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Echocardiographic and biomarker characteristics in diabetes, coronary artery disease or both: insights from HOMAGE trial

Luca Monzo[1*], Masatake Kobayashi[1,2], João Pedro Ferreira[1,3], Zohra Lamiral[1], Christian Delles[4], Andrew L. Clark[5], Frank Edelmann[6,7,8], Arantxa González[9,10], Stephane Heymans[11], Pierpaolo Pellicori[15], Johannes Petutschnigg[6,7,8], Job A. J. Verdonschot[11], Patrick Rossignol[1,12,13,14], John G. F. Cleland[15], Faiez Zannad[1], Nicolas Girerd[1*] and on behalf of the HOMAGE "Heart Omics in AGEing" Trial Committees and Investigators

Abstract

Background Coronary artery disease (CAD) and diabetes mellitus (DM) can induce changes in myocardial structure and function, thereby increasing the risk of heart failure (HF). We aimed to identify the alterations in echocardiographic variables and circulating biomarkers associated with DM, CAD, or both and to assess the effect of spironolactone on them.

Methods The "Heart OMics in AGEing" (HOMAGE) trial evaluated the effect of spironolactone on circulating markers of fibrosis over 9 months of follow-up in people at risk for HF. From the initial population ($N=527$) of the HOMAGE trial, a total of 495 participants (mean age 74 years, 25% women) were categorized according to clinical phenotype (DM-/CAD + vs. DM+/CAD- vs. DM+/CAD+), while the DM-/CAD- group was excluded due to the low sample size ($N=32$). Multivariable linear regression analysis was used to assess the relations between variables and DM/CAD status.

Results At baseline, participants with DM, whether or not they had CAD, showed lower markers of type I collagen synthesis (procollagen type I C-terminal propeptide; β [95% CI]: DM+/CAD-: -6.973 [-13.778; -0.167]; DM+/CAD+: -9.039 [-15.174; -2.903]), reduced left ventricular volumes (β [95% CI]: end-diastolic, DM+/CAD-: -6.323 [-9.696; -2.951]; DM+/CAD+: -2.503 [-5.531; 0.526]; end-systolic, DM+/CAD-: -2.905 [-4.817; -0.992]; DM+/CAD+: -1.400 [-3.120; 0.320]) and higher levels of galectin-3 (Exponential β [95% CI]: DM+/CAD-: 1.127 [1.050; 1.209]; DM+/CAD+: 1.118 [1.048; 1.192]), and growth differentiation factor-15 (Exponential β [95% CI]: DM+/CAD-: 1.542 [1.360; 1.747]; DM+/CAD+: 1.535 [1.370; 1.720]), along with an elevated E/e' ratio (β [95% CI]: DM+/CAD-: 1.355 [0.462; 2.248]; DM+/CAD+: 0.879 [0.067; 1.690]), compared with DM-/CAD + individuals (all $p<0.05$). At follow-up, the effect of spironolactone on echocardiographic variables and circulating biomarkers was not significantly different across DM/CAD phenotypes

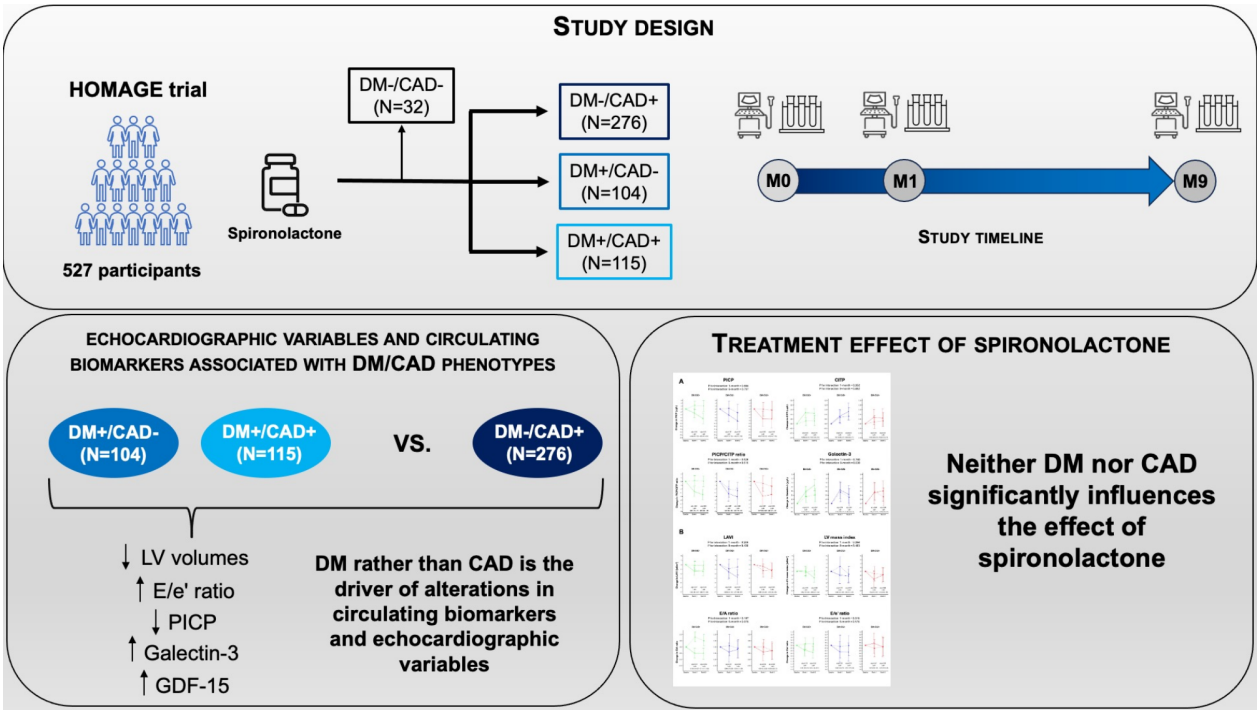
*Correspondence:
Luca Monzo
l.monzo@chru-nancy.fr
Nicolas Girerd
n.girerd@chru-nancy.fr

Full list of author information is available at the end of the article

(all p-interaction > 0.05), except for a more pronounced reduction in GDF-15 in the DM+/CAD + group at the 1-month visit (p-interaction = 0.03).

