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The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation provides a better definition of cardiovascular burden associated with CKD than the Modification of Diet in Renal Disease (MDRD) Study formula in subjects with type 2 diabetes

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ABSTRACT

Objective: The chronic kidney disease (CKD)-Epidemiology Collaboration (EPI) equation was shown to be more accurate than the Modification of Diet in Renal Disease (MDRD) Study formula for estimating glomerular filtration rate (GFR) in the general population. This study was aimed at assessing cardiovascular disease (CVD) burden associated with CKD in type 2 diabetes, using these two GFR estimating formulas for CKD definition.

Methods: This cohort study examined 15,773 Caucasian patients with type 2 diabetes participating in the Renal Insufficiency And Cardiovascular Events Italian Multicenter Study (NCT00715481) and attending the baseline visit in 19 diabetes clinics in years 2007–2008. Serum creatinine was assessed by the modified Jaffe method. Albuminuria was measured by immunonephelometry or immunoturbidimetry. CKD was defined as an estimated GFR (eGFR) <60 mL/min/1.73 m^2 and/or micro/macroalbuminuria.

Results: Prevalence of impaired eGFR and CKD decreased from 18.7% to 17.2% ($P = 0.0012$) and from 37.5% to 36.3% ($P = 0.077$), respectively, with the CKD-EPI, as compared with the MDRD Study equation. Subjects with impaired eGFR or CKD with the MDRD Study equation only showed lower CVD prevalence rates and coronary heart disease risk scores, mainly driven by prevailing female sex, younger age and shorter diabetes duration, as compared with those with both formulas, whereas opposite figures were observed in patients falling into these categories with the CKD-EPI equation only.

Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; CVD, cardiovascular disease; NKF, National Kidney Foundation; KDOQI, Kidney Disease Outcomes Quality Initiative; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; CKD-EPI, CKD epidemiology collaboration; eGFR, estimated GFR; T2DM, type 2 diabetes; RIACE, Renal Insufficiency And Cardiovascular Events; IDMS, isotope-dilution mass spectrometry; AER, albumin excretion rate; BP, blood pressure; HbA_{1c}, glycated hemoglobin; UKPDS, UK Prospective Diabetes Study; CHD, coronary heart disease.

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Estimating GFR in patients with type 2 diabetes using the CKD-EPI equation provides a better definition of CVD burden associated with CKD not only in individuals reclassified upward, but also in those reclassified downward.

1. Introduction

Chronic kidney disease (CKD) is recognized as a major public health concern worldwide, due to the increased risk of progression to end-stage renal disease (ESRD) requiring dialysis or kidney transplant as well as of cardiovascular disease (CVD) morbidity and mortality, since its earliest stages [1]. For clinical and epidemiological purposes, CKD is currently classified into 5 stages, according to the National Kidney Foundation (NKF)'s Kidney Disease Outcomes Quality Initiative (KDOQI), based on the presence or absence of kidney damage, as manifested by either pathological abnormalities or disease markers such as micro or macroalbuminuria, and glomerular filtration rate (GFR), as calculated by the use of estimating equations from serum creatinine measurements [2]. The four-variable Modification of Diet in Renal Disease (MDRD) Study formula [3,4] is the most widely used equation for reporting results of serum creatinine measurements by clinical laboratories as well as for estimating CKD prevalence in epidemiological surveys.

However, this equation was derived from subjects with CKD and, when applied to the general population, it was shown to systematically underestimate GFR in individuals with measured values $\geq$60 mL/min/1.73 m^2, thus resulting in overdiagnosis of CKD and overestimation of its prevalence [5]. To provide more accurate GFR estimates, a new equation using the same four variables as the MDRD Study equation was recently developed and validated in pooled populations with diverse clinical characteristics [6]. This formula, the CKD Epidemiology Collaboration (CKD-EPI) equation, was shown to be more accurate, especially for higher GFR values [7], and also to provide lower estimates of CKD prevalence and to categorize more appropriately individuals with respect to renal and CVD risk, as compared with the MDRD Study equation. In particular, a variable proportion of subjects with estimated GFR (eGFR) <60 mL/min/1.73 m^2 were reclassified upward, thus reducing the prevalence of CKD in the general population from approximately 13% to 11% [6,8]. Moreover, reclassified individuals were more frequently younger, female and at lower risk than those who were not reclassified, though age- and sex-adjusted risks for all-cause mortality, ESRD and CVD events were greatly attenuated [8,9]. However, the CKD-EPI formula may not perform equally in different populations and in subjects with various clinical conditions, such as type 2 diabetes mellitus (T2DM).

