**Supplementary Data**

**Title:**

**Cardiovascular mortality can be predicted by heart rate turbulence in hemodialysis patients**

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| **Supplemental Table 1.** Detailed intake of antihypertensive medications overall and by categories of heart rate turbulence (HRT) |
| **Parameter** | **Total group****(n = 290)** | **Heart rate turbulence (HRT)** |  |
| **Category 0****(n = 161)** | **Category 1****(n = 88)** | **Category 2****(n = 41)** | ***P*** |
| Antihypertensive medication | 258 (89.0) | 137 (85.1) | 81 (92.0) | 40 (97.6) | 0.041 |
|  - ACEI | 108 (37.2) | 62 (38.5) | 34 (38.6) | 12 (29.3) | 0.52 |
|  - ARB | 71 (24.5) | 34 (21.1) | 23 (26.1) | 14 (34.1) | 0.20 |
|  - CCB | 123 (42.4) | 70 (43.5) | 31 (35.2) | 22 (53.7) | 0.13 |
|  - Vasodilator | 44 (15.2) | 24 (14.9) | 11 (12.5) | 9 (22.0) | 0.38 |
|  - *ß*-blocker | 183 (63.1) | 93 (57.8) | 61 (69.3) | 29 (70.7) | 0.11 |
|  - Diuretics | 170 (58.6) | 82 (50.9) | 61 (69.3) | 27 (65.9) | 0.011 |
|  - Others | 41 (14.1) | 21 (13.0) | 12 (13.6) | 8 (19.5) | 0.56 |
| n (%) for categorical data. Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensinreceptor blocker; CCB, calcium channel blocker. Others included drugs other than ACEI, ARB, CCB, Vasodilators, *ß*-blocker or diuretics (e.g. α-blocker, renin inhibitor). |

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| **Supplemental Table 2.** Cohort description in relation to excluded patients and study cohort |
| **Parameter** | **Study population** **(n = 290)** | **Excluded patients** **(n = 229)** | ***P*** |
| Age [years] | 63.9 [50.7 - 73.8] | 73.0 [58.9 - 79.9] | <0.001 |
| Gender [male] | 190 (65.5) | 168 (73.4) | 0.06 |
| Body mass index [kg/m2] | 25.0 [22.4 - 28.7] | 25.5 [22.8 - 28.9] | 0.42 |
| Dialysis vintage [months] | 46.0 [24.0 - 78.3] | 41.0 [19.0 - 79.5] | 0.31 |
| Ultrafiltration rate [ml/h] | 483.0 ± 259.5 | 511.2 ± 265.2 | 0.22 |
| Net ultrafiltration [l] | 1.7 ± 1.2 | 1.9 ± 1.3 | 0.027 |
| Kt/V | 1.46 [1.21 - 1.65] | 1.46 [1.23 - 1.67] | 0.75 |
| Systolic blood pressure [mmHg] | 137.0 [123.0 - 149.0] | 132.0 [115.0 - 145.0] | 0.020 |
| Diastolic blood pressure [mmHg] | 75.1 ± 14.6 | 68.5 ± 14.7 | <0.001 |
| Heart rate [bpm] | 73.7 [65.6 - 80.9] | 71.9 [64.8 - 81.6] | 0.35 |
| Blood urea nitrogen [mg/dl] | 62.8 ± 16.5 | 59.2 ± 16.8 | 0.014 |
| Phosphate [mmol/l] | 1.74 ± 0.49 | 1.74 ± 0.58 | 0.85 |
| Total calcium [mmol/l] | 2.27 ± 0.18 | 2.26 ± 0.21 | 0.61 |
| Calcium *x* phosphate [mmol2/l2] | 3.93 ± 1.12 | 3.94 ± 1.36 | 0.98 |
| Creatinine [mg/dl] | 8.81 ± 2.83 | 7.98 ± 2.62 | 0.001 |
| High-sensitivity CRP [mg/dl] | 0.38 [0.16 - 0.90] | 0.62 [0.23 - 1.22] | 0.001 |
| Albumin [g/dl] | 4.02 ± 0.40 | 3.92 ± 0.42 | 0.007 |
| Parathyroid hormone [pg/ml] | 238.5 [127.4 - 402.9] | 184.9 [99.1 - 365.2] | 0.047 |
| Leukocytes [G/l] | 6.97 ± 2.06 | 6.94 ± 6.60 | 0.88 |
| Total cholesterol [mg/dl] | 177.0 [154.0 - 207.0] | 171.0 [139.0 - 200.0] | 0.019 |
| Charlson Comorbidity Index [0-21] | 2.0 [1.0 - 5.0] | 5.0 [2.0 - 8.0] | <0.001 |
| Diabetes mellitus | 99 (34.1) | 110 (48.0) | 0.002 |
| History of myocardial infarction | 47 (16.2) | 56 (24.5) | 0.02 |
| Left ventricular hypertrophy | 76 (26.2) | 76 (33.2) | 0.10 |
| Heart failure | 31 (10.7) | 68 (29.7) | <0.001 |
| Peripheral artery disease | 55 (19.0) | 68 (29.7) | 0.004 |
| Hypertension | 271 (93.4) | 218 (95.2) | 0.40 |
| Coronary heart disease | 88 (30.3) | 99 (43.2) | 0.002 |
| Cerebral vascular disease | 41 (14.1) | 44 (19.2) | 0.12 |
| Smoking [ever] | 79 (27.4) | 39 (19.7) | 0.051 |
| Antihypertensive medication | 258 (89.0) | 213 (93.0) | 0.11 |
| Statin | 104 (36.4) | 92 (40.2) | 0.38 |
| n (%) for categorical data, mean ± standard deviation or median [interquartile range] for continuous data, as appropriate. Abbreviations: CRP, c-reactive protein. |

