SUPPLEMENTARY

Supplementary Table S1 – Risk of bias of individual studies by revised Cochrane Risk Assessment tool

Study name	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result
GALACTIC-HF	-	-	-	-	-
COSMIC-HF	-	-	-	-	-
VICTORIA	-	-	-	-	-
SOCRATES-REDUCEI	-	-	-	-	-
EMPEROR-Reduced	-	-	-	-	-
EMPERIAL-Reduced	-	-	-	-	-
Empire HF	-	-	-	-	+/-
SUGAR-DM-HF	-	-	-	-	+/-
EMPA-TROPISM (ATRU-4)	-	-	-	-	+/-
DAPA-HF	-	-	-	-	-
DECLARE-TIMI 58 subgroup HFrEF	-	-	-	-	-
DEFINE-HF	-	-	-	-	-
TOTAL	-	-	-	-	-

Each field should be graded as: Low - /High + /Some concerns +/- (please use the corresponding signs pasting them: -/+/-/ +)

Information at:

https://methods.cochrane.org/bias/resources/cochrane-risk-bias-tool

https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool?authuser=0

https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2?authuser=0

Supplementary Table S2: League table showing pooled HRs for primary and secondary endpoints (sensitivity analysis – NMA on HR estimates).

Endpoint	Placebo	SGLT2i	Vericiguat	Omecamtiv mecarbil
CV death or HF hospitalization				
	Placebo	0.74 (0.67-0.81)	0.89 (0.82-0.98)	0.92 (0.86-0.99)
	1.35 (1.23-1.49)	SGLT2i	1.21 (1.06-1.38)	1.25 (1.11-1.40)
	1.12 (1.02-1.23)	0.83 (0.73-0.94)	Vericiguat	1.03 (0.92-1.16)
	1.09 (1.01-1.17)	0.80 (0.71-0.90)	0.97 (0.86-1.09)	Omecamtiv mecarbil
CV death				
	Placebo	0.82 (0.67-0.99)	0.93 (0.71-1.21)	1.01 (0.79-1.29)
	1.23 (1.01-1.49)	SGLT2i	1.14 (0.82-1.58)	1.24 (0.90-1.69)
	1.08-0.83-1.40)	0.88 (0.63-1.22)	Vericiguat	1.09 (0.76-1.56)
	0.99 (0.77-1.27)	0.81 (0.59-1.11)	0.92 (0.64-1.32)	Omecamtiv mecarbil
All-cause death				
	Placebo	0.82 (0.69-0.98)	0.95 (0.74-1.22)	1.00 (0.79-1.26)
	1.22 (1.02-1.46)	SGLT2i	1.16 (0.85-1.57)	1.22 (0.91-1.64)
	1.05 (0.82-1.35)	0.86 (0.64-1.17)	Vericiguat	1.05 (0.75-1.48)
	1.00 (0.79-1.26)	0.82 (0.61-1.10)	0.95 (0.68-1.34)	Omecamtiv mecarbil
HF hospitalization				
	Placebo	0.69 (0.62-0.77)	0.90 (0.81-1.00)	0.95 (0.87-1.03)
	1.45 (1.30-1.62)	SGLT2i	1.30 (1.12-1.52)	1.38 (1.20-1.58)
	1.11 (1.00-1.23)	0.77 (0.66-0.89)	Vericiguat	1.06 (0.92-1.21)
	1.05 (0.97-1.15)	0.73 (0.63-0.84)	0.95 (0.83-1.08)	Omecamtiv mecarbil