This study was aimed at assessing CVD burden associated with CKD in a large cohort of Italian type 2 diabetic subjects, using the two GFR estimating formulas for CKD definition.

2. Subjects and methods

2.1. Study population

We used the anamnestic, clinical and laboratory data obtained at the baseline visit for the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicenter Study, an observational, prospective cohort study on eGFR as independent predictor of CVD morbidity and mortality in T2DM (registered with ClinicalTrials.gov, NCT00715481; URL http://clinicaltrials.gov/ct2/show/NCT00715481). The study protocol was approved by the locally appointed ethics committees. The RIACE population consists of 15,773 Caucasian patients with T2DM (America Diabetes Association criteria) visiting consecutively 19 hospital-based Diabetes Clinics of the National Health Service throughout Italy (see on-line appendix) in years 2007–2008. Exclusion criteria were dialysis or renal transplantation.

2.2. eGFR and albuminuria

GFR was estimated using both the four-variable MDRD Study [3] and the CKD-EPI [6] equations. Serum (and urine) creatinine was measured by the modified Jaffe method. One-to-three measurements were obtained and the mean value was used in case of multiple measures, which were performed in a 3-to-6-month period. As recommended [4], one of two versions of MDRD Study equation were used, depending on whether or not serum creatinine methods had been calibrated to be isotope-dilution mass spectrometry (IDMS)-traceable. For GFR estimation with the CKD-EPI formula, non-IDMS serum creatinine values were standardized using the following equation: $-0.166 + 1.10x$ (measured serum creatinine [mg/dL]). To derive this equation, 201 frozen samples previously analyzed using a non-IDMS method were re-assayed by an IDMS reference method [8]. Patients were then assigned to one of the following classes of eGFR (mL/min/1.73 m^2): 1 ($\geq$90); 2 (60–89); 3 (30–59); 4 (15–29); and 5 (<15). Patients assigned to classes 4 and 5 were pooled together for cross-classification by eGFR or CKD.

Albumin excretion rate (AER) was obtained from timed (24 h) urine collections or calculated from albumin/creatinine ratio in early-morning, first-voided urine samples using a conversion formula developed in type 1 diabetes [10] and preliminary validated in a subgroup of subjects from the RIACE cohort. Albumin concentration was measured in fresh urine samples by immunonephelometry or immunoturbidimetry, in the absence of symptoms and signs of urinary tract infection or other interfering clinical conditions. As recommended [11], the analytical coefficient of variation (CV) of both methods was largely <15%, i.e. 2.1–5.2% and 3.4–8.1%, with a detection limit of 1.7 mg/L and 3.0 mg/L, for immunonephelometry and immunoturbidimetry, respectively. As an external quality control, 50 samples from each centre were re-analyzed at the reference laboratory to verify that the CVs between the peripheral and the central values were <15% at least in the relevant clinical range of 15–500 mg/L. Higher CVs were observed almost exclusively for very low albumin concentrations, with no impact on patient classification into classes of albuminuria. One to three measurements for each patient were obtained; in case of multiple measurements, which were performed in a 3-to-6-month interval, the geometric mean of 2-to-3 values was used for analysis. Patients were then assigned to one of the following classes of albuminuria (mg/24 h): normoalbuminuria (AER <30), microalbuminuria (AER 30-299), or macroalbuminuria (AER $\geq$300). In addition, normoalbuminuric subjects were further classified as having normal (AER <10) or low albuminuria (AER 10-29), according to the recent NKF definition [12].

Based on eGFR and AER values, patients were finally classified has having no CKD or CKD stages 1–5, according to the NFK's KDOQI classification [2].

