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Supplementary Table S1—Spearman’s correlations between log-transformed and standardized biomarkers and clinical variables in SURDIAGENE patients

Circulating biomarker	Age	Diabetes duration	SBP	HbA_{1c}	eGFR	ACR	MR-proADM	sTNFR1	NT-proBNP
MR-proADM	0.46 (<0.0001)	0.22 (<0.0001)	0.10 (0.0005)	-0.03 (0.28)	-0.61 (<0.0001)	0.28 (<0.0001)	1.0		
sTNFR1	0.32 (<0.0001)	0.17 (<0.0001)	0.09 (0.003)	0.005 (0.88)	-0.51 (<0.0001)	0.27 (<0.0001)	0.72 (<0.0001)	1.0	
NT-proBNP	0.55 (<0.0001)	0.25 (<0.0001)	0.10 (0.0004)	-0.10 (0.001)	-0.46 (<0.0001)	0.29 (<0.0001)	0.56 (<0.0001)	0.38 (<0.0001)	1.0

Results are Spearman’s correlation coefficients (P value)

SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate by CKD EPI equation; uACR, urinary albumin-to-creatinine ratio; MR-proADM, Mid-regional-pro-adrenomedullin; NT-proBNP; N-terminal prohormone brain natriuretic peptide; sTNFR1, soluble Tumor Necrosis Factor receptor 1

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Supplementary Table S2-Summary of the fixed effects for predicting annual estimated glomerular filtration rate (eGFR) decline using a multivariate linear mixed model

Effects	β coefficient	Standard error	P-value
At Baseline			
Intercept	73.78	0.61	<0.0001
Female vs Male	-1.40	0.94	0.14
Age	-6.34	0.49	<0.0001
SBP	-1.07	0.48	0.02
HbA1c	0.07	0.45	0.87
uACR	-1.36	0.56	0.01
MR-proADM	-7.45	0.77	<0.0001
NT-proBNP	-0.70	0.61	0.25
sTNFR1	-4.33	0.72	<0.0001
Variable (per year)			
Time	-2.83	0.15	<0.0001
Female vs Male	0.72	0.23	0.002
HbA1c	-0.42	0.11	0.0002
uACR	-0.93	0.13	<0.0001
NT-proBNP	-0.28	0.13	0.03
sTNFR1	-0.39	0.14	0.004

Increments are for 1 SD increase except for Time as per 1 year

MR-proADM, Mid-regional-pro-adrenomedullin; sTNFR1, soluble Tumor Necrosis Factor receptor 1; NT-proBNP; N-terminal prohormone brain natriuretic peptide

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Supplementary Table S3- Risk of renal function loss ($\geq 40\%$ GFR drop) and rapid renal function decline ($<5\text{ml/min/year}$) according to biomarkers in patients of the SURDIAGENE cohort without baseline cardiovascular history

Variables	Model 1		Model 2		Model 3	
Hazard ratio for renal function loss ($\geq 40\%$ GFR drop)*						
MR-proADM (per 1 SD)	2.18 (1.94-2.44)	<0.0001	2.14 (1.88-2.43)	<0.0001	2.14 (1.83-2.49)	<0.0001
sTNFR1 (per 1 SD)	2.01 (1.8-2.25)	<0.0001	1.84 (1.64-2.08)	<0.0001	1.74 (1.51-2.00)	<0.0001
NT-proBNP (per 1 SD)	1.96 (1.74-2.2)	<0.0001	1.80 (1.56-2.07)	<0.0001	1.54 (1.33-1.79)	<0.0001
Odds ratio of rapid renal function decline ($<5\text{ml/min/year}$) ‡						
MR-proADM (per 1 SD)	1.94 (1.63-2.31)	<0.0001	2.07 (1.7-2.53)	<0.0001	2.54 (1.94-3.31)	<0.0001
sTNFR1 (per 1 SD)	1.98 (1.66-2.36)	<0.0001	1.96 (1.62-2.36)	<0.0001	2.25 (1.75-2.87)	<0.0001
NT-proBNP (per 1 SD)	1.69 (1.42-2.01)	<0.0001	1.78 (1.44-2.19)	<0.0001	1.52 (1.21-1.91)	0.0004

Ratios are presented with 95% confidence interval and P Value.

* Cox model, † logistic model.

Model 1 = univariate

Model 2 = Age, Sex, Diabetes duration, Systolic blood pressure, HbA_{1c}

Model 3 = model 2 + eGFR +uACR

MR-proADM, Mid-regional-pro-adrenomedullin; sTNFR1, soluble Tumor Necrosis Factor receptor 1; NT-proBNP; N-terminal prohormone brain natriuretic peptide

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Supplementary Table S4- Risk of renal function loss ($\geq 40\%$ GFR drop) according to biomarkers in patients of the SURDIAGENE cohort without baseline cardiovascular disease (CVD) history (1) excluding patients with incident major cardiovascular event (2) accounting for incident cardiovascular disease as a time varying covariate (3) censoring data at the time cardiovascular disease.

