Inflammation, Body Mass Index, and Cardiovascular Outcomes in Chronic Kidney Disease and Type 2 Diabetes

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Background

- Systemic inflammation appears to be a key driver of residual cardiovascular (CV) risk in persons with chronic kidney disease (CKD) and type 2 diabetes (T2D).
- However, the extent to which low-grade systemic inflammation is associated with obesity in this population remains underexplored.

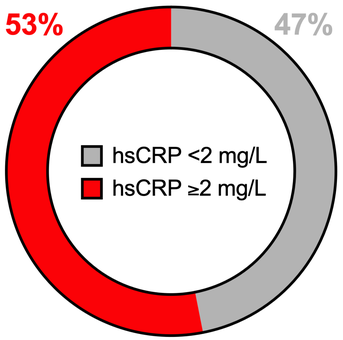
Objectives

- In this participant-level pooled analysis of the global, randomized, phase 3 FIDELIO-DKD and FIGARO-DKD trials (FIDELITY), we examined:
  1. Predictors of baseline high-sensitivity C-reactive protein (hsCRP) levels
  2. Associations between BMI and hsCRP
  3. Associations between hsCRP and adverse CV outcomes, by BMI
  4. Effect of finerenone on CV outcomes, by hsCRP

Methods

- FIDELIO-DKD and FIGARO-DKD enrolled adults with albuminuric CKD and T2D
- Participants with available BMI (≥18.5 kg/m^2) and hsCRP were included
- First, the associational strength of baseline covariates and baseline hsCRP was examined using linear regression with standardized beta coefficients
- Second, the association between baseline BMI and 1) baseline hsCRP; and 2) the odds of an elevated hsCRP was examined using multivariable-adjusted linear and logistic regression
- Third, multivariable-adjusted associations between hsCRP and the cardiovascular composite outcome (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure) were assessed, overall and by BMI
- The effect of finerenone on cardiovascular outcomes across the spectrum of baseline hsCRP was evaluated using Poisson regression with restricted cubic splines

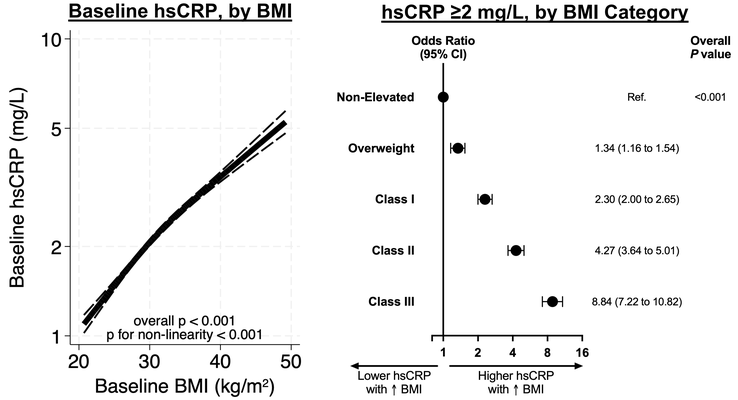
Baseline Characteristics in FIDELITY (n=12,864), by Baseline hsCRP



Higher baseline hsCRP associated with:

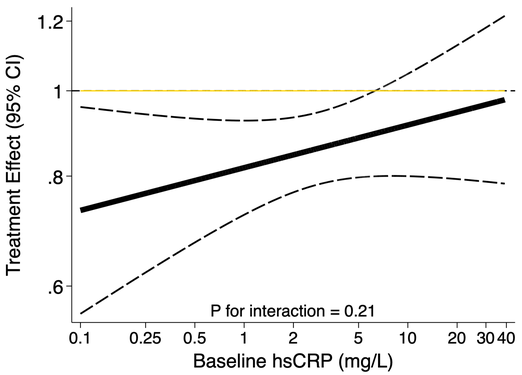
- Female sex
- White and Black race
- Higher BMI and WHtR
- Higher HbA_{1c}
- Higher LDL-C and triglyceride levels
- Lower HDL-C levels
- Longer diabetes duration
- History of HF and AF
- Higher prevalence of insulin and diuretic use