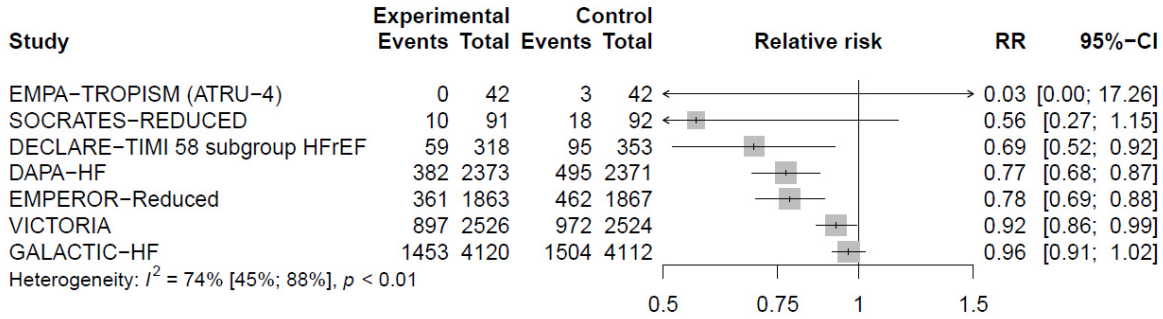
Values are reported as pooled hazard ratios and 95% confidence intervals. The pooled effect estimates obtained from the network meta-analysis are reported for column intervention relative to raw.
HR = hazard ratio; NMA = network meta-analysis.

Supplementary Table S3: League table showing pooled risk ratios for primary and secondary endpoints (sensitivity analysis – NMA including phase 3 trials only).

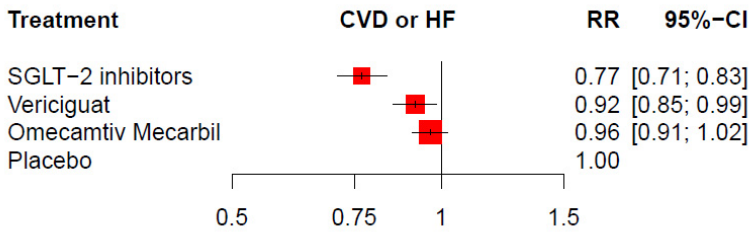
Endpoint	Placebo	SGLT2i	Vericiguat	Omecamtiv mecarbil
CV death or HF hospitalization				
	Placebo	0.78 (0.71-0.85)	0.92 (0.86-0.99)	0.96 (0.91-1.02)
	1.29 (1.18-1.40)	SGLT2i	1.19 (1.06-1.33)	1.24 (1.12-1.38)
	1.08 (1.01-1.17)	0.84 (0.75-0.94)	Vericiguat	1.05 (0.95-1.15)
	1.04 (0.98-1.09)	0.81 (0.73-0.89)	0.96 (0.87-1.05)	Omecamtiv mecarbil
CV death				
	Placebo	0.87 (0.77-0.99)	0.94 (0.83-1.06)	1.01 (0.93-1.10)
	1.15 (1.01-1.30)	SGLT2i	1.08 (0.90-1.28)	1.16 (0.99-1.35)
	1.07 (0.94-1.02)	0.93 (0.78-1.11)	Vericiguat	1.08 (0.93-1.25)
	0.99 (0.91-1.08)	0.86 (0.74-1.01)	0.93 (0.80-1.08)	Omecamtiv mecarbil
All-cause death				
	Placebo	0.88 (0.79-0.99)	0.96 (0.86-1.07)	1.00 (0.99-1.08)
	1.13 (1.01-1.26)	SGLT2i	1.08 (0.93-1.27)	1.13 (0.99-1.29)
	1.04 (0.94-1.16)	0.92 (0.79-1.08)	Vericiguat	1.04 (0.91-1.19)
	1.00 (0.93-1.08)	0.88 (0.77-1.01)	0.96 (0.84-1.09)	Omecamtiv mecarbil
HF hospitalization				
	Placebo	0.72 (0.65-0.81)	0.92 (0.85-1.01)	0.97 (0.90-1.04)
	1.38 (1.24-1.54)	SGLT2i	1.28 (1.11-1.47)	1.34 (1.17-1.52)
	1.08 (0.99-1.18)	0.78 (0.68-0.90)	Vericiguat	1.05 (0.94-1.17)
	1.03 (0.97-1.11)	0.75 (0.66-0.85)	0.96 (0.86-1.07)	Omecamtiv mecarbil

Values are reported as pooled risk ratios and 95% confidence intervals. The pooled effect estimates obtained from the network meta-analysis are reported for column intervention relative to raw.

