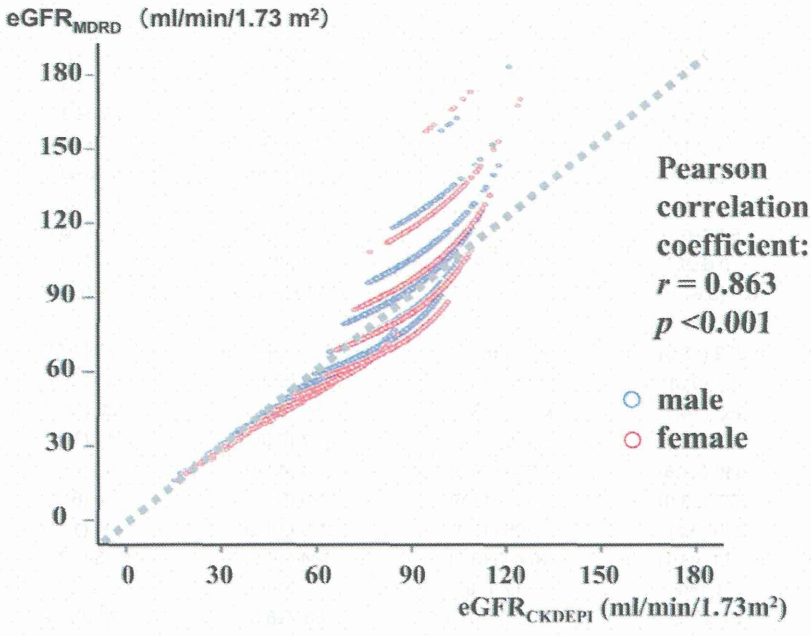

Figure 2. Relationship between eGFRCKDEPI and eGFRMDRD. Points along the diagonal dotted line, accordance between eGFRCKDEPI and eGFRMDRD; points below the diagonal dotted line, underestimation by eGFRMDRD; points over the diagonal dotted line, overestimation by eGFRMDRD. eGFRCKDEPI, estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Study equation; eGFRMDRD, eGFR calculated using the Modification of Diet in Renal Disease (MDRD) study equation.

Methods

Subjects

The subjects were participants of the Iwate-Kenpoku cohort (Iwate-KENCO) study. The Iwate KENCO Study was designed to determine the effects of traditional risk factors and new biomarkers on cardiovascular morbidity and mortality in the Japanese general population. The study area is a typical rural area of Japan (**Figure S1**) with a low move-out/move-in population and a high proportion of elderly people. The methodology of the Iwate-KENCO study has been described elsewhere.[21,22] The initial surveys were carried out from 2002 to 2004. The original cohort study members consisted of 26,469 participants. We excluded participants who lacked data for serum creatinine (n=143), participants with a history of MI or stroke (n=984), and participants who lacked data for at least 1 factor that was used for analysis as an explanatory variable (n=785). Finally, we analyzed data from 24,560 participants (**Figure 1**). The study was approved by the Medical Ethics Committee of Iwate Medical University and conducted in accordance with the guidelines of the Declaration of Helsinki.

Measurements

The initial examinations consisted of a questionnaire, measurements of blood pressure and anthropometric data, and blood tests. Serum creatinine level was measured using an enzymatic assay on an automated analyzer (HITACHI 7700). The methods for measuring serum lipid profile, plasma glucose level, and plasma glycosylated hemoglobin (HbA_{1c}) have been previously described.[21] In this analysis, HbA_{1c} level (National Glycohemoglobin Standardization Program [NGSP] equivalent value) was modified by adding 0.4% to the estimated value (the Japan Diabetes Society [JDS] value) according to the Guidelines of the JDS.[23] Urine albumin was assessed quantitatively using an immunonephelometric method (N-antiserum albumin, Dade Behring) and urine creatinine was measured quantitatively on enzymatic colorimetric test.[24] The urine albumin-creatinine ratio (UACR) was used because the accuracy of the ratio in comparison to 24-h urine sample has been demonstrated in previous studies.[25,26] The data-gathering methodology has been previously described.[21]

Classification and Definition

eGFR was calculated using both MDRD and CKD-EPI equations modified by a Japanese coefficient (eGFRCKDEPI and eGFRMDRD) as shown in **Table S1**.[10,11] Participants were divided into 4 categories (1, $\geq 90\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$; 2, 60–$89\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$; 3a, 45–$59\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$; 3b+, $<45\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$) according to both GFR based on eGFRCKDEPI and on eGFRMDRD. Albuminuria was defined as the presence of microalbuminuria or macroalbuminuria. Microalbuminuria was defined as a UACR of 30–299 mg/g and macroalbuminuria was defined as a UACR ≥300 mg/g.

Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure ≥90 mmHg, use of antihypertensive agents or a combination of these. Diabetes was defined as plasma glucose ≥200 mg/dl, plasma HbA_{1c} (NSGP equivalent value) ≥6.5%, use of anti-diabetes agents or a combination of these. Dyslipidemia was defined as serum total cholesterol (TC) ≥220 mg/dl, serum high-density-lipoprotein cholesterol (HDLC) <40 mg/dl, use of anti-hyperlipidemia agents or a combination of these. Regular alcohol drinking was defined as drinking ≥5 days/week. Exercise habit was defined as doing exercise for at least 60 min 8 days per month.

