CLINICAL INVESTIGATIONS

Age, Renal Dysfunction, Cardiovascular Disease, and Antihyperglycemic Treatment in Type 2 Diabetes Mellitus: Findings from the Renal Insufficiency and Cardiovascular Events Italian Multicenter Study

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OBJECTIVES: To assess the distribution of antihyperglycemic treatments according to age and renal function and its relationship with cardiovascular disease in type 2 diabetes mellitus (T2DM).

DESIGN: Cross-sectional analysis.

SETTING: Nineteen hospital-based diabetes mellitus clinics in 2007 and 2008.

PARTICIPANTS: Fifteen thousand seven hundred thirty-three individuals with T2DM from the Renal Insufficiency and Cardiovascular Events (RIACE) Italian Multicenter Study.

MEASUREMENTS: Current antihyperglycemic treatments were recorded. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Albuminuria was measured using immunonephelometry or immunoturbidimetry. Prevalence of major acute cardiovascular events was calculated according to age quartiles, treatments, and categories of eGFR (1 = ≥90; 2 = 60–89; 3 = 30–59; and 4 = <30 mL/min per 1.73 m^2).

RESULTS: Across age quartiles, eGFR declined progressively at a time-linear rate, with an acceleration in older adults, whereas albuminuria increased; age and eGFR were associated with cardiovascular events independently of other confounders. With increasing age, percentage of participants using lifestyle treatments for their T2DM and taking metformin or glitazones fell; percentage taking sulphonylureas and repaglinide rose, and percentage taking insulin remained stable. In eGFR categories 3 and 4, use of metformin was 41.4% and 14.5%, respectively, and that of sulphonylureas was 34.2% and 18.1%, respectively. Inappropriate prescription of these agents, especially sulphonylureas, increased with age. Metformin was independently associated with lower prevalence of cardiovascular disease for any age quartile and eGFR category than all other treatments.

CONCLUSION: In real-life conditions, use of agents that are not recommended in elderly adults with diabetes mellitus with moderate to severe renal impairment is frequent, but metformin is associated with lower cardiovascular event rates even in these individuals. **J Am Geriatr Soc 61:1253–1261, 2013.**

Key words: age; glomerular filtration rate; albuminuria; cardiovascular disease; oral hypoglycemic agents

Diabetes mellitus is the leading cause of renal dysfunction, accounting for up to 50% of new cases of end-stage renal disease (ESRD) in developed countries.[1] The number of people with ESRD with type 2 diabetes mellitus (T2DM) is rapidly increasing because of the rising

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DOI: 10.1111/jgs.12381

0002-8614/13/$15.00

incidence of the disease and longer survival as a result of improved treatment.[2]

Among factors influencing the rate of decline of renal function in individuals with T2DM, hyperglycemia seems to play an important role, based on the evidence that intensive glucose control is effective in preventing or delaying renal impairment in individuals with type 1 diabetes mellitus[3] and T2DM.[4] Most clinical trials of strict glycemic control excluded individuals with chronic kidney disease (CKD), consistent with the product labels of the drugs tested, but a recent study showed that, in individuals with diabetes mellitus with an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1.73 m^2, the relative risk of developing ESRD was higher with a glycosylated hemoglobin (HbA_1c) level of greater than 9% than with a level of less than 7%.[5] Moreover, although in participants with T2DM in the UK Prospective Diabetes Study the benefits on renal outcomes were independent of the antihyperglycemic agent(s) used,[4] a recent large retrospective study showed that the risk of eGFR decline, ESRD, or death was higher with sulphonylureas than with metformin or rosiglitazone.[6]

Renal impairment limits the use of certain oral hypoglycemic agents (OHAs) because it increases the risk of serious drug adverse effects. Because metformin is excreted unchanged through urine, it accumulates as renal function worsens, favoring the occurrence of lactic acidosis.[7] In addition, the active metabolites of the sulphonylureas glimepiride and glyburide may reach high plasma concentrations in case of renal dysfunction, potentially enhancing the risk of severe hypoglycemia,[7] itself favored by low glycogen stores and impaired renal gluconeogenesis.[8] Finally, glitazones, which the liver metabolizes, may exacerbate fluid retention and the risk of fractures associated with renal insufficiency.[7] Therefore, these OHAs are contraindicated—or should be used with caution—in individuals with poor renal function,[7] although the specific eGFR thresholds are still debated. Use of repaglinide is allowed, because of its predominant liver metabolism,[9] and insulin can be used safely in individuals with CKD with dose adjustment.[7]

The choice of the antihyperglycemic agent(s) is particularly challenging in older adults because eGFR decreases with normal aging,[10] and CKD occurs more frequently in elderly individuals, especially if they have diabetes mellitus or hypertension.[11] Moreover, other age-related comorbidities, particularly if they require hospitalization, may favor the occurrence of drug adverse effects through several mechanisms, including further loss of renal function due to dehydration, infection, or administration of nephrotoxic drugs or contrast media.[12]

Cardiovascular disease (CVD) is the main cause of morbidity and mortality in individuals with T2DM, with impaired kidney function[13] and increasing age[14] conferring additional CVD risk. Previous studies and meta-analyses have suggested that use of sulphonylureas, particularly glibenclamide, might be associated with greater CVD burden,[15,16] but other studies failed to demonstrate this relationship,[17,18] whereas metformin was shown to be protective.[19,20] Moreover, use of glitazones is associated with greater risk of congestive heart failure (CHF),[21] and rosiglitazone was suspended because of excess all-cause and CVD mortality.[22] Whether insulin is proatherogenic is still debated, and no conclusive evidence is available.[23]

Despite the increasing emphasis on personalized medicine, most evidence-based data come from trials excluding individuals with certain comorbidities, especially CKD, and few large studies have assessed the distribution of antihyperglycemic treatments in real-life conditions in relation to age, degree of renal function, and prevalent CVD. Therefore, this study was aimed at addressing this in the large cohort of individuals with T2DM from the Renal Insufficiency and Cardiovascular Events (RIACE) Italian Multicenter Study.

