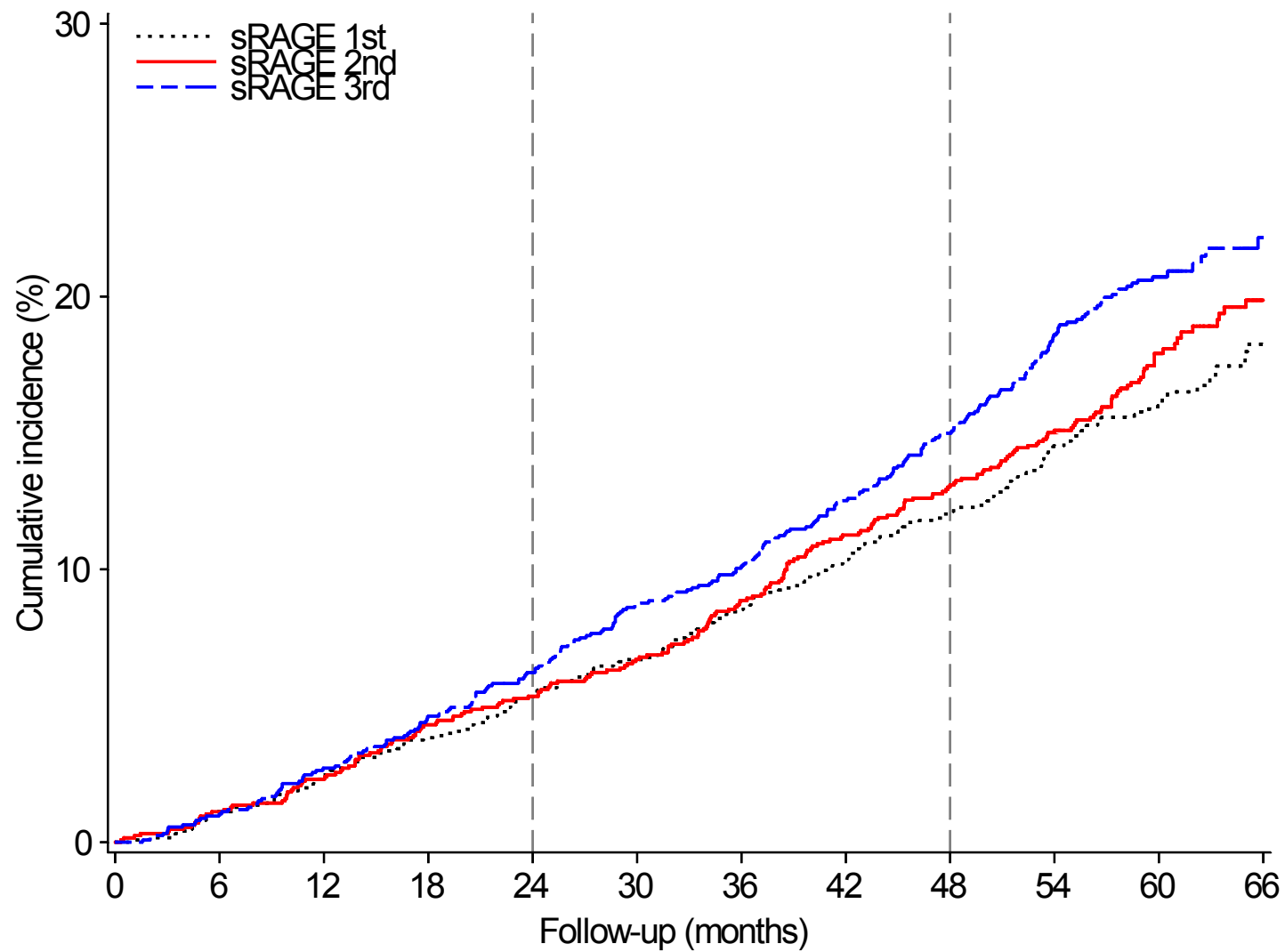Supplementary Figure 1A. Kaplan Meier curve showing all cause death among patients in the random sub-cohort (n=3500) divided into sRAGE thirds

Supplementary Figure 1B. Kaplan Meier curve showing major cardiovascular events among patients in the random sub-cohort (n=3500) divided into sRAGE thirds.