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| **Supplemental Table 3.** Unadjusted hazards ratios of baseline parameters for cardiovascular mortality |
| **Parameter** | **HR (95% CI)** | ***P*** |
| Age [10 years] | 1.40 (1.01-1.95) | 0.047 |
| Gender [male] | 2.12 (0.71-6.33) | 0.18 |
| Body mass index [kg/m2] | 1.00 (0.93-1.09) | 0.96 |
| Dialysis vintage [months] | 0.99 (1.00-1.00) | 0.84 |
| Ultrafiltration rate [ml/h] | 1.00 (1.00-1.00) | 0.21 |
| Net ultrafiltration [l] | 0.76 (0.52-1.12) | 0.16 |
| Kt/V | 0.46 (0.14-1.53) | 0.20 |
| Systolic blood pressure [mmHg] | 1.01 (0.99-1.03) | 0.59 |
| Diastolic blood pressure [mmHg] | 1.01 (0.98-1.04) | 0.46 |
| Heart rate [bpm] | 1.00 (1.00-1.00) | 0.98 |
| Blood urea nitrogen [mg/dl] | 0.98 (0.95-1.01) | 0.18 |
| Phosphate [mmol/l] | 0.87 (0.34-2.25) | 0.78 |
| Total calcium [mmol/l] | 10.5 (0.73-149.4) | 0.08 |
| Calcium *x* phosphate [mmol2/l2] | 1.02 (0.68-1.52) | 0.92 |
| Creatinine [mg/dl] | 0.87 (0.74-1.02) | 0.08 |
| High-sensitivity CRP [mg/dl] | 1.28 (1.06-1.55) | 0.011 |
| Albumin [g/dl] | 0.87 (0.28-2.72) | 0.80 |
| Parathyroid hormone [pg/ml] | 1.00 (1.00-1.00) | 0.41 |
| Leukocytes [G/l] | 1.41 (1.17-1.70) | <0.001 |
| Total cholesterol [mg/dl] | 1.00 (0.99-1.01) | 0.67 |
| High-density lipoprotein cholesterol [mg/dl]\* | 1.01 (0.98-1.04) | 0.52 |
| Low-density lipoprotein cholesterol [mg/dl]\* | 1.00 (0.99-1.02) | 0.53 |
| Charlson Comorbidity Index [0-21] | 1.29 (1.15-1.45) | <0.001 |
| Diabetes mellitus | 0.62 (0.26-1.49) | 0.28 |
| History of myocardial infarction | 0.13 (0.06-0.32) | <0.001 |
| Left ventricular hypertrophy | 2.10 (0.62-7.18) | 0.24 |
| Heart failure | 0.33 (0.12-0.90) | 0.030 |
| Peripheral artery disease | 0.26 (0.11-0.63) | 0.003 |
| Hypertension | 0.05 (0.00-122.32) | 0.44 |
| Coronary heart disease | 0.21 (0.09-0.53) | 0.001 |
| Cerebral vascular disease | 0.46 (0.17-1.27) | 0.14 |
| Smoking [ever] | 0.68 (0.27-1.70) | 0.41 |
| Antihypertensive medication | 0.04 (0.00-19.90) | 0.31 |
| Statin | 1.77 (0.74-4.25) | 0.20 |
| Abbreviations: CI, confidence interval; HR, hazard ratio. \*Missing values n=60. |