METHODS

Study Population

Baseline data from the RIACE Italian Multicenter Study (registered with ClinicalTrials.gov, NCT00715481; http://clinicaltrials.gov/ct2/show/NCT00715481), an observational, prospective cohort study on the effect of eGFR on CVD morbidity and mortality in T2DM were used. The study population consisted of 15,933 individuals with T2DM (defined according to American Diabetes Association criteria) consecutively attending 19 hospital-based diabetes clinics of the National Health Service throughout Italy in 2007 and 2008. Exclusion criteria were dialysis or renal transplantation. After exclusion of 160 individuals with missing or implausible data, 15,773 individuals were included in the cross-sectional analysis. The locally appointed ethics committees approved the study protocol.

Clinical Determinations

All individuals participated in a structured interview, and the following parameters were recorded: age; smoking status (never, former, current); known duration of T2DM; and current antihyperglycemic, antihypertensive, and lipid-lowering treatment and antiplatelet and anticoagulant therapy, with indication of the class of drug. Participants were also asked to report previous major acute CVD events; including myocardial infarction; stroke; foot ulcer or gangrene; amputation; coronary, carotid, and lower limb revascularization; surgery for aortic aneurysm; and comorbidities. An ad hoc committee in each center adjudicated CVD events based on hospital discharge records.[24]

Body mass index (BMI) was calculated from weight and height measured using a scale and a stadiometer. Blood pressure (BP) was measured using a mercury sphygmomanometer on the right arm after at least 5 minutes of rest, and pulse pressure was calculated. An expert ophthalmologist assessed the presence of diabetic retinopathy (DR) using funduscopy in mydriasis and classified it as absent, nonadvanced (including mild and moderate nonproliferative DR), or advanced (maculopathy, preproliferative and proliferative DR or history of previous photocoagulation, and blindness, if less than 1/10 normal vision or 20/200 on the Snellen test).

Analytical Determinations

HbA_1c was measured using high-performance liquid chromatography using Diabetes Control and Complications Trial–aligned methods; triglyceride, total cholesterol, and high-density lipoprotein cholesterol (HDL-C) levels were determined using standard analytical methods; and low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula.

Renal function was assessed as previously detailed.[25,26] Serum creatinine was measured using the modified Jaffe method. One to three measurements were obtained for each participant, and eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation,[27] using mean serum creatinine in case of multiple measures. Participants were then assigned to one of the following categories of eGFR: $\geq$ 90 mL/min per 1.73 m^2 or less (category 1), 60 to 89 mL/min per 1.73 m^2 (category 2), 30 to 59 mL/min per 1.73 m^2 (category 3), and less than 30 mL/min per 1.73 m^2 (category 4). Albumin excretion rate (AER) was obtained from timed (24-hour) urine collections or calculated from albumin: creatinine ratio (A/C) in early-morning, first-void urine samples in the absence of symptoms and signs of urinary tract infection or other interfering clinical conditions. Albuminuria was measured in one to three fresh urine samples for each participant using immunonephelometry or immunoturbidimetry; in the case of multiple measurements, the geometric mean was used for analysis. Participants were classified into three categories of albuminuria (mg/24 h): normoalbuminuria (AER < 30), microalbuminuria (AER 30–299), or macroalbuminuria (AER $\geq$ 300).

Statistical Analysis

Participants were divided into age quartiles and eGFR categories. Distribution of classes of drugs in the whole cohort and in each age quartile and eGFR category were then calculated. Participants were also classified into five groups according to antihyperglycemic regimen: no pharmacological treatment; metformin alone; metformin in combination with insulin; any other OHA (including combinations with metformin); and insulin, alone or in combination with any other OHA. Data are reported as medians with interquartile ranges for continuous variables and number of cases and percentages for categorical variables. Group values were compared using one-way analysis of variance or, in case of variables with a skewed distribution, using the Kruskal-Wallis test. Pearson chi-square or, when indicated, Fisher exact tests were applied to categorical variables.

A multiple logistic model was used to assess the association between age, T2DM duration, and measures of renal function (eGFR and albuminuria) and prevalent CVD, independent of each other and of other CVD risk factors, complications, and treatments. CVD prevalence according to age quartile and eGFR category was then calculated in participants treated with metformin only versus any other pharmacological treatment (including combination therapies with metformin) and in individuals treated with metformin, alone or in combination, versus those who were not. Logistic regression analysis was applied to calculate the odds ratio (OR) and its 95% confidence interval (CI) for CVD according to treatment in any age quartile and eGFR category. Categories 3 and 4 were grouped because of the small number of participants taking metformin in category 4. Multiple logistic models were also used to estimate the independent association between metformin treatment and CVD. Covariates were age and age at T2DM diagnosis, male sex, smoking, T2DM duration, HbA_1c, antihyperglycemic treatment, triglycerides, HDL-C, BMI, eGFR, albuminuria, and retinopathy. Hypertension (high systolic or diastolic BP or specific treatment) and dyslipidemia (high LDL-C or statin treatment) were also included in the model.

