Influence of ejection fraction on biomarker expression and response to spironolactone in people at risk of heart failure: findings from the HOMAGE trial

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Abstract

Background: Left ventricular ejection fraction (LVEF) can provide hemodynamic information and may influence the response to spironolactone and other heart failure (HF) therapies.

Aims: To study the patient characteristics and circulating protein associations with LVEF, and whether LVEF influenced the response to spironolactone.

Methods: HOMAGE enrolled patients aged >60 years at high risk of developing HF with a LVEF ≥45%. 527 patients were randomized to either spironolactone or standard-of-care for ≈9 months. 276 circulating proteins were measured using Olink® technology.

Results: 364 patients had available LVEF determined by the Simpson's bi-plane method. The respective LVEF tertiles were: Tertile1:<60% (N=122), Tertile2:60-65% (N=121), and Tertile3:>65% (N=121). Patients with a LVEF>65% had smaller LV chamber size and volumes, and lower natriuretic peptide levels. Compared to patients with a LVEF<60%, those with LVEF>65% had higher levels of circulating c-c motif chemokine ligand-23 and interleukin-8, and lower levels of tissue plasminogen activator, BNP, S100 calcium binding protein A12, and collagen type I alpha 1 chain (COL1A1)**.** Spironolactone significantly reduced the circulating levels of BNP and COL1A1 without significant treatment-by-LVEF heterogeneity: BNP change β=-0.36 Log_2 and COL1A1 change β=-0.16 Log_2 (P<0.0001 for both; interactionP>0.1 for both). Spironolactone increased LVEF from baseline to month 9 by 1.1%, P=0.007.

Conclusion: Patients with higher LVEF had higher circulating levels of chemokines

and inflammatory markers and lower levels of stretch, injury, and fibrosis markers. Spironolactone reduced the circulating levels of natriuretic peptides and type 1 collagen, and increased LVEF.

Key-words: ejection fraction, spironolactone, inflammation, fibrosis.

Introduction

Left ventricular ejection fraction (LVEF) is the ratio of stroke volume to end-diastolic volume of the left ventricle (LV); LVEF can thus provide relevant hemodynamic information, but does not reflect the contractility of the LV.[1]

Over the last two decades, LVEF has been incorporated as an inclusion criterion in heart failure (HF) trials. Patients with HF and reduced EF have been found to benefit markedly from neurohormonal antagonists, whereas HF patients with normal EF have not benefited as markedly as their reduced EF counterparts.[2]

Given the influence of LVEF in the response to HF treatments, studies have explored the relation between patients' characteristics and biomarker expression across the range of LVEF. Some studies suggested that patients with HF who have higher EF have more extra-cardiac comorbidities and higher expression of pathways related to inflammation than patients with lower EF.[3]

The Heart Omics in AGEing (HOMAGE; NCT02556450) trial enrolled people at high risk of developing HF to test the effect of spironolactone (vs. usual care) on circulating markers of fibrosis, natriuretic peptides, blood pressure and cardiac structure and function.[4] Spironolactone reduced the circulating levels of procollagen type-I C-terminal propeptide (PICP) and increased collagen type-I C-terminal telopeptide (CITP), reflecting a decreased in the synthesis and an increase in the degradation of type-I collagen, respectively. In addition, spironolactone reduced blood pressure, NT-pro BNP and left atrial volume, while improving LVEF at 9 months.[5]

In the Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function (TOPCAT) enrolling patients with HF and a preserved EF (HFpEF), the effect of spironolactone was influenced by LVEF, whereby patients with EF below 55-60% may have benefited from spironolactone.[6] Compared to TOPCAT, HOMAGE enrolled less symptomatic patients with a higher LVEF on average (63% in HOMAGE vs. 56% in TOPCAT).[5, 7]

Given the previously documented differences in patients' characteristics, biomarker expression, and response to spironolactone across LVEF, we aim to study the influence of LVEF on circulating proteins and outcomes in the HOMAGE trial.

Methods

Trial design and population

The HOMAGE trial was a prospective, randomised, open-label, blinded-endpoint (PROBE), multicentre design, in which people at high risk of developing HF were randomly assigned to receive either spironolactone or standard of care/"control" - not receiving spironolactone or other MRA (ClinicalTrials.gov Identifier: NCT02556450). The rationale, trial design and main results have been published.[4, 5]

The study was approved by all relevant ethics committees and regulatory bodies. All participants provided written informed consent prior to study-specific procedures.

The main entry criteria included age of 65 or older (amended to 60 years during the course of the trial), cardiovascular risk defined by the presence of coronary artery disease or at least 2 of the following: diabetes mellitus, treated hypertension, microalbuminuria or an abnormal ECG, and a NT-proBNP between 125 and 1,000ng/L or a BNP between 35 and 280ng/L. The main exclusion criteria were

glomerular filtration rate (eGFR) <30 mL/minute/1.73m2, serum potassium >5.0 mmol/L, left ventricular ejection fraction <45%, a diagnosis of HF or treatment with loop diuretics, and atrial fibrillation/flutter.

A total of 527 patients was randomized (265 to spironolactone and 262 to standard of care). The median (percentile$_{25\text{-}75}$) follow-up time was 8.9 (6.0-9.2) months.

Echocardiographic measurements

Echocardiograms were recorded, de-identified and transferred to a core laboratory (University Hospital of Nancy). Blind to treatment allocation, a single experienced echocardiographer (E. B.) measured the echocardiographic variables (including LVEF) using dedicated software (Echo PAC, GE Healthcare). Measurements were repeated at least 2 months later, blind to the first measurement. All recordings with suboptimal images and/or with differences >10% were reviewed by a senior cardiologist (N. G.) to mitigate measurement error.

The main LVEF assessment was performed using the Simpson's bi-plane method (N =364). As supplementary analysis, we report the findings from estimates of LVEF calculated from single plane in 4-chamber view images (N =456).

Proteomic biomarkers

Baseline and month 9 (or "last visit") plasma samples were analysed for 276 protein biomarkers by the TATAA-biocenter using the Olink Proseek® Multiplex cardiovascular (CVD) II, CVD III, and inflammation panels. The proteins were determined using high-throughput Olink Proseek® Multiplex 96x96 kits, which measures 92 manually selected proteins simultaneously in 1µl of plasma per kit. Each kit uses a proximity extension assay (PEA) technology with dual-recognition DNA-coupled readout, where 92 oligonucleotide-labelled antibody probe pairs are

allowed to bind to their respective target in the sample. The platform provides Log_2 normalized protein expression (NPX) values with relative quantification. A detailed description of the Olink® technology is depicted on the website: https://www.olink.com/. The abbreviations, full names and respective Olink® multiplex panels of the studied proteins are described in the ***Supplemental Table 1***. In addition, serum PICP was measured using the METRA EIA kit (Quidel Corporation), plasma NT-pro BNP and high sensitivity troponin T (hs-TnT) were assessed by electro-chemiluminescent assays (Roche diagnostics). The assays were performed blinded to treatment allocation.

Statistical analyses

We compared the characteristics of the patients across tertiles of LVEF at baseline using the appropriate tests for continuous and categorical variables. To assess whether the biomarkers were expressed differently between patients with higher (top tertile) and lower (bottom tertile) LVEF, logistic regression analyses were performed comparing the top LVEF tertile (outcome) with the bottom LVEF tertile (referent) with each circulating protein as an independent variable plus age, sex, systolic blood pressure, heart rate, body mass index (BMI) and eGFR as adjustment covariates. To complement the previous step, ordered logistic regression analyses with LVEF tertiles as outcome variable were also performed. To identify the proteins with stronger association with higher (vs. lower) LVEF, a multivariable stepwise forward selection procedure was applied with all the circulating proteins with a P-value <0.05 in the previous step included in the model and the adjustment variables “forced” in the model. A P-value <0.05 was required for a protein to enter and stay in the final model. After selecting the “top” proteins with different expression by LVEF, we have tested whether spironolactone affected the levels of the proteins throughout the

follow-up, using analysis of covariance (ANCOVA) to compare the difference in changes between the control and spironolactone groups. To study whether LVEF could influence the response to spironolactone on the main outcomes of the study, we performed ANCOVA with a treatment-by-LVEF interaction term. The effect of spironolactone on LVEF throughout the follow-up was assess using a mixed effect model with LVEF as dependent variable (measured at baseline, 1 month, and 9 months), treatment (spironolactone vs. control) as independent fixed-effects variable, and age, sex, systolic blood pressure, heart rate, BMI and eGFR as adjustment covariates; the random intercepts were set at the patient "ID" level with an unstructured covariance matrix, meaning that all variances and covariances could vary freely between patients. Statistical analyses were performed using Stata® (version 17, StataCorp LP).

Bioinformatical and network analyses

We used knowledge-based network analysis with induced network approach by consensuspathDB (CPDB) online server (accessed on 25 November 2021) from Max Planck Institute for Molecular Genetics to identify the links among the circulating proteins with different expression according to LVEF tertiles, based on known knowledge of interactions (protein interactions and biochemical interactions).[7] The network analysis also identifies additional proteins limited to the first-degree interactors (intermediate nodes) linking our input proteins (seed nodes), with exclusion of low-confidence interactions and quantified by a z-score ≤20 calculated for each intermediate node. The Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) database was used to add further nodes to the network. Functional enrichment (GO biological processes) was performed using proteins that were significantly higher or lower in patients with higher vs. lower LVEF at baseline

on a genetic background including only the proteins on the measured OLINK panels to correct for the selected proteins. We only included identified GO-processes when the protein-protein interaction (PPI) enrichment P-value was <0.05.

Results

Patients' characteristics

A total of 364 patients had available baseline LVEF as determined by the Simpson's bi-plane method. The respective LVEF tertiles were: Tertile 1: <60% (N =122), Tertile 2: 60-65% (N =121), and Tertile 3: >65% (N =121). Compared to patients with a LVEF <60% (Tertile 1), those with a LVEF >65% (Tertile 3) had smaller left ventricular end-diastolic diameter (LVEDD) 46.5 vs. 49.4 mm, lower left ventricular end-diastolic and end-systolic volumes indexed to body surface area (LVEDVi and LVESVi) 39.1 vs. 45.6 ml/m^2 and 12.2 vs. 20.7 ml/m^2, respectively, lower NT-pro BNP levels 159.5 vs. 258.0 pg/mL and were more likely to use thiazides 23.1 vs. 12.3%. ***Table 1***. A similar pattern of associations was observed with LVEF tertiles determined from the 4-chamber view only. ***Supplemental Table 2***.

Circulating proteins associated with LVEF

After multivariable stepwise selection with adjustment for clinical variables, compared to patients with a LVEF <60% (Tertile 1), those with a LVEF >65% (Tertile 3) had higher levels of circulating c-c motif chemokine ligand 23 (CCL23; β =+1.79 Log_2 NPX) and interleukin 8 (IL8; β =+0.58 Log_2 NPX), and lower levels of circulating tissue plasminogen activator (TPA; β =-0.83 Log_2 NPX), brain natriuretic peptide (BNP; β =-0.46 Log_2 NPX), S100 calcium binding protein A12 (ENRAGE; β =-0.62 Log_2 NPX) and collagen type I alpha 1 chain (COL1A1; β =-0.92 Log_2 NPX. ***Table 2***. The full list of individual (1-by-1 testing) proteins associated with a LVEF >65% vs.

<60% with adjustment for clinical variables is shown in ***Supplemental Table 3***. Other proteins retained in the multivariable stepwise model included tumor necrosis factor β (TNFβ), CD6, monocyte chemotactic protein 3 (MCP3) and renin (REN), which were higher among patients with LVEF >65% compared to those with LVEF <60%. NT-pro BNP and procollagen type I carboxy-terminal propeptide (PICP) were lower among patients with LVEF >65% compared to those with LVEF <60% (P <0.05 for all). Similar associations were found with ordered logistic regression across LVEF categories (***Supplemental Table 4***), and with LVEF determined from the 4-chamber view only (***Supplemental Tables 5 & 6***). COL1A1 and PICP were well correlated (Rho =0.61, P <0.0001).

There was a significant enrichment of protein-protein interactions among the selected proteins (PPI enrichment p-value =0.0009). A cluster of chemokines was higher in patients with LVEF >65% (*GO:0030593: neutrophil chemotaxis*, FDR 0.00021; CXCL8, CCL23 and CCL7). The circulating chemokines were connected to a lower circulating level of COL1A1 through 3 matrix-metalloproteinases (MMP) which were induced into the network. Even when the network was limited to proteins which remained significant after adjusting for clinical variables, the network showed the same pattern. ***Figure 1***.

Spironolactone effect on top proteins associated with LVEF

Spironolactone reduced the circulating levels of BNP and COL1A1 without significant treatment-by-LVEF heterogeneity: spironolactone vs. control month 9 BNP change β =-0.36 Log_2 NPX and COL1A1 change β =-0.16 Log_2 NPX (P <0.0001 for both; interaction P >0.1 for both). Spironolactone did not significantly change the circulating levels of CCL23, TPA, ENRAGE, and IL8. ***Table 3***.

Spironolactone effect on LVEF

Compared with control, spironolactone increased LVEF in the overall group from baseline to month 9 by 1.1%, P =0.007. The effect of spironolactone on LVEF was more pronounced among patients with LVEF <60% at baseline (Tertile 1) =1.9% and less among patients with LVEF >65% at baseline (Tertile 3) =0.3%, but without significant spironolactone-by-LVEF interaction P =0.24. ***Figure 2***.

The effect of spironolactone on LVEF was not mediated statistically by reductions in BNP or COLA1A1. ***Supplemental Table 7***.

Spironolactone effect on main outcomes of interest by LVEF tertiles

The effect of spironolactone (vs. control) to reduce systolic blood pressure (SBP), PICP, NT-proBNP and left atrial volume indexed to body surface area (LAVi) was not modified by LVEF (interaction P >0.1 for all). ***Table 4***.

Discussion

Our study showed that among patients at risk of developing HF, those with higher LVEF had higher levels of circulating chemokines and inflammatory proteins and lower levels of BNP, collagen type I and proteins related to vascular and endothelial function. Spironolactone reduced the circulating levels of BNP, collagen type I, SBP, and LAVi, irrespective of LVEF, but it did not significantly change the levels of inflammatory proteins. In addition, spironolactone increased LVEF from baseline to month 9, an effect that was more pronounced among patients with lower baseline LVEF. These findings may help better understanding the pathophysiology of patients with preserved EF, particularly those with “supranormal” EF who may have a pro-inflammatory profile with lower expression of fibrosis and myocardial volume overload markers.

Patients with HFpEF and LVEF above 60-65% have been shown to experience an attenuated response to several agents that have been tested in HFpEF, at least regarding HF hospitalizations. The attenuated response at the higher end of LVEF was seen for candesartan in the CHARM-Preserved trial,[8] sacubitril/valsartan in the PARAGON-HF trial,[9] spironolactone in the TOPCAT trial,[6] and, more recently, empagliflozin in the EMPEROR-Preserved trial;[10] still, in EMPEROR-Preserved the attenuation of effect with empagliflozin seemed to have occurred only in patients with EF of 65% or greater.[11] The mechanisms by which patients at the higher end of the EF spectrum do not respond similarly to patients with lower EFs, using the same agents, are not well-established. Some studies have suggested that patients with higher EFs constitute a different phenotype with high ventricular-arterial stiffening with aging and hypertension as contributing factors (e.g., in HOMAGE the higher the LVEF the more frequent was the use of thiazide-type diuretics).[12] Such patients have smaller LV diameter and lower systolic and diastolic volumes; thus, the LV end-diastolic pressures may be lower.[13] Mechanistic studies have shown that patients with higher LVEF have a pro-inflammatory profile,[14] with lower expression of cardiac stretch and injury markers.[3, 15]

Patients participating in HOMAGE did not have overt HF signs and symptoms, but did have high natriuretic peptides and alterations of cardiac structure and function.[5] To a great extent, the present study replicates previous findings in HFpEF and expands the phenotyping of patients with “normal and supranormal” EF. In HOMAGE, compared to patients in the lower LVEF tertile (<60%), those in the upper tertile of LVEF (i.e., >65%) had smaller LV with lower systolic and diastolic volumes and natriuretic peptide levels, suggesting that these patients have lower LV end-diastolic pressures. The expression of chemokines and pro-inflammatory markers

(CCL23 and IL8) was also higher among patients in the upper LVEF tertile. CCL23 is a chemokine serving as chemotactic factor for monocytes/macrophages, dendritic cells and lymphocytes, which may play a role both as a circulating and tissue inflammatory molecule, up-regulating the release of pro-inflammatory cytokines such as TNFα.[16] IL8 is a major mediator of inflammatory response, involved in neutrophil chemotaxis, angiogenesis, atherogenesis, and cancer.[17] In patients with chronic HF, IL8 was independently associated with poor outcomes.[18] In HOMAGE, both the CCL23 and IL8 levels were not significantly modified by spironolactone.

Patients in the upper LVEF tertiles expressed lower circulating levels of BNP and collagen type I, which is also in concordance with prior HF studies showing that patients with higher EF had lower levels of cardiac stretch and injury markers.[3, 15, 19] In HOMAGE, spironolactone significantly reduced collagen type I-related biomarkers (both COL1A1 and PICP) and natriuretic peptides (both BNP and NT-pro BNP),[5, 20] irrespective of LVEF. The effect of spironolactone to reduce SBP and LAVi was also not influenced by baseline LVEF.

Beyond the lower levels of BNP and collagen type I, patients in the upper LVEF tertile also expressed lower circulating levels of TPA and ENRAGE. TPA is produced by vascular endothelial cells and activates clot dissolution in the presence of fibrin by converting plasminogen to plasmin.[21] Higher TPA levels have been associated with higher risk of cardiovascular events.[22] ENRAGE is involved in calcium-dependent signal transduction pathways and may act in the regulation of cytoskeletal components.[23] Higher ENRAGE levels have been associated with poor cardiovascular and HF outcomes.[24] In HOMAGE, both the TPA and ENRAGE levels were not significantly changed with spironolactone treatment.

