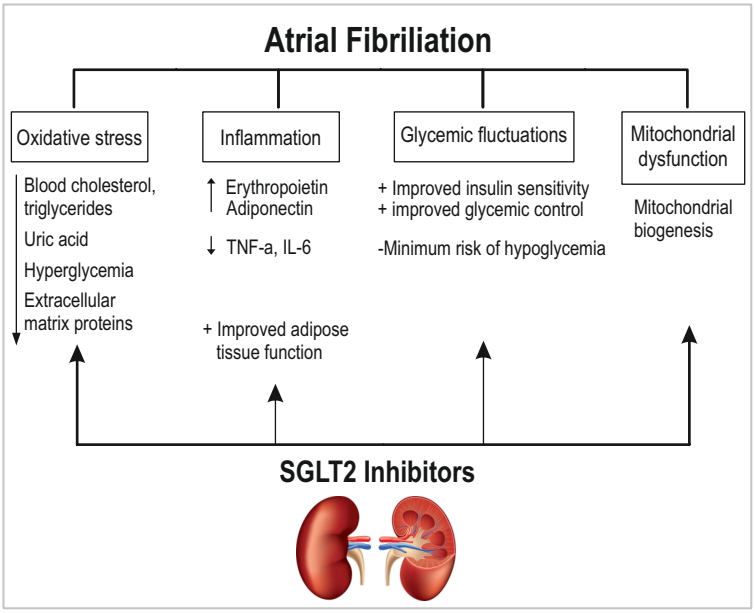
Reactive oxygen species (ROS), originating from mitochondrial dysfunction, are pro-arrhythmic and are related to AF onset and progression. Experimental studies of SGLT2is have demonstrated their positive effects on atrial structural and electrical remodelling by improving mitochondrial function and mitochondrial biogenesis acting as a preventive agent against DM-related AF.

SGLT2is reduce obesity, oxidative stress, systemic inflammation, and sympathetic overdrive—all significant contributors to the initiation and development of AF.

Glycemic variations such as hypoglycemia have been linked to an increased risk of AF in DM patients and this risk is negligible with SGLT2is compared to other glucose-lowering agents due to its insulin independent action.

SGLT2is action of natriuresis, diuresis, reduce the atrial volume. The reduction in uric acid levels also helps preventing AF onset and progression.

SGLT2is have also been shown to produce a beneficial reduction in epicardial fat as this pathogenic tissue has been related to coronary artery disease but also increased AF incidence and severity. A study demonstrated that patients who received Dapagliflozin presented significant epicardial fat volume reduction.



Erythropoietin can produce favorable hemodynamic and myocardial energetic alterations, adding an extra systematic anti-inflammatory/pro-angiogenic effect, promoting cardioprotection. This has been validated through a clinical study which demonstrated a beneficial impact in red blood cell production induced by increased erythropoietin secretion in patients receiving a SGLT2i.

SGLT2is delivers further cardiovascular benefits in human physiology by soothing inflammasome activity corroborated through an experimental study where a SGLT2i mitigated NLPR3-associated overproduction of cytokines IL-1β and IL-18 as well as smooth muscle cell migration and proliferation.

➡ **Clinical evidences:**

1. In the DECLARE-TIMI 58 trial, Dapagliflozin decreased the incidence of AF by 19% in patients with type 2 diabetes. Dapagliflozin offered beneficial effect to AF episodes and hospitalizations. It also reduced the total number atrial flutter (AFL) episodes.
2. Other SGLT2is studied in landmark trials showed beneficial effect on HF-related outcomes in both patients with and without AF.
3. In a population based propensity score-matched cohort study consisting of 79,150 DM patients receiving SGLT2is compared DM patients receiving DDP-4 inhibitors, it was shown that there was a 17% reduction of new-onset AF in the SGLT2i arm. Similar findings were obtained in the CVD REAL Nordic study, with Dapagliflozin.
4. Metanalysis of four CV safety trials, three renal outcome trials and one HF trial, showed that participants who received SGLT-2i demonstrated a significantly lower incidence of AF in participants with and without DM. Other metanalyses [(16 studies, 38,335 DM patients); (20 studies, 63604 DM patients)] found similar results in support of SGLT2is.