2.3. Other parameters

The following information was collected by a structured interview: age, family history of diabetes, hypertension, dyslipidemia, and premature CVD in a first degree relative, smoking status, known

diabetes duration, current treatments, and previous documented major acute CVD events, including myocardial infarction, stroke, ulcer or gangrene, amputation, coronary, carotid, and lower limb revascularization, and surgery for aortic aneurysm. CVD events were adjudicated based on hospital discharge records or specialist visits by an *ad hoc* committee in each center.

Body mass index was calculated from the weight and height measured during the physical examination. Blood pressure (BP) was then measured after the patient had been seated for at least 5 min.

Glycated hemoglobin (HbA_{1c}) was measured by high performance liquid chromatography using DCCT-aligned methods, whereas triglycerides, HDL and total cholesterol were assessed by standard methods and LDL cholesterol was calculated using the Friedwald formula.

Retinopathy was assessed by an expert ophthalmologist with ophtalmoscopy or high-quality stereoscopic photographs.

2.4. Statistical analysis

The distribution of eGFR classes and CKD stages in the RIACE cohort was compared for GFR estimated using the MDRD Study and CKD-EPI equations in all patients. Distribution of eGFR categories was also stratified by AER and sex, whereas prevalence of CKD stages was examined for men and women separately as well as for the following age classes: <55, 55–64, 65–74, and ≥75 years.

Participants were then classified into 4 mutually exclusive groups depending on the presence of eGFR <60 mL/min/1.73 m^2 or CKD according to the MDRD Study or CKD-EPI equation only, to both equations or to neither one. Values of CVD risk factors were calculated for these groups and global CVD risk was estimated in patients without a previous CVD event using the UK Prospective Diabetes Study (UKPDS) 10-year coronary heart disease (CHD) risk score [13]. Clinical characteristics of subjects in these groups were compared using the Mann–Whitney *U*-test or χ^2 test, for continuous and variables, respectively. Prevalence rates with the two formulas were compared using the paired preferences test.

Data are expressed as median [interquartile range] or number of cases and percentage, as appropriate. All statistical analyses were performed using SPSS 10.0 statistical software.

3. Results

The main clinical characteristics of patients from the RIACE population were: age 67 [59–73] years; male/female ratio 57/43; diabetes duration 11 [5–20] years; HbA_{1c} 7.30 [6.51–8.28] %; subjects on diet alone 13.5%, oral hypoglycemic agents 61.4%, insulin 15.5%, and combined therapy 9.6%; subjects on anti-hypertensive treatment 70.7% (58.1% on blockers of the renin-angiotensin system); subjects on lipid-lowering treatment 46.2% (42.5% on statins).

The number of subjects reclassified upward for eGFR was higher with the CKD-EPI than with the MDRD Study equation, i.e. 9.9% (1,563) vs. 1.8% (291) from class 2 to class 1, and 2.0% (311) vs. 0.4% (67) from class 3 to class 2. This was not the case with the percentage of patients passing from class 4 to class 3 (all to class 3b, i.e. 30–44 mL/min/1.73 m^2), that was higher with the MDRD Study (48, 0.3%) than with the CKE-EPI (2, <0.1%) equation. As a result, the number of subjects with impaired eGFR (i.e. <60 mL/min/1.73 m^2), decreased (8.2% reduction) from 18.7% (2959) to 17.2% (2715) using the CKD-EPI instead of the MDRD Study formula ($P = 0.0012$) (Table 1). When stratified by AER, no significant trend was observed (Supplemental Table 1).

As a consequence of eGFR reclassification, the number of subjects reclassified upward for CKD was higher with the CKD-EPI than with the MDRD Study equation, i.e. 1.5% (234) vs. 0.3% (44) from stage 3 to no CKD, 1.8% (283) vs. 0.5% (75) from stage 2 to stage 1, and 0.5% (77) vs. 0.1% (23) from stage 3 to stage 2. Conversely, the number of patients with stage 4 CKD passing to stage 3 was higher with the MDRD Study (48, 0.3%) than with the CKD-EPI (2, <0.1%) equation. As a result, the number of subjects with CKD decreased (3.2% reduction) from 37.5% (5,908) to 36.3% (5,718) using the CKD-EPI instead of the MDRD Study formula ($P = 0.077$) (Table 2). This decrease in CKD prevalence was almost exclusive of female sex (3.0% vs. 0.2% reduction in males), whereas the percentage of CKD subjects was higher with the MDRD Study formula than with the CKD-EPI equation in the age classes <55, 55–64 and 65–74 years, but not among the oldest patients (≥75 years) (Supplemental Table 2).

