1

Introduction and aim of the thesis

INTRODUCTION

Heart failure (HF) affects over 26 million people worldwide.[1] HF mortality and hospitalization rates remain high despite the availability of current pharmacological and device interventions that have rapidly advanced in recent years.[2] Therefore, further agents that, when added to the standard care of therapy, improve long term prognosis and extend life expectancy of patients with HF are urgently needed.

HF is often accompanied by other comorbidities such as hypertension, diabetes mellitus, obesity, hyperlipidemia, metabolic syndrome, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), stroke and anemia.[3,4] Analysis from European Society of Cardiology Heart Failure Pilot Survey revealed that around 74% of HF patients have more than 1 comorbidity.[5] The large burden of comorbidities have been associated with increased mortality in HF.[2,6,7] Intriguingly, more than half of the hospitalizations for patients with HF are related to comorbid conditions rather than the HF condition itself.[8]

It has been known that preventing HF hospitalizations and improving functional capacity are considered as important aspect in the management of HF. Current guideline and consensus paper have now included modification of risk factors in order to delay the onset of HF.[2,9] In HF, modification of lifestyle and related comorbidities become important as it contributes to change the HF epidemiology.[10]

CARDIOVASCULAR EFFECTS OF NON-CARDIOVASCULAR DRUGS IN HEART FAILURE

Polypharmacy is common among HF patients, with average 6.8 prescription medication per day.[11,12] Unfortunately, several classes of drugs have been shown to potentially induce HF in patients without any history of cardiovascular disease (CVD) or provoke the incidence of HF in patients with impaired left ventricular function.[13–15] Also, drugs that were not intentionally designed to treat HF may have the effects on the CV system.

Sodium-glucose co-transporter inhibitors

Despite effectively lowering the blood glucose, some anti-diabetic drugs can paradoxically increase adverse CV events in patients with HF.[16–18] In response to the concerns of increased CV risk, the U.S. Food and Drug Administration (FDA) and other regulatory agencies have requested large cardiovascular outcomes trials (CVOTs) for all new diabetic medication.[19]

Currently, oral anti-diabetic drug sodium-glucose co-transporter inhibitors (SGLT2i) received a lot of attention after showing reduction of mortality and HF hospitalization when added to standard care of therapy in patients with and without diabetes.[20–23] Therefore, it is

possible that the benefits of SGLT2i will expand to non-diabetic HF as well. Many hypotheses have been proposed, but the definitive mechanisms remain poorly understood. Several dedicated HF trial (NCT03057977, NCT03057951, NCT03619213) are currently underway to assess the effects of SGLT2i in HF.

Factor Xa inhibitor

HF has been acknowledged as a prothrombotic state because the elements of Virchow's triad: aberrations in blood flow, blood vessel and blood components, that can promote thrombosis, are present in HF.[24,25] Patients with HF are at higher risk of LV thrombi, stroke and venous thromboembolism, even in the setting of sinus rhythm.[26–28] Previous studies have reported that coagulation factors such as Factor Xa (FXa) and thrombin can also target protease activated receptors (PARs) in the myocardium, and it has been suggested that their activation may contribute to maladaptive cardiac remodeling and promote HF progression.[29–32] However, the direct evidence on the role of PAR signaling in HF is limited.[31,32] Additionally, it is unknown whether anticoagulant therapy, such as FXa inhibitor, may amend PAR activation and/or influence disease progression in HF. The potential consequence of FXa inhibition in HF have not been studied to date.

Ketone bodies

Ketone bodies are endogenous metabolites that are produced by the liver, in particular under conditions of prolonged fasting, insulin deprivation and extreme exercise.[33] Circulating ketone concentrations as well as the cardiac uptake of ketone bodies are increased in patients with HF, both in HF with reduced (HFrEF) and preserved (HFpEF) ejection fraction.[34–36] Experimental evidence suggests in the failing heart energy metabolism is re-programmed towards increased oxidation of ketone bodies as a fuel source.[37] Indeed, mice which are unable to oxidize ketone bodies in their hearts develop more severe cardiac dysfunction in response to myocardial infarction (MI) and pressure overload.[38] Accordingly, interventions that enhance circulating ketone levels result in increased ketone oxidation in the myocardium and improve cardiac function.[38–41] Recent advances in our understanding of these mechanisms will aid in the development of novel therapies, including metabolic manipulations that could prevent and treat HF.