A two-tailed $P < .05$ was considered significant. All statistical analyses were performed using SPSS 13.0 software (SPSS, Inc., Chicago, IL).

RESULTS

The median age of the cohort was 67 (range 59–73), the median T2DM duration was 11 years (range 5–20 years), and the male:female ratio was 57:43 9,225 (58.5%) were aged 65 and older. Clinical characteristics according to age quartiles are shown in Table 1. Older participants had longer T2DM duration; lower BMI, waist girth, and triglyceride levels; and higher HDL-C than younger participants. Systolic BP levels and pulse pressure tended to increase with age; the percentage of smokers decreased; and rates of treatments to lower glucose, BP, and lipids and antiplatelet and anticoagulant treatments increased. As expected, serum creatinine increased and eGFR declined progressively as a function of age (Table 1), equally in men and women, at an approximately linear rate of 1.1 mL/min per 1.73 m^2 until approximately age 65, after which it dropped more than linearly (Figure 1). As a consequence, prevalence of eGFR categories varied significantly across age quartiles, from predominance of category 1 (eGFR $\geq$ 90 mL/min per 1.73 m^2) in younger participants to more than one-third of the oldest individuals belonging to categories 3 and 4 (eGFR < 60 mL/min per 1.73 m^2; Figure S1). Prevalence of micro- and macroalbuminuria also increased significantly with age (Table 1). Similar findings were observed when participants were stratified according to eGFR category: age, T2DM duration, triglyceride levels, and prevalence rates of micro- and macro-albuminuria, retinopathy, and treatments increased, whereas HDL-C levels and eGFR decreased (Table S1).

When the cohort was grouped according to antihyperglycemic treatment, T2DM duration was longer, and HbA_1c, albuminuria, and eGFR worsened moving from lifestyle treatment only to insulin treatment through OHAs (Table S2). In the whole cohort, the majority of participants were taking metformin, followed by sulphonylureas, insulin, and lifestyle treatments. When participants taking each class of drugs were stratified according to age quartile, a significant trend toward greater use of sulphonylureas was observed, together with fewer participants using lifestyle treatment and taking metformin and glitazones and slightly more taking repaglinide, the sole meglitinide derivative available in Italy. No significant change with age was detected in use of insulin and the

Table 1. Clinical Characteristics of the Renal Insufficiency and Cardiovascular Events Italian Multicenter Study Participant According to Age Quartile

