

SUPPLEMENTARY DATA

Supplemental Table 1. Sensitivity analysis; Discrimination and reclassification statistics (95% CIs) for 5-year risk of heart failure after addition of biomarkers to a model containing clinical risk factors after excluding patients with past history of hospitalization for heart failure

	C-statistic	IDI	Relative IDI (%)	NRI	
				Continuous	Categorical [†]
Base model*	0.8007 (0.7585, 0.8430)				
Base model plus IL-6	0.8098 (0.7690, 0.8506) <i>P</i> = 0.11	0.015 (0.0005, 0.030) <i>P</i> = 0.04	5.39 (0.17, 1.49)	0.383 (0.176, 0.567) <i>P</i> <0.001	0.013 (-0.067, 0.078) <i>P</i> = 0.48
Base model plus hs-CRP	0.8125 (0.7713, 0.8538) <i>P</i> = 0.17	0.028 (0.011, 0.048) <i>P</i> <0.001	9.90 (3.82, 17.05)	0.264 (0.074, 46.4) <i>P</i> = 0.01	0.042 (-0.025, 0.114) <i>P</i> = 0.23
Base model plus hs-cTnT	0.8092 (0.7682, 0.8501) <i>P</i> = 0.29	0.010 (-0.004, 0.023) <i>P</i> = 0.15	3.68 (-1.20, 8.29)	0.427 (0.240, 0.606) <i>P</i> <0.001	0.013 (-0.087, 0.110) <i>P</i> = 0.34
Base model plus NT-proBNP	0.8747 (0.8441, 0.9052) <i>P</i> <0.001	0.099 (0.056, 0.145) <i>P</i> <0.001	35.1 (18.8, 52.1)	0.783 (0.615, 0.949) <i>P</i> <0.001	0.234 (0.117, 0.343) <i>P</i> <0.001
Base model plus IL-6, hs-CRP, and hs-cTnT	0.8231 (0.7834, 0.8628)				
Addition of NT-proBNP to base model plus IL-6, hs-CRP, and hs-cTnT	0.8768 (0.8462, 0.9074) <i>P</i> <0.001	0.086 (0.044, 0.130) <i>P</i> <0.001	26.1 (13.4, 40.3)	0.661 (0.491, 0.834) <i>P</i> <0.001	0.209 (0.105, 0.316) <i>P</i> <0.001
Base model plus NT-proBNP	0.8747 (0.8441, 0.9052)				
Addition of IL-6, hs-CRP, and hs-cTnT to base model plus NT-proBNP	0.8768 (0.8462, 0.9074) <i>P</i> = 0.70	0.035 (0.016, 0.056) <i>P</i> <0.001	9.14 (4.22, 14.69)	0.342 (0.117, 0.526) <i>P</i> <0.001	0.007 (-0.055, 0.064) <i>P</i> = 0.47

Results were derived from the random subcohort (n = 2,871).

Biomarkers were log transformed.

* Base model included the same variables in Table 2 (see caption for Table 2), except for history of hospitalization for heart failure.

[†] Using cutoff points of 5% and 10% 5-year risk.

Abbreviations: IDI, integrated discrimination improvement; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; IL-6, interleukin-6; NRI, net reclassification improvement; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

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Supplemental Table 2. Sensitivity analysis; Discrimination and reclassification statistics (95% CIs) for 5-year risk of heart failure after addition of biomarkers to a model containing clinical risk factors after excluding patients with NT-proBNP levels >400 pg/mL

