

At baseline, echocardiography was performed in all patients and images were stored in a digital cine-loop format for off-line analysis following recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging relative to the cardiac chamber and right heart measurements¹

From standard 2D views, left ventricular (LV) structure and function were evaluated (including apical four-chamber, apical two-chamber and parasternal long- and short-axis views). Ventricular dimensions, wall thickness, mass and geometry were determined from 2D parasternal short- and long-axis views. LV volumes, stroke volume and ejection fraction were calculated using the biplane method (modified Simpson's rule). All cardiac chamber volumes and mass measurements were indexed to body surface area.

Left atrial (LA) volume was assessed by the biplane area-length method from apical 2- and 4-chamber views at end-systole and was indexed to body surface area (LA volume index, LAVi). LA area (cm²) was estimated from the apical views. If LA volume was not available, LA area was used to evaluate remodeling. Patients with either LAVi > 40 ml/m² or LA area > 20 cm² were considered to have dilated LA.

Pulsed-wave Doppler obtained at the tip of mitral leaflets was used to assess the peak velocities of early (E) and late (A) wave of transmitral flow and E-wave deceleration time (DT). The average of septal and lateral annular velocities (e') was measured using tissue Doppler imaging (TDI). The peak E-wave velocity and the average of septal and lateral e' were used to calculate the E/e' ratio. LV outflow tract (LVOT) time velocity integral, isovolumic relaxation time (IVRT) and color M-mode of early diastolic mitral inflow into the left ventricle (Flow propagation velocity, Vp) were acquired from apical four- and five-

¹ Lang RM *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; 16(3):233-70.

chamber views. Pulmonary venous flow (PVF) was sampled using pulsed-wave Doppler at 1 cm into the orifice of the right upper pulmonary vein.

TAPSE (in mm) measurement was performed to estimate right ventricular (RV) function and pulmonary arterial systolic pressure (PASP) was calculated using the peak velocity of tricuspid regurgitation (TR) and the maximum IVC diameter (IVC baseline) and respiratory variation (Ratio IVC inspiration / IVC baseline) measured 3 cm before merger with the right atrium.

Overall, echocardiographic data were complete in >75% of patients, except for A (and E/A ratio) (which were available in 70% and 61% of the population, respectively).

Supplemental table 1 Participating centers MEDIA-DHF

Nancy Clinical Investigation Centre, University of Lorraine, France (and EDDH European Drug Development Hub, Nancy, France as project manager)
Lariboisière Hospital, Paris, France
Free University Medical Centre, Amsterdam, The Netherlands
CHARITE, universitätsmedizin Berlin, Berlin Germany
University of Porto, Porto, Portugal
University of Maastricht, Maastricht, The Netherlands
Hartcentrum ZNA, Antwerp, Belgium
Cardiff University, Cardiff, United Kingdom
Foundation for Applied Medical Research, Pamplona, Spain
University of Eastern PIEMONTE Medical School, Novara, Italy
University of Brescia, Brescia, Italy
University of Perugia, Perugia, Italy
University College Dublin, National University of Ireland, Dublin, Ireland
University Debrecen, Debrecen, Hungary
Oslo University Hospital, Norway

