**Furosemide and spironolactone doses and hyponatremia in patients with heart failure**

**Supplementary material**

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This supplement has been provided by the authors to give readers additional information about the findings of the study.

1. **Fig. S.1** Patients taking spironolactone according to dose and coadministration with furosemide
2. **Fig. S.2** Distribution of study patients according to hydrochlorothiazide dose and hyponatremia
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**Fig. S.1**

**Fig. S.2**

**Table S.1**

Univariate correlations of clinical variables with serum NT-proBNP levels.

|  |  |  |
| --- | --- | --- |
|  | *r* | *p* |
| GFR (ml/min/1.73 m2) | 0.164 | 0.047\* |
| Cardiac troponin I (ng/ml) | 0.039 | 0.67 |
| Furosemide dose (mg) | -0.032 | 0.70 |
| Hydrochlorothiazide dose (mg) | 0.276 | 0.001\* |
| Spironolactone dose (mg) | 0.021 | 0.80 |
| LVEF (%) | -0.313 | <0.001\* |
| Serum sodium (mmol/L) | -0.049 | 0.55 |

*NT-pro BNP*: N-terminal pro brain natriuretic peptide, *GFR*: glomerular filtration rate, *LVEF*: left ventricular ejection fraction.

*r* and *p* values were obtained from the linear regression analysis.

\* Statistically significant differences (*p*<0.05)

**Table S.2**

Multivariate analysis of the predicting association of clinical factors with occurrence of hyponatremia (Model 1\*)

|  |  |  |  |
| --- | --- | --- | --- |
|  | *OR* (95% *CI*) | *p* | |
| Age (per 10-year increase) | 1.116 (1.009 – 1.237) | | 0.03† |
| Alcohol consumption | 1.113 (1.005 – 1.282) | | 0.04† |
| Male sex | 0.952 (0.865 – 1.052) | | 0.35 |
| Kidney failure | 1.044 (0.940 – 1.165) | | 0.40 |
| LVEF ≤ 45% | 1.080 (0.978 – 1.185) | | 0.13 |
| Arterial hypertension | 0.932 (0.838 – 1.033) | | 0.18 |
| Diabetes mellitus | 1.119 (1.015 – 1.232) | | 0.02† |
| Previous AMI | 1.068 (0.962 – 1.213) | | 0.19 |
| Current smoking | 1.066 (0.947 – 1.256) | | 0.23 |
| Furosemide | 1.022 (0.919 – 1.134) | | 0.69 |
| Hydrochlorothiazide | 0.957 (0.840 – 1.071) | | 0.39 |
| Spironolactone | 1.079 (0.971 – 1.247) | | 0.13 |
| β-blocker | 0.979 (0.894 – 1.075) | | 0.67 |
| Calcium antagonist | 0.918 (0.824 – 1.021) | | 0.12 |
| ARB | 1.047 (0.923 – 1.247) | | 0.36 |
| ACEI | 1.069 (0.967 – 1.176) | | 0.19 |
| Aspirin | 0.968 (0.876 – 1.067) | | 0.50 |
| Digoxin | 0.960 (0.852 – 1.071) | | 0.43 |

Odds ratios (*OR*) and *p* values were obtained from the logistic regression analysis. *CI*: Confidence Interval, *LVEF*: left ventricular ejection fraction, *AMI*: acute myocardial infarction, *ARB*: angiotensin II receptor I blocker, *ACEI*: angiotensin converting enzyme-inhibitor

\* The use of each drug was included as dichotomous variable

† Statistically significant differences (*p*<0.05)