Characteristic	Age Quartile				
n (%)	1 (≤59), n = 3,995 (25.3%)	2 (60–66), n = 3,767 (23.9%)	3 (67–73), n = 4,151 (26.3%)	4 (≥74), n = 3,860 (24.5%)	*P*-Value
Male, n (%)	2,506 (63)	2,225 (59)	2,324 (56)	1,905 (50)	<.001
Age, median (IQR)	54 (49–57)	63 (61–65)	70 (68–72)	78 (75–81)	<.001
Smoking, n (%)					
No	2,044 (51)	2,047 (54)	2,458 (59)	2,379 (62)	<.001
Former	997 (25)	1,088 (29)	1,209 (29)	1,140 (29)	
Current	954 (24)	632 (17)	484 (12)	341 (9)	
Age at diabetes mellitus diagnosis, median (IQR)	45 (39–51)	53 (46–59)	57 (49–63)	61 (51–59)	<.001
Diabetes mellitus duration, years, median (IQR)	6 (3–11)	10 (5–17)	12 (6–21)	18 (8–27)	<.001
Glycosylated hemoglobin,%, median (IQR)	7.30 (6.44–8.40)	7.26 (6.51–8.18)	7.28 (6.55–8.18)	7.38 (6.61–8.29)	<.003
Body mass index, kg/m^2, median (IQR)					
All	29.0 (25.9–32.9)	28.6 (25.7–32.0)	28.3 (25.7–31.6)	27.3 (24.6–30.4)	<.001
Men	28.1 (25.5–30.9)	28.1 (25.5–30.9)	27.9 (25.5–30.6)	26.7 (24.5–29.6)	<.001
Women	30.2 (26.4–34.9)	29.6 (26.0–33.8)	29.2 (26.0–32.9)	27.9 (24.8–31.2)	<.001
Waist circumference, cm, median (IQR)					
All	103 (96–111)	102 (96–109)	101 (96–108)	99 (94–105)	<.001
Men	102 (96–110)	102 (96–108)	101 (96–107)	99 (94–105)	<.001
Women	104 (96–113)	103 (95–110)	102 (96–109)	99 (93–105)	<.001
Triglycerides, mg/dL, median (IQR)	128 (90–184)	120 (86–169)	116 (85–162)	113 (83–156)	<.001
HDL-C, mg/dL, median (IQR)					
All	46 (38–55)	48 (40–57)	49 (41–58)	50 (42–59)	<.001
Men	43 (37–52)	45 (38–54)	46 (39–55)	47 (39–55)	<.001
Women	50 (42–60)	52 (44–61)	52 (44–62)	53 (44–63)	<.001
Low-density lipoprotein cholesterol, mg/dL, median (IQR)	108 (87–130)	106 (85–128)	104 (84–125)	106 (86–127)	<.001
Non-HDL-C, mg/dL, median (IQR)	136 (113–161)	133 (108–156)	129 (108–154)	130 (109–155)	<.001
Systolic BP, mmHg, median (IQR)	130 (120–140)	140 (128–150)	140 (130–150)	140 (130–150)	<.001
Diastolic BP, mmHg, median (IQR)	80 (72–85)	80 (70–85)	80 (70–83)	80 (70–80)	<.001
Pulse pressure, mmHg, median (IQR)	50 (45–60)	60 (50–70)	60 (50–70)	60 (50–70)	<.001
Albuminuria, mg/24 h, median (IQR)	11.7 (6.0–25.9)	12.89 (6.1–30.2)	13.6 (6.8–33.6)	16.8 (8.0–45.0)	.005
Albuminuria, n (%)					<.001
Normoalbuminuria	3,099 (77.6)	2,821 (74.9)	3,045 (73.4)	2,573 (66.7)	
Microalbuminuria	735 (18.4)	772 (20.5)	936 (22.5)	1,054 (27.3)	
Macroalbuminuria	161 (4.0)	174 (4.6)	170 (4.1)	233 (6.0)	
Serum creatinine, mg/dL, median (IQR)	0.84 (0.70–0.99)	0.90 (0.75–1.01)	0.90 (0.79–1.10)	0.97 (0.80–1.18)	<.001
Estimated glomerular filtration rate, mL/min per 1.73 m^2, median (IQR)	98.7 (85.9–106.0)	88.7 (74.8–96.0)	80.8 (64.8–90.3)	68.3 (52.7–82.4)	<.001
Retinopathy, n (%)					<.001
No	3,296 (82.5)	2,899 (77.0)	3,166 (76.3)	2,915 (75.5)	
Nonadvanced	365 (9.1)	458 (12.2)	556 (13.4)	578 (15.0)	
Advanced	334 (8.4)	410 (10.9)	429 (10.3)	367 (9.5)	
Any cardiovascular event, n (%)	566 (14.2)	793 (21.1)	1,053 (25.4)	1243 (32.2)	<.001
Antihyperglycemic treatments, n (%)					
Lifestyle	662 (16.6)	539 (14.3)	515 (12.4)	410 (10.6)	<.001
Metformin only	1,087 (27.2)	926 (24.6)	753 (20.5)	539 (14.0)	<.001
Metformin plus insulin	350 (8.8)	352 (9.3)	362 (8.7)	229 (5.9)	<.001
Oral hypoglycemic agents	1,274 (31.9)	1,381 (36.7)	1,725 (41.6)	1,896 (49.1)	<.001
Insulin	622 (15.6)	569 (15.1)	696 (16.8)	786 (20.4)	<.001
BP-lowering agents, n (%)	2,242 (56.1)	2,635 (69.9)	3,168 (76.3)	3,105 (80.4)	<.001
Renin-angiotensin system blockers, n (%)	1,867 (46.7)	2,197 (58.3)	2,623 (63.2)	2,478 (64.2)	<.001
Lipid-lowering agents, n (%)	1,559 (39.0)	1,850 (49.1)	2,115 (51.0)	1,762 (45.6)	<.001
Statins, n (%)	1,360 (34.0)	1,711 (45.4)	1,974 (47.6)	1,652 (42.8)	<.001
Antiplatelet drugs, n (%)	1,050 (26.3)	1,435 (38.1)	1,851 (44.6)	1,961 (50.8)	<.001
Anticoagulant drugs, n (%)	66 (1.7)	119 (3.2)	204 (4.9)	284 (7.4)	<.001

IQR = interquartile range; HDL-C = high-density lipoprotein cholesterol; BP = blood pressure.

alpha-glucosidase inhibitor acarbose. When participants were further stratified according to eGFR category, the percentage of subjects in categories 3 (eGFR 30–59 mL/min per 1.73 m^2) and 4 (eGFR < 60 mL/min per 1.73 m^2) who were taking sulphonylureas increased with age quartile, whereas that taking insulin decreased. Moreover, the