Supplemental table 2 Overview of biomarkers measured at baseline in MEDIA-DHF

Organ damage panel	
5'-AMP-activated protein kinase subunit beta-1 (PRKAB1) Q9Y478	Kidney Injury Molecule (KIM1) Q96D42
Adhesion G-protein coupled receptor G1 (ADGRG1) Q9Y653	Leukotriene A-4 hydrolase (LTA4H) P09960
Aldolase dehydrogenase, dimeric NADP-preferring (ALDH3A1) P30838	Linker for activation of T-cells family member 2 (LAT2) Q9GZY6
Anterior gradient protein 2 homolog (AGR2) O95994	Lutropin subunit beta (LHB) P01229
Apoptosis-inducing factor 1, mitochondrial (AIFM1) O95831	Macrophage erythroblast attachment (MAEA) Q7L5Y9
B-cell scaffold protein with ankyrin repeats (BANP1) Q8NDB2	Macrophage-capping protein (CAPG) P40121
BHL-3-interacting domain death agonist (BIL3) P55957	Melanoma-associated antigen D1 (MAGED1) Q9Y9V3
BMP and activin membrane-bound inhibitor homolog (BAMBI) Q13145	Methionine aminopeptidase 1 (METAP1) P53582
Calcitonin (CALCA) P01258	Mevlonate kinase (MVK) Q03426
Calreticulin (CALR) P27797	Mitogen-activated protein kinase kinase kinase 5 (MAP4K5) Q9Y4E4
Carbonic anhydrase 12 (CA12) O43570	Mothers against decapentaplegic homolog 1 (SMAD1) Q15797
Carbonic anhydrase 14 (CA14) Q9ULX7	NAD-dependent protein deacetylase sirtuin-5, mitochondrial (SIRT5) Q9NNA8
Casain kinase 1 isoform delta (CSNK1D) P48730	NEDD8 ultimate bustle 1 (NUB1) Q9Y5A7
Claspin (CLSPN) Q9HAW4	Neutrophil cytosol factor 2 (NCF2) P19878
CMP-N-acetylneuraminic-beta-galactosidase-alpha-2,3-sialyltransferase 1 (ST3GAL1) Q11201	Nibin (NBN) O60934
Cocaine esterase (CES2) O00748	Nitric oxide synthase, endothelial (NOS3) P29474
Contactin-2 (CNTN2) Q02246	Nucleobindin-2 (NUCB2) P80303
Corticosterone (CRH) P08830	Parvalbumin alpha (PVALB) P20472
C-type lectin domain family 1 member A (CLEC1A) Q8NC01	Paxillin (PXN) P49023
C-type natriuretic peptide (NPPC) P23582	Peptidyl-prolyl cis-trans isomerase FKBP1B (FKBP1B) P68106
Desmoglein-4 (DSG4) Q86536	Perilipin-1 (PLIN1) O60240
Dipeptidyl aminopeptidase-like protein 6 (DPP6) P42658	Placenta growth factor (PGF) P49763
DNA topoisomerase 2-beta (TOP2B) Q01880	Platelet-derived growth factor C (PDGFC) Q9NRA1
Ectonucleoside triphosphate diphosphohydrolase 2 (ENTPD2) Q9Y3L3	Pleiotrophin (PTN) P21246
Ectonucleoside triphosphate diphosphohydrolase 6 (ENTPD6) O75354	Phosphatidylinositol 3,4,5-trisphosphate 5-phosphatase 2 (DNPL1) O15357
EGF-like repeat and discoidin I-like domain-containing protein 3 (EDIL3) O43854	Plasma domain-containing protein 1 (PLNDC1) Q8IUK5
Enteropeptidase (TMPRSS15) P98073	Polypeptide N-acetylglucosaminyltransferase 10 (GALNT10) Q86581
Epidermal growth factor-like protein 7 (EGFL7) Q9UHF1	Probetacellulin (BTC) P35070
Erbin (ERBB2) Q96RT1	Programmed cell death protein 1 (PDCD1) Q15116
Erythropoietin (EPO) P01588	Prolonged-density lipoprotein receptor-related protein 1 (LRP1) Q07954
Fatty acid-binding protein 9 (FABP9) Q02758	Proteasome subunit alpha type-1 (PSMA1) P25786
Forkhead box protein O1 (FOXO1) Q12778	Protein amniotic (AMN) Q9BXJ7
Fructose-2,6-bisphosphatase TIGAR (TIGAR) Q9NQ88	Protein foxB (FOXB) P53539
Haematopoietic prostaglandin D synthase (HPGDS) O60760	Protein max (MAX) P61244
Inactive tyrosine-protein kinase 7 (PTK7) Q13308	Protein phosphatase 1B (PP1B) O75688
Integrin beta-1-binding protein 1 (ITGB1BP1) O14713	[Pyruvate dehydrogenase (acetyl-transferring)]-phosphatase 1, mitochondrial (PDPI) Q9P0J1
Interferon-inducible double-stranded RNA-dependent protein kinase activator A (PRKRA) O75569	Ras association domain-containing protein 2 (RASSF2) P50749
Renin receptor (ATP6AP2) O75787	Ras GTPase-activating protein 1 (RASAP1) P20956
	Receptor-type tyrosine-protein phosphatase eta (PTPRJ) Q12913
	EGF-containing fibulin-like extracellular matrix protein 1 (EFEMP1)

	REST corepressor 1 (RCOR1) Q9UKL0	Q12805
	Retinoic acid receptor responder protein 1 (RARRES1) P49768	Endoglin (ENG) P17813
	Ribonucleoside-diphosphate reductase subunit M2 B (RRM2B) Q7LG56	Ferritin-B (FETUB) Q9UGM5
	Serpins A9 (SERPINA9) Q86WD7	Ficolin-2 (FCN2) Q15485
0	Serum paraoxonase/arylesterase 2 (PON2) Q15165	Glutaminyl-peptidyl cyclotransferase (QPCT) Q16769
1	Syntaxin-8 (STX8) Q9UN80	Granulysin (GNLY) P22749
2	Syntaxin-binding protein 3 (STXBP3) O00186	Growth arrest-specific protein 6 (GAS6) Q14393
3	Troponin I, cardiac muscle (TNNT3) P19429	Hepatocyte growth factor receptor (MET) P08381
4	Tyrosine-protein kinase Fes/Fps (FES) P07332	Ig lambda-2 chain C regions (IGLC2) P0CG05
5	Tyrosine-protein kinase Fgr (FGR) P09769	Insulin-like growth factor-binding protein 3 (IGFBP3) P17936
6	Tyrosine-protein kinase Yes (YES1) P07947	Insulin-like growth factor-binding protein 6 (IGFBP6) P24592
7	Vascular endothelial growth factor C (VEGFC) P49767	Integrin alpha-M (ITGAM) P11215
8	Vasohibin-1 (VASH1) Q7L8A9	Intercellular adhesion molecule 1 (ICAM1) P05362
9	Wiskott-Aldrich syndrome protein (WAS) P42768	Intercellular adhesion molecule 3 (ICAM3) P32942
0		Interleukin-7 receptor subunit alpha (IL7R) P16871
1		Latent-transforming growth factor beta-binding protein 2 (LTBP2) Q14767
2	Cardiometabolic panel	Leukocyte immunoglobulin-like receptor subfamily B member 1 (LILRB1) Q8NHL6
3	Angiotensin (ANG) P03950	Leukocyte immunoglobulin-like receptor subfamily B member 2 (LILRB2) Q8N423
4	Angiotensin-related protein 3 (ANGPTL3) Q9Y5C1	Leukocyte immunoglobulin-like receptor subfamily B member 3 (LILRB3) O75023
5	Apolipoprotein M (APOM) O95445	Lithostathine-1-alpha (LSTHA) P05451
6	Beta-Ala-His dipeptidase (CNDP1) Q96KN2	Liver carboxylesterase 1 (CES1) P23141
7	Beta-galactoside alpha-2,6-sialyltransferase 1 (ST6GAL1) P15907	Low affinity immunoglobulin gamma Fc region receptor II-a (FCGR2A) P12318
8	Cadherin-1 (CDH1) P12830	Low affinity immunoglobulin gamma Fc region receptor III-B (FCGR3B) O75015
9	Carbonic anhydrase 1 (CA1) P00915	L-selectin (SELL) P14151
0	Carbonic anhydrase 3 (CA3) P07451	Lymphatic vessel endothelial hyaluronate receptor 1 (LYVE1) Q9Y3Y7
1	Carbonic anhydrase 4 (CA4) P22748	Lysosomal Pro-X carboxypeptidase (PRCP) P42785
2	Cartilage acidic protein 1 (CRTAC1) Q9NQ79	Mannose-binding protein C (MBL2) P11226
3	Cartilage oligomeric matrix protein (COMP) P49747	Mast/stem cell growth factor receptor Kit (KIT) P10721
4	C-C motif chemokine 5 (CCL5) P13501	Membrane cofactor protein (CD46) P13529
5	C-C motif chemokine 14 (CCL14) Q16627	Membrane primary amine oxidase (AOC3) Q16853
6	C-C motif chemokine 18 (CCL18) P55774	Metalloproteinase inhibitor 1 (TIMP1) P01033
7	CD59 glycoprotein (CD59) P13987	Microfibrillar-associated protein 5 (MFAP5) Q13361
8	Coagulation factor VII (F7) P08709	Multiple epidermal growth factor-like domains protein 9 (MEGF9) Q9H1U4
9	Coagulation factor XI (F11) P03951	Neural cell adhesion molecule 1 (NCAM1) P13591
0	Collagen alpha-1(XVIII) chain (COL18A1) P39060	Neural cell adhesion molecule LI-like protein (CHL1) O00533
1	Complement C1q tumor necrosis factor-related protein 1 (C1QTNF1) Q9BXJ1	Neurogenic locus notch homolog protein 1 (NOTCH1) P46331
2	Complement C2 (C2) P06681	Neuropilin-1 (NRP1) O14786
3	Complement factor H-related protein 5 (CFHR5) Q9BXK6	Neutrophil defensin 1 (DEFB1) P19665
4	Complement receptor type 2 (CR2) P20023	Neutrophil gelatinase-associated lipocalin (LCN2) P60188
5	Cystatin-C (CST3) P01034	Nidogen-1 (NID1) P14543
6	Dipeptidyl peptidase 4 (DPP4) P27487	Oncostatin-M-specific receptor subunit beta (OSMR) Q99650