Subjects showing impaired eGFR or CKD with the MDRD Study equation only were younger and predominantly female and had shorter diabetes duration and lower UKPDS 10-year CHD risk score, as compared subjects with impaired eGFR or CKD according to both equation. They were also less frequently on insulin or combined treatment, and had a lower prevalence of albuminuria, hypertension, and dyslipidemia (not for CKD subjects), CVD and diabetic retinopathy. Most of these features were similar to those of subjects without reduced eGFR or CKD, despite lower eGFR values (Tables 3 and 4).

An opposite picture was observed in patients showing impaired eGFR or CKD with the CKD-EPI equation only, i.e. almost exclusively male sex and older age, longer diabetes duration, and higher insulin use (only for impaired eGFR), prevalence of albuminuria and CVD (but not of hypertension, dyslipidemia, and retinopathy), and UKPDS 10-year CHD risk scores, as compared with patients with impaired eGFR or CKD with the MDRD Study equation only and with those without impaired eGFR or CKD. More importantly, prevalence of CVD (for impaired eGFR only) and the UKPDS 10-year CHD risk scores were significantly higher than those of patients with impaired eGFR or CKD with both equations, despite better preservation of renal function and lower prevalence of hypertension (for impaired eGFR only), dyslipidemia, and retinopathy (for CKD only) (Tables 3 and 4).

Finally, the 48 patients reclassified downward from class 3 to class 4 eGFR (and from stage 3 to stage 4 CKD) with the CKD-EPI equation, as compared with those showing an eGFR <30 with both formulas, were older (78 [72–84] vs. 74 [68–80] years), more frequently male (60.4% vs. 47.7%) and with higher CVD prevalence (56.3% vs. 46.1%), particularly CHD (45.8% vs. 25.8%) and peripheral artery disease (20.8% vs. 13.7%), and 10-year CHD risk score (0.48 [0.31–0.63] vs. 0.37 [0.24–0.63]).

4. Discussion

Prevalence of impaired eGFR and CKD decreased with the CKD-EPI, as compared with the MDRD Study equation. Subjects with impaired eGFR or CKD with the MDRD Study equation only showed lower CVD prevalence rates and CHD risk scores, mainly driven by prevailing female sex, younger age and shorter diabetes duration, as compared with those with both formulas, whereas opposite figures were observed in patients falling into these categories with the CKD-EPI equation only.

Monitoring eGFR decrease from normal to mild-to-moderate reduction is particularly important in subjects with increased risk of development and progression of CKD, such as patients with T2DM, especially in view of the increasing evidence that impaired eGFR is associated with increased CVD risk [14,15] and, in the majority of these individuals, occurs in the absence of albuminuria [15–17]. In fact, the NKF has recently acknowledged that identifying subjects with impaired renal function based on the presence of an eGFR <60 mL/min/1.73 m^2, without concomitant evidence of

Table 1
Comparison of eGFR categories using the CKD-EPI and MDRD Study equations in the RIACE cohort. Subjects reclassified upward and downward with the CKD-EPI equation are indicated in light and dark grey, respectively.

CKD-EPI eGFR (mL/min/1.73 m^2)	MDRD Study eGFR (mL/min/1.73 m^2)				Total
	≥90	60–89	30–59	<30	
≥90	4371 (27.7%)	1563 (9.9%)	0 (0%)	0 (0%)	5934 (37.6%)
60–89	291 (1.8%)	6522 (41.3%)	311 (2.0%)	0 (0%)	7124 (45.2%)
30–59	0 (0%)	67 (0.4%)	2,342 (14.8%)	2 (0.1%)	2411 (15.3%)
<30	0 (0%)	0 (0%)	48 (0.3%)	256 (1.6%)	304 (1.9%)
Total	4662 (29.6%)	8152 (51.7%)	2701 (17.1%)	258 (1.6%)	15,773 (100.0%)

Table 2
Comparison of CKD stages using the CKD-EPI and MDRD Study equations in the RIACE cohort. Subjects reclassified upward and downward with the CKD-EPI equation are indicated in light and dark grey, respectively.

