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REVIEW

Chronic kidney disease in type 2 diabetes: Lessons from the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study

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Abstract The Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study is an ongoing observational survey that examines the role of estimated glomerular filtration rate (eGFR) as an independent predictor of cardiovascular and renal outcomes in 15,773 Italian subjects with type 2 diabetes. The analysis of data collected at the enrollment visit provided a picture of chronic kidney disease (CKD) and its association with other complications, risk factors for cardiovascular disease (CVD) and treatments in a large contemporary cohort. Main results of this analysis were that (a) non-albuminuric renal impairment is the predominant clinical phenotype in patients, particularly women, with reduced eGFR; (b) concordance between CKD and diabetic retinopathy is low, with only a minority of patients with renal dysfunction presenting with any or advanced retinal lesions; (c) the non-albuminuric form is associated with a significant prevalence of CVD, especially at the level of the coronary vascular bed; (d) CKD is associated with hemoglobin (Hb) A_{1c} variability more than with average HbA_{1c}, whereas retinopathy and CVD are not; (e) in elderly individuals with moderate-to-severe eGFR reduction, use of agents which are not recommended, such as sulphonylureas and metformin, is still frequent; and (f) though complications are generally more prevalent in men (except non-albuminuric renal impairment) women show a less favorable CVD risk profile and achieve therapeutic targets to a lesser extent than men, despite the fact that treatment intensity is not lower. These data update existing information on the natural history of CKD in patients with type 2 diabetes.

Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; CVD, cardiovascular disease; GFR, glomerular filtration rate; RIACE, Renal Insufficiency And Cardiovascular Events; eGFR, estimated GFR; BP, blood pressure; BMI, body mass index; HbA_{1c}, hemoglobin A_{1c}; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; DR, diabetic retinopathy; NPDR, non-proliferative DR; PDR, proliferative DR; ACE-I, angiotensin-converting inhibitors; ARBs, angiotensin II receptor blockers; UKPDS, UK Prospective Diabetes Study; CAD, coronary artery disease.

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Introduction

Chronic kidney disease (CKD) is a major complication of both type 1 and type 2 diabetes. It occurs in approximately one third of diabetic patients and has become the leading cause of end-stage renal disease (ESRD) worldwide [1]. Since its early stages, CKD is also associated with an increased risk of death, particularly from cardiovascular disease (CVD), and subjects with type 2 diabetes and mild-to-moderate renal impairment are more likely to die of CVD than to progress to ESRD [2], though recent findings seem to favor progression [3].

CKD is defined as abnormalities of kidney structure or function, such as persistent proteinuria or reduced glomerular filtration rate (GFR), present for >3 months. Albuminuria has long been recognized as the hallmark of diabetic nephropathy, preceding GFR decline [4]. Therefore, albuminuria has assumed a central role in the screening, diagnosis and management of CKD in patients with diabetes [5]. However, a growing body of evidence has indicated that GFR loss may occur also in normoalbuminuric subjects [6], in type 1 [7] and especially in type 2 [8–13] diabetes (Table 1). Thus, albuminuria and reduced GFR should be considered as "twin manifestations" of diabetic nephropathy, representing complementary, if overlapping, features of kidney damage in diabetes [14]. Both albuminuria and reduced GFR are powerful and independent predictors of CVD morbidity and mortality and adverse renal outcomes in the general population [15–17] and in diabetic subjects [12,13,18]. Thus, it is of pivotal importance to detail the clinical phenotypes and investigate the prognostic implications of the albuminuric and non-albuminuric forms of CKD in subjects with type 2 diabetes.

The Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study

The RIACE Italian Multicenter Study is an observational, prospective cohort study aimed at assessing the impact of estimated GFR (eGFR) on CVD morbidity and mortality (primary endpoint) and renal outcome (secondary endpoint), independently of albuminuria and other CVD risk factors, in subjects with type 2 diabetes over a 4-year follow-up.