LVEF was significantly increased with spironolactone treatment from baseline to month 9 (LVEF change =1.1%), despite the absence of a significant interaction, the effect of spironolactone to improve LVEF was more pronounced among patients in the lower LVEF tertile (LVEF <60%), who had more margin for improvement. Spironolactone has been shown to improve systolic function, determined by LV longitudinal strain, in the TOPCAT trial.[25] However, in a subset of 239 patients enrolled in TOPCAT, LVEF was not significantly improved with spironolactone treatment during 12 to 18 months (LVEF change: +0.6%, P =0.33).[26] In the ALDO-DHF trial, spironolactone improved LVEF at 12 months by +1.6% (P =0.04).[27] These findings, together with HOMAGE, suggest that spironolactone may have, at least, a modest effect to improve LVEF in patients with preserved ejection fraction.

Limitations

Despite the external replication of our main findings, these results should be regarded as hypothesis-generating given the post-hoc nature of our study, the relatively small sample size of LVEF tertiles, and the lack of mechanism confirmation at a cellular level. As per inclusion criteria, HOMAGE included only asymptomatic patients with a LVEF of 45% or greater and these findings cannot be generalized to symptomatic patients or those with lower ejection fractions; still, tertile 1 (LVEF <60%) include patients with “mildly reduced” or “mid-range” LVEF who may present a phenotype similar to patients with reduced EF.[28] We did not find treatment effect modification by LVEF categories (regarding collagen markers, natriuretic peptides and blood pressure); however, HOMAGE was a mechanistic trial to evaluate the impact of spironolactone on circulating collagen markers in a low-risk population who did not experience HF hospitalizations or fatal events. Therefore, the findings of TOPCAT could not be replicated herein.

Conclusions

In patients at risk of developing HF enrolled in the HOMAGE trial, those with higher LVEF had higher levels of circulating inflammatory markers and lower levels of stretch, injury, and fibrosis markers. These finding support a different phenotype of patients with “supranormal” EF, which may help explaining why such patients may not respond to HF therapies.

Ethics approval and consent to participate

The study was approved by all relevant ethics committees and regulatory bodies. All participants provided written informed consent prior to study specific procedures.

Consent for publication

There is no data of individual persons included in the manuscript.

Competing interests

The authors have no relevant conflicts of interest to disclose with regards to the content of this manuscript.

References

(1) Folse, R.; Braunwald, E. Determination of fraction of left ventricular volume ejected per beat and of ventricular end-diastolic and residual volumes. Experimental and clinical observations with a precordial dilution technic. *Circulation* **1962**, *25*, 674-685. DOI: 10.1161/01.cir.25.4.674 From NLM.
(2) McDonagh, T. A.; Metra, M.; Adamo, M.; Gardner, R. S.; Baumbach, A.; Böhm, M.; Burri, H.; Butler, J.; Čelutkienė, J.; Chioncel, O.; et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* **2021**, *42* (36), 3599-3726. DOI: 10.1093/eurheartj/ehab368 From NLM.
(3) Tromp, J.; Westenbrink, B. D.; Ouwerkerk, W.; van Veldhuisen, D. J.; Samani, N. J.; Ponikowski, P.; Metra, M.; Anker, S. D.; Cleland, J. G.; Dickstein, K.; et al. Identifying Pathophysiological Mechanisms in Heart Failure With Reduced Versus Preserved Ejection Fraction. *J Am Coll Cardiol* **2018**, *72* (10), 1081-1090. DOI: 10.1016/j.jacc.2018.06.050 From NLM.
(4) Pellicori, P.; Ferreira, J. P.; Mariottoni, B.; Brunner-La Rocca, H. P.; Ahmed, F. Z.; Verdonschot, J.; Collier, T.; Cuthbert, J. J.; Petutschnigg, J.; Mujaj, B.; et al. Effects of spironolactone on serum markers of fibrosis in people at high risk of developing heart failure: rationale, design and baseline characteristics of a proof-of-concept, randomised, precision-medicine, prevention trial. The Heart OMics in AGing (HOMAGE) trial. *Eur J Heart Fail* **2020**. DOI: 10.1002/ejhf.1716.
(5) Cleland, J. G. F.; Ferreira, J. P.; Mariottoni, B.; Pellicori, P.; Cuthbert, J.; Verdonschot, J. A. J.; Petutschnigg, J.; Ahmed, F. Z.; Cosmi, F.; Brunner La Rocca, H. P.; et al. The effect of spironolactone on cardiovascular function and markers of fibrosis in people at increased risk of developing heart failure: the heart 'OMics' in AGEing (HOMAGE) randomized clinical trial. *Eur Heart J* **2020**. DOI: 10.1093/eurheartj/ehaa758 From NLM.
(6) Solomon, S. D.; Claggett, B.; Lewis, E. F.; Desai, A.; Anand, I.; Sweitzer, N. K.; O'Meara, E.; Shah, S. J.; McKinlay, S.; Fleg, J. L.; et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. *Eur Heart J* **2016**, *37* (5), 455-462. DOI: 10.1093/eurheartj/ehv464 From NLM.
(7) Pitt, B.; Pfeffer, M. A.; Assmann, S. F.; Boineau, R.; Anand, I. S.; Claggett, B.; Clausell, N.; Desai, A. S.; Diaz, R.; Fleg, J. L.; et al. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* **2014**, *370* (15), 1383-1392. DOI: 10.1056/NEJMoa1313731 From NLM.
(8) Lund, L. H.; Claggett, B.; Liu, J.; Lam, C. S.; Jhund, P. S.; Rosano, G. M.; Swedberg, K.; Yusuf, S.; Granger, C. B.; Pfeffer, M. A.; et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. *Eur J Heart Fail* **2018**, *20* (8), 1230-1239. DOI: 10.1002/ejhf.1149 From NLM.
(9) Solomon, S. D.; Vaduganathan, M.; B, L. C.; Packer, M.; Zile, M.; Swedberg, K.; Rouleau, J.; M, A. P.; Desai, A.; Lund, L. H.; et al. Sacubitril/Valsartan Across the Spectrum of Ejection Fraction in Heart Failure. *Circulation* **2020**, *141* (5), 352-361. DOI: 10.1161/circulationaha.119.044586 From NLM.
(10) Packer, M.; Butler, J.; Zannad, F.; Filippatos, G.; Ferreira, J. P.; Pocock, S. J.; Carson, P.; Anand, I.; Doehner, W.; Haass, M.; et al. Effect of Empagliflozin on Worsening Heart Failure Events in Patients with Heart Failure and a Preserved Ejection Fraction: The EMPEROR-Preserved Trial. *Circulation* **2021**. DOI: 10.1161/circulationaha.121.056824 From NLM.

(11) Butler, J.; Packer, M.; Filippatos, G.; Ferreira, J. P.; Zeller, C.; Schnee, J.; Brueckmann, M.; Pocock, S. J.; Zannad, F.; Anker, S. D. Effect of empagliflozin in patients with heart failure across the spectrum of left ventricular ejection fraction. *Eur Heart J* **2021**. DOI: 10.1093/eurheartj/ehab798 From NLM.
(12) Kawaguchi, M.; Hay, I.; Fetics, B.; Kass, D. A. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. *Circulation* **2003**, *107* (5), 714-720. DOI: 10.1161/01.cir.0000048123.22359.a0 From NLM.
(13) Gori, M.; Iacovoni, A.; Senni, M. Haemodynamics of Heart Failure With Preserved Ejection Fraction: A Clinical Perspective. *Card Fail Rev* **2016**, *2* (2), 102-105. DOI: 10.15420/cfr.2016:17:2 From NLM.
(14) Paulus, W. J.; Tschope, C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* **2013**, *62* (4), 263-271. DOI: 10.1016/j.jacc.2013.02.092 From NLM.
(15) Tromp, J.; Khan, M. A.; Klip, I. T.; Meyer, S.; de Boer, R. A.; Jaarsma, T.; Hillege, H.; van Veldhuisen, D. J.; van der Meer, P.; Voors, A. A. Biomarker Profiles in Heart Failure Patients With Preserved and Reduced Ejection Fraction. *J Am Heart Assoc* **2017**, *6* (4). DOI: 10.1161/jaha.116.003989 From NLM.
(16) Hwang, J.; Son, K. N.; Kim, C. W.; Ko, J.; Na, D. S.; Kwon, B. S.; Gho, Y. S.; Kim, J. Human CC chemokine CCL23, a ligand for CCR1, induces endothelial cell migration and promotes angiogenesis. *Cytokine* **2005**, *30* (5), 254-263. DOI: 10.1016/j.cyto.2005.01.018 From NLM.
(17) Apostolakis, S.; Vogiatzi, K.; Amanatidou, V.; Spandidos, D. A. Interleukin 8 and cardiovascular disease. *Cardiovasc Res* **2009**, *84* (3), 353-360. DOI: 10.1093/cvr/cvp241 From NLM.
(18) Nymo, S. H.; Hulthe, J.; Ueland, T.; McMurray, J.; Wikstrand, J.; Askevold, E. T.; Yndestad, A.; Gullestad, L.; Aukrust, P. Inflammatory cytokines in chronic heart failure: interleukin-8 is associated with adverse outcome. Results from CORONA. *Eur J Heart Fail* **2014**, *16* (1), 68-75. DOI: 10.1093/eurjhf/hft125 From NLM.
(19) Martos, R.; Baugh, J.; Ledwidge, M.; O'Loughlin, C.; Conlon, C.; Patle, A.; Donnelly, S. C.; McDonald, K. Diastolic heart failure: evidence of increased myocardial collagen turnover linked to diastolic dysfunction. *Circulation* **2007**, *115* (7), 888-895. DOI: 10.1161/circulationaha.106.638569 From NLM.
(20) Ferreira, J. P.; Verdonschot, J.; Wang, P.; Pizard, A.; Collier, T.; Ahmed, F. Z.; Brunner-La-Rocca, H. P.; Clark, A. L.; Cosmi, F.; Cuthbert, J.; et al. Proteomic and Mechanistic Analysis of Spironolactone in Patients at Risk for HF. *JACC Heart Fail* **2021**. DOI: 10.1016/j.jchf.2020.11.010 From NLM.
(21) Danesh, J.; Whincup, P.; Walker, M.; Lennon, L.; Thomson, A.; Appleby, P.; Rumley, A.; Lowe, G. D. Fibrin D-dimer and coronary heart disease: prospective study and meta-analysis. *Circulation* **2001**, *103* (19), 2323-2327. DOI: 10.1161/01.cir.103.19.2323 From NLM.
(22) Tofler, G. H.; Massaro, J.; O'Donnell, C. J.; Wilson, P. W. F.; Vasan, R. S.; Sutherland, P. A.; Meigs, J. B.; Levy, D.; D'Agostino, R. B., Sr. Plasminogen activator inhibitor and the risk of cardiovascular disease: The Framingham Heart Study. *Thromb Res* **2016**, *140*, 30-35. DOI: 10.1016/j.thromres.2016.02.002 From NLM.
(23) Oesterle, A.; Bowman, M. A. S100A12 and the S100/Calgranulins: Emerging Biomarkers for Atherosclerosis and Possibly Therapeutic Targets. *Arterioscler*

Thromb Vasc Biol **2015**, *35* (12), 2496-2507. DOI: 10.1161/atvbaha.115.302072 From NLM.
(24) He, Y. Y.; Yan, W.; Liu, C. L.; Li, X.; Li, R. J.; Mu, Y.; Jia, Q.; Wu, F. F.; Wang, L. L.; He, K. L. Usefulness of S100A12 as a prognostic biomarker for adverse events in patients with heart failure. *Clin Biochem* **2015**, *48* (4-5), 329-333. DOI: 10.1016/j.clinbiochem.2014.11.016 From NLM. Saito, T.; Hojo, Y.; Ogoyama, Y.; Hirose, M.; Ikemoto, T.; Katsuki, T.; Shimada, K.; Kario, K. S100A12 as a marker to predict cardiovascular events in patients with chronic coronary artery disease. *Circ J* **2012**, *76* (11), 2647-2652. DOI: 10.1253/circj.cj-12-0093 From NLM.
(25) Shah, A. M.; Claggett, B.; Sweitzer, N. K.; Shah, S. J.; Anand, I. S.; Liu, L.; Pitt, B.; Pfeffer, M. A.; Solomon, S. D. Prognostic Importance of Impaired Systolic Function in Heart Failure With Preserved Ejection Fraction and the Impact of Spironolactone. *Circulation* **2015**, *132* (5), 402-414. DOI: 10.1161/circulationaha.115.015884 From NLM.
(26) Shah, A. M.; Claggett, B.; Sweitzer, N. K.; Shah, S. J.; Deswal, A.; Anand, I. S.; Fleg, J. L.; Pitt, B.; Pfeffer, M. A.; Solomon, S. D. Prognostic Importance of Changes in Cardiac Structure and Function in Heart Failure With Preserved Ejection Fraction and the Impact of Spironolactone. *Circ Heart Fail* **2015**, *8* (6), 1052-1058. DOI: 10.1161/circheartfailure.115.002249 From NLM.
(27) Edelmann, F.; Wachter, R.; Schmidt, A. G.; Kraigher-Krainer, E.; Colantonio, C.; Kamke, W.; Duvinage, A.; Stahrenberg, R.; Durstewitz, K.; Loffler, M.; et al. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. *Jama* **2013**, *309* (8), 781-791. DOI: 10.1001/jama.2013.905 From NLM.
(28) Savarese, G.; Stolfo, D.; Sinagra, G.; Lund, L. H. Heart failure with mid-range or mildly reduced ejection fraction. *Nat Rev Cardiol* **2021**, 1-17. DOI: 10.1038/s41569-021-00605-5 From NLM.

Table 1. Baseline patients' characteristics by tertiles of LVEF

Characteristic	LVEF tertiles			P-value
	<60%	60-65%	>65%	
N.	122	121	121	
Age, years	72.1 (68.3, 77.4)	73.4 (69.3, 78.7)	71.5 (68.2, 76.9)	0.12
Men, n (%)	94 (77.0%)	95 (78.5%)	84 (69.4%)	0.21
CAD, n. (%)	95 (77.9%)	90 (74.4%)	85 (70.2%)	0.40
Hypertension, n. (%)	88 (72.1%)	90 (74.4%)	98 (81.0%)	0.25
Diabetes, n. (%)	48 (39.3%)	52 (43.0%)	53 (43.8%)	0.76
BMI, Kg/m^2	27.4 (25.0, 30.2)	28.2 (25.1, 31.6)	28.3 (25.3, 31.8)	0.20
Waist circ., cm	100.0 (93.0, 108.0)	101.5 (95.0, 109.0)	101.5 (95.0, 111.0)	0.30
SBP, mmHg	140.0 (128.0, 152.0)	141.0 (130.0, 156.0)	142.0 (129.0, 159.0)	0.23
DBP, mmHg	79.0 (73.0, 85.0)	79.0 (72.0, 84.0)	77.0 (70.0, 84.0)	0.17
Heart rate, bpm	62.0 (56.0, 69.0)	58.0 (54.0, 65.0)	59.0 (54.0, 66.0)	0.022
LVEF, % *	55.0 (52.3, 58.1)	62.9 (61.6, 64.0)	68.5 (66.4, 71.5)	<0.001
LVMi, g/m^2	100.6 (87.6, 115.5)	93.8 (81.1, 111.8)	88.9 (77.8, 101.6)	0.001
LAVi, ml/m^2	31.2 (27.3, 37.2)	30.9 (24.3, 37.7)	30.6 (25.9, 35.6)	0.35
E/e'	9.1 (7.3, 11.9)	9.4 (7.9, 11.1)	9.5 (8.0, 11.6)	0.75
E/A ratio	0.8 (0.6, 1.0)	0.9 (0.7, 1.0)	0.9 (0.7, 1.0)	0.004
LVEDD, mm	49.4 (46.1, 53.9)	47.4 (44.2, 50.3)	46.5 (44.2, 50.2)	<0.001
LVEDV, ml/m^2	45.6 (38.3, 54.5)	41.7 (37.4, 48.5)	39.1 (33.3, 45.7)	<0.001
LVESV, ml/m^2	20.7 (16.8, 24.9)	15.6 (13.3, 18.0)	12.2 (9.8, 14.5)	<0.001
eGFR, $ml/min/1.73m^2$	75.5 (64.2, 85.3)	70.5 (60.9, 82.9)	76.1 (66.5, 88.1)	0.061
eGFR <60, n. (%)	21 (17.2%)	27 (22.3%)	22 (18.2%)	0.56
Urea, mmol/L	8.6 (5.7, 13.6)	10.0 (6.1, 15.0)	8.5 (5.8, 13.6)	0.13
Hemoglobin, g/dl	14.0 (13.1, 14.9)	14.3 (13.5, 15.2)	13.8 (13.0, 14.7)	0.064
Sodium, mmol/L	140.0 (138.0, 141.0)	140.0 (138.0, 141.0)	139.0 (137.0, 141.0)	0.13
Potassium, mmol/L	4.4 (4.1, 4.6)	4.3 (4.1, 4.6)	4.3 (4.1, 4.5)	0.36
NT-pro BNP, pg/mL	258.0 (153.4, 451.9)	194.0 (121.4, 298.8)	159.5 (111.8, 288.3)	<0.001
Anti-platelet, n. (%)	96 (78.7%)	97 (80.2%)	98 (81.0%)	0.90
Beta-blocker, n. (%)	86 (70.5%)	83 (68.6%)	85 (70.2%)	0.94
ACEi/ARB, n. (%)	91 (74.6%)	94 (77.7%)	93 (76.9%)	0.84
CCB, n. (%)	23 (18.9%)	22 (18.2%)	24 (19.8%)	0.95
Thiazide, n. (%)	15 (12.3%)	16 (13.2%)	28 (23.1%)	0.040
Statin, n. (%)	104 (85.2%)	99 (81.8%)	103 (85.1%)	0.71

Legend: CAD, coronary artery disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; LVM, left ventricular mass indexed to body surface area; LAV, left atrial volume indexed to body surface area; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; eGFR, estimated glomerular filtration rate; ACEi/ARB, angiotensin converting enzyme/angiotensin receptor blocker; CCB, calcium channel blocker; *LVEF analyzed by the Simpson bi-plane method.

