

Diuretic therapy as prognostic enrichment factor for clinical trials in patients with heart failure with reduced ejection fraction

Clinical Research in Cardiology

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Supplementary Table 1: Prognostic value of furosemide in predicting the primary outcome using Harrell's C-Index

Model for furosemide dose (mg)	C-index (95 %CI)	P-value
Global	0.595 (0.574 - 0.617)	<0.0001
HFH subgroup	0.571 (0.545 - 0.596)	<0.0001
CVH subgroup	0.606 (0.559 - 0.653)	<0.0001
BNP subgroup	0.582 (0.503 - 0.661)	0.043

Supplementary Table 2: Treatment effect on cardiovascular death or hospitalization for heart failure and secondary outcomes according to enrichment criteria and diuretic use.

Parameter		CVD HFH		HHF		CVD		Death		CVH		CVD CVH	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
According to timing in HFH	Interaction with drug		0.0217		0.0634		0.18		0.25		0.09		0.029
	30-180 (n=807)	0.83 (0.63 - 1.09)		0.83 (0.60 - 1.16)		0.88 (0.61 - 1.28)		0.83 (0.59 - 1.18)		0.93 (0.71 - 1.21)		0.92 (0.72 - 1.17)	
	<30 (n=689)	0.53 (0.40 - 0.70)		0.53 (0.38 - 0.75)		0.62 (0.43 - 0.89)		0.63 (0.44 - 0.89)		0.67 (0.50 - 0.88)		0.63 (0.49 - 0.80)	
According to timing in CVH	Interaction with drug		0.92		0.84		0.51		0.19		0.41		0.31
	30-180 (n=596)	0.68 (0.44 - 1.03)		0.51 (0.30 - 0.86)		1.03 (0.57 - 1.88)		1.23 (0.72 - 2.11)		0.72 (0.52 - 0.99)		0.71 (0.52 - 0.97)	
	<30 (n=246)	0.70 (0.40 - 1.24)		0.56 (0.27 - 1.16)		0.75 (0.35 - 1.61)		0.68 (0.33 - 1.40)		0.56 (0.34 - 0.91)		0.54 (0.34 - 0.84)	
According to enrichment criteria	Interaction with drug		0.77		0.34		0.65		0.38		0.13		0.22
	CVH (n=842)	0.68 (0.48 - 0.95)		0.52 (0.34 - 0.80)		0.90 (0.56 - 1.44)		0.99 (0.64 - 1.51)		0.66 (0.50 - 0.87)		0.65 (0.50 - 0.83)	
	HFH (n=1496)	0.66 (0.55 - 0.81)		0.67 (0.53 - 0.85)		0.74 (0.57 - 0.95)		0.72 (0.57 - 0.92)		0.79 (0.65 - 0.96)		0.76 (0.64 - 0.91)	
	Elevated BNP (n=384)	0.54 (0.30 - 0.95)		0.42 (0.20 - 0.86)		0.61 (0.28 - 1.32)		0.62 (0.31 - 1.23)		0.46 (0.27 - 0.79)		0.50 (0.31 - 0.83)	
According to enrichment criteria and timing	Interaction with drug		0.20		0.22		0.52		0.28		0.10		0.062
	Reference CVH 30-180 (n=596)	0.67 (0.44 - 1.03)		0.51 (0.30 - 0.86)		1.03 (0.57 - 1.88)		1.23 (0.72 - 2.11)		0.72 (0.52 - 0.99)		0.71 (0.52 - 0.97)	
	HFH <30 (n=689)	0.52 (0.39 - 0.69)		0.53 (0.38 - 0.74)		0.62 (0.43 - 0.88)		0.63 (0.44 - 0.88)		0.66 (0.50 - 0.88)		0.62 (0.49 - 0.80)	
	HFH 30-180 (n=807)	0.83 (0.63 - 1.09)		0.83 (0.60 - 1.15)		0.88 (0.61 - 1.28)		0.83 (0.59 - 1.18)		0.93 (0.71 - 1.21)		0.92 (0.72 - 1.17)	
	CVH <30 (n=246)	0.69 (0.39 - 1.23)		0.55 (0.26 - 1.15)		0.74 (0.34 - 1.59)		0.68 (0.33 - 1.39)		0.56 (0.34 - 0.91)		0.53 (0.34 - 0.83)	
Elevated BNP (n=384)	0.54 (0.30 - 0.95)		0.42 (0.20 - 0.86)		0.61 (0.28 - 1.32)		0.62 (0.31 - 1.23)		0.46 (0.27 - 0.79)		0.50 (0.31 - 0.83)		
According to loop diuretics use	Interaction with drug		0.36		0.70		0.50		0.40		0.20		0.29
	Ref No (n=647)	0.81 (0.51 - 1.27)		0.68 (0.38 - 1.22)		0.94 (0.51 - 1.72)		0.98 (0.55 - 1.74)		0.89 (0.62 - 1.29)		0.83 (0.59 - 1.17)	
	Yes (n=2090)	0.64 (0.54 - 0.77)		0.61 (0.49 - 0.75)		0.75 (0.60 - 0.95)		0.76 (0.61 - 0.94)		0.69 (0.58 - 0.81)		0.68 (0.59 - 0.79)	
According to loop diuretics dose	Interaction with drug		0.64		0.51		0.41		0.39		0.17		0.42
	Ref none (n=647)	0.81 (0.51 - 1.27)		0.68 (0.38 - 1.22)		0.94 (0.51 - 1.72)		0.98 (0.55 - 1.74)		0.89 (0.62 - 1.29)		0.83 (0.59 - 1.17)	
	1-40 (n=1411)	0.63 (0.51 - 0.79)		0.54 (0.41 - 0.72)		0.83 (0.62 - 1.11)		0.82 (0.63 - 1.08)		0.63 (0.51 - 0.77)		0.65 (0.54 - 0.79)	
	>40 (n=657)	0.65 (0.50 - 0.86)		0.68 (0.50 - 0.93)		0.63 (0.43 - 0.92)		0.64 (0.45 - 0.91)		0.79 (0.61 - 1.02)		0.74 (0.58 - 0.94)	