Outcome Measures

In this cohort study, the endpoints were all-cause death, incident MI and incident stroke. To ascertain subjects' vital status, follow-up surveys were performed in 2006 and 2009. The investigators visited each municipality and reviewed the Basic Resident Register sheets in each local government to confirm the dates of death and move-out of participants. Persons who were known to be alive at the end of follow-up and those who had moved away from the study area were treated as censored

Table 1. Subject Characteristics vs. CKD Stage

CKD stage (ml·min^{-1}·1.73 m^{-2})	eGFR ≥90	60≤eGFR<90	45≤eGFR<60	eGFR <45
CKD-EPI equation (no. subjects)	2,504	20,607	1,259	190
Age (years)	43.0±9.0	63.9±9.3	73.0±7.6	75.2±6.8
BMI (kg/m^2)	23.3±3.6	24.1±3.2	24.3±3.3	24.6±3.4
SBP (mmHg)	116±17.7	128±19.9	133±19.8	134±21.5
TC (mg/dl)	189±33.7	202±32.6	202±33.2	200±38.6
HDLC (mg/dl)	61.4±14.5	59.6±14.9	55.6±14.4	53.3±14.4
HbA_{1c} (mg/dl)	5.33±0.77	5.53±0.66	5.59±0.65	5.64±0.68
SCr (mg/dl)	0.6±0.1	0.7±0.1	1.0±0.1	1.4±0.3
UACR† (mg/g)	10.7 (6.6–19.1)	14.9 (8.5–29.3)	18.8 (9.5–47.2)	56.2 (20.0–317)
Comorbid conditions and habits (%)				
Microalbuminuria	332 (13.3)	4,668 (22.7)	374 (29.7)	77 (40.5)
Macroalbuminuria	21 (0.8)	351 (1.7)	66 (5.2)	49 (25.8)
Hypertension	352 (14.1)	8,653 (42.0)	752 (59.7)	123 (64.7)
Diabetes mellitus	76 (3.0)	1,070 (5.2)	87 (6.9)	19 (10.0)
Dyslipidemia	540 (21.6)	7,600 (36.9)	534 (42.4)	92 (48.4)
Current smoker	577 (23.0)	2,395 (11.6)	120 (9.5)	16 (8.4)
Past smoker	230 (9.2)	2,295 (11.1)	230 (18.3)	34 (17.9)
Regular drinker	579 (23.1)	3748 (18.2)	184 (14.6)	25 (13.2)
MDRD equation (no. subjects)	4,449	17,128	2,711	272
Age (years)	56.2±12.2	62.7±10.9	68.7±8.5	73.3±8.2
BMI (kg/m^2)	23.8±3.5	24.0±3.2	24.4±3.3	24.6±3.4
SBP (mmHg)	124±20.1	127±20.0	131±19.6	134±20.9
TC (mg/dl)	197±33.5	201±32.8	204±32.9	201±38.3
HDLC (mg/dl)	60.7±14.8	59.7±14.9	57.1±14.7	54.2±13.8
HbA_{1c} (mg/dl)	5.54±0.90	5.50±0.61	5.54±0.58	5.62±0.71
SCr (mg/dl)	0.5±0.1	0.7±0.1	0.9±0.1	1.3±0.3
UACR (mg/g)†	15.3 (8.9–30.8)	14.0 (8.1–27.4)	15.4 (8.2–35.5)	38.7 (14.8–180)
Comorbid conditions and habits (%)				
Microalbuminuria	1,076 (24.2)	3,594 (21.0)	677 (25.0)	104 (38.2)
Macroalbuminuria	66 (1.5)	263 (1.5)	103 (3.8)	55 (20.2)
Hypertension	1,452 (32.6)	6,805 (39.7)	1,451 (53.5)	172 (63.2)
Diabetes mellitus	273 (6.1)	815 (4.8)	137 (5.1)	27 (9.9)
Dyslipidemia	1,396 (31.4)	6,090 (35.6)	1,151 (42.5)	129 (47.4)
Current smoker	743 (16.7)	2,110 (12.3)	237 (8.7)	18 (6.6)
Past smoker	402 (9.0)	1,952 (11.4)	398 (14.7)	37 (13.6)
Regular drinker	944 (21.2)	3,175 (18.5)	387 (14.3)	30 (11.0)

Data given as mean±SD, n (%) or †median (interquartile range).
AMI, acute myocardial infarction; BMI, body mass index; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycosylated hemoglobin; HDLC, high-density lipoprotein cholesterol; MDRD, Modification of Diet in Renal Disease; SBP, systolic blood pressure; SCr, serum creatinine; TC, total cholesterol; UACR, urinary albumin to creatinine ratio.

cases.

Stroke events were identified by assessing the Iwate Prefecture Stroke Registration program, which included the entire area where the subjects lived. Details of this registry have been described previously.[22,27] The medical records of all medical facilities within the survey area were verified every year to ensure complete capture of all data from 2006 to 2009 by the physicians and trained research nurses. Incidents of acute MI (AMI) were identified by accessing data from Northern Iwate Heart Disease Registry Consortium, which has been collecting data since 2002. The registration of AMI was based on the criteria of the MONICA study. Details of this registry have been described previously.[22,28] To verify the accuracy of the data, physicians and trained research nurses also checked the medical records of the referral hospitals.

Statistical Analysis

The relationship between $eGFR_{CKDEPI}$ and $eGFR_{MDRD}$ was illustrated using a scatter diagram. Pearson correlation coefficient (r) between $eGFR_{CKDEPI}$ and $eGFR_{MDRD}$ was calculated. Concordance between each corresponding CKD stage according to $eGFR_{CKDEPI}$ and $eGFR_{MDRD}$, was examined on a cross-table for the 4 CKD categories of $eGFR_{CKDEPI}$ and $eGFR_{MDRD}$. Baseline characteristics are listed according to CKD stage based on both $eGFR_{CKDEPI}$ and $eGFR_{MDRD}$ and according to endpoint category. Risk factor-related variables are expressed as mean±SD, proportions (expressed as percentages) or median (interquartile range). Proportion of each CKD stage was compared between GFR_{CKDEPI} and $eGFR_{MDRD}$ by chi-square test.

