

Supplemental Material

Supplemental Table 1. Protein names from Olink® CVDII panel sorted in alphabetical order

Protein full name	Entry name	Uniprot ID**
Angiotensin-converting enzyme 2	ACE2	Q9BYF1
Adisintegrin and metalloproteinase with thrombospondin motifs 13	ADAMTS13	Q76LX8
ADM	ADM	P35318
Agouti-related protein	AGRP	O00253
Protein AMBP	AMBP	P02760
Angiopoietin-1	ANG1	Q15389
Bone morphogenetic protein 6	BMP6	P22004
Natriuretic peptides B	BNP	P16860
Carbonic anhydrase 5A, mitochondrial	CA5A	P35218
C-C motif chemokine 17	CCL17	Q92583
C-C motif chemokine 3	CCL3	P10147
T-cell surface glycoprotein CD4	CD4	P01730
CD40 ligand	CD40L	P29965
SLAM family member 5	CD84	Q9UIB8
Carcinoembryonic antigenrelated cell adhesion molecule 8	CEACAM8	P31997
Chymotrypsin C	CTRC	Q99895
Cathepsin L1	CTSL1	P07711
C-X-C motif chemokine 1 (CVD2)	CXCL1	P09341
Decorin	DCN	P07585
2,4-dienoyl-CoA reductase, mitochondrial	DECR1	Q16698
Dickkopf-related protein 1	DKK1	O94907
Fatty acid-binding protein, intestinal	FABP2	P12104
Fibroblast growth factor 21 (CVD2)	FGF21	Q9NSA1
Fibroblast growth factor 23 (CVD2)	FGF23	Q9GZV9
Follistatin	FS	P19883
Galectin-9	GAL9	O00182
Growth/differentiation factor 2	GDF2	Q9UK05
Growth hormone	GH	P01241
Gastric intrinsic factor	GIF	P27352
Lactoylglutathione lyase	GLO1	Q04760
Gastrotropin	GT	P51161
Hydroxyacid oxidase 1	HAOX1	Q9UJM8
Proheparin-binding EGF-like growth factor	HBEGF	Q99075
Heme oxygenase 1	HO1	P09601
Osteoclast-associated immunoglobulin-like receptor	HOSCAR	Q8IYS5
Heat shock 27 kDa protein	HSP27	P04792
Alpha-L-iduronidase	IDUA	P35475
Low affinity immunoglobulin gamma Fc region receptor II-b	IGGFCRECEPT ORIB	P31994
Pro-interleukin-16	IL16	Q14005
Interleukin-17D	IL17D	Q8TAD2
Interleukin-18 (CVD2)	IL18	Q14116
Interleukin-1 receptor antagonist protein	IL1RA	P18510

