Time patterns of repeat non-fatal events and death in heart failure trials:

Implications for improving future research

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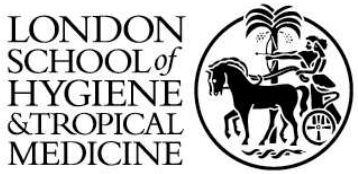

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Disclosures

- Audinga-Dea Hazewinkel is a Post-Doc Research Fellow funded by AstraZeneca (AZ supervisor Ulrica Wilderäng)

- This presentation is based on research using data from Boehringer-Ingelheim that has been made available by a VIVLI DATA USE AGREEMENT. Vivli has not contributed to or approved, and is not in any way responsible for, the contents of this publication.

Background

- In heart failure trials, common choices for primary outcomes are
  - Heart failure hospitalisation (HFH)
  - Composite of HFH and cardiovascular (CV) death
- First event or repeat events (including recurrent HFHs)
- Common presumptions:
  1. Analysing all events instead of only first will enhance statistical power (e.g., in analysis using Anderson-Gill, Negative Binomial)
  2. Repeat events are independent within-patient

Objectives

- Study patterns of heart failure hospitalisations (HFHs) over time
  - Relationship between first HFH and subsequent HFHs
  - Time clustering of HFHs for patients with >1 HFH

- Estimate treatment effects
  - Use assumption-free methods: win ratio and Area Under the Curve
  - Use first event only versus total events
  - Use number of HFHs versus total days spent in hospital