CVD, cardiovascular death; HFH, heart failure hospitalization; CVH, cardiovascular hospitalization; BNP, B-type natriuretic peptide

Supplementary figures

Figure 1

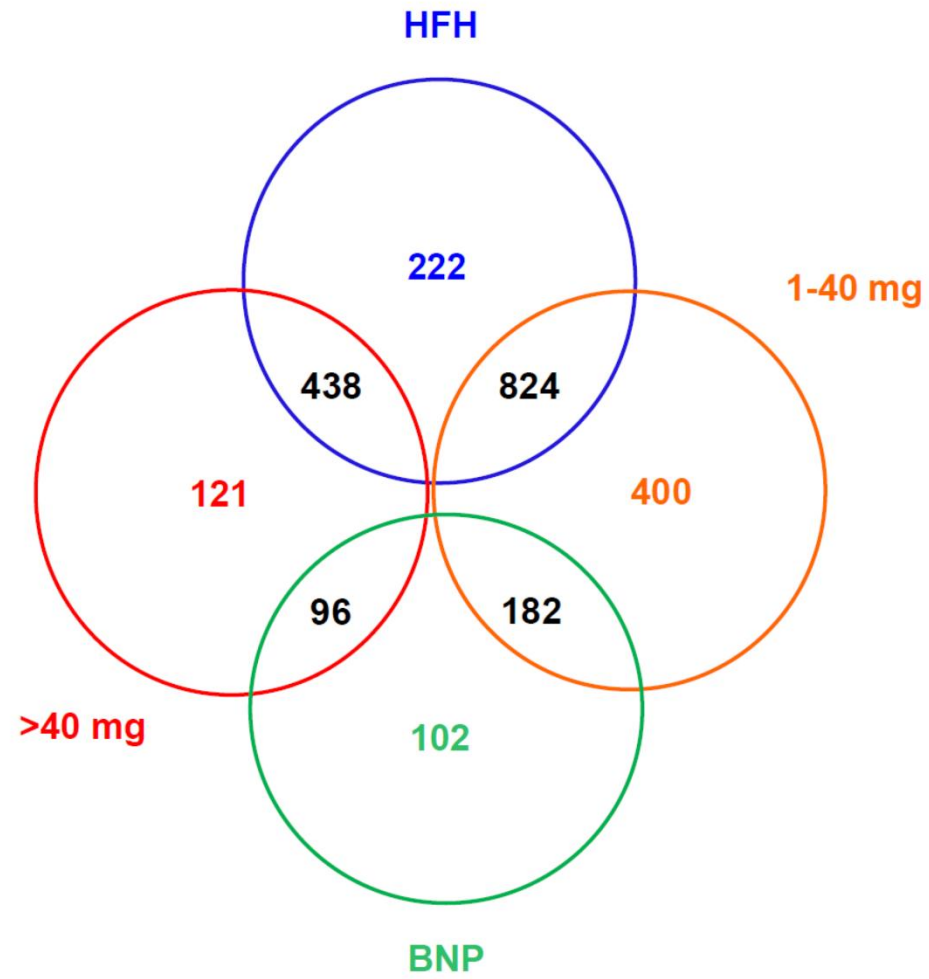


Figure 2

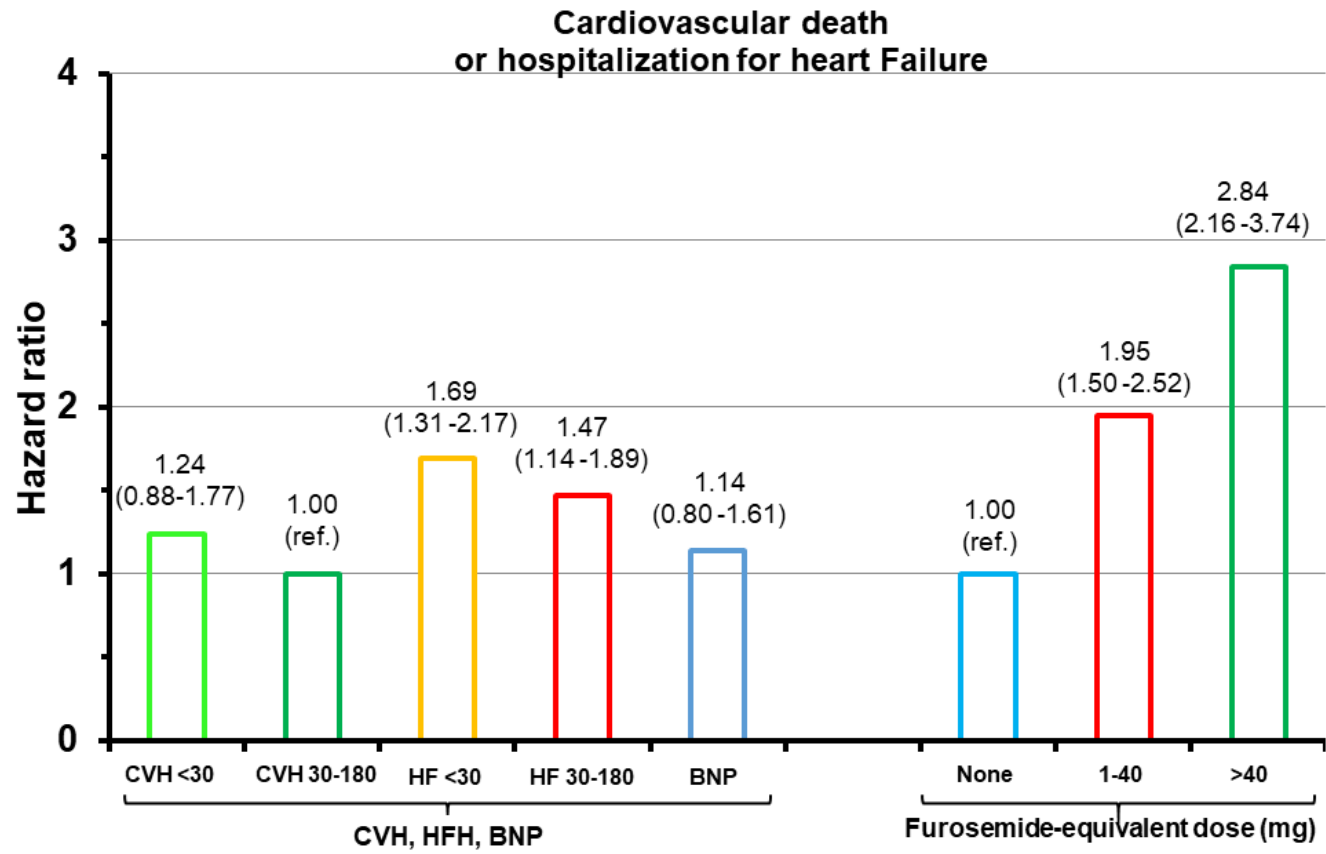
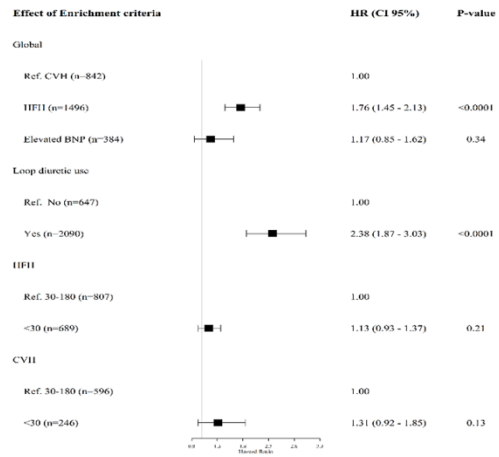
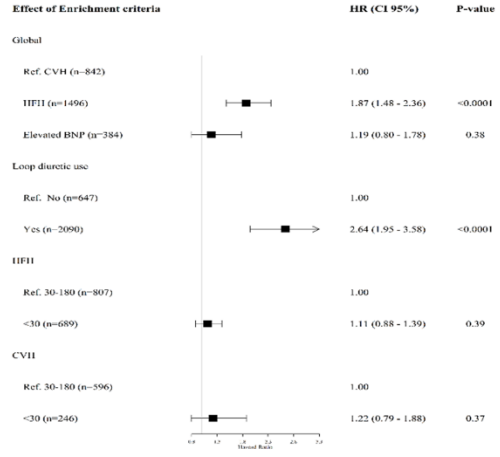


