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Challenge Your Thinking

Dose-exposure-response analysis of finerenone on serum potassium and cardiovascular outcomes among patients with heart failure: Insights from FINEARTS-HF

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Background

- Finerenone reduces the risk of total heart failure events and cardiovascular death among patients with HF with mildly reduced or preserved ejection fraction
- Finerenone is also known to reduce NT-proBNP and raise serum potassium, compared with placebo
- Whether the effects of finereone are dose/exposure dependent is not clear

FINEARTS-HF Study design

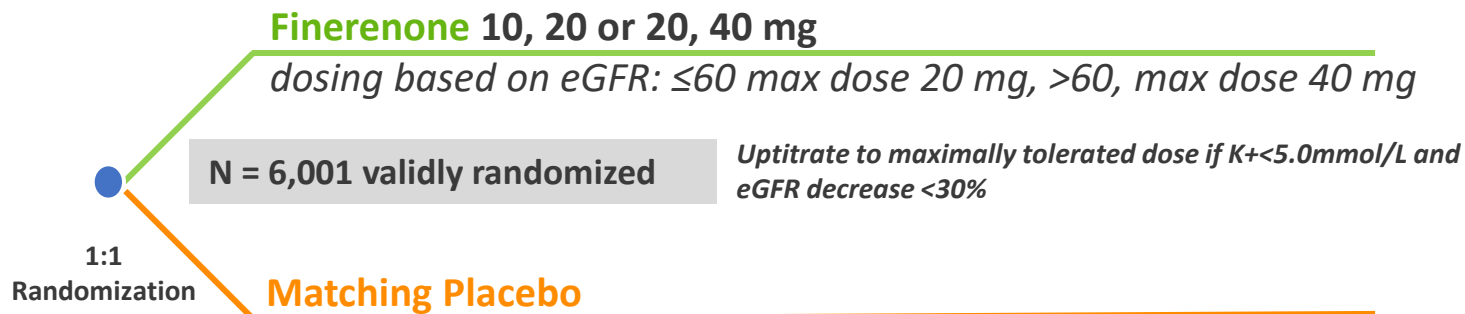
Randomized, double-blind, placebo-controlled trial of patients with HFmrEF/HFpEF

Key Inclusion Criteria

- Symptomatic HF with LVEF \geq 40%
- Age \geq 40 yrs
- Elevated natriuretic peptide levels
- Structural heart disease (LA \uparrow or LVH)
- Diuretics in the 30d prior to randomization

Key Exclusion Criteria

- eGFR $<$ 25 mL/min/1.73 m²
- Potassium $>$ 5.0 mmol/L
- Symptomatic hypotension
- MRA use 30d prior to randomization



Visits: Month 1, then 3-monthly for first 12 months, 4-monthly visits thereafter

FINEARTS-HF Dosing Algorithm – serum K

| Serum / plasma potassium (K ⁺ mmol/L) | Action to be taken | |
|--|--|--|
| First sample: | | |
| <5.0 | Increase to the next higher dose level (or continue at maximum permitted dose level) | |
| ≥5.0 to <5.5 | Continue the current dose level | |
| ≥5.5 to <6.0 | Down-titrate to the next lower dose if possible; if patient is already on dose level 1, interrupt study intervention. K ⁺ should be re-checked within 72 h of initial K ⁺ result awareness; follow option a | |
| ≥6.0 | Interrupt study intervention and K ⁺ should be re-checked within 72 h of initial K ⁺ result awareness; follow option b | |
| Second and subsequent sample: | | |
| Option a | <5.5 | Continue current dose |
| | ≥5.5 | Down-titrate to the next lower dose if possible, or interrupt study intervention and recheck K ⁺ |
| Option b | <5.5 | Restart at dose level 1 |
| | ≥5.5 | Continue to withhold study intervention, further monitoring of K ⁺ . Restart at dose level 1 ONLY if K ⁺ is <5.0 mmol/L |