Peptidyl-glycine alpha-oxidizing monooxygenase (PAM) P19021	C-C motif chemokine 17 (CCL17) Q82583
Phospholipid transfer protein (PLTP) P55058	CD40 ligand (CD40-L) P28963
Plasma serine protease inhibitor (SERPINA5) P05154	Chymotrypsin C (CTRC) Q99895
Platelet glycoprotein Ib alpha chain (GP1BA) P07359	C-X-C motif chemokine 1 (CXCL1) P09341
Platelet-activating factor acetylhydrolase (PLA2G7) Q13093	Decorin (DCN) P07585
Plexin-B2 (PLXNB2) O15031	Dickkopf-related protein 1 (Dkk-1) Q94907
Procollagen C-endopeptidase enhancer 1 (PCOLCE) Q15113	Fatty acid-binding protein, intestinal (FABP2) P12104
Prolyl endopeptidase FAP (FAP) Q12884	Fibroblast growth factor 21 (FGF-21) Q9NSA1
Receptor-type tyrosine-protein phosphatase S (PTPRS) Q13332	Fibroblast growth factor 23 (FGF-23) Q9GZV9
Regenerating islet-derived protein 3-alpha (REG3A) Q06141	Follistatin (FS) P19883
Serum amyloid A-4 protein (SAA4) P35542	Galactin-9 (Gal-9) O00182
SPARC-like protein 1 (SPARCL1) Q14515	Gastric intrinsic factor (GIF) P27352
Superoxide dismutase [Cu-Zn] (SOD1) P00441	Gastrotropin (GT) P51161
T-cell immunoglobulin and mucin domain-containing protein 4 (TIMD4) Q96H15	Growth hormone (GH) P01241
Tenascin (TNC) P24821	Growth differentiation factor 2 (GDF-2) Q9UK05
Tenascin-X (TNXB) P22105	Heat shock 27 kDa protein (HSP 27) P04792
Thrombospondin-4 (THBS4) P35443	Heme oxygenase 1 (HO-1) P09601
Thyroxine-binding globulin (SERPINA7) P05543	Hydroxynitric oxidase 1 (HAOX1) Q9UJMS
Transcobalamin-2 (TCN2) P20062	Interleukin-1 receptor antagonist protein (IL-1ra) P18510
Transforming growth factor beta receptor type 3 (TGFB3) Q03167	Interleukin-1 receptor-like 2 (IL1RL2) Q9H239
Transforming growth factor-beta-induced protein ig-h3 (TGFB1) Q15582	Interleukin-4 receptor subunit alpha (IL-4RA) P24394
Trypsin-2 (PRSS2) P07478	Interleukin-6 (IL6) P03231
Tyrosine-protein kinase receptor Tie-1 (TIE1) P35590	Interleukin-17D (IL-17D) Q8TAD2
Uromodulin (UMOD) P07911	Interleukin-18 (IL-18) Q14116
Vascular cell adhesion protein 1 (VCAM1) P19320	Interleukin-27 (IL-27) Q9NEV9
Vasorin (VASN) Q6EMK4	Q14213
Vitamin K-dependent protein C (PROC) P04070	Kidney Injury Molecule (KIM1) Q98L42
	Lactoylglutathione lyase (GLO1) Q04760
Cardiovascular II panel	Lectin-like oxidized LDL receptor 1 (LOX-1) P78380
2,4-dienoyl-CoA reductase, mitochondrial (DECR1) Q16698	Leptin (LEP) P41159
A disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAM-TS13) Q76LN8	Lipoprotein lipase (LPL) P06858
ADM (ADM) P35318	Low affinity immunoglobulin gamma Fc region receptor II-b (IgG Fc receptor II-b) P31994
Agouti-related protein (AGRP) O00253	Lymphotactin (XCL1) P47992
Alpha-L-iduronidase (IDUA) P35475	Macrophage receptor MARCO (MARCO) Q9UEW3
Angiotensin-1 (ANG-1) Q15389	Matrix metalloproteinase-7 (MMP-7) P09237
Angiotensin-1 receptor (TIE2) Q02763	Matrix metalloproteinase-12 (MMP-12) P39900
Angiotensin-converting enzyme 2 (ACE2) Q9BYF1	Melusin (ITGB1BP2) Q9UKP3
Bone morphogenetic protein 6 (BMP-6) P22004	Natriuretic peptide B (BNP) P16860
Brother of CDO (Protein BOC) Q9BWV1	NF-kappa-B essential modulator (NEMO) Q9Y6K9
Carbonic anhydrase 3A, mitochondrial (CA3A) P35218	Osteoclast-associated immunoglobulin-like receptor (hOSCAR) Q8IYS5
Carcinoembryonic antigen-related cell adhesion molecule 8 (CEACAM8) P31997	Pappalysin-1 (PAPPA) Q13219
Cathepsin L1 (CTSL1) P07711	Pentraxin-related protein PTX3 (PTX3) P26022
C-C motif chemokine 3 (CCL3) P10147	Placenta growth factor (PGF) P49763