AIMS AND OUTLINE OF THE THESIS

The primary aims of this thesis are:

1. To evaluate the cardiac and renal effects of sodium-glucose co-transporter inhibitors in non-diabetic HF.
2. To evaluate the effects of anticoagulation with factor Xa inhibitor in HF.
3. To evaluate the effects of ketone ester supplementation in HF.

In **Chapter 2** and **3**, we investigate the cardiac and renal effects of sodium-glucose co-transporter inhibitors (SGLT2i) in non-diabetic HF. For this purpose, we perform deep cardiac and renal phenotyping of SGLT2i empagliflozin in non-diabetic rats with HF after myocardial infarction (MI). Furthermore, in **Chapter 4**, we describe the current knowledges regarding the potential effects of SGLT2i as treatment for atrial fibrillation in diabetes.

In **Chapter 5**, we study the role of factor Xa (FXa) inbibitor in HF. For this purpose, we use FXa inhibitor apixaban in a well-established rat model of chronic post-MI HF. In **Chapter 6**, we examine the effects of oral ketone ester supplementation in HF. In doing so, we use oral ketone ester as a prevention and treatment strategies in pre-clinical models of HF. In **Chapter 7**, we review the cardiovascular properties of ketone bodies in cardiovascular disease (CVD).

Finally, we discuss the main findings and conclusion of this thesis, as well as the future perspectives, in **Chapter 8**.

REFERENCES

1. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, Nodari S, Lam CSP, Sato N, Shah AN, Gheorghiade M. The Global Health and Economic Burden of Hospitalizations for Heart Failure. *J Am Coll Cardiol* 2014;**63**:1123–1133.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, Meer P van der. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016;**37**:2129–2200.
3. Wal HH van der, Deursen VM van, Meer P van der, Voors AA. Comorbidities in Heart Failure. *Handbook of Experimental Pharmacology* 2017. p. 35–66.
4. Sturm HB, Haaijer-Ruskamp FM, Veeger NJ, Baljé-Volkers CP, Swedberg K, Gilst WH Van. The relevance of comorbidities for heart failure treatment in primary care: A European survey. Eur. J. Heart Fail. 2006.
5. Deursen VM van, Urso R, Laroche C, Damman K, Dahlström U, Tavazzi L, Maggioni AP, Voors AA. Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. *Eur J Heart Fail* 2014;**16**:103–111.
6. Mentz RJ, Felker GM. Noncardiac Comorbidities and Acute Heart Failure Patients. *Heart Fail Clin* 2013;**9**:359–367.
7. Mentz RJ, Kelly JP, Lueder TG von, Voors AA, Lam CSP, Cowie MR, Kjeldsen K, Jankowska EA, Atar D, Butler J, Fiuzat M, Zannad F, Pitt B, O'Connor CM. Noncardiac Comorbidities in Heart Failure With Reduced Versus Preserved Ejection Fraction. *J Am Coll Cardiol* 2014;**64**:2281–2293.
8. Dunlay SM, Redfield MM, Weston SA, Therneau TM, Hall Long K, Shah ND, Roger VL. Hospitalizations After Heart Failure Diagnosis. *J Am Coll Cardiol* 2009;**54**:1695–1702.
9. Aggarwal M, Bozkurt B, Panjrath G, Aggarwal B, Ostfeld RJ, Barnard ND, Gaggin H, Freeman AM, Allen K, Madan S, Massera D, Litwin SE. Lifestyle Modifications for Preventing and Treating Heart Failure. *J Am Coll Cardiol* 2018;**72**:2391–2405.
10. Andersson C, Vasan RS. Epidemiology of cardiovascular disease in young individuals. *Nat Rev Cardiol* 2018;**15**:230–240.
11. Masoudi FA, Baillie CA, Wang Y, Bradford WD, Steiner JF, Havranek EP, Foody JM, Krumholz HM. The Complexity and Cost of Drug Regimens of Older Patients Hospitalized With Heart Failure in the United States, 1998-2001. *Arch Intern Med* 2005;**165**:2069.
12. Rich MW. Pharmacotherapy of heart failure in the elderly: adverse events. *Heart Fail Rev* 2012;**17**:589–595.
13. Feenstra J, Grobbee DE, Remme WJ, Stricker BHC. Drug-induced heart failure. *J Am Coll Cardiol* 1999;**33**:1152–1162.
14. Slørdal L, Spigset O. Heart failure induced by non-cardiac drugs. *Drug Saf* 2006;**29**:567–586.
15. Page RL, O'Bryant CL, Cheng D, Dow TJ, Ky B, Stein CM, Spencer AP, Trupp RJ, Lindenfeld J. Drugs That May Cause or Exacerbate Heart Failure. *Circulation* 2016;**134**.
16. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. *Lancet* 2007;**370**:1129–1136.
17. Home PD, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJV. Rosiglitazone Evaluated for Cardiovascular Outcomes — An Interim Analysis. *N Engl J Med* 2007;**357**:28–38.
18. Nissen SE, Wolski K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. *N Engl J Med* 2007;**356**:2457–2471.
19. The Food and Drug Administration. Diabetes Mellitus -- Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. 2008. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diabetes-mellitus-evaluating-cardiovascular-risk-new-antidiabetic-therapies-treat-type-2-diabetes

20. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015;**373**:2117–2128.
21. Neal B, Perkovic V, Mahaffey KW, Zeeuw D de, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 2017;**377**:644–657.
22. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde A-M, Sabatine MS. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2019;**380**:347–357.
23. McMurray JJ V, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, Böhm M, Chiang C-E, Chopra VK, Boer RA de, Desai AS, Diez M, Drozdz J, Dukát A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2019;**381**:1995–2008.
24. Gurbel PA, Tantry US. Antiplatelet and Anticoagulant Agents in Heart Failure. *JACC Hear Fail* 2014;**2**:1–14.
25. Zeitler EP, Eapen ZJ. Anticoagulation in Heart Failure: a Review. *J Atr Fibrillation* 2015;**8**:1250.
26. Freudenberger RS, Hellkamp AS, Halperin JL, Poole J, Anderson J, Johnson G, Mark DB, Lee KL, Bardy GH. Risk of Thromboembolism in Heart Failure. *Circulation* 2007;**115**:2637–2641.
27. Piazza G, Goldhaber SZ, Lessard DM, Goldberg RJ, Emery C, Spencer FA. Venous Thromboembolism in Heart Failure: Preventable Deaths During and After Hospitalization. *Am J Med* 2011;**124**:252–259.
28. Lip GY, Gibbs CR. Does heart failure confer a hypercoagulable state? Virchow's triad revisited. *J Am Coll Cardiol* 1999;**33**:1424–1426.
29. Spronk HMH, Jong AM De, Verheule S, Boer HC De, Maass AH, Lau DH, Rienstra M, Hunnik A van, Kuiper M, Lumeij S, Zeemering S, Linz D, Kamphuisen PW, Cate H Ten, Crijns HJ, Gelder IC Van, Zonneveld AJ van, Schotten U. Hypercoagulability causes atrial fibrosis and promotes atrial fibrillation. *Eur Heart J* 2017;**38**:38–50.
30. Spronk HMH, Jong AM de, Crijns HJ, Schotten U, Gelder IC Van, Cate H ten. Pleiotropic effects of factor Xa and thrombin: what to expect from novel anticoagulants. *Cardiovasc Res* 2014;**101**:344–351.
31. Moshal KS, Tyagi N, Moss V, Henderson B, Steed M, Ovechkin A, Aru GM, Tyagi SC. Early induction of matrix metalloproteinase-9 transduces signaling in human heart end stage failure. *J Cell Mol Med* 2005;**9**:704–713.
32. Moshal KS, Tyagi N, Henderson B, Ovechkin A V, Tyagi SC. Protease-activated receptor and endothelial-myocyte uncoupling in chronic heart failure. *Am J Physiol Heart Circ Physiol* 2005;**288**:H2770-7.
33. Puchalska P, Crawford PA. Multi-dimensional Roles of Ketone Bodies in Fuel Metabolism, Signaling, and Therapeutics. *Cell Metab* 2017;**25**:262–284.
34. Bedi KC, Snyder NW, Brandimarto J, Aziz M, Mesaros C, Worth AJ, Wang LL, Javaheri A, Blair IA, Margulies KB, Rame JE. Evidence for Intramyocardial Disruption of Lipid Metabolism and Increased Myocardial Ketone Utilization in Advanced Human Heart Failure. *Circulation* 2016;**133**:706–716.
35. Aubert G, Martin OJ, Horton JL, Lai L, Vega RB, Leone TC, Koves T, Gardell SJ, Krüger M, Hoppel CL, Lewandowski ED, Crawford PA, Muoio DM, Kelly DP. The Failing Heart Relies on Ketone Bodies as a Fuel. *Circulation* 2016;**133**:698–705.
36. Voros G, Ector J, Garweg C, Droogne W, Cleemput J Van, Peersman N, Vermeersch P, Janssens S. Increased Cardiac Uptake of Ketone Bodies and Free Fatty Acids in Human Heart Failure and Hypertrophic Left Ventricular Remodeling. *Circ Heart Fail* 2018;**11**:e004953.
37. Mudaliar S, Alloju S, Henry RR. Can a Shift in Fuel Energetics Explain the Beneficial Cardiorenal Outcomes in the EMPA-REG OUTCOME Study? A Unifying Hypothesis. *Diabetes Care* 2016;**39**:1115–1122.
38. Horton JL, Davidson MT, Kurishima C, Vega RB, Powers JC, Matsuura TR, Petucci C, Lewandowski ED, Crawford PA, Muoio DM, Recchia FA, Kelly DP. The failing heart utilizes 3-hydroxybutyrate as a metabolic stress defense. *JCI Insight* 2019;**4**.