	C-statistic	IDI	Relative IDI (%)	NRI	
				Continuous	Categorical [†]
Base model*	0.8215 (0.7674, 0.8755)				
Base model plus IL-6	0.8252 (0.7714, 0.8791) <i>P</i> = 0.44	0.001 (-0.014, 0.018) <i>P</i> = 0.23	0.42 (-4.65, 6.20)	0.215 (-0.051, 0.492) <i>P</i> = 0.12	-0.001 (-0.077, 0.060) <i>P</i> = 0.77
Base model plus hs-CRP	0.8226 (0.7696, 0.8756) <i>P</i> = 0.90	0.002 (-0.010, 0.012) <i>P</i> = 0.51	0.59 (-3.08, 4.22)	0.131 (-0.131, 0.402) <i>P</i> = 0.33	-0.014 (-0.098, 0.062) <i>P</i> = 0.75
Base model plus hs-cTnT	0.8223 (0.7682, 0.8764) <i>P</i> = 0.63	0.004 (-0.005, 0.015) <i>P</i> = 0.39	1.38 (-1.87, 4.92)	0.199 (-0.057, 0.463) <i>P</i> = 0.12	0.015 (-0.062, 0.092) <i>P</i> = 0.58
Base model plus NT-proBNP	0.8640 (0.8162, 0.9119) <i>P</i> = 0.009	0.042 (0.009, 0.079) <i>P</i> = 0.02	15.0 (3.31, 28.0)	0.503 (0.268, 0.740) <i>P</i> <0.001	0.194 (0.082, 0.315) <i>P</i> = 0.002
Base model plus IL-6, hs-CRP, and hs-cTnT	0.8264 (0.7737, 0.8791)				
Addition of NT-proBNP to base model plus IL-6, hs-CRP, and hs-cTnT	0.8647 (0.8171, 0.9123) <i>P</i> = 0.01	0.036 (0.007, 0.070) <i>P</i> = 0.02	12.6 (2.10, 24.8)	0.400 (0.145, 0.651) <i>P</i> = 0.002	0.231 (0.109, 0.373) <i>P</i> = 0.002
Base model plus NT-proBNP	0.8640 (0.8162, 0.9119)				
Addition of IL-6, hs-CRP, and hs-cTnT to base model plus NT-proBNP	0.8647 (0.8171, 0.9123) <i>P</i> = 0.88	0.0002 (-0.009, 0.010) <i>P</i> = 0.10	0.06 (-2.91, 3.01)	0.151 (-0.128, 0.425) <i>P</i> = 0.26	0.049 (-0.022, 0.131) <i>P</i> = 0.19

Results were derived from the random subcohort (n = 2,643).

Biomarkers were log transformed.

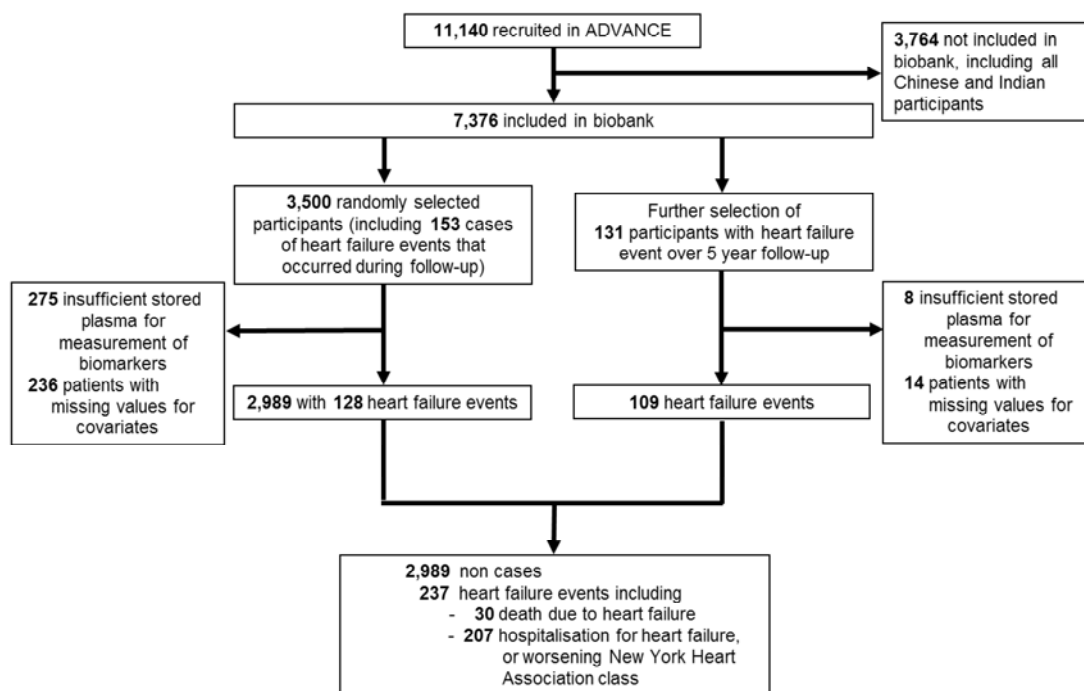
* Base model included the same variables in Table 2 (see caption for Table 2).