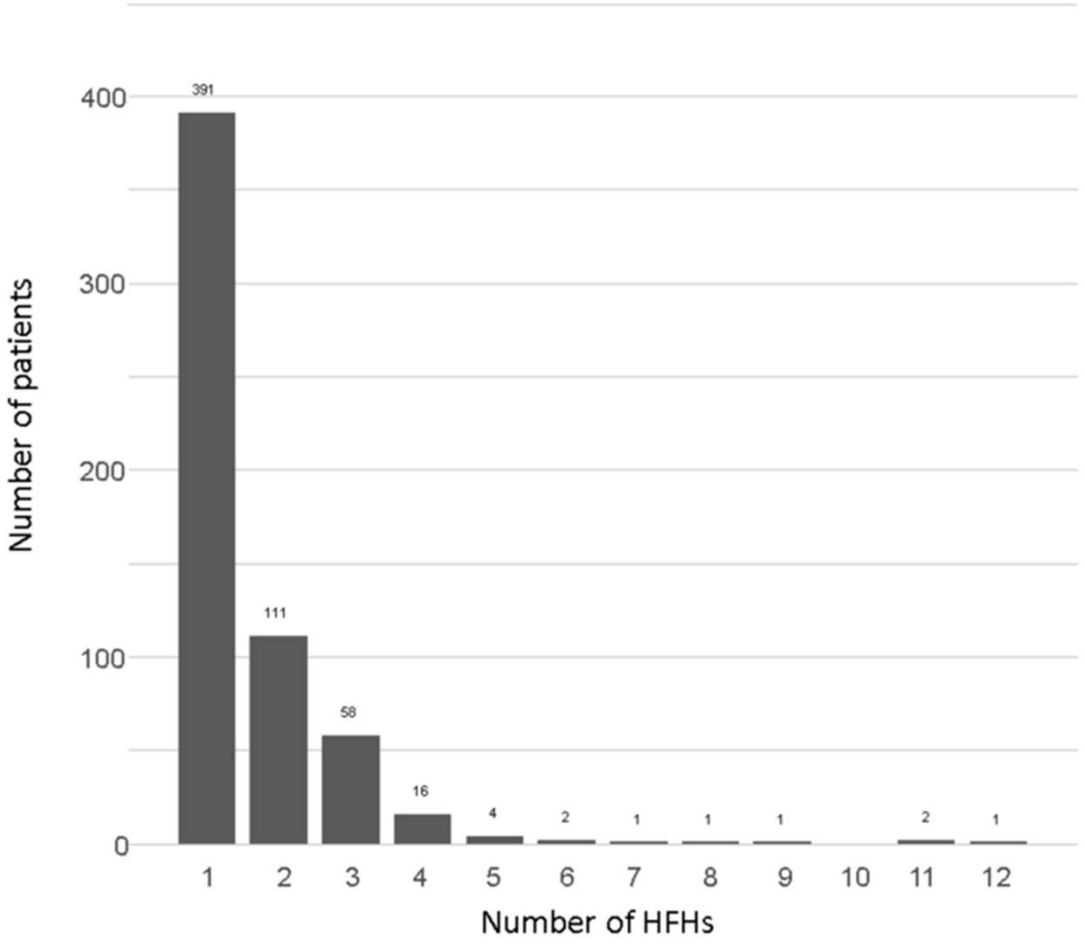
Data

- **EMPEROR-Reduced** and EMPEROR-Preserved trials in chronic heart failure with **reduced**/preserved ejection fraction

- **3730** randomised to empagliflozin vs placebo
- Primary outcome: first HFH/CVD
- Median follow-up time **15.7 months**
- **389 (10%)** experienced CV death
- **588 (16%)** with 1 or more HFHs
- **941** in total

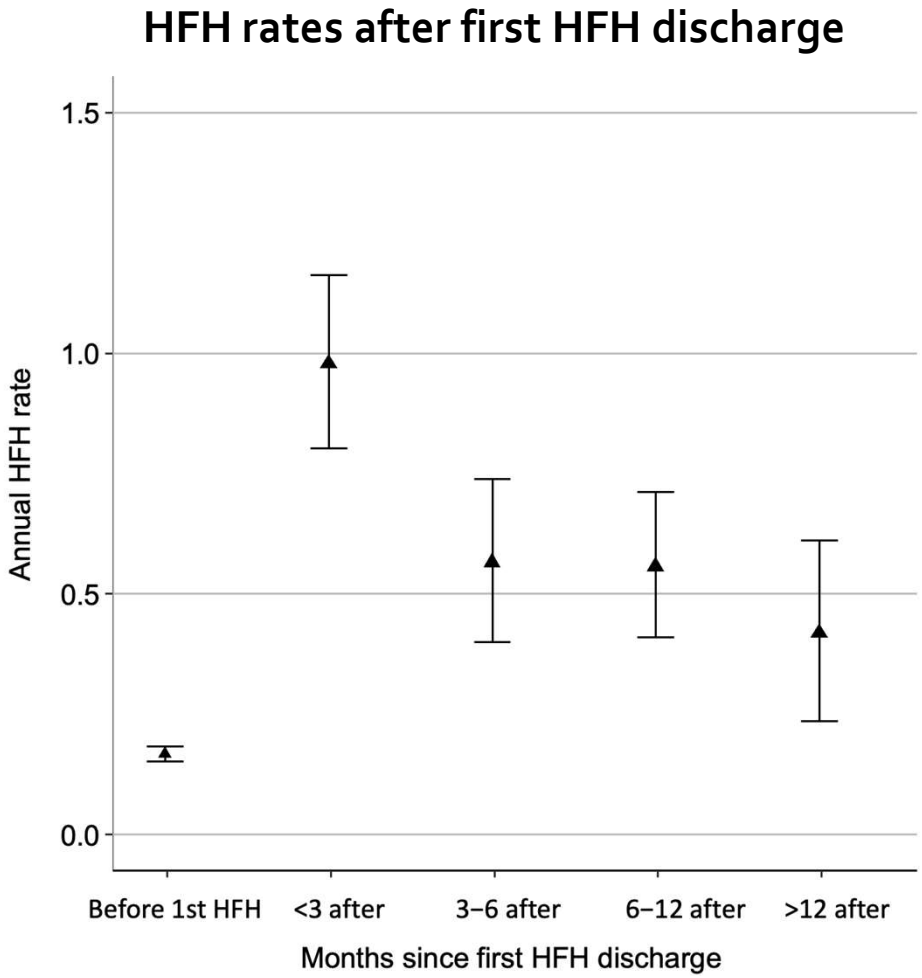
Data

- EMPEROR-Reduced
- Number of HFHs per patient
- 588 patients with ≥ 1 HFHs
- 3142 patients with no HFHs



Relationship between first HFH and subsequent HFHs

- Increased HFH rate in the first three months following first HFH discharge
- HFH rate remains significantly elevated over time
- Incidence of a first HFH is much lower