Variables	Multivariate model 3*	P value
	HR (95%CI)	
#1 no history of CVD at baseline and no incident major cardiovascular event (n=754)		
MR-proADM (per 1 SD)	2.19 (1.81-2.64)	<0.0001
sTNFR1 (per 1 SD)	1.70 (1.43-2.01)	<0.0001
NT-proBNP (per 1 SD)	1.45 (1.19-1.76)	0.0002
#2 no history of CVD at baseline and incident CVD outcome as a time varying covariate (n=919)		
MR-proADM (per 1 SD)	2.16 (1.83-2.56)	<0.0001
sTNFR1 (per 1 SD)	1.76 (1.51-2.06)	<0.0001
NT-proBNP (per 1 SD)	1.45 (1.24-1.71)	<0.0001
#3 no history of CVD at baseline and censoring data at the time CVD outcome (n=919)		
MR-proADM (per 1 SD)	2.11 (1.81-2.45)	<0.0001
sTNFR1 (per 1 SD)	1.75 (1.52-2.02)	<0.0001
NT-proBNP (per 1 SD)	1.51 (1.30-1.75)	<0.0001

Hazard Ratios are presented with 95% confidence interval and P Value.

CVD is defined as non-fatal myocardial or non-fatal stroke.

Major cardiovascular event is defined as outcome of cardiovascular death or non-fatal myocardial or non-fatal stroke during follow-up

*Adjustments were performed for age, sex, diabetes duration, systolic blood pressure, HbA_{1c}, eGFR and uACR.

MR-proADM, Mid-regional-pro-adrenomedullin; sTNFR1, soluble Tumor Necrosis Factor receptor 1; NT-proBNP; N-terminal prohormone brain natriuretic peptide

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Supplementary Table S5-C-statistics, relative integrated discrimination improvement index (rIDI) using individual biomarkers or their combination for prediction of renal function loss ($\geq 40\%$ GFR drop) and of rapid renal function decline (< -5 ml/min/year) in patients of the SURDIAGENE cohort without baseline cardiovascular history

Variables	C-statistics with biomarker	Difference in C-statistics (95% CI)	Likelihood ratio P value	Relative IDI (95% CI)	P value
Dependent variable = renal function loss ($\geq 40\%$ GFR drop)					
MR-proADM	0.761	0.038 (0.022-0.057)	<0.0001	0.425 (0.191-0.726)	<0.0001
sTNFR1	0.752	0.028 (0.012-0.046)	<0.0001	0.253 (0.089-0.466)	<0.0001
NT-proBNP	0.744	0.021 (0.007-0.038)	<0.0001	0.135 (0.021-0.283)	0.004
MR-proADM + NT-proBNP	0.766	0.043 (0.023-0.065)	<0.0001	0.446 (0.198-0.744)	<0.0001
MR-proADM + sTNFR1	0.764	0.041 (0.022-0.063)	<0.0001	0.448 (0.211-0.752)	<0.0001
NT-proBNP + sTNFR1	0.762	0.038 (0.019-0.059)	<0.0001	0.333 (0.130-0.571)	<0.0001
MR-proADM+ sTNFR1+ NT-proBNP	0.769	0.045(0.026-0.069)	<0.0001	0.486 (0.218-0.771)	<0.0001
Dependent variable = rapid renal function decline (< -5 ml/min/year)					
MR-proADM	0.784	0.051 (0.026-0.079)	<0.0001	0.457 (0.231-0.947)	<0.0001
sTNFR1	0.782	0.049 (0.024-0.077)	<0.0001	0.419 (0.240-0.962)	<0.0001
NT-proBNP	0.753	0.020 (0.002-0.045)	<0.0001	0.103 (0.037-0.460)	0.02
MR-proADM + NT-proBNP	0.786	0.052 (0.026-0.082)	<0.0001	0.455 (0.252-1.000)	<0.0001
MR-proADM + sTNFR1	0.795	0.061 (0.034-0.091)	<0.0001	0.563 (0.332-1.000)	<0.0001
NT-proBNP + sTNFR1	0.786	0.053 (0.027-0.085)	<0.0001	0.456 (0.297-1.000)	<0.0001
MR-proADM+ sTNFR1+ NT-proBNP	0.795	0.062 (0.033-0.093)	<0.0001	0.561 (0.351-1.000)	<0.0001