[†] Using cutoff points of 5% and 10% 5-year risk.

Abbreviations: IDI, integrated discrimination improvement; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; IL-6, interleukin-6; NRI, net reclassification improvement; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

SUPPLEMENTARY DATA

Supplementary Figure 1. The case-cohort study design and data availability.

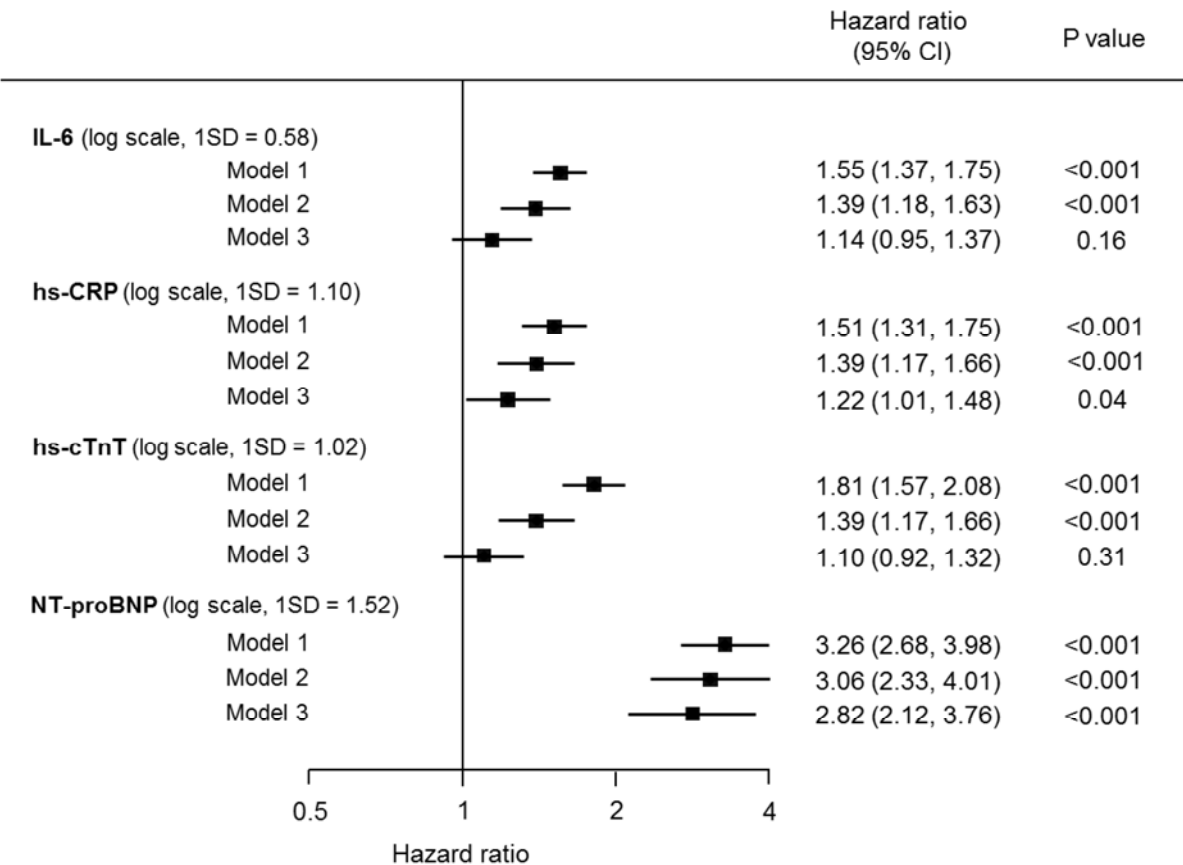


SUPPLEMENTARY DATA

Supplementary Figure 2. Sensitivity analysis; Adjusted hazard ratios and 95% CIs for heart failure according to a one standard deviation increment in biomarkers after excluding patients with past history of hospitalization for heart failure.

Abbreviations: ECG, electrocardiogram; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; IL-6, interleukin-6; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation.

Hazard ratios were adjusted for the variables in Figure 2 (see caption for Figure 2). Model 2 was adjusted for the variables except for history of hospitalization for heart failure.