Analytic Approach

- For data visualization, finerenone dose was considered as the dose administered before the respective PD measurement
- Non-linear mixed effects models were fit to explore relationships of repeated measures of dose/exposure with outcomes
- Serum potassium
 - Thresholds of >5.5 and >6.0 mmol/L
- NT-proBNP
 - Ratio of current concentration to baseline
- Clinical Events
 - Repeated time to event analyses (CV death & total HF events)

Results

N=6,001



Mean eGFR 62 ± 20
mL/min/1.73 m²

n=3,168 eGFR >60
Finerenone 20 -> 40 mg/day

n=2,833 eGFR ≤60
Finerenone 10 -> 20 mg/day

Mean prescribed dose
 33 ± 9 mg/day

Mean prescribed dose
 16 ± 4 mg/day



Finerenone
concentrations
n=6,658 measurements



Serum K⁺
n=123,720 measurements

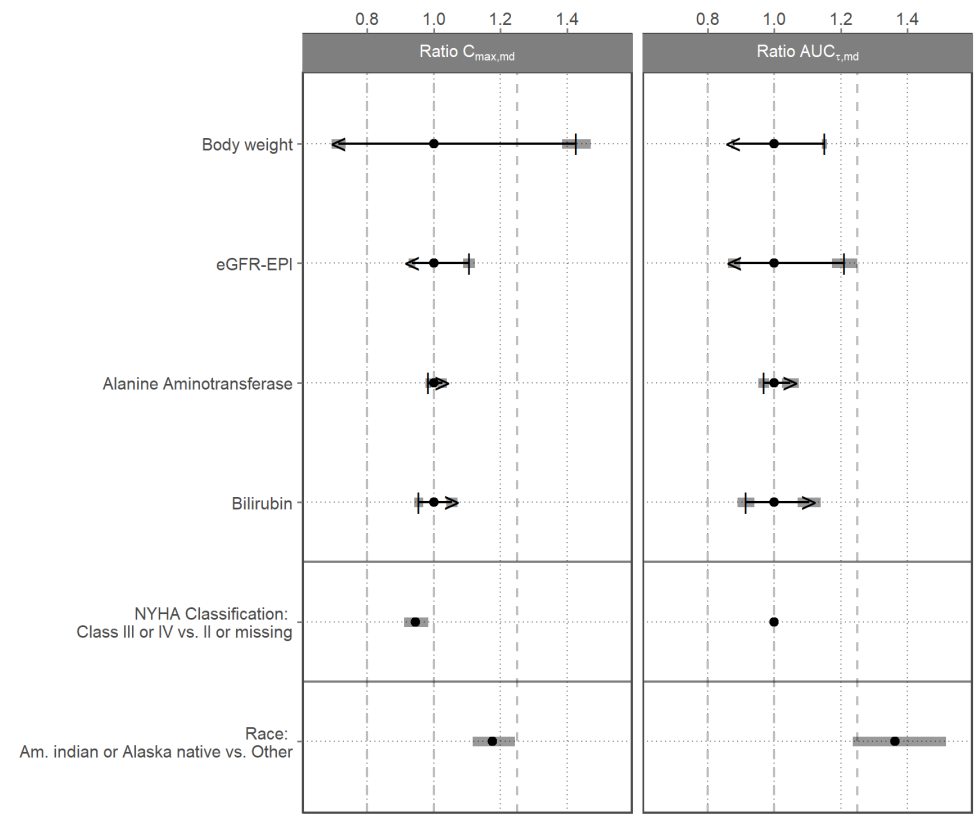
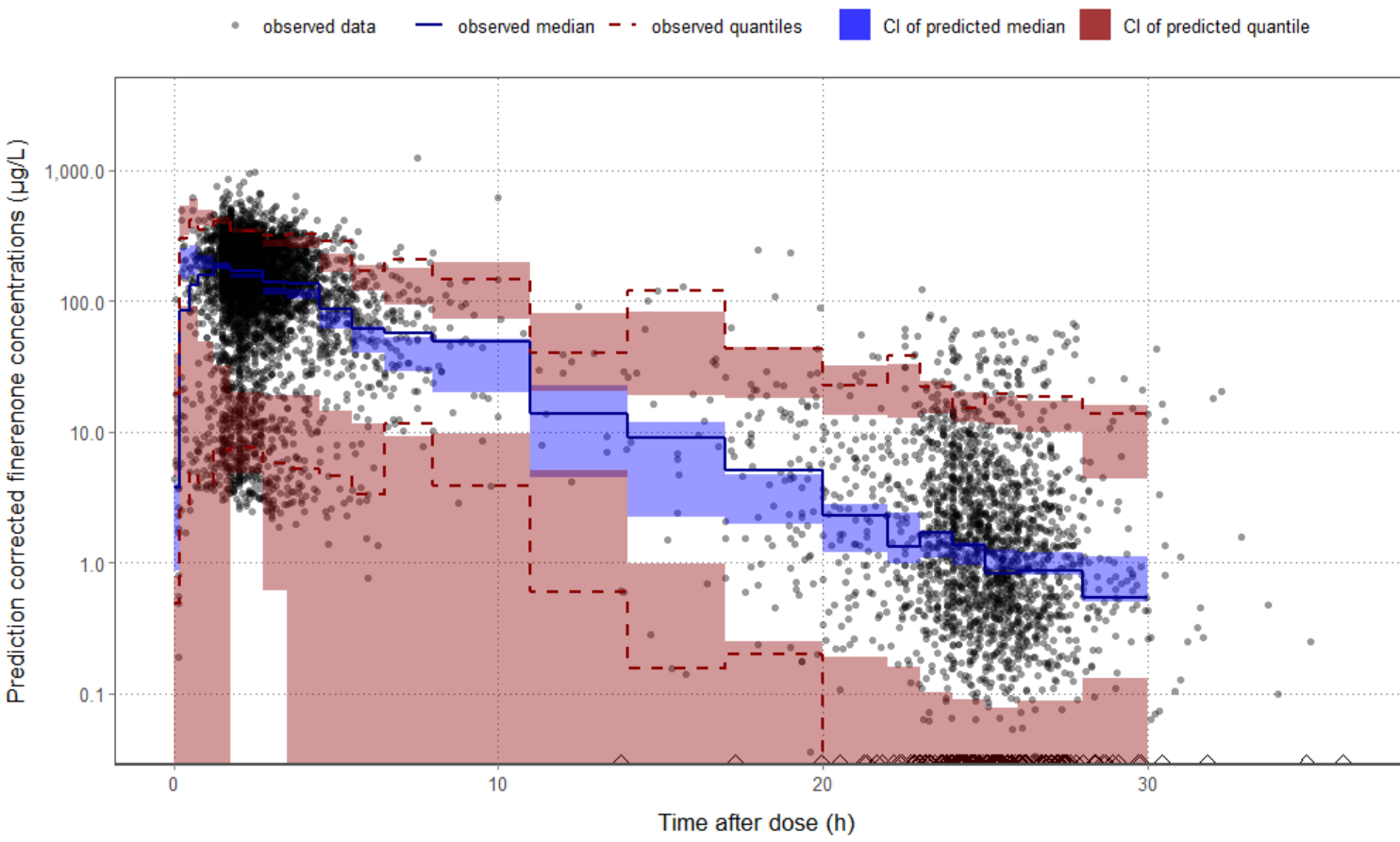


