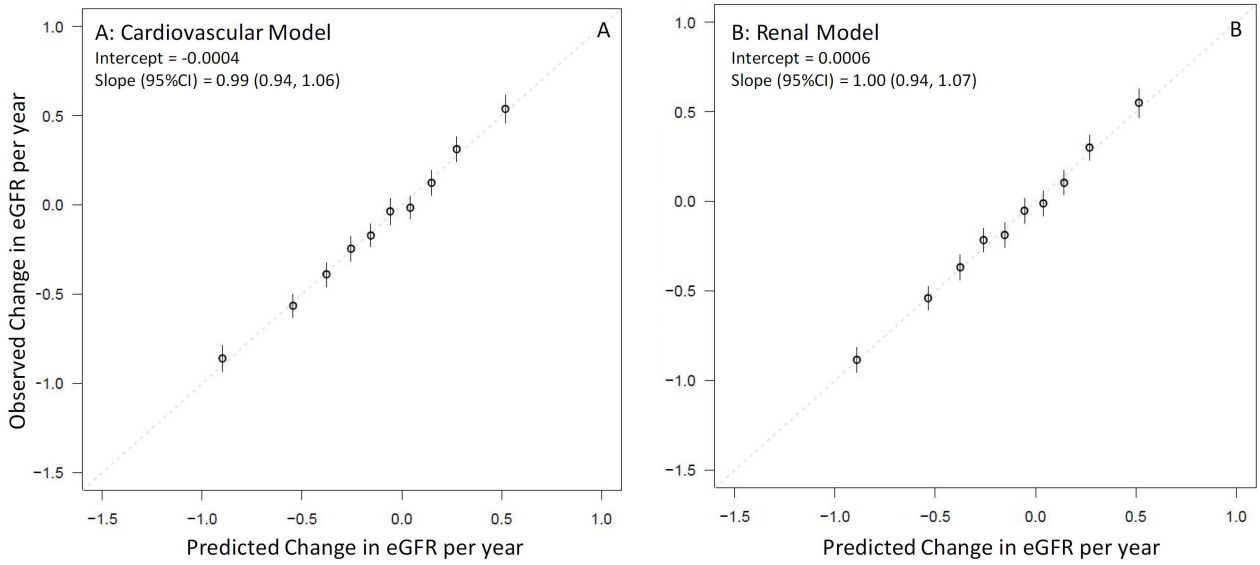
SUPPLEMENTARY DATA

Supplementary Figure S1

Calibration plot comparing the observed change in eGFR per year to the predicted value based on either the cardiovascular model (Panel A) or the renal model (Panel B) in all 7482 participants. The mean and 95% confidence intervals for the predicted change value are shown for each decile of the mean observed value.



SUPPLEMENTARY DATA

Supplementary Table S1. Participants in the ORIGIN Renal Biomarker Study

Characteristics	Participants/Concentration
N	7482
Male	4939 (66.0)
Mean Age (years)	63.5 (7.8)
Men ≥ 55 or Women ≥ 65 years	5218 (69.7)
Region	
N. America or Australia	1263 (16.9)
S. America	2461 (32.9)
Europe	3421 (45.7)
India	337 (4.5)
Current Smoking	901 (12.0)
Prior diabetes	6073 (81.2)
Hypertension	5901 (78.9)
Prior Cardiovascular Event	4402 (58.8)
Mean Blood Pressure	146 (22)/ 85 (12)
Mean Arterial Pressure (SD)	105 (14)
Reported/Measured Micro or Macroalbuminuria	2290 (30.6)
Mean Log2 (albumin/creatinine)	-0.15 (1.61)
Mean LDL Cholesterol (mmol/L)	2.89 (1.02)
Mean HDL Cholesterol (mmol/L)	1.18 (0.32)
Mean BMI (kg/m^2)	30.1 (5.3)
Mean HbA1c (%)	6.49 (0.94)
Mean eGFR (ml/min/1.73m^2)	77.8 (21.3)
eGFR < 60 (%)	1405 (18.8)
eGFR $\geq$ 60 (%)	6077 (81.2)
ACE-I or ARB	5152 (68.9)
Allocation to Glargine	3716 (49.7)

Results are expressed as N(%), Mean (SD) or Median (IQR)

SUPPLEMENTARY DATA

Supplementary Table S2. Independent Biomarkers of Annual Change in eGFR Adjusted for Baseline eGFR in N=7482

