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High prevalence of advanced retinopathy in patients with type 2 diabetes from the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicenter Study☆

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ABSTRACT

Aims: The natural history of diabetic complications, including diabetic retinopathy (DR), is changing due to improved care. This study aimed at assessing prevalence of advanced DR and its correlation with risk factors and complications in subjects with type 2 diabetes from the Renal Insufficiency and Cardiovascular Events (RIACE) Italian Multicenter Study.
Methods: This study enrolled 15,773 patients visiting consecutively 19 Diabetes Clinics in years 2007–2008. DR was assessed by dilated fundoscopy and classified according to the Global Diabetic Retinopathy Project Group.
Results: Advanced DR was observed in 9.8% of patients (4.2% pre-proliferative, 4.2% proliferative, 1.3% maculopathy, 0.1% blindness). Advanced DR was independently associated with hemoglobin (Hb) A_{1c}, diabetes duration and treatment, particularly with insulin, hypertension, previous cardiovascular disease (CVD), albuminuria and, inversely, age, age at diabetes diagnosis, smoking and estimated glomerular filtration rate. Maculopathy alone was associated with female gender, but not HbA_{1c}, hypertension and age.

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Abbreviations: DR, diabetic retinopathy; PDR, proliferative DR; DMO, diabetic macular edema; CKD, chronic kidney disease; RIACE, Renal Insufficiency and Cardiovascular Events; eGFR, estimated GFR; CVD, cardiovascular disease; BP, blood pressure; BMI, body mass index; HbA_{1c}, hemoglobin A_{1c}; AER, albumin excretion rate; A/C, albumin/creatinine ratio; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; OR, odd ratios; CI, confidence interval; DAI, Diabetes and Informatics; ETDRS, Early Treatment Diabetic Retinopathy Study.

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Conclusions: We found an alarming high prevalence of advanced DR in subjects with type 2 diabetes from the RIACE cohort, suggesting that the expected favorable effect of improved diabetes management has not emerged yet. Independent correlates of advanced DR were indexes of glycemic exposure, hypertension, CVD, albuminuria and, inversely, age at diagnosis and smoking.

1. Introduction

Diabetic retinopathy (DR) is a common and highly specific microvascular complication of diabetes mellitus and represents the leading cause of blindness among working-age individuals in developed countries [1]. DR occurs both in type 1 and type 2 diabetes and is strictly related to the duration of the disease: virtually all individuals diagnosed with diabetes at less than 30 years of age [2] and more than 70% of individuals diagnosed aged 30 years or older [3] develop DR after 15 years of diabetes duration. However, there are substantial differences between type 1 and type 2 diabetes in terms of clinical presentation, prevalence, and, at least in part, risk factors of DR.

Proliferative DR (PDR) is the most common sight-threatening lesion in type 1 diabetes [4], whereas diabetic macular edema (DME) is the primary cause of loss of visual acuity [5] and usually precedes PDR [6] in type 2 diabetes. Prevalence of any DR is higher in type 1 than in type 2 diabetes and also in males than in females, as recently shown in a Swedish cohort [7]. However, prevalence estimates are quite variable across the world [8] and it is unclear whether recent improvements in diabetes care have resulted in significant reduction of this complication and particularly of its sight-threatening lesions. Re-analysis of individuals under poor control in 25 years of follow-up revealed only minor improvements following implementation of improved care [9], even though an intensive glucose control early in the course of the disease produced significant and persistent benefits on microvascular complications including DR, both in type 1 [10] and in type 2 [11] diabetes. In addition to the extent and duration of chronic hyperglycemia [12,13], other risk factors for DR are hypertension [13,14] and dyslipidemia [15]; conversely, the role of age, gender and smoking is controversial and seems to differ between type 1 and type 2 diabetes [16,17].

This study was aimed at assessing real-life prevalence and correlates of advanced DR, including severe non-PDR, PDR and maculopathy, in the large cohort of Caucasian patients with type 2 diabetes from the Renal Insufficiency and Cardiovascular Events (RIACE) Italian Multicenter Study.