Interleukin-1 receptor-like 2	IL1RL2	Q9HB29
Interleukin-27	IL27	Q8NEV9
Interleukin-4 receptor subunit alpha	IL4RA	P24394
Interleukin-6 (CVD2)	IL6	P05231
Melusin	ITGB1BP2	Q9UKP3
Kidney injury molecule 1	KIM1	Q96D42
Leptin	LEP	P41159
Lectin-like oxidized LDL receptor 1	LOX1	P78380
Lipoprotein lipase	LPL	P06858
Macrophage receptor MARCO	MARCO	Q9UEW3
Tyrosine-protein kinase Mer	MERTK	Q12866
Matrix metalloproteinase-12	MMP12	P39900
Matrix metalloproteinase-7	MMP7	P09237
NF-kappa-B essential modulator	NEMO	Q9Y6K9
Pappalysin-1	PAPPA	Q13219
Proteinase-activated receptor 1	PAR1	P25116
Poly [ADP-ribose] polymerase 1	PARP1	P09874
Platelet-derived growth factor subunit B	PDGFSUBUNIT B	P01127
Programmed cell death 1 ligand 2	PDL2	Q9BQ51
Polymeric immunoglobulin receptor	PIGR	P01833
Placenta growth factor	PLGF	P49763
Prolargin	PRELP	P51888
Brother of CDO	PROTEINBOC	Q9BWV1
Serine protease 27	PRSS27	Q9BQR3
Prostasin	PRSS8	Q16651
P-selectin glycoprotein ligand 1	PSGL1	Q14242
Pentraxin-related protein PTX3	PTX3	P26022
Receptor for advanced glycosylation end products	RAGE	Q15109
Renin	REN	P00797
Stem cell factor (CVD2)	SCF	P21583
Serpin A12	SERPINA12	Q8IW75
SLAM family member 7	SLAMF7	Q9NQ25
Superoxide dismutase [Mn], mitochondrial	SOD2	P04179
Sortilin	SORT1	Q99523
Spondin-2	SPON2	Q9BUD6
Proto-oncogene tyrosine-protein kinase Src	SRC	P12931
Serine/threonine-protein kinase 4	STK4	Q13043
Tissue factor	TF	P13726
Protein-glutamine gamma-glutamyltransferase 2	TGM2	P21980
Thrombospondin-2	THBS2	P35442
Thrombopoietin	THPO	P40225
Angiopoietin-1 receptor	TIE2	Q02763
Thrombomodulin	TM	P07204
Tumor necrosis factor receptor superfamily member 10A	TNFRSF10A	O00220
Tumor necrosis factor receptor superfamily member 11A	TNFRSF11A	Q9Y6Q6
Tumor necrosis factor receptor superfamily member 13B	TNFRSF13B	O14836
TNF-related apoptosis-inducing ligand receptor 2	TRAILR2	O14763

Vascular endothelial growth factor D	VEGFD	O43915
V-set and immunoglobulin domain-containing protein 2	VSIG2	Q96IQ7
Lymphotactin	XCL1	P47992

Legend: *CVDII: cardiovascular II panel; **UniProt ID from UniProt Knowledgebase

Supplemental Table 2. Clinical variables and their association with worsening kidney function

Variable	Beta coef. (95%CI)	Z	P
Anemia	1.39 (0.96 to 1.82)	6.4	0.00001
Previous HFH	0.79 (0.37 to 1.22)	3.7	0.0002
Diuretic use	0.74 (0.31 to 1.16)	3.4	0.001
eGFR <60	0.42 (-0.02 to 0.85)	1.9	0.06
Hypertension	0.43 (-0.03 to 0.88)	1.9	0.065
Alogliptin	1.13 (-0.25 to 2.52)	1.6	0.108
Insulin	0.37 (-0.08 to 0.82)	1.6	0.111
Female	0.28 (-0.13 to 0.68)	1.3	0.183
Duration of diabetes >7yr	0.17 (-0.26 to 0.60)	0.8	0.447
Smoker	-0.05 (-0.69 to 0.60)	-0.1	0.891
Age >65yr	-0.32 (-0.74 to 0.10)	-1.5	0.136
Metformin	-0.36 (-0.79 to 0.06)	-1.7	0.096
Statin	-0.71 (-1.28 to -0.14)	-2.5	0.014

Legend: HFH, heart failure hospitalization; eGFR, estimated glomerular filtration rate.
 Light Green: variables with P-value ≤ 0.0001

Supplemental Table 3. Biomarkers associated with worsening kidney function $\geq 40\%$ from baseline in a mixed random effects logistic regression model