39. Yurista SR, Silljé HHW, Oberdorf-Maass SU, Schouten E, Pavez Giani MG, Hillebrands J, Goor H van, Veldhuisen DJ van, Boer RA de, Westenbrink BD. Sodium-glucose co-transporter 2 inhibition with empagliflozin improves cardiac function in non-diabetic rats with left ventricular dysfunction after myocardial infarction. *Eur J Heart Fail* 2019;**21**:862–873.
40. Gormsen LC, Svart M, Thomsen HH, Søndergaard E, Vendelbo MH, Christensen N, Tolbod LP, Harms HJ, Nielsen R, Wiggers H, Jessen N, Hansen J, Bøtker HE, Møller N. Ketone Body Infusion With 3-Hydroxybutyrate Reduces Myocardial Glucose Uptake and Increases Blood Flow in Humans: A Positron Emission Tomography Study. *J Am Heart Assoc* 2017;**6**:e005066.
41. Nielsen R, Møller N, Gormsen LC, Tolbod LP, Hansson NH, Sorensen J, Harms HJ, Frøkiær J, Eiskjaer H, Jespersen NR, Mellemkjaer S, Lassen TR, Pryds K, Bøtker HE, Wiggers H. Cardiovascular Effects of Treatment With the Ketone Body 3-Hydroxybutyrate in Chronic Heart Failure Patients. *Circulation* 2019;**139**:2129–2141.