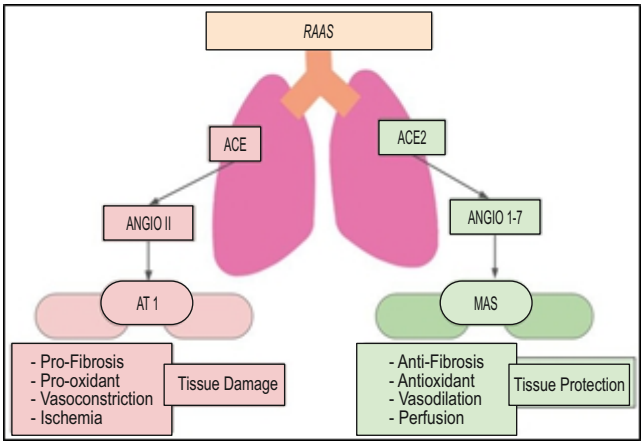
Information above demonstrates the potentially beneficial impact of SGLT2i on the incidence of AF.

Source: Chang SN, et al. JAHA. 2023; 12(10): e027764; Asrial AA, et al. J Clin Med. 2023; 12(18): 5898; Karamichalakis N, et al. J. Cardiovasc. Dev. Dis. 2022, 9(8), 236.

EFFECT OF OLMEBLU (OLMESARTAN) ON THE MAS AXIS CONTRIBUTING TO ITS RENOPROTECTIVE ACTIONS

Hypertension is one of the most important risk factors for chronic kidney disease (CKD). Both hypertension and CKD are intrinsically related, as hypertension is a strong determinant of worse renal outcomes and renal function decline aggravates hypertension. The interrelation between hypertension and CKD is bidirectional where persistently high blood pressure can accelerate the progression of CKD and the progressive decline of the eGFR can conversely interfere with the achievement of adequate BP control.

Physiologically, the BP is controlled by the ***Renin Angiotensin Aldosterone System (RAAS)*** pathway and the well-known components of the "classical" RAAS pathway include angiotensinogen, angiotensin I, angiotensin II, renin and the angiotensin converting enzyme (ACE).



Among this, angiotensin II is the major effector molecule exerting its biological actions via the angiotensin type I receptor (AT1 receptor) through which it causes an elevation in the BP.

In addition, there is also a "non-classical" RAAS pathway, also referred to as the ***MAS axis pathway*** which includes an ACE related carboxypeptidase called the ACE2, an enzyme similar to ACE along with the products angiotensin (1-7) that binds to the MAS receptor. ACE2 catalyzes the cleavage of angiotensin I to inactive angiotensin (1-9) and subsequently to the active angiotensin (1-7) which is known to be protective and counter-regulates the angiotensin II actions through the activation of the MAS receptor.

It has been suggested that the "non-classical" RAAS pathway involving the ACE2, its product angiotensin (1-7) and the MAS receptor plays a protective role. The cardiovascular system and the renal system are the major sources for the angiotensin (1-7) production and it along with the ACE2 have multifaceted effects on the heart and the kidney.

Protective effect of the MAS axis pathway on the kidney

Hypertensive kidney disease is a clinical condition that causes damage to the kidneys because of chronic elevated BP. The renal pathological changes are gradual and progressive, characterized by glomerular damage, followed by glomerular sclerosis and interstitial fibrosis.

