Supplemental Material

Data S1

Appendix

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Table S1. Definitions of adverse outcomes.

Adverse outcomes	Definition
Death	Deaths were classified as either cardiovascular or non-cardiovascular origin. All deaths were assumed to be of cardiovascular origin unless a non-cardiovascular reason could be established. Cardiovascular deaths included cardiac deaths (e.g. cardiogenic shock, arrhythmia/sudden death, cardiac rupture) and other vascular deaths (e.g. stroke, pulmonary embolism, ruptured aortic aneurysm, or dissection). All hemorrhagic deaths were classified as cardiovascular deaths. Non-cardiovascular deaths included all deaths due to a clearly documented non-cardiac and non-vascular cause such as respiratory failure (excluding cardiogenic pulmonary edema), infection/sepsis, neoplasm, liver failure, renal failure, and trauma (including suicide and homicide).
Hospitalization for heart failure	Hospitalization for acute heart failure was defined as any hospitalization for acute heart failure that was associated with at least one overnight stay. If it was not clear whether the reason for a patient's hospitalization was acute heart failure or not, this event was in doubt be classified as acute heart failure. The following references mentioned under clinical examination, or in the progress entry were used as an indication for heart failure: leg swelling/leg edema, distension of the neck veins, positive hepato-jugular reflux, rales, and 3rd heart sound.
Stroke	Stroke was categorized as ischemic stroke, intracerebral hemorrhage, or undetermined stroke. Ischemic stroke was defined as a rapid onset of focal neurological dysfunction with clinical, imaging or pathological evidence of focal infarction of the brain, retina (excluding anterior ischemic optic neuropathy [AION]), or spinal cord explaining the dysfunction. Clinical evidence of infarction was based on symptoms persisting ≥24 hours or until death, and exclusion of other etiologies (such as brain infection, trauma, tumor, seizure, severe metabolic disease, or degenerative neurological disease). Intracerebral hemorrhage was defined as a rapid onset of focal or global neurological dysfunction and/or headache attributable to a focal collection of blood within the brain parenchyma or ventricular system that was not caused by trauma. If the type of stroke could not be determined by imaging or other means (e.g., lumbar puncture, neurosurgery, or autopsy) but was judged to fulfil the stroke definition above, the stroke was classified as undetermined stroke.
Systemic embolism	A systemic arterial embolism was considered to have occurred when there was clear evidence of abrupt occlusion of a systemic artery consistent with an embolic event. Pulmonary embolism or deep vein thrombosis were not reported. Two criteria were required for an event to be defined as Systemic Arterial Embolism: 1. Clinical signs and symptoms consistent with embolic arterial occlusion 2. At least one of the following objective findings: - Surgical report indicating evidence of arterial embolism - Pathological specimens related to embolism removal - Imaging evidence consistent with arterial embolism - Autopsy reports
Myocardial infarction	Myocardial infarction (MI) was defined according to the universal definition of MI as rise and/or fall of cardiac troponin with at least one value above the 99th percentile of the upper reference limit in a clinical setting consistent with myocardial ischemia, and with at least one of the following: - Symptoms of ischemia - New ST elevation at the J point in two contiguous leads >0.1 mV except for V2-V3. For leads V2-V3 the following cut points apply: ≥0.2 mV in men ≥40 years, ≥0.25 mV in men <40 years and ≥0.15 mV in women on ECG - New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads and/or T inversion ≥0.1 mV in two contiguous leads with prominent R wave or R/S ratio >1. - New left bundle brunch block on ECG - Development of pathological Q waves on ECG - Imaging evidence of new loss of viable myocardium or new regional wall motion - Identification of an intracoronary thrombus by angiography or autopsy

Table S2. Association of BMP10 concentration and adverse outcomes – multivariable model additionally adjusted for NT-proBNP.