Supplementary Figure 1C. Kaplan Meier curve showing incident nephropathy among patients in the random sub-cohort (n=3500) divided into thirds, on the basis of tertiles of sRAGE levels.
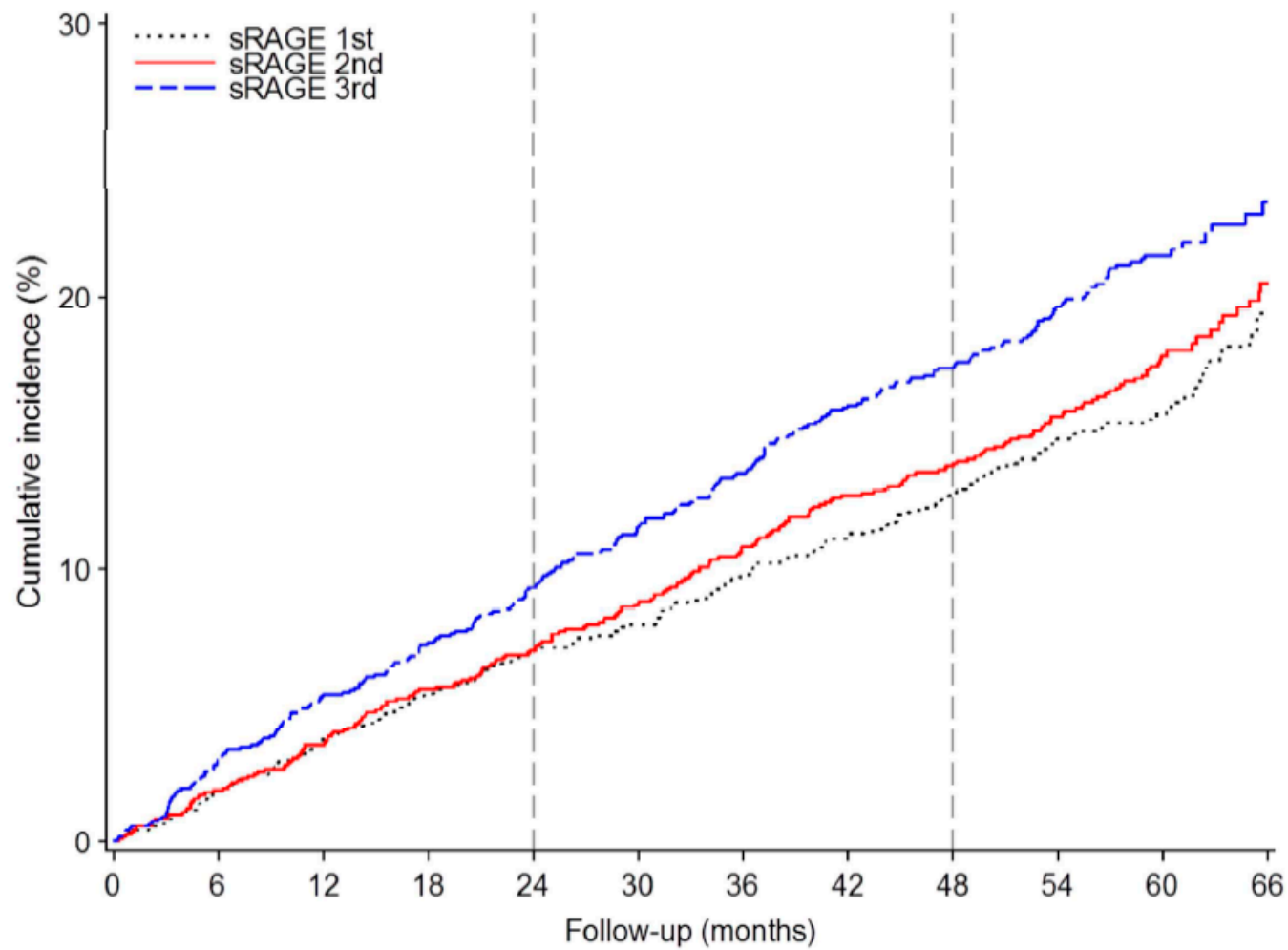