CKD-EPI CKD Stage	MDRD Study CKD stage					Total
	No CKD	1	2	3	4-5	
No CKD	9821 (62.3%)	0 (0%)	0 (0%)	234 (1.5%)	0 (0%)	10,055 (63.8%)
1	0 (0%)	977 (6.2%)	283 (1.8%)	0 (0%)	0 (0%)	1260 (8.0%)
2	0 (0%)	75 (0.5%)	1,591 (10.1%)	77 (0.5%)	0 (0%)	1743 (11.1%)
3	44 (0.3%)	0 (0%)	23 (0.1%)	2342 (14.8%)	2 (0.1%)	2411 (15.3%)
4–5	0 (0%)	0 (0%)	0 (0%)	48 (0.3%)	256 (1.6%)	304 (1.9%)
Total	9865 (62.5%)	1052 (6.7%)	1897 (12.0%)	2701 (17.1%)	258 (1.7%)	15,773 (100.0%)

Table 3
Clinical characteristics of patients with eGFR <60 mL/min/1.73 m^2 according to the MDRD Study (Group 1) or CKD-EPI (Group 2) equation only, to both equations (Group 3), and to neither one (Group 4).

	G1	G2	G3	G4	P[a] G1 vs.	P[a] G2 vs.
n	311	67	2648	12,747	NA	NA
Male sex (%)	17.7	94.0	48.9	59.2	G3 <0.001	G3 <0.001
					G4 <0.001	G4 <0.001
Age (years)	67 [62–71]	81 [78–85]	74 [68–79]	65 [58–72]	G3 <0.001	G3 <0.001
					G4 0.009	G4 <0.001
Diab. duration (years)	11 [5–20]	21 [9–30]	16 [8–26]	10 [4–19]	G3 <0.001	G3 0.06
					G4 0.04	G4 <0.001
Insulin ± OHA (%)	29.9	43.5	38.5	22.2	G3 0.002	G3 0.49
					G4 0.001	G4 0.02
HbA_{1c} (%)	7.4 [6.6–8.7]	7.5 [6.5–8.2]	7.5 [6.7–8.5]	7.3 [6.5–8.2]	G3 0.86	G3 0.36
					G4 0.03	G4 0.73
Alb (%)	24.8	34.3	45.7	23.0	G3 <0.001	G3 0.07
					G4 0.46	G4 0.03
HT (%)	80.4	71.6	88.4	66.8	G3 <0.001	G3 <0.001
					G4 <0.001	G4 0.40
DL (%)	51.1	35.8	54.9	44.3	G3 0.21	G3 0.002
					G4 0.02	G4 0.16
CVD (%)	23.2	41.8	39.0	19.8	G3 <0.001	G3 0.64
					G4 0.14	G4 <0.001
DR (%)	24.4	20.9	32.3	20.0	G3 0.02	G3 0.14
					G4 0.13	G4 0.79
eGFR MDRD (mL/min/1.73 m^2)	58.7 [57.9–59.3]	61.2 [60.6–61.7]	48.8 [39.9–54.0]	83.6 [73.1–97.1]	NA	NA
eGFR CKD-EPI (mL/min/1.73 m^2)	62.2 [60.9–63.5]	58.9 [58.1–59.6]	48.5 [38.8–54.6]	88.7 [77.5–97.7]	NA	NA
Serum creat. (mg/dL)	1.0 [0.97–1.04]	1.20 [1.15–1.21]	1.32 [1.14–1.57]	0.85 [0.72–0.97]	G3 <0.001	G3 <0.001
					G4 <0.001	G4 <0.001
UKPDS 10-year risk[b]	0.17 [0.11–0.27]	0.58 [0.45–0.72]	0.31 [0.19–0.49]	0.19 [0.11–0.31]	G3 <0.001	G3 <0.001
					G4 0.005	G4 <0.001

OHA, oral hypoglycemic agents; Alb, albuminuria; HT, hypertension; DL, dyslipidemia; DR, diabetic retinopathy.
[a] Mann–Whitney *U*-test or χ^2 test.
[b] Estimated in patients without a previous CVD event.

albuminuria or reference to age, might lead to inappropriate diagnosis of CKD, due to inaccuracy of GFR estimates, which do not account properly for the effect of aging [18].