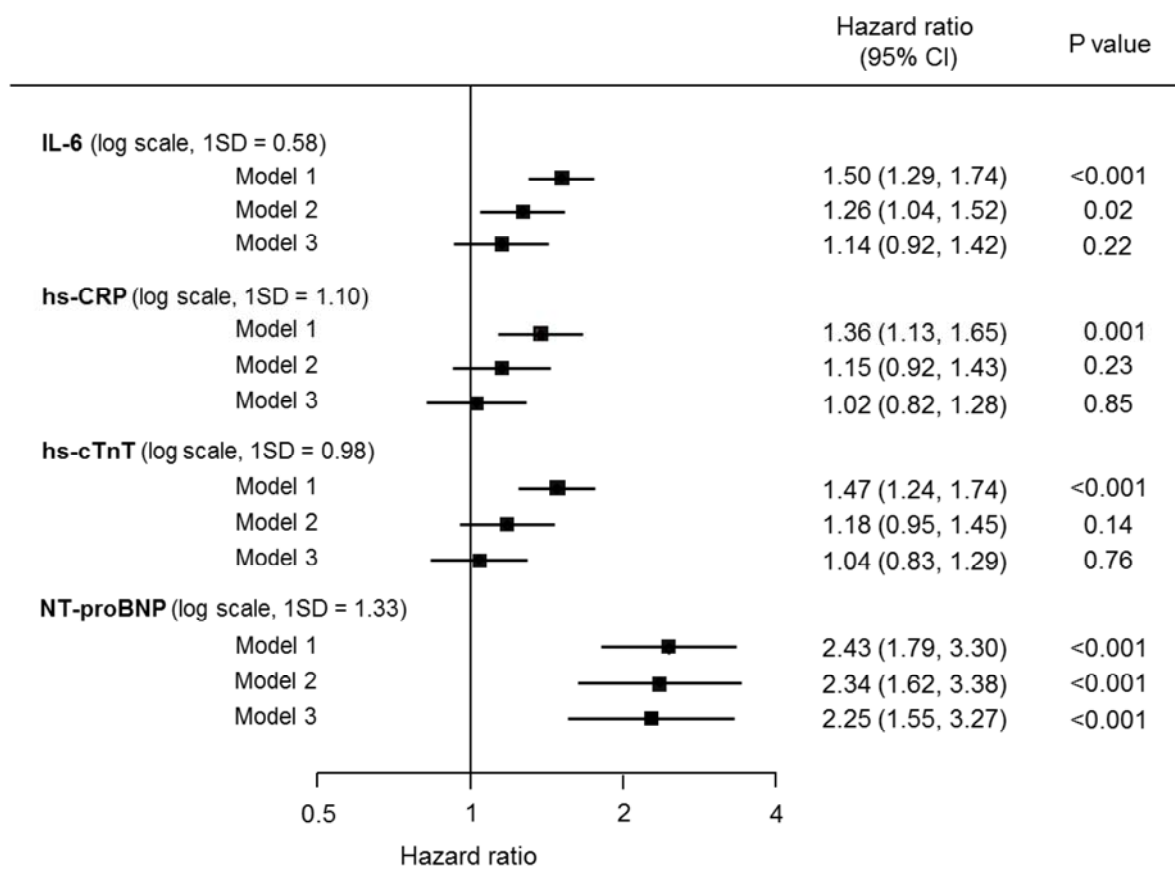


SUPPLEMENTARY DATA

Supplementary Figure 3. Sensitivity analysis; Adjusted hazard ratios and 95% CIs for heart failure according to a one standard deviation increment in biomarkers after excluding patients with NT-proBNP levels >400 pg/mL.

Abbreviations: ECG, electrocardiogram; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; IL-6, interleukin-6; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation.

Hazard ratios were adjusted for the variables in Figure 2 (see caption for Figure 2).



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Supplementary Figure 4. Adjusted hazard ratios and 95% CIs for heart failure according to a one standard deviation increment in NT-proBNP, stratified by sex, age, duration of diabetes, history of myocardial infarction, and a history of hospitalization for heart failure.

Abbreviations: DM, diabetes mellitus; HF, heart failure; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Hazard ratios were adjusted for the variables in model 2 (see caption for Figure 2), except for myocardial infarction, where insulin was dropped from the model to allow convergence.

