

Supplemental Table 1. Hazard Ratios (95% Confidence Intervals) for Cardiovascular Disease and Mortality by Category of Percent Change in Filtration Markers Over a Six-Year Period Adjusted for First Measurement of Covariates and Filtration Marker^a

Filtration Marker	Category of Percent Change in Filtration Marker			
	< -30%	-30% to -10%	-9.9% to +9.9%	≥ +10%
Total Cardiovascular Disease (1,922/9,712) ^b				
eGFR _{Cys}	1.72 (1.46, 2.03)	1.22 (1.11, 1.35)	1 [Reference]	0.95 (0.80, 1.14)
1/β ₂ -Microglobulin	2.11 (1.79, 2.49)	1.32 (1.19, 1.46)	1 [Reference]	1.10 (0.94, 1.29)
Three Marker Average ^c	2.20 (1.84, 2.64)	1.27 (1.15, 1.40)	1 [Reference]	1.06 (0.84, 1.33)
Coronary Heart Disease (835/9,452) ^b				
eGFR _{Cys}	1.64 (1.28, 2.10)	1.16 (1.00, 1.35)	1 [Reference]	0.88 (0.67, 1.15)
1/β ₂ -Microglobulin	1.80 (1.38, 2.36)	1.33 (1.14, 1.54)	1 [Reference]	1.24 (0.99, 1.56)
Three Marker Average ^c	2.33 (1.77, 3.05)	1.39 (1.19, 1.61)	1 [Reference]	1.40 (1.01, 1.94)
Ischemic Stroke (442/9,609) ^b				
eGFR _{Cys}	1.55 (1.08, 2.20)	1.23 (1.00, 1.52)	1 [Reference]	1.06 (0.74, 1.52)
1/β ₂ -Microglobulin	1.84 (1.28, 2.62)	1.21 (0.97, 1.49)	1 [Reference]	1.33 (0.98, 1.81)
Three Marker Average ^c	1.66 (1.11, 2.47)	1.23 (1.00, 1.50)	1 [Reference]	0.96 (0.58, 1.59)

Heart Failure (1,139/9,531) ^b				
eGFR _{Cys}	2.14 (1.75, 2.63)	1.38 (1.21, 1.58)	1 [Reference]	0.94 (0.74, 1.18)
1/β ₂ -Microglobulin	2.81 (2.30, 3.44)	1.48 (1.30, 1.69)	1 [Reference]	1.06 (0.86, 1.31)
Three Marker Average ^c	2.90 (2.34, 3.58)	1.25 (1.10, 1.42)	1 [Reference]	0.92 (0.67, 1.25)
All-Cause Mortality (2,285/9,716) ^b				
eGFR _{Cys}	2.31 (2.01, 2.65)	1.24 (1.12, 1.36)	1 [Reference]	1.04 (0.88, 1.22)
1/β ₂ -Microglobulin	2.51 (2.18, 2.89)	1.28 (1.17, 1.41)	1 [Reference]	0.97 (0.83, 1.13)
Three Marker Average ^c	2.73 (2.34, 3.19)	1.28 (1.17, 1.40)	1 [Reference]	1.06 (0.85, 1.32)
Cardiovascular Disease Mortality (696/9,716) ^b				
eGFR _{Cys}	2.30 (1.80, 2.93)	1.31 (1.10, 1.56)	1 [Reference]	0.92 (0.69, 1.23)
1/β ₂ -Microglobulin	2.65 (2.06, 3.40)	1.48 (1.25, 1.76)	1 [Reference]	1.12 (0.85, 1.47)
Three Marker Average ^c	3.38 (2.62, 4.36)	1.49 (1.26, 1.76)	1 [Reference]	1.37 (0.96, 1.94)
Non-Cardiovascular Disease Mortality (1,540/9,716) ^b				
eGFR _{Cys}	2.26 (1.91, 2.69)	1.19 (1.07, 1.34)	1 [Reference]	1.08 (0.88, 1.32)
1/β ₂ -Microglobulin	2.43 (2.04, 2.90)	1.22 (1.09, 1.37)	1 [Reference]	0.91 (0.75, 1.10)
Three Marker Average ^c	2.46 (2.02, 3.00)	1.20 (1.08, 1.34)	1 [Reference]	0.92 (0.70, 1.22)

eGFR_{Cys}, estimated glomerular filtration rate based on cystatin C

Bold font for hazard ratio (95% confidence interval) indicates statistical significance.