2. Subjects, materials and methods

2.1. Design

The RIACE Italian Multicenter Study is an observational, prospective cohort study on the impact of estimated GFR (eGFR) on morbidity and mortality from cardiovascular disease (CVD) in subjects with type 2 diabetes. The study protocol was approved by the locally appointed ethics committees. Here, we report a cross-sectional analysis of DR data collected at the baseline visit.

2.2. Patients

The RIACE cohort consisted of 15,933 Caucasian patients with type 2 diabetes (defined by the American Diabetes Association criteria), attending consecutively 19 hospital-based Diabetes Clinics of the National Health Service throughout Italy (see online Appendix) in years 2007–2008. Exclusion criteria were dialysis or renal transplantation.

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The quality and completeness of data were controlled and 160 patients were excluded due to missing or implausible values; data from the remaining 15,773 patients were subsequently analyzed.

2.3. Risk factors

All patients underwent a structured interview in order to collect the following information: age, smoking status, known diabetes onset and duration, current glucose-, blood pressure (BP)- and lipid-lowering therapy, with indication of the class of drug.

Weight and height were assessed and body mass index (BMI) was calculated, then BP was measured with a sphygmomanometer after a 5 min of rest. Hemoglobin (Hb) A_{1c} was measured by high performance liquid chromatography using DCCT-aligned methods; triglycerides, total and HDL cholesterol were determined by standard analytical methods; LDL cholesterol was calculated by the Friedwald formula.

2.4. Complications

The presence of DR was assessed by an expert ophthalmologist with dilated fundoscopy. Patients were classified into the following categories: absent DR, mild, moderate or severe non-PDR, PDR, or maculopathy, according to the Global Diabetic Retinopathy Project Group [18]. Patients were classified based on the actual fundus appearance or the retinal disease condition which had eventually required a previous photocoagulation or surgical treatment. For further analysis, patients with non-PDR of mild (microaneurysms only) or moderate (microaneurysms and other microvascular lesions) degree were classified as having non-advanced DR, whereas those with severe non-PDR or pre-PDR (i.e. microaneurysms/hemorrhages in four quadrants, or venous beadings in two

quadrants, or intraretinal microvascular abnormalities in one quadrant), PDR (i.e. neovascularisation from the disc or from elsewhere, vitreous hemorrhages or tractional retinal detachment), maculopathy (retinal thickening or hard exudates distant from, approaching or involving the center of the macula), or blindness (if less than 1/10 normal vision or 20/200 on the Snellen test) were either grouped into the advanced, sight-threatening DR category or considered separately as patients with severe non-PDR or PDR and patients with maculopathy. Subjects with maculopathy and non-advanced DR were classified as having maculopathy, whereas those with maculopathy and severe non-PDR or PDR were classified as having one of the latter conditions. DR grade was assigned based on the worst eye.

The presence of CKD was assessed by measuring albuminuria and serum creatinine. As previously detailed [19], albumin excretion rate (AER) was obtained from timed (24 h) urine collections or calculated from albumin/creatinine ratio (A/C) in early-morning, first-voided 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 patient by immunonephelometry or immunoturbidimetry and, in case of multiple measurements, the geometric mean was used for analysis. Patients were then assigned to one of the following categories 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). Serum (and urine) creatinine was measured by the modified Jaffe method. One to three measurements were obtained for each patients and eGFR was calculated by the four-variable Modification of Diet in Renal Disease (MDRD) Study equation or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, using the mean serum creatinine value in case of multiple measures, as reported in previous publications [19,20]. Patients were then assigned to one of the following categories of eGFR (mL/min/1.73 m^2): 1 ($\geq$90); 2 (60–89); 3 (30–59); 4 (15–29); and 5 ($<$15). Finally, subjects were classified as having no CKD or CKD stages 1–5, based on the presence or absence of micro or macroalbuminuria and the value of eGFR, according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative [21]. Patients assigned to CKD stages (and GFR classes) 4 and 5 were pooled together.

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, 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 [22].