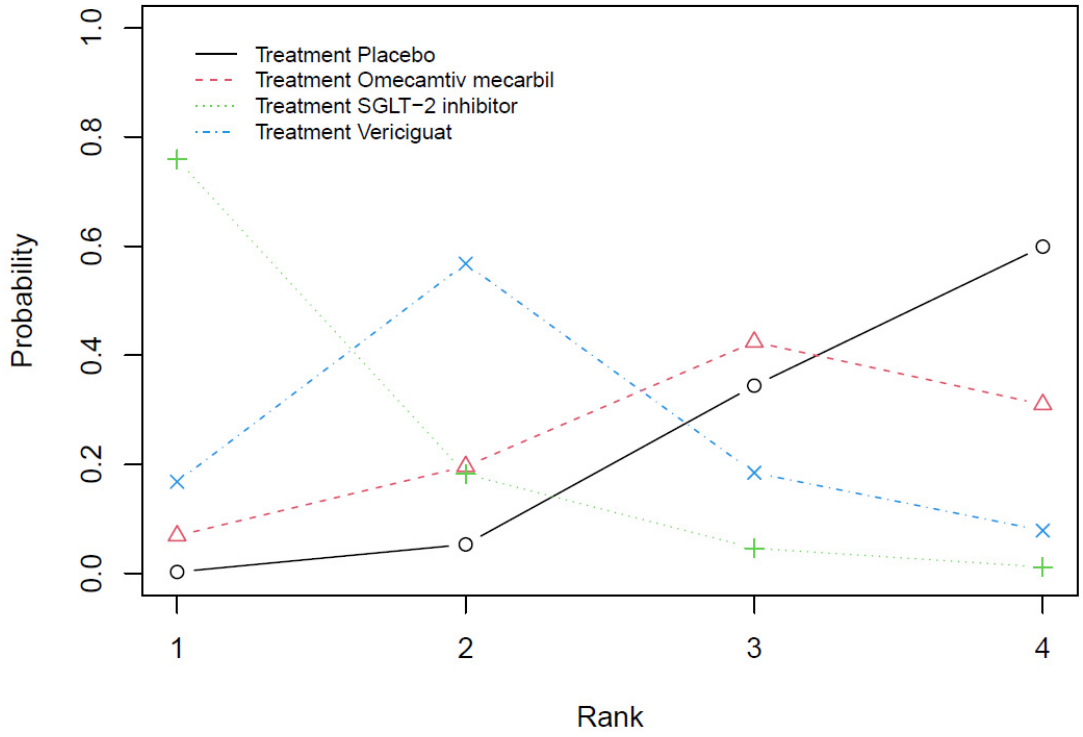
Supplementary Figure S1: Forest plot summarizing data from individual studies for primary endpoint (main analysis).



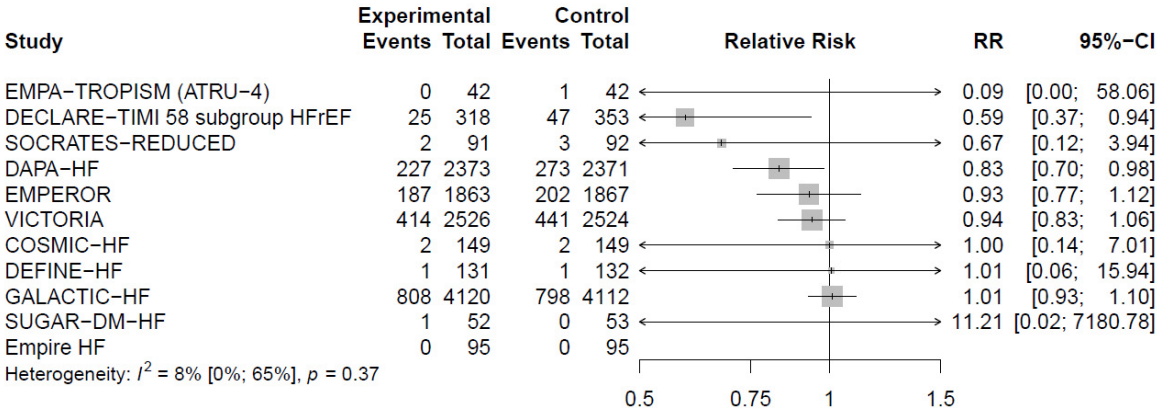
Supplementary Figure S2: Forest plot of each treatment versus PLACEBO for primary endpoint (main analysis).



