**Table S1. Risk of incident fragility fractures across quartiles of cardiovascular biomarkers (CT-proAVP, CT-proET-1, MR-proADM and MR-proANP) in multivariable-adjusted Cox regression model.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Biomarkers** | **Sample size, n** | **Adjusted Hazard Ratio**  **(95% CI)** | **P-value** | **C-statistic (95% CI)** |
| **CT-proAVP** |  | **P<0.001\*** |  | **0.668**  **(0.545-0.792)** |
| Q1 (1-4 pmol/l) | 1352 | *Reference* | - |  |
| Q2 (4-7 pmol/l) | 1353 | 0.91 (0.77-1.08) | 0.284 |  |
| Q3 (7-12 pmol/l) | 1352 | 0.83 (0.68-0.99) | 0.043 |  |
| Q4 (12-489 pmol/l) | 1352 | 1.02 (0.84-1.23) | 0.836 |  |
| **CT-proET-1** |  | **P<0.001\*** |  | **0.666**  **(0.541-0.789)** |
| Q1 (4-60 pmol/l) | 1352 | *Reference* | - |  |
| Q2 (60-68 pmol/l) | 1352 | 0.96 (0.79-1.16) | 0.644 |  |
| Q3 (68-78 pmol/l) | 1352 | 0.98 (0.80-1.20) | 0.832 |  |
| Q4 (78-432 pmol/l) | 1352 | 1.08 (0.86-1.37) | 0.506 |  |
| **MR-proADM** |  | **P<0.001\*** |  | **0.668**  **(0.545-0.794)** |
| Q1 (0.12-0.61 nmol/l) | 1353 | *Reference* | - |  |
| Q2 (0.61-0.70 nmol/l) | 1354 | 1.09 (0.89-1.33) | 0.413 |  |
| Q3 (0.70-0.84 nmol/l) | 1354 | 1.12 (0.91-1.39) | 0.284 |  |
| Q4 (0.84-4.38 nmol/l) | 1353 | 1.14 (0.89-1.48) | 0.305 |  |
| **MR-proANP** |  | **P<0.001\*** |  | **0.669**  **(0.548-0.796)** |
| Q1 (22-77 pmol/l) | 1353 | *Reference* | - |  |
| Q2 (77-104 pmol/l) | 1354 | 1.05 (0.86-1.28) | 0.615 |  |
| Q3 (104-146 pmol/l) | 1354 | 1.20 (0.98-1.46) | 0.076 |  |
| Q4 (146-1681 pmol/l) | 1354 | 1.31 (1.06-1.63) | 0.015 |  |

Adjusted for age, gender, body mass index (BMI), systolic blood pressure, heart rate, anti-hypertensive treatment, smoking, diabetes, prevalent fractures, history of cerebro-cardiovascular disease and self-reported physical activity. CI, confidence interval; CT-pro-AVP, copeptin; CT-proET-1, C-terminal endothelin-1; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide. \*P-value for trend across quartiles.

**Table S2. Influence of age, gender and antihypertensive treatment on the relationship between cardiovascular biomarker and fracture risk.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Biomarker** | **Gender** | | **Age** | | **Antihypertensive treatment** | |
| **β(SE)** | **P-value** | **β(SE)** | **P-value** | **β(SE)** | **P-value** |
| **CT-proAVP** | -0.135(0.07) | 0.047 | 0.003(0.006) | 0.65 | 0.07(0.03) | **0.013** |
| **CT-proET1** | -0.15(0.06) | 0.019 | 0.003(0.006) | 0.49 | -0.04(0.06) | 0.5 |
| **MR-proADM** | -0.225(0.06) | <0.0001 | -0.001(0.005) | 0.78 | 0.06(0.07) | 0.33 |
| **MR-proANP** | -0.178(0.07) | 0.009 | 0.01(0.005) | **0.03** | -0.05(0.07) | 0.46 |

CT-pro-AVP, copeptin; CT-proET-1, C-terminal endothelin-1; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; SE, standard error; standardized beta (β).