2.5. *Statistical analysis*

Data are expressed as median (interquartile range) for continuous variables and number of cases and percentages for categorical variables. Patients were stratified by DR grading, i.e. no, non-advanced and advanced. Prevalence of DR stages was calculated in the whole cohort and by quartiles of age at diabetes onset, disease duration and HbA_{1c}. The following statistical tests were applied: one-way ANOVA and Kruskall–Wallis for parametric and non-parametric continuous variables, respectively, and Pearson Chi square for categorical variables.

Logistic regression analyses with stepwise (forward and, in selected cases, also backward) variable selection were performed to identify factors independently associated with non-advanced or advanced DR, the latter further divided into pre-PDR + PDR and maculopathy, as compared with no DR. Further analyses were performed comparing factors associated with advanced vs. non-advanced DR. Covariates were age, gender, smoking status, known diabetes duration or age at diabetes diagnosis, HbA_{1c}, hypertension, dyslipidemia, triglycerides, HDL cholesterol, previous major acute CVD events and either CKD phenotypes or individual eGFR and albuminuria categories. Hypertension was defined as systolic BP $\geq$ 140 mmHg and/or diastolic BP $\geq$ 90 and/or anti-hypertensive treatment. Dyslipidemia was defined as high LDL cholesterol and/or lipid-lowering treatment, whereas high triglycerides and low HDL cholesterol were considered separately. Results of these analyses were expressed as odd ratios (ORs) with their 95% confidence interval (CI). The p value cut-offs for variable entry and removal from the model were $p < 0.05$ and $p > 0.10$, respectively.

All p values were two-sided, and a p value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, Illinois, USA).

3. Results

No signs of DR were detected in the vast majority of patients from the RIACE cohort (78.2%), though a high percentage of individuals with any DR showed advanced lesions (Table 1).

Subjects with advanced or non-advanced DR were slightly older, more frequently male (not significantly) and non-smokers, had lower age at diabetes onset, much longer diabetes duration, higher HbA_{1c}, systolic BP, albuminuria, and serum creatinine (only those with advanced DR), and lower total and LDL-cholesterol, diastolic BP, and eGFR values. Moreover, patients with DR had a higher prevalence of major acute CVD events and were more frequently on lipid-lowering drugs and anti-hypertensive agents, including angiotensin-converting enzyme inhibitors/angiotensin II-receptor blockers

Table 1 – Prevalence (number of cases and percentage) of stages of DR.

Stages	*n*	%
No DR	12,276	77.8
Non-advanced DR	1957	12.4
Advanced DR	1540	9.8
Pre-proliferative	660	4.2
Proliferative	658	4.2
Maculopathy alone	205	1.3
Blindness	17	0.1

DR = diabetic retinopathy.

Table 2 – Clinical characteristics of subjects with no, non-advanced and advanced DR.