Figure 3

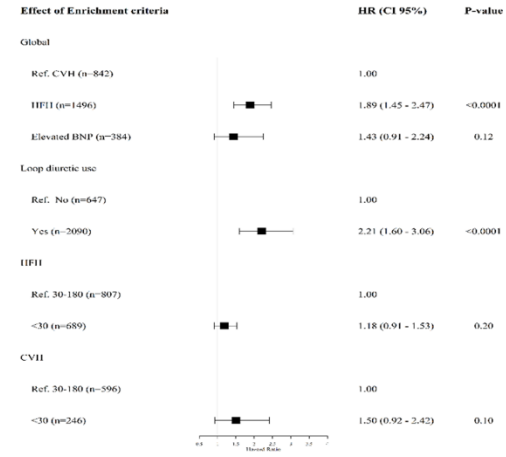
CVD/HFH



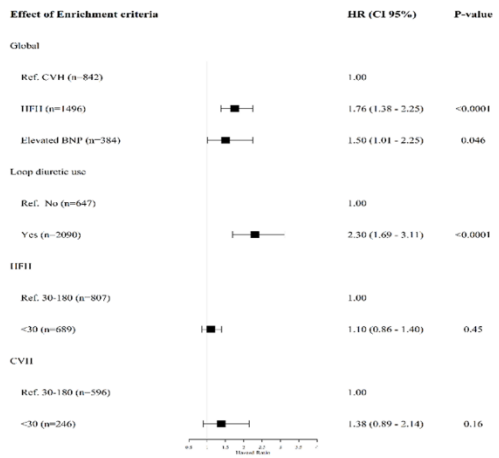
HFH



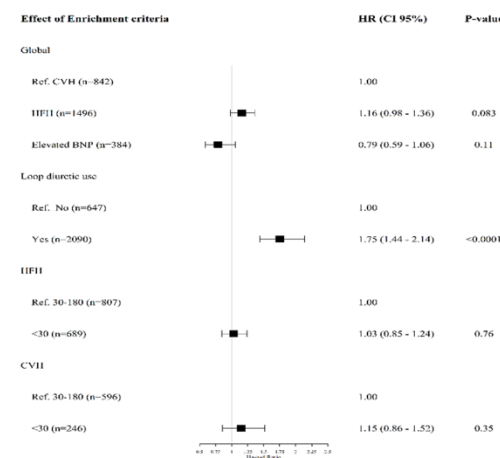
CVD



Death



CVH



CVD/CVH