We defined follow-up time as the period from the initial survey to the first outcome or end of observation. Individuals

Table 2. Baseline Subject Characteristics vs. Endpoint

	All subjects	No events survivor	Died	Incident AMI	Incident stroke
Subjects (n)	24,560	22,246	851	78	605
Age (years)	62.3±11.4	61.3±11.3	71.3±9.0	70.3±7.6	69.9±8.1
Male	8,368 (34.1)	7,334 (33.0)	320 (37.6)	55 (70.5)	96 (36.0)
BMI (kg/m^2)	24.0±3.3	24.0±3.3	23.5±3.5	24.3±3.2	24.3±3.5
SBP (mmHg)	127±20.1	126±20.0	133±20.5	134±19.8	138±20.6
TC (mg/dl)	201±33.0	201±33.0	192±33.9	206±32.6	198±32.7
HDLC (mg/dl)	59.5±14.9	59.7±14.8	56.4±15.4	51.3±14.2	57.5±14.9
HbA$_{1c}$ (%)	5.52±0.67	5.50±0.65	5.63±0.91	5.77±0.72	5.67±0.83
SCr (mg/dl)	0.7±0.2	0.7±0.2	0.8±0.2	0.8±0.2	0.7±0.2
eGFR$_{CKDEPI}$ (ml·min^{-1}·1.73m^{-2})	77.6±10.6	78.4±10.3	71.0±12.0	69.3±10.8	72.2±10.3
eGFR$_{MDRD}$ (ml·min^{-1}·1.73m^{-2})	75.9±15.4	76.5±15.2	71.8±16.8	68.3±14.1	72.1±15.1
UACR (mg/g)†	14.5 (8.2–29.1)	14.0 (8.0–27.4)	19.5 (10.4–49.6)	20.4 (9.3–51.9)	22.8 (12.6–51.8)
Comorbid conditions and habits					
Microalbuminuria	5,453 (22.6)	4,664 (21.3)	273 (34.0)	24 (32.4)	218 (37.8)
Macroalbuminuria	487 (2.0)	373 (1.7)	47 (5.5)	4 (5.1)	29 (4.8)
Hypertension	9,881 (40.2)	8,529 (38.3)	447 (52.5)	51 (65.4)	412 (68.1)
Diabetes mellitus	1,252 (5.1)	1,028 (4.6)	88 (10.3)	8 (10.3)	60 (9.9)
Dyslipidemia	8,770 (35.7)	7,945 (35.7)	274 (32.2)	35 (44.9)	215 (35.5)
Current smoker	3,110 (12.7)	2,761 (12.4)	184 (21.6)	19 (24.4)	108 (17.9)
Past smoker	2,789 (11.4)	2,451 (11.0)	176 (20.7)	16 (20.5)	97 (16.0)
Regular drinker	4,537 (18.5)	4,085 (18.4)	217 (25.5)	15 (19.2)	155 (25.6)
CKD stage based on eGFR$_{CKDEPI}$ (ml·min^{-1}·1.73m^{-2})					
GFR ≥90	2,508 (10.2)	2,470 (11.1)	26 (3.1)	1 (1.3)	11 (1.8)
60≤GFR<90	20,612 (83.9)	18,716 (84.1)	695 (81.7)	62 (79.5)	521 (86.1)
45≤GFR<60	1,259 (5.1)	951 (4.3)	96 (11.3)	14 (17.9)	61 (10.1)
GFR <45	190 (0.8)	118 (0.5)	34 (4.0)	1 (1.3)	12 (2.0)
CKD stage based on eGFR$_{MDRD}$ (ml·min^{-1}·1.73m^{-2})					
GFR ≥90	4,453 (18.1)	4,209 (18.9)	112 (13.2)	5 (6.4)	69 (11.4)
60≤GFR<90	17,133 (69.7)	15,582 (70.0)	568 (66.7)	48 (61.5)	428 (70.7)
45≤GFR<60	2,711 (11.0)	2,280 (10.2)	132 (15.5)	24 (30.8)	94 (15.5)
GFR <45	272 (1.1)	184 (0.8)	39 (4.6)	1 (1.3)	14 (2.3)

Data given as mean±SD, n (%) or †median (interquartile range).
Abbreviations as in Table 1.

who were free of outcomes by 5-year follow-up were subjected to censoring. Receiver operating characteristic (ROC) curves were drawn and the areas under the curves (AUROC) were calculated for each equation to compare the discrimination abilities of the 2 models. Crude, sex- and age-adjusted, and multivariate-adjusted mortality and incidence rates of AMI and stroke (/1,000 person-years) were determined in the 4 groups according to eGFR (CKD stages 1, 2, 3a and 3b+) on Poisson regression analysis. Multivariate-adjusted mortality and incidence rates were estimated after adjusting for age, sex, SBP, body mass index, TC, HDLC, HbA$_{1c}$, existence of albuminuria, smoking habit, regular drinking habit and exercise habit.

Relative risks for all-cause death, incident AMI, and incident stroke were estimated in each category and compared with the reference group (60≤eGFR<90 ml·min^{-1}·1.73 m^{-2}) in a Cox regression model for the same explanatory variables as those used in Poisson regression analysis separately for the 2 models of eGFR$_{CKDEPI}$ and eGFR$_{MDRD}$ CKD stage. The performances of the multivariate models were quantified using Harrell's concordance statistics (Harrell's C).[14] The Akaike information criterion (AIC)[29] and Bayesian information criterion (BIC)[30] were also estimated for these models. We also quantified the degree of correct reclassification by estimating net reclassification improvement (NRI) using cross-categories of eGFR for both equations.[20,31]

All P-values were 2-tailed, and P<0.05 was considered to be statistically significant. Statistical analysis was performed using PASW version 18.0 (IBM Japan, Tokyo, Japan) and STATA version STATA/SE 11 (STATA, College Station, TX, USA).