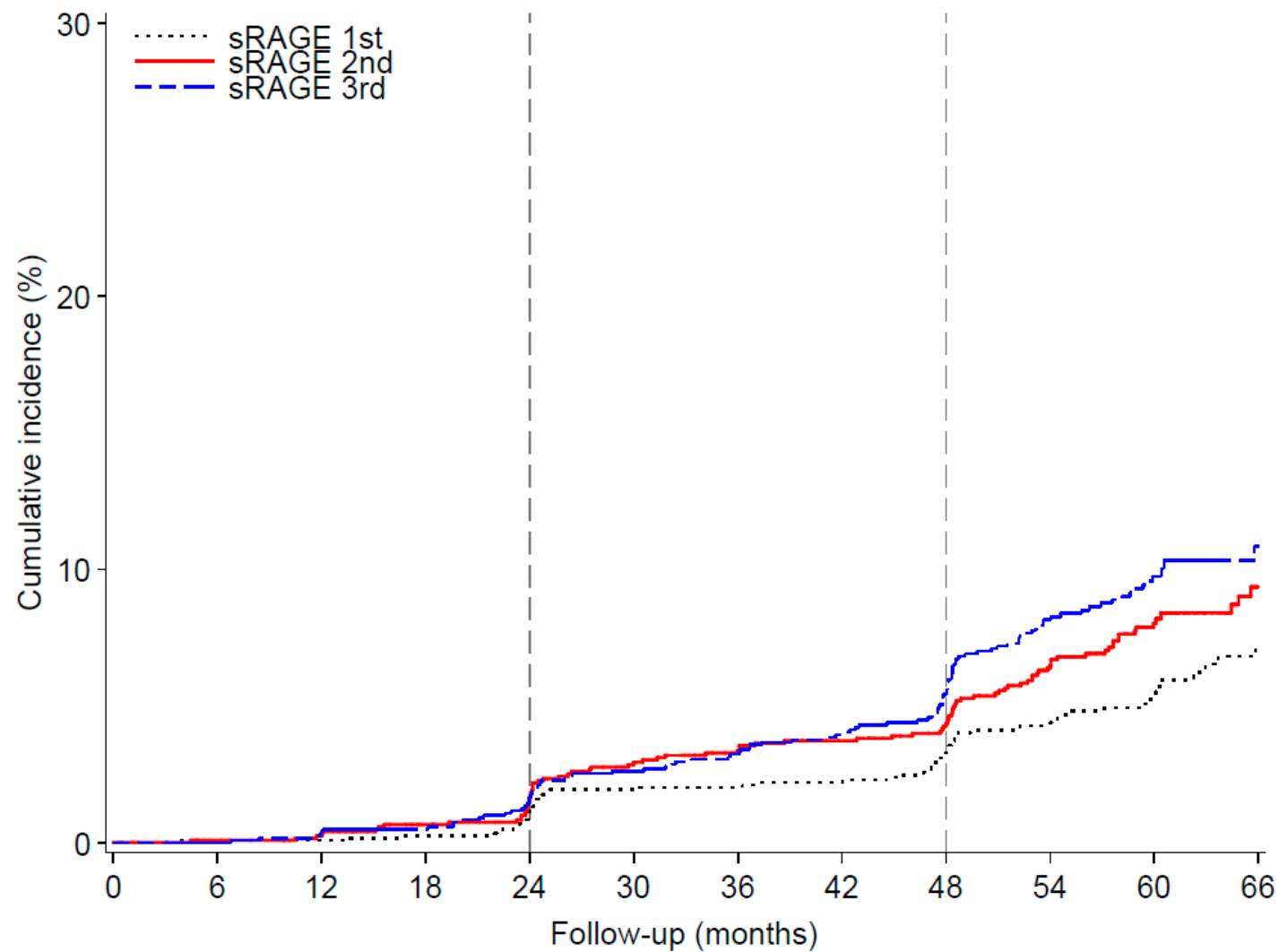**Supplementary Figure 2 A. Kaplan Meier curve showing all cause death among patients in the random sub-cohort (n=3500) divided into thirds, on the basis of tertiles of AGE levels.**