* Adjusted for 8 risk factors

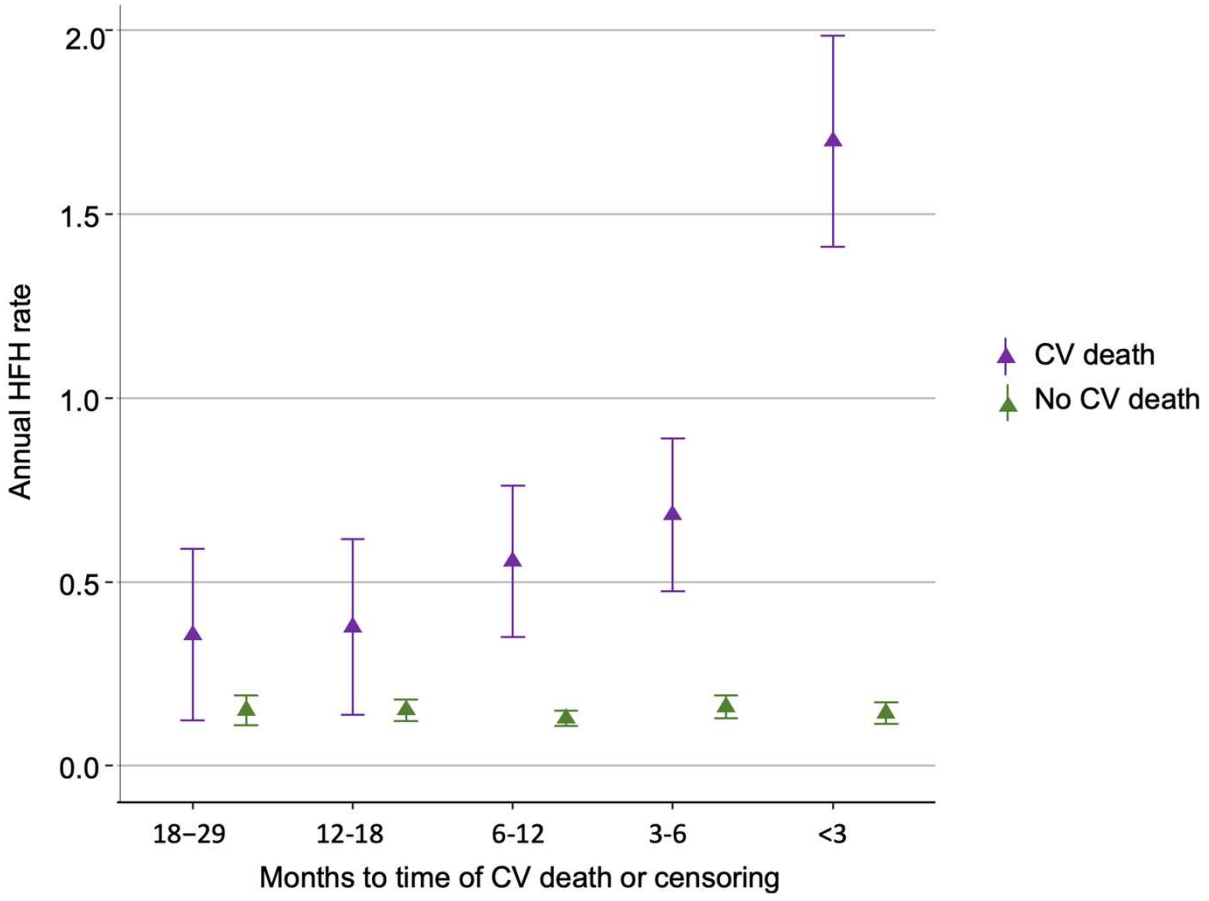
Time clustering of HFHs for patients with >1 HFH

- We developed a method that compares observed time between consecutive HFHs to the expected time if
  - HFHs were truly independent within-patient
  - i.e. they occur randomly over time (Poisson process, constant event rate)
- Is this a plausible assumption?