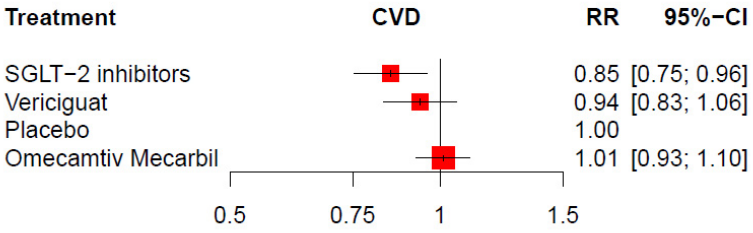
Supplementary Figure S3: Cumulative probability rank plots for each treatment being the best with respect to primary endpoint (main analysis).



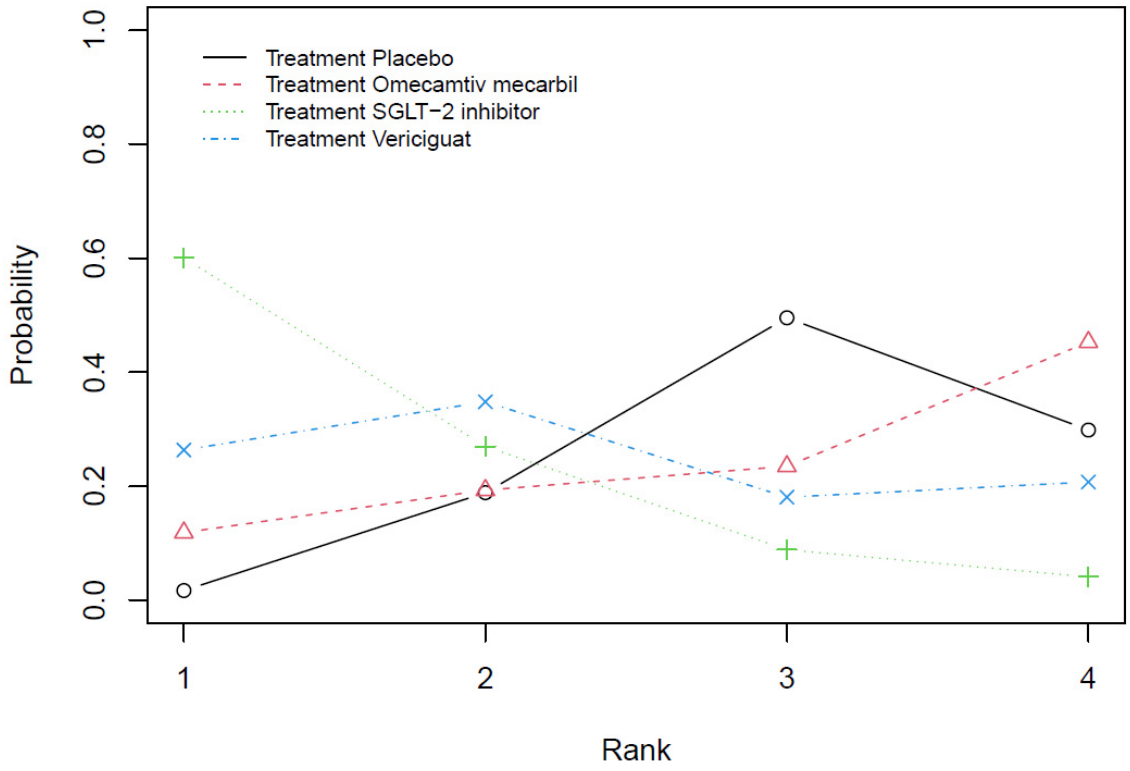
Supplementary Figure S4: Forest plot summarizing data from individual studies for CV death (main analysis).