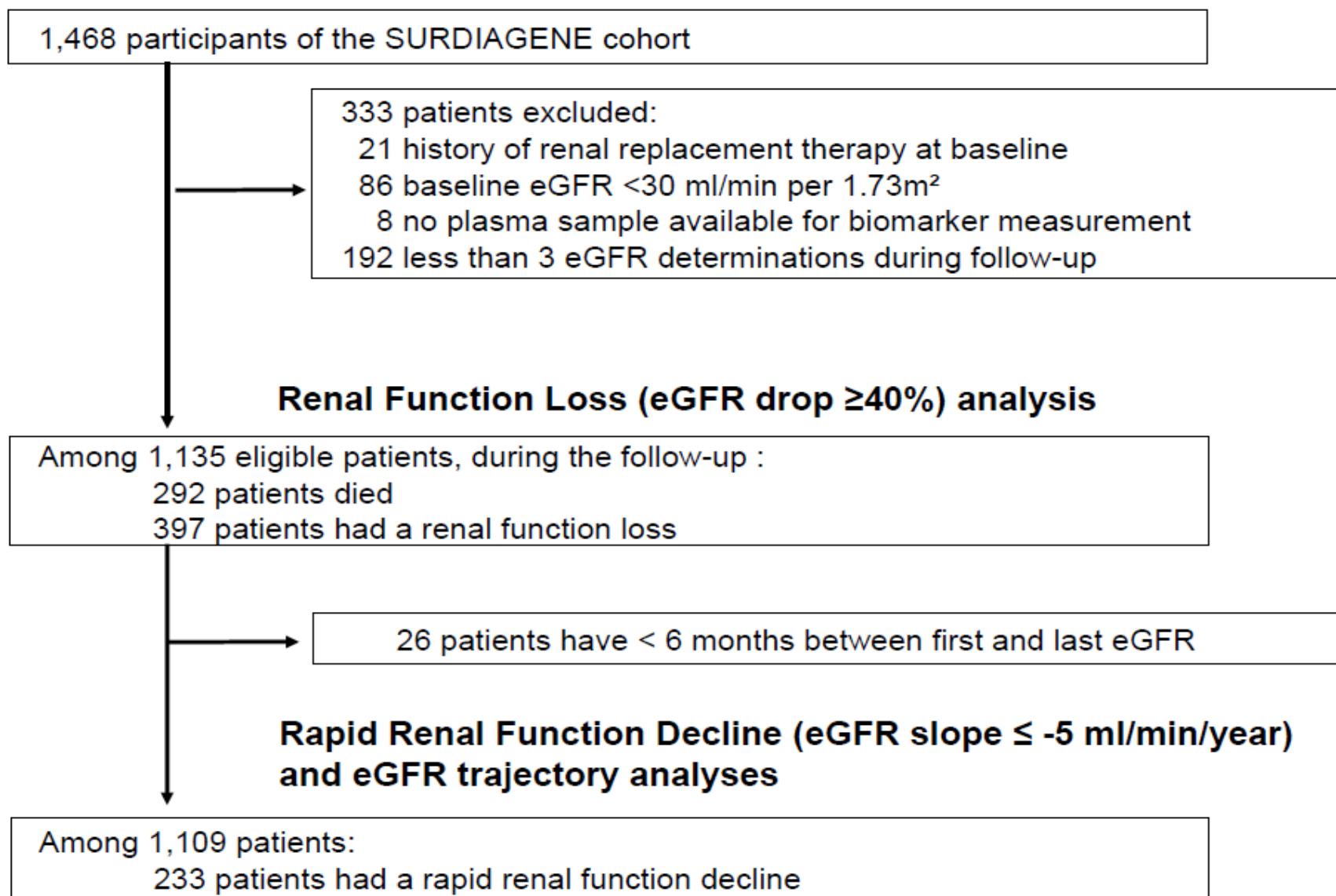
Reference model = age, sex, diabetes duration, systolic blood pressure, HbA1c, eGFR , uACR.

C-statistics reference =0.723 and 0.733 for renal function loss and rapid renal function decline.