Supplementary Figure 2B. Kaplan Meier curve showing major cardiovascular events among patients in the random sub-cohort (n=3500) divided into thirds, on the basis of tertiles of AGE levels.
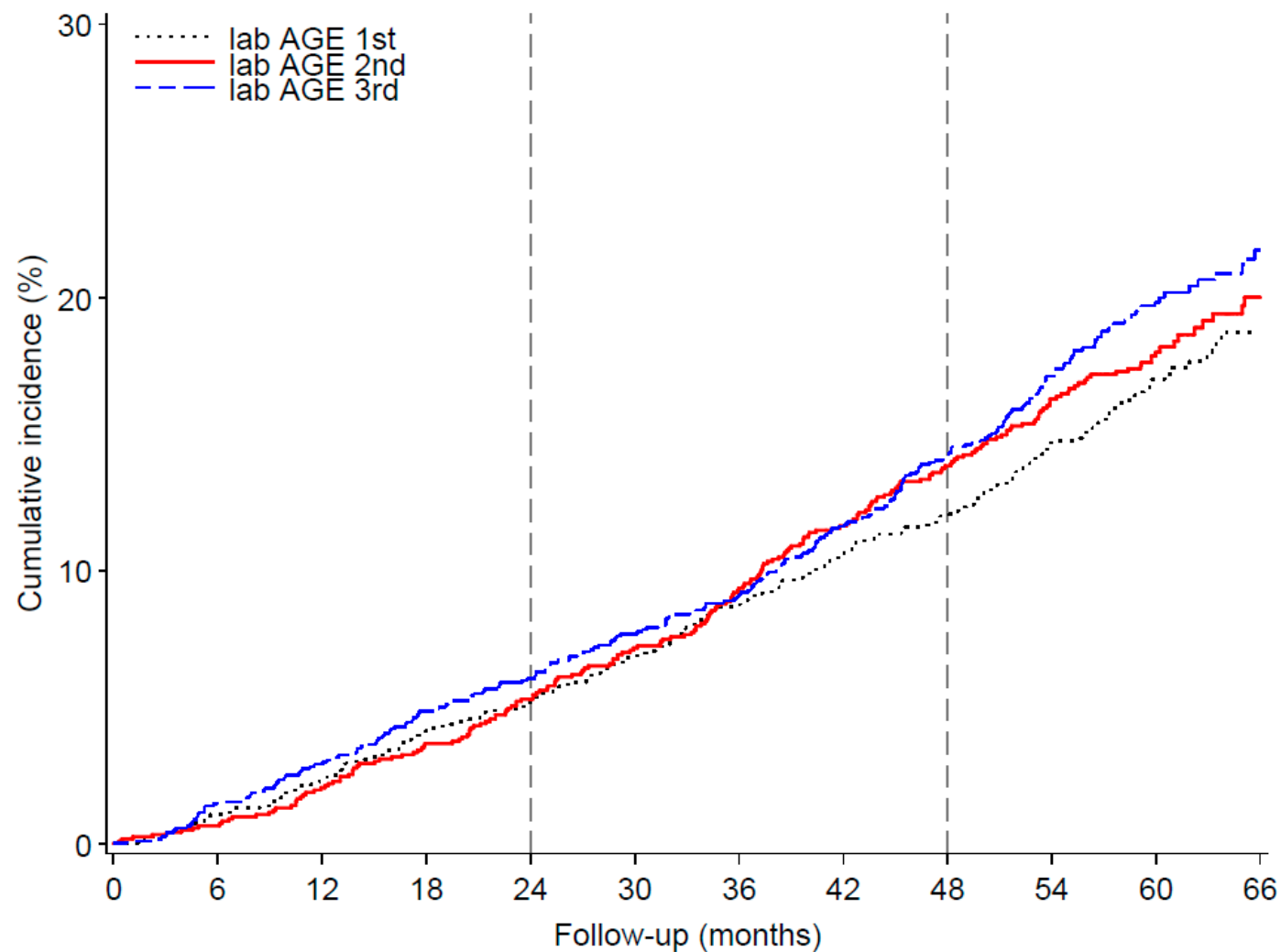
Supplementary Figure 2C. Kaplan Meier curve showing incident nephropathy among patients