Preventing fibrosis

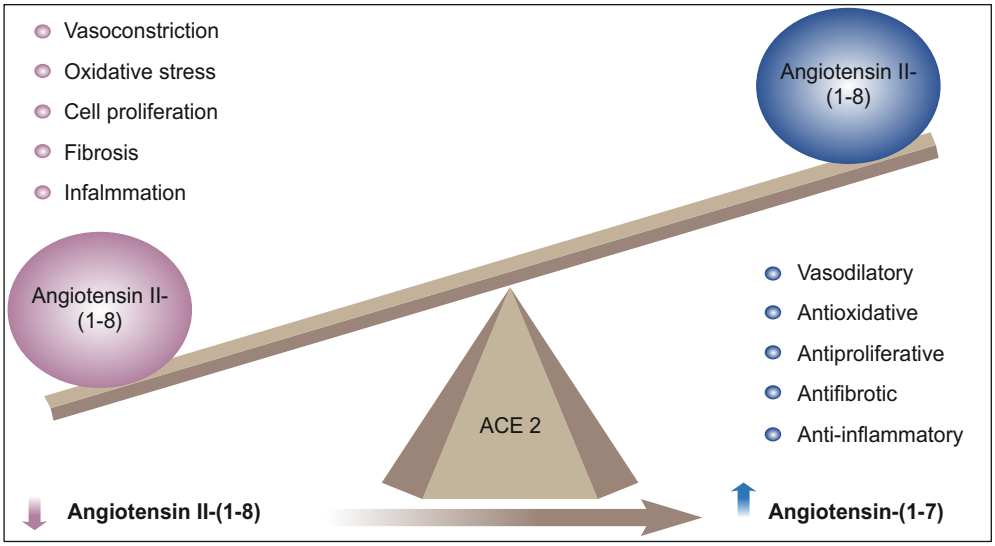
Fibrosis is initiated when the macrophages release profibrogenic cytokines and growth factors that stimulate the fibroblasts for laying down extracellular matrix (ECM) at the sites of injury. The most well characterized profibrotic mediators is TGFβ and the TGFβ expression is upregulated in the hypertensive kidney making it more susceptible to fibrotic changes. TGFβ also affects the integrity of glomerular basement membrane (GBM) through the induction of vascular endothelial growth factor (VEGF-A) and disrupts the uptake of the filtered albumin by the proximal tubular epithelial cells leading to microalbuminuria. This TGFβ has been shown to be significantly suppressed by angiotensin (1-7), it therefore participates in preventing fibrosis by regulating the TGFβ synthesis. It also significantly attenuates the *Fibroblast Growth Factor (FGF)* pathway and carries out its antifibrotic role.

Collagen degradation

Collagen synthesis and degradation co-exist in the repairing tissue. Enhanced collagen production and reduced collagen degradation facilitate collagen deposition. The function of *tissue inhibitor of metalloproteinases (TIMPs)* is to inhibit the metalloproteinase activity and promote collagen accumulation. TIMP-1 and TIMP-2 are upregulated in the hypertensive kidney which are significantly attenuated by the angiotensin (1-7) and hence promote collagen degradation and reducing fibrosis in the hypertensive kidney.

Reducing oxidative stress

Oxidative stress often occurs in the injured tissue which plays an important role in the inflammatory and fibrogenic responses. Elevated expression of NADPH oxidase and iNOS in the hypertensive kidney contributes to the activation of local oxidative stress. Angiotensin (1-7) significantly suppresses the expression of NADPH oxidase suggesting that it confers antioxidant properties in the hypertensive kidney.



Effect of Olmesartan on Angiotensin (1-7) and microalbuminuria

Olmesartan inhibits albuminuria & glomerular hypertrophy independently of the BP through enhancement of ACE2/Ang (1-7)/Mas axis pathway & suppression of ROS generation apart from its original action on the AT1 receptor blockade. Supporting this, a clinical study conducted on 80 participants were randomized to receive either Olmesartan or Amlodipine. It was observed that the Ang (1-7) levels as well as the ACE2 levels were significantly increased among patients taking Olmesartan. Olmesartan also demonstrated an increase in the plasma renin activity (PRA) and significantly reduced the aldosterone levels.

Olmesartan through its action on the "non-classical" RAAS pathway, exerts its reno-protective effects independent of its action on BP control. It helps in reducing albuminuria, glomerular hypertrophy & prevents a decline in kidney function through the reduction in fibrosis & reduction in oxidative stress.

Source: Kim et al. Diabetol Metab Syndr 2023; 15: 43; Ichikawa H et al. Int Heart J 2018; 59: 1445-1453; Chen Y et al. Am J Hypertens 2019; 32(5): 460-467; Georgianos P & Agarwal R. Nephrology Dialysis Transplantation 2023; Scurt FG et al. Kidney Int Rep 2019; 4: 1373-1386; www. Ncbi.nlm.nih.gov/books/NBK563255.

CARDIOPROTECTIVE EFFECTS OF K-GLIM (GLIMEPIRIDE) VIA ITS ACTION ON EPOXYEICOSATRIENOIC ACID (EET)

It has been observed that patients with diabetes have a higher incidence of heart failure (HF) with statistical data showing, the prevalence is 4 times higher than the general population.