Risk Factor	CV Clinical Model Beta (95%CI)	Renal Clinical Model Beta (95%CI)	Combined Model Beta (95%CI)
Alpha-1-Microglobulin	-0.129 (-0.159, -0.099)	-0.157 (-0.185, -0.128)	-0.154 (-0.183, -0.126)
NT-proBNP	-0.094 (-0.114, -0.074)	-0.081 (-0.101, -0.062)	-0.085 (-0.105, -0.065)
IGFBP4	-0.112 (-0.144, -0.080)[a]	-0.110 (-0.142, -0.078)[b]	-0.119 (-0.151, -0.086)[c]
Growth/Differentiation Factor 15	-0.080 (-0.109, -0.052)	-0.091 (-0.118, -0.064)	-0.090 (-0.118, -0.062)
RAGE	-0.053 (-0.077, -0.029)	-0.052 (-0.077, -0.027)	-0.064 (-0.088, -0.040)
Myoglobin	-0.077 (-0.102, -0.052)	-0.073 (-0.098, -0.048)	-0.075 (-0.100, -0.049)
Growth-Regulated alpha protein	0.059 (0.034, 0.083)	0.058 (0.033, 0.082)	0.057 (0.032, 0.081)
Fibulin-1C	-0.060 (-0.085, -0.034)	-0.048 (-0.073, -0.023)	N/A
Urokinase-type Plasminogen Activator	0.034 (0.010, 0.059)	N/A	N/A
Apolipoprotein A-IV	-0.054 (-0.078, -0.030)	-0.057 (-0.081, -0.032)	-0.055 (-0.079, -0.030)
Kidney Injury Molecule-1	-0.035 (-0.052, -0.018)	N/A	N/A
Apolipoprotein A-II	0.063 (0.038, 0.087)	0.065 (0.041, 0.089)	0.069 (0.044, 0.094)
Retinol-binding protein 4	-0.054 (-0.082, -0.027)	N/A	N/A
Fas Ligand	-0.086 (-0.124, -0.048)	-0.099 (-0.138, -0.060)	-0.099 (-0.138, -0.060)
Eotaxin-1	-0.047 (-0.070, -0.023)	-0.052 (-0.075, -0.028)	-0.049 (-0.073, -0.025)
Beta Amyloid 1-40	N/A	-0.057 (-0.081, -0.032)	-0.055 (-0.080, -0.029)

These biomarkers were identified by forward selection. Variables included in the combined clinical model were: age, sex, prior CV event, prior diabetes, prior hypertension, mean arterial pressure, current smoking, former smoking, body mass index, log2 (albumin/creatinine), cholesterol levels, LDL/HDL, baseline eGFR ,and HbA1c. There was a significant interaction between IGF BP4 and glargine allocation. For the CV model[a] after accounting for this interaction (P=0.002), beta (glargine)=-0.177(-0.225,-0.129), and beta (standard care)= -0.058 (-0.100, -0.015). For the renal model[b] after accounting for this interaction (P=0.0008), beta (glargine)=-0.168(-0.215, -0.121) and beta (standard care) = -0.060 (-0.103, -0.018). For the combined model[c] after accounting for this interaction (P=0.0007), beta (glargine) =-0.180 (-0.228, -0.132) and beta (standard care) = -0.066 (-0.109, -0.024).

SUPPLEMENTARY DATA

Supplementary Table S3. Variance of the Annual Change in eGFR that is Explained by the Clinical Variables Alone and by the Clinical Variables Plus the Identified Biomarkers (R^2)

	Clinical Variables Alone	Clinical Variables + Selected Biomarkers	Difference in Log-Likelihood	P
CV Clinical Model	0.040 (0.032, 0.050)	0.158 (0.141, 0.174)	967 (837, 1098)	<0.0001
Renal Clinical Model	0.053 (0.043, 0.063)	0.155 (0.139, 0.172)	849 (733, 966)	<0.0001

R^2 and the difference in log-likelihood were estimated from 1000 samples of the data using bootstrapping with replacement; A log-likelihood value > 37.7 for the CV model with 15 biomarkers, and a value > 34.5 for the renal model with 13 biomarkers would indicate significance at an alpha=0.001.

SUPPLEMENTARY DATA

Supplementary Table S4. HR of Death and of the Renal Composite Outcome for every 0.1 ml/min/1.73 m^2 Predicted Annual Decline in eGFR based on Clinical Risk Factors and Biomarkers

	Death HR (95%CI)	Original Renal Composite[a] HR (95%CI)	New Renal Composite[b] HR (95%CI)
Cardiovascular Model	1.13 (1.12, 1.14)	1.11 (1.10, 1.12)	1.28 (1.25, 1.31)
Renal Model	1.13 (1.12, 1.14)	1.10 (1.09, 1.12)	1.27 (1.25, 1.31)

[a]renal replacement therapy, renal death, renal failure, albuminuria category progression, or doubling of serum creatinine from baseline; [b]renal replacement therapy, renal death, renal failure, or doubling of serum creatinine from baseline

SUPPLEMENTARY DATA

Supplementary Table S5. Renal Dysfunction Model Performance For Predicting Death or the Renal Composite Outcome

	Clinical Risk Factors C (95%CI)	Clinical Risk Factors Plus Biomarkers C (95%CI)	Net Reclassification Improvement (95%CI)	IDI (95%CI)*
Death				
Cardiovascular Model	0.62 (0.60, 0.63)	0.67 (0.66, 0.69)	0.192 (0.153, 0.232)	0.040 (0.033, 0.047)
Renal Model	0.67 (0.65, 0.68)	0.68 (0.67, 0.70)	0.027 (0, 0.065)	0.000 (0, 0.007)
Renal Composite				
Cardiovascular Model	0.61 (0.59, 0.62)	0.63 (0.61, 0.64)	0.031 (0.020, 0.042)	0.017 (0.010, 0.024)
Renal Model	0.60 (0.59, 0.62)	0.62 (0.61, 0.64)	0.050 (0.041, 0.060)	0.017 (0.010, 0.023)

*integrated discrimination improvement