**Table S3** - **Risk of incident fragility fractures by quartiles of cardiovascular biomarkers (CT-proAVP, CT-proET-1, MR-proADM and MR-proANP) in multivariable-adjusted Cox regression model: gender subgroup analysis.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Biomarkers** | **Women**  **(sample, n=1639;**  **incident fractures, n=484)** | | | **Men**  **(sample, n=3776;**  **incident fractures, n=546)** | | |
| **Adjusted Hazard Ratio**  **(95% CI)** | **P-value** | **C-statistic**  **(95% CI)** | **Adjusted Hazard Ratio**  **(95% CI)** | **P-value** | **C-statistic**  **(95% CI)** |
| **CT-proAVP** | | | **0.668**  **(0.544-0.793)** |  | | **0.666**  **(0.542-0.790)** |
| Q1  (1-4 pmol/l) | *Reference* | 0.035\* |  | *Reference* | 0.341\* |  |
| Q2  (4-7 pmol/l) | 0.89 (0.71-1.11) | 0.312 |  | 1.03 (0.78-1.36) | 0.846 |  |
| Q3  (7-12 pmol/l) | 0.78 (0.60-1.02) | 0.073 |  | 0.96 (0.73-1.23) | 0.791 |  |
| Q4  (12-489 pmol/l) | 1.26 (0.95-1.67) | 0.115 |  | 1.17 (0.90-1.52) | 0.251 |  |
| **CT-proET-1** | | | **0.667**  **(0.543-0.793)** |  | | **0.666**  **(0.541-0.792)** |
| Q1  (4-60 pmol/l) | *Reference* | 0.568\* |  | *Reference* | 0.003\* |  |
| Q2  (60-68 pmol/l) | 1.05 (0.81-1.37) | 0.710 |  | 0.96 (0.74-1.23) | 0.766 |  |
| Q3  (68-78 pmol/l) | 1.13 (0.87-1.47) | 0.341 |  | 1.05 (0.81-1.36) | 0.721 |  |
| Q4  (78-432 pmol/l) | 1.21 (0.91-1.59) | 0.187 |  | 1.46 (1.12-1.90) | 0.004 |  |
| **MR-proADM** | | | **0.668**  **(0.545-0.792)** |  | | **0.670**  **(0.549-0.795)** |
| Q1  (0.12-0.61 nmol/l) | *Reference* | 0.182\* |  | *Reference* | 0.009\* |  |
| Q2  (0.61-0.70 nmol/l) | 1.08 (0.81-1.43) | 0.591 |  | 1.17 (0.90-1.53) | 0.229 |  |
| Q3  (0.70-0.84 nmol/l) | 1.28 (0.98-1.69) | 0.071 |  | 1.15 (0.88-1.50) | 0.315 |  |
| Q4  (0.84-4.38 nmol/l) | 1.32 (0.98-1.79) | 0.067 |  | 1.56 (1.17-2.06) | 0.002 |  |
| **MR-proANP** | | | **0.664**  **(0.539-0.789)** |  | | **0.666**  **(0.543-0.790)** |
| Q1  (22-77 pmol/l) | *Reference* | 0.478\* |  | *Reference* | <0.0001\* |  |
| Q2  (77-104 pmol/l) | 1.24 (1.02-1.50) | 0.878 |  | 1.14 (0.87-1.50) | 0.346 |  |
| Q3  (104-146 pmol/l) | 0.99 (0.75-1.30) | 0.929 |  | 1.52 (1.16-1.99) | 0.002 |  |
| Q4  (146-1681 pmol/l) | 1.17 (0.87-1.58) | 0.291 |  | 1.75 (1.33-2.31) | <0.0001 |  |

CT-pro-AVP, copeptin; CT-proET-1, C-terminal endothelin-1; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide; \*P for trend.

**Table S4. Risk of incident fragility fractures by quartiles of MR-proANP in multivariable-adjusted Cox regression model: median age subgroup analysis.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Biomarkers** | **Age≥68 years** | |  | **Age<68 years** | |  |
| **Adjusted Hazard Ratio**  **(95% CI)** | **P-value** | **C-statistic**  **(95% CI)** | **Adjusted Hazard Ratio**  **(95% CI)** | **P-value** | **C-statistic**  **(95% CI)** |
| **MR-proANP** |  |  | **0.658 (0.539-0.790)** |  | | **0.653 (0.536-0.756)** |
| Q1 (22-77 pmol/l) | *Reference* | 0.001\* |  | *Reference* | 0.449\* |  |
| Q2 (77-104 pmol/l) | 1.08 (0.82-1.43) | 0.567 |  | 1.15 (0.86-1.52) | 0.345 |  |
| Q3 (104-146 pmol/l) | 1.27 (0.98-1.65) | 0.071 |  | 1.29 (0.95-1.75) | 0.106 |  |
| Q4 (146-1681 pmol/l) | 1.60 (1.22-2.08) | 0.001 |  | 1.14 (0.79-1.67) | 0.480 |  |

AHT, antihypertensive treatment; CT-proAVP, copeptin; \*P for trend.