**Table S.3**

Multivariate analysis of the predicting association of clinical factors with occurrence of hyponatremia (Model 2\*)

|  |  |  |
| --- | --- | --- |
|  | *OR* (95% *CI*) | *p* |
| Age (per 10-year increase) | 1.115 (1.006 – 1.239) | 0.03† |
| Alcohol consumption | 1.114 (1.007 – 1.146) | 0.03† |
| Male sex | 0.939 (0.853 – 1.041) | 0.24 |
| Kidney failure | 1.043 (0.943 – 1.158) | 0.39 |
| LVEF ≤ 45% | 0.945 (0.994 – 1.001) | 0.27 |
| Arterial hypertension | 0.934 (0.841 – 1.035) | 0.19 |
| Diabetes mellitus | 1.109 (1.003 – 1.224) | 0.04† |
| Previous AMI | 1.057 (0.949 – 1.198) | 0.28 |
| Current smoking | 1.066 (0.947 – 1.255) | 0.22 |
| Furosemide + spironolactone | 1.113 (1.007 – 1.272) | 0.04† |
| Hydrochlorothiazide | 0.930 (0.810 – 1.036) | 0.16 |
| β-blocker | 0.984 (0.899 – 1.079) | 0.75 |
| Calcium antagonist | 0.923 (0.814 – 1.023) | 0.12 |
| ARB | 1.053 (0.931 – 1.258) | 0.30 |
| ACEI | 1.067 (0.966 – 1.173) | 0.21 |
| Aspirin | 0.973 (0.881 – 1.073) | 0.58 |
| Digoxin | 0.955 (0.848 – 1.062) | 0.36 |

Odds ratios (*OR*) and *p* values were obtained from the logistic regression analysis. *CI*: Confidence Interval, *LVEF*: left ventricular ejection fraction, *AMI*: acute myocardial infarction, *ARB*: angiotensin II receptor I blocker, *ACEI*: angiotensin converting enzyme-inhibitor

\* The use of each drug, as well as combination of furosemide and spironolactone, were included as

dichotomous variable

† Statistically significant differences (*p*<0.05)

**Table S.4**

Multivariate analysis of the predicting association of clinical factors with serum NT-proBNP levels.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Model 1\* |  |  | Model 2\*\* |  |
|  | *β* | *p* |  | *β* | *p* |
| Predictors |  |  |  |  |  |
| Age (years) | 0.078 | 0.39 |  | 0.095 | 0.32 |
| Alcohol consumption | 0.034 | 0.69 |  | 0.030 | 0.73 |
| Male sex | -0.104 | 0.24 |  | -0.049 | 0.59 |
| GFR (ml/min/1.73 m2) | -0.458 | <0.0001† |  | -0.492 | <0.0001† |
| LVEF (%) | -0.173 | 0.04† |  | -0.193 | 0.02† |
| Cardiac troponin I (ng/ml) | 0.177 | 0.04† |  | 0.178 | 0.04† |
| Arterial hypertension | 0.051 | 0.58 |  | 0.077 | 0.42 |
| Diabetes mellitus | 0.057 | 0.52 |  | 0.027 | 0.76 |
| Previous AMI | -0.002 | 0.98 |  | 0.008 | 0.93 |
| Current smoking | 0.031 | 0.71 |  | 0.052 | 0.54 |
| Furosemide | 0.037 | 0.71 |  | 0.006 | 0.95 |
| Spironolactone | 0.312 | <0.0001† |  | 0.275 | 0.003† |
| Hydrochlorothiazide | 0.035 | 0.67 |  | 0.064 | 0.44 |
| Calcium antagonist | -0.130 | 0.13 |  | -0.129 | 0.15 |
| ARB | -0.168 | 0.053 |  | -0.173 | 0.051 |
| ACEI | -0.096 | 0.27 |  | -0.090 | 0.31 |
| Digoxin | -0.079 | 0.38 |  | -0.055 | 0.53 |

*NT-pro BNP*: N-terminal pro brain natriuretic peptide, *GFR*: glomerular filtration rate, *LVEF*: left ventricular ejection fraction, *AMI*: acute myocardial infarction*, ARB*: angiotensin II receptor I blocker, *ACEI*: angiotensin converting enzyme-inhibitor. *β* and *p* values were obtained from the multiple regression analysis

\* Model 1 includes furosemide, spironolactone and hydrochlorothiazide as dichotomous variables

\*\* Model 2 includes furosemide, spironolactone and hydrochlorothiazide with their doses (mg)

† Statistically significant differences (*p*<0.05)