Results

Figure 2 shows a scatter graph of eGFR$_{CKDEPI}$ and eGFR$_{MDRD}$. The overall correlation between eGFR$_{CKDEPI}$ and eGFR$_{MDRD}$ was relatively good (r=0.863, P<0.001.). Using eGFR$_{CKDEPI}$ as the gold standard, eGFR$_{MDRD}$ mildly to moderately underestimated GFR in persons with eGFR$_{CKDEPI}$ 45–90 ml·min^{-1}·1.73 m^{-2}. Because most of the present participants belonged to this category, eGFR$_{MDRD}$ was likely to underestimate GFR in the total subjects. In contrast, eGFR$_{MDRD}$ moderately to greatly overestimated GFR in persons with eGFR$_{CKDEPI}$ 90–120 ml·min^{-1}·1.73 m^{-2}, especially in female participants. Table S2 is a cross-table of the 4 CKD categories of eGFR$_{CKDEPI}$ and eGFR$_{MDRD}$. Underestimation of eGFR$_{MDRD}$ was observed in 30%

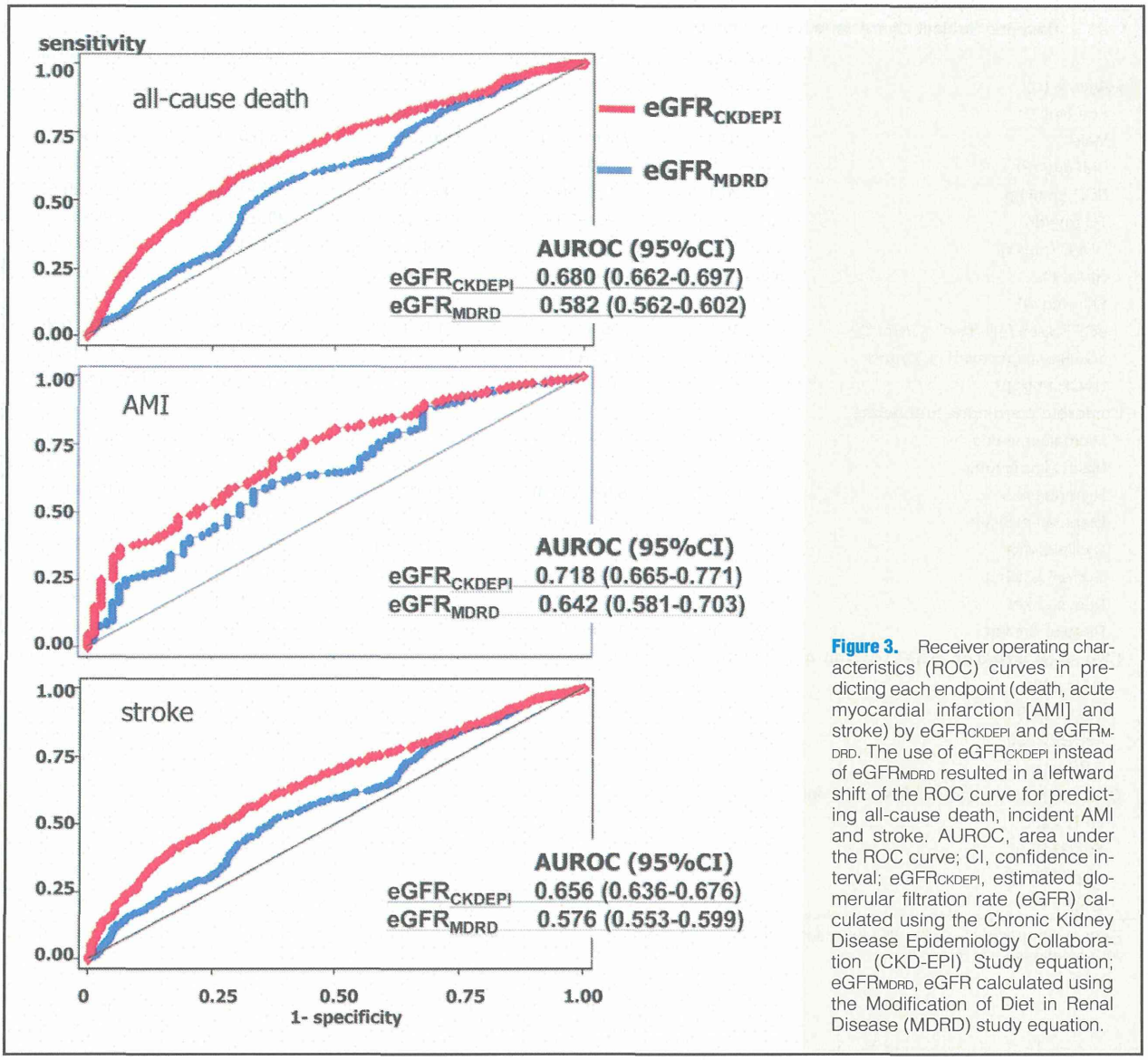

Figure 3. Receiver operating characteristics (ROC) curves in predicting each endpoint (death, acute myocardial infarction [AMI] and stroke) by eGFR$_{CKDEPI}$ and eGFR$_{MDRD}$. The use of eGFR$_{CKDEPI}$ instead of eGFR$_{MDRD}$ resulted in a leftward shift of the ROC curve for predicting all-cause death, incident AMI and stroke. AUROC, area under the ROC curve; CI, confidence interval; eGFR$_{CKDEPI}$, estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Study equation; eGFR$_{MDRD}$, eGFR calculated using the Modification of Diet in Renal Disease (MDRD) study equation.

of subjects in stage 1 (eGFR ≥90 ml·min^{-1}·1.73 m^{-2}) and in 7% of subjects in stage 2 (69–89 ml·min^{-1}·1.73 m^{-2}) using eGFR$_{CKDEPI}$ as the gold standard, while eGFR$_{MDRD}$ was overestimated in 13% of subjects in stage 2. Subclassification and age-stratification of CKD stage showed that significantly different age distributions between corresponding CKD stage based on eGFR$_{CKDEPI}$ and eGFR$_{MDRD}$ contributed to over/underestimations. We have already listed the concordance/discordant results of CKD stage in detail elsewhere.[32]

Table 1 lists baseline characteristics vs. CKD stage based on eGFR$_{CKDEPI}$ and on eGFR$_{MDRD}$, and also the differences in baseline characteristics in each CKD stage between the models using eGFR$_{CKDEPI}$ and eGFR$_{MDRD}$. Age distributions were very different between the 2 models. In stage 1 (eGFR ≥90 ml·min^{-1}·1.73 m^{-2}), mean age was 43.0 years and had a narrow distribution in the eGFR$_{CKDEPI}$ model, while it was 56.2 years with a wide distribution in the eGFR$_{MDRD}$ model. The difference in mean age in CKD stage 1 was >13 years. Higher age with a narrower age distribution was observed in CKD stage 3a and stage 3b+ in the eGFR$_{CKDEPI}$ model compared to the eGFR$_{MDRD}$ model.