Relationship between HFH and CV death

- Amongst patients with CV death
  - acceleration in HFH incidence over time as death approache
  - Partly due to in-hospital CV death (72/389)
- Amongst patients who stay alive (or non-CV death)
  - lower incidence of HFH, constant over time

HFH rates leading up to time of CV death or censoring



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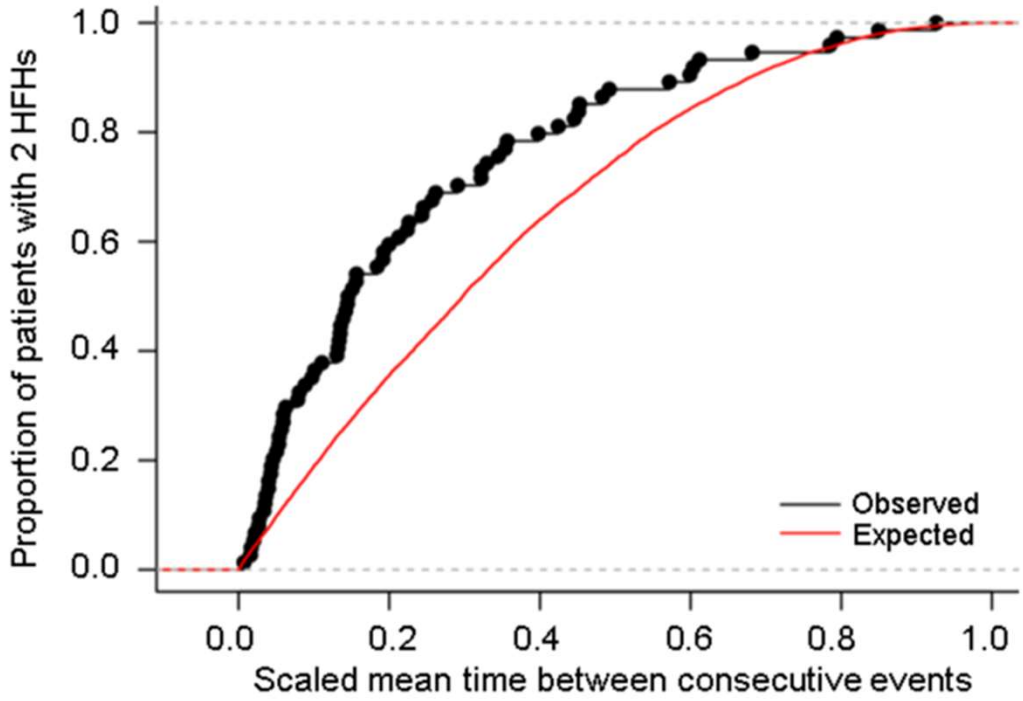
Time clustering of HFHs for patients with >1 HFH

- We developed a method that compares observed time between consecutive HFHs to the expected time if
  - HFHs were truly independent within-patient
  - i.e. they occur randomly over time (Poisson process, constant event rate)
- Restrict focus to censored patients (i.e. no acceleration of events near end of follow-up)
- Estimate clustering in patients with specific number of events (e.g., 2 events, 3 events, 4 events, etc.)
- Then pool results

Time clustering of HFHs for patients with >1 HFH

- Example: 2 events
- Cumulative distribution plot of observed and expected times between consecutive HFHs
- Scaled as a proportion of follow-up



The time between consecutive HFHs is on average 23.5% shorter ($p<0.00001$) than would be expected if within-patient HFHs were distributed randomly over time

Estimating treatment effects: win ratio

- Need an assumption-free method
- Choose a hierarchical composite outcome → win ratio analysis
- Three alternative hierarchical composites:
  - (1) CV death, (2) Time to 1st HFH
  - (1) CV death, (2) Number of HFHs
  - (1) CV death, (2) Cumulative days spent in hospital due to HF

Estimating treatment effects: win ratio

- Example: (1) CV death, (2) Time to 1st HFH
- All patient pairs (one empagliflozin, one placebo: 1863 x 1867 = 3 478 221 pairs) are compared first on level (1) CV death:
  - **win** if placebo patient experiences CV death and empagliflozin patient does not, or if placebo patient experiences CV death earlier
  - **loss** if the converse is true
  - **tie** if neither patient experiences CV death
- If tied for (1) CV death, patients are compared on the same basis for level (2) Time to 1st HFH
- Win ratio = total wins / total losses