The RIACE cohort consisted of 15,773 Caucasian non-dialytic patients with type 2 diabetes, attending consecutively 19 hospital-based Diabetes Clinics of the National Health Service throughout Italy (see on-line appendix) in years 2007–2008. Patients had a median age of 67 years (interquartile range 59–73), a median diabetes duration of 11 years (5–20), and a male/female ratio of 57/43.

All patients underwent a structured interview to collect information about age, smoking status, known diabetes onset and duration, current glucose-, blood pressure (BP)- and lipid-lowering therapy. Moreover, body mass index (BMI), BP, hemoglobin A_{1c} (HbA_{1c}), triglycerides, and total, HDL and LDL cholesterol were assessed.

The presence of CKD was evaluated by measuring albuminuria and serum creatinine; GFR was estimated from creatinine by the four-variable Modification of Diet in Renal Disease (MDRD) Study formula [19] or the recently developed Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [20]. Patients were then assigned to one of the following categories of albuminuria (mg/24 h): normoalbuminuria (<30), microalbuminuria (30–299), or macroalbuminuria (≥300); and to one of the following categories of eGFR (mL/min/1.73 m^2): 1 (≥90); 2 (60–89); 3 (30–59); 4 (15–29); and 5 (<15). Finally, based on albuminuria and eGFR levels, patients were stratified according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative classification in no CKD and stages 1–5 CKD [21].

The presence of diabetic retinopathy (DR) was assessed by dilated fundoscopy. Patients were classified into absent DR, mild, moderate or severe non-proliferative DR (NPDR), proliferative DR (PDR), or maculopathy, according to the Global Diabetic Retinopathy Project Group [22]. For further analysis, patients with NPDR of mild or moderate degree were classified as having non-advanced DR, whereas those

Table 1 Incidence and prevalence (%) of non-albuminuric renal impairment in diabetic patients.

Studies	Patients (n)	DM (type)	Follow-up (years)	Renal impairment[a]	Non-albuminuric renal impairment	Renal impairment with no albuminuria nor DR
Longitudinal						
Molitch ME et al. (DCCT/EDIC), 2010 [7]	1.439	1	19	6.2	24	
Retnakaran R et al. (UKPDS), 2006 [8]	4.006	2	15	28	51	
Cross-sectional						
Kramer HJ et al. (NHANES III), 2003 [9]	1.197	2	NA	13	36	30
MacIsaac RJ et al., 2004 [10]	301	2	NA	36	39	29
Thomas MC et al. (NEFRON-11), 2009 [11]	3.893	2	NA	23	55	
Ninomiya T et al. (ADVANCE), 2009 [12]	10.640	2	NA	19	62	
Drury PL et al. (FIELD), 2011 [13]	9.795	2	NA	5.3	59	
Penno G et al. (RIACE), 2011 [23]	15.773	2	NA	18.8	55.6	43.2

DM = diabetes mellitus; DR = diabetic retinopathy; DCCT/EDIC = Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications; UKPDS = UK Prospective Diabetes Study; NHANES III= Third National Health and Nutrition Examination Survey; NEFRON-11 = National Evaluation of the Frequency of Renal Impairment cOexisting with NIDDM-11; ADVANCE = Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes; RIACE = Renal Insufficiency And Cardiovascular Events.

[a] eGFR <60 ml/min/1,73 m^2.