Serum NT-proBNP
n=16,971 measurements

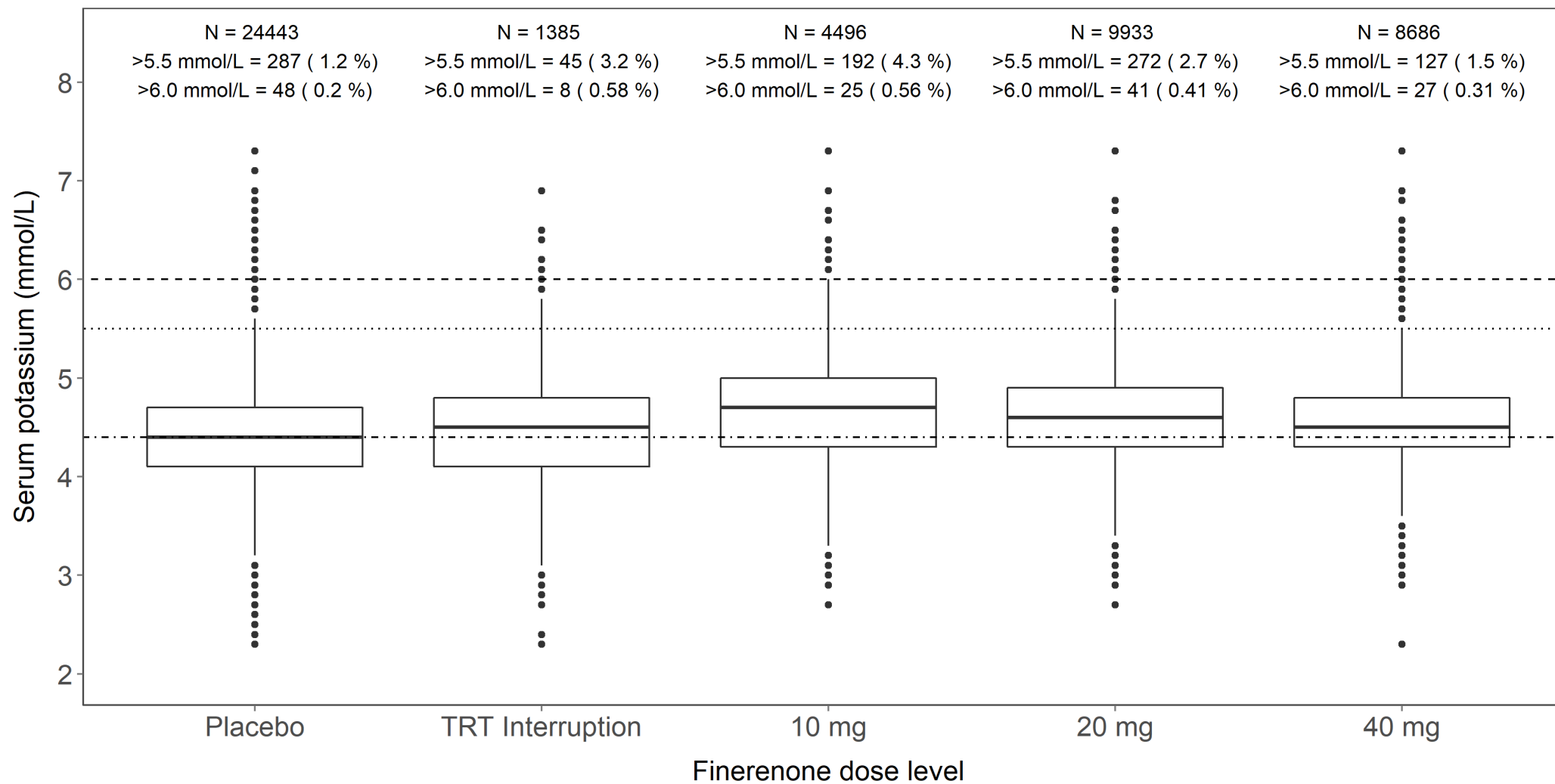


CV death & total HF