in the random sub-cohort (n=3500) divided into thirds, on the basis of tertiles of AGE levels.
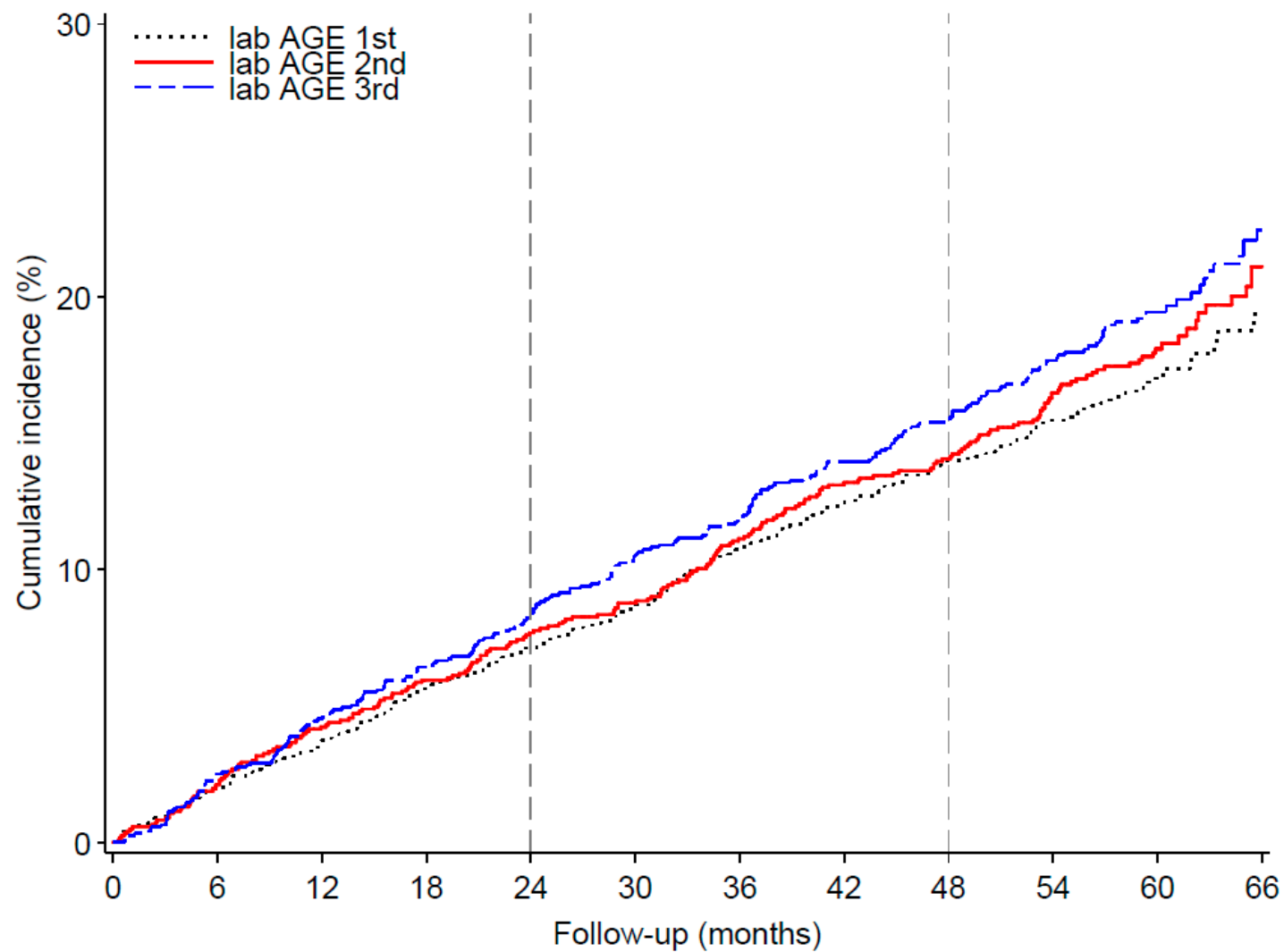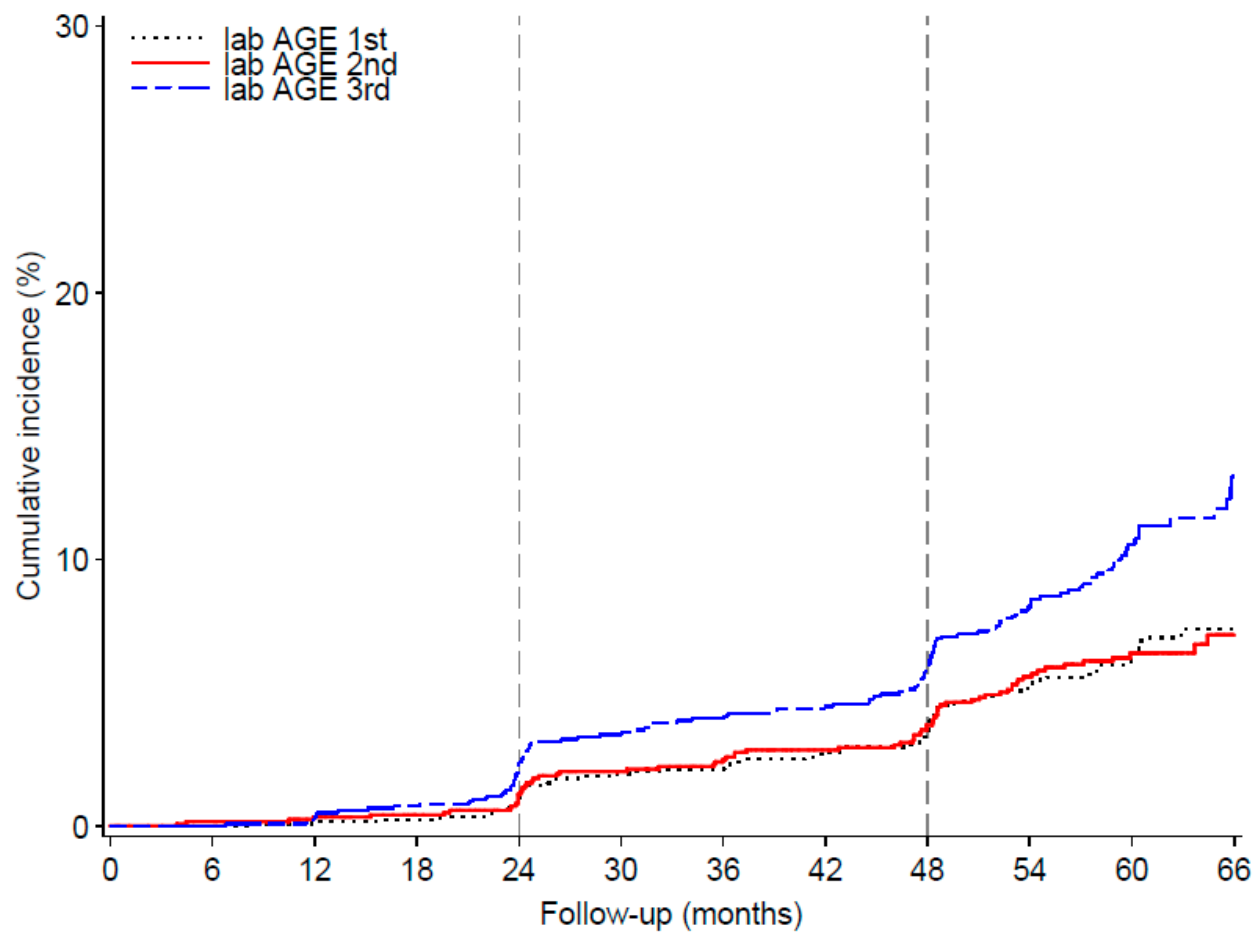
Supplementary Figure 3A. Levels of sRAGE and AGEs (as in Table 3) and the hazard ratio for death (following multivariable adjustment, see text).