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| **Supplemental Table 4.** Explorative analysis of risk variables with cardiovascular mortality |
| **Variable** | **Unit** | **Exploratory Model 5** | **Exploratory Model 6** | **Exploratory Model 7** | **Exploratory Model 8** | **Exploratory Model 9** | **Exploratory Model 10** |
| **HR (95% CI)** | ***P*** | **HR (95% CI)** | ***P*** | **HR (95% CI)** | ***P*** | **HR (95% CI)** | ***P*** | **HR (95% CI)** | ***P*** | **HR (95% CI)** | ***P*** |
| Age | 10 year | 1.07 (0.73-1.57) | 0.74 | 1.17 (0.79-1.74) | 0.43 | 1.13 (0.76-1.70) | 0.55 | 1.05 (0.71-1.54) | 0.82 | 1.07 (0.73-1.58) | 0.72 | 1.04 (0.70-1.55) | 0.85 |
| High-sensitivity CRP | 1 mg/dl | 1.23 (1.00-1.51) | 0.046 | - | - | - | - | - | - | - | - | - | - |
| Leukocytes | 1 G/l | - | - | 1.46 (1.17-1.81) | 0.001 | - | - | - | - | - | - | - | - |
| History of myocardial infarction | present | - | - | - | - | 6.79 (2.77-16.65) | <0.001 | - | - | - | - | - | - |
| Heart failure | present | - | - | - | - | - | - | 2.26 (0.82-6.25) | 0.12 | - | - | - | - |
| Peripheral artery diseases | present | - | - | - | - | - | - | - | - | 2.37 (0.94-5.96) | 0.07 | - | - |
| Coronary artery disease | present | - | - | - | - | - | - | - | - | - | - | 3.57 (1.42-8.98) | 0.007 |
| HRT category 1 vs 0 |  | 7.57 (1.51-37.96) | 0.01 | 8.58 (1.68-43.75) | 0.01 | 5.75 (1.19-27.87) | 0.03 | 7.48 (1.48-37.75) | 0.02 | 7.46 (1.51-36.95) | 0.014 | 6.96 (1.14-34.05) | 0.017 |
| HRT category 2 vs 0 |  | 16.98 (3.44-83.75) | 0.001 | 13.06 (2.65-64.46) | 0.002 | 16.01 (3.31-77.49) | 0.001 | 17.04 (3.41-85.17) | 0.001 | 13.56 (2.70-68.06) | 0.002 | 15.23 (3.13-74.20) | 0.001 |
| Additional exploratory models were built if a variable was predictive for cardiovascular mortality in univariate analysis.  |

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| **Supplemental Table 5.** Exploratory association of HRT with cardiovascular mortality |
| **Variable** | **Adjusted Model 3\*** | **Adjusted Model 4\*** |
| **HR (95% CI)** | ***P*** | **HR (95% CI)** | ***P*** |
| HRT category 1 vs 0 | 7.76 (1.53-39.22) | 0.013 | 6.86 (1.37-34.36) | 0.019 |
| HRT category 2 vs 0 | 17.49 (3.49-87.51) | <0.001 | 11.41 (2.19-59.58) | 0.004 |
| \*Note: Due to the presence of 5 and 6 variables in relation the 20 cardiovascular mortality events in adjusted Model 3 and 4, respectively, this model could potentially be overfitted.Adjusted Model 3: Age, albumin, high-sensitivity CRP, calcium *x* phosphate, HRT.Adjusted Model 4: Age, albumin, high-sensitivity CRP, calcium *x* phosphate, Charlson Comorbidity Index, HRT.Abbreviations: CI, confidence interval; HR, hazard ratio; HRT, heart rate turbulence. |