Adverse outcomes	BMP10 ng/ml	Multivariable model* additionally adjusted for NT-proBNP[§] HR (95% CI)
All-cause death	Continuous	1.34 (1.13; 1.59), p <0.001
	Quartile I	Reference
	Quartile II	1.29 (0.87; 1.92)
	Quartile III	1.37 (0.92; 2.03)
	Quartile VI	1.76 (1.18; 2.64)
	p linear trend	0.007
	p quadratic trend	1.0
	p cubic trend	0.43
MACE	Continuous	1.24 (1.08; 1.44), p = 0.003
	Quartile I	Reference
	Quartile II	1.16 (0.87; 1.55)
	Quartile III	1.22 (0.91; 1.63)
	Quartile VI	1.46 (1.07; 1.98)
	p linear trend	0.02
	p quadratic trend	0.87
	p cubic trend	0.54

BMP10 = bone morphogenetic protein 10, CI = confidence interval, HR = hazard ratio, MACE = major adverse cardiovascular events (composite of hospitalization for heart failure, cardiovascular death, stroke, systemic embolism, myocardial infarction). [§]NT-proBNP was log-transformed.

*adjusted for age, sex, body mass index, heart rate, systolic blood pressure, rhythm at baseline (sinus rhythm, atrial fibrillation, other), current smoking, history of diabetes, coronary artery disease, hypertension, heart failure, stroke/transient ischemic attack, oral anticoagulation, antiplatelet therapy, and estimated glomerular filtration rate. n = 2184.

Table S3. Association of BMP10 concentration and adverse outcomes – multivariable model additionally adjusted for study centre.

Adverse outcomes	BMP10 ng/ml	Multivariable model* additionally adjusted for study centre HR (95% CI)
All-cause death	Continuous	1.60 (1.36; 1.87), p <0.001
	Quartile I	Reference
	Quartile II	1.49 (1.00; 2.22)
	Quartile III	1.73 (1.17; 2.56)
	Quartile VI	2.55 (1.71; 3.81)
	p linear trend	<0.001
	p quadratic trend	0.96
	p cubic trend	0.33
MACE	Continuous	1.51 (1.32; 1.73), p <0.001
	Quartile I	Reference
	Quartile II	1.29 (0.97; 1.73)
	Quartile III	1.52 (1.14; 2.03)
	Quartile VI	2.07 (1.53; 2.80)
	p linear trend	<0.001
	p quadratic trend	0.79
	p cubic trend	0.53

BMP10 = bone morphogenetic protein 10, CI = confidence interval, HR = hazard ratio, MACE = major adverse cardiovascular events (composite of hospitalization for heart failure, cardiovascular death, stroke, systemic embolism, myocardial infarction).

*adjusted for age, sex, body mass index, heart rate, systolic blood pressure, rhythm at baseline (sinus rhythm, atrial fibrillation, other), current smoking, history of diabetes, coronary artery disease, hypertension, heart failure, stroke/transient ischemic attack, oral anticoagulation, antiplatelet therapy, and estimated glomerular filtration rate. n = 2184.

Table S4. Association of NT-proBNP categories and adverse outcomes.

Adverse outcomes	NT-proBNP	Number of events	Patient-years	Incidence rate per 100 patient-years	Age- and sex-adjusted model HR (95% CI)	Multivariable adjusted model* HR (95% CI)
All-cause death	Continuous§	395	9618	4.11	1.80 (1.63; 1.98), p <0.001	1.59 (1.40; 1.79), p <0.001
	Low (<300 ng/l)	37	3220	1.15	Reference	Reference
	Intermediate (300-900 ng/l)	87	2713	3.21	2.05 (1.39; 3.02)	1.79 (1.19; 2.71)
	High (>900 ng/l)	271	3685	7.35	3.99 (2.79; 5.70)	2.79 (1.83; 4.27)
	p linear trend				<0.001	<0.001
	p quadratic trend				0.85	0.62
MACE	Continuous§	605	8648	7.00	1.73 (1.60; 1.86), p <0.001	1.64 (1.49; 1.81), p <0.001
	Low (<300 ng/l)	58	3124	1.86	Reference	Reference
	Intermediate (300-900 ng/l)	155	2440	6.35	2.81 (2.07; 3.81)	2.59 (1.88; 3.56)
	High (>900 ng/l)	392	3084	12.71	4.93 (3.70; 6.57)	4.01 (2.86; 5.63)
	p linear trend				<0.001	<0.001
	p quadratic trend				0.03	0.02
Hospitalization for heart failure	Continuous§	362	8929	4.05	2.01 (1.82; 2.22), p <0.001	1.91 (1.67; 2.17), p <0.001
	Low (<300 ng/l)	22	3172	0.69	Reference	Reference
	Intermediate (300-900 ng/l)	89	2537	3.51	4.28 (2.67; 6.86)	3.68 (2.27; 5.95)
	High (>900 ng/l)	251	3220	7.80	8.50 (5.43; 13.31)	6.35 (3.88; 10.42)
	p linear trend				<0.001	<0.001
	p quadratic trend				0.01	0.01
Cardiovascular death	Continuous§	254	9618	2.64	1.88 (1.66; 2.12), p <0.001	1.62 (1.39; 1.90), p <0.001
	Low (<300 ng/l)	17	3220	0.53	Reference	Reference
	Intermediate (300-900 ng/l)	52	2713	1.92	2.56 (1.47; 4.44)	2.23 (1.22; 4.06)
	High (>900 ng/l)	185	3685	5.02	5.54 (3.32; 9.24)	3.72 (2.03; 6.82)
	p linear trend				<0.001	<0.001
	p quadratic trend				0.66	0.46