Association Between Baseline BMI and hsCRP



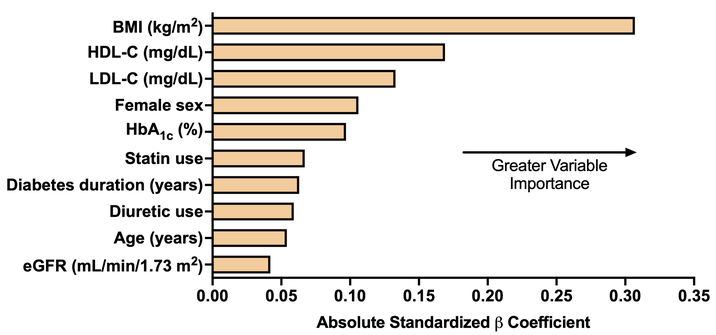
Models adjusted for age, sex, race, eGFR, log-transformed UACR, history of ASCVD, statin use, SGLT2i use, and GLP-1RA use

Effect of Finerenone on Cardiovascular Outcomes, by hsCRP



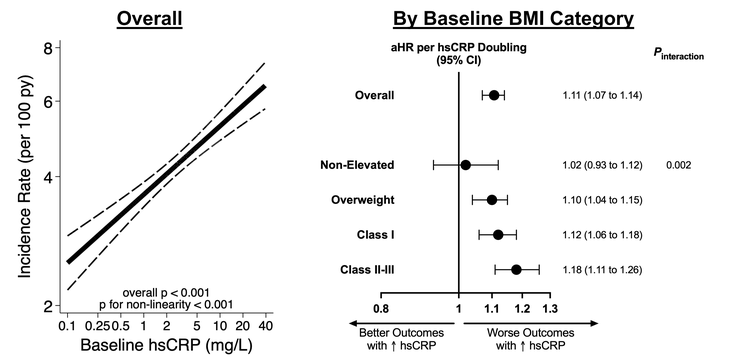
Treatment effect (and 95% CI) of finerenone vs. placebo according to baseline hsCRP estimated via Poisson regression

Predictors of Baseline hsCRP Levels



Standardized beta coefficients extracted from linear regression model adjusted for age, sex, race, BMI, systolic blood pressure, diastolic blood pressure, glycated hemoglobin, eGFR, log-transformed UACR, smoking status, diabetes duration, history of HF, history of MI, history of stroke, history of PAD, atrial fibrillation, baseline LDL-C, baseline HDL-C, baseline triglyceride levels, statin use, aspirin use, NSAID use, metformin use, insulin use, SGLT2i use, and GLP-1RA use.

Association Between hsCRP and Cardiovascular Outcomes, Overall and by BMI



Forest plot (right) shows the association between baseline hsCRP (per doubling) and the composite cardiovascular outcome. aHRs and 95% CI estimated through Cox proportional hazards regression, adjusted for baseline BMI (spline variable with 3 knots; overall model alone), age, sex, race, estimated glomerular filtration rate, glycated hemoglobin, systolic blood pressure, diabetes duration, smoking history, statin use, sodium-glucose co-transporter 2 inhibitor use, and glucagon-like peptide-1 receptor agonist use, randomized treatment, and the protocol-specified stratification factors

Key Findings

In this FIDELITY analysis, BMI was the dominant predictor of baseline hsCRP levels; hsCRP levels were steeply and positively associated with BMI

Baseline BMI appeared to modify hsCRP-outcome associations; hsCRP appeared to be associated with adverse CV outcomes principally among persons with elevated BMI

Finerenone consistently reduced adverse CV outcomes, irrespective of baseline hsCRP

Funding

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These findings suggest obesity is a major driver of low-grade systemic inflammation in persons with CKD and T2D, with potential implications for screening and treatment efforts