n=2,366 events

Pharmacokinetics of finerenone

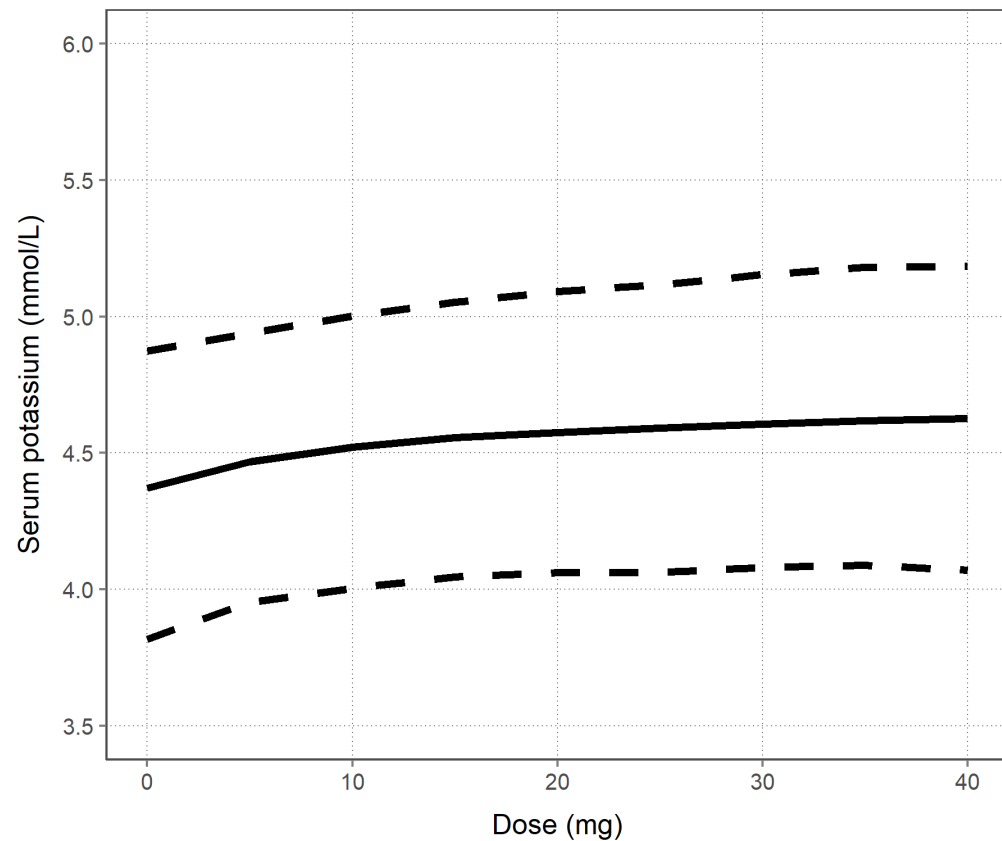


