When and how to make use of recurrent events in cardiovascular trials

Supplemental Appendix

Contents

Appendix Table 1: Results on additional statistical analyses of five cardiovascular trials used as case studies in this article

Trial	Chosen secondary outcome	First events / subsequent events	Analysis considering only first event	Analyses using information on repeat events			
			Cox proportional model (first event only) Hazard ratio	LWYY model hazard ratio	Negative binomial model rate ratio	Joint frailty model hazard ratio	Ratio of AUC (areas under the curve AUC)
EMPEROR-Preserved	HFH	611 (259 vs 352) / 337 (148 vs 189)	0.71 (0.60–0.83); p<0.001; z=4.20	0.75 (0.62-0.90) P=0.0023; z=3.05	0.73 (0.60-0.89) P=0.0017; z=3.13	0.73 (0.61-0.88) P=0.0009 ; z=3.33	Not performed for technical reasons*
CHARM-Preserved	HFH	508 (230 vs 278) / 435 (164 vs 271)	0.80 (0.68-0.96) p=0.015; z=2.43	0.71 (0.58-0.88); p=0.0018; z=3.11	0.68 (0.54-0.86) p=0.0012; z=3.24	0.69 (0.56-0.85) p= 0.0006; z=3.44	0.69 (0.50-0.94), p=0.018, z=2.36
AFFIRM-AHF	HFH	320 (142 vs. 178) / 191 (75 vs. 116)	0.73 (0.59-0.92) p=0.006; z=2.74	0.72 (0.57-0.91) p=0.006, z=2.77	0.73 (0.56-0.94) p=-0.016, z=-2.42	0.746 (95% CI: 0.5999, 0.929), p=0.0090	0.75 (0.57-0.99), p=0..043, z=2.03
COAPT	CVD or HFH	290 (115 vs. 175) / 296 (104 vs. 192)	0.56 (0.44-0.70) P<0.001; z=4..9	0.56 (0.44-0.72) p<0.001; z=4.6	0.52 (0.39-0.69) P<0.001; z=4.50	n/a contains fatal event	Not performed for technical reasons*
REDUCE-IT	CV death, non-fatal stroke, or non-fatal MI	1065 (459 vs 606) / 260 (99 vs 161)	0.74 (0.65-0.83) p<0.001; z=4.83	0.72 (0.63-0.82) p<0.001; z=4.77	0.72 (0.63-0.82) p<0.001; z=4.82	n/a contains a fatal event	0.74 (0.62-0.89) p<0.001; z=-3.15

*Unable to install statistical software for AUC on the same machine as the study database

List of abbreviations: AFFIRM-AHF= A Randomised, Double-blind Placebo Controlled Trial Comparing the Effect of Intravenous Ferric Carboxymaltose on Hospitalisations and Mortality in Iron Deficient Subjects Admitted for Acute Heart Failure; EMPEROR-Preserved :The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Preserved Ejection Fraction (EMPEROR-Preserved); CHARM = Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity; COAPT= Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation Trial; CVD=Cardiovascular death; HFH=heart failure hospitalisation; REDUCE-IT= Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial

Appendix Table 2: Hazard ratio for time to first event for selected outcomes by trial (using a Cox proportional hazards model)

Study	Endpoint	Hazard ratio (95% confidence interval)	P-value
EMPEROR-Preserved	CVD	0.91 (0.76-1.09)	0.295
	HFH	0.71 (0.60-0.83)	<0.0001
CHARM-Preserved	CVD	0.99 (0.80-1.22)	0.92
	HFH	0.80 (0.68-0.96)	0.015
AFFIRM-AHF	CVD	0·94 (0·68–1·29)	0·687
	HFH	0.73 (0.59-0.92)	0.006
COAPT	HFH	0.52 (0.40-0.67)	<0.0001
	CVD	0.61 (0.46-0.81)	<0.0001
REDUCE-IT	CV Death	0.80 (0.66-0.98)	0.033
	Fatal or non-fatal stroke	0.72 (0.55-0.93)	0.013
	Fatal or non-fatal MI	0.69 (0.58-0.81)	<0.0001
	Coronary Revascularization	0.66 (0.58-0.76)	<0.0001
	Unstable Angina	0.68 (0.53-0.87)	0.0019

