**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**

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**Figure 2**

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**Figure 3**

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