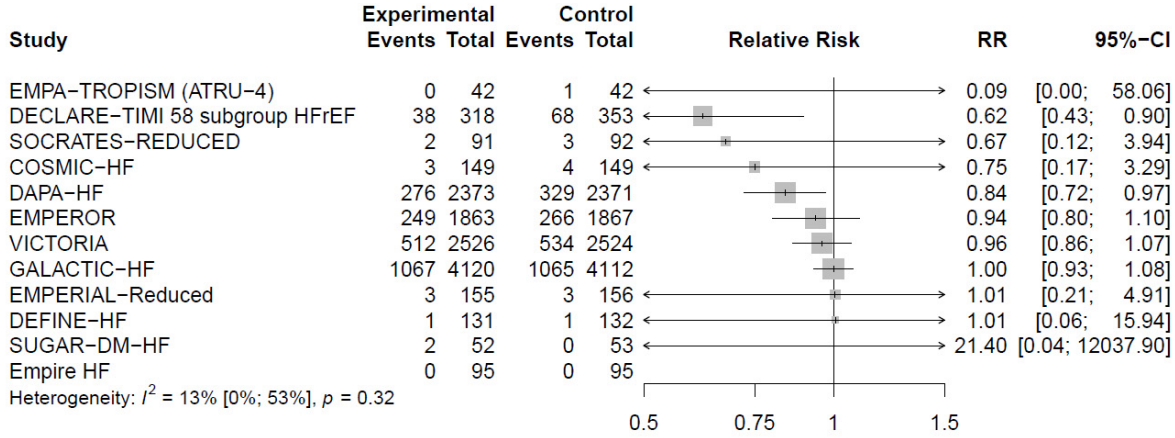
Supplementary Figure S5: Forest plot of each treatment versus PLACEBO for CV death (main analysis).



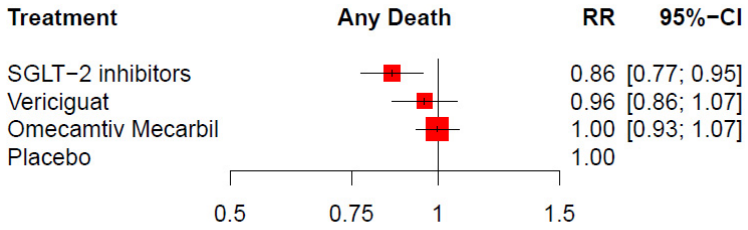
Supplementary Figure S6: Cumulative probability rank plots for each treatment being the best with respect to CV death (main analysis).