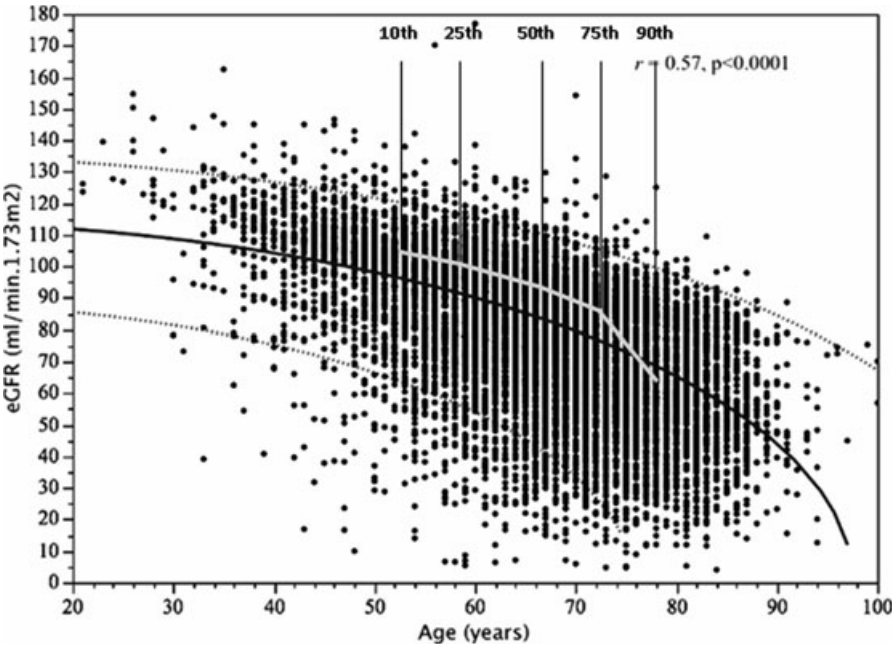

Figure 1. Nonlinear regression analysis of the relationship between age and estimate glomerular filtration rate (eGFR); the fit equation is $eGFR^2 = 13{,}060 - 1.372 \times age^2$, $P < .001$. The gray line connects the median values at the indicated percentiles.

proportion of individuals in these eGFR categories and treated with metformin tended to increase, except than in the fourth age quartile (Table 2).

In the whole cohort, prevalence of CVD was 23.2% and increased progressively with age (Table 1) and eGFR (Table S1). Age (odds ratio (OR) = 1.023, 95% CI = 1.018–1.028) and, inversely, eGFR (OR = 0.989, 95% CI = 0.987–0.991) were significantly associated ($P < .001$) with prevalent CVD, independently of each other and of other CVD correlates, including male sex; T2DM duration; smoking habits; albuminuria; retinopathy; and glucose, BP, and lipid control and related treatments. Prevalence of CVD was lower ($P < .001$) in participants treated with metformin (20.2%) than in those on any other drug (32.4%) and in subjects taking metformin alone (18.6%) than in those undergoing any other pharmacological treatment (26.6%), including individuals taking any OHA (27.1%) or insulin (36.8%) without metformin. CVD prevalence, although increasing with age and eGFR, was almost uniformly lower in participants taking metformin alone or in combination than in participants taking drugs other than metformin in each age quartile and eGFR category (Figure 2). Similar data were obtained when comparing participants treated with metformin only with those taking any other pharmacological treatment (Figure S2). Unadjusted ORs for each age quartile and eGFR category showed a powerful inverse association between metformin and no metformin ($P < .001$ in all cases) and to a lesser extent between metformin alone and any other pharmacological treatment ($P < .01$–$.001$) with previous CVD events (not shown). In the multiple logistic models, the adjusted ORs for CVD remained significant in participants treated with metformin (i.e., the association was independent of known predictors of CVD events, including age, T2DM duration, renal function, other CVD risk factors, complications, and treatments; Table 3).

DISCUSSION

This observational study describes the clinical characteristics of a cohort of outpatients with T2DM and the distribution of antihyperglycemic treatments in these individuals according to age, degree of renal dysfunction, and prevalent CVD, under real-life conditions.

Older age was associated with a progressively lower BMI, waist circumference, and triglyceride levels and slightly but significantly higher HDL-C. These differences are likely to reflect the progressive loss of lean body mass in elderly or frail individuals[28] and a selection bias whereby individuals with larger waist circumference and higher triglyceride levels and lower HDL-C levels die earlier and are therefore removed from a cross-sectional cohort. The lower percentage of smokers with older age might also be a function of better adherence, survivor bias, and temporal trends in the smoking habits of the population, whereas the higher pulse pressure reflects the greater prevalence of hypertension and arterial stiffness in elderly adults.[29] The accelerated decline of eGFR that occurred in men and women after age 65, associated with greater prevalence of micro- and macro-albuminuria and duration of T2DM, probably reflects the superimposition of diabetic kidney disease onto age-related loss of nephron units.[11,30]

An important finding of this study is the distribution of antihyperglycemic treatments according to age and degree of renal dysfunction, in keeping with surveys from other countries reporting that OHAs,[31] especially metformin,[32,33] are frequently prescribed inappropriately in real-life conditions. In eGFR category 4, for example, 24.4% of participants were taking OHAs—sulphonylureas, metformin, or both—and 16.4% were taking repaglinide. As far as eGFR category 3 is concerned, 53.8% of participants were taking metformin, sulphonylureas, or both,

Table 2. Antihyperglycemic Treatments of the Renal Insufficiency and Cardiovascular Events Italian Multicenter Study Participants According to Age Quartile and Estimated Glomerular Filtration Rate (eGFR) Category