Conclusions Among HOMAGE trial participants, diabetes was a powerful driver of biomarker and echocardiographic alterations irrespectively of CAD. These alterations were mainly related to the domains of inflammation and diastolic function.

Graphic abstract Summary of the study design and key findings. Abbreviations: CAD, coronary artery disease; DM, diabetes mellitus; LV, left ventricular; M0, baseline; M1, 1-month follow-up; M9, 9-month follow-up; PICP, procollagen type I C-terminal propeptide.



Keywords Collagen markers, Echocardiography, Heart failure, Diabetes, Coronary artery disease

Introduction

Coronary artery disease (CAD) is a major risk factor for the development of heart failure (HF) [1]. CAD is a frequent complication of diabetes mellitus (DM) and the main mechanism by which diabetes causes changes to cardiac structure [2]. Nevertheless, DM can contribute, along with other risk factors (mainly hypertension), to left ventricular (LV) dysfunction and HF development, even in the absence of overt CAD [3, 4].

Previous studies have demonstrated that both DM and CAD possess unique proteomic profiles, particularly regarding inflammatory, immunological, and collagen catabolic processes, which could be instrumental in the development of HF [5, 6]. Anyway, how DM and CAD interact to affect cardiac remodelling and the onset of HF is not understood. If there are key pathophysiological differences between subjects with DM, CAD, or both, then specific disease progression traits, such as myocardial fibrosis, may give insights into the effect of specific treatments with the potential to delay or prevent the onset of HF. Notably, biomarkers can reflect key pathophysiological processes, offering valuable insights into the mechanisms contributing to the progression toward HF [7]. Specifically, procollagen peptides (i.e., type I and type III) and collagen type I C-terminal telopeptide (CITP) provide information on myocardial fibrosis and collagen turnover [8], while galectin-3 and growth differentiation factor-15 (GDF-15) are involved in pro-inflammatory signalling [9, 10]. Natriuretic peptides and cardiac troponins are well-established indicators of myocardial stress and injury [11].

In the "Heart OMics in AGEing" (HOMAGE) trial, spironolactone reduced type I collagen metabolism and improved cardiac remodelling in people at risk for HF [8], with an excellent safety profile [12]. This study analysed data from the HOMAGE trial to investigate the

echocardiographic and circulating biomarker profiles of patients with DM, CAD, or both, aiming to identify distinctive patterns associated with these conditions. Additionally, we explored whether the effects of spironolactone varied across the DM/CAD subgroups.

Methods

Trial design and study population

The design and main results of the HOMAGE trial have previously been reported [8, 13]. Briefly, the HOMAGE trial was a randomized, open-label, blinded-endpoint, multicentre trial, investigating the effects of spironolactone on markers of collagen metabolism and cardiovascular structure and function in people at increased risk of developing HF. A total of 527 individuals aged > 65 years (amended to > 60 years) with established CAD or at least two criteria indicative of cardiovascular disease, including type 2 DM, hypertension under treatment, microalbuminuria, or an abnormal electrocardiogram (including LV hypertrophy, QRS duration > 120 ms, or abnormal Q-waves) were included. Additionally, patients were required to have plasma concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP) between 125 and 1000 ng/L or brain natriuretic peptide (BNP) between 35 and 280 ng/mL (to exclude individuals at low risk of developing HF or those with advanced disease warranting further investigation). CAD was defined as a history of myocardial infarction, coronary arterial angioplasty, or coronary artery bypass, while DM was defined as requiring treatment with antidiabetic drugs. Patients with known HF, an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2, serum potassium > 5.0 mmol/L, LV ejection fraction < 45%, atrial fibrillation, prescribed loop diuretics, or cardiovascular events in the prior 3 months were excluded. Patients were randomly allocated to either spironolactone or control in addition to their background medical therapy. Spironolactone was initiated at 25 mg/day and titrated to 50 mg/day, if tolerated, on top of usual care. After randomization, patient visits were scheduled at 1 and 9 months, for clinical assessment, collection of blood samples, electrocardiogram, and echocardiographic examination [13].

The current post-hoc analysis included 495 participants categorized according to their clinical phenotype as having: (a) CAD without DM (DM-/CAD+; $N = 276$); (b) DM without CAD (DM+/CAD-; $N = 104$); (c) DM and CAD (DM+/CAD+; $N = 115$). The group of participants without DM and CAD (DM-/CAD-) was excluded from the analysis because of the low sample size ($N = 32$).

Echocardiography and circulating biomarkers

Echocardiograms were analysed offline by a single experienced operator using dedicated software (Echo PAC, GE Healthcare) and blinded to clinical data, according to current recommendations [14, 15]. The reproducibility of echocardiographic measurements is high, as previously reported [16]. Blind to clinical data and randomization, procollagen type I C-terminal propeptide (PICP) was measured by enzyme immunoassay (METRA; Quidel Corporation®; limit of detection [LoD] = 2 µg/L); while procollagen type III N-terminal propeptide (PIIINP) and CITP by radioimmunoassay (Orion Diagnostica®, Espoo, Finland; PIIINP: LoD = 0.3 µg/L; CITP: LoD = 0.4 µg/L). Galectin-3 was measured by enzyme-linked immunosorbent assay (BG Medicine®, Inc., Waltham, USA; LoD = 1.13 µg/L, limit of quantitation [LoQ] = 1.32 µg/L). High-sensitivity troponin T (hsTnT), NT-proBNP, and GDF-15 were measured by electro-chemi-luminescence (ELECSYS® 2010 analyser; Roche Diagnostics, Mannheim, Germany; hsTnT: LoD = 5 ng/L, LoQ = 13 ng/L; NT-proBNP: LoD = 5 pg/mL, LoQ = 50 pg/mL; GDF-15: LoD and LoQ = 400 ng/L). All intra-assay variations were < 10%.