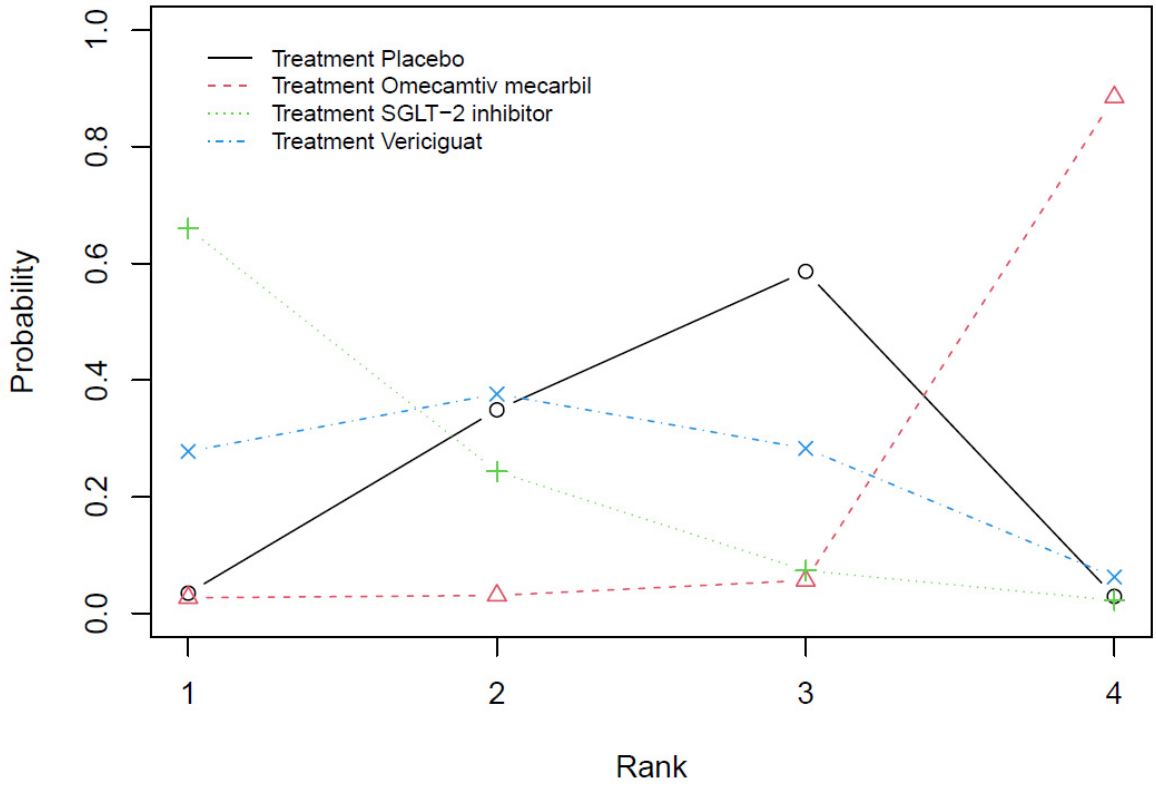
Supplementary Figure S7: Forest plot summarizing data from individual studies for all-cause death (main analysis).



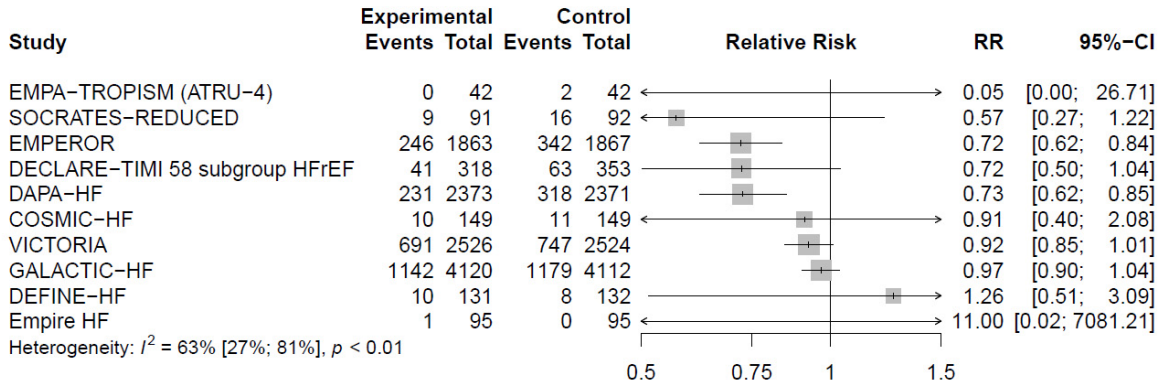
Supplementary Figure S8: Forest plot of each treatment versus PLACEBO for all-cause death (main analysis).



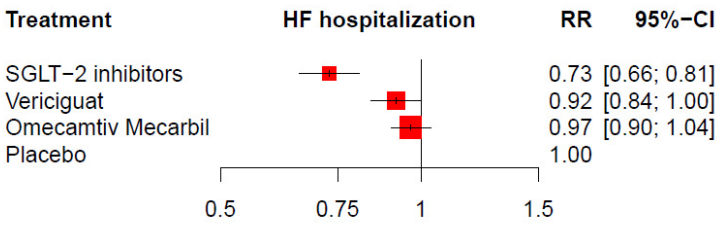
Supplementary Figure S9: Cumulative probability rank plots for each treatment being the best with respect to all-cause death (main analysis).