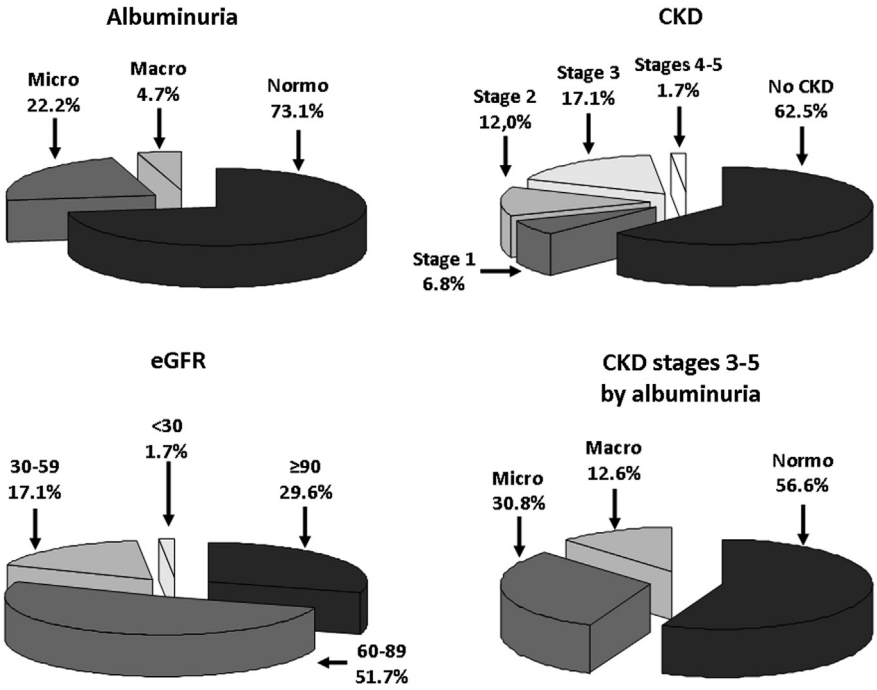

Figure 1 Prevalence of albuminuria and eGFR (ml/min/1.73 m^2) categoried and CKD stages (with stratification of subjects with Stages 3–5 CKD by albuminuria) in the RIACE cohort. Categories of albuminuria (mg/24 h or mg/g creatinine): normoalbuminuria < 30; microalbuminuria 30–299; macroalbuminuria > 300.

with severe NPDR, PDR, maculopathy, or blindness were grouped into the advanced, sight-threatening DR category.

Prevalent CVD was assessed from medical history by recording previous documented major acute CVD events, including myocardial infarction, stroke, foot ulcer or gangrene, amputation, coronary, carotid, and lower limb revascularization.

Here, we report a summary of the analyses of baseline data from the RIACE Study that have provided important information on the prevalence, clinical features and correlates of CKD in a large, contemporary cohort of Italian patients with type 2 diabetes.

Nephropathy

Prevalence of normoalbuminuria was 73.1%, that of microalbuminuria was 22.2%, and that of macroalbuminuria was 4.7%. Prevalence of eGFR categories 1 to 4–5 was 29.6%, 51.7%, 17.1%, and 1.6%, respectively. Based on both albuminuria and eGFR, 62.5% of subjects had no CKD, whereas 37.5% had CKD, 18.7% of stages 1–2 (albuminuria with eGFR ≥60 ml/m/1.73 m^2), and 17.8% of stages 3–5 (eGFR <60 ml/m/1.73 m^2). The majority of patients with reduced eGFR (56.6%) were normoalbuminuric, whereas only 30.8% were microalbuminuric and 12.8% were macroalbuminuric [23] (Fig. 1). Of subjects with reduced eGFR, 68.5% had no DR, 16.0% had non-advanced DR, and 15.5% had advanced DR; moreover, only 18.2% had both albuminuria and DR, whereas 43.2% had neither albuminuria nor DR, i.e. two major criteria for establishing the "diabetic" nature of renal damage and excluding the need for renal biopsy.