In the RIACE cohort, a higher proportion of subjects with T2DM were reclassified upward with the CKD-EPI than with the MDRD Study equation, thus confirming that the former provides higher GFR estimates than the latter for values around or above 60 mL/min/1.73 m^2, as previously shown for the general population [6,8]. However, due to the lack of direct GFR measures, our study was not designed to verify whether the CKD-EPI equation performs better than the MDRD Study formula in estimating GFR in T2DM subjects and that the systematic bias introduced by the use of demographics in these equations when applied to such an old population is lower with the newer formula. A recent small survey using GFR measurements by the ^{51}Cr-EDTA single-injection method showed that both equations performed less well in patients with T2DM than in normal individuals and that bias was similar with the two formulas, though only subjects with normal renal function were examined and bias was significantly higher for the highest GFR values [19]. Thus, further investigation is required to assess accuracy and precision of the CKD-EPI equation in T2DM individuals over the full GFR range.

Table 4
Clinical characteristics of patients with CKD according to presence or absence of albuminuria and GFR estimation by the MDRD Study (Group 1) or CKD-EPI (Group 2) equation only, to both equations (Group 3), and to neither one (Group 4).

	G1	G2	G3	G4	P[a] G1 vs.	P[a] G2 vs.
n	234	44	5,677	9,818	NA	NA
Male sex (%)	11.1	97.7	60.0	55.8	G3 <0.001	G3 <0.001
					G4 <0.001	G4 <0.001
Age (years)	67 [63–71]	81 [77–84]	70 [63–76]	65 [58–71]	G3 <0.001	G3 <0.001
					G4 <0.001	G4 <0.001
Diab. duration (years)	11 [5–20]	21 [8.3–29.5]	14 [6–23]	9 [4–18]	G3 0.001	G3 0.04
					G4 0.04	G4 <0.001
Insulin ± OHA (%)	24.4	25.0	34.0	20.1	G3 0.002	G3 0.21
					G4 0.11	G4 0.41
HbA_{1c} (%)	7.3 [6.4–8.5]	7.3 [6.4–8.1]	7.5 [6.7–8.6]	7.2 [6.5–8.1]	G3 0.008	G3 0.08
					G4 0.28	G4 0.9
HT (%)	88.9	84.1	91.5	79.0	G3 0.16	G3 0.08
					G4 <0.001	G4 0.41
DL (%)	72.2	50.0	65.0	59.2	G3 0.02	G3 0.04
					G4 <0.001	G4 0.22
CVD (%)	20.5	36.4	32.6	17.7	G3 <0.001	G3 0.60
					G4 0.27	G4 0.001
DR (%)	20.5	13.6	31.1	17.1	G3 0.002	G3 0.04
					G4 0.24	G4 0.71
eGFR MDRD (mL/min/1.73 m^2)	58.6 [57.9–59.3]	61.3 [60.6–61.8]	62.2 [49.7–83.5]	83.9 [73.4–97.0]	NA	NA
eGFR CKD-EPI (mL/min/1.73 m^2)	62.2 [60.9–63.6]	58.9 [58.2–59.7]	63.1 [49.4–88.0]	89.1 [78.1–97.9]	NA	NA
Serum creat. (mg/dL)	1.0 [0.97–1.02]	1.20 [1.16–1.22]	1.06 [0.87–1.30]	0.84 [0.71–0.95]	G3 0.002	G3 0.002
					G4 <0.001	G4 <0.001
UKPDS 10-year risk[b]	0.16 [0.11-0.25]	0.56 [0.42-0.72]	0.27 [0.17-0.44]	0.18 [0.10-0.29]	G3 <0.001	G3 <0.001
					G4 0.29	G4 <0.001

OHA, oral hypoglycemic agents; HT, hypertension; DL, dyslipidemia; DR, diabetic retinopathy.
[a] Mann–Whitney *U*-test or χ^2 test.
[b] Estimated in patients without a previous CVD event.