Table 2. Top proteins associated with LVEF

Protein (Log_2 NPX)	**Coefficient (95%CI) LVEF: >65% vs. <60%**	**P-value**
CCL23	+1.79 (+0.95 to +2.63)	<0.0001
TPA	-0.83 (-1.27 to -0.39)	<0.0001
BNP	-0.46 (-0.75 to -0.18)	0.002
ENRAGE	-0.62 (-1.05 to -0.18)	0.005
COL1A1	-0.92 (-1.67 to -0.18)	0.015
IL8	+0.58 (+0.09 to +1.07)	0.019

Legend: CCL23, c-c motif chemokine ligand 23; TPA, tissue plasminogen activator; BNP, brain natriuretic peptide; ENRAGE, S100 calcium binding protein A12; COL1A1, collagen type I alpha 1 chain; IL8, interleukin 8.
LVEF obtained with Simpson bi-plane method.
Multivariable stepwise forward logistic regression model with age, sex, systolic blood pressure, heart rate, body mass index, and eGFR “forced” into the model, and all circulating proteins with a P-value of <0.05 in the 1-by-1 analysis entered in the model (BNP, NT-pro BNP, CCL23, COL1A1, TPA, TNFB, PICP, IL8, CD6, MCP3, ENRAGE, REN; see Supplemental Table 3).

Table 3. Effect of spironolactone on the top proteins associated with LVEF

Protein (Log_2 NPX)	**Month 1**	**Month 9**	**Treatment-by-LVEF interaction P**
CCL23	-0.04 (-0.11 to +0.02) P =0.21	+0.01 (-0.06 to +0.08) P =0.72	0.72
TPA	+0.03 (-0.15 to +0.21) P =0.74	+0.11 (-0.07 to +0.29) P =0.24	0.20
BNP	-0.45 (-0.61 to -0.29) P <0.0001	-0.36 (-0.52 to -0.19) P <0.0001	0.60
ENRAGE	+0.03 (-0.08 to +0.15) P =0.57	-0.05 (-0.16 to +0.06) P =0.39	0.60
COL1A1	-0.09 (-0.15 to -0.03) P =0.005	-0.16 (-0.23 to -0.10) P <0.0001	0.89
IL8	-0.01 (-0.12 to +0.09) P =0.81	-0.09 (-0.20 to +0.01) P =0.078	0.67

Legend: CCL23, c-c motif chemokine ligand 23; TPA, tissue plasminogen activator; BNP, brain natriuretic peptide; ENRAGE, S100 calcium binding protein A12; COL1A1, collagen type I alpha 1 chain; IL8, interleukin 8.
LVEF obtained with Simpson bi-plane method.
Caption: BNP and COL1A1 were decreased with spironolactone over time, without effect modification by LVEF.

Table 4. Effect of spironolactone on main outcomes by LVEF tertiles

Outcome/LVEF tertile	Coefficient (95%CI)	Treatment-by-LVEF interaction P
SBP change (mmHg)		
LVEF <60%	-7.3 (-13.1 to -1.5)	0.48
LVEF 60-65%	-12.1 (-17.7 to -6.6)	
LVEF >65%	-10.6 (-16.3 to -4.9)	
PICP change (µg/l)		
LVEF <60%	-12.4 (-20.0 to -5.0)	0.54
LVEF 60-65%	-7.6 (-15.2 to 0.0)	
LVEF >65%	-7.0 (-14.4 to +0.4)	
NT-pro BNP change (pg/ml)		
LVEF <60%	-78 (-194 to +39)	0.90
LVEF 60-65%	-99 (-215 to +18)	
LVEF >65%	-61 (-177 to +55)	
LAVi change (ml/m^2)		
LVEF <60%	-2.8 (-5.1 to -0.4)	0.76
LVEF 60-65%	-1.5 (-3.7 to +0.6)	
LVEF >65%	-2.0 (-4.3 to +0.3)	

Legend: SBP, systolic blood pressure; PICP, procollagen type I carboxy-terminal propeptide; LAVi, left atrial volume indexed to body surface area.
Change from baseline to month 9.

Figure 1. Network analysis relating the top proteins associated with LVEF

Legend: CCL23, c-c motif chemokine ligand 23; TPA, tissue plasminogen activator; BNP, brain natriuretic peptide; ENRAGE, S100 calcium binding protein A12; COL1A1, collagen type I alpha 1 chain; IL8, interleukin 8; REN, renin; MMP, matrix metalloproteinase; SPARC, secreted protein acidic and cysteine rich; DCN, decorin.

Figure 2. Spironolactone effect on LVEF by tertiles of LVEF

Legend: Ctrl, control; Spiro., spironolactone; 0, baseline; M1, month 1; M9, month 9.
Spironolactone vs. Control effect on LVEF:
Tertile 1 LVEF <60%:
M1 =+0.7 (-0.8 to +2.2) %, P =0.34; M9 =+1.9 (+0.5 to +3.4) %, P =0.011.
Tertile 2 LVEF 60-65%:
M1 =-1.2 (-2.6 to +0.3) %, P =0.12; M9 =+1.1 (-0.2 to +2.5) %, P =0.098.
Tertile 3 LVEF >65%:
M1 =-0.8 (-2.1 to +0.6) %, P =0.27; M9 =+0.3 (-1.1 to +1.7) %, P =0.64.
Spironolactone-by-LVEF interaction P =0.24.
Overall effect:
M1 =-0.4 (-1.3 to +0.4) %, P =0.31; M9 =+1.1 (+ 0.3 to +1.9) %, P =0.007.
Overall joint P-value =0.012.
Caption: Spironolactone improved LVEF from baseline to month 9.

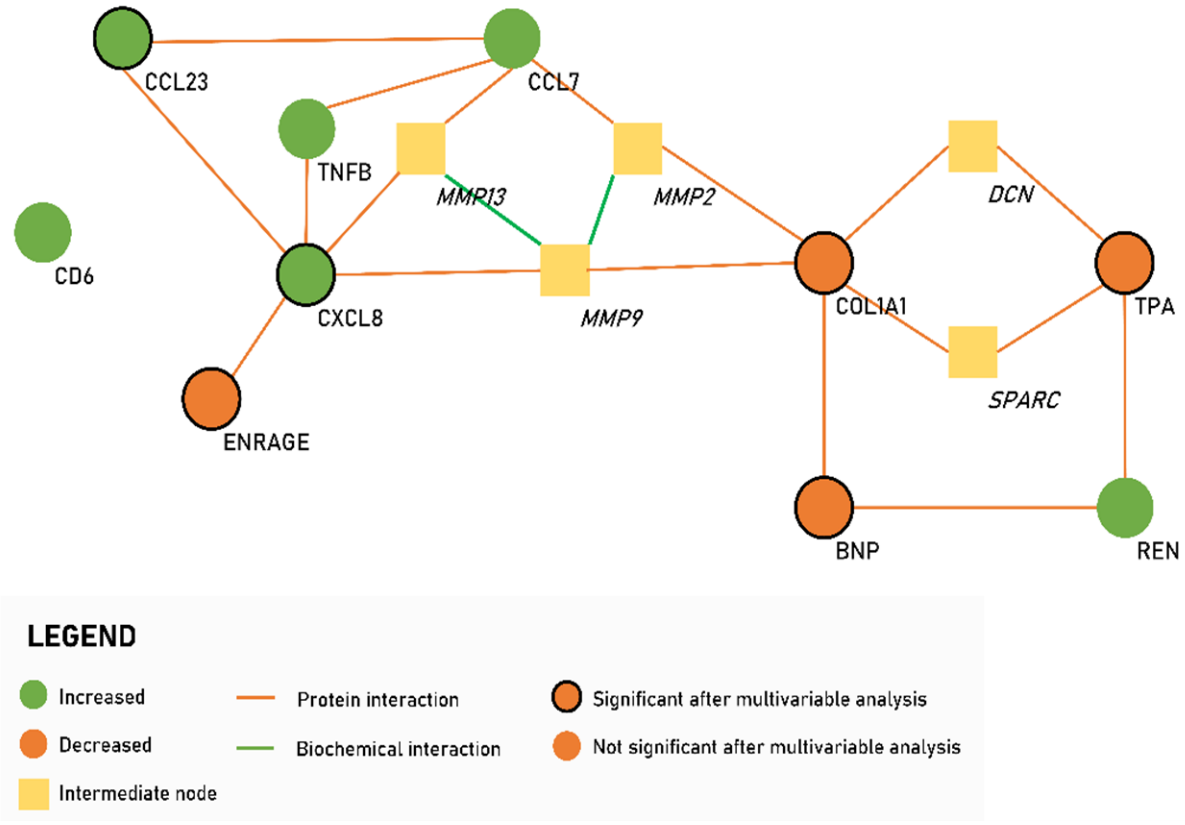

Figure 1

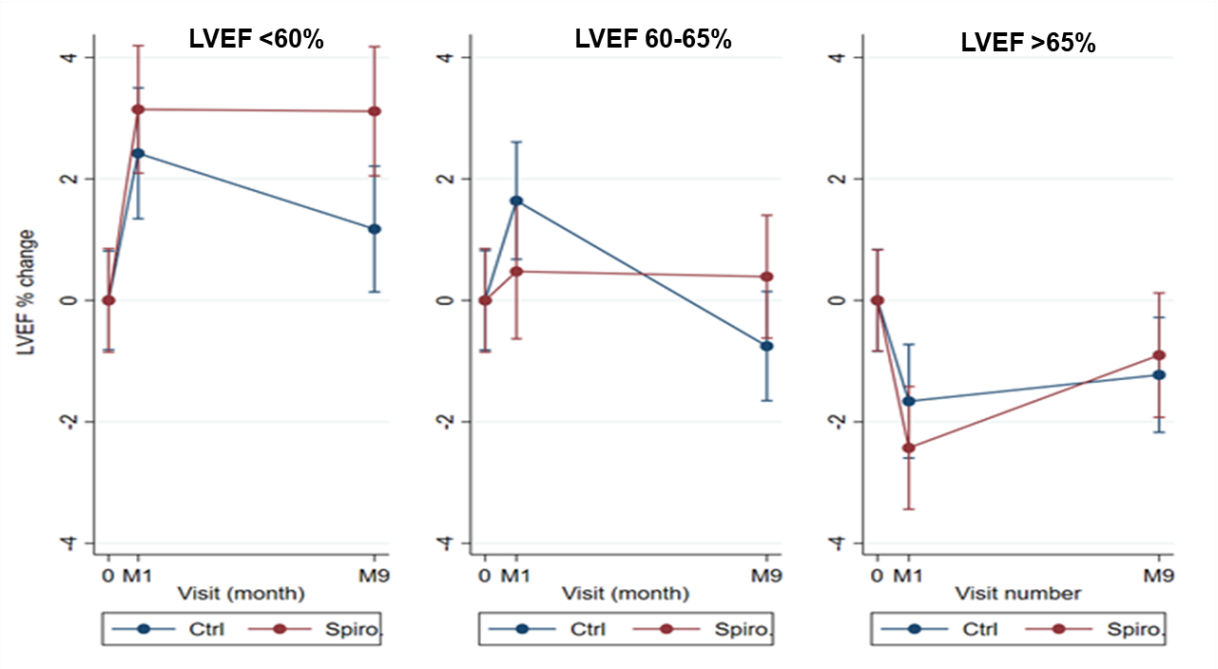

Figure 2

Supplemental Material

Supplemental Table 1. Protein names and respective Olink® panel sorted in alphabetical order

Protein full name	Entry name	Olink® Panel*	Uniprot ID**
Angiotensin-converting enzyme 2	ACE2	CVD II	Q9BYF1
Adenosine Deaminase	ADA	INF	P00813
Adisintegrin and metalloproteinase with thrombospondin motifs 13	ADAMTS13	CVD II	Q76LX8
ADM	ADM	CVD II	P35318
Agouti-related protein	AGRP	CVD II	O00253
CD166 antigen	ALCAM	CVD III	Q13740
Protein AMBP	AMBP	CVD II	P02760
Angiopoietin-1	ANG1	CVD II	Q15389
Aminopeptidase N	APN	CVD III	P15144
Axin-1	AXIN1	INF	O15169
Tyrosine-protein kinase receptor UFO	AXL	CVD III	P30530
Azurocidin	AZU1	CVD III	P20160
Brain-derived neurotrophic factor	BDNF	INF	P23560
Beta-nerve growth factor	BETANGF	INF	P01138
Bleomycin hydrolase	BLMHYDROLASE	CVD III	Q13867
Bone morphogenetic protein 6	BMP6	CVD II	P22004
Natriuretic peptides B	BNP	CVD II	P16860
Eukaryotic translation initiation factor 4E-binding protein 1	BP1_4E	INF	Q13541
Carbonic anhydrase 5A, mitochondrial	CA5A	CVD II	P35218
Caspase-3	CASP3	CVD III	P42574
Caspase 8	CASP8	INF	Q14790
Eotaxin-1	CCL11	INF	P51671
C-C motif chemokine 15	CCL15	CVD III	Q16663
C-C motif chemokine 16	CCL16	CVD III	O15467
C-C motif chemokine 17	CCL17	CVD II	Q92583
C-C motif chemokine 19	CCL19	INF	Q99731
C-C motif chemokine 20	CCL20	INF	P78556
C-C motif chemikine 22	CCL22	CVD III	O00626
C-C motif chemokine 23	CCL23	INF	P55773
C-C motif chemokine 24	CCL24	CVD III	O00175
C-C motif chemokine 25	CCL25	INF	O15444
C-C motif chemokine 28	CCL28	INF	Q9NRJ3
C-C motif chemokine 3	CCL3	CVD II	P10147
C-C motif chemokine 4	CCL4	INF	P13236
Scavenger receptor cysteine-rich type 1 protein M130	CD163	CVD III	Q86VB7
Natural killer cell receptor 2B4	CD244	INF	Q9BZW8
T-cell surface glycoprotein CD4	CD4	CVD II	P01730
CD40L receptor	CD40	INF	P25942
CD40 ligand	CD40L	CVD II	P29965
T-cell surface glycoprotein CD5	CD5	INF	P06127
T cell surface glycoprotein CD6	CD6	INF	P30203
SLAM family member 5	CD84	CVD II	Q9UIB8
Complement component C1q receptor	CD93	CVD III	Q9NPY3
CUB domain-containing protein 1	CDCP1	INF	Q9H5V8
Cadherin-5	CDH5	CVD III	P33151

Carcinoembryonic antigenrelated cell adhesion molecule 8	CEACAM8	CVD II	P31997
Chitinase-3-like protein 1	CHI3L1	CVD III	P36222
Chitotriosidase-1	CHIT1	CVD III	Q13231
Contactin-1	CNTN1	CVD III	Q12860
Collagen alpha-1(I) chain	COL1A1	CVD III	P02452
Carboxypeptidase A1	CPA1	CVD III	P15085
Carboxypeptidase B	CPB1	CVD III	P15086
Macrophage colony-stimulating factor 1	CSF1	INF	P09603
Cystatin D	CST5	INF	P28325
Cystatin-B	CSTB	CVD III	P04080
Chymotrypsin C	CTRC	CVD II	Q99895
Cathepsin D	CTSD	CVD III	P07339
Cathepsin L1	CTSL1	CVD II	P07711
Cathepsin Z	CTSZ	CVD III	Q9UBR2
Fractalkine	CX3CL1	INF	P78423
C-X-C motif chemokine 1 (CVD2)	CXCL1	CVD II	P09341
C-X-C motif chemokine 10	CXCL10	INF	P02778
C-X-C motif chemokine 11	CXCL11	INF	O14625
C-X-C motif chemokine 16	CXCL16	CVD III	Q9H2A7
C-X-C motif chemokine 5	CXCL5	INF	P42830
C-X-C motif chemokine 6	CXCL6	INF	P80162
C-X-C motif chemokine 9	CXCL9	INF	Q07325
Decorin	DCN	CVD II	P07585
2,4-dienoyl-CoA reductase, mitochondrial	DECR1	CVD II	Q16698
Dickkopf-related protein 1	DKK1	CVD II	O94907
Azurocidin	DLK1	CVD III	P80370
Delta and Notch-like epidermal growth factor-related receptor	DNER	INF	Q8NFT8
Epidermal growth factor receptor	EGFR	CVD III	P00533
Protein S100-A12	ENRAGE	INF	P80511
Epithelial cell adhesion molecule	EPCAM	CVD III	P16422
Ephrin type-B receptor 4	EPHB4	CVD III	P54760
Fatty acid-binding protein, intestinal	FABP2	CVD II	P12104
Fatty acid-binding protein, adipocyte	FABP4	CVD III	P15090
Tumor necrosis factor receptor superfamily member 6	FAS	CVD III	P25445
Fibroblast growth factor 19	FGF19	INF	O95750
Fibroblast growth factor 21 (CVD2)	FGF21	CVD II	Q9NSA1
Fibroblast growth factor 23 (CVD2)	FGF23	CVD II	Q9GZV9
Fibroblast growth factor 5	FGF5	INF	P12034
Fms-related tyrosine kinase 3 ligand	FLT3L	INF	P49771
Follistatin	FS	CVD II	P19883
Galectin-3	GAL3	CVD III	P17931
Galectin-4	GAL4	CVD III	P56470
Galectin-9	GAL9	CVD II	O00182
Growth/differentiation factor 15	GDF15	CVD III	Q99988
Growth/differentiation factor 2	GDF2	CVD II	Q9UK05
Growth hormone	GH	CVD II	P01241
Gastric intrinsic factor	GIF	CVD II	P27352
Lactoylglutathione lyase	GLO1	CVD II	Q04760
Granulins	GRN	CVD III	P28799