Platelet-derived growth factor subunit B (PDGF subunit B) P01127	Caspase-3 (CASP-3) P42574
Poly [ADP-ribose] polymerase 1 (PARP-1) P09874	Cathepsin D (CTSD) P07339
Polymorphic immunoglobulin receptor (PIgR) P01833	Cathepsin Z (CTSZ) Q9UBR2
Programmed cell death 1 ligand 2 (PD-L2) Q9BQ51	C-C motif chemokine 15 (CCL15) Q16663
Proteasome-binding EGF-like growth factor (HB-EGF) Q99075	C-C motif chemokine 16 (CCL16) O15467
Pro-interleukin-16 (IL16) Q14005	Note: New assay under development N/A
Prolargin (PRELP) P51888	C-C motif chemokine 24 (CCL24) O00175
Prostatein (PRSS5) Q16651	CD166 antigen (ALCAM) Q13740
Protein AMBP (AMBP) P02760	Chitinase-3-like protein 1 (CH3L1) P36222
Proteinase-activated receptor 1 (PAR-1) P25116	Chitinotriose-1 (CHIT1) Q13231
Protein-glutamine gamma-glutamyltransferase 2 (TGM2) P21980	Collagen alpha-1(I) chain (COL1A1) P02452
Proto-oncogene tyrosine-protein kinase Src (SRC) P12931	Complement component C1q receptor (CD93) Q9NPY3
P-selectin glycoprotein ligand 1 (PSGL-1) Q14242	Contractin-1 (CNTN1) Q12860
Receptor for advanced glycosylation end products (RAGE) Q15109	C-X-C motif chemokine 16 (CXCL16) Q9H2A7
Renin (REN) P00797	Cystatin-B (CSTB) P04080
Serine protease 27 (PRSS27) Q9BQR3	Elastin (ELN) P19957
Serine/threonine-protein kinase 4 (STK4) Q13043	Ephrin type-B receptor 4 (EPHB4) P54760
Serpin A12 (SERPINA12) Q8RW75	Epidermal growth factor receptor (EGFR) P00533
SLAM family member 5 (CD84) Q9UIB8	Epithelial cell adhesion molecule (Eg-CAM) P16422
SLAM family member 7 (SLAMF7) Q9NQ25	E-selectin (SELE) P16581
Sortilin (SORT1) Q99523	Fatty acid-binding protein, adipocyte (FABP4) P15090
Spondin-2 (SPON2) Q9BUD6	Galactin-3 (Gal-3) P17931
Stem cell factor (SCF) P21583	Galactin-4 (Gal-4) P56470
Superoxide dismutase [Mn], mitochondrial (SOD2) P04179	Granulin (GRN) P28799
T-cell surface glycoprotein CD4 (CD4) P01730	Growth differentiation factor 15 (GDF-15) Q99988
Thrombospondin TM P07204	Insulin-like growth factor-binding protein 1 (IGFBP-1) P08833
Thrombospondin (THPO) P40225	Insulin-like growth factor-binding protein 2 (IGFBP-2) P18065
Thrombospondin-2 (THBS2) P35442	Insulin-like growth factor-binding protein 7 (IGFBP-7) Q16270
Tissue factor (TF) P13726	Integrin beta-2 (ITGB2) P05107
TNF-related apoptosis-inducing ligand receptor 2 (TRAIL-R2) O14763	Intercellular adhesion molecule 2 (ICAM-2) P13598
Tumor necrosis factor receptor superfamily member 10A (TNFRSF10A) O00220	Interleukin-1 receptor type 1 (IL-1RT1) P14778
Tumor necrosis factor receptor superfamily member 11A (TNFRSF11A) Q9Y6Q6	Interleukin-1 receptor type 2 (IL-1RT2) P27930
Tumor necrosis factor receptor superfamily member 13B (TNFRSF13B) Q14836	Interleukin-2 receptor subunit alpha (IL-2-RA) P01589
Tyrosine-protein kinase Mer (MERTK) Q12866	Interleukin-6 receptor subunit alpha (IL-6RA) P08887
Vascular endothelial growth factor D (VEGFD) O43915	Interleukin-17 receptor A (IL-17RA) Q96F46
V-set and immunoglobulin domain-containing protein 2 (VSIG2) Q96IQ7	Interleukin-18-binding protein (IL-18BP) O95998
Cardiovascular III panel	Functional adhesion molecule A (JAM-A) Q9Y624
Aminopeptidase N (AP-N) P15144	Kallikrein-6 (KLK6) Q92876
Anrocidin (AZU1) P20160	Low-density lipoprotein receptor (LDL receptor) P01130
Bleomycin hydrolase (BLM hydrolase) Q13867	Lymphotxin-beta receptor (LTBR) P36941
Cadherin-5 (CDH5) P33151	Matrix extracellular phosphoglycoprotein (MEPE) Q9NQ76
Carboxypeptidase A1 (CPA1) P15085	Matrix metalloproteinase-2 (MMP-2) P08253
Carboxypeptidase B (CPB1) P15086	Matrix metalloproteinase-3 (MMP-3) P08254