Stroke and systemic embolism	Continuous§	114	9406	1.21	1.35 (1.15; 1.60), p <0.001	1.26 (1.01; 1.57), p = 0.04
	Low (<300 ng/l)	12	3191	0.38	Reference	Reference
	Intermediate (300-900 ng/l)	41	2639	1.55	3.38 (1.76; 6.50)	2.95 (1.47; 5.89)
	High (>900 ng/l)	61	3576	1.71	3.29 (1.72; 6.28)	2.37 (1.09; 5.15)
	p linear trend				<0.001	0.03
	p quadratic trend				0.01	0.004
Stroke	Continuous§	107	9427	1.14	1.34 (1.12; 1.59), p <0.001	1.25 (0.99; 1.57), p = 0.06
	Low (<300 ng/l)	11	3196	0.34	Reference	Reference
	Intermediate (300-900 ng/l)	39	2644	1.48	3.50 (1.77; 6.90)	3.08 (1.50; 6.34)
	High (>900 ng/l)	57	3587	1.59	3.34 (1.70; 6.55)	2.51 (1.12; 5.61)
	p linear trend				<0.001	0.02
	p quadratic trend				<0.001	0.004
Myocardial infarction	Continuous§	81	9459	0.86	1.28 (1.05; 1.55), p = 0.01	1.31 (1.02; 1.69), p = 0.04
	Low (<300 ng/l)	15	3194	0.47	Reference	Reference
	Intermediate (300-900 ng/l)	21	2663	0.79	1.36 (0.69; 2.67)	1.27 (0.63; 2.58)
	High (>900 ng/l)	45	3602	1.25	1.86 (1.00; 3.48)	1.87 (0.86; 4.06)
	p linear trend				0.05	0.11
	p quadratic trend				0.98	0.79

CI = confidence interval, HR = hazard ratio, MACE = major adverse cardiovascular events (composite of hospitalization for heart failure, cardiovascular death, stroke, systemic embolism, myocardial infarction). NT-proBNP = N-terminal prohormone of brain natriuretic peptide. n = 2219 (Low NT-proBNP n = 697, Intermediate NT-proBNP n = 617, High NT-proBNP n = 905). § NT-proBNP was log-transformed. * adjusted for age, sex, body mass index, heart rate, systolic blood pressure, rhythm at baseline (sinus rhythm, atrial fibrillation, other), current smoking, history of diabetes, coronary artery disease, hypertension, heart failure, stroke/transient ischemic attack, oral anticoagulation, antiplatelet therapy, and estimated glomerular filtration rate. n = 2184.

Figure S1. Histogram of BMP10.

Overall distribution of BMP10 concentration. BMP10 = bone morphogenetic protein 10.