Biomarker	Beta coef. (95%CI)	Z	P
KIM1	0.84 (0.66-1.03)	9.1	0.00001
PGF	1.81 (1.31-2.32)	7.1	0.00001
TRAILR2	1.06 (0.76-1.36)	6.9	0.00001
TNFRSF11A	1.26 (0.89-1.63)	6.6	0.00001
TM	2.07 (1.46-2.68)	6.6	0.00001
TNFRSF10A	1.49 (1.03-1.95)	6.4	0.00001
IL4RA	1.29 (0.88-1.69)	6.2	0.00001
uNGAL	0.33 (0.22-0.44)	6	0.00001
TF	1.82 (1.22-2.43)	5.9	0.00001
VSIG2	0.9 (0.56-1.24)	5.1	0.00001
RAGE	1.02 (0.6-1.45)	4.7	0.00001
AMBP	2.19 (1.25-3.13)	4.6	0.00001
VEGFD	1.21 (0.69-1.73)	4.5	0.00001
XCL1	0.61 (0.31-0.9)	4	0.0001
AGRP	0.66 (0.34-0.98)	4	0.0001
BNP	0.2 (0.1-0.3)	4	0.0001
CD4	1.18 (0.61-1.75)	4	0.0001
SPON2	2.11 (1.02-3.21)	3.8	0.0001
MERTK	0.86 (0.4-1.32)	3.7	0.0003
BOC	1.21 (0.55-1.88)	3.6	0.0003
GAL9	1.02 (0.46-1.57)	3.6	0.0004
PRSS8	1.22 (0.54-1.91)	3.5	0.0004
MMP7	0.29 (0.12-0.47)	3.3	0.001
PRELP	1.43 (0.55-2.31)	3.2	0.0014
V-GT	0.37 (0.15-0.6)	3.2	0.0013
PRSS27	0.54 (0.19-0.88)	3.1	0.0022
DCN	1.23 (0.45-2.02)	3.1	0.002
TNFRSF13B	0.65 (0.23-1.06)	3.1	0.0022
CA5A	0.29 (0.1-0.47)	3.1	0.0022
uKIM1	0.24 (0.08-0.39)	2.9	0.0034
PAR1	0.44 (0.15-0.74)	2.9	0.0034
SCF	0.68 (0.22-1.14)	2.9	0.0037
IL16	0.4 (0.12-0.68)	2.8	0.005
LPL	0.55 (0.16-0.93)	2.8	0.0051
CEACAM8	0.3 (0.07-0.52)	2.6	0.0089
FABP2	0.35 (0.09-0.61)	2.6	0.0084
HOSCAR	1.15 (0.28-2.03)	2.6	0.0097
TROPONIN I	0.12 (0.02-0.21)	2.4	0.0181
IL17D	0.51 (0.09-0.93)	2.4	0.0172
PTX3	0.43 (0.08-0.78)	2.4	0.0165
MMP12	0.33 (0.06-0.59)	2.4	0.0153
REN	0.28 (0.04-0.51)	2.3	0.0205