Finerenone dose and serum K

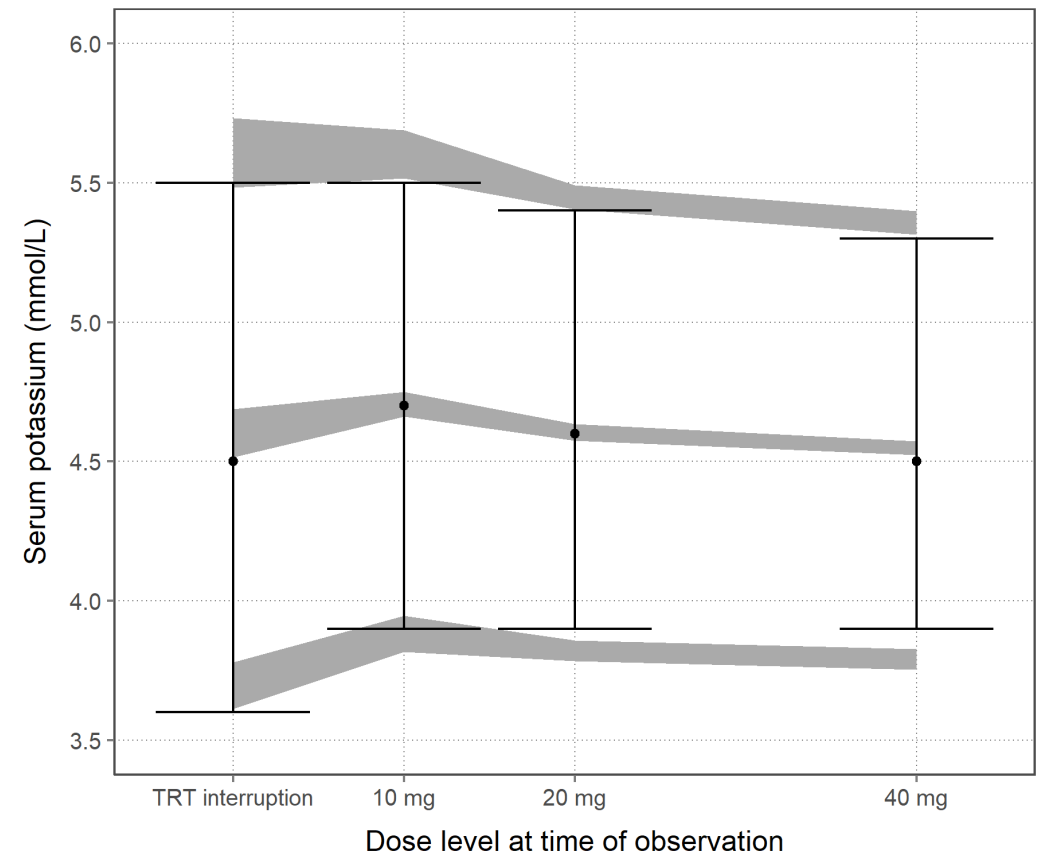


Simulation studies – dose and serum K