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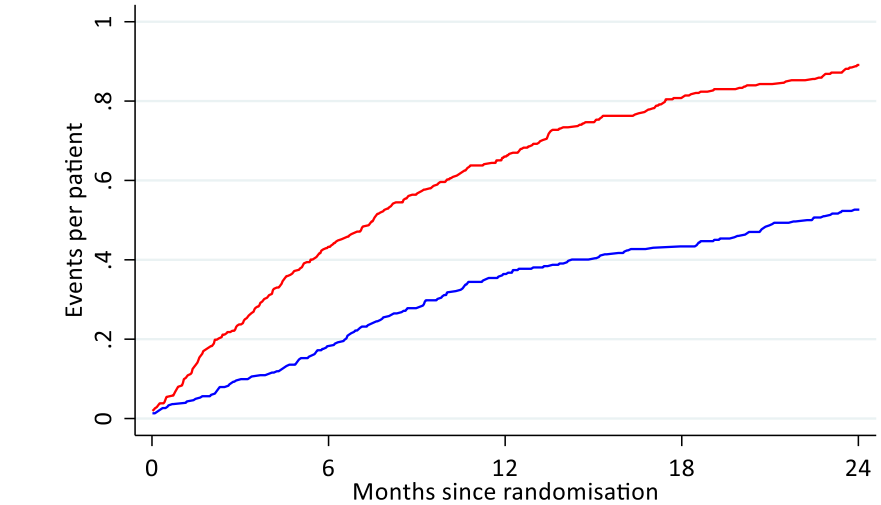
Supplementary Appendix

Appendix Figure 1: Mean cumulative function for number of heart failure hospitalisations per patient in COAPT using the method of Ghosh and Lin[31]



No. at risk			
Control	302	236	124
Device	312	219	88

Appendix A: Statistical programming code for sample size calculations

Statistical programming code for sample size calculations in Stata for selected repeat events methodologies

Central scenario for all examples

Trial similar to assumptions used for AFFIRM-AHF:

- Repeat non-fatal outcome variable
- Duration of 1-year
- Annualized rate of 0.7 per person year in the control group
- Rate is expected to vary from patient to patient, i.e. some patients are higher risk. We expect 33% of events to occur in the 10% most frail patients. To account for this we assume a dispersion parameter of 1.
- Expected incidence rate ratio comparing treatment to control of 0.75

Note that all calculations included here do not include adjustment for crossover or loss to follow-up. These would need to be accounted for in the usual way

Example 1: power calculation if analysis is with a negative binomial model.

```
. ssc install power_twrates_zhu //installing relevant package from ssc archive
. power tworates_zhu, power(0.8) alpha(0.05)  overdispersion(1) r1(0.7) irr(0.75)
```

Note: we would expect similar numbers of patients are required if analysis is instead using an LWYY model

Example 2: power calculation if analysis is using the win ratio

```
. ssc install winratiotest //installing relevant package from ssc archive
. wrpower , power(0.8) alpha(0.05) outcome(repeat mean(0.525 0.7) win(less) dispersion(1))
```

Example 3

Suppose we take the central scenario, but we additionally want to include cardiovascular death as part of the outcome. We expect cardiovascular death to occur in 10% of patients in the control group, and we anticipate the hazard associated with cardiovascular death to be 0.9. We wish to include cardiovascular death as the most important outcome in the hierarchy, and then non-fatal HFH.

```
. ssc install winratiotest //installing relevant package from ssc archive
. wrpower , power(0.8) alpha(0.05) outcome(tte eventprob(0.1) hr(0.9) win(late))  outcome(repeat
mean(0.525 0.7) win(less) dispersion(1))
```

Example 4:

With an annualized event rate is 0.7 and a dispersion parameter of 1 then the expected proportion with at least 1 event in the control group is 0.42. One can then calculate power with a Cox model, but should note that it is not directly comparable to the calculation in Example 1 because the hazard ratio here is marginal, whereas the hazard ratio in Example 1 is conditional.

```
.power cox, power(0.8)  alpha(0.05) eventprob(0.42) hratio(0.75)
```

Appendix B: Methods for identifying eligible studies for review

We searched the PubMed database using the following search terms:

#1: "2019/06/01"[Date - Publication] : "2023/01/01"[Date - Publication])

#2: ("The New England journal of medicine"[Journal]) OR ("Lancet (London, England)"[Journal])) OR ("Nature medicine"[Journal])

#3: (heart failure) OR (heart-failure)

#4: (trial) OR (randomised trial)) OR (randomized trial)

#5: Search: #1 and #2 and #3 and #4

This searched yielded:

- 91 potentially eligible studies.
- 20 were not trial reports
- 47 were excluded because the study population was not patients with heart failure, or because heart failure hospitalisation was not part of the primary outcome
- This left 24 eligible publication covering 18 unique studies (i.e. 6 were duplicate publications).
- These 18 eligible studies. Four trials did not present any analysis using repeat events (COACH, SODIUM-HF, REVIVED-BCIS2, RELAX-AHF 2). Fourteen trials listed on the following page are included in Table 3.

Appendix C: Acronyms and references for the trials surveyed in Table 3

Study acronym	Full name
AFFIRM-AHF[1]	A Randomised, Double-blind Placebo Controlled Trial Comparing the Effect of Intravenous Ferric Carboxymaltose on Hospitalisations and Mortality in Iron Deficient Subjects Admitted for Acute Heart Failure
DELIVER[2]	Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure
DAPA-HF[3]	Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure
EMPEROR-Reduced[4]	Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) trial
EMPEROR-Preserved[5]	Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Preserved Ejection Fraction (EMPEROR-Preserved) trial
EMPULSE[5]	A Study to Test the Effect of Empagliflozin in Patients Who Are in Hospital for Acute Heart Failure
GUIDE-HF[6]	Haemodynamic-GUIDEed management of Heart Failure (GUIDE-HF) trial
IRONMAN[7]	Effectiveness of Intravenous Iron Treatment versus Standard Care in Patients with Heart Failure and Iron Deficiency
PARAGON-HF[8]	
REDUCE LAP-HF II[9]	Atrial shunt in patients with heart failure and preserved or mildly reduced ejection fraction
SCORED[10]	Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk
SOLOIST-WHF[11]	Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure
STRONG-HF[12]	Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure
VICTORIA[13]	Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction

References:

1. Ponikowski P, Kirwan B-A, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. Lancet. 2020;396:1895–1904.

2. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2022;387:1089–1098.

3. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2019;381:1609–1620.

4. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020;383:1413–1424.

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6. Voors A, Angermann C, Teerlink J, et al. Efficacy and Safety of Empagliflozin in Hospitalized Heart Failure Patients: Main Results from The Empulse Trial. Nat Med. 2022;55:172.

7. Lindenfeld J, Zile MR, Desai AS, et al. Haemodynamic-guided management of heart failure (GUIDE-HF): a randomised controlled trial. Lancet. 2021;398:991–1001.

8. Kalra PR, Cleland JGF, Petrie MC, et al. Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial. Lancet. 2022;400:2199–2209.

9. Shah SJ, Borlaug BA, Chung ES, et al. Atrial shunt device for heart failure with preserved and mildly reduced ejection fraction (REDUCE LAP-HF II): a randomised, multicentre, blinded, sham-controlled trial. Lancet. 2022;399:1130–1140.

10. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. N Engl J Med. 2021;384:129–139.

11. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N Engl J Med. 2021;384:117–128.

12. Mebazaa A, Davison B, Chioncel O, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. Lancet. 2022;400:1938–1952.

13. Armstrong PW, Pieske B, Anstrom KJ, et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2020;382:1883–1893.