Statistical analysis

Categorical variables are presented as frequencies (percentages) and continuous variables as median (25th and 75th percentiles). Comparisons of baseline characteristics between clinical phenotypes were analysed using analysis of variance, Kruskal–Wallis and χ^2 tests, as appropriate. Multivariable linear regression analysis was used to assess the relations between variables and DM/CAD status, after adjustment for potential confounders, including study treatment (spironolactone), age, sex, body mass index (BMI), hypertension status, eGFR, angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs), betablockers, and statins. Additionally, when evaluating the relationships between absolute changes in variables from baseline to 1 month and 9 months and DM/CAD status, further adjustments were made for the baseline values of the respective variables. Normality was assessed using the Shapiro-Wilk test. Variables that were not normally distributed were log-transformed prior to analysis, and the results of the regression analysis were expressed as the exponential transformation of the beta coefficients (Exp β). Analysis of covariance (ANCOVA) was used to compare the absolute changes in echocardiographic variables and circulating biomarkers from baseline to 1 month and 9 months of follow-up between the control and spironolactone group, adjusting for confounders (study treatment, age, sex, BMI, hypertension status, and eGFR) as well as the baseline values of the studied variables. Interaction between spironolactone effect and clinical phenotypes was also assessed. No adjustments were made for multiple comparisons to account for type I error, given the exploratory nature of this subanalysis.

Table 1 Baseline characteristics according to DM/CAD status

	DM-/CAD+ (*N* = 276)	DM+/CAD- (*N* = 115)	DM+/CAD+ (*N* = 104)	*p*-value
Demographics and medical history				
Age, years	73 ± 6	75 ± 7	73 ± 6	< 0.001
Female sex, n (%)	50 (21)	46 (40)	13 (13)	< 0.001
Hypertension, n (%)	178 (65)	113 (98)	90 (87)	< 0.001
Current smokers, n (%)	27 (10)	8 (7)	8 (8)	0.63
Previous MI, n (%)	165 (60)	0 (0)	51 (49)	< 0.001
Percutaneous coronary intervention, n (%)	198 (72)	0 (0)	69 (26)	< 0.001
Coronary artery bypass graft, n (%)	95 (34)	0 (0)	41 (39)	< 0.001
Stroke/TIA, n (%)	14 (5)	7 (6)	7 (7)	0.78
Medications				
Spironolactone, n (%)	138 (50)	58 (50)	52 (50)	1.00
ACE inhibitors, n (%)	145 (53)	62 (54)	56 (54)	0.96
Angiotensin receptor blockers, n (%)	59 (21)	41 (36)	28 (27)	0.014
Beta-blockers, n (%)	218 (79)	46 (40)	83 (80)	< 0.001
Thiazide diuretics, n (%)	21 (8)	35 (30)	19 (18)	< 0.001
Calcium channel blockers, n (%)	49 (18)	31 (27)	23 (22)	0.12
Lipid-lowering therapy, n (%)	256 (93)	68 (59)	100 (96)	< 0.001
Aspirin, n (%)	226 (82)	49 (43)	82 (79)	< 0.001
Any antiplatelet (including aspirin), n (%)	244 (88)	60 (52)	89 (86)	< 0.001
Anti-diabetic drugs*, n (%)	0 (0)	114 (99)	95 (91)	< 0.001
SGLT2 inhibitors	0 (0)	0 (0.0)	1 (1)	0.20
GLP1-RA	0 (0)	2 (2)	1 (1)	0.079
Insulin	0 (0)	29 (26)	24 (25)	< 0.001
Sulfonylureas	0 (0)	23 (20)	15 (16)	< 0.001
DPP-4 inhibitors	0 (0)	14 (12)	16 (15)	< 0.001
Biguanides	0 (0)	100 (88)	81 (85)	< 0.001
Glinides	0 (0)	4 (4)	2 (2)	0.005
Physical examination and symptoms				
BMI, Kg/m^2	27.8 ± 4.2	29.7 ± 6.1	30.9 ± 5.2	< 0.001
NYHA class, n (%)				0.015
I	223 (82)	107 (93)	82 (80)	
II	41 (15)	6 (5)	19 (19)	
III	7 (3)	2 (2)	1 (1)	
Heart rate, bpm	60 ± 9	66 ± 10	62 ± 10	< 0.001
SBP, mmHg	140 ± 21	147 ± 20	142 ± 19	0.005
DBP, mmHg	79 ± 11	77 ± 9	78 ± 11	0.27
Blood tests				
eGFR (CKD-EPI), ml/min/1,73 m^2	72.9 ± 14.4	69.7 ± 18.5	75.1 ± 16.2	0.12
Urea, mg/dL	7.6 ± 3.1	8.7 ± 2.9	8.4 ± 3.5	< 0.001
Sodium, mmol/L	139.4 ± 2.8	139.3 ± 2.9	138.7 ± 2.7	0.067
Potassium, mmol/L	4.4 ± 0.3	4.2 ± 0.4	4.4 ± 0.4	< 0.001
Haemoglobin, gr/dL	14.2 ± 1.3	13.4 ± 1.4	14.2 ± 1.3	< 0.001
Total cholesterol, mg/dL	147 [112; 174]	152 [107; 188]	135 [101; 159]	0.031
HbA1c, %	5.8 [5.5; 6.1]	6.3 [5.8; 7.3]	6.7 [6.3; 7.3]	< 0.001
PICP, µg/L	85.6 ± 26.9	81.9 ± 25.6	77.3 ± 21.6	0.018
PIIINP, µg/L	4.1 ± 1.6	4.4 ± 2.0	4.3 ± 1.7	0.37
Hs-troponin T, ng/L	13.4 ± 9.5	16.6 ± 9.5	19.3 ± 23.3	< 0.001
CITP, µg/L	3.6 [2.8; 4.7]	4.0 [2.9; 5.8]	3.6 [2.6; 4.6]	0.037
PICP/CITP ratio	22.3 [17.0; 29.0]	19.3 [13.2; 26.5]	20.7 [16.1; 27.9]	0.007
Galectin-3, µg/L	15.3 [12.9; 18.2]	17.5 [15.0; 21.3]	16.9 [13.9; 18.2]	< 0.001
GDF-15, ng/L	1212 [939; 1584]	2121 [1346; 2857]	1792 [1398; 2659]	< 0.001
NT-proBNP, ng/L	215 [134; 351]	209 [137; 377]	184 [113; 314]	0.42
Echocardiography				