CCL3	0.3 (0.04-0.56)	2.3	0.0232
HO1	0.44 (0.05-0.82)	2.2	0.0257
HSP27	0.35 (0.04-0.67)	2.2	0.0278
ACE2	0.28 (0.02-0.54)	2.1	0.0355
ADM	0.25 (0.01-0.49)	2	0.0415
IL27	0.44 (0.01-0.88)	2	0.0438
IDUA	0.31 (-0.02-0.64)	1.8	0.0663
FGF21	0.12 (-0.01-0.26)	1.8	0.0751
CTSL1	0.51 (-0.04-1.06)	1.8	0.071
PAPPA	0.26 (-0.06-0.58)	1.6	0.1078
IL6	0.15 (-0.05-0.34)	1.5	0.1414
LOX1	0.17 (-0.06-0.4)	1.5	0.1383
PDL2	0.3 (-0.11-0.71)	1.4	0.1533
TGM2	0.16 (-0.07-0.4)	1.4	0.1678
GH	0.07 (-0.03-0.17)	1.3	0.183
IL18	0.19 (-0.12-0.5)	1.2	0.2218
GLO1	0.12 (-0.08-0.32)	1.2	0.236
IGGFCRECEPTORIIB	0.12 (-0.08-0.32)	1.2	0.2382
BMP6	0.16 (-0.13-0.45)	1.1	0.2696
THPO	0.21 (-0.16-0.58)	1.1	0.2614
SLAMF7	0.14 (-0.14-0.42)	1	0.3367
FS	0.2 (-0.18-0.57)	1	0.3099
PIGR	0.65 (-0.7-1.99)	0.9	0.3461
FGF23	0.08 (-0.12-0.27)	0.8	0.429
CCL17	0.06 (-0.08-0.2)	0.8	0.4116
THBS2	0.3 (-0.52-1.11)	0.7	0.4745
DKK1	0.06 (-0.15-0.28)	0.6	0.5562
SRC	0.03 (-0.1-0.16)	0.4	0.6677
GIF	0.03 (-0.13-0.2)	0.4	0.6746
SORT1	0.07 (-0.4-0.54)	0.3	0.7721
NEMO	0.02 (-0.12-0.16)	0.3	0.738
STK4	0.01 (-0.08-0.1)	0.2	0.8733
GDF2	0.03 (-0.27-0.34)	0.2	0.8313
IL1RL2	0.03 (-0.42-0.48)	0.1	0.8948
ANG1	0 (-0.13-0.13)	0	0.9866
PDGFSUBUNITB	0 (-0.12-0.13)	0	0.9929
CD84	0 (-0.31-0.31)	0	0.9953
CD40L	0 (-0.12-0.12)	-0.1	0.956
IL1RA	-0.01 (-0.26-0.24)	-0.1	0.9485
MARCO	-0.02 (-0.58-0.54)	-0.1	0.9463
HAOX1	0 (-0.13-0.12)	-0.1	0.9506
SOD2	-0.22 (-1.45-1.02)	-0.3	0.7319
ITGB1BP2	-0.01 (-0.1-0.07)	-0.3	0.7759
HBEGF	-0.04 (-0.25-0.16)	-0.4	0.6745
DECR1	-0.05 (-0.18-0.08)	-0.7	0.4748
TIE2	-0.26 (-0.9-0.38)	-0.8	0.4195

SERPINA12	-0.06 (-0.2-0.08)	-0.8	0.3957
PSGL1	-0.34 (-0.94-0.27)	-1.1	0.2742
LEP	-0.11 (-0.3-0.09)	-1.1	0.289
PARP1	-0.1 (-0.28-0.07)	-1.1	0.2508
CTRC	-0.13 (-0.35-0.08)	-1.2	0.2115
CXCL1	-0.08 (-0.2-0.04)	-1.3	0.2024
ADAMTS13	-0.59 (-1.35-0.17)	-1.5	0.1307

Caption: Models adjusted on all variables depicted in the Supplemental Table 2 plus visit by treatment interaction.

Light Green: variables with P-value ≤ 0.0001

Supplemental Table 4. Biomarkers associated with eGFR slope in a mixed random effects linear regression model