T2DM subjects reclassified both upward and downward with the CKD-EPI equation showed CVD prevalence rates and CHD risk scores which were higher and lower, respectively, than those of CKD individuals who were not reclassified. These data indicate that the CKD-EPI equation provides a better definition of global CVD burden associated with CKD in these individuals, as compared with the MDRD Study formula, though it remains unresolved whether this is attributable to a higher accuracy of the newer equation. Interestingly, most of the clinical characteristics of the individuals reclassified upward with the CKD-EPI equation (i.e. those having impaired GFR or CKD with the MDRD Study formula only) were similar to those of subjects without impaired GFR or CKD with both formulas, despite lower GFR values. Conversely, subjects reclassified downward with the CKD-EPI formula (i.e. those having impaired GFR or CKD with the CKD-EPI equation only) had higher CVD prevalence rates and CHD risk scores than those of patients with impaired eGFR or CKD with both equations, despite clinical features were not worse (or were even better) and renal function was better preserved. The different CVD risk carried by individuals reclassified in both directions appeared to be predominantly driven by differences in sex and age, since subjects reclassified upward were mainly females and had a younger age, as previously shown in the general population [8,9], whereas those reclassified downward were almost exclusively males and had a much older age. In addition, differences in terms of severity of diabetes burden, as identified by disease duration and partly by insulin usage (but not by HbA_{1c} levels at the time of the visit), might have contributed to the decreased and increased CVD risk, respectively. This is also in keeping with a previous report showing that clinical variables between reclassified subjects and those with or without CKD with both formulas disappeared after adjustment for age and sex, except for burden of diabetes and fasting plasma glucose and HbA_{1c} levels [8]. Presence or absence of albuminuria in reclassified subjects did not impact significantly on these differences, though prospective surveys have clearly shown the role of albuminuria in predicting renal and CVD outcomes in the general population [20] and diabetic individuals [21].

In addition, this study indicates for the first time that, for eGFR values around or below 30 mL/min/1.73 m^2, application of the CKD-EPI equation results in lower GFR estimates than the MDRD Study equation, with reclassification downward from class 3 to class 4 eGFR of 48 vs. 2 individuals. Previous studies in the general population showed a better performance of the CKD-EPI than the MDRD Study equation when estimates were compared with measured GFR using urinary or plasma clearance of exogenous filtration markers. However, this was the case for higher GFR values, whereas bias was similar with the two formulas for levels <30 mL/min/1.73 m^2 [6]. Thus, it would be particularly important to compare performance of the two formulas versus direct GFR measurements in patients with T2DM within this low eGFR range, in order to verify whether lower GFR estimates provided by the CKD-EPI equation predict GFR more reliably in these individuals. Correct reclassification of these subjects would improve the ability of clinicians to adjust drug dosages and identify individuals who may be at increased risk of side effects of medications or diagnostic procedures. Our data indicate that, also in these patients, reclassification with the CKD-EPI equation predicts more reliably the CVD burden associated with CKD, with increased risk driven predominantly by sex and age.

Main limitations of this study include the cross-sectional design and the lack of centralized measurements. Though the analysis of the follow-up data of this survey will provide more reliable information about the performance of the two equations in predicting the long-term renal and CVD outcomes, cross-sectional data from the RIACE cohort clearly indicate that the CKD-EPI equation provides a better definition of CVD burden associated with CKD than the MDRD Study formula in patients with T2DM. Variations due to the different assay methods may have also influenced the results, though findings were similar with IDMS- and non-IDMS-traceable methods for measuring serum creatinine as well as with the two techniques for assessing albuminuria. Moreover, though albuminuria was assessed using a single specimen in 74.2% of subjects, concordance rate between the first value and the geometric mean of multiple measurements was >90% [22].

In conclusion, these data show that estimating GFR in patients with T2DM using the CKD-EPI equation, as compared with the MDRD Study formula, in addition to resulting in reduced CKD prevalence, provides a better definition of global CVD burden, in terms of CVD prevalence and CHD risk score, which applies not only to subjects reclassified upward, but also to those reclassified downward with the newer equation, and appears to be driven mainly or exclusively by sex, age, and diabetes duration. Whether this is due to a more accurate GFR estimation with the CKD-EPI equation remains to be elucidated by comparison with direct GFR measurements.

Conflict of interest

The authors declare no potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.atherosclerosis.2011.04.035.

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