8

Summary and future perspectives

SUMMARY

Heart Failure (HF) is a clinical syndrome that represents the final stage of most cardiac diseases, and the incidence of HF is approaching epidemic proportions.[1–3] Despite improved pharmacologic and device management of patients with HF, we are still unable to restore cardiac function in most patients nor can we rejuvenate the heart.[4,5] Thus, clinical and preclinical investigations are still needed to establish innovative therapies that could tackle this problem. Furthermore, polypharmacy becomes prevalent in HF patients because HF can be complex and often accompanied with more than 1 comorbidity.[6] As the number of comorbidities increases, the therapeutic regimens are also more complex.[7] On the other hand, drugs that are not prescribed to treat HF may potentially affect the cardiovascular (CV) system.[8–11] Cardiologists should therefore be aware of the effects and the possible interaction that may arise from the use of these drugs.

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) have received a lot of attention due to their reported CV benefits in patients with type 2 diabetes (T2D), including patients with HF at baseline.[12–14] Since SGLT2i are antidiabetic drugs, it is unclear whether the CV benefits can be translated to non-diabetic subjects. In **Chapter 2**, we investigated the role of sodium-glucose co-transporter 2 inhibitors (SGLT2i) empagliflozin (EMPA) in the context of non-diabetic HF. To determine the effects of EMPA on cardiac function and metabolic parameters in non-diabetic setting, we treated non-diabetic rats with left ventricular (LV) dysfunction after myocardial infarction (MI) with EMPA or vehicle for 10 weeks. In this chapter, we demonstrated that EMPA improves cardiac function in non-diabetic rats with HF and this is associated with the reversal of the metabolic derangements observed in the failing myocardium. EMPA also enhanced the circulating and cardiac oxidation of ketone bodies as an additional fuel source. Interestingly, EMPA did not induce hypoglycemia.

SGLT2i also have been shown to prevent the progression of renal disease in patients with T2D.[13–16] In contrast, it has also been warned that SGLT2i may induce endocrine changes that may increase fracture risk in these patients.[17–19] Unlike in diabetic subjects, the renal effects of SGLT2i in the non-diabetic context have not been well described. In **Chapter 3**, using the same animals used in **Chapter 2**, we performed deep renal phenotyping to determine the effects (safety) of EMPA on renal structure and function in non-diabetic rats with LV dysfunction after MI. In this chapter, we showed that EMPA promotes diuresis without affecting renal structure and function or causing substantial electrolyte imbalance in a non-diabetic setting, which is in line with the findings from DAPA-HF trial.[20] Furthermore, we did not find evidence for increased bone mineral resorption suggesting that EMPA does not affect bone health. Our study therefore provides robust evidence that SGLT2 inhibition with EMPA has the potential to improve cardiac performance in non-diabetic failing hearts, and provides further mechanistic insights that suggest that SGLT2i may be both safe and beneficial in HF patients without diabetes. The findings in **Chapter 2** and **Chapter 3** are summarized in *Figure 1*.

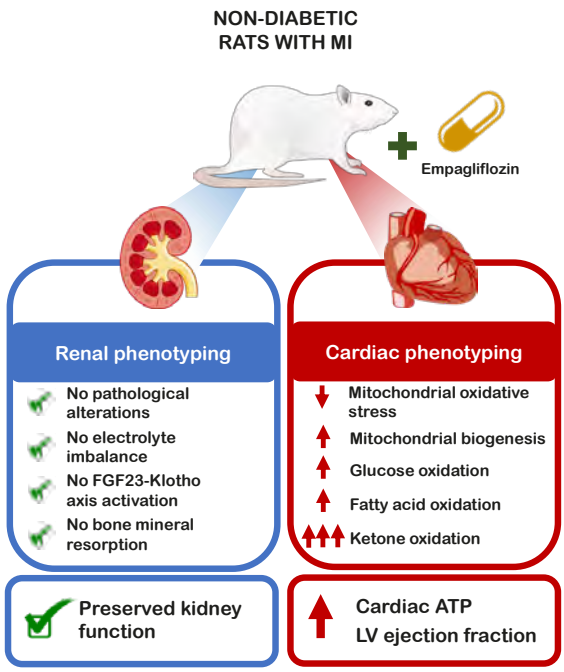

FIGURE 1. Cardiac and renal effects of sodium-glucose co-transporter inhibitors empagliflozin in non-diabetic rats with LV dysfunction after myocardial infarction