After completion of 5-year follow-up, the observed patient-years were 136,961. The mean follow-up period was 5.6 years. There were 851 deaths, 78 cases of AMI and 605 cases of stroke during the observation period. **Table 2** lists baseline characteristics of participants stratified by endpoint. The mean age of subjects who died during the observation period was 71.3 years, which was 10 years older than that of subjects who survived without events. The mean age of subjects in whom AMI or stroke occurred was approximately 70 years, which was 9 years older than that of survivors with no events. For the total subjects, differences in prevalence of CKD stage between eGFR$_{CKDEPI}$ and eGFR$_{MDRD}$ were large in stage 1 (10.2% vs. 18.1%, χ^2=633, P<0.001) and stage 2 (83.9% vs. 69.7%, χ^2=1,382, P<0.001). The proportion of subjects with eGFR <60 ml·min^{-1}·1.73 m^{-2} was 5.9% for eGFR$_{CKDEPI}$ and 12.1% for eGFR$_{MDRD}$ (χ^2=584, P<0.001).

Figure 3 shows ROC curves for predicting each endpoint

Table 3. Events (Death or Incidence) and Mortality/Incidence Rates vs. eGFR

CKD stage (ml·min^{-1}·1.73 m^{-2})	eGFR ≥90	60≤eGFR<90	45≤eGFR<60	eGFR <45
CKD-EPI equation (n)	2,504	20,607	1,259	190
Death				
No. events (crude)	26 (1.86)	695 (6.04)	96 (14.0)	34 (33.4)
Sex- and age-adjusted (95% CI)	6.68 (4.05–9.30)	3.03 (2.66–3.41)	3.26 (2.43–4.08)	6.65 (4.14–9.16)
Multivariate-adjusted (95% CI)	7.21 (4.32–10.1)	3.70 (3.17–4.23)	4.09 (3.01–5.16)	7.50 (4.62–10.4)
AMI				
No. events (crude)	1 (0.07)	62 (0.54)	14 (2.06)	1 (0.98)
Sex- and age-adjusted (95% CI)	0.18 (0.00–0.53)	0.34 (0.22–0.47)	0.72 (0.22–1.23)	0.31 (0.00–0.95)
Multivariate-adjusted (95% CI)	0.15 (0.00–0.45)	0.27 (0.14–0.40)	0.50 (0.11–0.89)	0.19 (0.00–0.58)
Stroke				
No. events (crude)	11 (0.79)	521 (4.58)	61 (9.14)	12 (12.1)
Sex- and age-adjusted (95% CI)	2.27 (0.91–3.64)	2.92 (2.54–3.30)	3.19 (2.23–4.15)	3.71 (1.50–5.92)
Multivariate-adjusted (95% CI)	2.61 (1.03–4.20)	3.56 (2.99–4.12)	4.01 (2.75–5.27)	4.17 (1.66–6.69)
MDRD equation (n)	4,449	17,128	2,711	272
Death				
No. events (crude)	112 (4.47)	568 (5.95)	132 (8.88)	39 (26.6)
Sex- and age-adjusted (95% CI)	4.21 (3.40–5.02)	3.04 (2.65–3.43)	3.02 (2.38–3.66)	6.46 (4.19–8.73)
Multivariate-adjusted (95% CI)	4.80 (3.82–5.78)	3.73 (3.18–4.27)	3.79 (2.94–4.64)	7.36 (4.72–10.0)
AMI				
No. events (crude)	5 (0.20)	48 (0.50)	24 (1.62)	1 (0.68)
Sex- and age-adjusted (95% CI)	0.21 (0.02–0.39)	0.32 (0.20–0.45)	0.77 (0.35–1.19)	0.26 (0.00–0.80)
Multivariate-adjusted (95% CI)	0.17 (0.01–0.33)	0.26 (0.13–0.39)	0.56 (0.20–0.92)	0.17 (0.00–0.52)
Stroke				
No. events (crude)	69 (2.77)	428 (4.53)	94 (6.43)	14 (9.76)
Sex- and age-adjusted (95% CI)	2.81 (2.13–3.48)	2.88 (2.49–3.26)	2.89 (2.19–3.59)	3.25 (1.46–5.04)
Multivariate-adjusted (95% CI)	3.19 (2.37–4.00)	3.56 (2.98–4.14)	3.64 (2.70–4.59)	3.68 (1.63–5.72)

Crude, crude mortality/incidence rates; multivariate-adjusted, multivariate-adjusted mortality/incidence rates (/1,000 person-years); sex- and age-adjusted, sex- and age-adjusted mortality/incidence rates (/1,000 person-years). Multivariate adjustment for risk factors: age, SBP, BMI, TC, HDLC, HbA$_{1c}$, smoking habit and regular drinking habit.
CI, confidence interval. Other abbreviations as in Table 1.

