

Supplemental Methods

Biomarker testing. Blood samples used for measurement of plasma natriuretic peptide levels were collected within 48 hours of admission. The samples were collected into plastic tubes containing ethylenediaminetetraacetic acid (EDTA-2Na, 1.5 mg/ml) and aprotinin (500 kallikrein inhibitor units/ml) and stored at 4°C. After centrifugation, the collected plasma samples were stored at -80°C until measurements were made.

Measurement of two BNP forms. Plasma total BNP and proBNP were measured using the chemiluminescence enzyme immunoassays (CLEIAs) as previously described^{8, 15}. Briefly, in both CLEIAs, an antibody recognizing a common epitope in the C-terminal region of proBNP and mature BNP was used as a capture antibody. An antibody recognizing the N-terminal region of proBNP and one recognizing the ring region of BNP were used as detection antibodies in the proBNP and total BNP CLEIAs, respectively. Glycosylated proBNP with a relative molecular mass of 32 kDa (HyTest, Turku, Finland) served as the standard. Intra-assay (8 replicates) and inter-assay (10 replicates) coefficients of variation of the standard peptide at 2.6, 8.9, and 76.7 pmol/l (pM) were in the ranges of 1.5-5.4% and 4.1-5.5%, respectively, in the proBNP assay.

Cyclic guanosine monophosphate (cGMP) and other laboratory markers. The second messenger mediating the effects of ANP and BNP, cGMP, was measured using a radioimmunoassay assay kit (Yamasa Co, Tokyo, Japan). Estimated glomerular filtration rate (eGFR) was calculated using the equation for Japanese individuals: $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$ ($\times 0.739$ for females) (unit, ml/min/1.73 m²)¹⁵.

Echocardiography. Echocardiography was routinely performed when the patients were admitted to the hospital. Left ventricular (LV) dimensions were measured according to American Society of Echocardiography guidelines¹⁸. LV ejection fraction (EF) was measured using the modified Simpson's

method or the semiquantitative two-dimensional visual estimate method, as previously described¹⁹.