Estimating treatment effects: win ratio

Outcome	win ratio (95% CI)	Z	P-value
(1) CV death; (2) Time to 1st HFH	1.340 (1.160 to 1.547	3.99	<0.0001
(1) CV death; (2) Number of HFHs	1.335 (1.156 to 1.541)	3.94	<0.0001
(1) CV death; (2) Cumulative days in hospital due to HF	1.330 (1.153 to 1.534)	3.91	<0.0001

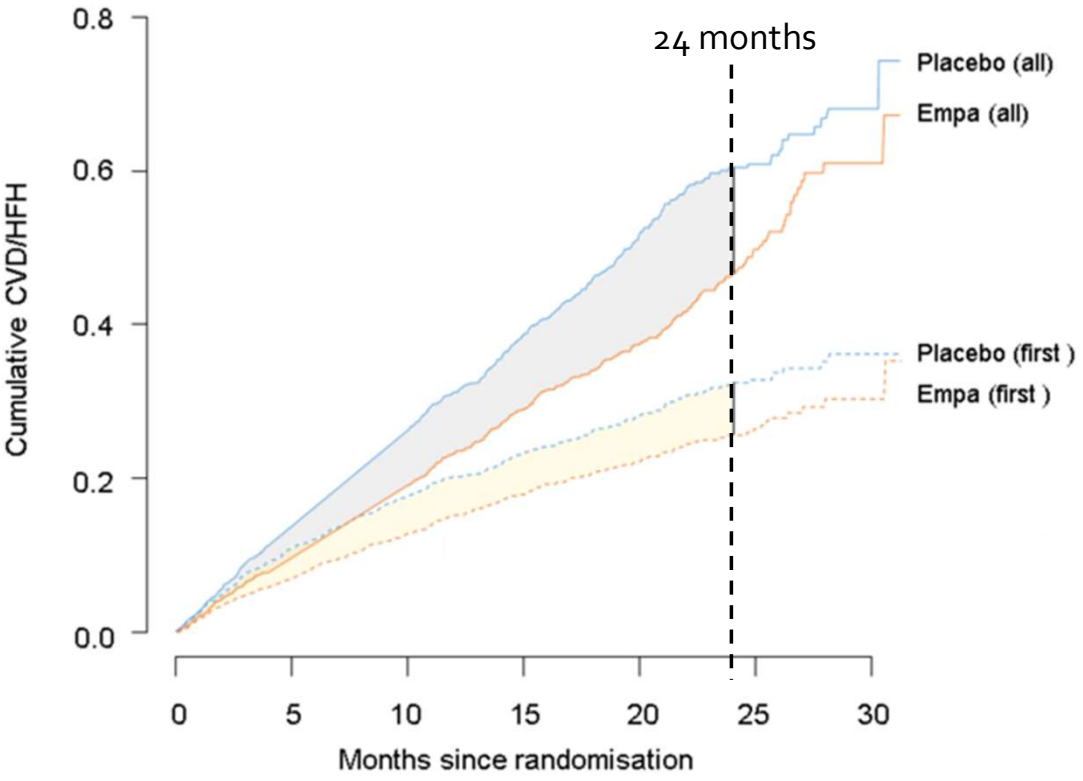
- Comparable win ratios and Z-scores
- No advantage in using repeat HFHs over first HFH
- No advantage in using cumulative HFH duration over number of HFHs

Estimating treatment effects: Area Under The Curve

- Average amount of time between primary outcome occurring and fixed milestone time
- For first events: restricted mean event time lost (RMLT); area under the cumulative incidence curve
- For repeat events: area under the mean cumulative function (AUC)
- Ratio of RMLT/AUC: relative measure of treatment benefit (<1 indicates benefit)

Cumulative incidence over time of

- **first events (first of HFH/CVD)**
- **repeat events (all HFHs and CVD)**



Estimating treatment effects: Area Under The Curve

- RMLT: Composite outcome of first HFH or CV death
- AUC: Composite outcome of all HFHs and CV death
- Milestone time of 24 months (an arbitrary choice)

Outcome	RMLT/AUC (95% CI)	Z	P-value
First HFH or CV death	0.764 (0.674 to 0.866)	4.23	<0.00001
All HFHs and CV death	0.739 (0.628 to 0.867)	3.64	<0.0001