In Chapter 4, we hypothesise that that SGLT2i could reflect a mitochondrial targeted therapy to reduce the burden of atrial fibrillation (AF) in patients with diabetes. This commentary discusses a paper by Shao et al, which demonstrated that SGLT2i EMPA attenuate structural and electrical remodelling of atrial tissue, associated with mitochondrial biogenesis in diabetic rats.[21] In **Chapter 4**, we discussed the mechanistic implications of this study and also describe how SGLT2i could potentially prevent AF in T2D. We argue that mitochondria-targeted therapy could serve as a promising therapeutic target in AF, especially in diabetic patients.

In heart failure (HF) patients, the incidence of left ventricular (LV) thrombi, ischemic strokes, and other thromboembolic events is increased, suggesting that is HF should be considered to be a hypercoagulable state.[22–26] To further investigate the role of FXa inhibitor in HF, in **Chapter 5**, we conducted animal experimentation in which we treated rats with heart failure after a large anterior wall myocardial infarction with apixaban or vehicle for 10 weeks.

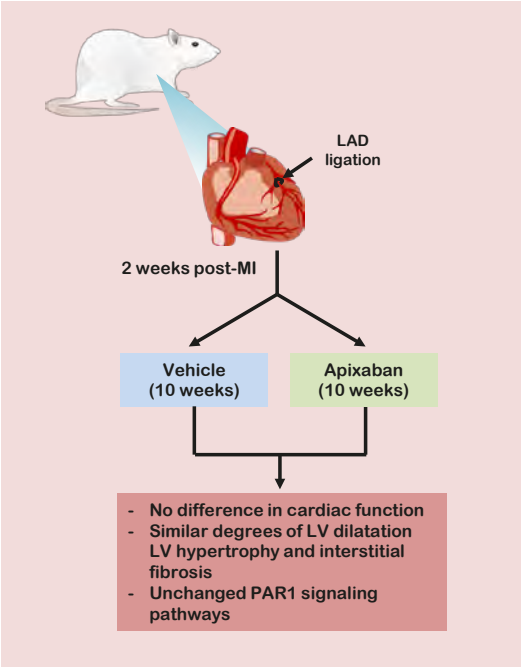

FIGURE 2. Cardiovascular effects of factor Xa inhibitor apixaban in rats with heart failure after myocardial infarction.

As expected, apixaban treatment resulted in a significant reduction in FXa activity. Nevertheless, the reductions in FXa activity with apixaban did not affect the activity of PAR1 signaling pathways in hearts from rats with or without HF. Furthermore, apixaban did not influence cardiac function and cardiac remodeling after MI. Our results confirm and provide mechanistic insights explaining the neutral outcomes of the COMMANDER HF trial.[27] Moreover, our results do not support the use of FXa inhibitors in HF patients with the aim to modulate the severity of HF. The results are summarized in *Figure* 2.

In patients with HF, metabolic roadblocks in fat and carbohydrate metabolism occur, which reduce the myocardial capacity to generate ATP.[28–30] This results in myocardial energy deficiency, and the failing heart is often compared with an engine out of fuel.[31] In **Chapter 6**, we investigated the effect of oral ketone ester (KE) supplementation on cardiac function in pre-clinical models of HF. In this chapter we demonstrated that we were able to attenuate cardiac remodeling and improve cardiac function through chronic oral supplementation with KE in two different pre-clinical models of HF. Additionally, treatment with KE also normalized myocardial ATP production. These findings suggest that treatment with KE could benefit patients with HF. The results are summarized in figure 3.