Gastrotropin	GT	CVD II	P51161
Hydroxyacid oxidase 1	HAOX1	CVD II	Q9UJM8
Proheparin-binding EGF-like growth factor	HBEGF	CVD II	Q99075
Glial cell line-derived neurotrophic factor	HGDNF	INF	P39905
Hepatocyte growth factor	HGF	INF	P14210
Heme oxygenase 1	HO1	CVD II	P09601
Osteoclast-associated immunoglobulin-like receptor	HOSCAR	CVD II	Q8IYS5
Heat shock 27 kDa protein	HSP27	CVD II	P04792
Intercellular adhesion molecule 2	ICAM2	CVD III	P13598
Alpha-L-iduronidase	IDUA	CVD II	P35475
Insulin-like growth factor-binding protein 1	IGFBP1	CVD III	P08833
Insulin-like Growth Factor-Binding Protein 2	IGFBP2	CVD III	P18065
Insulin-like growth factor-binding protein 7	IGFBP7	CVD III	Q16270
Low affinity immunoglobulin gamma Fc region receptor II-b	IGGFCRECEPTORIIB	CVD II	P31994
Interleukin-10	IL10	INF	P22301
Interleukin-10 receptor subunit alpha	IL10RA	INF	Q13651
Interleukin-10 receptor subunit beta	IL10RB	INF	Q08334
Interleukin-12 subunit beta	IL12B	INF	P29460
Interleukin-13	IL13	INF	P35225
Interleukin-15 receptor subunit alpha	IL15RA	INF	Q13261
Pro-interleukin-16	IL16	CVD II	Q14005
Interleukin-17A	IL17A	INF	Q16552
Interleukin-17C	IL17C	INF	Q9P0M4
Interleukin-17D	IL17D	CVD II	Q8TAD2
Interleukin-17 receptor A	IL17RA	CVD III	Q96F46
Interleukin-18 (CVD2)	IL18	CVD II	Q14116
Interleukin-18-binding protein	IL18BP	CVD III	O95998
Interleukin-18 receptor 1	IL18R1	INF	Q13478
Interleukin-1 receptor antagonist protein	IL1RA	CVD II	P18510
Interleukin-1 receptor-like 2	IL1RL2	CVD II	Q9HB29
Interleukin-1 receptor type 1	IL1RT1	CVD III	P14778
Interleukin-1 receptor type 2	IL1RT2	CVD III	P27930
Interleukin-20 receptor subunit alpha	IL20RA	INF	Q9UHF4
Interleukin-27	IL27	CVD II	Q8NEV9
Interleukin-2 receptor subunit alpha	IL2RA	CVD III	P01589
Interleukin-4 receptor subunit alpha	IL4RA	CVD II	P24394
Interleukin-6 (CVD2)	IL6	CVD II	P05231
Interleukin-6 receptor subunit alpha	IL6RA	CVD III	P08887
Interleukin-7	IL7	INF	P13232
Interleukin-8	IL8	INF	P10145
Melusin	ITGB1BP2	CVD II	Q9UKP3
Integrin beta-2	ITGB2	CVD III	P05107
Junctional adhesion molecule A	JAMA	CVD III	Q9Y624
Kidney injury molecule 1	KIM1	CVD II	Q96D42
Kallikrein-6	KLK6	CVD III	Q92876
Latency-associated peptide transforming growth factor beta 1	LAPTGFBETA1	INF	P01137
Low-density lipoprotein receptor	LDLRECEPTOR	CVD III	P01130
Leptin	LEP	CVD II	P41159

Leukemia inhibitory factor receptor	LIFR	INF	P42702
Lectin-like oxidized LDL receptor 1	LOX1	CVD II	P78380
Lipoprotein lipase	LPL	CVD II	P06858
Lymphotoxin-beta receptor	LTBR	CVD III	P36941
Macrophage receptor MARCO	MARCO	CVD II	Q9UEW3
Myoglobin	MB	CVD III	P02144
Monocyte chemotactic protein 1	MCP1_CVD3	CVD III	P13500
Monocyte chemotactic protein 2	MCP2	INF	P80075
Monocyte chemotactic protein 3	MCP3	INF	P80098
Monocyte chemotactic protein 4	MCP4	INF	Q99616
Matrix extracellular phosphoglycoprotein	MEPE	CVD III	Q9NQ76
Tyrosine-protein kinase Mer	MERTK	CVD II	Q12866
Matrix metalloproteinase-1	MMP1	INF	P03956
Matrix metalloproteinase-10	MMP10	INF	P09238
Matrix metalloproteinase-12	MMP12	CVD II	P39900
Matrix metalloproteinase-2	MMP2	CVD III	P08253
Matrix metalloproteinase-3	MMP3	CVD III	P08254
Matrix metalloproteinase-7	MMP7	CVD II	P09237
Matrix metalloproteinase-9	MMP9	CVD III	P14780
Myeloperoxidase	MPO	CVD III	P05164
NF-kappa-B essential modulator	NEMO	CVD II	Q9Y6K9
Neurogenic locus notch homolog protein 3	NOTCH3	CVD III	Q9UM47
Neurotrophin-3	NT3	INF	P20783
N-terminal prohormone brain natriuretic peptide	NTPROBNP	CVDII	P16860
Osteoprotegerin	OPG_CVD3	CVD III	O00300
Osteopontin	OPN	CVD III	P10451
Oncostatin-M	OSM	INF	P13725
Plasminogen activator inhibitor 1	PAI	CVD III	P05121
Pappalysin-1	PAPPA	CVD II	Q13219
Proteinase-activated receptor 1	PAR1	CVD II	P25116
Poly [ADP-ribose] polymerase 1	PARP1	CVD II	P09874
Proprotein convertase subtilisin/kexin type 9	PCSK9	CVD III	Q8NBP7
Platelet-derived growth factor subunit A	PDGFSUBUNITA	CVD III	P04085
Platelet-derived growth factor subunit B	PDGFSUBUNITB	CVD II	P01127
Programmed cell death 1 ligand 1	PDL1	INF	Q9NZQ7
Programmed cell death 1 ligand 2	PDL2	CVD II	Q9BQ51
Platelet endothelial cell adhesion molecule	PECAM1	CVD III	P16284
Peptidoglycan recognition protein 1	PGLYRP1	CVD III	O75594
Elafin	PI3	CVD III	P19957
Polymeric immunoglobulin receptor	PIGR	CVD II	P01833
Perlecan	PLC	CVD III	P98160
Placenta growth factor	PLGF	CVD II	P49763
Paraoxonase (PON 3)	PON3	CVD III	Q15166
Prolargin	PRELP	CVD II	P51888
Brother of CDO	PROTEINBOC	CVD II	Q9BWV1
Serine protease 27	PRSS27	CVD II	Q9BQR3
Prostasin	PRSS8	CVD II	Q16651
Myeloblastin	PRTN3	CVD III	P24158

P-selectin glycoprotein ligand 1	PSGL1	CVD II	Q14242
Pulmonary surfactant-associated protein D	PSPD	CVD III	P35247
Pentraxin-related protein PTX3	PTX3	CVD II	P26022
Receptor for advanced glycosylation end products	RAGE	CVD II	Q15109
Retinoic acid receptor responder protein 2	RARRES2	CVD III	Q99969
Renin	REN	CVD II	P00797
Resistin	RETN	CVD III	Q9HD89
Stem cell factor (CVD2)	SCF	CVD II	P21583
Secretoglobin family 3A member 2	SCGB3A2	CVD III	Q96PL1
E-selectin	SELE	CVD III	P16581
P-selectin	SELP	CVD III	P16109
Serpin A12	SERPINA12	CVD II	Q8IW75
Tyrosine-protein phosphatase non-receptor type substrate 1	SHPS1	CVD III	P78324
SIR2-like protein 2	SIRT2	INF	Q8IXJ6
Signaling lymphocytic activation molecule	SLAMF1	INF	Q13291
SLAM family member 7	SLAMF7	CVD II	Q9NQ25
Superoxide dismutase [Mn], mitochondrial	SOD2	CVD II	P04179
Sortilin	SORT1	CVD II	Q99523
Spondin-1	SPON1	CVD III	Q9HCB6
Spondin-2	SPON2	CVD II	Q9BUD6
Proto-oncogene tyrosine-protein kinase Src	SRC	CVD II	P12931
Sulfotransferase 1A1	ST1A1	INF	P50225
ST2 protein	ST2	CVD III	Q01638
STAM-binding protein	STAMPB	INF	O95630
Serine/threonine-protein kinase 4	STK4	CVD II	Q13043
Tissue factor	TF	CVD II	P13726
Trefoil factor 3	TFF3	CVD III	Q07654
Tissue factor pathway inhibitor	TFPI	CVD III	P10646
Transforming growth factor alpha	TGFALPHA	INF	P01135
Protein-glutamine gamma-glutamyltransferase 2	TGM2	CVD II	P21980
Thrombospondin-2	THBS2	CVD II	P35442
Thrombopoietin	THPO	CVD II	P40225
Angiopoietin-1 receptor	TIE2	CVD II	Q02763
Metalloproteinase inhibitor 4	TIMP4	CVD III	Q99727
Trem-like transcript 2 protein	TLT2	CVD III	Q5T2D2
Thrombomodulin	TM	CVD II	P07204
Tumor necrosis factor	TNF	INF	P01375
TNF-beta	TNFB	INF	P01374
Tumor necrosis factor receptor 1	TNFR1	CVD III	P19438
Tumor necrosis factor receptor 2	TNFR2	CVD III	P20333
Tumor necrosis factor receptor superfamily member 10A	TNFRSF10A	CVD II	O00220
Tumor necrosis factor receptor superfamily member 10C	TNFRSF10C	CVD III	O14798
Tumor necrosis factor receptor superfamily member 11A	TNFRSF11A	CVD II	Q9Y6Q6
Tumor necrosis factor receptor superfamily member 13B	TNFRSF13B	CVD II	O14836
Tumor necrosis factor receptor superfamily member 14	TNFRSF14	CVD III	Q92956

Tumor necrosis factor receptor superfamily member 9	TNFRSF9	INF	Q07011
Tumor necrosis factor ligand superfamily member 13B	TNFSF13B	CVD III	Q9Y275
Tumor necrosis factor ligand superfamily member 14	TNFSF14	INF	O43557
Tissue-type plasminogen activator	TPA	CVD III	P00750
Transferrin receptor protein 1	TR	CVD III	P02786
TNF-related apoptosis-inducing ligand	TRAIL	INF	P50591
TNF-related apoptosis-inducing ligand receptor 2	TRAILR2	CVD II	O14763
TNF-related activation-induced cytokine	TRANCE	INF	O14788
Tartrate-resistant acid phosphatase type 5	TRAP	CVD III	P13686
Tumor necrosis factor (Ligand) superfamily, member 12	TWEAK	INF	O43508
Urokinase-type plasminogen activator	UPA_CVD3	CVD III	P00749
Urokinase plasminogen activator surface receptor	UPAR	CVD III	Q03405
Vascular endothelial growth factor A	VEGFA	INF	P15692
Vascular endothelial growth factor D	VEGFD	CVD II	O43915
V-set and immunoglobulin domain-containing protein 2	VSIG2	CVD II	Q96IQ7
von Willebrand factor	VWF	CVD III	P04275
Lymphotactin	XCL1	CVD II	P47992

Supplemental Table 2. Baseline patients' characteristics by tertiles of LVEF

Characteristic	LVEF tertiles			P-value
	<60%	60-65%	>65%	
N.	152	152	152	
Age, years	72.8 (68.5, 78.1)	72.6 (68.4, 77.8)	72.8 (68.0, 78.0)	0.99
Men, n (%)	124 (81.6%)	111 (73.0%)	109 (71.7%)	0.095
CAD, n. (%)	114 (75.0%)	114 (75.0%)	107 (70.4%)	0.58
Hypertension, n. (%)	117 (77.0%)	109 (71.7%)	126 (82.9%)	0.067
Diabetes, n. (%)	57 (37.5%)	60 (39.5%)	71 (46.7%)	0.23
BMI, Kg/m^2	27.4 (25.3, 31.2)	28.0 (25.0, 31.5)	28.3 (25.3, 31.8)	0.70
Waist circ., cm	101.5 (93.0, 110.0)	100.5 (95.0, 109.0)	102.0 (95.0, 111.0)	0.46
SBP, mmHg	140.0 (128.0, 154.0)	139.0 (126.0, 156.0)	144.5 (130.0, 159.0)	0.098
DBP, mmHg	80.0 (73.0, 88.0)	78.0 (70.0, 84.0)	76.5 (70.0, 84.0)	0.008
Heart rate, bpm	63.0 (56.0, 69.0)	59.0 (54.0, 65.0)	59.0 (54.0, 66.0)	0.031
LVEF, % *	53.9 (49.6, 57.0)	62.6 (61.3, 64.2)	69.3 (67.5, 71.9)	<0.001
LVM, g/m^2	96.9 (84.2, 113.8)	91.8 (79.1, 109.4)	93.8 (79.0, 112.3)	0.099
LAV, ml/m^2	30.4 (25.5, 36.5)	29.8 (25.3, 35.3)	30.7 (25.6, 37.1)	0.80
E/e'	8.9 (7.3, 11.5)	9.3 (7.7, 11.3)	9.6 (7.9, 11.8)	0.30
E/A ratio	0.8 (0.7, 1.0)	0.9 (0.7, 1.0)	0.9 (0.7, 1.1)	0.004
LVEDD, mm	49.8 (46.2, 54.0)	46.9 (43.6, 50.1)	46.5 (44.0, 50.6)	<0.001
LVEDV, ml/m^2	46.6 (37.0, 54.5)	40.6 (35.2, 47.7)	40.8 (34.6, 47.6)	<0.001
LVESV, ml/m^2	20.8 (17.1, 25.4)	15.5 (12.9, 17.8)	12.3 (10.0, 14.5)	<0.001
eGFR, ml/min/1.73m^2	70.6 (62.5, 83.1)	72.3 (61.5, 86.3)	74.2 (63.3, 86.0)	0.50
eGFR <60, n. (%)	33 (21.7%)	30 (19.7%)	32 (21.1%)	0.91
Urea, mmol/L	8.4 (5.8, 14.3)	8.0 (5.7, 13.6)	8.9 (5.8, 13.9)	0.93
Hemoglobin, g/dl	14.0 (13.3, 14.9)	14.0 (13.1, 15.0)	13.8 (12.9, 14.7)	0.20
Sodium, mmol/L	140.0 (138.0, 141.0)	139.5 (138.0, 141.0)	139.0 (138.0, 141.0)	0.34
Potassium, mmol/L	4.4 (4.1, 4.6)	4.3 (4.1, 4.6)	4.3 (4.1, 4.5)	0.54
NT-pro BNP, pg/mL	251.8 (160.5, 405.5)	183.9 (121.4, 293.4)	196.4 (128.9, 303.2)	<0.001
Anti-platelet, n. (%)	112 (73.7%)	120 (78.9%)	125 (82.2%)	0.19
Beta-blocker, n. (%)	110 (72.4%)	103 (67.8%)	108 (71.1%)	0.66
ACEi/ARB, n. (%)	123 (80.9%)	115 (75.7%)	118 (77.6%)	0.53
CCB, n. (%)	28 (18.4%)	32 (21.1%)	32 (21.1%)	0.80
Thiazide, n. (%)	22 (14.5%)	20 (13.2%)	33 (21.7%)	0.096
Statin, n. (%)	122 (80.3%)	126 (82.9%)	132 (86.8%)	0.30

Legend: CAD, coronary artery disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; LVM, left ventricular mass indexed to body surface area; LVH, left ventricular hypertrophy; LAV, left atrial volume indexed to body surface area; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; eGFR, estimated glomerular filtration rate; ACEi/ARB, angiotensin converting enzyme/angiotensin receptor blocker; CCB, calcium channel blocker; *LVEF analyzed in 4 cavities.

Supplemental Table 3. Association of circulating proteins with LVEF (logistic regression: upper vs. lower tertile) assessed with the Simpson bi-plane method

Protein	Coefficient (95%CI) LVEF: >65% vs. <60%	P-value
BNP	-0.44 (-0.7 to -0.19)	0.0006
NTPROBNP	-0.56 (-0.9 to -0.22)	0.0014
CCL23	0.91 (0.29 to 1.53)	0.0041
COL1A1	-0.91 (-1.55 to -0.26)	0.0057
TPA	-0.47 (-0.81 to -0.13)	0.0065
TNFB	0.82 (0.2 to 1.45)	0.0101
PICP	-0.74 (-1.35 to -0.13)	0.0183
IL8	0.5 (0.08 to 0.91)	0.0195
CD6	0.57 (0.04 to 1.09)	0.0334
MCP3	0.55 (0.04 to 1.06)	0.0358
ENRAGE	-0.39 (-0.75 to -0.02)	0.0382
REN	0.32 (0 to 0.63)	0.0482
ST1A1	0.3 (0 to 0.61)	0.051
NOTCH3	-0.71 (-1.42 to 0)	0.0514
MEPE	-0.69 (-1.38 to 0.01)	0.0536
CCL3	0.42 (-0.01 to 0.85)	0.0573
HOSCAR	-1.04 (-2.12 to 0.04)	0.0602
NRTN	-1.13 (-2.38 to 0.11)	0.0751
IL1RA	0.46 (-0.06 to 0.98)	0.0813
TGFALPHA	-0.74 (-1.58 to 0.1)	0.0833
TRAIL	0.8 (-0.12 to 1.71)	0.0874
PAR1	0.5 (-0.08 to 1.08)	0.0901
GAL3	-0.6 (-1.29 to 0.1)	0.0918
SPON1	-0.72 (-1.56 to 0.12)	0.0936
CD5	0.52 (-0.09 to 1.13)	0.096
MCP1	0.53 (-0.1 to 1.17)	0.0973
OPG	0.58 (-0.13 to 1.28)	0.1085
TROPONIN T	-0.31 (-0.7 to 0.07)	0.1131
STK4	0.17 (-0.04 to 0.38)	0.1145
IL18R1	0.47 (-0.12 to 1.05)	0.1216
TR	-0.31 (-0.7 to 0.08)	0.1221
PGF	0.66 (-0.19 to 1.52)	0.1275
OPN	-0.44 (-1 to 0.13)	0.1291
PDL2	0.57 (-0.18 to 1.32)	0.1343
TFF3	0.45 (-0.15 to 1.05)	0.1392
CXCL16	0.7 (-0.24 to 1.63)	0.1439
CCL4	0.3 (-0.1 to 0.7)	0.1465
FGF19	-0.23 (-0.53 to 0.08)	0.1466
IL13	-0.33 (-0.79 to 0.12)	0.1513
MCP2	0.31 (-0.11 to 0.73)	0.1528
TFPI	0.47 (-0.18 to 1.13)	0.1577
LAPTGFBETA1	0.42 (-0.17 to 1)	0.1623