Variable	No DR	Non-advanced DR	Advanced DR	p^*
N (%)	12,276 (77.8)	1957 (12 4)	1540 (9.8)	
Age, years	66 (59–73)	68 (61–75)	67 (60–73)	<0.0001
Male gender, *n* (%)	6959 (56.7)	1131 (57.8)	870 (56.5)	0.635
Smoking, *n* (%)				0.024
Never	6903 (56.2)	1101 (56.3)	924 (60.0)	
Former	3460 (28.2)	554 (28.3)	420 (27.3)	
Current	1913 (15.6)	302 (15.4)	196 (12.7)	
Age at diabetes diagnosis, years	54 (47–62)	49 (42–56)	48 (40–55)	<0.0001
Diabetes duration, years	9 (4–17)	19 (11–26)	19 (11–26)	<0.0001
HbA_{1c}, %	7.2 (6.4–8.1)	8.1 (7.1–8.8)	8.1 (6.9–9.0)	<0.0001
[nmol/mol]	[55 (47–65)]	[65 (54–73)]	[65 (52–75)]	<0.0001
BMI, kg/m^2				
Males	27.8 (25.2–30.8)	27.7 (25.3–30.8)	28.2 (25.6–31.2)	0.225
Females	28.9 (25.5–32.8)	29.2 (25.9–33.3)	30.6 (26.4–34.3)	<0.0001
Triglycerides, mmol/l	1.33 (0.97–1.88)	1.26 (0.92–1.86)	1.37 (0.99–1.93)	<0.0001
Total cholesterol, mmol/l	4.75 (4.14–5.40)	4.60 (4.00–5.28)	4.65 (4.03–5.95)	<0.0001
HDL cholesterol, mmol/l				
Males	1.16 (0.98–1.40)	1.19 (0.98–1.41)	1.14 (0.96–1.37)	0.066
Females	1.34 (1.14–1.60)	1.34 (1.11–1.60)	1.32 (1.11–1.55)	0.046
LDL cholesterol, mmol/l	2.76 (2.24–3.33)	2.64 (2.09–3.22)	2.65 (2.14–3.20)	<0.0001
SBP, mmHg	136 (125–150)	140 (130–150)	140 (130–154)	<0.0001
DBP, mmHg	80 (70–85)	79 (70–80)	79 (70–80)	<0.0001
Albuminuria, mg/24 h	12.3 (6.0–27.1)	17.0 (4.6–49.9)	25.9 (9.7–110.3)	<0.0001
Serum creatinine, μmol/l	79.56 (67.18–91.94)	79.56 (68.95–97.24)	84.86 (70.72–106.08)	<0.0001
eGFR MDRD, ml/min/1.73 m^2	79.2 (66.2–93.5)	75.8 (60.9–91.6)	72.3 (55.9–88.9)	<0.0001
eGFR CKD-EPI, ml/min/1.73 m^2	85.1 (69.5–96.1)	80.8 (62.6–93.2)	77.0 (56.9–92.4)	<0.0001
CKD, *n* (%)	4 094 (33.3)	911 (46.6)	903 (58.6)	<0.0001
Any CVD event, *n* (%)	2494 (20.3)	623 (31.8)	538 (34.9)	<0.0001
AMI, *n* (%)	1229 (10.0)	287 (14.7)	242 (15.7)	<0.0001
Stroke, *n* (%)	353 (2.9)	80 (4.1)	82 (5.3)	<0.0001
Foot ulcer/gangrene, *n* (%)	250 (2.0)	119 (6.1)	163 (10.6)	<0.0001
Coronary revascularization, *n* (%)	1113 (9.1)	265 (13.5)	206 (13.4)	<0.0001
Carotid revascularization, *n* (%)	565 (4.6)	204 (10.4)	98 (6.4)	<0.0001
Lower limb revascularization, *n* (%)	255 (2.1)	104 (5.3)	97 (6.3)	<0.0001
Lipid-lowering treatment, *n* (%)	5548 (45.2)	949 (48.5)	789 (51.2)	<0.0001
Anti-hypertensive treatment, *n* (%)	8408 (68.5)	1513 (77.3)	1229 (79.8)	<0.0001
ACE-I/ARB treatment, *n* (%)	6770 (55.1)	1312 (67.0)	1083 (70.3)	<0.0001

One-way ANOVA and Kruskall–Wallis for parametric and non-parametric (triglycerides, albuminuria, serum creatinine, eGFR) continuous variables; Pearson Chi square for categorical variables. CKD phenotypes were identified using the MDRD Study formula for eGFR calculation. DR = diabetic retinopathy; HbA_{1c} = heamoglobin A_{1c}; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; eGFR = estimated GFR; MDRD = Modification of Diet in Renal Disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CKD = chronic kidney disease; CVD = cardiovascular disease; AMI = acute myocardial infarction; ACE-I = ACE-inhibitors; ARB = angiotensin II-receptor blockers.

* Values are median (interquartile range) or *n* (%).

(Table 2). Prevalence of both advanced and non-advanced DR increased from the highest to the lowest quartile of age at diabetes onset and from the lowest to the highest quartile of diabetes duration and HbA_{1c} (Fig. 1).