Biomarker	Beta coef. (95%CI)	Z	P
PGF	-4.77 (-5.4--4.15)	-15	0.00001
KIM1	-1.35 (-1.58--1.12)	-11.5	0.00001
TNFRSF11A	-2.54 (-3--2.08)	-10.8	0.00001
TM	-3.71 (-4.39--3.02)	-10.6	0.00001
TRAILR2	-2.62 (-3.12--2.12)	-10.2	0.00001
SPON2	-5.85 (-7.02--4.69)	-9.9	0.00001
TF	-3.61 (-4.35--2.87)	-9.6	0.00001
RAGE	-2.34 (-2.83--1.85)	-9.4	0.00001
IL4RA	-2.59 (-3.16--2.02)	-8.9	0.00001
AMBP	-4.82 (-5.93--3.7)	-8.5	0.00001
TNFRSF10A	-2.45 (-3.04--1.86)	-8.1	0.00001
PRSS8	-3.19 (-3.96--2.42)	-8.1	0.00001
VSIG2	-1.52 (-1.93--1.11)	-7.3	0.00001
BNP	-0.45 (-0.57--0.33)	-7.2	0.00001
VEGFD	-1.67 (-2.17--1.18)	-6.6	0.00001
MMP7	-0.67 (-0.88--0.46)	-6.4	0.00001
BOC	-2.35 (-3.08--1.62)	-6.3	0.00001
CD4	-2.16 (-2.83--1.48)	-6.3	0.00001
GAL9	-2.12 (-2.8--1.44)	-6.1	0.00001
MERTK	-1.71 (-2.26--1.16)	-6.1	0.00001
FABP2	-0.86 (-1.15--0.57)	-5.8	0.00001
SCF	-1.46 (-1.96--0.96)	-5.7	0.00001
PRSS27	-1.19 (-1.6--0.77)	-5.6	0.00001
MMP12	-0.91 (-1.23--0.59)	-5.5	0.00001
DCN	-2.51 (-3.45--1.57)	-5.2	0.00001
AGRP	-1.04 (-1.44--0.65)	-5.2	0.00001
IL17D	-1.55 (-2.15--0.95)	-5.1	0.00001
PDL2	-1.2 (-1.69--0.72)	-4.9	0.00001
PRELP	-1.72 (-2.48--0.96)	-4.4	0.00001
XCL1	-0.73 (-1.06--0.4)	-4.4	0.00001
ADM	-0.51 (-0.75--0.28)	-4.2	0.00001
uNGAL	-0.3 (-0.44--0.16)	-4.1	0.00001
TROPONIN I	-0.24 (-0.36--0.12)	-4	0.0001
LPL	-0.68 (-1.03--0.32)	-3.8	0.0002
CTSL1	-1.26 (-1.92--0.6)	-3.8	0.0002
PIGR	-2.84 (-4.34--1.34)	-3.7	0.0002
FGF21	-0.3 (-0.46--0.14)	-3.6	0.0003
V-GT	-0.51 (-0.78--0.23)	-3.6	0.0003
IL16	-0.6 (-0.93--0.27)	-3.6	0.0004
HOSCAR	-1 (-1.65--0.34)	-3	0.0029
CCL3	-0.47 (-0.79--0.15)	-2.9	0.0039
GDF2	-0.54 (-0.91--0.17)	-2.9	0.0041

CA5A	-0.34 (-0.57--0.1)	-2.8	0.0059
ACE2	-0.44 (-0.76--0.12)	-2.7	0.0076
TNFRSF13B	-0.69 (-1.2--0.18)	-2.7	0.0076
LEP	-0.31 (-0.55--0.07)	-2.5	0.0124
HO1	-0.4 (-0.82-0.02)	-1.9	0.059
FGF23	-0.23 (-0.49-0.04)	-1.7	0.0945
THBS2	-0.71 (-1.67-0.24)	-1.5	0.143
CTRC	-0.18 (-0.44-0.08)	-1.4	0.1706
SLAMF7	-0.24 (-0.57-0.1)	-1.4	0.1718
PAR1	-0.13 (-0.41-0.14)	-1	0.3401
IL18	-0.18 (-0.55-0.19)	-0.9	0.3469
PAPPA	-0.16 (-0.55-0.22)	-0.8	0.4084
uKIM1	-0.07 (-0.24-0.11)	-0.7	0.4573
IL6	-0.09 (-0.34-0.16)	-0.7	0.476
IGGFCRECEPTORIIIB	-0.08 (-0.31-0.15)	-0.7	0.5002
THPO	-0.14 (-0.56-0.29)	-0.6	0.5252
IL27	-0.12 (-0.64-0.4)	-0.5	0.6453
BMP6	-0.06 (-0.36-0.25)	-0.4	0.7195
CEACAM8	-0.03 (-0.31-0.25)	-0.2	0.8334
MARCO	-0.07 (-0.76-0.61)	-0.2	0.8364
FS	-0.03 (-0.47-0.41)	-0.1	0.8865
SERPINA12	0.02 (-0.15-0.18)	0.2	0.8366
GH	0.01 (-0.11-0.13)	0.2	0.8484
ADAMTS13	0.18 (-0.61-0.97)	0.4	0.6576
REN	0.06 (-0.21-0.32)	0.4	0.6814
IDUA	0.07 (-0.31-0.46)	0.4	0.7057
HSP27	0.06 (-0.27-0.39)	0.4	0.7197
GIF	0.07 (-0.12-0.27)	0.7	0.4775
PTX3	0.17 (-0.25-0.59)	0.8	0.4406
IL1RL2	0.25 (-0.29-0.78)	0.9	0.3651
DKK1	0.11 (-0.13-0.35)	0.9	0.3724
SORT1	0.29 (-0.23-0.82)	1.1	0.277
LOX1	0.15 (-0.12-0.41)	1.1	0.2855
IL1RA	0.17 (-0.14-0.47)	1.1	0.2875
TGM2	0.17 (-0.1-0.45)	1.2	0.2175
HAOX1	0.11 (-0.05-0.26)	1.3	0.1822
ANG1	0.12 (-0.02-0.27)	1.6	0.1004
TIE2	0.65 (-0.13-1.44)	1.6	0.1041
PSGL1	0.62 (-0.13-1.37)	1.6	0.1047
CCL17	0.13 (-0.03-0.29)	1.6	0.1211
PDGFSUBUNITB	0.13 (-0.01-0.27)	1.8	0.0691
SOD2	1.53 (-0.02-3.07)	1.9	0.0532
SRC	0.15 (0-0.3)	1.9	0.0563
GLO1	0.25 (0.01-0.48)	2.1	0.0388
PARP1	0.24 (0.05-0.42)	2.5	0.0113
CXCL1	0.18 (0.04-0.33)	2.5	0.0117