DLK1	0.32 (-0.13 to 0.76)	0.1632
FGF23	-0.37 (-0.89 to 0.16)	0.1688
IL17C	-0.3 (-0.73 to 0.13)	0.1711
BOC	0.59 (-0.26 to 1.44)	0.1739
CSF1	0.76 (-0.34 to 1.87)	0.1765
CSF1	0.76 (-0.34 to 1.87)	0.1765
GDF2	0.47 (-0.21 to 1.16)	0.1766
ALCAM	0.64 (-0.29 to 1.58)	0.1769
OPG	0.51 (-0.25 to 1.26)	0.191
CDCP1	0.29 (-0.15 to 0.73)	0.1983
CCL17	0.16 (-0.08 to 0.4)	0.2004
VWF	-0.13 (-0.34 to 0.07)	0.2016
IL1RL2	0.41 (-0.23 to 1.04)	0.2074
CX3CL1	0.4 (-0.23 to 1.03)	0.2093
IL20	0.5 (-0.29 to 1.28)	0.2135
CITP	-0.33 (-0.85 to 0.2)	0.2252
CCL15	-0.33 (-0.88 to 0.21)	0.2288
GDNF	0.38 (-0.24 to 1)	0.233
MMP9	-0.41 (-1.07 to 0.26)	0.2334
AMBP	0.87 (-0.56 to 2.3)	0.2348
PIGR	-0.95 (-2.53 to 0.63)	0.2373
LEP	0.23 (-0.15 to 0.6)	0.2377
IL2RA	-0.37 (-0.99 to 0.25)	0.2397
CPB1	-0.21 (-0.57 to 0.15)	0.2455
IL1RT2	0.42 (-0.29 to 1.12)	0.2463
TRAILR2	0.4 (-0.28 to 1.09)	0.2495
FABP4	0.29 (-0.2 to 0.77)	0.2502
NEMO	0.12 (-0.08 to 0.31)	0.2539
LIF	-0.89 (-2.43 to 0.64)	0.2546
MCP4	0.23 (-0.17 to 0.63)	0.2595
IFNGAMMA	46.67 (-34.5 to 5127.89)	0.2601
PGLYRP1	-0.28 (-0.78 to 0.22)	0.2663
CXCL1	0.11 (-0.08 to 0.3)	0.2673
BMP6	0.29 (-0.23 to 0.82)	0.2685
GH	0.08 (-0.06 to 0.23)	0.2705
CD163	0.3 (-0.24 to 0.84)	0.2709
TM	0.46 (-0.36 to 1.29)	0.2714
DKK1	0.21 (-0.17 to 0.59)	0.2752
FABP2	0.17 (-0.14 to 0.49)	0.28
SRC	0.14 (-0.11 to 0.39)	0.2812
CSTB	0.33 (-0.27 to 0.93)	0.282
PAPPA	-0.26 (-0.74 to 0.22)	0.2831
CXCL1	0.11 (-0.09 to 0.31)	0.2841
CD40	0.32 (-0.27 to 0.9)	0.2882
IL18	-0.27 (-0.79 to 0.24)	0.2923
CXCL6	0.16 (-0.14 to 0.47)	0.2927

IL18	-0.27 (-0.77 to 0.23)	0.2955
CXCL9	0.21 (-0.19 to 0.6)	0.302
PRELP	-0.64 (-1.87 to 0.58)	0.3049
AXIN1	0.1 (-0.09 to 0.29)	0.307
GT	0.19 (-0.18 to 0.55)	0.3098
CHIT1	-0.12 (-0.35 to 0.11)	0.3133
MCP1	0.28 (-0.27 to 0.82)	0.3189
CST5	0.25 (-0.27 to 0.77)	0.3436
FGF23	-0.24 (-0.75 to 0.26)	0.3458
MARCO	0.54 (-0.58 to 1.67)	0.3462
CD40L	0.09 (-0.1 to 0.28)	0.3512
IL12B	0.19 (-0.21 to 0.59)	0.3541
OSM	-0.14 (-0.43 to 0.16)	0.355
CXCL5	0.07 (-0.08 to 0.21)	0.3556
CA5A	0.13 (-0.15 to 0.42)	0.3615
GRN	0.34 (-0.4 to 1.07)	0.3662
IL5	0.12 (-0.15 to 0.39)	0.3726
UPA	0.34 (-0.41 to 1.1)	0.3741
SHPS1	0.29 (-0.35 to 0.92)	0.3791
TF	0.36 (-0.45 to 1.16)	0.3837
CXCL10	0.16 (-0.2 to 0.53)	0.3869
CPA1	-0.14 (-0.47 to 0.18)	0.3875
IGGFCRECEPTORIIB	0.14 (-0.17 to 0.45)	0.3876
IL24	0.21 (-0.27 to 0.69)	0.3929
ANG1	0.09 (-0.12 to 0.29)	0.3935
CD244	0.26 (-0.35 to 0.88)	0.4009
TNFRSF11A	0.28 (-0.39 to 0.95)	0.4069
IL6	-0.15 (-0.5 to 0.21)	0.4208
IL1RT1	-0.3 (-1.02 to 0.43)	0.4264
TNFRSF10C	-0.22 (-0.75 to 0.32)	0.4269
TNFRSF14	0.23 (-0.34 to 0.79)	0.4284
BETANGF	-0.29 (-1.01 to 0.43)	0.4285
PRSS8	0.32 (-0.48 to 1.12)	0.4301
CASP8	0.17 (-0.26 to 0.61)	0.432
FGF5	0.71 (-1.07 to 2.49)	0.4354
PARP1	0.15 (-0.23 to 0.53)	0.4369
IL27	-0.27 (-0.96 to 0.41)	0.4373
CNTN1	-0.27 (-0.97 to 0.42)	0.4397
DECR1	0.07 (-0.11 to 0.25)	0.4406
VEGFD	0.28 (-0.44 to 1)	0.4478
GP6	-0.12 (-0.44 to 0.2)	0.4538
TNFR2	0.24 (-0.39 to 0.88)	0.4546
CD8A	-0.15 (-0.53 to 0.24)	0.4554
TRAP	0.26 (-0.42 to 0.94)	0.457
CCL19	0.11 (-0.19 to 0.41)	0.4645
TSLP	-0.59 (-2.16 to 0.99)	0.4648

IL6	-0.13 (-0.48 to 0.22)	0.4662
MMP3	0.16 (-0.28 to 0.6)	0.4682
IDUA	0.21 (-0.36 to 0.78)	0.469
TRANCE	0.16 (-0.28 to 0.6)	0.469
EPHB4	-0.3 (-1.12 to 0.52)	0.4758
SLAMF7	0.13 (-0.24 to 0.51)	0.4827
TGM2	-0.1 (-0.39 to 0.19)	0.4827
CXCL11	0.11 (-0.19 to 0.4)	0.4834
HAOX1	0.07 (-0.13 to 0.27)	0.484
GAL4	0.15 (-0.27 to 0.58)	0.4879
VEGFA	0.27 (-0.49 to 1.02)	0.4885
TNFRSF10A	0.24 (-0.45 to 0.93)	0.4923
ADA	0.21 (-0.4 to 0.82)	0.4973
LOX1	-0.15 (-0.59 to 0.29)	0.4989
ICAM2	-0.21 (-0.81 to 0.4)	0.5041
CD4	-0.28 (-1.12 to 0.56)	0.5093
TLT2	-0.17 (-0.69 to 0.34)	0.5113
IL22RA1	-0.29 (-1.14 to 0.57)	0.5132
FAS	0.23 (-0.46 to 0.92)	0.5134
HBEGF	0.12 (-0.24 to 0.48)	0.5165
MMP2	-0.23 (-0.94 to 0.48)	0.5187
ITGB1BP2	0.06 (-0.13 to 0.25)	0.5252
SCF	-0.25 (-1.02 to 0.52)	0.5279
APN	0.24 (-0.53 to 1.02)	0.5357
CTSD	-0.17 (-0.73 to 0.39)	0.5413
SERPINA12	-0.12 (-0.52 to 0.28)	0.5502
SCGB3A2	-0.11 (-0.47 to 0.25)	0.5536
CCL11	-0.18 (-0.76 to 0.41)	0.555
PDGFSUBUNITB	0.05 (-0.12 to 0.22)	0.5631
IL33	0.76 (-1.82 to 3.35)	0.5633
MMP7	0.15 (-0.36 to 0.65)	0.5637
IL7	0.09 (-0.22 to 0.41)	0.5683
SCF_INF	-0.22 (-0.99 to 0.54)	0.5709
TIMP4	-0.16 (-0.74 to 0.41)	0.5758
IGFBP1	0.08 (-0.21 to 0.38)	0.579
FS	-0.18 (-0.81 to 0.46)	0.5841
CCL24	-0.08 (-0.38 to 0.22)	0.591
ADM	0.22 (-0.58 to 1.01)	0.5912
MMP10	-0.13 (-0.58 to 0.33)	0.5923
TNFSF13B	-0.17 (-0.81 to 0.46)	0.5951
CTSZ	0.18 (-0.51 to 0.88)	0.6066
TNFSF14	0.12 (-0.34 to 0.57)	0.6083
ITGB2	0.15 (-0.42 to 0.72)	0.61
SOD2	-0.55 (-2.67 to 1.57)	0.6112
PSPD	0.08 (-0.22 to 0.37)	0.6141
CD93	-0.21 (-1.03 to 0.61)	0.616

PAI	-0.06 (-0.3 to 0.18)	0.6187
DNER	0.24 (-0.7 to 1.17)	0.6203
SELE	0.1 (-0.32 to 0.52)	0.6281
PDL1	0.16 (-0.49 to 0.81)	0.6285
RETN	-0.12 (-0.59 to 0.36)	0.6299
STAMBP	0.06 (-0.19 to 0.32)	0.6319
IL4RA	-0.17 (-0.9 to 0.57)	0.6518
IL18BP	0.16 (-0.56 to 0.89)	0.6551
THPO	0.16 (-0.55 to 0.87)	0.6556
IL10RB	0.17 (-0.6 to 0.95)	0.6617
KIM1	-0.07 (-0.39 to 0.25)	0.6663
LDLRECEPTOR	0.11 (-0.4 to 0.63)	0.668
RARRES2	0.18 (-0.63 to 0.98)	0.6704
FLT3L	0.12 (-0.42 to 0.66)	0.6722
MPO	0.2 (-0.74 to 1.14)	0.6767
JAMA	0.05 (-0.17 to 0.26)	0.6798
IL6RA	-0.13 (-0.75 to 0.49)	0.682
EPCAM	-0.06 (-0.33 to 0.22)	0.6847
HGF	0.14 (-0.53 to 0.81)	0.689
SLAMF1	-0.09 (-0.53 to 0.35)	0.6929
LTBR	-0.15 (-0.92 to 0.62)	0.7037
PDGFSUBUNITA	0.04 (-0.18 to 0.27)	0.704
ARTN	0.13 (-0.52 to 0.78)	0.7042
TNF	-0.16 (-1.02 to 0.69)	0.7059
CASP3	0.03 (-0.14 to 0.21)	0.7098
SIRT2	0.04 (-0.15 to 0.22)	0.7102
TNFR1	0.14 (-0.59 to 0.86)	0.7103
ST2	-0.09 (-0.6 to 0.41)	0.7169
SORT1	0.17 (-0.74 to 1.07)	0.7188
PRTN3	0.16 (-0.76 to 1.08)	0.7301
CCL20	0.05 (-0.22 to 0.31)	0.739
CD84	0.08 (-0.41 to 0.58)	0.7406
CCL16	0.07 (-0.36 to 0.51)	0.7407
PON3	0.08 (-0.4 to 0.56)	0.7417
IL4	0.07 (-0.34 to 0.48)	0.7426
PTX3	-0.09 (-0.65 to 0.47)	0.7475
GLO1	0.06 (-0.29 to 0.4)	0.7505
GIF	0.04 (-0.2 to 0.27)	0.7509
IL1ALPHA	-0.13 (-0.91 to 0.65)	0.7528
IGFBP7	0.11 (-0.58 to 0.81)	0.7534
MMP1	-0.04 (-0.29 to 0.21)	0.7561
THBS2	-0.16 (-1.23 to 0.91)	0.7683
GAL9	-0.13 (-1.01 to 0.74)	0.7692
IL15RA	0.13 (-0.79 to 1.06)	0.7759
AXL	-0.1 (-0.79 to 0.59)	0.7795
CHI3L1	-0.04 (-0.33 to 0.25)	0.782

PI3	0.06 (-0.39 to 0.5)	0.7934
SELP	0.04 (-0.26 to 0.33)	0.7949
NT3	-0.06 (-0.55 to 0.43)	0.7967
BLMHYDROLASE	0.07 (-0.5 to 0.65)	0.7978
FGF21	0.03 (-0.18 to 0.23)	0.8039
DCN	-0.1 (-0.91 to 0.7)	0.8058
IL17A	-0.04 (-0.37 to 0.29)	0.8075
AGRP	-0.06 (-0.58 to 0.45)	0.8096
KLK6	-0.08 (-0.72 to 0.57)	0.8107
TNFRSF9	0.07 (-0.51 to 0.65)	0.8113
HO1	-0.08 (-0.75 to 0.59)	0.814
FGF21	0.03 (-0.2 to 0.26)	0.8154
PCSK9	-0.09 (-0.82 to 0.65)	0.8166
MERTK	0.08 (-0.61 to 0.77)	0.8169
PLC	0.11 (-0.88 to 1.1)	0.8275
BP1	-0.03 (-0.35 to 0.28)	0.8316
AZU1	0.04 (-0.35 to 0.43)	0.8326
LIFR	0.09 (-0.76 to 0.95)	0.8327
UPA	0.07 (-0.63 to 0.76)	0.8473
PSGL1	0.08 (-0.8 to 0.96)	0.8624
RAGE	0.05 (-0.61 to 0.72)	0.8711
IL16	0.04 (-0.5 to 0.59)	0.8802
SPON2	-0.1 (-1.42 to 1.22)	0.8828
IL10RA	0.03 (-0.41 to 0.47)	0.8881
IL17D	-0.05 (-0.84 to 0.73)	0.8935
PRSS27	-0.04 (-0.58 to 0.5)	0.8942
GDF15	-0.03 (-0.45 to 0.39)	0.8955
MMP12	-0.02 (-0.39 to 0.35)	0.8979
ADAMTS13	0.07 (-1.04 to 1.19)	0.8982
CCL28	-0.05 (-0.81 to 0.71)	0.8984
CCL25	-0.03 (-0.55 to 0.49)	0.8993
CDH5	-0.04 (-0.73 to 0.65)	0.9019
CTRC	0.02 (-0.31 to 0.36)	0.9035
VSIG2	0.02 (-0.39 to 0.44)	0.9079
TNFRSF13B	-0.04 (-0.66 to 0.59)	0.9116
LPL	-0.02 (-0.56 to 0.51)	0.9352
TIE2	-0.04 (-0.93 to 0.86)	0.9356
PECAM1	0.01 (-0.29 to 0.32)	0.9384
CEACAM8	-0.01 (-0.44 to 0.42)	0.9603
HSP27	0.01 (-0.53 to 0.55)	0.9668
ACE2	0.01 (-0.39 to 0.41)	0.9694
IGFBP2	0.01 (-0.46 to 0.48)	0.9698
CTSL1	-0.01 (-0.78 to 0.76)	0.9712
TWEAK	-0.01 (-0.77 to 0.74)	0.9744
EGFR	0.02 (-0.99 to 1.02)	0.9752
IL17RA	0.01 (-0.43 to 0.44)	0.9775

IL2RB	0.01 (-0.66 to 0.68)	0.9813
MB	0.01 (-0.44 to 0.45)	0.9814
XCL1	0 (-0.46 to 0.45)	0.9838
P3NP	0 (-0.45 to 0.46)	0.9929
IL20RA	0 (-0.64 to 0.65)	0.994
IL10	0 (-0.39 to 0.39)	0.9984
UPAR	0 (-0.7 to 0.7)	0.9997
IL2	0 (0 to 0)	1

Supplemental Table 4. Association of circulating proteins with LVEF (ordered logistic regression: per tertile increase) assessed with the Simpson bi-plane method

Protein	Coefficient (95%CI) Ordered logistic	P-value
BNP	-0.31 (-0.5 to -0.13)	0.0008
NTPROBNP	-0.4 (-0.65 to -0.14)	0.0023
CCL23	0.68 (0.24 to 1.13)	0.0027
TNFB	0.65 (0.2 to 1.1)	0.0046
CD6	0.55 (0.16 to 0.93)	0.0056
IL8	0.43 (0.12 to 0.75)	0.0071
TPA	-0.32 (-0.55 to -0.08)	0.0094
MCP3	0.45 (0.11 to 0.78)	0.0098
CCL3	0.35 (0.06 to 0.64)	0.0194
COL1A1	-0.56 (-1.05 to -0.08)	0.0229
ST1A1	0.25 (0.03 to 0.47)	0.0274
CD5	0.55 (0.06 to 1.04)	0.0278
REN	0.27 (0.02 to 0.51)	0.0348
PICP	-0.47 (-0.93 to -0.02)	0.0405
PGF	0.63 (0.01 to 1.25)	0.045
PAR1	0.45 (0.01 to 0.88)	0.0452
TFPI	0.5 (0 to 1)	0.0515
LAPTGFBETA1	0.43 (0 to 0.86)	0.0524
CSF1	0.79 (-0.01 to 1.6)	0.0531
CSF1	0.79 (-0.01 to 1.6)	0.0531
IL18R1	0.44 (-0.01 to 0.88)	0.0534
TRAIL	0.67 (-0.01 to 1.34)	0.0536
IL1RA	0.35 (-0.01 to 0.71)	0.0566
OPG	0.52 (-0.03 to 1.08)	0.0636
MCP1	0.41 (-0.03 to 0.84)	0.065
ENRAGE	-0.23 (-0.48 to 0.02)	0.0674
CDCP1	0.29 (-0.03 to 0.61)	0.0772
CCL4	0.25 (-0.03 to 0.53)	0.0777
CXCL16	0.65 (-0.08 to 1.38)	0.0799
TFF3	0.41 (-0.05 to 0.87)	0.0815
NOTCH3	-0.48 (-1.02 to 0.06)	0.0831
STK4	0.13 (-0.02 to 0.29)	0.0917
ALCAM	0.6 (-0.1 to 1.3)	0.0927
PDL2	0.45 (-0.08 to 0.99)	0.0952
GAL3	-0.42 (-0.91 to 0.08)	0.0978
TRAILR2	0.45 (-0.09 to 0.99)	0.1033
IL13	-0.15 (-0.35 to 0.04)	0.1162
IL20	0.47 (-0.12 to 1.06)	0.1212
CX3CL1	0.33 (-0.1 to 0.77)	0.1344
CSTB	0.33 (-0.1 to 0.77)	0.1365
BOC	0.5 (-0.16 to 1.15)	0.1379
SPON1	-0.47 (-1.1 to 0.15)	0.1395