Multiple logistic regression analysis with stepwise variable selection (Table 3) indicated that diabetes duration, HbA_{1c}, diabetes treatment (particularly with insulin, alone or in combination with oral agents), hypertension, any previous CVD event and, inversely, age, smoking and triglyceride levels were independently associated with advanced DR. Albuminuria correlated more strongly than eGFR with advanced DR. Independent correlates of non-advanced DR were the same, except eGFR and smoking. When forced in the regression model in place of age and diabetes duration, age at diabetes diagnosis was also inversely associated with both advanced (OR per year 0.961 [95% CI 0.956–0.966]) and non-advanced (0.965 [0.961–0.970]) DR. On multiple logistic regression analysis comparing factors independently associated with advanced vs. non-advanced DR, the most significant correlates of advanced DR were former and current smoking (0.834 [0.711–0.978] and 0.700 [0.568–0.863], respectively), insulin treatment, either combined or alone (2.135 [1.426–3.197] and 2.171 [1.463–3.222], respectively), micro and macroalbuminuria (1.492 [1.245–1.788] and 2.110 [1.622–2.746], respectively), and, in the backward model only, eGFR < 60 ml/min/1.73 m^2 (not shown). When pre-PDR + PDR and maculopathy were

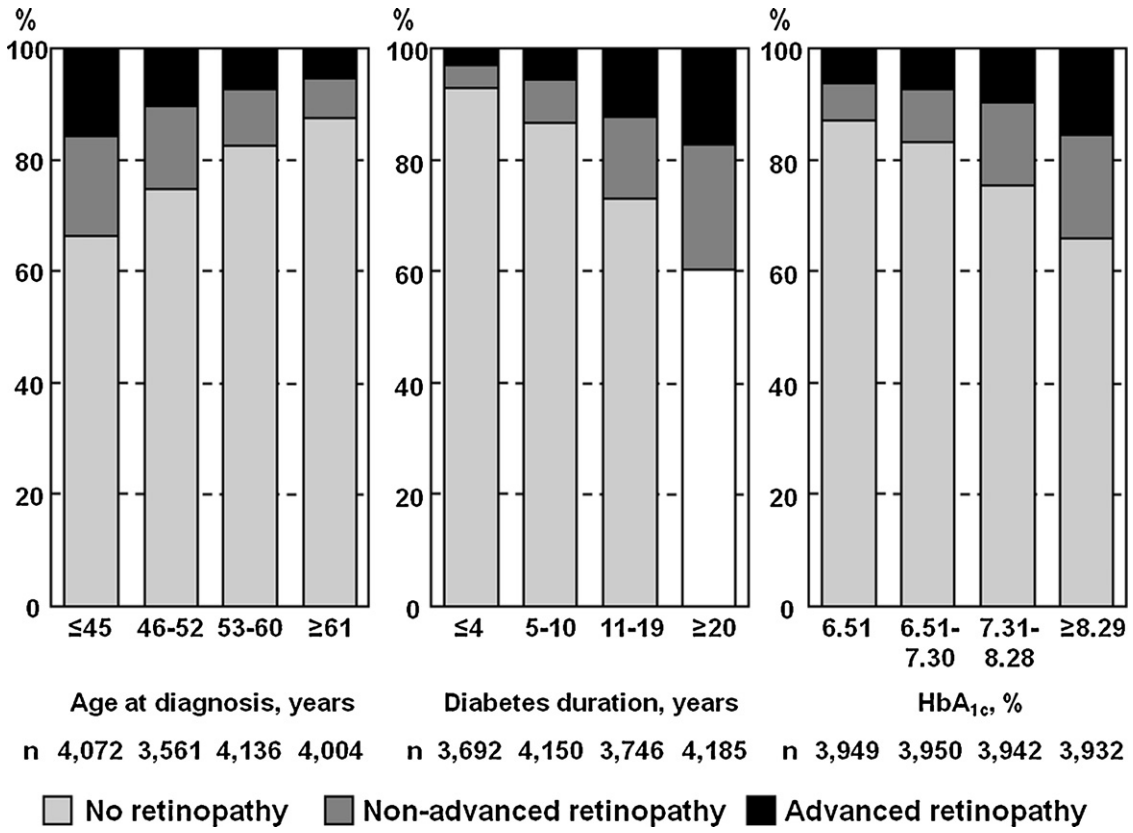

Fig. 1 – Prevalence of DR stages by quartiles of age at diabetes diagnosis, diabetes duration and HbA_{1c}. DR = diabetic retinopathy; *n* = number of subjects in each quartile.

considered separately, correlates did not change for pre-PDR + PDR, whereas maculopathy was associated with female gender, but not with HbA_{1c} and hypertension nor, inversely, with age, smoking and triglycerides (Table 4). When all covariates were forced in the model, ORs for excluded variables were found to be close to 1 (not shown).