^a Adjusted for age, sex, race, body mass index, systolic blood pressure, anti-hypertensive medication use, diabetes status, total cholesterol, high-density lipoprotein cholesterol, current cigarette smoking status, first measurement of the respective filtration marker. eGFR was included in the model as linear spline terms with two knots at 60 and 90 mL/min/1.73 m². For the three marker average, all three filtration markers (eGFR-creatinine, eGFR-cystatin C, 1/ β_2 -microglobulin) were included in the model. All covariates were assessed at ARIC study visit 2 (1990-1992).

^b Analyses exclude prevalent cases of the respective outcome.

^c Three Marker Average: mean of percent change in estimated glomerular filtration rate-creatinine, estimated glomerular filtration rate-cystatin C, and 1/ β_2 -microglobulin

Supplemental Table 2. Hazard Ratios (95% Confidence Intervals) for Cardiovascular Disease and Mortality by Category of Percent Change in Filtration Markers Over a Six-Year Period Adjusted for First Measurement of Covariates Only^a

Filtration Marker	Category of Percent Change in Filtration Marker			
	< -30%	-30% to -10%	-9.9% to +9.9%	≥ +10%
Total Cardiovascular Disease (1,922/9,712) ^b				
eGFR _{Cr}	2.03 (1.76, 2.34)	1.07 (0.96, 1.18)	1 [Reference]	1.17 (0.95, 1.44)
eGFR _{Cys}	1.75 (1.48, 2.06)	1.16 (1.05, 1.28)	1 [Reference]	1.19 (1.00, 1.41)
1/β ₂ -Microglobulin	2.14 (1.81, 2.52)	1.31 (1.19, 1.45)	1 [Reference]	1.14 (0.98, 1.34)
Three Marker Average ^c	2.35 (1.96, 2.81)	1.24 (1.12, 1.36)	1 [Reference]	1.26 (1.01, 1.58)
Coronary Heart Disease (835/9,452) ^b				
eGFR _{Cr}	2.20 (1.78, 2.71)	1.07 (0.91, 1.25)	1 [Reference]	1.27 (0.93, 1.72)
eGFR _{Cys}	1.68 (1.32, 2.16)	1.11 (0.95, 1.29)	1 [Reference]	1.09 (0.84, 1.42)
1/β ₂ -Microglobulin	1.84 (1.40, 2.40)	1.32 (1.13, 1.54)	1 [Reference]	1.28 (1.02, 1.60)
Three Marker Average ^c	2.46 (1.88, 3.22)	1.35 (1.17, 1.57)	1 [Reference]	1.68 (1.23, 2.29)
Ischemic Stroke (442/9,609) ^b				
eGFR _{Cr}	1.71 (1.27, 2.30)	0.95 (0.77, 1.17)	1 [Reference]	0.99 (0.62, 1.57)

eGFR _{Cys}	1.57 (1.10, 2.24)	1.17 (0.95, 1.45)	1 [Reference]	1.33 (0.94, 1.87)
1/β ₂ -Microglobulin	1.85 (1.29, 2.65)	1.20 (0.97, 1.48)	1 [Reference]	1.38 (1.02, 1.87)
Three Marker Average ^c	1.76 (1.19, 2.62)	1.20 (0.98, 1.47)	1 [Reference]	1.19 (0.74, 1.94)
Heart Failure (1,139/9,531) ^b				
eGFR _{Cr}	2.33 (1.95, 2.80)	1.21 (1.06, 1.38)	1 [Reference]	1.22 (0.93, 1.59)
eGFR _{Cys}	2.19 (1.79, 2.68)	1.29 (1.13, 1.47)	1 [Reference]	1.20 (0.96, 1.50)
1/β ₂ -Microglobulin	2.92 (2.39, 3.56)	1.47 (1.29, 1.68)	1 [Reference]	1.10 (0.89, 1.36)
Three Marker Average ^c	3.13 (2.53, 3.86)	1.21 (1.07, 1.38)	1 [Reference]	1.12 (0.83, 1.52)
All-Cause Mortality (2,285/9,716) ^b				
eGFR _{Cr}	1.93 (1.69, 2.20)	1.05 (0.96, 1.15)	1 [Reference]	1.06 (0.87, 1.30)
eGFR _{Cys}	2.33 (2.03, 2.68)	1.17 (1.07, 1.29)	1 [Reference]	1.30 (1.12, 1.52)
1/β ₂ -Microglobulin	2.54 (2.21, 2.93)	1.28 (1.16, 1.40)	1 [Reference]	1.03 (0.88, 1.20)
Three Marker Average ^c	2.90 (2.49, 3.38)	1.25 (1.15, 1.37)	1 [Reference]	1.31 (1.06, 1.62)
Cardiovascular Disease Mortality (696/9,716) ^b				
eGFR _{Cr}	2.50 (2.01, 3.10)	1.14 (0.96, 1.35)	1 [Reference]	1.00 (0.68, 1.47)
eGFR _{Cys}	2.39 (1.88, 3.05)	1.21 (1.01, 1.43)	1 [Reference]	1.28 (0.97, 1.69)