Treatment According to eGFR Category	All	Age Quartile				*P*-Value Among Quartiles
		1 (≤59), n = 3,995	2 (60–66), n = 3,767	3 (67–73), n = 4,151	4 (≥74), n = 3,860	
	n (%)					
Total	15,773 (100)	3,995 (25.3)	3,767 (23.9)	4,151 (26.3)	3,860 (24.5)	
Lifestyle	2,126 (13.5)	662 (16.6)	539 (14.3)	515 (12.4)	410 (10.6)	<.001
1	875 (14.8)	456 (16.3)	252 (14.2)	128 (11.7)	39 (14.2)	.003
2	999 (14.0)	181 (17.9)	255 (15.6)	316 (13.7)	247 (11.4)	<.001
3	229 (9.5)	20 (12.2)	29 (9.0)	66 (9.7)	114 (6.2)	.64
4	23 (7.6)	5 (20.8)	3 (7.9)	5 (6.8)	10 (6.0)	.08
Metformin	8703 (55.2)	2,355 (58.9)	2,244 (59.6)	2,330 (56.1)	1,774 (46.0)	<.001
1	3,694 (62.3)	1,733 (61.9)	1,118 (63.1)	682 (62.5)	161 (58.8)	.54
2	3,966 (55.7)	561 (55.6)	969 (59.3)	1,336 (57.9)	1,100 (50.6)	<.001
3	999 (41.4)	59 (36.0)	153 (47.4)	298 (43.9)	489 (39.3)	.01
4	44 (14.5)	2 (8.3)	4 (10.5)	14 (18.9)	24 (14.3)	.49
Sulphonylureas	5,278 (33.5)	1,017 (25.5)	1,160 (30.8)	1,466 (35.3)	1,635 (42.4)	<.001
1	1,838 (31.0)	733 (26.2)	569 (32.1)	419 (38.4)	117 (42.7)	<.001
2	2,560 (35.9)	245 (24.3)	503 (30.8)	840 (36.4)	972 (44.7)	<.001
3	825 (34.2)	37 (22.6)	85 (26.3)	197 (29.0)	506 (40.6)	<.001
4	55 (18.1)	2 (8.3)	3 (7.9)	10 (13.5)	40 (23.8)	.04[a]
Repaglinide	1,534 (9.7)	318 (8.0)	345 (9.2)	427 (10.3)	444 (11.5)	<.001
1	485 (8.2)	214 (7.6)	133 (7.5)	104 (9.5)	34 (7.7)	.01
2	666 (9.4)	83 (8.2)	161 (9.8)	227 (9.8)	195 (9.0)	.39
3	333 (13.8)	20 (12.2)	43 (13.3)	87 (12.8)	183 (14.7)	.61
4	50 (16.5)	1 (4.2)	8 (21.1)	9 (12.2)	32 (19.0)	.17
Acarbose	171 (1.1)	42 (1.1)	33 (0.9)	46 (1.1)	50 (1.3)	.36
1	66 (1.1)	32 (1.1)	17 (1.0)	14 (1.3)	3 (1.1)	.88
2	58 (0.8)	8 (0.8)	13 (0.8)	10 (0.9)	27 (1.2)	.42
3	42 (1.7)	1 (0.6)	1 (0.3)	20 (1.5)	20 (1.6)	.26
4	5 (1.6)	1 (4.2)	2 (5.3)	2 (1.1)	0 (0)	.06
Glitazones	560 (3.6)	198 (5.0)	165 (4.4)	138 (3.3)	59 (1.5)	<.001
1	261 (4.4)	143 (5.1)	71 (4.0)	42 (3.9)	5 (1.8)	.03
2	244 (3.4)	51 (5.1)	81 (5.0)	74 (3.2)	38 (1.8)	<.001
3	53 (2.2)	4 (2.4)	12 (3.7)	22 (3.2)	15 (1.2)	.004[a]
4	2 (0.7)	0 (0)	1 (2.6)	0 (0)	1 (0.6)	.40
Insulin	3,966 (25.1)	972 (24.3)	921 (24.4)	1,058 (25.5)	1,015 (26.3)	.15
1	1,282 (21.6)	625 (22.3)	394 (22.3)	220 (20.2)	43 (15.7)	.04
2	1,641 (23.0)	257 (25.5)	377 (23.1)	525 (22.8)	482 (22.2)	.22
3	864 (35.8)	74 (45.1)	125 (38.7)	267 (39.3)	398 (32.0)	<.001
4	179 (58.9)	16 (66.7)	25 (65.8)	46 (62.2)	92 (54.8)	.41

Percentages of subjects undergoing the various antihyperglycemic treatments for each eGFR category refer to all individuals in that category in the whole cohort or in each age quartile.

[a] Fisher exact test.

with 21.9% receiving both drugs, a combination similar to the rate of participants with an eGFR greater than 60 mL/min per 1.73 m^2 (23.4% and 24.8% in eGFR categories 1 and 2, respectively) and that exposes individuals with even moderate impairment of renal function to a high risk of hypoglycemia.[7] Moreover, drugs frequently used in elderly adults, such as antimicrobial agents, may enhance the hypoglycemic effect of these compounds.[34] This practice persists despite recent evidence that discontinuation of long-acting sulphonylureas in elderly adults with renal insufficiency does not compromise glycemic control[35] and the availability of new OHAs, such as the dipeptidyl peptidase-IV inhibitors, which individuals with CKD can take, with or without dose adjustment.[36] More importantly, the current survey showed that prescription of metformin and particularly sulphonylureas in subjects with an eGFR greater than 60 mL/min per 1.73 m^2 increases with aging, despite the fact that age and age-related comorbidities confer a greater risk of adverse effects such as lactic acidosis and hypoglycemia.