- Stronger evidence (greater Z-score) when using time-to-first
- No advantage in using repeat HFHs over first HFH

Key findings

- Clear evidence of time-clustering of repeat HFHs
- After a first HFH, risk of subsequent HFH is markedly elevated, especially early on
- No apparent gain in power by analysing repeat HFHs instead of just time to first
- No advantage from using cumulative days in hospital instead of number of HFHs
- Win ratio and Area Under the Curve method give similar results
- Comparable results in EMPEROR-Preserved (not shown)

Conclusions

1. Commonly used repeat events methods such as Anderson-Gill and Negative Binomial unrealistically assume in-patient events are independent
   - Implications of this require further work
   - Win ratio and Area Under the Curve are assumption-free
2. Time for a rethink on how to best make use of recurrent events in heart failure trials?
3. Need to study how these findings relate to other diseases with recurrent events

References

EMPEROR TRIALS:

- Packer M *et al.* (2020). EMPEROR-Reduced Trial. *N Engl J Med*. 383:1413-1424.
- Anker SD *et al.* (2021). EMPEROR-Preserved. *N Engl J Med*. 385:1451-1461.

EMPEROR-Reduced CVD/HFH risk score:

- Pocock SJ *et al.* (2021). *Eur Heart J. 42:*4455-4464.

Win ratio:

- Pocock SJ *et al*. (2012). *Eur Heart J*, *33:*176-182.

Area Under the Curve:

- Claggett BL *et al*. (2022). *NEJM Evid*, *1(10)*

Recurrent versus first events in heart failure trials:

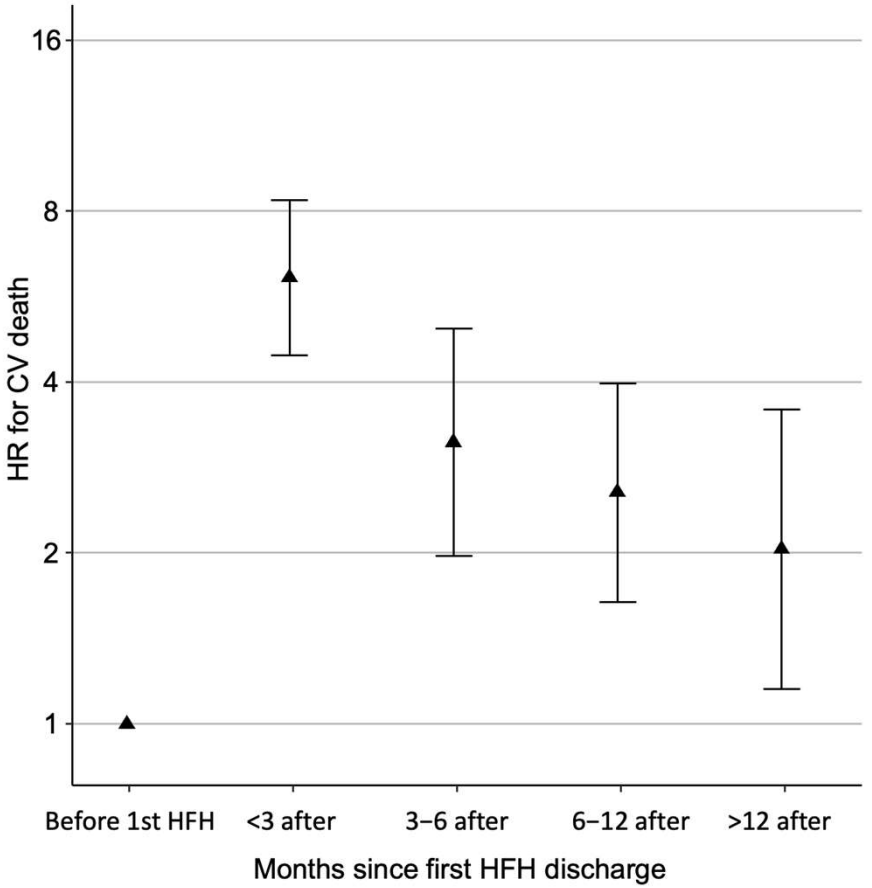
- Gregson J *et al*. (2023). *J Am Coll Cardiol*. 82:1445-1463.
- Claggett B *et al.* (2018). *Circulation.* 138:570-577.