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| **Supplemental Table 6.** Unadjusted and adjusted hazards ratios of ln transformed frequency-domain heart rate variability measures for cardiovascular mortality |
| **Cardiovascular mortality risk** |
| **Parameter** | **Unit** | **Univariate** | **Adjusted Model 1** | **Adjusted Model 2** |
| **HR (95% CI)** | ***P*** | **HR (95% CI)** | ***P*** | **HR (95% CI)** | ***P*** |
| Total Power | ln(ms2) | 0.67 (0.35-1.30) | 0.24 | 0.72 (0.36-1.42) | 0.34 | 0.95 (0.49-1.85) | 0.89 |
| ULF | ln(ms2) | 0.68 (0.36-1.28) | 0.23 | 0.74 (0.39-1.40) | 0.35 | 0.95 (0.51-1.78) | 0.87 |
| VLF | ln(ms2) | 0.70 (0.41-1.20) | 0.19 | 0.75 (0.43-1.29) | 0.30 | 0.92 (0.52-1.62) | 0.78 |
| LF | ln(ms2) | 0.72 (0.46-1.11) | 0.14 | 0.71 (0.45-1.12) | 0.14 | 0.81 (0.51-1.31) | 0.40 |
| HF | ln(ms2) | 0.94 (0.63-1.41) | 0.75 | 0.82 (0.53-1.26) | 0.36 | 0.91 (0.58-1.42) | 0.67 |
| Model 1: age, albumin; model 2: age, Charlson Comorbidity Index. Abbreviations: CI, confidence interval; ULF, ultra-low frequency; VLF, very low frequency; LF, low frequency; HF, high frequency. |

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| **Supplemental Table 7.** Association of severe autonomic failure (SAF) with cardiovascular mortality in univariate and multivariable analysis |
| **Variable** |  | **Univariate** | **Adjusted Model 1** | **Adjusted Model 2** |
| **HR (95% CI)** | ***P*** | **HR (95% CI)** | ***P*** | **HR (95% CI)** | ***P*** |
| Severe autonomic failure 1 vs 0 |  | 5.95 (2.47-14.36) | <0.001 | 5.11 (2.09-12.49) | <0.001 | 3.36 (1.25-9.03) | 0.016 |
| Adjusted model 1 includes: Age, albumin and severe autonomic failure. Adjusted model 2 includes: Age, Charlson Comorbidity Index and severe autonomic failure. Severe autonomic failure is assumed if HRT category 2 and deceleration capacity ≤ 4.5 ms are present (n=36). Abbreviations: CI, confidence interval; HR, hazard ratio |

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| **Supplemental Table 8.** Ln transformed frequency-domain measures of heart rate variability at baseline in patients overall and grouped by survival state |
| **Parameter** | **Unit** | **Overall** | **Cardiovascular mortality** |
| **Survivor (n=270)** | **Non-survivor (n=20)** |
| Total Power | ln(ms2) | 8.95±0.69 | 8.96±0.69 | 8.78±0.57 |
| ULF | ln(ms2) | 8.76±0.72 | 8.77±0.72 | 8.58±0.65 |
| VLF | ln(ms2) | 6.48±0.82 | 6.50±0.83 | 6.23±0.65 |
| LF | ln(ms2) | 5.56±0.98 | 5.58±1.00 | 5.21±0.69 |
| HF | ln(ms2) | 4.74±0.98 | 4.75±1.09 | 4.63±0.89 |
| Values are expressed as mean ± standard deviation. ULF, ultra-low frequency; VLF, very low frequency; LF, low frequency; HF, high frequency. |

**Supplemental Figure 1.** Cumulative cardiovascular mortality curves stratified by heart rate turbulence (HRT) including HRT category non-calculable.

The number of patients of the individual groups involved in the analysis at 1, 2 and 3 years are shown under the graph. 3-year cardiovascular mortality rates were 0.9%, 1.9%, 10.2%, and 22.0% for those with HRT category non-calculable (n.c.), 0, 1, and 2, respectively. There was no significant difference in the survival probability of patients in HRT category 0 and HRT category non-calculable (χ2=0.25, log-rank p=0.62).