Matrix metalloproteinase-9 (MMP-9) P14780	von Willebrand factor (vWF) P04275
Metalloproteinase inhibitor 4 (TIMP4) Q99727	
Monocyte chemoattractant protein 1 (MCP-1) P13500	Inflammation panel
Myeloblastin (PRTN3) P24158	Adenosine Deaminase (ADA) P00813
Myeloperoxidase (MPO) P05164	Artemin (ARTN) Q5T4W7
Myoglobin (MB) P02144	Axin-1 (AXIN1) O15169
Neurogenic locus notch homolog protein 3 (Notch 3) Q9UM47	Beta-nerve growth factor (Beta-NGF) P01138
N-terminal prohomone brain natriuretic peptide (NT-proBNP) NA	Caspase-8 (CASP-8) Q14790
Osteopontin (OPN) P10451	C-C motif chemokine 3 (CCL3) P10147
Osteoprotegerin (OPG) O00300	C-C motif chemokine 4 (CCL4) P13236
Paraoxonase (PON3) Q15166	C-C motif chemokine 19 (CCL19) Q99731
Peptidoglycan recognition protein 1 (PGLYRP1) O75594	C-C motif chemokine 20 (CCL20) P78556
Perlecan (PLC) P98160	C-C motif chemokine 23 (CCL23) P55773
Plasminogen activator inhibitor 1 (PAI) P05121	C-C motif chemokine 25 (CCL25) O15444
Platelet endothelial cell adhesion molecule (PECAM-1) P16284	C-C motif chemokine 28 (CCL28) Q9NRJ3
Platelet-derived growth factor subunit A (PDGF subunit A) P04083	CD40L receptor (CD40) P15942
Proprotein convertase subtilisin/kexin type 9 (PCSK9) Q8NBP7	CUB domain-containing protein 1 (CDCP1) Q9H5V8
Protein delta homolog 1 (DLK-1) P60370	C-X-C motif chemokine 1 (CXCL1) P09341
P-selectin (SELP) P16109	C-X-C motif chemokine 5 (CXCL5) P42830
Pulmonary surfactant-associated protein D (SPSP-D) P35247	C-X-C motif chemokine 6 (CXCL6) P60162
Reelin (RELN) Q9HJ89	C-X-C motif chemokine 9 (CXCL9) Q07325
Retinoic acid receptor responder protein 2 (RARRES2) Q99969	C-X-C motif chemokine 10 (CXCL10) P02778
Scavenger receptor cysteine-rich type 1 protein M130 (CD163) Q86VB7	C-X-C motif chemokine 11 (CXCL11) O14625
Secretoglobulin family 3A member 2 (SCGB3A2) Q96PL1	Cystatin D (CST5) P28325
Spondin-1 (SPON1) Q9HCB6	Delta and Notch-like epidermal growth factor-related receptor (DNER) Q8NFT8
ST2 protein (ST2) Q01638	Eotaxin (CCL11) P51671
Tartrate-resistant acid phosphatase type 5 (TR-AP) P13886	Eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) Q13541
Tissue factor pathway inhibitor (TFPI) P10646	Fibroblast growth factor 21 (FGF-21) Q9NSA1
Tissue-type plasminogen activator (t-PA) P00750	Fibroblast growth factor 23 (FGF-23) Q9GZV9
Transferrin receptor protein 1 (TR) P02786	Fibroblast growth factor 5 (FGF-5) Q8NF90
Trefoil factor 3 (TFF3) Q07654	Fibroblast growth factor 19 (FGF-19) Q95750
Trem-like transcript 2 protein (TLT-2) Q5T2D2	Fms-related tyrosine kinase 3 ligand (Flt3L) P49771
Tumor necrosis factor ligand superfamily member 13B (TNFSF13B) Q9Y275	Fractalkine (CX3CL1) P78423
Tumor necrosis factor receptor 1 (TNF-R1) P19438	Glial cell line-derived neurotrophic factor (GDNF) P39905
Tumor necrosis factor receptor 2 (TNF-R2) P20333	Hepatocyte growth factor (HGF) P14210
Tumor necrosis factor receptor superfamily member 6 (FAS) P25445	Interferon gamma (IFN-gamma) P01579
Tumor necrosis factor receptor superfamily member 10C (TNFRSF10C) Q14798	Interleukin-1 alpha (IL-1 alpha) P01583
Tumor necrosis factor receptor superfamily member 14 (TNFRSF14) Q92916	Interleukin-2 (IL-2) P60568
Tyrosine-protein kinase receptor UFO (AXL) P30530	Interleukin-2 receptor subunit beta (IL-2RB) P14784
Tyrosine-protein phosphatase non-receptor type substrate 1 (SHP5-1) P78324	Interleukin-4 (IL-4) P05112
Urokinase plasminogen activator surface receptor (U-PAR) Q03405	Interleukin-5 (IL-5) P05113
Urokinase-type plasminogen activator (uPA) P00749	Interleukin-6 (IL-6) P05231