HBEGF	0.3 (0.08-0.53)	2.6	0.0089
NEMO	0.25 (0.1-0.41)	3.2	0.0015
CD84	0.57 (0.24-0.91)	3.3	0.0009
STK4	0.19 (0.08-0.29)	3.4	0.0006
CD40L	0.24 (0.1-0.38)	3.5	0.0005
ITGB1BP2	0.2 (0.1-0.29)	4.1	0.00001
DECR1	0.31 (0.17-0.46)	4.2	0.00001

Legend: eGFR, estimated glomerular filtration rate.

Caption: Models adjusted on all variables depicted in the Supplemental Table 2 plus visit by treatment interaction.

Light Green: variables with P-value ≤ 0.0001

Dark Green: variables common from the logistic model presented in the Supplemental Table 3.

Supplemental Table 5. Association of KIM-1 with total WKF events among patients with available UACR (n =2999) and after multiple imputation (n =5380)

Variables	Beta coef. (95%CI)	Z-score	P-value
Complete case n =2999			
KIM1 (per doubling concentration)	0.55 (0.35 to 0.75)	5.3	<0.0001
Age (per year)	-0.01 (-0.03 to 0.01)	-0.9	0.37
Male sex	0.15 (-0.23 to 0.53)	0.8	0.44
eGFR (per 10 ml/min)	0.04 (-0.05 to 0.14)	0.9	0.39
UACR (per doubling concentration)	0.17 (0.08 to 0.27)	3.7	<0.0001
Multiple imputation n =5380			
KIM1 (per doubling concentration)	0.62 (0.44 to 0.79)	6.9	<0.0001
Age (per year)	-0.01 (-0.01 to 0.02)	0.5	0.62
Male sex	0.25 (-0.09 to 0.59)	1.4	0.15
eGFR (per 10 ml/min)	0.01 (-0.01 to 0.01)	1.7	0.10
UACR (per doubling concentration)	0.17 (0.09 to 0.26)	3.9	<0.0001

Legend: KIM-1, kidney injury molecule-1; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

Model adjusted for the Kidney Failure Risk Equation (KFRE) including age, sex, eGFR, and UACR.