1/ β_2 -Microglobulin	2.69 (2.10, 3.45)	1.47 (1.24, 1.75)	1 [Reference]	1.21 (0.92, 1.58)
Three Marker Average ^c	3.69 (2.86, 4.75)	1.43 (1.21, 1.69)	1 [Reference]	1.81 (1.29, 2.53)
Non-Cardiovascular Disease Mortality (1,540/9,716) ^b				
eGFR _{Cr}	1.69 (1.43, 2.00)	1.03 (0.92, 1.15)	1 [Reference]	1.12 (0.89, 1.42)
eGFR _{Cys}	2.27 (1.92, 2.70)	1.15 (1.02, 1.29)	1 [Reference]	1.29 (1.07, 1.57)
1/ β_2 -Microglobulin	2.46 (2.07, 2.94)	1.21 (1.08, 1.36)	1 [Reference]	0.95 (0.79, 1.15)
Three Marker Average ^c	2.60 (2.13, 3.16)	1.18 (1.06, 1.32)	1 [Reference]	1.11 (0.84, 1.46)

eGFR_{Cr}, estimated glomerular filtration rate based on creatinine; eGFR_{Cys}, estimated glomerular filtration rate based on cystatin C

Bold font for hazard ratio (95% confidence interval) indicates statistical significance.

^a Adjusted for age, sex, race, body mass index, systolic blood pressure, anti-hypertensive medication use, diabetes status, total cholesterol, high-density lipoprotein cholesterol, current cigarette smoking status (all covariates assessed at study visit 2, 1990-1992)

^b Analyses exclude prevalent cases of the respective outcome.

^c Three Marker Average: mean of percent change in estimated glomerular filtration rate-creatinine, estimated glomerular filtration rate-cystatin C, and 1/ β_2 -microglobulin

Supplemental Table 3. Hazard Ratios (95% Confidence Intervals) for Cardiovascular Disease and Mortality by Category of Percent Change in Filtration Markers Over a Six-Year Period Adjusted for Last Measurement of Covariates and eGFR^a

Filtration Marker	Category of Percent Change in Filtration Marker			
	< -30%	-30% to -10%	-9.9% to +9.9%	≥ +10%
Total Cardiovascular Disease (1,922/9,712) ^b				
eGFR _{Cr}	1.91 (1.55, 2.36)	1.13 (0.99, 1.27)	1 [Reference]	1.25 (1.02, 1.55)
eGFR _{Cys}	1.52 (1.27, 1.82)	1.12 (1.01, 1.24)	1 [Reference]	1.22 (1.03, 1.45)
1/β ₂ -Microglobulin	1.87 (1.55, 2.26)	1.32 (1.19, 1.46)	1 [Reference]	1.11 (0.95, 1.30)
Three Marker Average ^c	2.04 (1.63, 2.55)	1.22 (1.10, 1.35)	1 [Reference]	1.25 (1.00, 1.57)
Coronary Heart Disease (835/9,452) ^b				
eGFR _{Cr}	1.75 (1.29, 2.39)	1.03 (0.85, 1.24)	1 [Reference]	1.39 (1.02, 1.90)
eGFR _{Cys}	1.38 (1.05, 1.81)	1.04 (0.89, 1.22)	1 [Reference]	1.15 (0.88, 1.49)
1/β ₂ -Microglobulin	1.40 (1.03, 1.90)	1.26 (1.08, 1.47)	1 [Reference]	1.26 (1.00, 1.58)
Three Marker Average ^c	1.90 (1.36, 2.65)	1.25 (1.07, 1.46)	1 [Reference]	1.71 (1.24, 2.34)
Ischemic Stroke (442/9,609) ^b				
eGFR _{Cr}	1.64 (1.07, 2.53)	1.01 (0.79, 1.31)	1 [Reference]	0.96 (0.60, 1.55)