MCP2	0.23 (-0.08 to 0.53)	0.1417
CD40	0.34 (-0.11 to 0.79)	0.1427
CCL17	0.14 (-0.05 to 0.32)	0.1428
IL1RT2	0.41 (-0.14 to 0.97)	0.145
DKK1	0.2 (-0.07 to 0.48)	0.1491
MEPE	-0.36 (-0.85 to 0.13)	0.1506
TROPONIN	-0.21 (-0.5 to 0.08)	0.1517
CXCL6	0.16 (-0.06 to 0.37)	0.1562
IL1RL2	0.34 (-0.13 to 0.81)	0.1569
CXCL1	0.11 (-0.04 to 0.25)	0.1605
OPG	0.41 (-0.17 to 0.99)	0.1643
TM	0.42 (-0.18 to 1.02)	0.1674
CST5	0.28 (-0.12 to 0.68)	0.1725
CXCL9	0.2 (-0.09 to 0.49)	0.1765
BMP6	0.28 (-0.13 to 0.68)	0.1771
TNFRSF11A	0.33 (-0.15 to 0.81)	0.1814
PARP1	0.2 (-0.09 to 0.49)	0.1838
NRTN	-0.32 (-0.79 to 0.15)	0.1856
DLK1	0.23 (-0.12 to 0.58)	0.1893
GDF2	0.33 (-0.17 to 0.82)	0.194
CD163	0.27 (-0.14 to 0.68)	0.1945
GDNF	0.33 (-0.17 to 0.83)	0.1952
AMBP	0.69 (-0.36 to 1.74)	0.1962
TNFRSF10A	0.36 (-0.19 to 0.9)	0.198
VWF	-0.1 (-0.25 to 0.05)	0.1998
CD244	0.31 (-0.16 to 0.78)	0.1998
NEMO	0.09 (-0.05 to 0.24)	0.2019
MCP4	0.18 (-0.1 to 0.47)	0.2023
CA5A	0.15 (-0.08 to 0.38)	0.2043
TRAP	0.33 (-0.18 to 0.84)	0.2106
CXCL5	0.07 (-0.04 to 0.18)	0.216
TNFR2	0.29 (-0.17 to 0.74)	0.2171
CASP8	0.2 (-0.12 to 0.51)	0.2235
GT	0.17 (-0.1 to 0.43)	0.2236
FGF23	-0.24 (-0.64 to 0.15)	0.2239
GRN	0.34 (-0.21 to 0.89)	0.2255
HOSCAR	-0.46 (-1.21 to 0.28)	0.2258
TNFRSF14	0.27 (-0.17 to 0.7)	0.2277
FGF5	0.78 (-0.49 to 2.04)	0.2291
VEGFA	0.33 (-0.21 to 0.88)	0.2299
MMP9	-0.3 (-0.79 to 0.19)	0.2349
MCP1	0.19 (-0.13 to 0.51)	0.2351
LIF	-0.29 (-0.78 to 0.2)	0.2407
HBEGF	0.16 (-0.11 to 0.43)	0.2421
AXIN1	0.08 (-0.06 to 0.22)	0.243
ANG1	0.09 (-0.06 to 0.24)	0.2538

CD40L	0.08 (-0.06 to 0.21)	0.2538
MARCO	0.49 (-0.36 to 1.35)	0.2567
LEP	0.15 (-0.11 to 0.41)	0.2584
TGFALPHA	-0.36 (-0.98 to 0.27)	0.2632
IL12B	0.16 (-0.12 to 0.44)	0.2712
FABP2	0.13 (-0.11 to 0.37)	0.2739
CXCL10	0.14 (-0.11 to 0.39)	0.2792
IL24	0.21 (-0.17 to 0.58)	0.2807
ADA	0.25 (-0.2 to 0.69)	0.2817
FGF19	-0.12 (-0.33 to 0.1)	0.2826
PDL1	0.27 (-0.22 to 0.76)	0.2865
CCL15	-0.23 (-0.65 to 0.19)	0.2874
CXCL11	0.11 (-0.09 to 0.31)	0.2895
SRC	0.1 (-0.08 to 0.28)	0.2981
IL18BP	0.29 (-0.25 to 0.83)	0.2989
SHPS1	0.25 (-0.23 to 0.72)	0.3026
TR	-0.15 (-0.45 to 0.14)	0.3036
TNFSF14	0.18 (-0.16 to 0.51)	0.3058
IL5	0.11 (-0.1 to 0.32)	0.3172
MMP3	0.16 (-0.16 to 0.49)	0.3174
GH	0.05 (-0.05 to 0.16)	0.3183
IFNGAMMA	0.85 (-0.83 to 2.52)	0.3204
IL17C	-0.15 (-0.45 to 0.15)	0.3272
PAPPA	-0.17 (-0.52 to 0.18)	0.3393
SORT1	0.31 (-0.32 to 0.93)	0.3395
FABP4	0.16 (-0.17 to 0.5)	0.3455
ITGB1BP2	0.07 (-0.07 to 0.2)	0.3475
TF	0.29 (-0.31 to 0.88)	0.3485
CPB1	-0.13 (-0.41 to 0.15)	0.3527
CITP	-0.18 (-0.58 to 0.21)	0.3565
FAS	0.24 (-0.27 to 0.75)	0.3613
CNTN1	-0.25 (-0.79 to 0.29)	0.3664
PRELP	-0.45 (-1.43 to 0.54)	0.3708
APN	0.28 (-0.33 to 0.88)	0.3728
IL15RA	0.33 (-0.39 to 1.04)	0.3755
IL7	0.11 (-0.13 to 0.34)	0.3778
IGGFCRECEPTORIIB	0.1 (-0.13 to 0.34)	0.3802
IL10RB	0.26 (-0.32 to 0.84)	0.3824
SLAMF7	0.12 (-0.16 to 0.41)	0.386
VEGFD	0.22 (-0.27 to 0.7)	0.386
CTSZ	0.21 (-0.28 to 0.7)	0.3962
TRANCE	0.13 (-0.17 to 0.44)	0.3966
THPO	0.23 (-0.3 to 0.75)	0.3988
LIFR	0.26 (-0.35 to 0.87)	0.4033
STAMBP	0.08 (-0.11 to 0.27)	0.4041
DECR1	0.05 (-0.07 to 0.18)	0.4059

GLO1	0.11 (-0.15 to 0.36)	0.4069
IL2RA	-0.16 (-0.55 to 0.23)	0.4091
PDGFSUBUNITB	0.05 (-0.07 to 0.18)	0.4182
CD84	0.16 (-0.23 to 0.54)	0.4261
CCL20	0.08 (-0.11 to 0.27)	0.4295
PGLYRP1	-0.15 (-0.53 to 0.23)	0.431
GAL4	0.13 (-0.2 to 0.46)	0.4349
TNFRSF10C	-0.16 (-0.55 to 0.24)	0.436
RARRES2	0.25 (-0.38 to 0.88)	0.437
ITGB2	0.16 (-0.25 to 0.57)	0.4377
CCL24	-0.08 (-0.3 to 0.13)	0.4426
PRSS8	0.23 (-0.36 to 0.82)	0.4457
UPA	0.21 (-0.33 to 0.74)	0.4478
TGM2	-0.09 (-0.32 to 0.14)	0.4507
TNFR1	0.21 (-0.34 to 0.75)	0.4582
HGF	0.17 (-0.27 to 0.61)	0.4582
CPA1	-0.1 (-0.36 to 0.16)	0.4607
FGF23	-0.15 (-0.54 to 0.24)	0.4645
IL22RA1	-0.2 (-0.73 to 0.33)	0.4676
HAOX1	0.06 (-0.1 to 0.21)	0.4697
OSM	-0.08 (-0.3 to 0.14)	0.4719
TNFRSF9	0.16 (-0.29 to 0.6)	0.4863
ADM	0.2 (-0.37 to 0.77)	0.4931
JAMA	0.06 (-0.11 to 0.23)	0.4949
IDUA	0.15 (-0.28 to 0.58)	0.4984
PIGR	-0.39 (-1.53 to 0.75)	0.5008
PON3	0.12 (-0.22 to 0.46)	0.5014
OPN	-0.14 (-0.54 to 0.27)	0.5068
SIRT2	0.05 (-0.09 to 0.19)	0.5079
SCGB3A2	-0.1 (-0.39 to 0.2)	0.5193
DNER	0.22 (-0.45 to 0.88)	0.5195
PRTN3	0.21 (-0.44 to 0.87)	0.5258
CCL19	0.07 (-0.14 to 0.28)	0.526
PDGFSUBUNITA	0.06 (-0.12 to 0.23)	0.5304
IGFBP1	0.07 (-0.14 to 0.27)	0.539
CASP3	0.04 (-0.09 to 0.17)	0.5402
MERTK	0.16 (-0.35 to 0.66)	0.5412
ARTN	0.18 (-0.41 to 0.77)	0.5459
GIF	0.05 (-0.12 to 0.22)	0.548
FGF21	0.05 (-0.1 to 0.2)	0.5495
MPO	0.21 (-0.47 to 0.88)	0.5503
SELP	0.07 (-0.16 to 0.3)	0.5612
VSIG2	0.09 (-0.21 to 0.38)	0.5634
IL16	0.12 (-0.28 to 0.51)	0.5634
MMP7	0.12 (-0.28 to 0.51)	0.564
CTSL1	0.16 (-0.4 to 0.72)	0.5741

TSLP	-0.2 (-0.91 to 0.5)	0.5751
BLMHYDROLASE	0.12 (-0.31 to 0.56)	0.5776
IGFBP7	0.16 (-0.42 to 0.75)	0.589
RAGE	0.13 (-0.37 to 0.62)	0.6155
SELE	0.08 (-0.24 to 0.4)	0.6196
EPCAM	-0.05 (-0.25 to 0.15)	0.6209
IL4	0.1 (-0.29 to 0.48)	0.6246
PLC	0.19 (-0.58 to 0.96)	0.6287
IL1ALPHA	-0.17 (-0.84 to 0.51)	0.6295
TLT2	-0.09 (-0.46 to 0.28)	0.6309
IL6	-0.06 (-0.31 to 0.19)	0.6311
IL18	-0.08 (-0.43 to 0.27)	0.657
CD93	-0.14 (-0.75 to 0.48)	0.6573
CHIT1	-0.03 (-0.19 to 0.12)	0.6579
UPAR	0.12 (-0.41 to 0.65)	0.6579
LDLRECEPTOR	0.09 (-0.31 to 0.48)	0.6684
IL33	0.41 (-1.45 to 2.26)	0.6693
IL20RA	0.08 (-0.27 to 0.43)	0.6697
FS	-0.1 (-0.56 to 0.36)	0.6709
PRSS27	0.08 (-0.3 to 0.46)	0.6761
ICAM2	-0.09 (-0.53 to 0.34)	0.6764
SCF	-0.11 (-0.65 to 0.43)	0.6866
CCL11	-0.09 (-0.51 to 0.34)	0.688
LOX1	-0.07 (-0.39 to 0.26)	0.69
IL27	-0.1 (-0.57 to 0.38)	0.6942
PECAM1	0.05 (-0.19 to 0.29)	0.6961
IL1RT1	-0.11 (-0.65 to 0.43)	0.7003
IL18	-0.07 (-0.42 to 0.28)	0.7029
NT3	-0.07 (-0.41 to 0.28)	0.7035
TWEAK	0.11 (-0.45 to 0.66)	0.7062
BETANGF	-0.12 (-0.72 to 0.49)	0.7099
MMP10	-0.07 (-0.41 to 0.28)	0.7111
RETN	-0.07 (-0.44 to 0.3)	0.7132
IL2	14.3 (-63.77 to 92.36)	0.7196
CTSD	-0.08 (-0.51 to 0.36)	0.732
GP6	-0.04 (-0.27 to 0.19)	0.7341
IL10RA	0.05 (-0.26 to 0.37)	0.7348
PSPD	0.04 (-0.19 to 0.27)	0.7375
MMP2	-0.1 (-0.66 to 0.47)	0.7413
CDH5	0.09 (-0.43 to 0.61)	0.7414
AZU1	0.05 (-0.23 to 0.33)	0.7422
ACE2	0.05 (-0.27 to 0.38)	0.7444
CTRC	0.04 (-0.2 to 0.28)	0.7457
SOD2	-0.25 (-1.74 to 1.25)	0.7472
TIE2	0.11 (-0.56 to 0.78)	0.7482
IL2RB	0.09 (-0.49 to 0.68)	0.753

PI3	0.06 (-0.3 to 0.41)	0.7576
DCN	0.1 (-0.52 to 0.71)	0.7599
AGRP	0.06 (-0.32 to 0.43)	0.7601
IGFBP2	0.05 (-0.3 to 0.41)	0.7604
LPL	0.06 (-0.33 to 0.44)	0.7625
CEACAM8	0.05 (-0.28 to 0.38)	0.776
FLT3L	0.06 (-0.38 to 0.5)	0.7823
IL17RA	0.05 (-0.28 to 0.37)	0.7866
GDF15	0.04 (-0.27 to 0.35)	0.7879
CD8A	-0.04 (-0.31 to 0.24)	0.7888
KLK6	0.06 (-0.39 to 0.51)	0.7949
SERPINA12	-0.04 (-0.3 to 0.23)	0.7952
SCF	-0.07 (-0.59 to 0.46)	0.8001
IL17A	-0.03 (-0.28 to 0.22)	0.8055
CD4	-0.08 (-0.75 to 0.59)	0.808
P3NP	0.04 (-0.31 to 0.4)	0.817
TIMP4	-0.05 (-0.45 to 0.36)	0.8225
IL4RA	-0.06 (-0.63 to 0.5)	0.8283
PSGL1	0.07 (-0.57 to 0.7)	0.841
THBS2	-0.09 (-0.93 to 0.76)	0.8411
KIM1	-0.02 (-0.27 to 0.22)	0.8448
HSP27	0.04 (-0.35 to 0.43)	0.8466
TNFSF13B	-0.05 (-0.52 to 0.43)	0.851
IL10	0.02 (-0.24 to 0.29)	0.855
BP1_4E	0.02 (-0.21 to 0.25)	0.8616
IL6RA	-0.04 (-0.51 to 0.43)	0.8671
GAL9	0.05 (-0.59 to 0.7)	0.8678
EGFR	0.06 (-0.71 to 0.84)	0.8698
MB	0.03 (-0.31 to 0.36)	0.8738
AXL	0.04 (-0.49 to 0.57)	0.8829
PAI	-0.01 (-0.21 to 0.18)	0.8926
MMP1	0.01 (-0.17 to 0.19)	0.9026
CHI3L1	0.01 (-0.2 to 0.22)	0.9118
CCL28	0.03 (-0.54 to 0.61)	0.9131
SPON2	0.06 (-0.96 to 1.08)	0.9134
CCL16	0.02 (-0.27 to 0.3)	0.9152
PCSK9	0.03 (-0.52 to 0.57)	0.9176
EPHB4	-0.03 (-0.6 to 0.54)	0.9197
TNFRSF13B	0.02 (-0.41 to 0.45)	0.9234
CCL25	0.02 (-0.38 to 0.41)	0.9282
SLAMF1	-0.02 (-0.34 to 0.31)	0.9285
PTX3	0.02 (-0.43 to 0.47)	0.9297
IL17D	0.02 (-0.39 to 0.42)	0.942
TNF	-0.01 (-0.45 to 0.43)	0.9543
MMP12	0.01 (-0.28 to 0.29)	0.9553
UPA	0.01 (-0.44 to 0.46)	0.9634

ST2	-0.01 (-0.39 to 0.38)	0.9731
XCL1	0 (-0.36 to 0.35)	0.9787
ADAMTS13	-0.01 (-0.82 to 0.8)	0.9851
LTBR	0 (-0.55 to 0.54)	0.9885
HO1	0 (-0.5 to 0.5)	0.9966

Supplemental Table 5. Association of circulating proteins with LVEF (logistic regression: upper vs. lower tertile) assessed with 4 cavities view

Protein	Coefficient (95%CI) LVEF: >65% vs. <60%	P-value
BNP	-0.32 (-0.55 to -0.1)	0.0053
NTPROBNP	-0.43 (-0.74 to -0.12)	0.006
REN	0.38 (0.09 to 0.68)	0.0098
COL1A1	-0.75 (-1.34 to -0.16)	0.0133
PAPPA	-0.54 (-0.99 to -0.1)	0.0173
PICP	-0.64 (-1.17 to -0.1)	0.0198
NOTCH3	-0.74 (-1.39 to -0.09)	0.0255
IL17RA	-0.46 (-0.87 to -0.05)	0.0266
CNTN1	-0.75 (-1.44 to -0.05)	0.0346
ENRAGE	-0.32 (-0.61 to -0.02)	0.0378
MEPE	-0.62 (-1.25 to 0.01)	0.0528
STK4	0.19 (0 to 0.38)	0.0536
IL5	0.23 (-0.01 to 0.47)	0.0603
IGGFCRECEPTORIIB	0.28 (-0.02 to 0.57)	0.064
TPA	-0.27 (-0.56 to 0.02)	0.069
PAR1	0.47 (-0.04 to 0.98)	0.0699
HOSCAR	-0.84 (-1.78 to 0.11)	0.0822
MCP3	0.39 (-0.05 to 0.83)	0.0855
GAL4	0.35 (-0.05 to 0.76)	0.0865
TFF3	0.44 (-0.09 to 0.97)	0.1029
SRC	0.19 (-0.04 to 0.42)	0.1046
GT	0.28 (-0.06 to 0.63)	0.1055
FGF21_INF	0.17 (-0.04 to 0.39)	0.1118
HAOX1	0.15 (-0.04 to 0.34)	0.1179
CDH5	-0.53 (-1.19 to 0.14)	0.1212
FGF21	0.15 (-0.04 to 0.34)	0.1242
TNFB	0.43 (-0.12 to 0.97)	0.1265
PSPD	0.22 (-0.07 to 0.51)	0.1383
TROPONIN	-0.28 (-0.66 to 0.1)	0.143
VWF	-0.13 (-0.31 to 0.05)	0.1532
SPON1	-0.51 (-1.23 to 0.2)	0.1588
IL1RA	0.32 (-0.13 to 0.76)	0.1604
OPG_INF	0.46 (-0.18 to 1.11)	0.1605
CCL17	0.16 (-0.07 to 0.38)	0.1642
OPN	-0.34 (-0.83 to 0.14)	0.1657
GH	-0.09 (-0.23 to 0.04)	0.1825
IL2RA	-0.37 (-0.91 to 0.17)	0.1835
LEP	0.22 (-0.11 to 0.55)	0.1854
CITP	-0.3 (-0.76 to 0.15)	0.1913
TRAILR2	0.41 (-0.21 to 1.03)	0.1936
CXCL16	0.55 (-0.28 to 1.39)	0.1951
GDNF	0.36 (-0.19 to 0.91)	0.2031