These findings are consistent with recent reports suggesting a worldwide increase in the prevalence of the non-albuminuric CKD phenotype among patients with type 2 diabetes [8,11–13], as compared with previous studies [9,10]. This growing prevalence of non-albuminuric renal impairment might be the consequence of changes in treatment, especially the wider use of angiotensin-converting inhibitors (ACE-I) and angiotensin II receptor blockers (ARBs) [9,11,23], due to their anti-proteinuric effect. However, in the RIACE cohort, the use of ACE-Is/ARBs was more frequent in subjects with albuminuric than with non-albuminuric renal impairment, likely due to an "indication effect" [23]. Moreover, this cross-sectional analysis did not allow to distinguish albuminuric patients who reverted to normoalbuminuria upon ACE-I/ARB treatment from persistently normoalbuminuric subjects. The increasing prevalence of the non-abuminuric phenotype may also reflect changes in the underlying pathology, with macroangiopathy prevailing over microangiopathy, also due to changes in treatment, particularly the tighter control of glucose, lipid, and BP levels that is being achieved in diabetic patients on the grounds of results of trials on intensive treatment. This hypothesis is consistent with the finding from the RIACE Study that non-albuminuric renal impairment showed no independent correlation with HbA_{1c} and a weaker association with DR than the albuminuric forms of CKD. It is also in agreement with results from the UK Prospective Diabetes Study (UKPDS) indicating that HbA_{1c} is an independent risk factor for albuminuria, but not for GFR impairment [8], and from the Third National Health and Nutrition Examination Survey showing that 30% of subjects with reduced eGFR have neither albuminuria nor DR [9]. It is also fits with the inverse

relationship between eGFR and intrarenal resistive index or indexes of systemic atherosclerosis in subjects with type 2 diabetes [24], though this association was independent of albuminuria [25,26].

However, in case of non-albuminuric renal impairment, definition of CKD relies solely upon GFR estimation, which may not precisely correct for sex and age. Subjects with the non-albuminuric phenotype are predominantly women, at variance with the albuminuric forms [11,23], and age was similar in CKD subjects with and without albuminuria from the RIACE cohort, though nonalbuminuric renal impairment was less frequent in those with <55 years [23]. These findings suggest that gender, more than age might lead to some misclassification of patients and overestimation of CKD.

To address methodological issues which may influence patients' classification and staging, reproducibility of albuminuria [27] and performance of the new CKD-EPI GFR estimating equation [28] were also explored in the RIACE cohort. Though multiple UAE measurements are recommended by current guidelines (at least three over a 3–6-month period) [5], due to the high pre-analytical, intra-individual biological variability of this parameter, repeated measures are difficult to obtain and avoidance would result in significant cost and time savings. Thus, concordance rate between the first value and the geometric mean of multiple measurements was assessed in 4062 subjects with at least two values (2310 with three values). Results showed that, despite coefficient of variation was high (32.5% [14.3–58.9]), concordance rate was 94.6% for normoalbuminuria, 83.5% for microalbuminuria, 91.1% for macroalbuminuria, and 90.6% for albuminuria (micro + macro) [27]. This suggests that a single UAE value, thought encumbered with high intra-individual variability, is an accurate predictor of nephropathy stage for clinical and epidemiological purposes. Reclassification of individuals from the RIACE cohort using the CKD-EPI equation instead of the MDRD Study formula resulted in reduced prevalence of impaired eGFR and CKD (17.2% vs. 18.7% and 36.3% vs. 37.5%, respectively). Moreover, the higher number of subjects who were reclassified upward with the CKD-EPI equation (i.e. those with impaired eGFR or CKD with the MDRD Study formula only) showed lower CVD prevalence rates and 10-year UKPDS coronary heart disease risk scores, as compared with those with both equations, whereas opposite figures were observed in the lower number of subjects who were reclassified downward (i.e. those with impaired eGFR or CKD with the CKD-EPI equation only), thus suggesting that the CKD-EPI equation provides a better definition of CVD burden associated with CKD [28].

