Supplemental Appendix 1

Main clinical and biochemical data of the MMKD study population.

	Whole group (n=173)	Non-progressors (n=110)	Progressors (n=63)	p-value [a]
Age (years)	46±12	45±12	49±11	0.07
Male gender (%)	67%	66%)	67%	0.97
Current smokers, n (%)	30 (17%)	16 (15%)	14 (22%)	0.20
Body mass index (kg/m²)	25.2 ± 3.7	24.9 ± 3.5	25.8 ± 4.0	0.14
Systolic blood pressure (mmHg)	137 ± 20	135 ± 17	138 ± 16	0.18
Diastolic blood pressure (mmHg)	87 ± 13	86 ± 10	87 ± 10	0.34
Serum creatinine (mg/dL)	2.14 ± 1.30 [1.19;1.67;2.75]	1.50 ± 0.70 [1.05;1.34;1.79]	3.24 ± 1.37 [2.19;2.95;4.30]	<0.001
Glomerular filtration rate (mL/min/1.73m²)	64±39 [36;56;90]	79±38 [51;74;99]	38±25 [20;33;46]	<0.001
Proteinuria (g/24h/1.73m²)	1.00 ± 0.92 [0.20; 0.70; 1.55]	0.86 ± 0.94 [0.14;0.44;1.24]	1.26 ± 0.83 [0.63;1.09;1.78]	<0.001
Hemoglobin (g/dL)	13.6 ± 1.8	14.1 ± 1.5	12.5 ± 1.7	<0.001
Serum albumin (g/dL)	4.6 ± 0.4	4.57 ± 0.43	4.54 ± 0.36	0.62
Calcium (mmol/L)	2.36 ± 0.21 [2.28; 2.35; 2.43]	2.38 ± 0.22 [2.30; 2.37; 2.44]	2.32 ± 0.17 [2.24; 2.31; 2.42]	0.03
Phosphate (mmol/L)	1.12 ± 0.4 [0.88;1.08;1.26]	1.04 ± 0.39 [0.86;1.01;1.14]	1.25 ± 0.27 [1.02;1.24;1.49]	<0.001
Parathormone (pmol/L)	12.4 ± 15.0 [3.9; 6.8; 14.5]	6.5 ± 5.4 [3.4; 5.0; 7.2]	22.6 ± 20.1 [8.6; 16.0; 26.0]	<0.001
High sensitivity C-reactive protein (mg/L)	0.27 ± 0.29	0.28 ± 0.32	0.26 ± 0.24	0.70
Fibroblast growth factor 23 intact (pg/mL)	47 ± 50 [23; 34; 56]	35 ± 28 [18;28;45]	70 ± 70 [33;48;78]	<0.001
Fibroblast growth factor 23 c-terminal (rU/mL)	186 ± 282 [49; 85; 183]	92 ± 113 [42;64;96]	351 ± 394 [101;190;487]	<0.001
ADMA (µMol/L)	0.47 ± 0.12	0.42 ± 0.09	0.55 ± 0.11	<0.001
SDMA (µMol/L)	0.96± 0.63 [0.48;0.73;1.26]	0.68 ± 0.37 [0.44;0.59;0.82]	1.45 ± 0.69 [0.92;1.38;1.78]	<0.001
L-Arginine (µMol/L)	64.2 ± 15.9 [54.5;62.8; 72.3]	62.7 ± 14.9 [54.2;61.7; 71.6]	66.8 ± 17.2 [54.7;65.1; 75.4]	0.158
L-Arginine / ADMA ratio	143.2 ± 40.4 [115.6;137.7;170.1]	153.7 ± 39.6 [129.8;150.4;177.1]	124.6 ± 34.9 [93.8;117.9;152.0]	<0.001

GFR denotes glomerular filtration rate measured by iohexol clearance, BMI; body-mass index. Data are presented as mean ± SD and 25th, 50th (median) and 75th percentiles for skewed variables where appropriate. [a]P value for comparison between progressors and non-progressors.

Supplemental Appendix 2 Univariate relationships (correlation coefficients and P values) of intact FGF23 and ADMA with demographic and clinical variables in the Southern Italy cohort.