4. Discussion

This study from a large Italian cohort shows that advanced DR (a) is present in almost 10% of contemporary subjects with type 2 diabetes, despite a relatively low prevalence of any DR (22.2%); and (b) correlates with indexes of glycemic exposure (i.e. HbA_{1c}, diabetes duration and treatment, especially with insulin), hypertension, CVD, albuminuria, and, inversely with age, age at diabetes diagnosis, smoking and eGFR.

A prevalence of any DR of 22.2% is lower than that reported for Caucasian patients with type 2 diabetes in a systematic review examining 359 studies from over 50 countries [5] and also in a recent pooled analysis using individual participant data from population-based studies around the world [23]. Moreover, this prevalence value is lower than that reported in two recent surveys: a population study in the catchment area of the eye clinic of Linköping University Hospital, Sweden (*n* = 10.877 with type 2 diabetes; prevalence 29.4%) [7], and a cross-sectional analysis of a US nationally representative sample of the National Health and Nutrition Examination Survey 2005–2008 (*n* = 1.006; prevalence 28.3%) [17]. As expected, prevalence in our study was also lower than that observed in subjects with childhood, adolescent or adult onset of type 1 diabetes from the prospective German Diabetes Documentation System Survey (*n* = 18.891; prevalence 27.4%) [16] as well as in other ethnic groups such as African Americans and Hispanics [24]. However, another large Italian survey conducted in years 1998–1999 on subjects with type 2 diabetes, the Diabetes and Informatics (DAI) Study and also using funduscopy instead of fundus photography, reported slightly lower figures (*n* = 19.468; prevalence 19.2%) [25]. Thus, prevalence of any DR in our study is likely underestimated due to the lower sensitivity of funduscopic examination as compared with fundus photography for detection of non-advanced DR.

The most important finding of our study is the quite high (9.8%) prevalence of advanced, sight-threatening forms of DR, including pre-PDR and PDR, maculopathy and blindness, though the few cases of blindness could not be definitively attributed to DR. Of note, this value is higher than that reported in the pooled analysis by Yau et al. for subjects with type 2 diabetes (6.92 [6.83–7.02]) [23] and also in the recent prospective German Diabetes Documentation System Survey for patients with type 1 diabetes (8.0%) [16]. This unexpected and alarming observation may be due to the high known diabetes duration of patients with advanced DR (median 19 years). In fact, in most of these subjects, onset of disease occurred before tight glucose control was implemented in

Table 3 – Logistic regression analysis with stepwise variable selection of independent correlates of non-advanced and advanced DR vs. no DR.

Variables	Non-advanced DR		Advanced DR	
	OR	95% CI	OR	95% CI
Age (x year)	0.989	0.984–.995	0.974	0.9680–0.981
Smoking				
Never	–	–	1.0	–
Former	–	–	0.833	0.727–0.955
Current	–	–	0.748	0.626–0.894
Diabetes duration (x year)	1.057	1.052–1.063	1.053	1.046–1.059
HbA_{1c}	1.164	1.125–1.204	1.079	1.039–1.121
Diabetes treatment				
Diet	1.0	–	1.0	–
OHA	2.0319	1.613–2.559	2.467	1.800–3.382
Insulin + OHA	3.252	2.527–4.185	7.045	5.076–9.777
Insulin	4.123	3.169–5.365	9.378	6.704–13.118
Triglycerides (x 0.113 mmol/l)	0.984	0.977–0.991	0.991	0.984–0.999
Hypertension	1.290	1.104–1.506	1.549	1.278–1.877
Previous CVD event	1.291	1.152–1.448	1.335	1.172–1.521
Albuminuria				
Normal albuminuria	1.0	–	1.0	–
Low albuminuria	1.157	1.023–1.309	1.136	0.976–1.322
Microalbuminuria	1.521	1.330–1.739	2.100	1.802–2.447
Macroalbuminuria	1.958	1.553–2.468	3.743	2.972–4.715
eGFR				
$\geq$90 ml/min/1.73 m^2	–	–	1.0	–
60–89 ml/min/1.73 m^2	–	–	1.085	0.935–1.258
30–59 ml/min/1.73 m^2	–	–	1.346	1.117–1.623
<30 ml/min/1.73 m^2	–	–	1.761	1.214–2.553

