Heart failure (HF) is a progressive syndrome causing chronic disability, requiring frequent hospitalisation and ultimately leading to death. It is experienced by approximately 60 million people worldwide. A distinction is made between a subtype of HF with reduced left ventricular ejection fraction (HFrEF) and with preserved ejection fraction (HFpEF). In the former subtype, systolic dysfunction predominates, while in the latter, the ability to generate contraction is preserved, but myocardial diastolic dysfunction occurs. HFpEF most commonly affects elderly, obese people with type 2 diabetes, with women much more commonly affected than men. The prognosis in both subtypes is poor. However, while treatments reducing mortality and hospitalisations proven in randomised multicentre trials have been widely implemented in HFrEF, there are no effective methods to reduce mortality in HFpEF, and treatment consists only of symptom relief.

Some hope is now being placed on inhibitors of the renal tubular sodium-glucose cotransporter-2 (SGLT2). Recently, SGLT2 inhibitors have been shown to effectively reduce mortality and morbidity in HFrEF, both in patients with and without type 2 diabetes. In one study, a reduction in the incidence of hospitalisation was also demonstrated in patients with HFpEF, stimulating further research to optimise treatment with SGLT2 inhibitors in these patients to achieve a reduction in mortality. The mechanisms of action of SGLT2 inhibitors in HF are very poorly understood, especially their extra-renal effects on the myocardium. It is also unknown whether inhibition of SGLT2 or dual inhibition of renal SGLT2 and myocardial SGLT1 would be more beneficial in HFpEF potentially affecting intracellular Na^+ and Ca^{2+} concentrations and the degree of fibrosis, both factors that strongly determine diastolic performance.

Hence, the aim of our project is to investigate in detail the effects of selective SGLT2 inhibition and dual SGLT2/SGLT1 inhibition on the development of HF progression and arrhythmic susceptibility in a rat model of HFpEF. We also want to comprehensively study for the first time the effects of flozins on the different stages of relaxation of heart muscle (active and passive) including the rate of Ca^{2+} elimination from the cytoplasm after contraction, the function of contractile apparatus proteins and cytoskeleton proteins and the amount and composition of the extracellular matrix.

To identify the mechanism of action of flozins, we also want to test whether the beneficial effects of flozins are due, at least in part, to their effects on Na^+ and Ca^{2+} transporters in cardiomyocytes other than SGLT1, such as Na^+/H^+ exchanger (NHE-1), L-type Ca^{2+} channels or the Na^+/Ca^{2+} exchanger (NCX). Finally, we plan to investigate whether diastolic dysfunction in HFpEF has the same course and severity in male and female individuals and whether treatment with flozins is similarly effective in both sexes. We will conduct our study in a rat model of HFpEF with associated metabolic abnormalities (obese ZSF-1 rats of both sexes, including females with a normal hormonal cycle and after ovariectomy*) in vivo, ex vivo* (perfused heart) and *in vitro* (isolated cardiomyocytes).

We hypothesise that dual inhibition of SGLT2 and SGLT1 will be more beneficial in HFpEF than selective blockade of SGLT2. We also hypothesise that the beneficial effects of the flozins are partly due to direct effects on transporters involved in the intracellular Na^+ and Ca2+ signalling, especially NHE-1 in cardiomyocytes. We hope that this project will answer the question of which therapeutic strategy using flozins and NHE-1 inhibitors is most effective in HFpEF, which stages of diastole are improved by this treatment and which require further correction, and whether the treatment should be the same in both sexes.

We believe it is particularly important to answer these questions as the number of patients with HFpEF is set to rise rapidly due to the ageing population and the epidemic of obesity and type 2 diabetes. Moreover, due to their longer life expectancy, they will be predominantly female. In the era of personalised medicine, every patient should receive effective treatment based on their condition and sex.