Table 4. Adjusted HR (95% CIs) for Endpoint According to eGFR Type

CKD stage (ml·min^{-1}·1.73 m^{-2})	eGFR ≥90	60≤eGFR<90	45≤eGFR<60	eGFR <45	Model parameters in multivariate-adjusted Cox regression analysis		
Estimated using CKD-EPI equation							
Subjects	2,504	20,607	1,259	190	AIC	BIC	Harrell's C
Death	1.93 (1.25–2.98)	Ref	1.12 (0.90–1.40)	2.05 (1.43–2.92)	15,858	15,947	0.739
AMI	0.55 (0.07–4.34)	Ref	1.86 (1.01–3.44)	0.71 (0.10–5.24)	1,449	1,538	0.790
Stroke	0.72 (0.38–1.36)	Ref	1.13 (0.86–1.48)	1.17 (0.66–2.10)	11,441	11,530	0.729
Estimated using MDRD equation							
Subjects (n)	4,449	17,128	2,711	272	AIC	BIC	Harrell's C
Death	1.28 (1.04–1.58)	Ref	1.03 (0.85–1.25)	1.99 (1.43–2.78)	15,863	15,952	0.737
AMI	0.65 (0.25–1.67)	Ref	2.14 (1.29–3.55)	0.65 (0.09–4.78)	1,446	1,536	0.797
Stroke	0.89 (0.68–1.15)	Ref	1.02 (0.82–1.28)	1.03 (0.00–0.45)	11,442	11,531	0.729

Data given as multivariate-adjusted HR (95% CI). Adjustment for risk factors: age, sex, SBP, BMI, TC, HDLC, HbA$_{1c}$, existence of albuminuria, smoking habit, regular drinking habit and exercise habit.
AIC, Akaike's information criterion; BIC, Baysian information criterion; Harrell's C, Harrell's concordance statistics; HR, hazard ratio. Other abbreviations as in Tables 1,2.

according to eGFR$_{CKDEPI}$ and eGFR$_{MDRD}$. The use of eGFR$_{CKDEPI}$ instead of eGFR$_{MDRD}$ results in a leftward shift of the ROC curve in prediction of all-cause death, incident AMI and stroke. AUROCs (95% confidence interval [95% CI]) for eGFR$_{CKDEPI}$ vs. eGFR$_{MDRD}$ were 0.680 (0.662–0.697) vs. 0.582 (0.562–0.602) in predicting all-cause death, 0.718 (0.665–0.771) vs. 0.642 (0.581–0.703) in predicting AMI and 0.656 (0.636–0.676) vs. 0.576 (0.553–0.599) in predicting stroke.

Table 3 lists number of events (death, AMI and stroke) and crude mortality and incidence rates, sex- and age-adjusted and multivariate-adjusted mortality and incidence rates, and their 95% CI (expressed as /1,000 person-years) in the 4 categories separately for the 2 models based on eGFR$_{CKDEPI}$ and on eGFR$_{MDRD}$. A clear steep linear relationship between eGFR

Table 5. Reclassification of eGFR Categories According to Endpoint

CKD stage	eGFR$_{CKDEPI}$				Total
	eGFR ≥90	60≤eGFR<90	45≤eGFR<60	eGFR <45	
eGFR$_{MDRD}$					
Participants who died					
GFR ≥90	25	87*	0	0	112
60≤GFR<90	1**	567	0	0	568
45≤GFR<60	0	41**	91	0	132
GFR <45	0	0	5**	34	39
Total	26	695	96	34	851
Participants who did not die					
GFR ≥90	1,741	2,596**	0	0	4,337
60≤GFR<90	737*	15,823	0	0	16,560
45≤GFR<60	0	1,493*	1,086	0	2,579
GFR <45	0	0	77*	156	233
Total	2,478	19,912	1,163	156	23,709
Participants who developed AMI					
GFR ≥90	1	4*	0	0	5
60≤GFR<90	0**	48	0	0	48
45≤GFR<60	0	10**	14	0	24
GFR <45	0	0	0**	1	1
Total	1	62	14	1	78
Participants who did not develop AMI					
GFR ≥90	1,765	2,679**	0	0	4,444
60≤GFR<90	738*	16,342	0	0	17,080
45≤GFR<60	0	1,524*	1,163	0	2,687
GFR <45	0	0	82*	189	271
Total	2,503	20,545	1,245	189	24,482
Participants who developed stroke					
GFR ≥90	10	59*	0	0	69
60≤GFR<90	1**	427	0	0	428
45≤GFR<60	0	35**	59	0	94
GFR <45	0	0	2**	12	14
Total	11	521	61	12	605
Participants who did not develop stroke					
GFR ≥90	1,756	2,624**	0	0	4,380
60≤GFR<90	737*	15,963	0	0	16,700
45≤GFR<60	0	1,499*	1,118	0	2,617
GFR <45	0	0	80*	178	258
Total	2,493	20,086	1,198	178	23,955

*Improved reclassification; **worse reclassification using the CKD-EPI equation instead of the MDRD equation. Units of GFR, $ml \cdot min^{-1} \cdot 1.73 m^{-2}$.
Abbreviations as in Table 1.

and crude mortality was observed for the eGFR$_{CKDEPI}$ model, while that for eGFR and crude mortality in the GFR$_{MDRD}$ model was more of a gradual slope.

The relationship between CKD stage and death risk was U-shaped in the sex- and age-adjusted models and multivariate-adjusted models, and the lowest mortality rate was observed in stage 2 (60–89 $ml \cdot min^{-1} \cdot 1.73 m^{-2}$) for both the eGFR$_{CKDEPI}$ and eGFR$_{MDRD}$ models. The adjusted mortality rate in stage 3a was almost identical to that in stage 2 for the eGFR$_{MDRD}$ model, while a slightly higher mortality rate in stage 3a than in stage 2 was observed for the eGFR$_{CKDEPI}$ model. Adjusted mortality rate was significantly higher in stage 1 than in stage 2 for the eGFR$_{CKDEPI}$ model, while it was not significantly higher in the eGFR$_{MDRD}$ model. Adjusted incidence rates of AMI and stroke were similar between the 2 models for each stage.