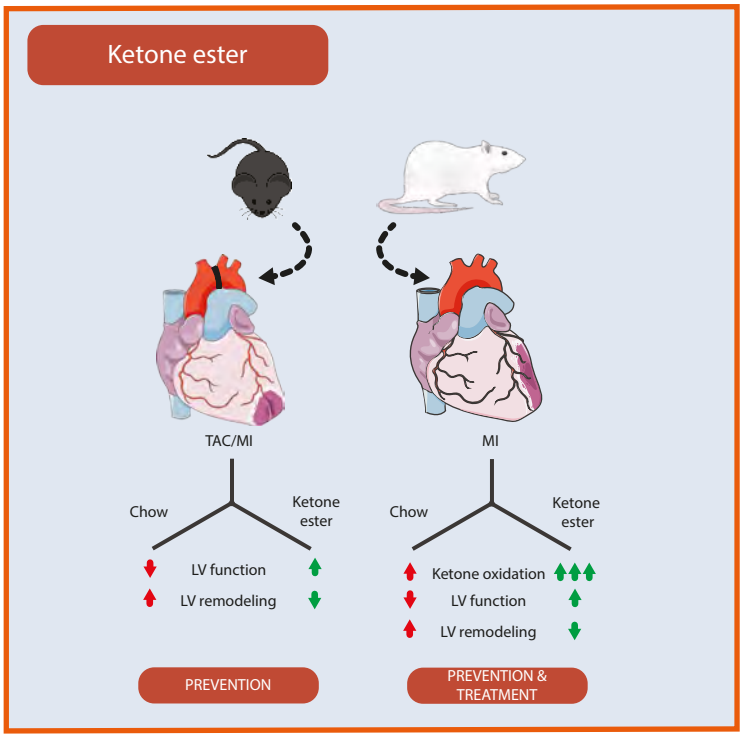

FIGURE 3. Cardiovascular effects of ketone ester in pre-clinical models of heart failure. Part of illustration elements courtesy of Servier Medical Art.

In **Chapter 7**, we provide an overview from available data from experimental and human studies evaluating the pleiotropic effects of ketone bodies that potentially contribute to its cardiovascular benefits. We concluded that the pleiotropic effects of ketone bodies extend far from cardiac energetics, and it could be mediated through their vasodilatory effect, anti-oxidant and anti-remodeling effects, mito-protective effects, and other possible mechanism on cardiovascular risk factors.

FUTURE PERSPECTIVES

SGLT2i were originally indicated as a treatment for diabetes before they were found to have unexpected benefits in HF. Currently, it is thought that the CV benefits of SGLT2i are actually beyond its glucose-lowering effects, therefore, it may also benefit non-diabetic HF patients. Our experimental study demonstrated that SGLT2i EMPA attenuate cardiac remodeling and fibrosis, normalize myocardial metabolic abnormalities and improve cardiac function in the post-MI, non-diabetic HF model. We also found that EMPA increases circulating ketone

bodies as well as cardiac ketone oxidation, and it was associated with increased myocardial ATP production. Based on this experimental study, we hypothesized that SGLT2i are safe and could be of benefits in non-diabetic patients with HF, and these effects could be mediated by mild ketosis seen during SGLT2i treatment. Similar observations have also been reported by others in non-diabetic porcine model of HF.[32] Therefore, we designed and performed an experimental study in which we treated rodent models of HF with ketone ester. We observed that ketone ester was effective both as preventive and treatment strategy in experimental HF. Moreover, KE could ameliorate cardiac remodeling and improve cardiac function. As expected, we observed an increase in cardiac ketone oxidation and normalization of myocardial ATP production during KE treatment. Taken together, it provides more insight on the ketosis-mediated effects during SGLT2i treatment and the potential use of KE in patients with HF.

Evidence suggests that patients with HF have a higher risk of thromboembolic events, including in the setting of sinus rhythm.[22,33,34] In fact, HF is the second leading cause of cardioembolic stroke after AF.[35] Thus, it sounds reasonable that oral anticoagulant therapy could benefit HF patients. However, several randomized trials failed to show benefits of oral anticoagulant in HF with sinus rhythm,[27,36] and it reflects to the current guidelines that do not support the use of anticoagulant in HF without AF, a prior thromboembolic event or known cardioembolic source.[2,37] Our experimental study confirms and clarifies why FXa inhibitor failed to provide benefits in HF patients with sinus rhythm.

In this thesis, we have addressed the cardiovascular effects of non-cardiovascular drugs (i.e SGLT2i, FXa inhibitor and ketone ester) in HF. We also have described the potential benefits of SGLT2i in diabetic AF and the cardioprotective properties of ketone bodies. However, the results may have been different in other species or other disease model (i.e HFpEF), therefore, further study in both animals and human is needed to better understand the benefits and its potential application. Nevertheless, our study provides molecular insights into the cardiovascular effects of SGLT2i, FXa inhibitor and KE in the failing heart.

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