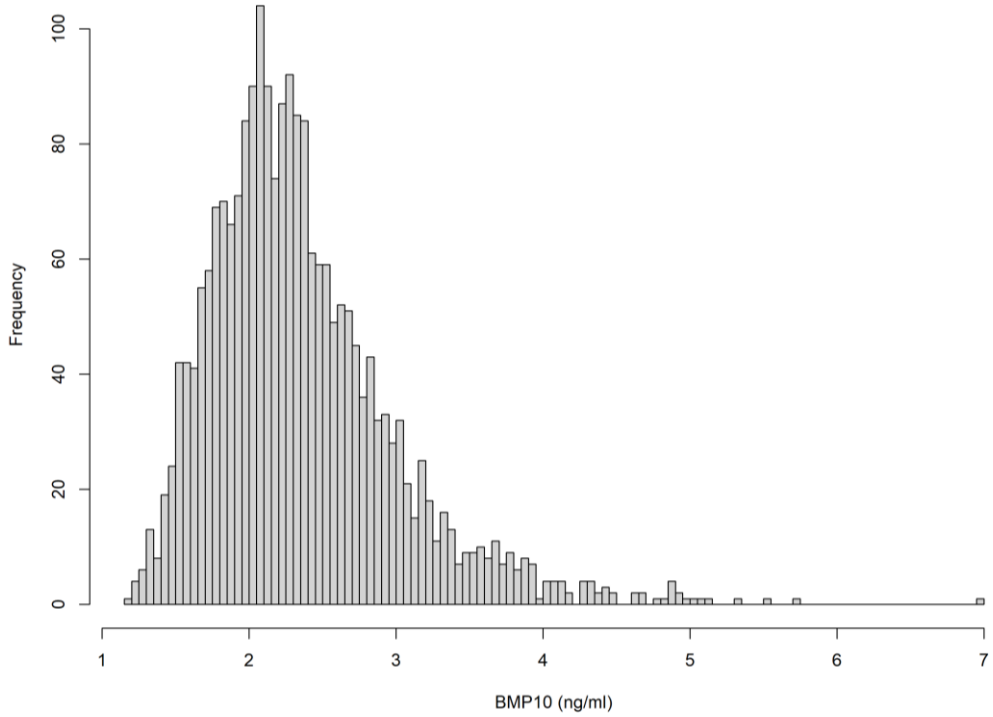

Figure S2. Histogram of NT-proBNP.

Overall distribution of NT-proBNP concentration. The excerpt shows only patients with NT-proBNP <5000 ng/l.

NT-proBNP = N-terminal prohormone of brain natriuretic peptide.

