Potassium, New-Onset Diabetes, and Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

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FINEARTS-HF

Background

- Hypokalemia is common in heart failure (HF) and may contribute to glucose intolerance
- However, the extent to which hypokalemia influences risks of new-onset diabetes in this population has not been rigorously explored

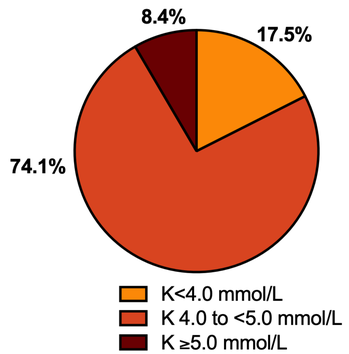
Objectives

- In this exploratory analysis of the global, randomized, phase 3 FINEARTS-HF trial, we examined:
  1. The association between serum potassium levels and incident diabetes
  2. Risks of new-onset diabetes after hypokalemia events
  3. Whether the benefit of finerenone, a nonsteroidal mineralocorticoid receptor antagonist, on new-onset diabetes is mediated through its effects on serum potassium levels

Methods

- **Study Population**: FINEARTS-HF enrolled adults with symptomatic chronic HF with mildly reduced or preserved ejection fraction
- Participants without diabetes at baseline were included in the analysis
- New-onset diabetes was defined as ≥2 glycated hemoglobin (HbA_{1c}) measurements ≥6.5% or new initiation of a glucose-lowering medication other than a sodium-glucose co-transporter 2 inhibitor
- Multivariable-adjusted Cox proportional hazards regression and Poisson regression models were used to examine the association between time-updated potassium and new-onset diabetes
- Cox proportional hazards regression models were used to assess the rate of new-onset diabetes after (versus before) incident hypokalemia (defined as a serum potassium <3.5 mmol/L)
- Causal mediation analysis estimated the percentage of the overall effect of finerenone on new-onset diabetes mediated by changes in time-updated serum potassium and hypokalemia events

Characteristics of FINEARTS-HF Participants without Diabetes (n=3,224), by Baseline Potassium



Lower baseline K associated with:

- Female sex
- Asian race
- Higher LVEF, eGFR, and UACR
- History of AF
- Lower use of beta blockers and ACEi/ARB/ARNI
- Greater use of SGLT2i

Risk of New-Onset Diabetes After Hypokalemia (K <3.5 mmol/L)

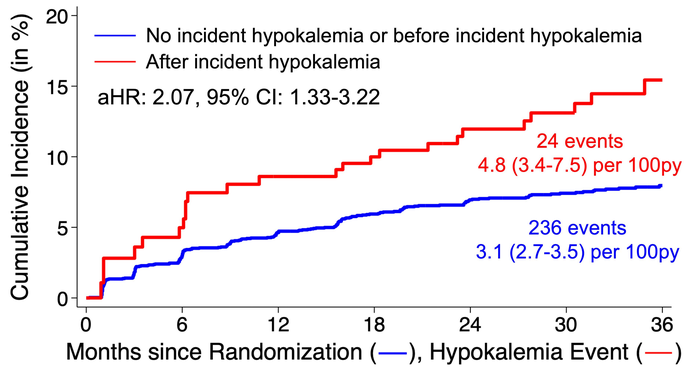
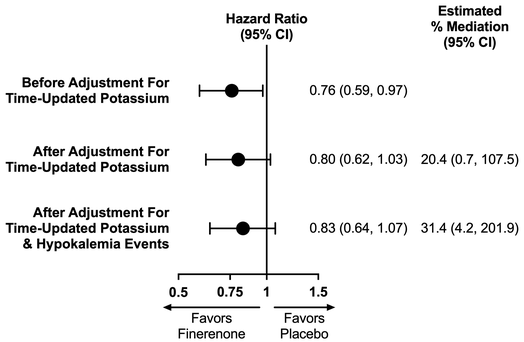


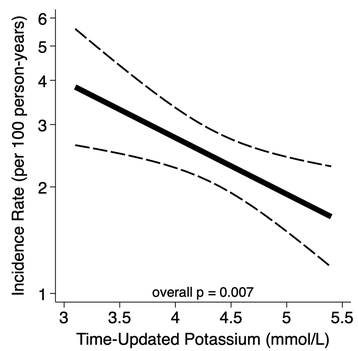
Figure shows the cumulative incidence of new-onset diabetes after incident hypokalemia, compared with before incident hypokalemia or among participants without incident hypokalemia, estimated through Cox proportional hazards models adjusted for the same covariates as in the second panel.

Mediation Analysis of Finerenone on New-Onset Diabetes



Forest plot in shows treatment effects of finerenone on new-onset diabetes, estimated through Cox proportional hazards regression models adjusted for baseline glycated hemoglobin, with and without accounting for time-updated potassium levels and hypokalemia safety events.

Time-Updated Potassium Levels and New-Onset Diabetes



Association between time-updated serum potassium and the incidence rate (and 95% CI) of new-onset diabetes (A), estimated through Poisson regression adjusted for baseline HbA_{1c}, randomized treatment, age, sex, baseline body mass index, geographic region, LVEF, smoking history, baseline eGFR, log-transformed NT-proBNP, log-transformed UACR, loop diuretic use, thiazide diuretic use, statin use, beta blocker use, and use of an renin-angiotensin inhibitor or angiotensin receptor-neprilysin inhibitor. These associations did not appear to be modified by randomized treatment ($P_{interaction}$=0.29).

Risk of New-Onset Diabetes After Serum Potassium <4.0 mmol/L

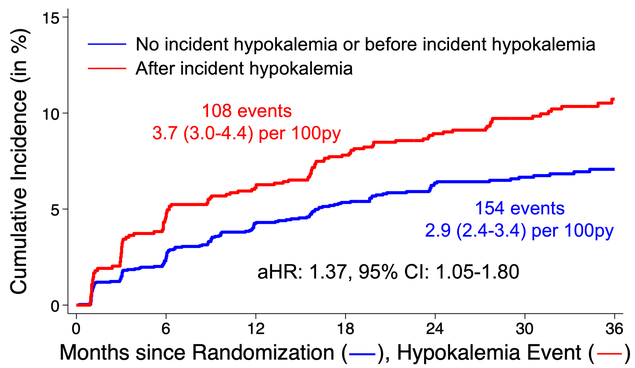


Figure shows the cumulative incidence of new-onset diabetes after incident hypokalemia, compared with before incident hypokalemia or among participants without incident hypokalemia, estimated through Cox proportional hazards models adjusted for the same covariates as in the second panel.

Key Findings

In this FINEARTS-HF analysis, lower time-updated potassium levels were associated with a higher rate of new-onset diabetes

Risks of new-onset diabetes additionally increased substantially after hypokalemia emergence

Benefits of finerenone on new-onset diabetes appeared to be only slightly mediated by its effects on serum potassium and hypokalemia events, suggesting these effects are largely mediated through other mechanistic pathways

Funding

FINEARTS-HF was sponsored by Bayer AG.

These findings enhance understanding of the adverse metabolic effects of hypokalemia in HFmrEF/HFpEF and suggest hypokalemia avoidance – including through finerenone treatment – may mitigate incident diabetes in this population