EXTRA SLIDES

Relationship between HFH and CV death

- Increased risk of CV death in the first three months following HFH discharge
- Risk of CV death remains significantly elevated over time
- Risk of CV death much lower in patients without any HFH

Risk of CV death following first HFH discharge

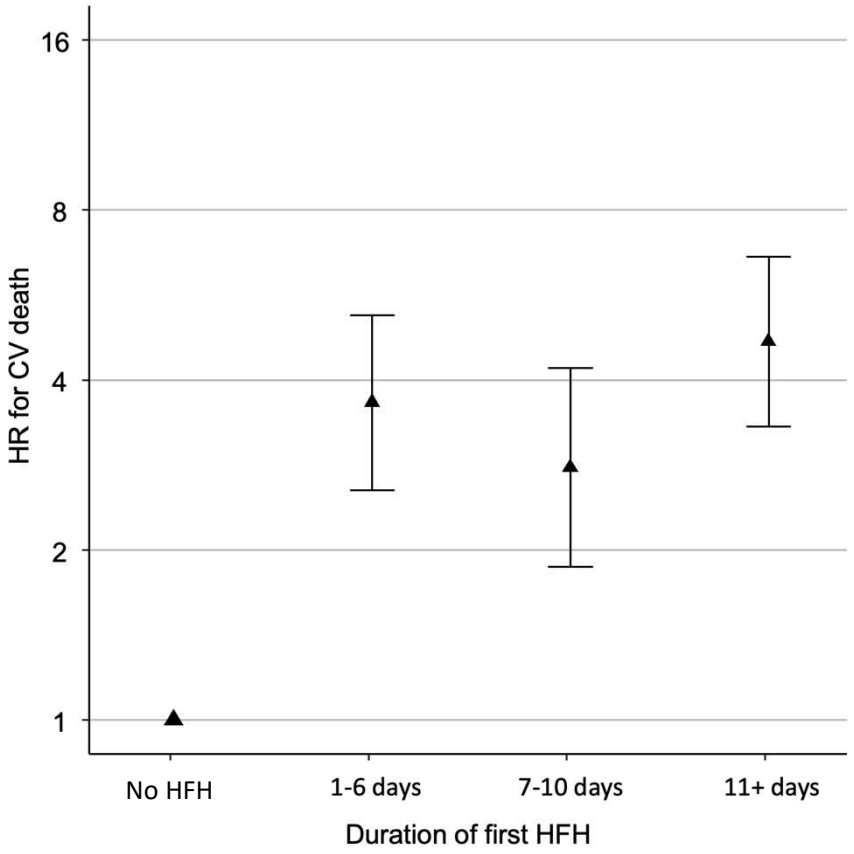


* Adjusted for 8 risk factors

Prognostic impact of length and number of HFHs

- HRs of CV death by
  1. Duration of first HFH
  2. Cumulative time spent in hospital
  3. Number of hospitalisations
- Relative to risk of CV death not preceded by an HFH

