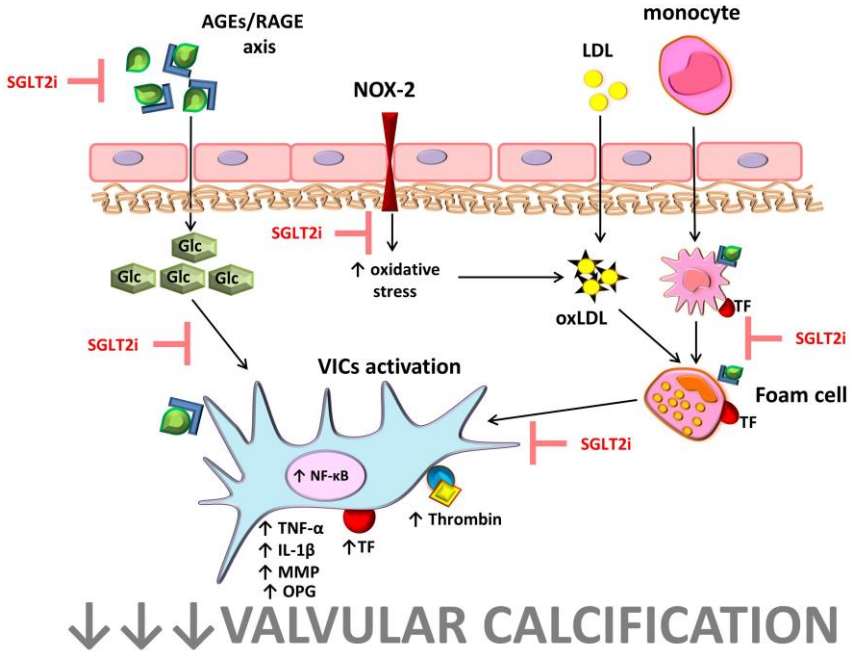
Flozins as potential inhibitors of aortic stenosis progression in patients with concomitant type 2 diabetes: impact on valvular calcification and remodeling in a non-randomized study

Aortic valve stenosis (AS) is the most common valvular disease in Western countries. Its prevalence increases with age, ranging 2-7% in subjects >65 years. Until the year 2030 about 4.5 million AS cases will be present worldwide, with no means to pharmacological treatment. To date, surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVI) are the only treatment options for AS. However, a predicted 30-day mortality for both procedures is relatively high and ranges from 4 to 8%.

As atherosclerotic-like process AS is associated with cardiovascular risk factors such as age, arterial hypertension, hypercholesterolemia or diabetes mellitus (DM). AS is considered an active inflammatory process, spread out in time, which occurs in response to damage of valvular endothelium and an influx of low-density lipoproteins (LDL), enhanced oxidative stress and monocytes infiltration, with subsequent transformation into foam cells. This results in the activation of valvular interstitial cells (VICs), being predominant cells of aortic valve and playing a pivotal role in pathologic alterations. VICs are responsible for different course of AS and atherosclerosis, therefore studies regarding atherosclerosis cannot be easily translated into AS. Under inflammatory condition, driven by nuclear factor (NF)-κB pathway, a master regulator of inflammatory responses, VICs differentiate and drive valvular calcification. Thus studies regarding therapeutic options affecting the pathways of VICs activation are highly warranted. A prevalence of DM is markedly higher among AS patients compared to the general population and still increases. The prevalence of DM concomitant to AS increased in US from 19.7% to 31.6% between the years 2009 and 2015. Available data suggest that poorly controlled DM in AS patients is associated with enhanced valvular oxidative stress, inflammation, and coagulation activation, which all together can accelerate AS progression. Moreover, increased valvular protein glycation due to an accumulation of advanced glycoxidation end products (AGEs) was suggested as a contributor to faster AS progression via NFκB-driven osteoblastic differentiation of VICs and activation of macrophages. Based on animal and human studies targeting an inhibition of the AGEs-RAGE axis using new antihyperglycemic agents, such as sodium-glucose cotransporter-2 inhibitors (SGLT-2i or flozins) have been proposed as therapies to reduce cardiovascular complications, including AS. Atherosclerotic mice treated with flozin had decreased serum levels of inflammatory cytokines. Moreover, flozins attenuated inflammation by downregulation of NF-κB pathway. Flozins reduced also cardiovascular risk in type 2 DM patients. However, the exact mechanism of this phenomenon has not been elucidated to date. Based on similarities between atherosclerosis and AS the goal of this project is to evaluate if empagliflozin may slower the rate of AS progression via reduced VICs activation and inhibited valvular inflammation. Results of this study might have practical implications supporting the role of flozins to retard AS progression, at least in subjects with mild-to-moderate AS.

Along with the micro-computed-tomography (micro-CT), we will perform a battery of advanced in vitro and ex vivo assays testing valvular calcification biology upon flozins treatment.

This project addresses an issue with major implications to human health and results of this study might have practical implications supporting the role of flozins to retard AS progression, at least in subjects with mild-to-moderate AS.



Potential effects of SGLT-2 inhibitors (i) on AS development/progression.