	Hazard ratio	95% CI	P-value
ALL CAUSE DEATH			
sRAGE value (log scale)	1.11	(1.00 - 1.22)	
Age in years			0.121
<=67	1.27	(1.06 - 1.52)	
>67	1.05	(0.93 - 1.18)	
Sex			0.880
Female	1.10	(0.93 - 1.30)	
Male	1.13	(1.00 - 1.27)	
Prior macrovascular event(s)			0.563
Yes	1.14	(0.97 - 1.34)	
No	1.08	(0.95 - 1.22)	
Prior microvascular event(s)			0.455
Yes	1.00	(0.76 - 1.33)	
No	1.12	(1.00 - 1.25)	
eGFR			0.782
<60	1.08	(0.89 - 1.32)	
>=60	1.12	(0.99 - 1.25)	
HbA1c			0.584
<7%	1.16	(0.98 - 1.38)	
>=7%	1.08	(0.96 - 1.22)	
Lab AGE value	0.97	(0.89 - 1.06)	
Age in years			0.778
<=67	0.99	(0.83 - 1.18)	
>67	0.96	(0.86 - 1.07)	
Sex			0.719
Female	0.97	(0.83 - 1.13)	
Male	0.98	(0.88 - 1.10)	
Prior macrovascular event(s)			0.431
Yes	1.02	(0.87 - 1.18)	
No	0.94	(0.84 - 1.06)	
Prior microvascular event(s)			0.677
Yes	1.06	(0.82 - 1.37)	
No	0.95	(0.86 - 1.05)	
eGFR			0.286
<60	1.04	(0.89 - 1.21)	
>=60	0.93	(0.83 - 1.05)	
HbA1c			0.241
<7%	0.92	(0.79 - 1.07)	
>=7%	1.00	(0.89 - 1.13)	