Table 1 (continued)

	DM-/CAD+ (*N* = 276)	DM+/CAD- (*N* = 115)	DM+/CAD+ (*N* = 104)	*p*-value
LVEDVi, mL/m^2	45.4 ± 11.8	38.6 ± 9.3	42.5 ± 9.5	< 0.001
LVESVi, mL/m^2	17.7 ± 6.9	14.5 ± 5.1	16.0 ± 4.8	< 0.001
LVEF, %	61.5 ± 6.7	62.7 ± 6.8	62.5 ± 6.4	0.31
LV mass index, g/m^2	94.6 ± 26.5	103.8 ± 28.9	99.0 ± 21.7	0.010
LAVI, mL/m^2	31.8 ± 7.7	32.7 ± 9.3	31.1 ± 8.8	0.46
E/A ratio	0.91 ± 0.31	0.84 ± 0.28	0.87 ± 0.29	0.11
E/e' ratio	9.3 ± 3.1	10.8 ± 3.4	10.4 ± 3.6	< 0.001
TAPSE, mm	22 ± 6	24 ± 7	21 ± 6	0.013

* data missing for 1 patient in the group DM+/CAD- and 9 patients in the group DM+/CAD+

Abbreviations: ACE, angiotensin converting enzyme; BMI, body mass index; NT-proBNP, N-terminal pro–B-type natriuretic peptide; CITP, collagen type I C-terminal telopeptide; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GDF-15, growth differentiation factor 15; GLP1-RA, glucagon-like peptide-1 receptor agonists; HbA1c, glycated haemoglobin; LAVI, left atrial volume index; LV, left ventricle; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PICP, procollagen type I C-terminal propeptide; PIIINP, procollagen type-III N-terminal propeptide; SGLT2, sodium-glucose cotransporter 2; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion; TIA, transient ischemic attack

The HOMAGE trial (NCT02556450) was approved by relevant ethics committees and regulatory bodies; all participants provided written, informed consent. Statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) and R software (the R Foundation for Statistical Computing) version 4.1.2. A two-sided p-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

The baseline characteristics of the study population according to DM/CAD status are shown in Table 1. Overall, the 495 participants included in the present analysis had a similar profile to those included in the HOMAGE trial (data not shown).

Among DM/CAD groups, participants with DM+/CAD- tended to be older, were more likely to be female, and had a larger prevalence of hypertension. Moreover, they had higher concentrations of galectin-3 and GDF-15, smaller LV volumes, higher LV mass index, and higher echocardiographic markers of elevated filling pressures (E/e' ratio) (all $p \leq 0.01$). Conversely, DM-/CAD + participants showed the higher markers of PICP ($p \leq 0.01$). Spironolactone treatment was equally distributed across the DM/CAD phenotypes (50% for all).

Association of echocardiographic variables and circulating biomarkers with clinical phenotypes

At baseline, subjects with diabetes (DM+), regardless of the presence of coexistent CAD, exhibited a positive association with galectin-3, GDF-15 concentrations and E/e' ratio, and an inverse association with PICP values, PICP/CITP ratio and LV volumes compared to participants without diabetes but with CAD (DM-/CAD+; reference group) (Table 2).

At the 1-month follow-up, only GDF-15 absolute change was higher in subjects with diabetes compared to those without diabetes, irrespective of CAD status (Additional file 1: Table S1). No significant differences in the absolute change of echocardiographic variables or circulating biomarkers were observed between groups at 9 months follow-up (all p-values > 0.05) (Table 3).

Effect of spironolactone

The effect of spironolactone on GDF-15 was greater in DM+/CAD + participants (p for interaction = 0.031) than in other clinical phenotypes at 1 month. At this timepoint, spironolactone had a greater effect on left atrial volume index (LAVI, mean difference [mdiff]: −1.30; 95% confidence interval [CI] − 2.58 to − 0.02] ml/m^2, p = 0.047), E/A ratio (mdiff: −0.13; [95% CI: −0.19 to − 0.07], p < 0.001), CITP (mdiff: 0.09, [95% CI: 0.03 to 0.15], p < 0.001) and PICP/CITP ratio (mdiff: -2.95, [95% CI: -4.73 to -1.17], p < 0.001) in DM-/CAD + subjects compared to other DM/CAD groups, although this differential effect never reach statistical significance (all p for interaction > 0.05) (Additional file 2: Table S2). At the 9-month follow-up, we found no significant treatment effect interaction across DM/CAD phenotypes, but only a slightly more pronounced effect of spironolactone on markers of collagen turnover (PICP, PICP/CITP ratio), galectin-3 and structural and functional cardiac remodelling variables (LAVI, LV mass, E/A ratio, and E/e' ratio) in DM-/CAD + subjects (all p for interaction > 0.05) compared to other clinical phenotypes (Fig. 1; Additional file 3: Table S3).