Association with retinopathy

While the vast majority of patients from the RIACE cohort (78.2%) showed no signs of DR, a high percentage of individuals with any DR had advanced lesions, which were observed in 9.8% of patients [29] (Fig. 2). Such an alarming high prevalence of advanced DR suggests that the expected favorable effect of improved diabetes management has not emerged yet. As expected, advanced DR was independently

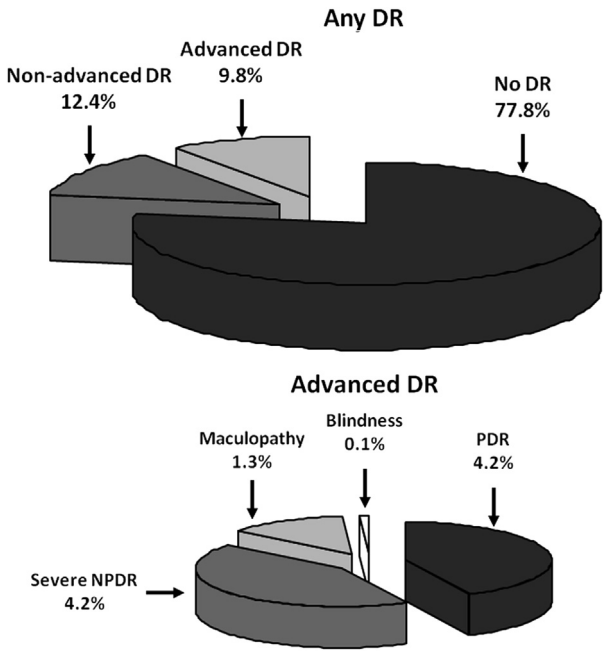

Figure 2 Prevalence of DR grades (with stratification of subjects with advanced DR by type of advanced lesion) in the RIACE cohort.

associated with glycemic exposure (HbA_{1c}, diabetes duration and treatment, particularly with insulin), hypertension, previous CVD, albuminuria and, inversely, with age and eGFR.

Concurrent assessment of DR and CKD showed that the majority of subjects (51.9%) had neither complication. Discordance between DR and CKD was observed in 36.6% of subjects, 10.6% with DR only and 26.0% with CKD only, whereas concordance was found only in 11.5% of individuals [30], a much lower percentage that in type 1 diabetes [31]. In subjects with both complications, stages 1–2, albuminuric stage ≥3 and non-albuminuric stage ≥3 CKD were detected in approximately 50%, 30% and 20% of individuals, respectively, thus confirming that DR is more frequently associated with the albuminuric than the non-albuminuric phenotypes [30]. Moreover, while CKD was detected in 58.6% of subjects with advanced DR, advanced DR was found only in 15.3% of individuals with any CKD (and any DR in approximately 30%), at variance with type 1 diabetes, in which DR occurs almost invariably in individuals with CKD [31]. This difference reflects the higher prevalence of non-albuminuric CKD in type 2 than in type 1 diabetes and the possible macroangiopatic nature of this phenotype. This interpretation was further supported by the finding that factors independently associated with presence of advanced DR in subjects with any CKD largely differed from those correlating with presence of any CKD in individuals with advanced DR [30].

Association with cardiovascular disease

One or more major acute CVD events were adjudicated in 23.2% of patients from the RIACE cohort. Events were more often myocardial infarction and coronary revascularization