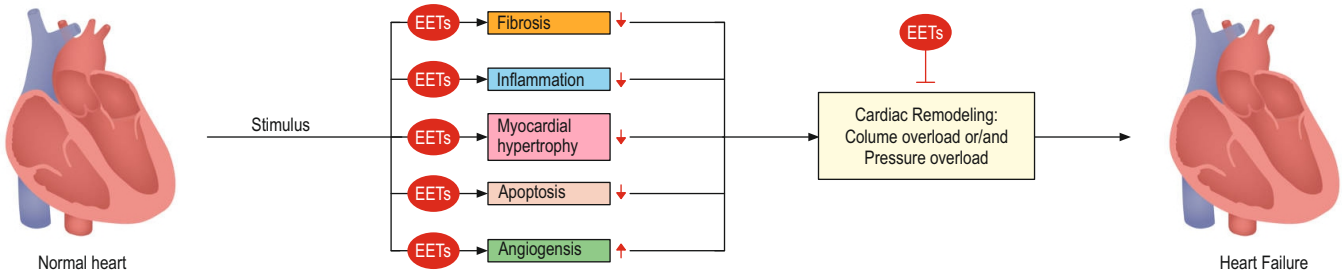
Type 2 diabetes (T2DM) also contributes to left ventricular dysfunction (LVD) and HF independent of coronary artery disease or hypertension. Moreover, T2DM is associated with myocardial fibrosis or increased collagen content and myocardial stiffness.

Role of Epoxyeicosatrienoic acid (EET) in cardiovascular protection

EETs are endogenous bioactive metabolites and are products of arachidonic acid (AA) metabolism through CYP 450 enzymes. EETs are reduced to less active dihydroxyeicosatrienoic acids (DHETs) by the enzyme *soluble epoxide hydrolase (sEH).*

EETs function as cardioprotective factors with exhibiting protective roles in inflammation, endothelial dysfunction, cardiac remodelling and fibrosis, the fundamental mechanisms of heart failure (HF), especially heart failure with preserved ejection fraction (HFpEF).

They improve cardiac mitochondrial function, decrease inflammation and oppose apoptosis to reduce cardiac fibrosis and hypertrophy.



Cardiac hypertrophy is a significant risk factor for HF and cardiomyocyte hypertrophy is a prerequisite for cardiac hypertrophy. EETs prevent cardiac hypertrophy by inhibiting the Ca+ mediated calcineurin/nuclear factor of activated T cells (NFAT) signaling *(key pathway in cell mediated adaptive immune response).* They protect against cardiac hypertrophy by AMPK2 and AKT1 activation that translocate into the nucleus to trigger the transcription and translation of atrial natriuretic peptide *(a hypotensive hormone that reduces blood pressure and cardiac hypertrophy)*. It has been observed that in cardiac hypertrophy there is an increased activity of sEH and decreased EETs in the cardiomyocytes, suggesting a critical role of EETs in the myocardium.

Effect of Glimepiride on EETs

It was shown that Glimepiride inhibits sEH significantly increasing the EET levels, decreasing the DHET levels and increasing the EET/DHET ratio. The results showed that the in-hospital CV mortality was 3.4% in the non-Glimepiride group and 0.9% in the Glimepiride group with a sub-group analysis showing that the CV mortality was lower among patients on a higher dose of Glimepiride (2-4 mg/d).

To summarize, the results of this study suggested that Glimepiride treatment is associated with reduced CV mortality, hospitalization and emergency visits for HF in patients with T2DM and coronary heart disease, especially in patients with LVD. This action of Glimepiride can be attributed to the inhibition of sEH and decreasing the EET degradation.

Source: He W et al. Eu J Preventive Cardiology 2023; 30(6): 474-487; Johnson R et al. Frontiers in Endocrinology: Advances in Res of CV Diseases 2022; Tanaka H et al. CV Diabetology 2020; 19(84); Dunlay SM et al. Circulation 2019; Zhang M et al. Biomedicine & Pharmacotherapy 2022; 153: 113326; Imig JD et al. biochemical Pharmacology 2022; 195: 114866.

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