Discussion

In this post-hoc analysis of the HOMAGE trial, we found that participants with diabetes, irrespective of the presence of CAD, had lower type I collagen synthesis (as demonstrated by lower PICP), and increased galectin-3 and GDF-15 levels at baseline as compared with DM-/CAD + individuals. In terms of cardiac structure and function, individuals with diabetes had smaller LV

Table 2 Association between baseline biomarkers and echocardiography parameters and DM/CAD status

Variables	DM+/CAD-		DM+/CAD+		
	Beta (95% CI)	*P*-value	Beta (95% CI)	*P*-value	Overall *p*-value*
Biomarkers					
PICP, µg/L	-6.973 (-13.778; -0.167)	0.045	-9.039 (-15.174; -2.903)	0.004	0.008
PIIINP, µg/L	0.114 (-0.348; 0.577)	0.63	-0.115 (-0.535; 0.305)	0.59	0.68
(Log) CITP, µg/L	1.052 (0.953; 1.162)	0.31	0.965 (0.882; 1.055)	0.44	0.32
(Log) PICP/CITP, ratio	0.867 (0.777; 0.968)	0.011	0.938 (0.849; 1.036)	0.21	0.035
(Log) Galectin-3, µg/L	1.127 (1.050; 1.209)	0.001	1.118 (1.048; 1.192)	< 0.001	< 0.001
(Log) GDF-15, ng/L	1.542 (1.360; 1.747)	< 0.001	1.535 (1.370; 1.720)	< 0.001	< 0.001
Echocardiography					
LVEDVi, mL/m^2	-6.323 (-9.696; -2.951)	< 0.001	-2.503 (-5.531; 0.526)	0.11	0.001
LVESVi, mL/m^2	-2.905 (-4.817; -0.992)	0.003	-1.400 (-3.120; 0.320)	0.11	0.009
LVEF, %	0.712 (-1.414; 2.837)	0.51	0.509 (-1.399; 2.417)	0.6	0.76
LV mass index, g/m^2	3.074 (-4.210; 10.357)	0.41	-2.382 (-8.806; 4.043)	0.47	0.42
LAVI, mL/m^2	-1.087 (-3.539; 1.366)	0.39	-1.345 (-3.573; 0.883)	0.24	0.43
E/A ratio	-0.014 (-0.099; 0.072)	0.76	-0.048 (-0.124; 0.028)	0.22	0.47
E/e' ratio	1.355 (0.462; 2.248)	0.003	0.879 (0.067; 1.690)	0.034	0.005
TAPSE, mm	1.358 (-0.456; 3.172)	0.14	-1.023 (-2.633; 0.587)	0.21	0.075

DM-/CAD+ group as reference.

When the dependent variable was log transformed, Exp(β) with 95% confidence intervals (CI) are reported. In this case, coefficient >1 and <1 indicate positive and negative association, respectively.

* Overall p-value for DM+ groups vs. DM-/CAD+ group

Analysis adjusted for: spironolactone treatment, sex, age, body mass index, hypertension status, estimated glomerular filtration rate, ACEi/ARBs, beta-blockers and statins use.

Abbreviations: ACEi, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CAD, coronary artery disease; CITP, collagen type I C-terminal telopeptide; DM, diabetes mellitus; GDF-15, growth differentiation factor 15; LAVI, left atrial volume index; LV, left ventricle; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; PICP, procollagen type I C-terminal propeptide; PIIINP, procollagen type-III N-terminal propeptide; TAPSE, tricuspid annular plane systolic excursion

volumes and increased echocardiographic markers of LV filling pressure, without sizably impact of CAD status, compared with DM-/CAD + participants. Overall, the treatment with spironolactone did not show a meaningful differential effect on these alterations according to DM/CAD phenotype (Graphical abstract).

The interplay between diabetes and CAD

The development of HF with preserved ejection fraction (HFpEF) has been previously attributed to a comorbidities-induced low-grade chronic inflammatory state, such as that seen in DM or CAD. This condition triggers a reduction in nitric oxide availability and coronary microvascular endothelial dysfunction, which stiffens cardiomyocytes and causes interstitial fibrosis, leading to increased diastolic LV filling pressures and ultimately resulting in HF [17]. Observational studies, such as the Framingham Heart Study, demonstrated that participants with DM face a 2- to 4-fold higher risk of developing HF compared to those without DM, even after adjustment for other cardiovascular risk factors [18]. Myocardial ischemia is a common pathway by which DM causes structural heart disease and HF [19]. In this context, hyperglycaemia and hyperinsulinemia accelerate atherosclerosis by promoting cell proliferation and inflammation [20], whereas changes towards a more atherogenic lipid profile and endothelial dysfunction are responsible for a shift toward a pro-thrombotic state [21]. Once CAD is established, the association with DM doubles the risk of developing HF compared with non-diabetics [22]. However, when DM is combined with other risk factors, such as hypertension, it can lead to LV dysfunction and HF, even without significant epicardial CAD [3, 4]. Notably, the coexistence of conditions such as obesity and hypertension significantly contributes to cardiac dysfunction by inducing macrophage polarization towards the pro-inflammatory M1 phenotype, resulting in alterations in circulating glucose and fatty acid substrates, lipotoxicity, and tissue hypoxia, which ultimately drive cardiac injury and the progression to HF [23].