1/2   1   2
Hazard ratio

Supplementary Figure 3B. Levels of sRAGE and AGEs and the hazard ratio for major cardiovascular events (following multivariable adjustment, see text).

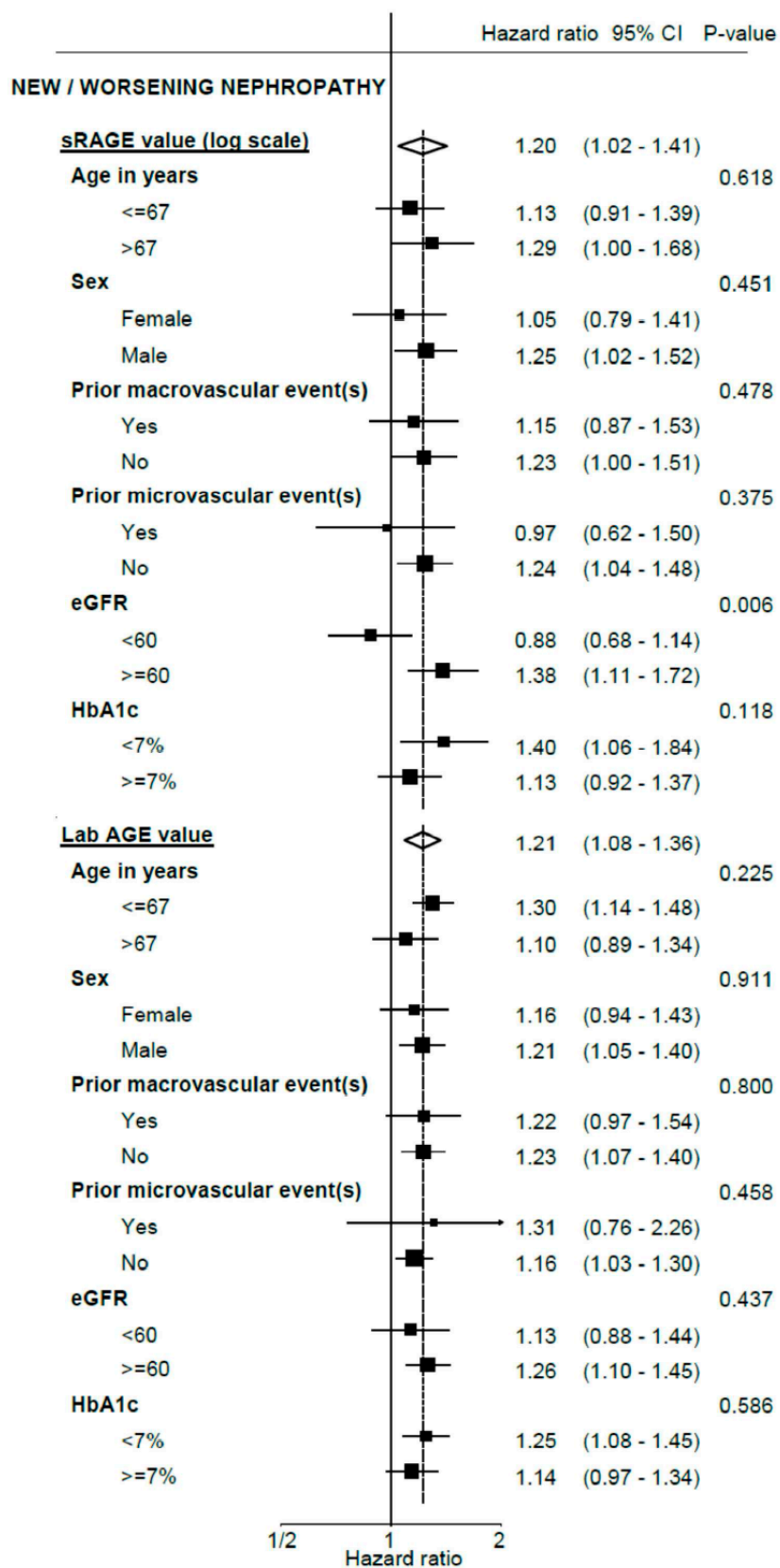|	Hazard ratio	95% CI	P-value
MAJOR CARDIOVASCULAR EVENTS			
sRAGE value (log scale)	1.08	(0.97 - 1.21)	
Age in years			0.281
<=67	1.20	(0.98 - 1.46)	
>67	1.03	(0.91 - 1.17)	
Sex			0.875
Female	1.09	(0.91 - 1.31)	
Male	1.11	(0.97 - 1.28)	
Prior macrovascular event(s)			0.137
Yes	1.17	(0.99 - 1.39)	
No	1.00	(0.87 - 1.15)	
Prior microvascular event(s)			0.524
Yes	1.02	(0.77 - 1.36)	
No	1.10	(0.97 - 1.23)	
eGFR			0.353
<60	1.00	(0.82 - 1.22)	
>=60	1.12	(0.98 - 1.28)	
HbA1c			0.455
<7%	1.17	(0.96 - 1.44)	
>=7%	1.03	(0.91 - 1.17)	
Lab AGE value	1.02	(0.93 - 1.12)	
Age in years			0.643
<=67	1.02	(0.86 - 1.22)	
>67	1.01	(0.90 - 1.13)	
Sex			0.826
Female	0.99	(0.85 - 1.15)	
Male	1.04	(0.93 - 1.17)	
Prior macrovascular event(s)			0.063
Yes	1.12	(0.98 - 1.27)	
No	0.93	(0.81 - 1.06)	
Prior microvascular event(s)			0.838
Yes	1.07	(0.80 - 1.43)	
No	1.00	(0.91 - 1.10)	
eGFR			0.320
<60	1.10	(0.94 - 1.29)	
>=60	0.98	(0.87 - 1.10)	
HbA1c			0.760
<7%	1.07	(0.93 - 1.23)	
>=7%	0.99	(0.87 - 1.13)	

Hazard ratio

Supplementary Figure 3C. Levels of sRAGE and AGEs (as in Table 3) and the hazard ratio for new or worsening nephropathy (following multivariable adjustment, see text).