eGFR _{Cys}	1.43 (0.97, 2.12)	1.17 (0.94, 1.44)	1 [Reference]	1.28 (0.91, 1.81)
1/β ₂ -Microglobulin	1.59 (1.06, 2.39)	1.24 (1.00, 1.54)	1 [Reference]	1.27 (0.93, 1.73)
Three Marker Average ^c	1.54 (0.95, 2.52)	1.25 (1.01, 1.55)	1 [Reference]	1.07 (0.65, 1.75)
Heart Failure (1,139/9,531) ^b				
eGFR _{Cr}	2.19 (1.68, 2.86)	1.30 (1.11, 1.53)	1 [Reference]	1.31 (1.00, 1.71)
eGFR _{Cys}	1.85 (1.48, 2.32)	1.24 (1.08, 1.42)	1 [Reference]	1.23 (0.99, 1.53)
1/β ₂ -Microglobulin	2.57 (2.05, 3.23)	1.48 (1.29, 1.69)	1 [Reference]	1.08 (0.87, 1.33)
Three Marker Average ^c	2.72 (2.08, 3.55)	1.19 (1.04, 1.36)	1 [Reference]	1.11 (0.82, 1.50)
All-Cause Mortality (2,285/9,716) ^b				
eGFR _{Cr}	1.68 (1.38, 2.04)	1.11 (0.99, 1.24)	1 [Reference]	1.10 (0.89, 1.34)
eGFR _{Cys}	2.02 (1.74, 2.35)	1.16 (1.06, 1.28)	1 [Reference]	1.33 (1.14, 1.56)
1/β ₂ -Microglobulin	2.21 (1.88, 2.60)	1.30 (1.19, 1.43)	1 [Reference]	0.98 (0.84, 1.14)
Three Marker Average ^c	2.51 (2.07, 3.05)	1.29 (1.17, 1.42)	1 [Reference]	1.26 (1.02, 1.56)
Cardiovascular Disease Mortality (696/9,716) ^b				
eGFR _{Cr}	1.97 (1.42, 2.75)	1.14 (0.93, 1.40)	1 [Reference]	1.05 (0.72, 1.55)
eGFR _{Cys}	1.85 (1.40, 2.43)	1.19 (1.00, 1.41)	1 [Reference]	1.32 (1.00, 1.74)

1/ β_2 -Microglobulin	2.10 (1.57, 2.82)	1.49 (1.25, 1.77)	1 [Reference]	1.19 (0.91, 1.56)
Three Marker Average ^c	2.81 (2.03, 3.89)	1.43 (1.20, 1.70)	1 [Reference]	1.75 (1.25, 2.46)
Non-Cardiovascular Disease Mortality (1,540/9,716) ^b				
eGFR _{Cr}	1.54 (1.20, 1.96)	1.12 (0.98, 1.28)	1 [Reference]	1.14 (0.90, 1.45)
eGFR _{Cys}	2.06 (1.71, 2.48)	1.14 (1.02, 1.28)	1 [Reference]	1.33 (1.10, 1.61)
1/ β_2 -Microglobulin	2.26 (1.85, 2.75)	1.24 (1.11, 1.39)	1 [Reference]	0.89 (0.74, 1.08)
Three Marker Average ^c	2.39 (1.87, 3.05)	1.23 (1.10, 1.38)	1 [Reference]	1.06 (0.80, 1.40)

eGFR_{Cr}, estimated glomerular filtration rate based on creatinine; eGFR_{Cys}, estimated glomerular filtration rate based on cystatin C

Bold font for hazard ratio (95% confidence interval) indicates statistical significance.

^a Adjusted for age, sex, race, body mass index, systolic blood pressure, anti-hypertensive medication use, diabetes status, total cholesterol, high-density lipoprotein cholesterol, current cigarette smoking status, last measurement of estimated glomerular filtration rate-creatinine as linear spline terms with two knots at 60 and 90 mL/min/1.73 m² (all covariates assessed at study visit 4, 1996-1998)

^b Analyses exclude prevalent cases of the respective outcome.

^c Three Marker Average: mean of percent change in estimated glomerular filtration rate-creatinine, estimated glomerular filtration rate-cystatin C, and 1/ β_2 -microglobulin