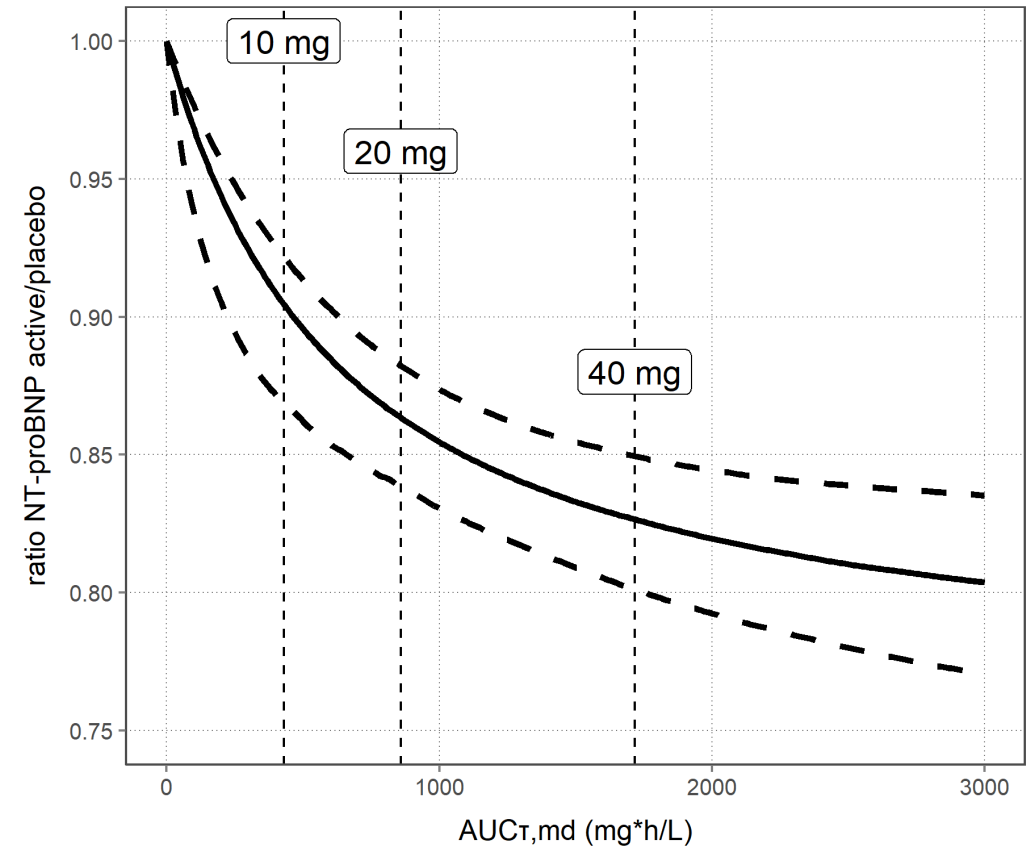
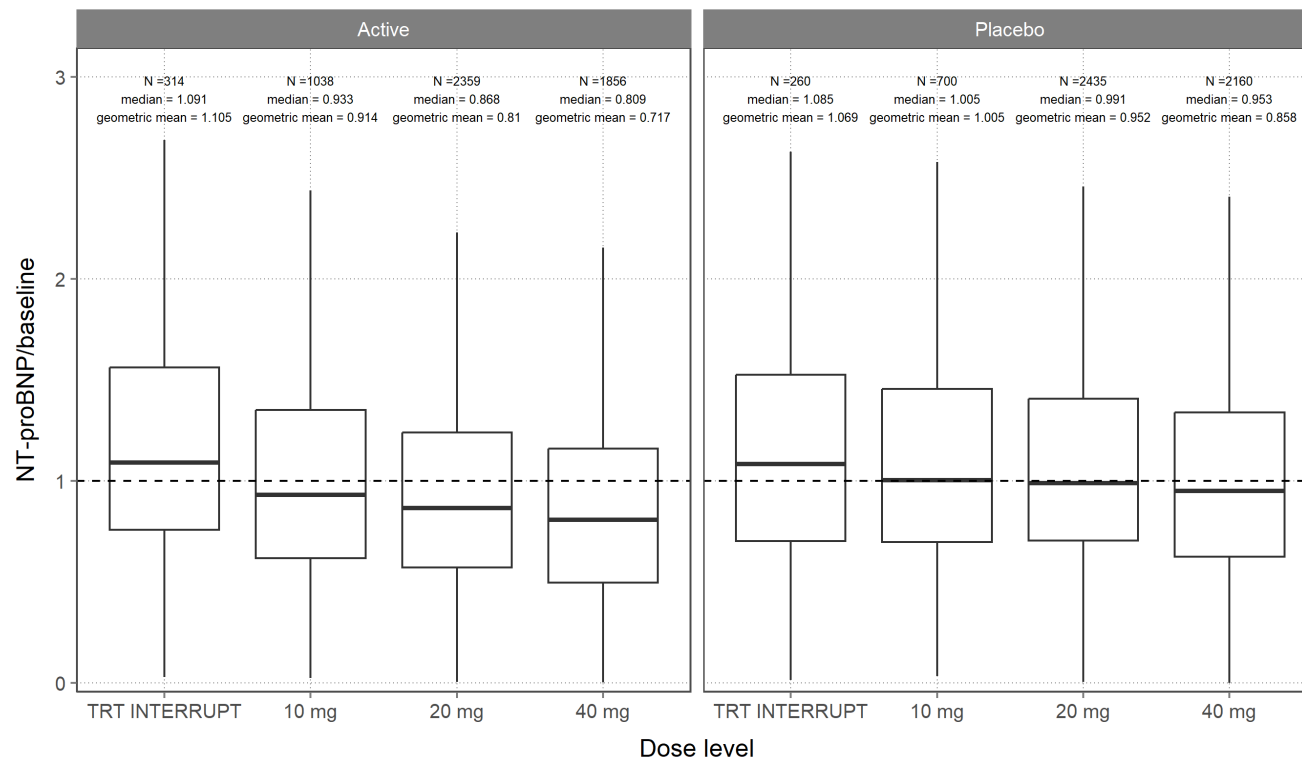
Without dose titration