However, current strict limitations on metformin use in individuals with impaired renal function have been recently disputed based on the lack of evidence that therapy with this agent is associated with a greater incidence of lactic acidosis or with higher levels of lactate than with other antihyperglycemic drugs, even in the presence of renal impairment or advanced age.[37] Metformin may accumulate in renal insufficiency but is not believed to be directly nephrotoxic; its use should be allowed also in individuals with stable CKD, provided that it is discontinued in the case of superimposed acute renal or liver failure or severe cardiovascular, respiratory, and hematological

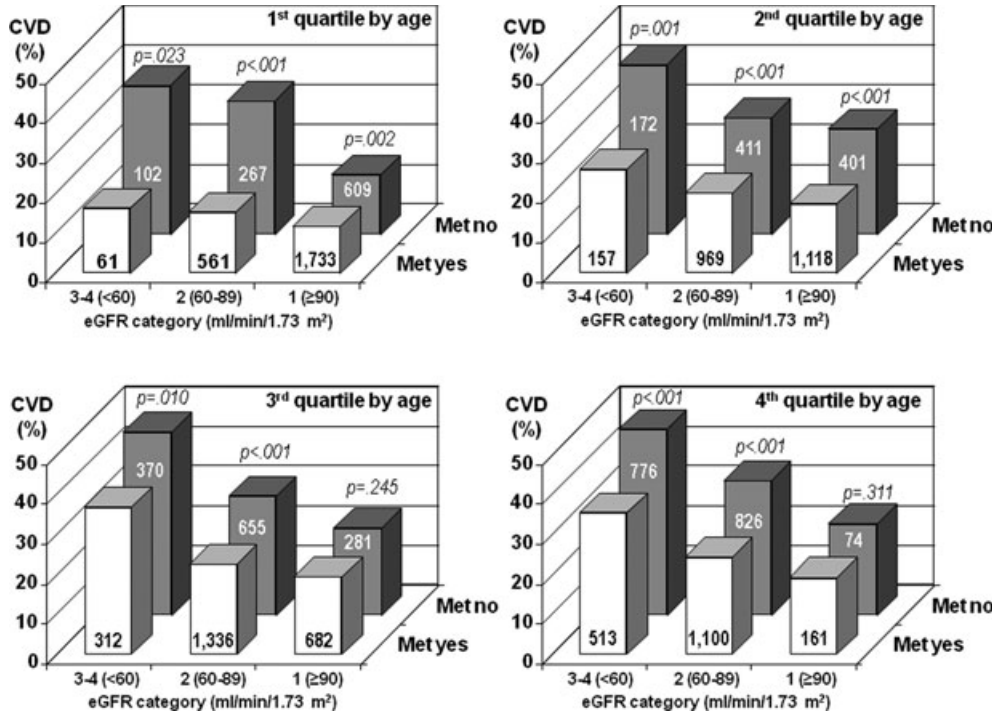

Figure 2. Prevalence of cardiovascular disease (CVD) according to quartiles of increasing age (1–4) according to estimated glomerular filtration rate (eGFR) category in participants taking metformin, alone or in combination (Met yes; n = 8,703) versus those taking drugs other than metformin (Met no; n = 4,944). Categories 3 and 4 were grouped because of the small number of participants taking metformin in category 4.

Table 3. Likelihood of Cardiovascular Disease According to Medication Regimen

	Metformin, Alone or in Combination (n = 8,703) vs No Metformin (n = 4,944)	Metformin Only (3,405) vs Other (n = 10,242)
Variable	**Odds Ratio (95% Confidence Interval) *P*-Value**	
Age	1.018 (1.012–1.023) <.001	1.018 (1.012–1.023) <.001
Male	1.727 (1.572–1.896) <.001	1.752 (1.596–1.924) <.001
Smoking (reference never)	1.0	1.0
Former	1.554 (1.412–1.710) <.001	1.545 (1.404–1.700) <.001
Current	1.137 (1.002–1.290) .046	1.132 (0.998–1.284) .054
Diabetes mellitus duration	1.018 (1.013–1.022) <.001	1.018 (1.014–1.023) <.001
Glycosylated hemoglobin	1.051 (1.021–1.081) .0007	1.053 (1.023–1.083) .0005
Triglycerides × 10 mg/dL	0.995 (0.990–1.000) .069	0.994 (0.989–1.000) .034
High-density lipoprotein cholesterol × 5 mg/dL	0.926 (0.910–0.942) <.001	0.927 (0.911–0.944) <.001
Dyslipidemia	1.690 (1.502–1.901) <.001	1.674 (1.489–1.883) <.001
Hypertension	2.304 (1.985–2.674) <.001	2.270 (1.957–2.634) <.001
Retinopathy (reference no)	1.0	1.0
Nonadvanced	1.358 (1.207–1.528) <.001	1.353 (1.203–1.521) <.001
Advanced	1.471 (1.294–1.672) <.001	1.466 (1.289–1.666) <.001
Estimated glomerular filtration rate	0.989 (0.987–0.991) <.001	0.987 (0.985–0.989) <.001
Albuminuria × 10 mg/24 h	1.001 (1.000–1.002) .003	1.001 (1.000–1.002) .002
Metformin treatment	0.667 (0.611–0.727) <.001	0.887 (0.798–0.987) .028

Body mass index excluded.

disorders compromising tissue oxygen supply.[38] However, it has been suggested that such risk should be weighed against the risks of the alternatives, in particular severe hypoglycemia in individuals taking sulphonylureas or insulin and fluid retention with CHF in those taking glitazones, and also with benefits that would be lost with metformin discontinuation.[39,40]