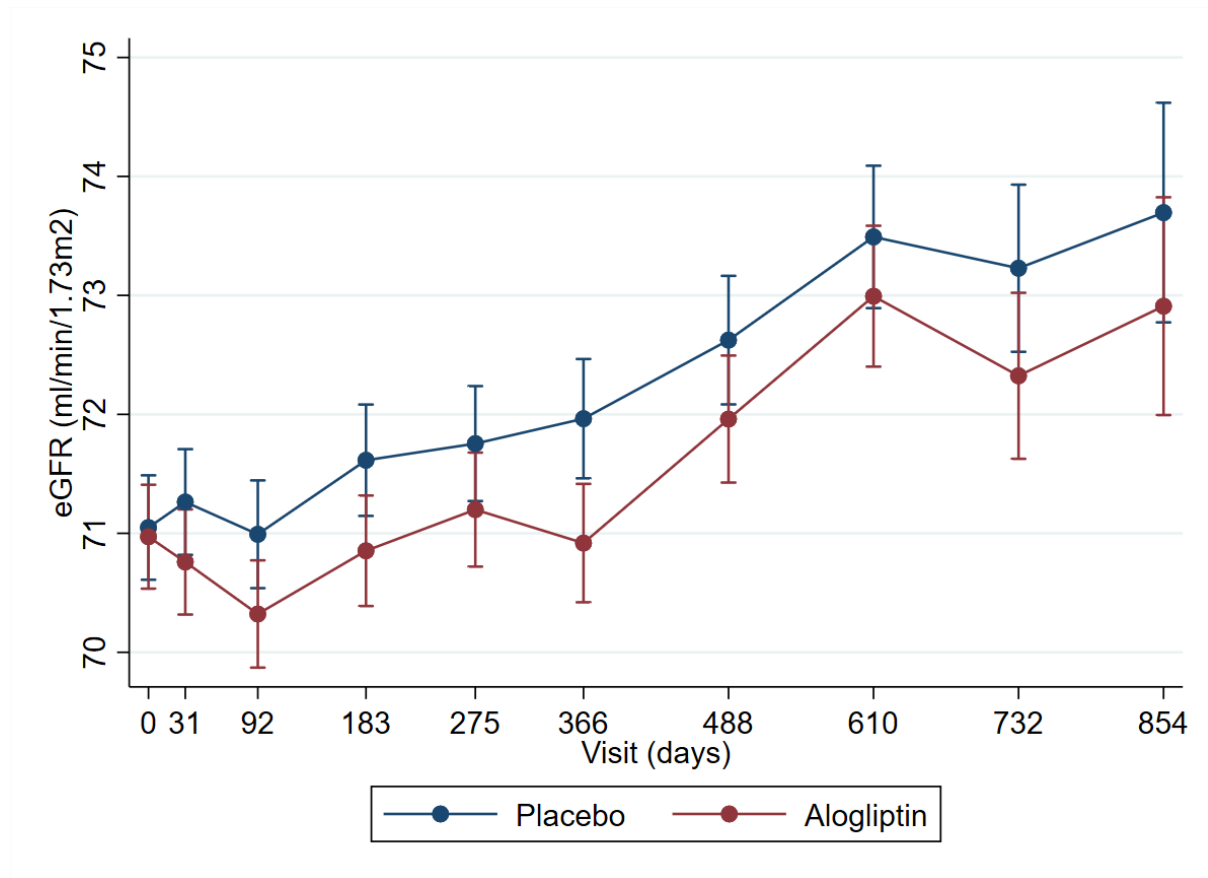
AUC of the KFRE model alone is =0.68. The AUC of KFRE+KIM-1 is =0.75. The p-value for the difference between the nested models is <0.0001.

Note: further adjustment on age, sex, baseline eGFR, anemia, diabetes duration, smoking, hypertension, prior HF hospitalization, use of diuretics, ACE/ARBs, insulin, metformin, statins, randomized treatment, diuretics, UACR, race, glycosylated

hemoglobin, and time since acute coronary syndrome does not change the results:

KIM-1 Beta per doubling concentration =0.53, Z-score =6.0.

Supplemental Figure 1. Effect of alogliptin (vs. placebo) on eGFR over time.



Legend: eGFR, estimated glomerular filtration rate.

eGFR slope of change (alogliptin vs. placebo) = -1.11 (-2.55 to 0.33), P =0.13.