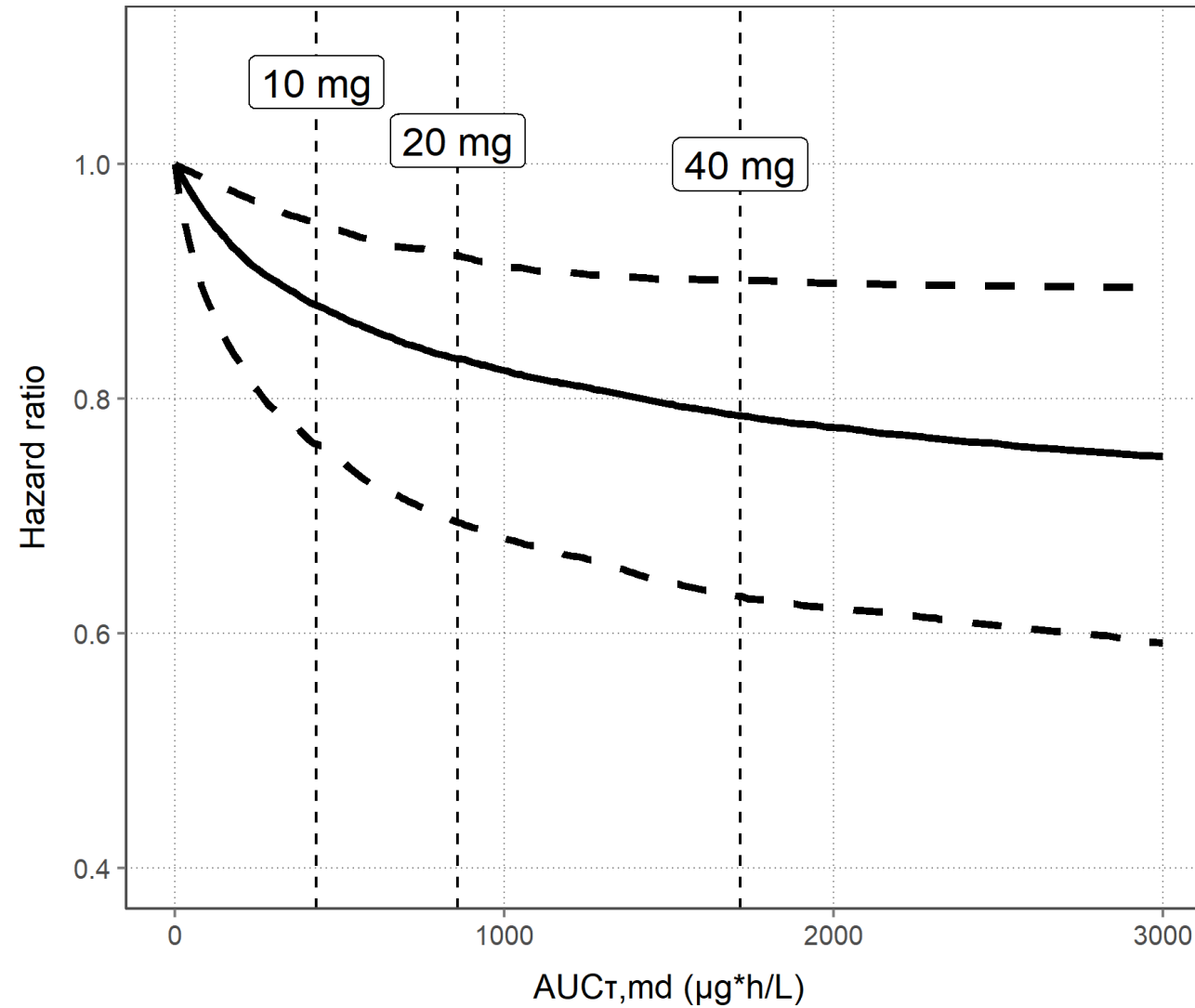
With dose titration



Dose-exposure and NT-proBNP



Dose-exposure and CV events



Conclusions

- The major determinants of higher finerenone exposure were lower body weight and lower eGFR
- Due to protocolized finerenone dose titration, higher doses did not lead to higher serum potassium concentrations
- Higher finerenone exposure was associated with a non-significant lower frequency of CV events and significantly greater reduction in NT-proBNP
- These data are consistent with prior results from CKD & T2DM, and should provide reassurance for appropriate prescribing and titration of finerenone in HFmrEF/HFpEF

Acknowledgements

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