Galectin-3 and GDF-15

Galectin-3, a potent cytokine expressed in various cells, plays a key role in mediating the inflammatory response [9]. Elevated levels of galectin-3 have been associated with an increased risk of incident HF in at-risk individuals [24]. In patients with DM, a condition characterized by a heightened systemic proinflammatory state [25], there is a significant increase in circulating galectin-3 levels [26]. In experimental models of diabetic

Table 3 Association between absolute change from baseline in biomarkers and echocardiography parameters at the 9-month follow-up and DM/CAD status

	DM+/CAD-		DM+/CAD+		
Variables	**Beta (95% CI)**	***P*-value**	**Beta (95% CI)**	***P*-value**	**Overall *p*-value***
Biomarkers					
PICP, µg/L	-2.802 (-8.736; 3.132)	0.36	-1.416 (-6.755; 3.924)	0.6	0.63
(Log) PIIINP, µg/L	1.013 (0.914; 1.123)	0.81	0.952 (0.867; 1.044)	0.29	0.48
(Log) CITP, µg/L	1.083 (0.988; 1.188)	0.09	0.973 (0.896; 1.057)	0.52	0.32
PICP/CITP, ratio	-2.338 (-4.572; -0.104)	0.04	-0.631 (-2.626; 1.364)	0.54	0.12
(Log) Galectin-3, µg/L	1.010 (0.959; 1.064)	0.71	1.017 (0.970; 1.066)	0.48	0.77
(Log) GDF-15, ng/L	1.058 (0.985; 1.136)	0.12	0.979 (0.917; 1.045)	0.53	0.13
Echocardiography					
LVEDVi, mL/m^2	-1.101 (-2.726; 0.523)	0.19	-0.832 (-2.213; 0.550)	0.24	0.28
LVESVi, mL/m^2	-0.548 (-1.360; 0.265)	0.19	-0.051 (-0.741; 0.640)	0.89	0.41
LVEF, %	0.511 (-1.118; 2.141)	0.54	-0.626 (-2.023; 0.772)	0.38	0.48
LV mass index, g/m^2	-2.136 (-5.852; 1.580)	0.26	-0.332 (-3.579; 2.916)	0.84	0.53
LAVI, mL/m^2	-0.427 (-1.990; 1.137)	0.59	-0.594 (-1.966; 0.779)	0.40	0.66
(Log) E/A ratio	0.984 (0.914; 1.059)	0.67	0.959 (0.900; 1.021)	0.19	0.42
(Log) E/e' ratio	1.002 (0.931; 1.078)	0.97	1.018 (0.954; 1.085)	0.60	0.86
TAPSE, mm	0.411 (-1.037; 1.860)	0.58	0.328 (-0.932; 1.589)	0.61	0.80

DM-/CAD+ group as reference.

When the dependent variable was log transformed, Exp(β) with 95% confidence intervals (CI) are reported. In this case, coefficient >1 and <1 indicate positive and negative association, respectively.

* Overall p-value for DM+ groups vs. DM-/CAD+ group

Analysis adjusted for: spironolactone treatment, sex, age, body mass index, hypertension status, estimated glomerular filtration rate, ACEi/ARBs, beta-blockers, statins, and baseline biomarkers/echocardiographic variables.

Abbreviations: ACEi, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CAD, coronary artery disease; CITP, collagen type I C-terminal telopeptide; DM, diabetes mellitus; GDF-15, growth differentiation factor 15; LAVI, left atrial volume index; LV, left ventricle; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; PICP, procollagen type I C-terminal propeptide; PIIINP, procollagen type-III N-terminal propeptide; TAPSE, tricuspid annular plane systolic excursion

cardiomyopathy, galectin-3 promoted myocardial apoptosis, oxidative stress, inflammation, and fibrosis in vivo and in vitro by the mechanism of reduction of NF-κB p65 activation [27]. Our study observed an increase in galectin-3 concentration without a corresponding increase in type 1 collagen synthesis in participants with diabetes compared to those without, suggesting an early involvement of galectin-3-related proinflammation pathways in DM. This stage may precede the progression to cardiac and vascular fibrosis, potentially serving as an early marker for subclinical disease and a target for preventive treatments [28].

Similar to galectin-3, participants with diabetes in HOMAGE trial showed an increased level of GDF-15 compared to non diabetics, regardless of CAD status. Prior studies in populations with diabetes have demonstrated an increase in GDF-15 levels [29], which are associated with impaired myocardial energetics and function [30, 31], as well as with an increased risk of incident HF [32, 33]. Elevated levels of GDF-15 in patients with diabetes were also associated with LV diastolic dysfunction and the onset of diabetic cardiomyopathy [34]. Furthermore, GDF-15 has also pro-atherogenic effects [35], and may serve as an indicator for the potential onset of CAD [36]. An analysis from the ARIC (Atherosclerosis Risk In Communities) study suggested that GDF-15 can be used for HF risk stratification among individuals with DM, thus allowing a better selection of candidates for effective HF prevention [10]. GDF-15 has also showed to be able to predict diastolic dysfunction in the very long-term [37] and to be a key mediator of the signalling of anorexia in established HF [38]. The ongoing GARDEN-TIMI 74 trial (NCT 05492500) is evaluating the effects of blocking GDF-15 in HF using the monoclonal antibody ponsegromab, with positive outcomes potentially paving the way for its application in earlier stages of HF.

Echocardiographic alterations in subjects at risk of HF

Participants with diabetes in the HOMAGE trial had smaller LV volumes and higher indirect markers of raised LV filling pressures (E/e' ratio) compared with non-diabetics. In DM, metabolic disturbances along with the influence of other risk factors can induce progressive changes in cardiac structure and function, including LV remodelling, and impaired LV systolic and diastolic function [39], ultimately serving as precursors to the development of HF [4, 40].