Interleukin-7 (IL-7) P13232	Thymic stromal lymphopoietin (TSLP) Q969D9
Interleukin-8 (IL-8) P10145	TNF-related activation-induced cytokine (TRANCE) O14788
Interleukin-10 (IL-10) P22301	TNF-related apoptosis-inducing ligand (TRAIL) P50591
Interleukin-10 receptor subunit alpha (IL-10RA) Q13651	Transforming growth factor alpha (TGF-alpha) P01135
Interleukin-10 receptor subunit beta (IL-10RB) Q08334	Tumor necrosis factor (Ligand) superfamily, member 12 (TNFRSF12) O43508
Interleukin-12 subunit beta (IL-12B) P29460	Tumor necrosis factor (TNF) P01375
Interleukin-13 (IL-13) P35225	Tumor necrosis factor ligand superfamily member 14 (TNFSF14) O43557
Interleukin-15 receptor subunit alpha (IL-15RA) Q13261	Tumor necrosis factor receptor superfamily member 9 (TNFRSF9) Q07011
Interleukin-17A (IL-17A) Q16552	Urokinase-type plasminogen activator (uPA) P00749
Interleukin-17C (IL-17C) Q9P0M4	Vascular endothelial growth factor A (VEGF-A) P15692
Interleukin-18 (IL-18) Q14116	
Interleukin-18 receptor 1 (IL-18R1) Q13478	
Interleukin-20 (IL-20) Q9NYY1	
Interleukin-20 receptor subunit alpha (IL-20RA) Q9UHF4	
Interleukin-22 receptor subunit alpha-1 (IL-22 RA1) Q8N6P7	
Interleukin-24 (IL-24) Q13007	
Interleukin-33 (IL-33) C95760	
Latency-associated peptide transforming growth factor beta-1 (LAP TGF-beta-1) P01137	
Leukemia inhibitory factor (LIF) P15018	
Leukemia inhibitory factor receptor (LIF-R) P42702	
Macrophage colony-stimulating factor 1 (CSF-1) P09603	
Matrix metalloproteinase-1 (MMP-1) P03956	
Matrix metalloproteinase-10 (MMP-10) P09238	
Monocyte chemoattractant protein 1 (MCP-1) P13500	
Monocyte chemoattractant protein 2 (MCP-2) P00075	
Monocyte chemoattractant protein 3 (MCP-3) P00098	
Monocyte chemoattractant protein 4 (MCP-4) Q99616	
Natural killer cell receptor 2B4 (CD244) Q9BZW8	
Neurotrophin-3 (NT-3) P20783	
Neurexin (NRTN) Q99748	
Oncostatin-M (OSM) P13725	
Osteoprotegerin (OPG) O00300	
Programmed cell death 1 ligand 1 (PD-L1) Q9NZQ7	
Protein S100-A12 (EN-RAGE) P80511	
Signaling lymphocytic activation molecule (SLAMF1) Q13291	
SIRT-like protein 2 (SIRT2) Q8IXJ6	
STAM-binding protein (STAMBP) O95630	
Stem cell factor (SCF) P21583	
Sulfotransferase 1A1 (ST1A1) P50225	
T cell surface glycoprotein CD6 isoform (CD6) Q8WWJ7	
T-cell surface glycoprotein CD5 (CD5) P06127	
T-cell surface glycoprotein CD8 alpha chain (CD8A) P01732	
TNF-beta (TNFB) P01374	

Supplemental table 3 Clinical variables in MEDLA-DHF

Sex
Age
Recently decompensated (< 60 days) HF
Smoking status
Alcohol consumption
Body mass index (BMI)
Systolic blood pressure (SBP)
Diastolic blood pressure (DBP)
Pulmonary rates
New York Heart Association (NYHA)
Peripheral edema
Jugular Venous Distension
Fatigue on exertion
Hepatomegaly
Heart rate
Previous HF hospitalization
Atrial fibrillation
Hypertension
Diabetes Mellitus
Coronary Artery Disease (CAD)
Stroke or Transient Ischemic Attack
Peripheral arterial disease
Chronic obstructive pulmonary disease
Total cholesterol
Anemia (defined as hemoglobin <12 g/dL in women and <13 g/dL following WHO definition)
Estimated glomerular filtration rate (MDRD)
ACE inhibitor or angiotensin receptor blocker
Betablocker
Loop diuretic
Thiazide diuretic
Mineralocorticoid receptor antagonist
Oral anticoagulant
Insulin
Statin
Left ventricular ejection fraction (LV)
LV end-diastolic index (LVEDVi)
LV end-systolic volume index (LVESVi)
left atrial volume index (LAVi)
tricuspid annular plane systolic excursion (TAPSE)
ratio of early mitral inflow E to annular velocity e' (E/e')
Excluded variables ($\geq 20\%$ missing)
pulmonary artery systolic pressure (PASP)
Ratio of the early (E) to late (A) ventricular filling velocities (E/A)
Waist circumference
Sodium
Potassium
CRP

Supplemental table 4 Average measure of biomarkers according to respective clusters