Table 4 lists relative risks for death, AMI and stroke according to CKD stage for both the eGFR$_{CKDEPI}$ and eGFR$_{MDRD}$ models. Also listed are the results of model assessment using post-estimation analysis. A typical U-shaped relationship between mortality risk and CKD stage was observed for eGFR$_{CKDEPI}$, and a J-shaped relationship between mortality risk and CKD stage was observed for eGFR$_{MDRD}$. Two-fold higher risk for death was observed in stage 1 and stage 3b+ (eGFR <45 $ml \cdot min^{-1} \cdot 1.73 m^{-2}$) in the eGFR$_{CKDEPI}$ model, while mildly elevated risk for death was observed in stage 1 in the eGFR$_{MDRD}$ model. Risks for AMI and stroke were similar in each stage regardless of eGFR type. Although AUROC indicated that eGFR$_{CKDEPI}$ accurately discriminated subjects into persons with events or not, all model parameters (AIC,

BIC and Harrell's C) were almost identical between the eGFRCKDEPI and eGFRMDRD models. This suggests that no superiority existed in prediction of events either in the eGFRCKDEPI model or the eGFRMDRD model on multivariate-adjusted Cox regression analysis.

Table 5 lists detailed cross-tabulated classifications (CKD stage based on eGFRCKDEPI and on eGFRMDRD) for calculating NRI separately by endpoint. For predicting all-cause death, NRI was estimated to be 6.7% and Z statistic was estimated to be 4.78 (P<0.001). The eGFRCKDEPI model reclassified risk categories better than the eGFRMDRD model. For predicting incident AMI, NRI was –9.1% and Z statistic was estimated to be –1.89 (P=0.029). Use of eGFRCKDEPI made reclassification worse than using eGFRMDRD. For predicting incident stroke, NRI was –0.3% and Z statistic was estimated to be –0.20 (P=0.421) and no improvement was observed by using eGFRCKDEPI instead of eGFRMDRD.

Discussion

We compared risk predictabilities of mortality and cardiovascular morbidity between 2 models using GFR based on eGFRCKDEPI and that based on eGFRMDRD. In univariate analysis, discriminating ability using eGFRCKDEPI was significantly higher than that using eGFRMDRD to predict future death, AMI and stroke events (**Figure 3**; P<0.01). To compare discrimination abilities of the 2 models using eGFRCKDEPI and eGFRMDRD in multivariate-adjusted analysis, we compared model parameters including Harrell's C, AIC and BIC between the Cox regression model for CKD stage based on eGFRCKDEPI and that based on eGFRMDRD. We could not identify better discriminating ability in the eGFRCKDEPI model than that in the eGFRMDRD model. NRI analysis indicated that the CKD-EPI equation was associated with a significantly positive NRI for predicting all-cause death, while it was not associated with a positive NRI for predicting AMI or stroke.

To capture discrimination, AUROC is the most common popular metric.[13] A larger AUROC indicates a more appropriate predictor for separating subjects into a diseased group and non-diseased group.[13] Harrell et al extended the concept of discrimination from the logistic regression setting to survival analysis and developed concordance C statistics.[14] To quantitatively estimate fitness of the model, information-theoretic methods, such as AIC and BIC, have been developed.[29,30] Lower AIC and BIC indicate more appropriate goodness of fit for predicting the endpoint in a multivariate-adjusted model. The c statistic (AUROC and Harrell's C, etc), however, may not be optimal in assessing models that predict future risk or stratify individuals into risk categories.[18]

The question of whether novel risk factors can contribute to overall risk prediction independent of traditional risk factors and the question of whether a new model can more accurately stratify individuals into higher or lower risk categories of clinical importance have been challenging us to developing new ways for assessing adequate model predictability.[15,16,18] Several studies have offered new methods of assessment of risk prediction regarding reclassification tables.[17–19] Pencina et al proposed a new method of statistical analysis named "the net reclassification improvement" (NRI).[20] Assessment of NRI enables determination of new risk factors that contribute to improvement of risk prediction. Although we failed to show superiority of the eGFRCKDEPI model in discrimination ability, we managed to identify statistically significantly better performance of the eGFRCKDEPI model compared to the eGFRMDRD model on NRI analysis.

Superiority in discriminating ability in the eGFRCKDEPI model disappeared after multivariate adjustment and we found similar predictability in the 2 models. Several confounding factors may attenuate superiority in predictive ability in the eGFRCKDEPI model. Poisson regression analysis showed that age adjustment drastically converted a positive and steep linear relationship between mortality and CKD stage into a U-shaped relationship in the eGFRCKDEPI model. We also showed that age distribution was different for corresponding CKD stage between the 2 models in the baseline characteristics on cross-sectional analysis. The age-adjusted model suggested that the contribution of age to prediction of death was greater in the eGFRCKDEPI model, and the difference in predictive ability between the 2 models was attenuated after age adjustment. Moreover, age adjustment made the risk for death higher in CKD stage 1, especially in the eGFRCKDEPI model.

All-cause mortality and cardiovascular morbidity rates were high in subjects with normal eGFR (eGFR ≥90 ml·min^{-1}·1.73 m^{-2}) compared to subjects in stage 2 (60–89 ml·min^{-1}·1.73 m^{-2}) in the present study. Although most previous studies identified a linear relationship between cardiovascular morbidity and mortality risk and CKD stage, recent studies have shown that there is a U-shaped relationship between death risk and CKD stage based on eGFR.[12,33–36] The ARIC study found elevated risk for death and cardiovascular disease in subjects with elevated eGFR. Risk elevation started at eGFR=120 ml·min^{-1}·1.73 m^{-2}, and the lowest risk for death was observed for eGFR 90–119 ml·min^{-1}·1.73 m^{-2}.[12] Tonelli et al reported that risk elevation started at eGFR=75 ml·min^{-1}·1.73 m^{-2} and that the lowest risk for death was observed for eGFR 60–74 ml·min^{-1}·1.73 m^{-2}.[33] Although reduced GFR has been shown to contribute to higher risks for all-cause death and cardiovascular mortality and morbidity in previous studies, whether elevated GFR contributes to high risks for all-cause death and cardiovascular mortality and morbidity has not been elucidated.

Serum creatinine level is affected not only by GFR but also by other factors such as muscle metabolism. Persons with muscle wasting secondary to an illness such as malignancy, malnutrition or inflammatory disease and other deconditioning situations have a low serum creatinine level with apparently overestimated eGFR. They possibly have high risks for all-cause death and cardiovascular morbidity and mortality. The association between high eGFR and poor prognosis might be attributable to overestimation of eGFR due to low serum creatinine level in persons with muscle wasting.