SLAMF1	-0.25 (-0.63 to 0.14)	0.2057
FABP4	0.26 (-0.15 to 0.67)	0.2119
DLK1	0.27 (-0.15 to 0.69)	0.2137
AMBP	0.74 (-0.45 to 1.93)	0.225
TIMP4	-0.32 (-0.84 to 0.2)	0.2262
DECR1	0.1 (-0.06 to 0.25)	0.2268
CXCL1	0.1 (-0.07 to 0.27)	0.2338
TNFRSF10A	0.39 (-0.26 to 1.03)	0.2363
GRN	0.42 (-0.28 to 1.11)	0.2385
FGF5	0.86 (-0.58 to 2.31)	0.2417
CX3CL1	0.32 (-0.22 to 0.86)	0.2459
TLT2	-0.28 (-0.76 to 0.2)	0.2603
TSLP	-2.48 (-6.82 to 1.87)	0.2643
CHIT1	-0.11 (-0.3 to 0.09)	0.2772
NEMO	0.1 (-0.08 to 0.27)	0.2786
VSIG2	0.2 (-0.16 to 0.57)	0.2809
ADAMTS13	-0.53 (-1.51 to 0.44)	0.2839
EGFR	-0.53 (-1.51 to 0.45)	0.2886
CCL4	0.19 (-0.16 to 0.55)	0.2894
BLMHYDROLASE	-0.29 (-0.81 to 0.24)	0.2907
ICAM2	-0.29 (-0.83 to 0.25)	0.2909
ANG1	0.1 (-0.09 to 0.29)	0.2924
CSF1	0.52 (-0.46 to 1.51)	0.299
CSF1	0.52 (-0.46 to 1.51)	0.299
TWEAK	-0.38 (-1.1 to 0.34)	0.2996
NT3	-0.23 (-0.66 to 0.2)	0.3004
CD4	-0.44 (-1.26 to 0.39)	0.3005
CXCL9	0.18 (-0.16 to 0.51)	0.3014
FLT3L	0.26 (-0.24 to 0.76)	0.3025
PRSS27	0.25 (-0.23 to 0.74)	0.3035
CCL23	0.26 (-0.25 to 0.78)	0.3164
CXCL1_INF	0.09 (-0.09 to 0.26)	0.3205
THBS2	-0.48 (-1.43 to 0.47)	0.3216
CD40L	0.08 (-0.08 to 0.25)	0.3221
CHI3L1	-0.13 (-0.4 to 0.13)	0.3266
MMP2	-0.33 (-0.99 to 0.33)	0.3269
APN	-0.35 (-1.06 to 0.36)	0.3319
MMP12	-0.17 (-0.52 to 0.18)	0.3323
SOD2	-0.84 (-2.56 to 0.88)	0.3365
CA5A	0.13 (-0.14 to 0.4)	0.3381
IL20RA	-0.32 (-0.96 to 0.33)	0.339
IL1ALPHA	1.49 (-1.57 to 4.55)	0.3391
PTX3	-0.26 (-0.78 to 0.27)	0.3414
IL2RB	0.28 (-0.3 to 0.85)	0.3437
CD93	-0.37 (-1.13 to 0.39)	0.3457
IL12B	0.17 (-0.19 to 0.54)	0.3481

TNFSF13B	-0.29 (-0.89 to 0.31)	0.3488
MCP1	0.25 (-0.27 to 0.77)	0.3544
FGF19	-0.13 (-0.39 to 0.14)	0.3557
IL4RA	0.31 (-0.35 to 0.97)	0.3587
TNFSF14	0.19 (-0.22 to 0.6)	0.3606
CTSD	-0.24 (-0.75 to 0.27)	0.3609
CD8A	-0.15 (-0.48 to 0.18)	0.3648
CD5	0.26 (-0.3 to 0.82)	0.3655
IL4	-0.18 (-0.56 to 0.21)	0.3692
ADM	0.32 (-0.38 to 1.02)	0.3701
HSP27	0.23 (-0.27 to 0.73)	0.3741
LPL	-0.2 (-0.65 to 0.25)	0.3752
TNFRSF11A	0.25 (-0.31 to 0.82)	0.38
CPA1	-0.13 (-0.43 to 0.16)	0.3802
GDF15	0.17 (-0.21 to 0.54)	0.3816
CST5	0.2 (-0.25 to 0.66)	0.3823
TGM2	-0.11 (-0.37 to 0.14)	0.3838
IL20	0.29 (-0.36 to 0.94)	0.3843
CXCL5	0.06 (-0.07 to 0.19)	0.3859
KLK6	-0.25 (-0.81 to 0.31)	0.3868
ST1A1	0.12 (-0.15 to 0.39)	0.3877
IL17A	-0.13 (-0.43 to 0.17)	0.3885
OPG	0.3 (-0.38 to 0.99)	0.3888
IDUA	0.23 (-0.3 to 0.76)	0.3905
PDGFSUBUNITB	0.07 (-0.09 to 0.23)	0.3923
GP6	-0.12 (-0.41 to 0.16)	0.3978
MMP9	-0.26 (-0.86 to 0.35)	0.4015
FGF23	-0.17 (-0.58 to 0.24)	0.4042
MCP4	0.15 (-0.21 to 0.51)	0.4172
IL8	0.15 (-0.21 to 0.51)	0.4201
SCF	0.27 (-0.39 to 0.94)	0.4233
DCN	-0.28 (-0.96 to 0.41)	0.4291
PDL2	0.27 (-0.4 to 0.94)	0.4305
PRELP	-0.45 (-1.57 to 0.68)	0.4353
ITGB1BP2	0.07 (-0.1 to 0.24)	0.4357
IL18R1	0.21 (-0.33 to 0.75)	0.4384
PLC	-0.35 (-1.25 to 0.54)	0.4397
LIF	-0.57 (-2.01 to 0.88)	0.4409
PGF	0.3 (-0.47 to 1.07)	0.4418
CXCL6	0.1 (-0.16 to 0.37)	0.4458
CDCP1	0.15 (-0.23 to 0.53)	0.4462
FGF23	-0.16 (-0.58 to 0.26)	0.4469
TGFALPHA	-0.27 (-1 to 0.46)	0.4659
PIGR	-0.49 (-1.8 to 0.83)	0.4687
IL10RB	0.25 (-0.43 to 0.93)	0.4691
AXIN1	0.06 (-0.11 to 0.23)	0.4717

SCGB3A2	-0.12 (-0.46 to 0.21)	0.4718
TRAP	0.22 (-0.39 to 0.83)	0.475
IL15RA	0.31 (-0.54 to 1.16)	0.4797
PRSS8	0.26 (-0.46 to 0.97)	0.4805
IGFBP7	-0.24 (-0.92 to 0.44)	0.4821
IL27	-0.21 (-0.81 to 0.38)	0.485
DKK1	0.12 (-0.22 to 0.45)	0.4934
IL6_INF	0.09 (-0.17 to 0.35)	0.4945
CEACAM8	-0.13 (-0.52 to 0.25)	0.4951
MCP2	0.13 (-0.25 to 0.51)	0.4982
EPHB4	-0.25 (-0.97 to 0.48)	0.5053
HO1	-0.19 (-0.75 to 0.37)	0.5086
IL6	0.09 (-0.17 to 0.35)	0.5089
UPA	-0.18 (-0.72 to 0.36)	0.5137
PGLYRP1	-0.15 (-0.59 to 0.3)	0.5158
MMP7	0.14 (-0.29 to 0.57)	0.5252
TNFRSF10C	-0.15 (-0.63 to 0.32)	0.5255
MARCO	0.34 (-0.71 to 1.39)	0.5299
AXL	0.21 (-0.45 to 0.87)	0.5323
LAPTGFBETA1	0.16 (-0.35 to 0.68)	0.533
SHPS1	0.18 (-0.39 to 0.74)	0.5356
IL17D	0.17 (-0.37 to 0.7)	0.5415
CD163	0.15 (-0.34 to 0.64)	0.5418
CCL3	0.11 (-0.23 to 0.44)	0.5424
IL17C	-0.11 (-0.47 to 0.25)	0.5471
IL1RT1	-0.2 (-0.85 to 0.46)	0.5549
IL6RA	0.17 (-0.4 to 0.74)	0.5572
FABP2	0.09 (-0.21 to 0.39)	0.563
GLO1	0.09 (-0.21 to 0.39)	0.5656
EPCAM	-0.07 (-0.33 to 0.18)	0.5778
MCP1	0.11 (-0.27 to 0.48)	0.5783
GIF	0.06 (-0.15 to 0.26)	0.5784
SCF	0.18 (-0.47 to 0.84)	0.583
TNFR2	0.16 (-0.41 to 0.72)	0.5859
TNF	-0.21 (-0.98 to 0.56)	0.5907
NRTN	0.16 (-0.44 to 0.76)	0.5972
LTBR	-0.18 (-0.87 to 0.5)	0.5982
IGFBP2	-0.11 (-0.51 to 0.3)	0.6
XCL1	0.11 (-0.31 to 0.52)	0.6107
HGF	0.15 (-0.44 to 0.73)	0.6196
CCL3	0.09 (-0.25 to 0.42)	0.6196
CCL24	-0.07 (-0.33 to 0.2)	0.6229
IL1RL2	0.14 (-0.43 to 0.72)	0.6242
JAMA	0.05 (-0.15 to 0.25)	0.6391
GAL3	-0.14 (-0.74 to 0.45)	0.6413
BP1_4E	-0.07 (-0.34 to 0.21)	0.6417

CASP3	0.04 (-0.12 to 0.2)	0.6434
IGFBP1	0.06 (-0.19 to 0.3)	0.6471
MMP1	0.05 (-0.16 to 0.26)	0.6508
CPB1	-0.07 (-0.39 to 0.24)	0.6551
ALCAM	0.19 (-0.67 to 1.05)	0.6599
CCL15	-0.12 (-0.63 to 0.4)	0.6612
VEGFA	0.15 (-0.51 to 0.8)	0.6618
IL10RA	0.08 (-0.28 to 0.43)	0.6675
TRAIL	0.17 (-0.62 to 0.97)	0.6688
IL33	0.56 (-2.02 to 3.13)	0.6719
CD6	0.1 (-0.38 to 0.59)	0.6753
ARTN	0.11 (-0.42 to 0.64)	0.679
TNFR1	0.13 (-0.51 to 0.78)	0.6818
MERTK	0.13 (-0.48 to 0.73)	0.6828
CTSL1	-0.13 (-0.77 to 0.51)	0.6857
IL18	0.09 (-0.34 to 0.52)	0.6863
ADA	0.11 (-0.42 to 0.64)	0.6898
THPO	0.13 (-0.5 to 0.75)	0.6908
AGRP	0.09 (-0.38 to 0.56)	0.6937
IL10	0.07 (-0.28 to 0.42)	0.708
SIRT2	0.03 (-0.14 to 0.2)	0.7124
CSTB	0.1 (-0.42 to 0.61)	0.7125
IFNGAMMA	2.14 (-9.31 to 13.59)	0.7137
SPON2	0.23 (-1.05 to 1.51)	0.7247
PI3	-0.07 (-0.48 to 0.33)	0.7293
TFPI	-0.11 (-0.7 to 0.49)	0.7303
CTRC	-0.05 (-0.34 to 0.24)	0.7406
FAS	-0.11 (-0.74 to 0.53)	0.7418
SELE	0.06 (-0.31 to 0.43)	0.7421
IL18	0.07 (-0.37 to 0.52)	0.7461
P3NP	-0.07 (-0.47 to 0.34)	0.7462
ACE2	0.06 (-0.3 to 0.42)	0.7492
TNFRSF9	0.08 (-0.41 to 0.57)	0.7504
TR	0.05 (-0.28 to 0.39)	0.7518
IL16	-0.07 (-0.53 to 0.39)	0.759
BETANGF	-0.11 (-0.79 to 0.58)	0.7593
IL22RA1	0.11 (-0.61 to 0.83)	0.7623
PCSK9	-0.1 (-0.74 to 0.54)	0.7632
TM	0.11 (-0.6 to 0.82)	0.7633
VEGFD	-0.1 (-0.72 to 0.53)	0.7636
SORT1	-0.12 (-0.89 to 0.66)	0.7638
GDF2	0.09 (-0.51 to 0.68)	0.771
BMP6	0.07 (-0.42 to 0.57)	0.772
CCL20	-0.03 (-0.27 to 0.2)	0.7723
FS	-0.08 (-0.63 to 0.47)	0.7763
SERPINA12	0.05 (-0.3 to 0.4)	0.7818

HBEGF	0.05 (-0.28 to 0.37)	0.7835
CASP8	-0.05 (-0.42 to 0.32)	0.7958
CCL16	0.05 (-0.32 to 0.41)	0.7963
MMP10	0.05 (-0.36 to 0.46)	0.8005
CD84	-0.05 (-0.51 to 0.41)	0.821
PECAM1	-0.03 (-0.32 to 0.26)	0.8267
ITGB2	-0.06 (-0.58 to 0.46)	0.8272
RAGE	-0.06 (-0.64 to 0.52)	0.8293
AZU1	-0.04 (-0.38 to 0.31)	0.8316
CCL19	0.03 (-0.24 to 0.3)	0.8399
OSM	-0.03 (-0.3 to 0.25)	0.8425
SLAMF7	0.03 (-0.3 to 0.37)	0.8426
TNFRSF14	0.05 (-0.47 to 0.57)	0.849
IL18BP	0.06 (-0.59 to 0.72)	0.8508
ST2	-0.04 (-0.52 to 0.43)	0.8569
IL13	-0.03 (-0.3 to 0.25)	0.858
CXCL10	0.03 (-0.31 to 0.36)	0.8681
KIM1	-0.02 (-0.32 to 0.27)	0.8685
TIE2	-0.07 (-0.86 to 0.73)	0.8718
PRTN3	-0.07 (-0.89 to 0.76)	0.8734
LIFR	-0.06 (-0.8 to 0.68)	0.8781
RETN	-0.03 (-0.47 to 0.41)	0.8847
SELP	-0.02 (-0.29 to 0.25)	0.8868
CD40	0.04 (-0.47 to 0.55)	0.8874
DNER	-0.06 (-0.87 to 0.75)	0.8884
PON3	0.03 (-0.4 to 0.47)	0.891
PDGFSUBUNITA	0.02 (-0.2 to 0.23)	0.8912
CCL11	0.03 (-0.47 to 0.54)	0.8938
TRANCE	-0.02 (-0.41 to 0.36)	0.8999
GAL9	0.05 (-0.79 to 0.89)	0.9032
PSGL1	-0.05 (-0.87 to 0.77)	0.9058
RARRES2	0.04 (-0.69 to 0.78)	0.9077
CXCL11	0.02 (-0.25 to 0.28)	0.9109
IL1RT2	-0.04 (-0.67 to 0.6)	0.911
MMP3	0.02 (-0.36 to 0.4)	0.9148
STAMBP	0.01 (-0.21 to 0.23)	0.9179
LDLRECEPTOR	-0.02 (-0.48 to 0.44)	0.9266
BOC	-0.03 (-0.82 to 0.75)	0.932
PDL1	0.02 (-0.53 to 0.58)	0.9327
UPA	-0.03 (-0.66 to 0.6)	0.9356
PAI	-0.01 (-0.24 to 0.23)	0.9405
CCL28	0.02 (-0.66 to 0.71)	0.944
MPO	-0.03 (-0.9 to 0.84)	0.9472
MB	-0.01 (-0.43 to 0.4)	0.9509
LOX1	-0.01 (-0.4 to 0.38)	0.9537
TF	-0.02 (-0.75 to 0.71)	0.9642

CCL25	-0.01 (-0.46 to 0.44)	0.9653
CTSZ	0.01 (-0.57 to 0.59)	0.9664
CD244	-0.01 (-0.53 to 0.51)	0.9671
UPAR	0.01 (-0.62 to 0.65)	0.9678
IL7	0.01 (-0.28 to 0.29)	0.9723
PARP1	0.01 (-0.31 to 0.32)	0.9746
IL24	0 (-0.37 to 0.38)	0.9846
TNFRSF13B	0 (-0.46 to 0.46)	0.9908
IL2	0 (0 to 0)	1

Supplemental Table 6. Association of circulating proteins with LVEF (ordered logistic regression: per tertile increase) assessed with 4 cavities view