A relevant and novel finding of the current study is the analysis of the interactions between age, T2DM duration, renal function, and prevalent CVD and the effect of antihyperglycemic treatments under real-life conditions. Although renal dysfunction was greater with older age, eGFR and age correlated with previous CVD events in the multiple regression model, suggesting that these variables

have an effect independent of each other and of other known predictors of CVD. Moreover, use of metformin, if inappropriate according to current recommendations, was nevertheless associated with a lower rate of prevalent CVD, even in elderly adults with renal dysfunction. The milder clinical phenotype and lower T2DM duration of participants treated with metformin might explain this association; although in the present series, the association was still significant after adjustment for a number of factors reflecting participant phenotype and physician propensity to prescribe metformin. The cross-sectional nature of the study, which does not allow any cause–effect relationship to be derived or a survival bias to be excluded, limits this finding. Lack of information about duration and dosage of treatments and drug adverse effects further limits this analysis, although in some animal models,[41,42] metformin was found to be protective against CVD. In humans, longitudinal clinical studies have shown that it is protective[19] or neutral.[18] A recent analysis of the national Veterans Health Administration databases linked to Medicare files showed that use of sulphonylureas for initial treatment of T2DM was associated with greater risk of CVD events or death than use of metformin.[43] More importantly, a cohort study from the Swedish National Diabetes Register showed that metformin use was associated with lower risk of CVD and all-cause mortality at any level of renal function than use of insulin and to a lesser extent with OHAs.[44] The current study lends reasonably good support to the conclusion that metformin is safe or even advantageous in terms of CVD risk in older adults with renal dysfunction, although large-scale, long-term randomized clinical trials are needed to confirm that metformin treatment in individuals with T2DM with stable CKD is more cost effective in terms of glycemic control, renal outcome, and CVD than other antihyperglycemic treatments.

Strengths of the current study include the large size of the cohort, the completeness of the data, and the analysis under real-life conditions of a contemporary data set. In addition to the cross-sectional design, a limitation is that this was not a geriatric population, although the majority of participants were aged 65 and older, and hence the lack of a comprehensive geriatric assessment including evaluation of cognitive and functional status, which are major determinants of medication prescription and adherence.

In conclusion, the present analysis highlights the fact that, even in a healthcare environment where diabetes specialists follow the majority of individuals with T2DM at hospital-based clinics, treatment recommendations penetrate clinical practice slowly and incompletely. Appropriateness of prescription of metformin and especially sulphonylureas according to degree of renal dysfunction is poor in elderly adults, despite the fact that occurrence of CKD increases with age, particularly in individuals with diabetes mellitus. Nevertheless, although the use of long-acting sulphonylureas in elderly adults with renal dysfunction is harmful, the risk of using metformin in CKD might be overestimated, also in view of preliminary observations, including the current data, which seem to suggest a favorable effect of this agent on CVD even in these individuals.

ACKNOWLEDGMENTS

The authors thank the RIACE Investigators for participating in this study (see the complete list as on-line Appendix).

Conflict of Interest: Anna Solini has received research grants from BMS/Astra Zeneca. Enzo Bonora is a consultant for BMS/Astra Zeneca, Boehringer-Ingelheim, Lilly, Gentili, Novartis, Novo, Roche, and Takeda and has received research grants from Menarini, Novo, and Takeda. Ele Ferrannini is a consultant for Astellas, BMS/Astra Zeneca, Boehringer-Ingelheim, Lilly, Merck Sharp & Dohme, Novartis, sanofi, and Takeda and has received research grants from Amylin, Boehringer-Ingelheim, Lilly, and Merck Sharp & Dohme.

This work was supported by the Research Foundation of the Italian Society of Diabetology; the Diabetes, Endocrinology and Metabolism Foundation; and unconditional grants from Eli-Lilly Italia, Takeda, Chiesi Farmaceutici, and Boehringer-Ingelheim.

This work was presented at the 72nd Scientific Sessions of the American Diabetes Association, Philadelphia, Pennsylvania, June 8–12, 2012, and published in abstract form in Diabetes 2012;61(Suppl 1):A140.

Author Contributions: Anna Solini, Giuseppe Penno, Ele Ferrannini, and Giuseppe Pugliese conceived and designed the study. Anna Solini, Giuseppe Penno, Enzo Bonora, Cecilia Fondelli, Emanuela Orsi, Roberto Trevisan, Monica Vedovato, Franco Cavalot, Mauro Cignarelli, Susanna Morano, and Giuseppe Pugliese acquired the data. Ele Ferrannini and Giuseppe Penno performed the statistical analysis. All authors participated in analysis and interpretation of results and approval of the final draft. Giuseppe Pugliese drafted the article and obtained funding. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Anna Solini is guarantor.

Sponsor's Role: The sponsors had no role in design and conduct of the study; collection, management, or interpretation of the data; or preparation, review, or approval of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Clinical characteristics of the RIACE study subjects by eGFR category.

Table S2. Clinical characteristics by anti-hyperglycemic treatment.

Figure S1. Prevalence of eGFR categories across age quartiles.

Figure S2. Prevalence of CVD in quartiles of increasing age (1st through 4th) by eGFR category* in subjects treated with metformin only (Met; n = 3,405) versus those on any other pharmacological treatment, including combination therapies with metformin (Other; n = 10,242). *Categories 3 and 4 were grouped due to the small number of patients on metformin in category 4.

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