**Supplementary information**

**Supplementary Table 1.** Biomarkers for HF monitored in the REALIsM-HF study

| Biomarker | Pathomechanism | Rationale for use in both HFpEF and HFrEF | Rationale for use in HFpEF | Rationale for use in HFrEF |
| --- | --- | --- | --- | --- |
| hsTnT | Cardiomyocyte stress and leakage | hsTnT reflects acute and chronic cardiac pathologies such as ischemia and cardiac toxicity [1, 2] | Serum hsTnT level was associated with event rate in patients with HF [3] | hsTnT levels were higher in HFrEF than in HFpEF [4] |
| Gal-3 | (Cardiac) fibroblast /cardiomyocyte stress  | Raised serum Gal-3 was a strong predictor of short-, mid-, and long-term mortality and HF-associated hospitalization in early- and late-stage HFpEF and HFrEF [5] |  |  |
| GDF15 | Cardiomyocyte stress  | Very low levels of GDF15 were detectable in the healthy myocardium, but GD15 was induced following ischemic injury [6] | Raised plasma GDF15 levels distinguish patients with HFpEF from healthy individuals (AUC 0.94). The NTproBNP/GDF15 ratio had the greatest utility in distinguishing between HFpEF and HFrEF [4] | In early HF, elevated plasma GDF15 levels correlated strongly with indices of myocardial remodeling (LVMI, LVEDD, LVEF, LA diameter). In chronic HF, raised GDF15 levels predicted mortality [7, 8] |
| sST2 | Myocardial stress  | In HF, expression of sST2 mRNA and protein was upregulated, and protein became detectable in serum [9] | In hypertensive patients, serum sST2 outperformed NTproBNP as an independent biomarker for the presence of HFpEF [10] | In severe chronic HF, increase in serum sST2 independently predicted mortality or transplantation [11] |
| NTproBNP | Pressure/volume overload | Integral part of AHA/ESC guidelines for the diagnosis of HF [12]. Levels on admission and at discharge carried important prognostic information in HFpEF and HFrEF, with low NTproBNP levels indicating very low risk of death. Used as a clinical endpoint in many clinical trials |  |  |
| hs-copeptin |  | Copeptin is secreted with vasopressin by the pituitary gland in a 1:1 stoichiometric ratio. Copeptin has a significantly longer half-life than biologically active vasopressin (several days vs minutes, respectively) and, thereby, is a surrogate biomarker for vasopressin [13] | Increased levels of copeptin were linked to excess mortality, and this link was maintained irrespective of the clinical signs of disease severity [14]. Copeptin was highly prognostic for 90-day adverse events in patients with acute HF [15] | Copeptin levels were significantly lower in HFpEF than in HFrEF. A 10 mL/min decline in glomerular filtration rate corresponded to a 17% increase in copeptin levels in patients with HFpEF [16] |
| IGFBP7 |  |  | Changes in IGFBP7 levels were significantly correlated with echocardiographic indicators of diastolic dysfunction and HFpEF [17] | Plasma IGFBP7 concentrations were associated with cardiac hypertrophy and prognostic for HF hospitalization and cardiovascular death [18]  |

AHA, American Heart Association; AUC, area under the curve; ESC, European Society of Cardiology; Gal-3, galectin 3; GDF15, growth/differentiation factor 15; HF, heart failure; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; hs-copeptin, high-sensitivity copeptin; hsTnT, high-sensitivity troponin T; IGFBP7, insulin-like growth factor-binding protein 7; LA, left atrium; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; mRNA, messenger ribonucleic acid; NTproBNP, N-terminal probrain natriuretic peptide; REALIsM-HF, Real-Life Multimarker Monitoring in Patients with Heart Failure; sST2, soluble suppression of tumorigenicity.

**Supplementary Figure legends**

**Supplementary Fig. 1.** Overview of the REALIsM-HF trial. 6MWD, 6-min walking distance; ePRO, electronic patient reported outcomes; HF, heart failure; QoL, quality of life; REALIsM-HF, Real-Life Multimarker Monitoring in Patients with Heart Failure.

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