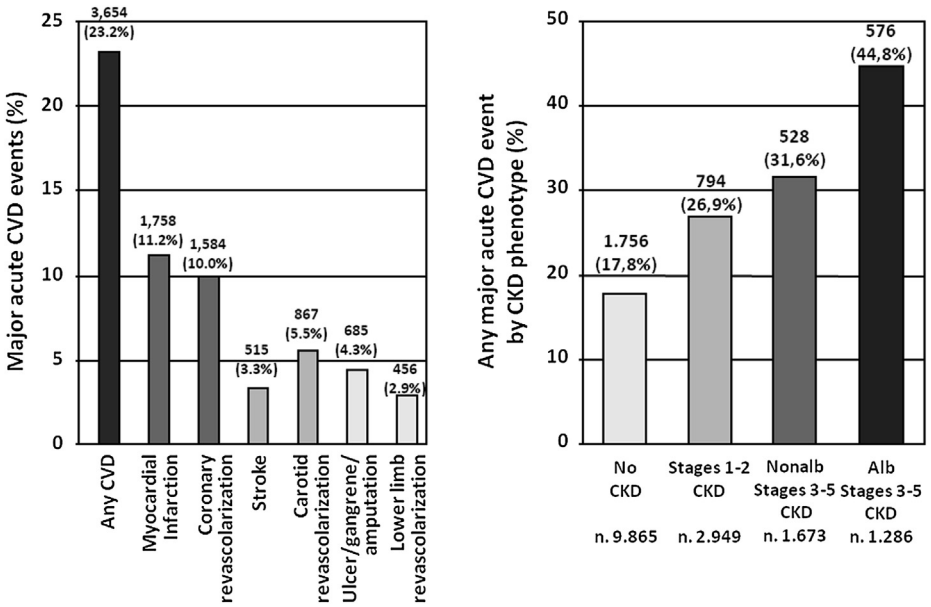

Figure 3 Prevalence of major acute CVD events and stratification of any CVD by CKD phenotype in the RIACE cohort.

(Fig. 3). Traditional CVD risk factors and DR correlated with presence of CVD, the prevalence of which was 26.9% in stages 1–2 CKD, 31.6% in non-albuminuric stage ≥3 and 44.8% in albuminuric stage ≥3 CKD (Fig. 3). Reduced eGFR without albuminuria was independently associated with a significant CVD burden, higher than albuminuria alone, whereas the combination of reduced eGFR and albuminuria marked a further increased risk of CVD events in an additive manner. The independent association of CVD with eGFR and albuminuria became significant for eGFR <60 mL/min/1.73 m^2 and micro or macroalbuminuria. However, when deciles of eGFR and albuminuria were considered, age- and gender-adjusted excess risk for a CVD event was significant for eGFR values <78 ml/min/1.73 m^2 (84 ml/min/1.73 m^2 when the two variables were included simultaneously) and albuminuria values ≥10.5 mg/24 h. This suggest that, in subjects with type 2 diabetes, even a mild reduction in eGFR and a small increase in albuminuria may predict the risk of a major acute CVD event [32].

Interestingly, even after accounting for the use of ACEIs/ARBs, albuminuria alone was not an independent correlate of coronary events, which were associated more strongly with non-albuminuric than with albuminuric renal impairment [32]. This is at variance with previous reports [12,13], showing that albuminuria is a strong predictor of coronary artery disease (CAD). Conversely, the association of coronary events with reduced eGFR is in keeping with the relation of a moderate-to-severe reduction in eGFR with the number of narrowed coronary arteries [33]. Moreover, in a cross-sectional analysis, this powerful association between CAD and impaired eGFR might reflect the unique bidirectional nature of heart–kidney interactions in the context of the cardiorenal syndrome [34]. This might also explain why, at variance with coronary events, cerebrovascular and peripheral events were associated more weakly with non-albuminuric than with albuminuric CKD [32]. Finally, the stronger association of coronary events with reduced eGFR than with albuminuria is consistent with the speculation that renal macrovascular involvement prevails in the non-albuminuric phenotype, which would be more frequently associated with coronary atherosclerosis than the albuminuric forms, likely characterized by microvascular lesions. This view was supported by the lack of association of coronary events with DR [32].

HbA_{1c} variability

At variance with "glucose variability", which relates to within-day fluctuations of glycemia, HbA_{1c} variability relates to changes in glycemia over longer time periods, i.e. with change in HbA_{1c} from one visit to the next [35]. HbA_{1c} variability during the 2-year period preceding recruitment added to average HbA_{1c} as an independent correlate of microalbuminuria, stages 1–2 CKD and any lower limb event, and was an independent predictor of macroalbuminuria, reduced eGFR, stages 3–5 albuminuric CKD and ulceration/gangrene, whereas average HbA_{1c} was not. The opposite was found for DR, any CVD, any coronary or cerebrovascular event, and myocardial infarction, whereas neither average HbA_{1c} nor HbA_{1c} variability affected non-albuminuric CKD and stroke [36,37]. However, HbA_{1c} variability in the RIACE cohort was much lower than in previous reports from subjects with type 1 [38,39] and type 2 [40,41] diabetes. This suggests that CKD is very sensitive to even small changes in HbA_{1c} variability. Conversely, the effect of changes of such magnitude on DR and CVD might be masked by that of average HbA_{1c} and possibly of other variables related to glycemic exposure, such as diabetes duration and

treatments, and wider fluctuations of HbA_{1c} over time might be required to influence these complications.