Protein	Coefficient (95%CI) Ordered logistic	P-value
BNP	-0.21 (-0.37 to -0.05)	0.012
REN	0.28 (0.06 to 0.5)	0.0129
NTPROBNP	-0.28 (-0.5 to -0.05)	0.0165
PAR1	0.46 (0.07 to 0.86)	0.0206
STK4	0.17 (0.03 to 0.31)	0.0207
MCP3	0.34 (0.05 to 0.63)	0.0215
COL1A1	-0.49 (-0.92 to -0.06)	0.0271
CCL17	0.19 (0.02 to 0.35)	0.0277
IL5	0.2 (0.02 to 0.39)	0.0333
PAPPA	-0.33 (-0.64 to -0.02)	0.0355
TFF3	0.45 (0.03 to 0.87)	0.0357
GT	0.25 (0.01 to 0.49)	0.0392
ENRAGE	-0.23 (-0.46 to -0.01)	0.0417
IL17RA	-0.31 (-0.6 to -0.01)	0.0436
PICP	-0.42 (-0.82 to -0.01)	0.0438
CXCL1	0.12 (0 to 0.25)	0.0573
GDNF	0.42 (-0.01 to 0.86)	0.058
TNFRSF10A	0.46 (-0.02 to 0.93)	0.0607
TRAILR2	0.46 (-0.02 to 0.95)	0.061
FGF21	0.15 (-0.01 to 0.31)	0.063
CNTN1	-0.44 (-0.91 to 0.03)	0.0692
FGF5	0.94 (-0.09 to 1.96)	0.0725
ANG1	0.12 (-0.01 to 0.26)	0.0741
SRC	0.15 (-0.02 to 0.31)	0.0788
OPG	0.43 (-0.05 to 0.91)	0.0821
NOTCH3	-0.41 (-0.88 to 0.05)	0.083
HAOX1	0.12 (-0.02 to 0.26)	0.084
TPA	-0.19 (-0.4 to 0.03)	0.0843
IGGFCRECEPTORIIB	0.19 (-0.03 to 0.4)	0.0862
TNFB	0.35 (-0.05 to 0.75)	0.0869
GAL4	0.26 (-0.04 to 0.56)	0.0873
CXCL1	0.11 (-0.02 to 0.25)	0.0912
CD40L	0.11 (-0.02 to 0.23)	0.0956
VWF	-0.11 (-0.24 to 0.02)	0.0976
MCP1	0.34 (-0.07 to 0.75)	0.0998
LEP	0.2 (-0.04 to 0.43)	0.1008
ST1A1	0.17 (-0.03 to 0.37)	0.1028
CSF1	0.59 (-0.14 to 1.32)	0.1124
CSF1	0.59 (-0.14 to 1.32)	0.1124
DECR1	0.1 (-0.02 to 0.21)	0.1158
CX3CL1	0.32 (-0.08 to 0.71)	0.117
NEMO	0.1 (-0.03 to 0.24)	0.1196

CXCL16	0.48 (-0.13 to 1.08)	0.122
PDGFSUBUNITB	0.09 (-0.02 to 0.21)	0.1237
DKK1	0.19 (-0.06 to 0.44)	0.1333
IL1RA	0.23 (-0.07 to 0.54)	0.1338
AMBP	0.7 (-0.22 to 1.61)	0.1353
IL8	0.2 (-0.06 to 0.47)	0.1386
IL20	0.44 (-0.14 to 1.03)	0.1387
CXCL5	0.08 (-0.02 to 0.17)	0.1408
TNFRSF11A	0.31 (-0.11 to 0.73)	0.1431
GRN	0.38 (-0.13 to 0.89)	0.1443
CCL23	0.29 (-0.1 to 0.69)	0.148
ITGB1BP2	0.09 (-0.03 to 0.22)	0.151
CXCL6	0.14 (-0.05 to 0.34)	0.151
PSPD	0.15 (-0.06 to 0.36)	0.1521
CST5	0.25 (-0.1 to 0.6)	0.1538
MEPE	-0.31 (-0.74 to 0.12)	0.1567
LAPTGFBETA1	0.27 (-0.1 to 0.64)	0.1579
HOSCAR	-0.48 (-1.16 to 0.19)	0.1604
TNFSF14	0.21 (-0.09 to 0.51)	0.1618
PRSS27	0.24 (-0.1 to 0.58)	0.1622
FABP4	0.2 (-0.08 to 0.48)	0.1649
VSIG2	0.18 (-0.09 to 0.45)	0.1845
GLO1	0.15 (-0.07 to 0.38)	0.1879
MCP4	0.17 (-0.08 to 0.43)	0.188
CCL4	0.16 (-0.09 to 0.4)	0.2036
VEGFA	0.31 (-0.17 to 0.8)	0.2052
CD5	0.27 (-0.15 to 0.69)	0.2109
GDF15	0.18 (-0.11 to 0.47)	0.2136
IL12B	0.16 (-0.09 to 0.42)	0.214
IL2RA	-0.22 (-0.57 to 0.13)	0.2196
IL15RA	0.39 (-0.24 to 1.02)	0.2219
CXCL9	0.15 (-0.1 to 0.4)	0.2313
AXIN1	0.08 (-0.05 to 0.2)	0.2328
CDH5	-0.28 (-0.74 to 0.18)	0.233
IL2RB	0.23 (-0.16 to 0.63)	0.2382
TROPONIN	-0.15 (-0.41 to 0.1)	0.2387
ADM	0.31 (-0.21 to 0.83)	0.2416
MMP1	0.09 (-0.07 to 0.25)	0.2451
FLT3L	0.23 (-0.16 to 0.62)	0.2463
IL17D	0.26 (-0.18 to 0.7)	0.2513
IDUA	0.22 (-0.16 to 0.6)	0.2545
IL6	0.11 (-0.08 to 0.31)	0.2563
PGF	0.31 (-0.23 to 0.84)	0.2579
CDCP1	0.16 (-0.12 to 0.44)	0.2616
CA5A	0.12 (-0.09 to 0.32)	0.2664
THPO	0.27 (-0.21 to 0.75)	0.2705

PDL2	0.26 (-0.21 to 0.73)	0.2786
TRAP	0.25 (-0.21 to 0.7)	0.2825
IL6	0.11 (-0.09 to 0.3)	0.2838
MCP1	0.18 (-0.15 to 0.51)	0.2848
MCP2	0.15 (-0.12 to 0.42)	0.2852
CITP	-0.18 (-0.52 to 0.15)	0.2897
IL4RA	0.26 (-0.22 to 0.75)	0.2928
HSP27	0.19 (-0.16 to 0.54)	0.2935
ADAMTS13	-0.38 (-1.1 to 0.34)	0.2962
HBEGF	0.13 (-0.11 to 0.37)	0.2966
SCF	0.25 (-0.23 to 0.73)	0.3016
ICAM2	-0.21 (-0.61 to 0.19)	0.3096
TGM2	-0.11 (-0.31 to 0.1)	0.3128
HGF	0.21 (-0.2 to 0.61)	0.316
CCL3	0.12 (-0.12 to 0.35)	0.3182
IL10RB	0.26 (-0.26 to 0.78)	0.3236
OPG	0.25 (-0.25 to 0.76)	0.3266
IL18R1	0.2 (-0.2 to 0.59)	0.3297
IL10	0.13 (-0.13 to 0.38)	0.3339
GH	-0.05 (-0.14 to 0.05)	0.3395
PRSS8	0.25 (-0.27 to 0.77)	0.3412
CASP3	0.06 (-0.06 to 0.17)	0.3465
SIRT2	0.06 (-0.07 to 0.19)	0.3507
IL4	-0.16 (-0.5 to 0.18)	0.3579
NT3	-0.14 (-0.45 to 0.16)	0.3585
SLAMF1	-0.13 (-0.43 to 0.16)	0.3638
CSTB	0.17 (-0.2 to 0.54)	0.3666
IL2	-16.12 (-51.46 to 19.21)	0.3711
ADA	0.18 (-0.21 to 0.57)	0.3716
CCL3	0.11 (-0.13 to 0.34)	0.3718
OPN	-0.16 (-0.51 to 0.19)	0.3735
DLK1	0.14 (-0.16 to 0.44)	0.3775
THBS2	-0.33 (-1.06 to 0.4)	0.3809
TNFSF13B	-0.19 (-0.61 to 0.24)	0.3848
JAMA	0.06 (-0.08 to 0.21)	0.3937
AGRP	0.15 (-0.19 to 0.49)	0.3965
FABP2	0.09 (-0.12 to 0.3)	0.4103
CD40	0.16 (-0.23 to 0.55)	0.4141
TLT2	-0.14 (-0.47 to 0.19)	0.4152
IL17A	-0.1 (-0.34 to 0.14)	0.416
FGF19	-0.08 (-0.27 to 0.11)	0.4264
CD93	-0.22 (-0.77 to 0.32)	0.4273
STAMBP	0.07 (-0.1 to 0.23)	0.4366
MERTK	0.18 (-0.27 to 0.62)	0.441
BMP6	0.13 (-0.21 to 0.47)	0.4454
SHPS1	0.16 (-0.25 to 0.57)	0.448

CD6	0.13 (-0.2 to 0.46)	0.4505
CTSD	-0.15 (-0.54 to 0.24)	0.4516
TM	0.2 (-0.32 to 0.71)	0.4563
TRAIL	0.23 (-0.37 to 0.82)	0.4571
TNFRSF9	0.14 (-0.23 to 0.5)	0.4628
CCL28	0.19 (-0.32 to 0.71)	0.4629
GIF	0.06 (-0.1 to 0.21)	0.4642
TSLP	-0.18 (-0.67 to 0.3)	0.4652
SCF	0.18 (-0.31 to 0.68)	0.4688
PDGFSUBUNITA	0.06 (-0.1 to 0.21)	0.4689
IL18	0.12 (-0.2 to 0.43)	0.4724
PDL1	0.15 (-0.27 to 0.58)	0.4761
SPON1	-0.19 (-0.72 to 0.34)	0.478
LIF	-0.16 (-0.62 to 0.29)	0.4834
EGFR	-0.24 (-0.93 to 0.44)	0.4848
TNFR2	0.14 (-0.27 to 0.55)	0.491
CD8A	-0.09 (-0.34 to 0.16)	0.494
PTX3	-0.14 (-0.54 to 0.26)	0.502
CCL11	0.14 (-0.26 to 0.53)	0.5028
HO1	-0.14 (-0.57 to 0.28)	0.5047
MMP7	0.11 (-0.22 to 0.45)	0.5057
ALCAM	0.21 (-0.41 to 0.83)	0.5066
IL1RL2	0.14 (-0.28 to 0.57)	0.5074
IGFBP1	0.06 (-0.12 to 0.25)	0.5119
PGLYRP1	-0.11 (-0.45 to 0.22)	0.5123
PIGR	-0.35 (-1.38 to 0.69)	0.5127
CPA1	-0.07 (-0.3 to 0.15)	0.5155
FGF23	-0.1 (-0.39 to 0.2)	0.5253
TNFRSF10C	-0.12 (-0.47 to 0.24)	0.5253
APN	-0.17 (-0.71 to 0.36)	0.5272
AXL	0.15 (-0.33 to 0.63)	0.5395
PON3	0.1 (-0.22 to 0.41)	0.5411
MMP3	0.09 (-0.2 to 0.38)	0.5429
MMP9	-0.14 (-0.57 to 0.3)	0.5434
TNFRSF14	0.12 (-0.27 to 0.51)	0.5444
MMP12	-0.07 (-0.32 to 0.17)	0.5512
TR	0.08 (-0.18 to 0.34)	0.553
CCL19	0.06 (-0.14 to 0.26)	0.5587
ACE2	0.08 (-0.2 to 0.36)	0.5605
CHIT1	-0.04 (-0.17 to 0.09)	0.5616
KLK6	-0.12 (-0.52 to 0.28)	0.562
GAL3	-0.13 (-0.57 to 0.32)	0.5742
MARCO	0.22 (-0.56 to 1)	0.5769
IL18	0.09 (-0.23 to 0.41)	0.5827
BOC	0.16 (-0.42 to 0.75)	0.5872
CD4	-0.16 (-0.75 to 0.43)	0.5928

FGF23	-0.08 (-0.37 to 0.22)	0.5955
BLMHYDROLASE	-0.1 (-0.49 to 0.28)	0.6005
RARRES2	0.15 (-0.42 to 0.73)	0.6025
IL7	0.06 (-0.16 to 0.28)	0.6041
MMP10	0.08 (-0.23 to 0.4)	0.6042
PLC	-0.17 (-0.84 to 0.49)	0.6052
TNFR1	0.13 (-0.36 to 0.62)	0.6062
IL27	-0.11 (-0.54 to 0.32)	0.6074
CXCL11	0.05 (-0.14 to 0.23)	0.6078
CD163	0.09 (-0.26 to 0.45)	0.6129
SLAMF7	0.06 (-0.19 to 0.31)	0.6221
IL10RA	0.07 (-0.2 to 0.33)	0.6225
CCL24	-0.05 (-0.24 to 0.14)	0.6261
UPAR	0.11 (-0.35 to 0.57)	0.6283
ARTN	0.1 (-0.33 to 0.53)	0.6446
SOD2	-0.3 (-1.6 to 0.99)	0.6462
UPA	-0.08 (-0.43 to 0.27)	0.6463
IL6RA	0.1 (-0.32 to 0.52)	0.6486
SERPINA12	0.06 (-0.2 to 0.32)	0.6577
TNF	-0.09 (-0.51 to 0.33)	0.6622
TNFRSF13B	0.08 (-0.3 to 0.46)	0.6752
GDF2	0.09 (-0.33 to 0.51)	0.6774
CD244	0.08 (-0.31 to 0.48)	0.6805
DNER	0.12 (-0.47 to 0.71)	0.6892
CHI3L1	-0.04 (-0.23 to 0.15)	0.6936
LOX1	0.06 (-0.24 to 0.35)	0.6937
CASP8	0.06 (-0.23 to 0.34)	0.7
SPON2	0.17 (-0.7 to 1.05)	0.7022
CCL16	0.05 (-0.22 to 0.32)	0.7032
SORT1	0.11 (-0.45 to 0.67)	0.7041
TIMP4	-0.06 (-0.4 to 0.27)	0.7042
RETN	-0.06 (-0.39 to 0.27)	0.707
TFPI	0.08 (-0.36 to 0.52)	0.7202
PI3	-0.06 (-0.37 to 0.26)	0.724
IL1RT1	-0.09 (-0.56 to 0.39)	0.725
XCL1	0.06 (-0.27 to 0.38)	0.7316
EPHB4	-0.09 (-0.62 to 0.44)	0.7403
TF	0.09 (-0.43 to 0.61)	0.7423
PAI	0.03 (-0.14 to 0.2)	0.7446
PARP1	0.04 (-0.19 to 0.27)	0.747
LIFR	0.09 (-0.45 to 0.62)	0.7493
MMP2	-0.08 (-0.58 to 0.42)	0.7499
SCGB3A2	-0.04 (-0.29 to 0.21)	0.7511
UPA	0.07 (-0.37 to 0.52)	0.7552
SELP	0.03 (-0.17 to 0.23)	0.756
IL18BP	0.08 (-0.41 to 0.56)	0.7565

TRANCE	0.04 (-0.23 to 0.32)	0.762
P3NP	-0.05 (-0.35 to 0.26)	0.7627
VEGFD	0.07 (-0.37 to 0.5)	0.7642
IFNGAMMA	0.23 (-1.29 to 1.76)	0.7649
IL33	0.28 (-1.58 to 2.14)	0.7681
IL1ALPHA	0.08 (-0.48 to 0.64)	0.7769
GAL9	0.08 (-0.5 to 0.66)	0.7839
NRTN	0.06 (-0.39 to 0.52)	0.7847
CD84	0.05 (-0.29 to 0.39)	0.7925
IL13	-0.02 (-0.21 to 0.16)	0.794
ST2	0.04 (-0.29 to 0.38)	0.7947
CEACAM8	-0.04 (-0.33 to 0.25)	0.7975
CXCL10	0.03 (-0.2 to 0.26)	0.7978
MPO	0.08 (-0.54 to 0.7)	0.8026
LTBR	-0.06 (-0.56 to 0.43)	0.803
IGFBP2	-0.04 (-0.35 to 0.27)	0.8053
FS	-0.05 (-0.47 to 0.36)	0.8063
GP6	-0.03 (-0.23 to 0.18)	0.8101
BETANGF	0.07 (-0.52 to 0.66)	0.8108
EPCAM	-0.02 (-0.2 to 0.15)	0.814
KIM1	-0.02 (-0.24 to 0.2)	0.8278
CTSZ	0.05 (-0.39 to 0.49)	0.8287
CTSL1	-0.05 (-0.56 to 0.45)	0.8307
IL17C	-0.03 (-0.3 to 0.24)	0.8344
LPL	-0.04 (-0.38 to 0.31)	0.8417
IL20RA	-0.03 (-0.35 to 0.28)	0.8459
IL16	0.03 (-0.32 to 0.39)	0.8504
BP1_4E	0.02 (-0.18 to 0.22)	0.8539
TIE2	0.05 (-0.54 to 0.65)	0.8587
CCL25	0.03 (-0.32 to 0.38)	0.8606
PECAM1	0.02 (-0.19 to 0.23)	0.8648
TWEAK	-0.04 (-0.52 to 0.44)	0.869
IGFBP7	-0.04 (-0.54 to 0.46)	0.8767
FAS	0.04 (-0.42 to 0.49)	0.8789
PCSK9	0.03 (-0.44 to 0.5)	0.8891
IL1RT2	0.03 (-0.47 to 0.53)	0.8946
CCL20	-0.01 (-0.19 to 0.16)	0.9
PRELP	-0.05 (-0.88 to 0.78)	0.9064
OSM	0.01 (-0.19 to 0.21)	0.9102
SELE	0.01 (-0.27 to 0.3)	0.9197
IL24	0.02 (-0.33 to 0.36)	0.9203
CPB1	-0.01 (-0.25 to 0.23)	0.9213
LDLRECEPTOR	-0.02 (-0.37 to 0.33)	0.9222
DCN	-0.02 (-0.53 to 0.5)	0.9521
MB	0.01 (-0.28 to 0.29)	0.9606
PRTN3	0.02 (-0.62 to 0.65)	0.9613

PSGL1	0.01 (-0.57 to 0.59)	0.9664
CTRC	0 (-0.21 to 0.22)	0.9675
CCL15	-0.01 (-0.37 to 0.36)	0.975
RAGE	0.01 (-0.42 to 0.43)	0.9767
ITGB2	0 (-0.38 to 0.37)	0.9821
TGFALPHA	0.01 (-0.54 to 0.55)	0.9824
IL22RA1	0.01 (-0.5 to 0.51)	0.9832
AZU1	0 (-0.27 to 0.26)	0.9897

Supplemental Table 7. Mediation analysis of proteins with potential mediator effect of spironolactone on LVEF change from baseline to month 9

Protein	**Coefficient (95%CI) LVEF change**	**P-value**
BNP		
Direct effect	0.19 (-0.38 to 0.76)	0.51
Indirect effect (spiro. via BNP)	-0.06 (-0.23 to 0.12)	0.52
COL1A1		
Direct effect	0.78 (-0.58 to 2.16)	0.26
Indirect effect (spiro. via COL1A1)	-0.12 (-0.34 to 0.10)	0.29