Cardiac damage in DKD/CKD mouse model resembles HFpEF and can be reduced by Standard-of-care treatment

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TNO innovation for life

Introduction

Cardiovascular damage is the major cause of death in CKD. TNO developed a diet-induced hypertension-accelerated DKD/CKD model resembling cardiovascular-kidney-metabolic syndrome including obesity, diabetes and hypertension and allows the study how the different components of this syndrome contribute to the development of cardiac damage.

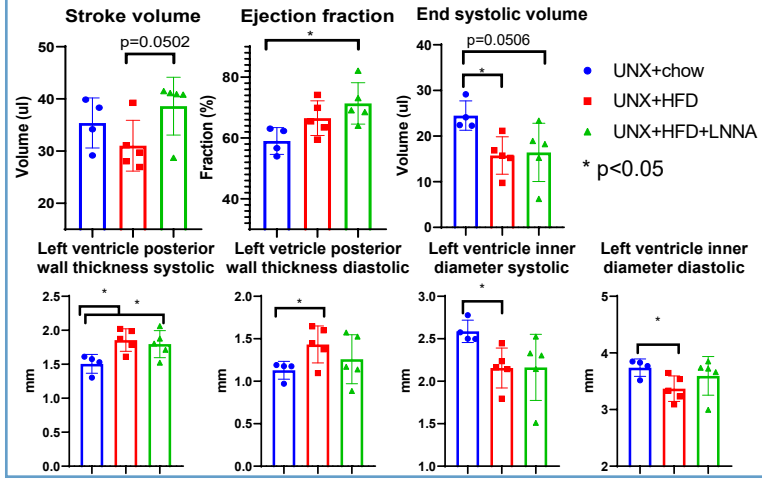
Aim

The aim of this study was 1) to functionally characterize cardiac damage in TNO's DKD/CKD model 2) to determine efficacy of standard-of-care combination therapy of a low dose of Lisinopril followed by on-top-off Dapagliflozin treatment on cardiac histopathology and 3) to induce dyslipidemia to resemble the cardiovascular-kidney-metabolic syndrome using an AAV-PCSK9 gain of function mutation injection.

Methods

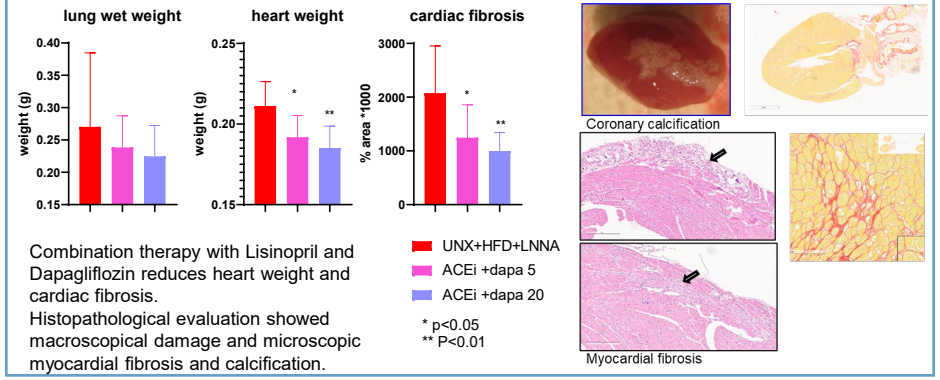
- Male KKAy mice underwent uninephrectomy (UNX). After recovery, mice received high fat diet (HFD) with or without the vasoconstrictor LNNA (50mg/L) for 16 weeks. In the standard-of-care intervention group, at wk 4 Lisinopril (2.5 mg/kg/day) was started. At week 8 Dapagliflozin (5 and 20 mg/kg/day). 1 group of mice received AAV-mPCSK9 (gain of function mutation) injection which reduces liver LDL receptor levels leading to high circulating cholesterol and increased susceptibility to atherosclerosis. At week 12, a subset of mice underwent cardiac imaging. GFR was measured using a transdermal measurement system.
- Pathology assessment includes quantitatively scoring of fibrosis using image analysis.

Combining obesity, diabetes and hypertension induces HFpEF



Cardiac imaging showed preserved ejection fraction, low end systolic volume and left ventricle inner diameter and posterior wall thickening, suggesting concentric hypertrophy and HFpEF. Data shown as mean ± SD.

Combination therapy reduces cardiac damage



Combination therapy with Lisinopril and Dapagliflozin reduces heart weight and cardiac fibrosis.
Histopathological evaluation showed macroscopical damage and microscopic myocardial fibrosis and calcification.

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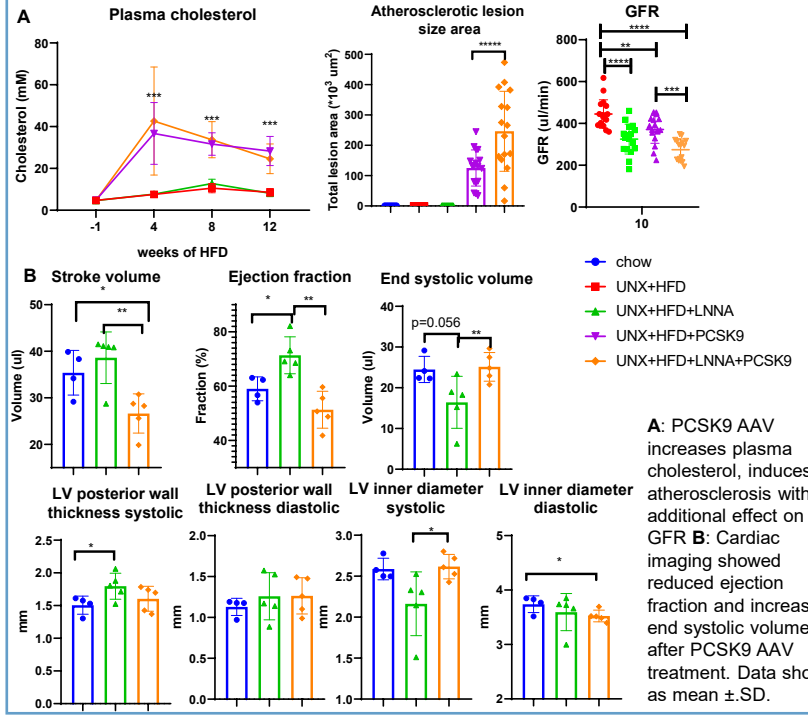
Combining dyslipidemia with obesity, diabetes and hypertension leads to CKD and suggests HFrEF



A: PCSK9 AAV increases plasma cholesterol, induces atherosclerosis with no additional effect on GFR **B**: Cardiac imaging showed reduced ejection fraction and increased end systolic volume after PCSK9 AAV treatment. Data shown as mean ±.SD.

Conclusions

TNO's translational DKD/CKD mouse model with UNX+HFD and LNNA exhibits features of HFpEF. Cardiac damage is reduced by combination therapy with a low dose of Lisinopril and Dapagliflozin. When inducing dyslipidemia the heart develops HFrEF. This shows the usability of the KKAy DKD/CKD mouse model for cardiac efficacy studies.