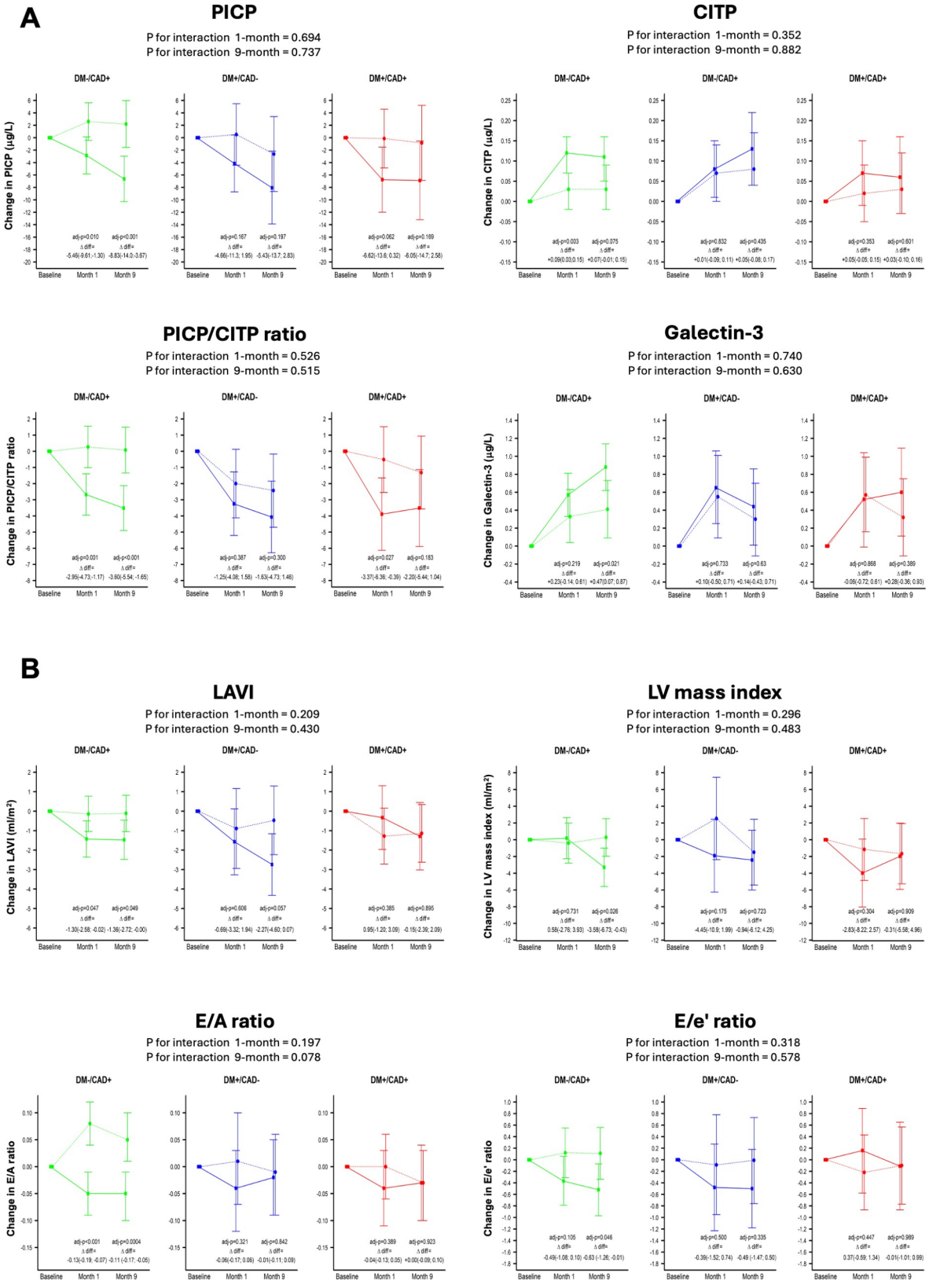


Fig. 1 (See legend on next page.)

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Fig. 1 Biomarker (**A**) and echocardiographic (**B**) changes with spironolactone at 1 month and 9 months follow-up by DM/CAD status. Continuous and dashed lines represent the change in the studied variable according to the treatment with spironolactone or placebo over follow-up, respectively. The measured values and their 95% confidence intervals at each time point are slightly offset to enhance readability. The interpolated line between the markers (squares or dots) represents the changing trend. p-values were adjusted for sex, age, body mass index, hypertension status, estimated glomerular filtration rate and baseline biomarkers/echocardiographic variables. Abbreviations: Adj-p, adjusted p-value; CAD, coronary artery disease; CITP, collagen type I C-terminal telopeptide; DM, diabetes mellitus; LAVI, left atrial volume index; LV, left ventricle; PICP, procollagen type I C-terminal propeptide

A recent clustering study involving two population-based cohorts revealed that participants with diastolic changes, characterized by a low LV end-diastolic volume and high E/e' ratio, faced a higher risk of cardiovascular (CV) mortality and HF hospitalization compared to individuals with predominantly normal echocardiographic parameters [41]. These patients also had elevated levels of circulating biomarkers related to inflammation, thus providing further biological plausibility for the hypothesized link between an increased systemic proinflammatory state, as seen in DM [25], and the development of diastolic dysfunction [17, 42, 43]. Another study in patients with diabetes showed that an echocardiographic phenotype characterized by diastolic dysfunction (marked by a high E/e' ratio and small LV volumes) was associated with a higher risk of CV hospitalization or death, compared to diabetics without echocardiographic signs of subtle myocardial alterations [44]. In this setting, diastolic function impairment has previously been considered as an early marker of HF development [40, 45]. Our findings suggest that diabetes affects diastolic function relatively independently from CAD. DM may actually be the primary driver of biological and diastolic alterations, eventually leading to HFpEF.