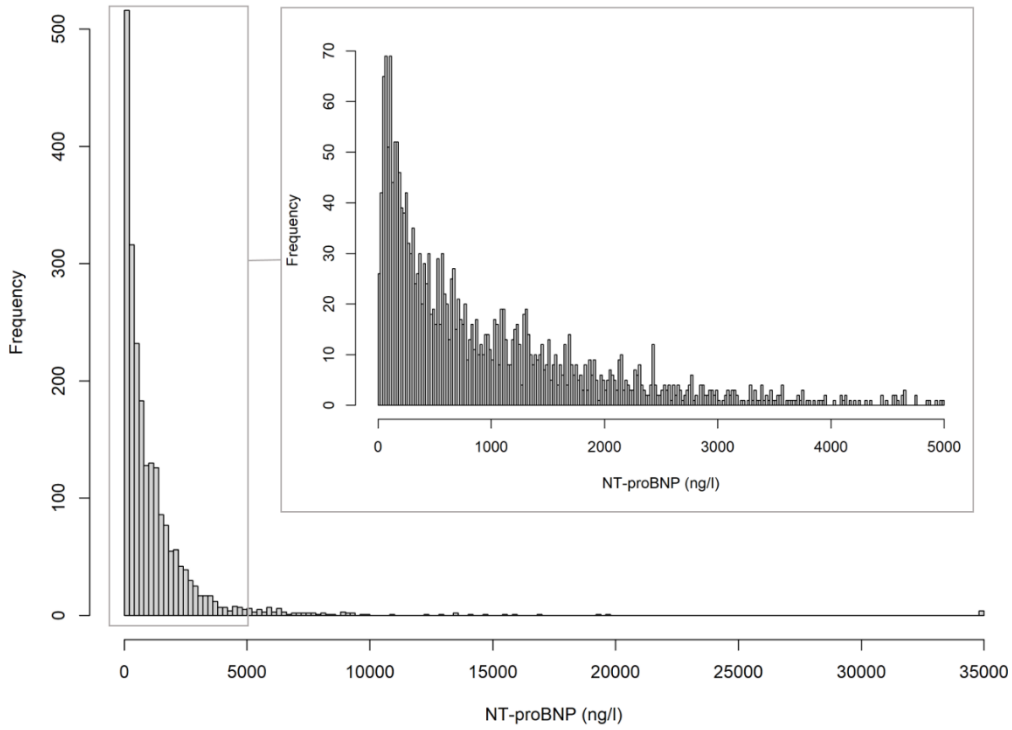

Figure S3. Violin boxplots of BMP10 according to AF type and rhythm.

(A) BMP10 concentration according to AF type. Non-paroxysmal AF type includes patients with persistent and permanent AF. p-value <0.001 (Mann-Whitney U test). **(B)** BMP10 concentration according to rhythm at baseline visit assessed with a resting 16-lead electrocardiogram of 5 min duration. p-value <0.001 (Kruskal-Wallis test). AF = atrial fibrillation, BMP10 = bone morphogenetic protein 10, SR = sinus rhythm.

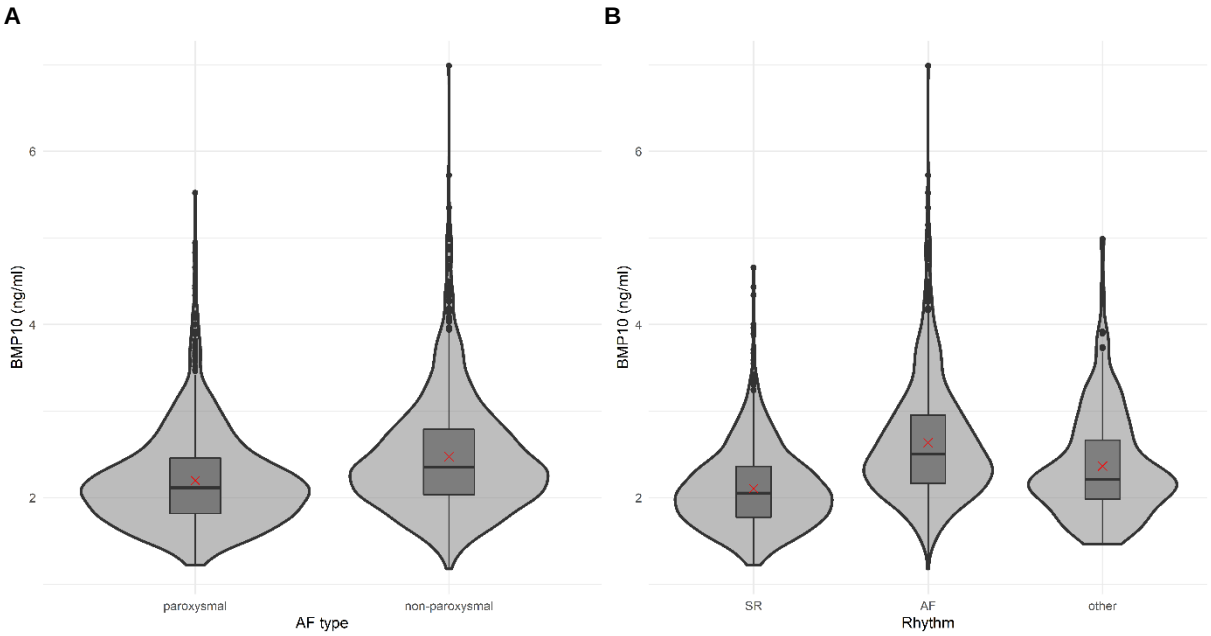

Figure S4. Scatterplot of BMP10 and NT-proBNP.

The correlation between BMP10 and NT-proBNP was calculated with the Spearman's rank correlation coefficient (0.59). NT-proBNP was log-transformed for the scatterplot. BMP10 = bone morphogenetic protein 10, NT-proBNP = N-terminal prohormone of brain natriuretic peptide.