1. Risk of CV death by duration of first HFH



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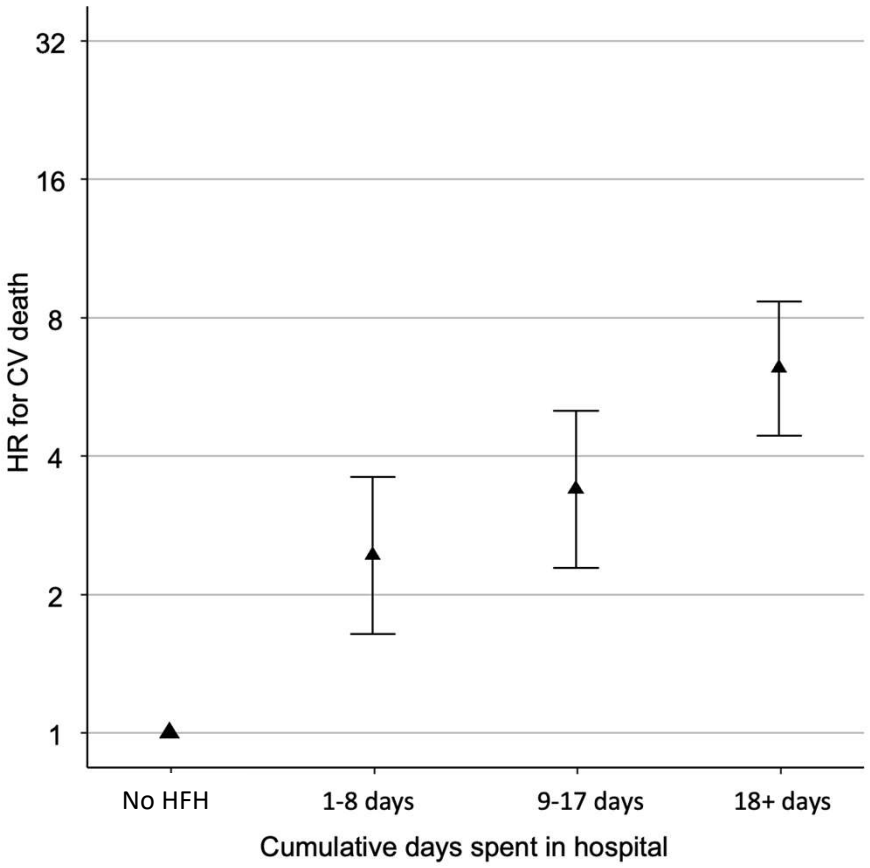
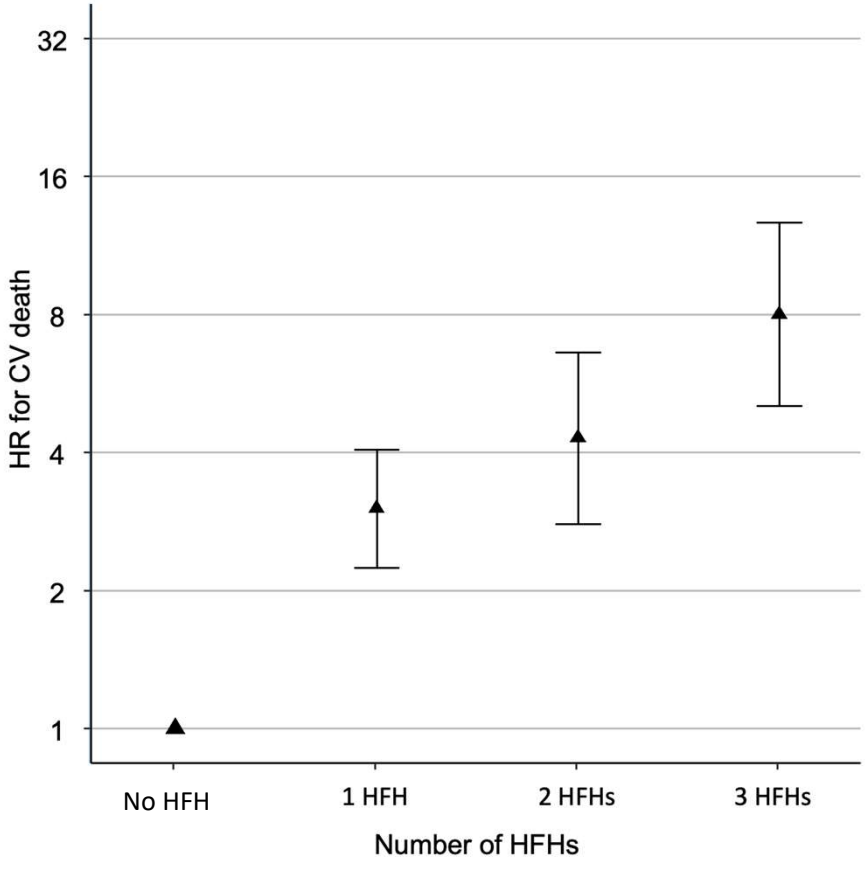
Prognostic impact of length and number of HFHs

2. Risk of CV death by cumulative days spent in hospital due to HF



3. Risk of CV death by number of HFHs



or 8 risk factors