	FGF23 Versus r(P)	**ADMA versus r(P)**
Age (years)	-0.06(0.08)	0.05(0.20)
Male gender (%)	0.01(0.78)	-0.09(0.02)
Smokers (%)	-0.006(0.88)	-0.003(0.93)
Diabetes (%)	-0.04(0.31)	-0.01(0.71)
With CV comorbidities (%)	-0.05(0.20)	-0.02(0.52)
On oral hypoglycemizing therapy (%)	-0.04(0.25)	-0.06(0.12)
On insulin therapy (%)	0.02(0.69)	0.08(0.03)
On anti-hypertensive treatment (%)	0.12(0.001)	0.02(0.54)
BMI (kg/m^2)	0.04(0.30)	0.03(0.49)
Systolic pressure (mmHg)	0.04(0.29)	-0.02(0.55)
Diastolic pressure (mmHg)	0.04(0.33)	-0.03(0.36)
Heart rate (beats/min)	0.03(0.40)	-0.04(0.25)
Creatinine (mg/dL)	0.53(<0.001)	0.17(<0.001)
$eGFR_{MDRD186}$ ($ml/min/1.73m^2$)	-0.48 (<0.001)	-0.21 (<0.001)
Urinary protein (g/24h)	0.11(0.003)	0.13(<0.001)
Glucose (mg/dL)	-0.06(0.13)	-0.02(0.52)
Cholesterol (mg/dL)	0.03(0.46)	-0.03(0.49)
HDL cholesterol (mg/dL)	-0.03(0.49)	0.01(0.77)
LDL cholesterol (mg/dL)	0.02(0.57)	-0.01(0.76)
Triglycerides (mg/dL)	0.07(0.05)	-0.04(0.26)
Hemoglobin (g/dL)	-0.19(<0.001)	-0.13(<0.001)
Albumin (g/dL)	-0.10(0.01)	-0.05(0.23)
hs-C Reactive Protein (mg/dL)	0.02(0.56)	0.007(0.85)
ADMA (µMol/L)	0.15(<0.001)	…
Calcium (mg/dL)	-0.004(0.91)	-0.11(0.003)
Phosphate (mg/dL)	0.29(<0.001)	0.20(<0.001)
Fractional phosphate excretion	0.21(<0.001)	-0.07(0.13)
PTH (pg/mL)	0.37(<0.001)	0.11(0.02)
FGF23 (pg/mL)	…	0.15(<0.001)
1.25 $(OH)_2$ D (pg/mL)	-0.31(<0.001)	-0.15(<0.001)
25 $(OH)_2$ D (pg/mL)	-0.26(<0.001)	-0.08(0.03)

Supplemental Appendix 3

a) Unadjusted and fully adjusted HR of FGF- 23 and ADMA for the risk of renal events in the Southern Italy cohort.

	Units of increase	**Unadjusted** (HR, 95% CI and P value)	**Fully adjusted** (HR, 95% CI and P value)
Intact FGF23	20 pg/ml	1.03 (1.02-1.05), P<0.001	1.02 (1.01-1.03), P=0.01
ADMA	0.1 µmol/L	1.14 (1.07-1.22), P<0.001	1.08 (1.01-1.16), P=0.03
$eGFR\text{-}_{MDRD186}$	1 ml/min/1.73m^2		0.97 (0.96-0.98), P<0.001
Age	1 year		0.99 (0.98-1.01), P=0.31
Anti-hypertensive treatment	0=no; 1=yes		1.43 (0.52-3.93), P=0.48
Triglycerides	20 mg/dL		0.98 (0.94-1.02), P=0.54
Hemoglobin	1 g/dL		0.96 (0.87-1.05), P=0.33
Albumin	1 g/dL		0.67 (0.48-0.93), P=0.02
Phosphate	1 mg/dL		1.02 (0.86-1.23), P=0.79
PTH	20 pg/mL		1.04 (1.01-1.07), P=0.01
1.25 (OH) Vitamin D	1 pg/ml		0.99 (0.98-1.01), P=0.72
25 (OH) Vitamin D	1 pg/ml		0.98 (0.95-1.00), P=0.09
Urinary protein	1 g/24h		1.20(1.12-1.30), P<0.001
Gender	0=F; 1=M		1.10 (0.82-1.46), P=0.52
Oral hypoglycemizing therapy	0=no; 1=yes		1.00(0.67-1.49), P=0.99
Insulin therapy	0=no; 1=yes		1.05(0.74-1.50), P=0.79
Calcium	1 mg/dL		0.79(0.66-0.95), P=0.01
BMI	1 kg/m^2		0.99(0.96-1.02), P=0.38
Systolic pressure	1 mmHg		1.01(0.99-1.02), P=0.06
LDL cholesterol	1 mg/dL		1.00(0.99-1.01), P=0.68
C-Reactive Protein	1 mg/L		0.99(0.97-1.00), P=0.13

Data are expressed as hazard ratio (HR), 95% confidence interval and P values.

b) Unadjusted and fully adjusted HR of FGF- 23 (intact and c-terminal) and ADMA for the risk of renal events in the MMKD cohort.

Variable (increment)	**HR (95% CI), P value**	**HR (95% CI), P value**	**HR (95% CI), P value**
Intact FGF23 (20 pg/mL)	1.25 (1.17-1.34) [a], <0.001	1.17 (1.09-1.26) [b], <0.001	--
C-terminal FGF23 (20 rU/mL)	1.06 (1.05-1.07) [a], <0.001	1.04 (1.02-1.05) [b], <0.001	--
ADMA (0.1 µMol/L)	2.48 (1.95-3.15) [a], <0.001	1.73 (1.30-2.31) [c], <0.001	1.70 (1.27-2.27) [d], <0.001

[a] Unadjusted
[b] Adjusted for age, sex, proteinuria and GFR (measured by iohexol clearance)
[c] Adjusted for age, sex, proteinuria, GFR (measured by iohexol clearance) and intact FGF23
[d] Adjusted for age, sex, proteinuria, GFR (measured by iohexol clearance) and c-terminal FGF23