Anti-hyperglycemic treatments

In the real-life conditions of the RIACE Study, use of agents that are not recommended in elderly diabetic subjects with moderate-to-severe renal impairment was still frequent [42]. In addition, prescription of these agents, especially sulphonylureas, increased with age. However, metformin was independently associated with a lower prevalence of cardiovascular disease at any age quartile and eGFR category than all other treatments, consistent with recent findings from a Swedish registry [43].

Gender differences

Prevalence of major acute CVD events in the RIACE cohort was higher in males than in females, coronary and peripheral more than cerebrovascular [44]. While prevalence of DR did not differ significantly between sexes, rates of albuminuria and reduced eGFR were higher in males and females, respectively; as a result, the albuminuric CKD phenotypes were more frequent in males, whereas the non-albuminuric form was more frequent in females [44]. Though CVD was more prevalent in men, women showed a less favorable CVD risk profile and a worse performance in achieving treatment targets for HbA_{1c}, LDL, HDL and non-HDL cholesterol, systolic BP, and particularly BMI and waist circumference [44], as reported in other cohorts [45,46]. However, at variance with these previous studies [45,46], females were more frequently on pharmacological treatments for hyperglycaemia, dyslipidaemia and particularly hypertension than males, and female gender remained an independent predictor for unmet therapeutic targets after adjustment for confounders [44]. Thus, in women with type 2 diabetes from the RIACE cohort, a more adverse CVD risk profile and a higher chance to fail treatment targets was not associated with disparities in treatments, as compared with men. This suggests that factors other than gender differences in treatment intensity are responsible for this general phenomenon.

Conclusions

The RIACE Study is an ongoing observational survey investigating the role of eGFR as an independent predictor of CVD and renal outcomes in Italian subjects with type 2 diabetes. The analysis of data collected at the enrollment visit has provided an updated picture of CKD and its association with other complications, CVD risk factors and treatments in this large contemporary cohort.

Results showed that non-albuminric renal impairment is the predominant clinical phenotype in patients with reduced eGFR and is not or weakly related to glycemic control and DR. As a consequence, overall concordance between CKD and DR is low, with only a minority of patients with renal dysfunction presenting with any or advanced DR. Moreover, the non-albuminuric form, which shows a CVD prevalence that is intermediate between albuminuria alone and albuminuria plus reduced eGFR, is associated more strongly with coronary events than the albuminuric forms, whereas the opposite occurs with cerebrovascular and peripheral events. CKD is also more sensitive to HbA_{1c} variability than DR and CVD. Despite eGFR decline with increasing age, use of agents such as sulphonylureas and metformin is quite frequent and, especially in case of sulphonylureas, increases with age, though metfomin treatment is associated with lower CVD prevalence even in elderly individuals with moderate-to-severe eGFR reduction. Finally, women show a less favorable CVD risk profile and a worse performance in achieving treatment targets, despite the fact that, in the RIACE cohort, this was not associated with lower treatment intensity as compared with men.

These data, which update existing information on the natural history of CKD in patients with type 2 diabetes, suggest that the course of this complication is changing, likely due to changes in treatment. In particular, the growing prevalence of non-albuminuric renal impairment prompts the need for future studies investigating the pathogenetic mechanisms, prognostic implications and therapeutic measures of this phenotype as compared with the classical albuminuric forms. The follow-up of the RIACE Study will hopefully contribute to fill this gap of knowledge by comparing the CVD and renal outcomes of non-albuminuric and albuminuric renal impairment.

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Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.numecd.2014.02.013.

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