**Table S5. Risk of incident fragility fractures by quartiles of MR-proANP in multivariable-adjusted Cox regression model: antihypertensive treatment subgroup analysis.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Biomarkers** | **AHT+** | | | **AHT-** | | |
| **Adjusted Hazard Ratio**  **(95% CI)** | **P-value** | **C-statistic**  **(95% CI)** | **Adjusted Hazard Ratio**  **(95% CI)** | **P-value** | **C-statistic**  **(95% CI)** |
| **CT-proAVP** |  | **0.003\*** | **0.654 (0.537-0.756)** |  | **0.908\*** | **0.655**  **(0.538-0.759)** |
| Q1  (1-4 pmol/l) | *Reference* |  |  | *Reference* |  |  |
| Q2  (4-7 pmol/l) | 0.79 (0.60-1.05) | 0.100 |  | 1.03 (0.83-1.29) | 0.760 |  |
| Q3  (7-12 pmol/l) | 0.78 (0.58-1.05) | 0.096 |  | 0.95 (0.75-1.20) | 0.682 |  |
| Q4  (12-489 pmol/l) | 1.20 (0.93-1.55) | 0.164 |  | 1.02 (0.78-1.33) | 0.870 |  |

AHT, antihypertensive treatment; CT-proAVP, copeptin; \*P for trend.

**Table S6. Fragility fracture risk in a population of 5415 older adults according to circulating levels of cardiovascular biomarkers, CT-pro-AVP, CT-proET-1, MR-pro-ADM and MR-pro-ANP, in multivariate Cox regression model stratified by fracture site.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Biomarkers** | **Hazard Ratio (95% CI)** | | | | |
| **Vertebral (n=104)** | **Upper (n=118)** | **Forearm (n=153)** | **Femoral (n=312)** | **Tibial (n=100)** |
| **C-Statistic (95%CI)** | **0.644**  **(0.529-0.766)** | **0.648**  **(0.536-0.770)** | **0.650**  **(0.539-0.773)** | **0.652**  **(0.543-0.776)** | **0.641**  **(0.525-0.760)** |
| **CT-proAVP** | 1.19  (0.97-1.45) | 0.97  (0.78-1.21) | 1.04  (0.81-1.33) | 1.12  (0.97-1.29) | 1.25  (0.97-1.59) |
| **CT-proET-1** | 0.90  (0.72-1.14) | 1.06  (0.87-1.28) | 0.94  (0.74-1.19) | 1.17  (1.01-1.35) | 1.25  (0.99-1.57) |
| **MR-proADM** | 1.12  (0.91-1.38) | 1.20  (0.97-1.49) | 0.97  (0.74-1.26) | 0.95  (0.79-1.14) | 1.02  (0.75-1.40) |
| **MR-proANP** | 1.14  (0.96-1.35) | 0.95  (0.78-1.15) | 0.99  (0.81-1.23) | 1.08  (0.96-1.21) | 0.71  (0.53-0.95) |

Adjusted for age, gender, body mass index, systolic blood pressure, heart rate, anti-hypertensive treatment, smoking, diabetes, prevalent fractures, history of cardio/cerebrovascular disease and physical activity. Only fracture site with incidence over 100 cases were analyzed. CI, confidence interval; CT-pro-AVP, copeptin; CT-proET-1, C-terminal endothelin-1; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide

**Table S7. Fragility fracture risk in a population of 5415 older adults according to circulating levels of cardiovascular biomarkers, CT-pro-AVP, CT-proET-1, MR-pro-ADM and MR-pro-ANP, in a Fine and Gray regression model with death as competing event.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Biomarkers** | **Hazard Ratio (95% CI)\*** | | |  |
| **Unadjusted** | **Adjusted for age and gender** | **Fully adjusted\*\*** | **C-statistic (95%CI) for Fully adjusted model** |
| **CT-proAVP** | 0.91  (0.83-0.99) | 1.02  (0.93-1.12) | 0.95  (0.86-1.04) | 0.551 (0.445-0.666) |
| **CT-proET-1** | 1.84  (1.43-2.38) | 1.44  (1.08-1.90) | 1.14  (0.61-1.44) | 0.554 (0.449-0.669) |
| **MR-proADM** | 2.02  (1.61-2.52) | 1.43  (1.10-1.85) | 1.31  (0.86-1.99) | 0.550 (0.444-0.664) |
| **MR-proANP** | 1.44  (1.29-1.62) | 1.23  (1.08-1.41) | 1.15  (0.98-1.35) | 0.558 (0.452-0.672) |

\*Hazard ratio is reported per 1 SD increase of log transformed biomarker concentration. \*\*Adjusted for age, gender, body mass index, systolic blood pressure, heart rate, antihypertensive treatment, diabetes, smoking, prevalent fractures, history of cerebro-cardiovascular disease and self-reported physical activity. CT-pro-AVP, copeptin; CTproET-1, C-terminal endothelin-1; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide.

**Table S8. Risk of incident fragility fractures across quartiles of cardiovascular biomarkers (CT-proAVP, CT-proET-1, MR-proADM and MR-proANP) in multivariable-adjusted Fine and Gray regression model with death as competing event.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Biomarkers** | **Sample size, n** | **Adjusted Hazard Ratio**  **(95% CI)** | **P-value** | **C-statistic**  **(95% CI)** |
| **CT-proAVP** |  |  |  | **0.542 (0.434-0.654)** |
| Q1 (1-4 pmol/l) | 1352 | *Reference* | - |  |
| Q2 (4-7 pmol/l) | 1353 | 0.93 (0.78-1.10) | 0.383 |  |
| Q3 (7-12 pmol/l) | 1352 | 0.82 (0.68-0.98) | 0.033 |  |
| Q4 (12-489 pmol/l) | 1352 | 0.99 (0.81-1.20) | 0.899 |  |
| **CT-proET-1** |  |  |  | **0.551 (0.441-0.661)** |
| Q1 (4-60 pmol/l) | 1352 | *Reference* | - |  |
| Q2 (60-68 pmol/l) | 1352 | 0.95 (0.78-1.16) | 0.623 |  |
| Q3 (68-78 pmol/l) | 1352 | 1.14 (0.79-1.20) | 0.818 |  |
| Q4 (78-432 pmol/l) | 1352 | 1.07 (0.82-1.38) | 0.863 |  |
| **MR-proADM** |  |  |  | **0.549 (0.439-0.660)** |
| Q1 (0.12-0.61 nmol/l) | 1353 | *Reference* | - |  |
| Q2 (0.61-0.70 nmol/l) | 1354 | 1.08 (0.89-1.32) | 0.437 |  |
| Q3 (0.70-0.84 nmol/l) | 1354 | 1.14 (0.91-1.41) | 0.242 |  |
| Q4 (0.84-4.38 nmol/l) | 1353 | 1.07 (0.82-1.38) | 0.636 |  |
| **MR-proANP** |  |  |  | **0.541 (0.432-0.652)** |
| Q1 (22-77 pmol/l) | 1353 | *Reference* | - |  |
| Q2 (77-104 pmol/l) | 1354 | 1.05 (0.87-1.28) | 0.600 |  |
| Q3 (104-146 pmol/l) | 1354 | 1.19 (0.98-1.45) | 0.084 |  |
| Q4 (146-1681 pmol/l) | 1354 | 1.23 (0.99-1.38) | 0.062 |  |

\*Hazard ratio is reported per 1 SD increase of log transformed biomarker concentration. \*\*Adjusted for age, gender, body mass index, systolic blood pressure, heart rate, antihypertensive treatment, diabetes, smoking, prevalent fractures, history of cerebro-cardiovascular disease and self-reported physical activity. CT-pro-AVP, copeptin; CTproET-1, C-terminal endothelin-1; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-atrial natriuretic peptide.