	Cluster 1 (N=229)	Cluster 2 (N=163)	p-value
TIE2	7.1 ± 0.3	7.3 ± 0.2	<0.001
ENTPD2	0.0 ± 0.2	0.1 ± 0.3	<0.001
CCL11	7.5 ± 0.4	7.8 ± 0.4	<0.001
TNFSF13B	5.7 ± 0.4	6.0 ± 0.5	<0.001
PDGFC	2.2 ± 0.4	2.3 ± 0.3	<0.001
SELL	7.5 ± 0.4	7.6 ± 0.4	0.006
PCSK9	1.8 ± 0.4	2.0 ± 0.4	<0.001
TWEAK	9.0 ± 0.5	9.1 ± 0.4	0.002
NOS3	1.3 ± 0.6	1.7 ± 0.6	<0.001
GNLY	0.5 ± 0.4	0.7 ± 0.5	<0.001
SELE	12.1 ± 0.6	12.3 ± 0.7	<0.001
SERPINA9	2.4 ± 0.6	2.8 ± 0.8	<0.001
AZU1	3.4 ± 0.8	3.8 ± 1.2	<0.001
SRC	6.5 ± 1.2	6.9 ± 1.0	0.001
ADGRG1	1.4 ± 1.0	2.2 ± 1.3	<0.001
FGF_21	5.7 ± 1.2	6.6 ± 1.5	<0.001
GH	7.6 ± 1.7	8.5 ± 1.6	<0.001

Legend: TIE2, angiopoietin-1 receptor; ENTPD2, ectonucleoside triphosphate diphosphohydrolase 2; CCL11, eotaxin; TNFSF13B, tumor necrosis factor ligand superfamily member 13B; PDGFC, platelet-derived growth factor C; SELL, L-selectin; PCSK9, proprotein convertase subtilisin/kexin type 9; TWEAK, tumor necrosis factor (Ligand) superfamily, member 12; NOS3, nitric oxide synthase; GNLY, granulysin; SELE, E-selectine; SERPINA9, serpin A9; AZU1, azurocidin; SRC, Proto-oncogene tyrosine-protein kinase Src; ADGRG1, adhesion G-protein coupled receptor G1; FGF_21_1, fibroblast growth factor 21; GH, growth hormone.

Biomarker results depict log2-normalized protein expression (NPX) data and an increase of 1 NPX confers therefore a doubling in concentration of the specific biomarker. For every biomarker the mean and standard deviation are listed.

Supplemental table 5 *Crude and adjusted hazards ratios for the baseline prediction of cardiovascular death and/or cardiovascular hospitalization at 1 year in MEDIA-DHF*

	UNIVARIATE ANALYSES		MULTIVARIATE ANALYSES	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Pulmonary rales	2.28 (1.34-3.86)	0.002	2.14 (1.25-3.68)	0.006
History of CAD	1.78 (1.06-2.99)	0.028	1.96 (1.15-3.42)	0.013
Previous HF hospitalization	1.75 (1.06-2.91)	0.030		
eGFR < 60 mL/min/1.73m ²	1.51 (1.30-1.76)	<0.001		
Anemia	1.50 (1.28-1.75)	<0.001		
E/e' > 9	3.37 (2.48-4.58)	<0.001		
Age (per 10 years)	1.00 (0.76-1.31)	0.99	0.93 (0.70-1.22)	0.59
Female sex	1.26 (0.73-2.16)	0.41	1.48 (0.83-2.63)	0.18

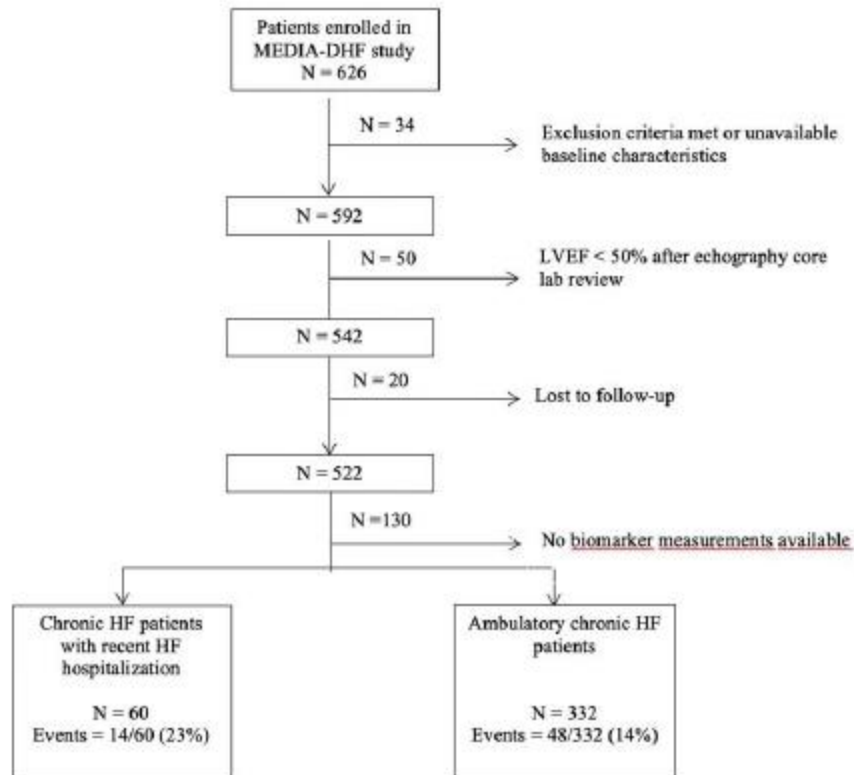
The table depicts pooled estimates derived after multiple imputation in 10 datasets. Anemia is defined following the WHO criteria for anemia (Hb < 12 g/dl in women; Hb < 13 in males).