The impact of spironolactone treatment

Previous analysis of the HOMAGE trial showed that DM did not significantly influence spironolactone effect, especially on proteomic markers [6]. In the analysis presented here, accounting for CAD does not alter the homogeneity of the spironolactone effect. Indeed, spironolactone treatment appears to similarly affect echocardiographic parameters and circulating biomarkers, regardless of DM/CAD status. The only outcome showing a significant interaction between DM/CAD status and treatment effect was GDF-15, with a trend towards more marked reduction at 1 month follow-up in the DM+/CAD + subgroup. Although we lack a definitive explanation for this finding, one possible interpretation could rely on the putative role of GDF-15 as an inflammation-induced central mediator of tissue tolerance and its increase during inflammatory states [46], such as CAD and DM. Indeed, the observed attenuation of GDF-15 levels in the DM+/CAD + subgroup might reflect a possible anti-inflammatory effect of spironolactone treatment [8, 47]. As GDF-15 levels were higher in DM+/CAD + patients at baseline, this suggests that this biomarker was more significantly reduced during the initial weeks of spironolactone treatment. Similarly, a more prominent effect of spironolactone on markers of collagen turnover was observed in the first month, as reported in the seminal HOMAGE paper [8]. However, this difference did not persist at later time points, raising questions about whether this result indicates a substantial differential biological impact of spironolactone in the short term or is simply due to chance.

Limitations

The main limitation of the current study is the post-hoc nature and the relatively moderate sample size; thus, it should be regarded as mechanistic and hypothesis-generating. Another notable limitation is the absence of a DM-/CAD- control group, due to the low sample size in this category ($N = 32$) within the studied cohort. Nonetheless, our analysis offers meaningful insights into the key differences between CAD and DM providing valuable information about the distinct alterations in echocardiographic variables and circulating biomarkers, as well as the effects of spironolactone on these parameters. The circulating levels of GDF-15 in the diabetic subgroup may have been impacted by metformin treatment (83%) [48]. However, this influence is unlikely to alter the demonstrated association between GDF-15 and the DM subgroup, a correlation also confirmed in other studies [29]. Due to the absence of a systematic examination to rule out ischemic cardiomyopathy in every patient, it's possible that some individuals labelled as "no CAD" could actually have undetected coronary atherosclerosis, microvascular disease or may have experienced a silent myocardial infarction in the past, potentially leading to errors in group classification. In the HOMAGE trial, some participants with elevated glycated haemoglobin levels (HbA1c ≥ 6.5%) were not labelled as diabetics (4.5%), as the trial inclusion criteria only considered those on anti-diabetic medications. Conversely, the largest part of those classified as diabetics showed well-controlled HbA1c levels. This scenario might have nuanced the observed impact of diabetes on structural and functional cardiac alterations in the study. Nonetheless, this reflects the clinical practice, where some patients may not receive treatment despite being diabetic, while others are under strict management. The use of a historical cohort, where newer antidiabetic treatments such as SGLT2 inhibitors and GLP-1 receptor agonists were not widely used, prevented us from evaluating their impact

on circulating biomarkers and echocardiographic variables across DM subgroups. We did not investigate the full spectrum of potential biomarkers involved in cardiac injury and remodelling, such as soluble suppression of tumorigenicity 2 (sST2), which may have led to the omission of valuable additional information [49]. The HOMAGE study enrolled patients at risk for HF, all of whom were over 60 years old and had comorbidities, with hypertension being notably the most prevalent among those with DM. These factors may have acted as confounders and could have contributed to our findings. Another potential confounder that could have impacted our results is the use of different antidiabetic treatment regimens across the studied population [50]. Finally, the expected low number of HF events in the HOMAGE population prevented us from evaluating the differential impact of circulating biomarkers and echocardiographic variables on clinical outcomes.

Conclusions

Among participants in the HOMAGE trial, CAD did not alter the association of diabetes with circulating biomarkers and echocardiographic changes, thus suggesting that diabetes was the primary driver of cardiac alterations in this population. These alterations were mainly related to the domains of chronic inflammation and diastolic function. Treatment effect of spironolactone was not significantly different across DM/CAD phenotypes.

Abbreviations

CAD	Coronary artery disease
CITP	Collagen type I C-terminal telopeptide
DM	Diabetes mellitus
GDF-15	Growth differentiation factor-15
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HOMAGE	Heart OMics in AGEing trial
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PICP	Procollagen type I C-terminal propeptide
PIIINP	Procollagen type-III N-terminal propeptide

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Consortia

HOMAGE "Heart Omics in AGEing" consortium.

Author contributions

LM, NG and FZ designed the study and drafted the manuscript. ZL, LM and NG analyzed the data. MK, JPF, FE, PP, JP and JAJV collected the data and substantially revised the manuscript. CD, SH, ALC, AG, PR, JGFC, FZ and NG gathered the funding, supervised the study at their respective location, interpreted the data and substantially revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

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

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Author details

[1]Centre d'Investigations Cliniques Plurithématique 1433 and Inserm U1116, CHRU Nancy, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Université de Lorraine, Nancy, France
[2]Department of Cardiology, Tokyo Medical University Hospital, Tokyo, Japan
[3]Department of Surgery and Physiology, Cardiovascular Research and Development Center, Faculty of Medicine, University of Porto, Porto, Portugal
[4]School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, UK
[5]Department of Cardiology, Castle Hill Hospital, University of Hull, East Riding of Yorkshire, UK
[6]Deutsches Herzzentrum der Charité, Klinik für Kardiologie, Angiologie & Intensivmedizin, Augustenburger Platz 1, 13353 Berlin, Germany
[7]Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Charitéplatz 1, 10117 Berlin, Germany
[8]DZHK (German Centre for Cardiovascular Research), Partner Site Berlin, Berlin, Germany
[9]Department of Pathology, Anatomy and Physiology Universidad de Navarra and IdiSNA, CIMA Universidad de Navarra, Pamplona, Spain
[10]CIBERCV, Carlos III Institute of Health, Madrid, Spain
[11]Department of Cardiology, Maastricht University Medical Center, Maastricht, The Netherlands
[12]Department of Medicine and Nephrology-Hemodialysis, Princess Grace Hospital, Monaco, Monaco
[13]M-CRIN (Monaco Clinical Research Infrastructure Network), Monaco, Monaco
[14]Monaco Private Hemodialysis Centre, Monaco, Monaco

[15]Robertson Centre for Biostatistics and Clinical Trials, Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK

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