Relative IDI, relative integrated discrimination improvement index; MR-proADM, Mid-regional-pro-adrenomedullin; sTNFR1, soluble Tumor Necrosis Factor receptor 1; NT-proBNP; N-terminal prohormone brain natriuretic peptide

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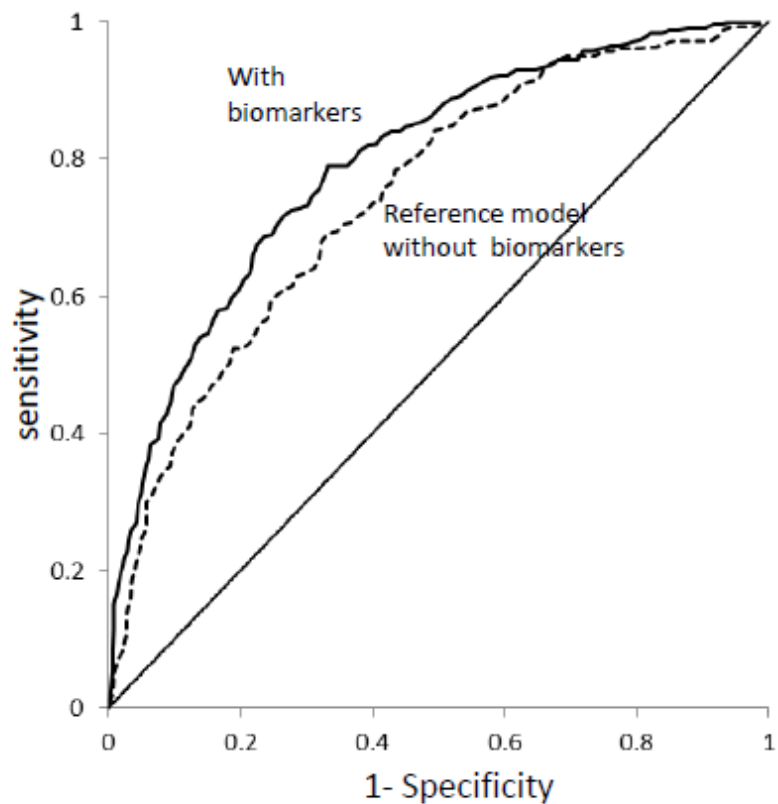
Supplementary Figure S1- Flow chart of the SURDIAGENE prospective cohort



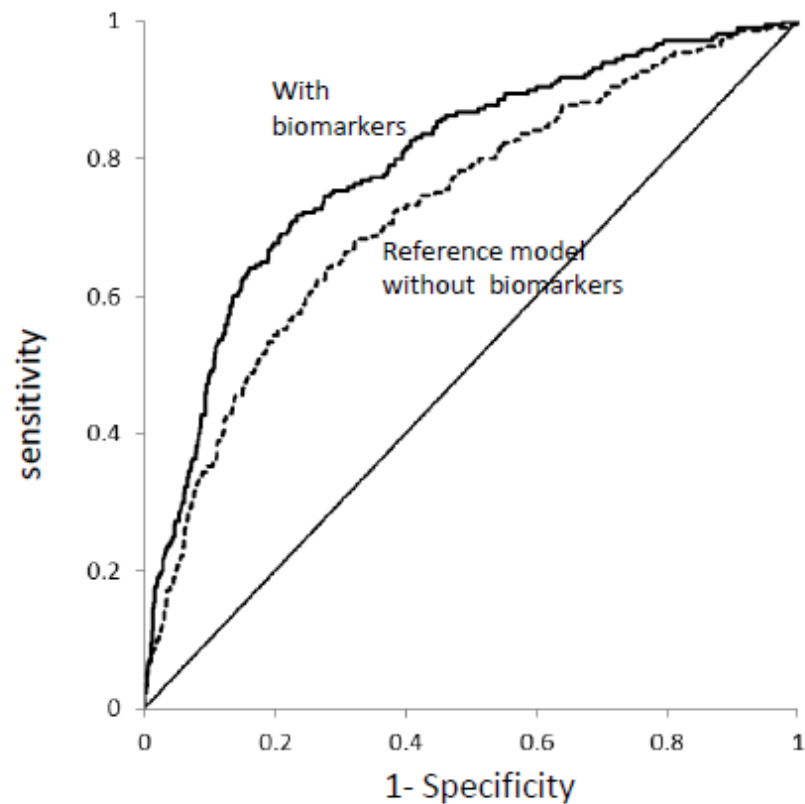
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Supplementary Figure S2 - Receiver operator characteristic (ROC) curves for 5-year Renal Function Loss (panel A) and Rapid Renal Function Decline (panel B). Area under the curve ROC are computed for prediction of risk with the use of traditional risk factors without biomarkers (reference model) and traditional risk factor with biomarkers. Reference model = age, sex, diabetes duration, systolic blood pressure, HbA1c, eGFR and uACR

A-Renal function loss (year-5)



B-Rapid renal function decline



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Supplementary Figure S3- Multivariable adjusted hazard ratio of Renal Function Loss ($\geq 40\%$ GFR drop) for (A) MR-proADM, and (B) sTNFR1 and (C) N-terminal pro-brain natriuretic peptide (NTproBNP) in subgroups. Adjustment was based on model 3 (age, sex, diabetes duration systolic blood pressure, HbA1c, eGFR and uACR).

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