Legend: HR, hazard ratio; CI, confidence interval; CAD, coronary artery disease; HF, heart failure; eGFR, estimated glomerular filtration rate; E/e', the ratio of early mitral inflow E to e'

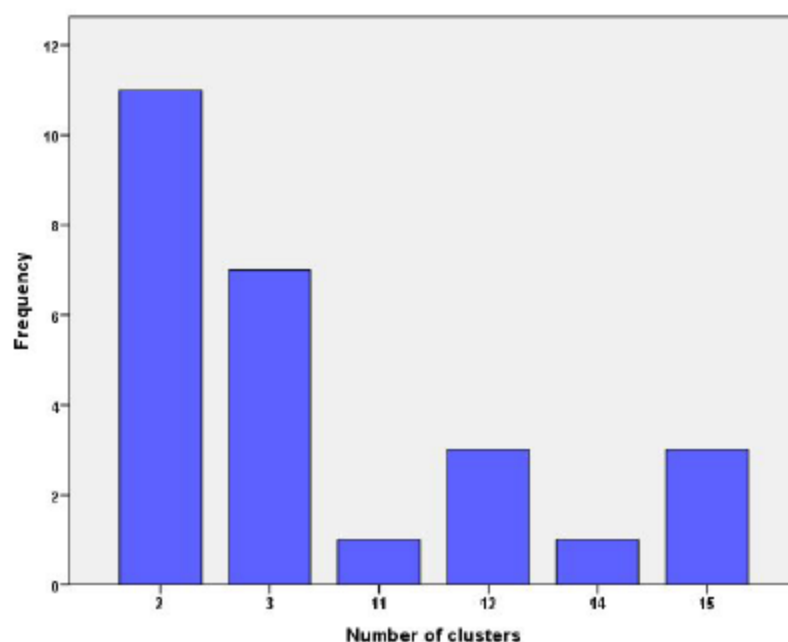
Supplemental table 6

Association between cluster assignment and cardiovascular outcomes after adjustment for additional clinical variables

	Additional adjusted variables on top of clinical + cluster model									
	Clinical	Clinical + cluster	+ prev HF hosp	+ anemia	+ SBP	NYHA 3/4	DM 2	ACE/ARB	BB	MRA
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Pulmonary rates	2.14 (1.25-3.68) p=0.006	2.17 (1.26-3.72) p=0.005	2.14 (1.24-3.67) p=0.006	2.85 (1.61-5.01) p<0.001	2.24 (1.29-3.88) p=0.004	2.19 (1.27-3.78) p=0.005	2.12 (1.23-3.66) p=0.007	2.19 (1.27-3.76) p=0.005	2.10 (1.22-3.63) p=0.008	2.17 (1.27-3.73) p=0.01
History of CAD	1.96 (1.15-3.42) p=0.013	2.01 (1.26-3.46) p=0.012	1.88 (1.09-3.26) p=0.024	1.84 (1.02-3.31) p=0.04	1.83 (1.05-3.20) p=0.034	2.05 (1.18-3.56) p=0.011	1.98 (1.15-3.42) p=0.014	2.02 (1.17-3.49) p=0.01	1.95 (1.12-3.38) p=0.02	2.02 (1.17-3.49) p=0.01
Age (per 10 years)	0.93 (0.70-1.22) p=0.059	0.88 (0.65-1.13) p=0.27	0.85 (0.65-1.12) p=0.26	0.86 (0.63-1.17) p=0.34	0.88 (0.66-1.17) p=0.38	0.84 (0.64-1.12) p=0.23	0.87 (0.66-1.16) p=0.26	0.83 (0.64-1.13) p=0.26	0.87 (0.65-1.15) p=0.33	0.87 (0.65-1.14) p=0.31
Female sex	1.48 (0.83-2.63) p=0.018	1.68 (0.93-3.02) p=0.085	1.80 (0.99-3.26) p=0.053	1.51 (0.80-2.89) p=0.34	1.71 (0.93-3.12) p=0.083	1.65 (0.91-2.98) p=0.09	1.70 (0.94-3.08) p=0.08	1.69 (0.94-3.04) p=0.08	1.69 (0.94-3.04) p=0.08	1.67 (0.92-3.00) p=0.09
Cluster 2		1.93 (1.12-3.32) p=0.018	1.81 (1.05-3.13) p=0.033	1.69 (0.93-3.07) p=0.087	2.04 (1.17-3.57) p=0.012	1.84 (1.06-3.19) p=0.029	1.90 (1.10-3.27) p=0.021	1.90 (1.10-3.28) p=0.02	1.86 (1.08-3.23) p=0.03	1.99 (1.15-3.42) p=0.01
Previous HF hosp			1.53 (0.89-2.65) p=0.13							
Anemia				1.21 (0.67-2.16) p=0.53						
SBP					0.99 (0.98-1.01) p=0.83					
NYHA 3 / 4						1.23 (0.65-2.31) p=0.53				
DM type 2							1.21 (0.71-2.08) p=0.49			
ACE/ARB								0.84 (0.45-1.58) p=0.59		
BB									1.29 (0.65-2.56) p=0.47	
MRA										0.60 (0.24-1.52) p=0.28

*Supplemental figure 1**Flowchart of patients included in study*

Supplemental figure 2 Optimal number of clusters determined using NbClust analysis



The optimal number of clusters determined by the *NbClust* package in R was 2. This package uses a total of 30 indices for determining the most optimal number of clusters from the results obtained by varying combinations of number of clusters, distance measures and clustering methods.