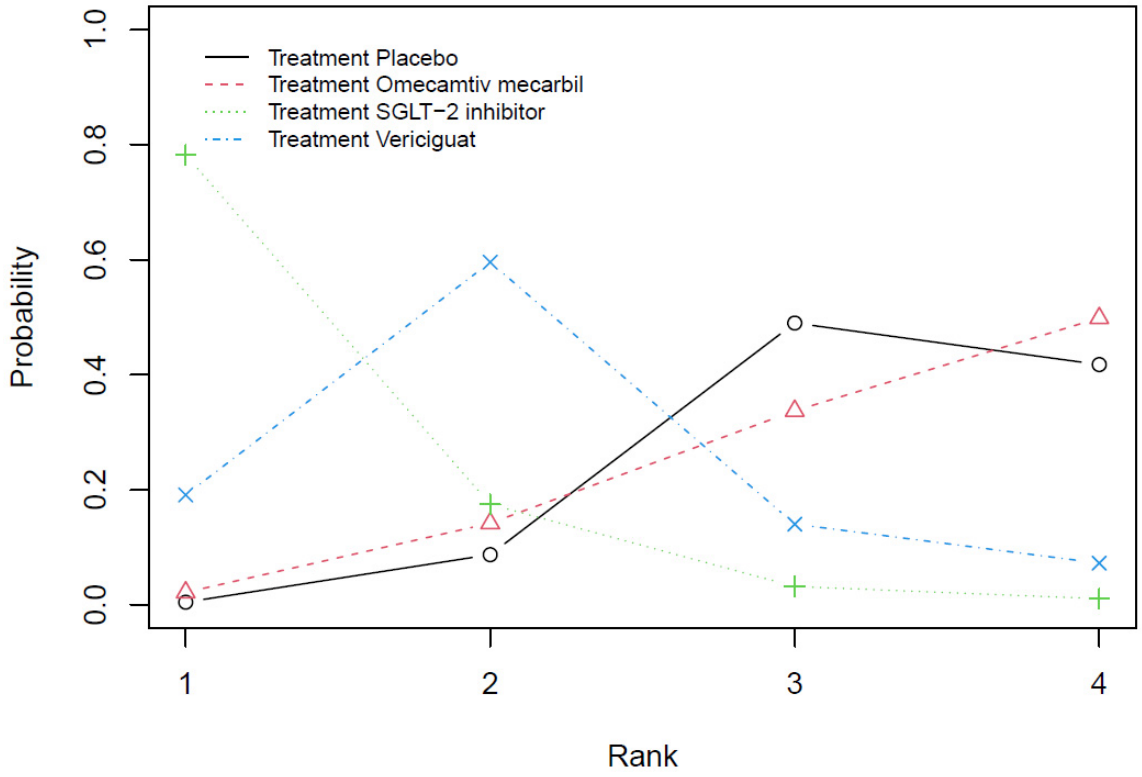
Supplementary Figure S10: Forest plot summarizing data from individual studies for HF hospitalization (main analysis).



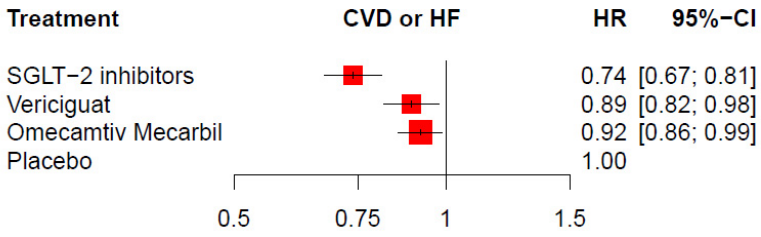
Supplementary Figure S11: Forest plot of each treatment versus PLACEBO for HF hospitalization (main analysis).



Supplementary Figure S12: Cumulative probability rank plots for each treatment being the best with respect to HF hospitalization (main analysis).



Supplementary Figure S13: Forest plot of each treatment versus PLACEBO for primary endpoint (sensitivity analysis – NMA on HR estimates).



Supplementary Figure S14: Forest plot of each treatment versus PLACEBO for primary endpoint (sensitivity analysis – NMA including phase 3 trials only).