	Hazard ratio	95% CI	P-value
NEW / WORSENING NEPHROPATHY			
<u>**sRAGE value (log scale)**</u>	1.20	(1.02 - 1.41)	
Age in years			0.618
<=67	1.13	(0.91 - 1.39)	
>67	1.29	(1.00 - 1.68)	
Sex			0.451
Female	1.05	(0.79 - 1.41)	
Male	1.25	(1.02 - 1.52)	
Prior macrovascular event(s)			0.478
Yes	1.15	(0.87 - 1.53)	
No	1.23	(1.00 - 1.51)	
Prior microvascular event(s)			0.375
Yes	0.97	(0.62 - 1.50)	
No	1.24	(1.04 - 1.48)	
eGFR			0.006
<60	0.88	(0.68 - 1.14)	
>=60	1.38	(1.11 - 1.72)	
HbA1c			0.118
<7%	1.40	(1.06 - 1.84)	
>=7%	1.13	(0.92 - 1.37)	
<u>**Lab AGE value**</u>	1.21	(1.08 - 1.36)	
Age in years			0.225
<=67	1.30	(1.14 - 1.48)	
>67	1.10	(0.89 - 1.34)	
Sex			0.911
Female	1.16	(0.94 - 1.43)	
Male	1.21	(1.05 - 1.40)	
Prior macrovascular event(s)			0.800
Yes	1.22	(0.97 - 1.54)	
No	1.23	(1.07 - 1.40)	
Prior microvascular event(s)			0.458
Yes	1.31	(0.76 - 2.26)	
No	1.16	(1.03 - 1.30)	
eGFR			0.437
<60	1.13	(0.88 - 1.44)	
>=60	1.26	(1.10 - 1.45)	
HbA1c			0.586
<7%	1.25	(1.08 - 1.45)	
>=7%	1.14	(0.97 - 1.34)	

1/2   1   2
Hazard ratio

SUPPLEMENTARY DATA

Supplementary Table 1. Hazard ratios for adverse events according to increasing levels of AGEs and sRAGE, restricted to only include patients those in the first or second third of sAGE (first results column) and to those in the first or second third of AGE (right results column).

Model	Outcome	sRAGE (log scale) (per 1 unit*)		Lab AGE value (per 100 RFU/mg protein*)	
		Hazard Ratio	P-value	Hazard Ratio	P-value
1	All cause death	1.12 (0.99, 1.27)	0.0778	1.08 (0.85, 1.36)	0.5275
	Major cardiovascular events	1.00 (0.88, 1.14)	0.9832	1.13 (0.90, 1.41)	0.3029
	New or worsening nephropathy	1.47 (1.13, 1.91)	0.0037	1.18 (0.82, 1.70)	0.3627
2	All cause death	1.09 (0.97, 1.24)	0.1509	1.02 (0.81, 1.30)	0.8441
	Major cardiovascular events	0.99 (0.87, 1.13)	0.8741	1.06 (0.84, 1.34)	0.6161
	New or worsening nephropathy	1.43 (1.11, 1.85)	0.0059	1.09 (0.74, 1.60)	0.6560
3	All cause death	1.04 (0.92, 1.18)	0.5112	0.99 (0.77, 1.27)	0.9512
	Major cardiovascular events	0.94 (0.83, 1.07)	0.3675	1.10 (0.86, 1.41)	0.4673
	New or worsening nephropathy	1.29 (1.00, 1.67)	0.0522	1.08 (0.69, 1.69)	0.7494
4	All cause death	1.11 (0.98, 1.25)	0.1070	0.98 (0.77, 1.24)	0.8551
	Major cardiovascular events	1.02 (0.89, 1.16)	0.8164	1.02 (0.80, 1.29)	0.8983
	New or worsening nephropathy	1.40 (1.08, 1.81)	0.0097	1.01 (0.68, 1.49)	0.9668
6	All cause death	1.06 (0.94, 1.20)	0.3360	1.05 (0.82, 1.34)	0.7225
	Major cardiovascular events	0.96 (0.84, 1.09)	0.5011	1.04 (0.82, 1.33)	0.7225
	New or worsening nephropathy	1.37 (1.06, 1.77)	0.0154	1.12 (0.76, 1.66)	0.5611
7	All cause death	1.08 (0.95, 1.22)	0.2249	1.03 (0.80, 1.32)	0.8339
	Major cardiovascular events	0.99 (0.87, 1.12)	0.8443	1.03 (0.80, 1.31)	0.8416
	New or worsening nephropathy	1.34 (1.04, 1.73)	0.0238	1.06 (0.72, 1.58)	0.7661

Model 1: adjusted for age, sex and randomised treatment groups; Model 2: as model 1, but adjusted additionally for duration of diabetes, current smoking, systolic BP, BMI, plasma glucose, HbA1c, total cholesterol, HDL-cholesterol and triglycerides, and history of macrovascular events; Model 3: as model 2, but additionally adjusted for ACR and eGFR (by the CKD-EPI equation); Model 4: as model 2, but adjusted additionally for sRAGE or AGE, as appropriate; Model 5: as model 4, but adjusted additionally for hs-cTnT, NT-proBNP, hs-CRP and use of beta-blockers; model 6: as model 5, but additionally adjusted for sRAGE or AGE, as appropriate.
Approximately one standard deviation (on the raw scale sRAGE was measured in pg/ml).