Aside from the possible contribution of difference in muscle mass to eGFR, increased GFR might have contributed to elevated risks for death and cardiovascular morbidity and mortality. Hostetter et al reported that reduced mass of nephrons by artificial ablation yielded a marked increase in GFR and contributed to structural hypertrophy in an animal study.[37] This suggested that early-stage kidney failure was accompanied by hyperfiltration. A cross-sectional study showed that higher eGFR correlated with presence of hyperfiltration among diabetic patients with microalbumimnuria,[38] and hyperfiltration status observed in diabetic children was thought to be associated with subsequent development of kidney dysfunction expressed as microalbuminuria.[39]

Whether higher eGFR is associated with early-stage renal failure in non-diabetic subjects has not been fully elucidated and whether higher eGFR is associated with elevated risks for cardiovascular morbidity and mortality has also not been elucidated until now. We have shown only that higher GFR based on eGFRCKDEPI was associated with higher risk for all-cause death in a general population. Whether the association be-

tween higher eGFR and an elevated risk for death reflects the true relationship between elevated actual measured GFR and an elevated risk for death due to cardiovascular disease should be examined.

Several limitations to the present study should be noted. We could not measure GFR directly, and we therefore compared risk predictability of CKD stage based on estimation using $eGFR_{CKDEPI}$ and estimation using $eGFR_{MDRD}$. Participants <40 years of age accounted for only 3.4% of the total subjects, and the number of persons diagnosed in K/DOQI CKD stage 1 category (GFR $\geq 90\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$) was only 747 (8.9% of the total subjects). Subject age was biased to middle-aged to elderly, and most of these participants had mildly reduced kidney function (K/DOQI CKD stage 2), therefore this might have contributed to uncertainty in risk predictability in persons in K/DOQI CKD stage 1. The subject group consisted of persons who underwent annual health check-ups and were in relatively good condition, and we could not perform accurate examination in persons who were diagnosed as having K/DOQI CKD stage 4+ because of the small sample size. The considerably low incidence rate of AMI in this cohort study, which was also observed in a previous study in Japan,[40] also contributed to uncertainty in risk predictability for AMI.

In conclusion, better discrimination was obtained using the $eGFR_{CKDEPI}$ model than the $eGFR_{MDRD}$ model in univariate analysis. NRI analysis indicated that the use of $eGFR_{CKDEPI}$ instead of $eGFR_{MDRD}$ offered a statistically significant improvement in prediction of death. The use of the new equation for eGFR instead of the old equation may contribute to accurate risk assessment.

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Disclosures

Conflict of Interest: None declared.

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Supplementary Files

Supplementary File 1

Figure S1. The study area.

Table S1. Formulas for Calculating eGFR Based on CKD-EPI Equation and MDRD Equation

Table S2. Cross-Tables of CKD Stage Based on eGFRCKDEPI and eGFRMDRD

Please find supplementary file(s);
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ORIGINAL ARTICLE

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Changes in Cognitive Function After Carotid Endarterectomy in Older Patients: Comparison With Younger Patients

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Abstract

Objective and subjective assessments of changes in cognition after carotid endarterectomy (CEA) were compared between older patients (≥76 years old) and younger patients (<76 years old). Patients underwent subjective cognitive assessment by a neurosurgeon and the patient's next of kin, and neuropsychological testing (five parameters) before and after surgery. Of 37 older patients studied, 4 (11%), 28 (75%), and 5 (14%) patients were defined as having subjectively improved, unchanged, and impaired cognition, respectively, following surgery. Differences in test scores (postoperative test score − preoperative test score: *Δ* score) in all neuropsychological tests were significantly lower in the older patients than in the 213 younger patients. The *Δ* score was able to statistically differentiate older patients with subjectively improved, unchanged, and impaired cognition after surgery. Receiver operating characteristic analysis showed that the *Δ* score cut-off point for detecting subjective improvement (upper cut-off point) and impairment (lower cut-off point) in cognition after surgery in older patients was identical to the mean or the mean +0.5 standard deviation (SD) and the mean −1.5 SD or the mean −1 SD, respectively, of the control value obtained from normal subjects. The upper and lower cut-off points were lower and higher, respectively, than those in younger patients. In conclusion, although neuropsychological test scores reflect the subjective assessment of postoperative change in cognition in older patients, the optimal cut-off points for the test scores to detect subjective improvement and impairment in cognition after CEA are different in older patients compared with younger patients.

Key words: carotid endarterectomy, cognition, neuropsychological test, elderly

Introduction

Carotid endarterectomy (CEA) reduces the risk of stroke in selected patients with carotid disease.[4] Numerous studies have investigated changes in cognitive function following CEA using objective neuropsychological testing and found that, while CEA may improve cognitive function,[9,17] cognitive impairment occurs in 10% to 30% of patients following CEA.[7,12,13,20] However, reports defined no clear criteria for determining significant cognitive improvement or impairment after surgery on neuropsychological test scores, because such postoperative changes may, in part, reflect the "practice effect" (an improvement in scores when patients are repeatedly tested).[12,17] In contrast, physicians and/or patients' families often report subjective postoperative improvements or impairments in cognition for patients undergoing CEA; indeed, patients <76 years old who underwent CEA experienced subjective improvement in 11% and impairment of cognition in 11% of cases after surgery.[22] Further, neuropsychological testing can detect subjective improvement and impairment in cognition after surgery if the optimal cut-off points for changes of the test scores are defined.[22]

CEA is an effective means of preventing stroke recurrence even in elderly patients.[3] However, whether cognitive function changes following CEA in such patients remains unclear. Several investigators showed significant improvement in cognitive performance scores after CEA,[1] but others demonstrated no significant differences in scores on cognitive tests before and after surgery.[10] Further, no studies have compared cognitive changes after CEA in

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