Variables excluded: gender, HDL cholesterol, dyslipidemia. DR = diabetic retinopathy; OR = odd ratio; CI = confidence interval; HbA_{1c} = hemoglobin A_{1c}; OHA = oral hypoglycemic agents; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate.

clinical care on the grounds of the evidence that it was effective in preventing microvascular complications of type 2 diabetes [26]. As a consequence, long-standing diabetic subjects developing advanced DR could have not been on intensive glycemic control from the time of diagnosis and, hence, they would have not benefited of the legacy effect associated with early achievement of glucose targets [11]. Thus, the positive effect of improvements in diabetes management with tighter control of risk factors on prevalence of advanced DR in patients with a recent diagnosis of diabetes might have been masked by the inclusion of subjects with long-standing disease, who could have also experienced many years of undiagnosed diabetes. This speculation is supported by the finding that, when considering only patients with less than 15 years of diabetes duration, prevalence of advanced DR fell to 5.7%, though further studies are required in order to verify whether the burden from sight-threatening lesions in type 2 diabetes is actually decreasing with improved diabetes care.

Finally, prevalence of maculopathy was lower than that reported previously in subjects with type 2 diabetes [5,7,17,23]. However, this finding is attributable to inter-study differences in the definition of maculopathy (see above). Thus, the more frequent macular involvement in patients with pre-PDR or PDR than in those with non-advanced DR accounts for the apparent low prevalence of maculopathy, especially if compared to that of pre-PDR + PDR (1.3% vs. 8.4%). In fact, any DME, either alone or associated with pre-PDR or PDR, was detected in 5.2% of subjects, more in accordance with previous reports.

In our study, presence of advanced and any DR was associated with markers of glycemic exposure, such as HbA_{1c} and particularly diabetes duration, with a 5–6% risk increase per year, and insulin treatment, either alone or combined with oral agents, with a 7–9-fold increase for advanced DR. These findings, as well as the association with hypertension, are consistent with previous reports [17,27,28]. Conversely, no association was found between non-advanced or advanced DR and lipid abnormalities, at variance with previous studies [15,28], though in agreement with another report [27]. Also male gender was not preferentially associated with DR, in contrast with results of other surveys [7,17], but consistent with data from the Early Treatment Diabetic Retinopathy Study (ETDRS) [28]. Indeed, presence of maculopathy correlated with female gender, in keeping with the DAI Study, showing that a higher prevalence of DR in females [25], and with the ETDRS, showing that female gender was among the risk factors associated with development of severe visual loss or vitrectomy before high-risk PDR [28]. Though DR was strongly associated with disease duration, it correlated inversely with age. This apparent discrepancy can be explained by the inverse association of DR with age at diabetes diagnosis,

Table 4 – Logistic regression analysis with stepwise variable selection of independent correlates of pre-PDR/PDR and maculopathy vs. no DR.

Variables	Pre-PDR/PDR		Maculopathy	
	OR	95% CI	OR	95% CI
Age (x year)	0.969	0.962–0.976	–	–
Female gender	–	–	1.613	1.206–2.158
Smoking				
Never	1.0	–	–	–
Former	0.806	0.696–0.934	–	–
Current	0.757	0.626–0.914	–	–
Diabetes duration (x year)	1.056	1.049–1.063	1.039	1.026–1.053
HbA_{1c}	1.082	1.040–1.127	–	–
Diabetes treatment				
Diet	1.0	–	1.0	–
OHA	2.830	1.963–4.079	1.327	0.721–2.442
Insulin + OHA	8.132	5.574–11.865	3.426	1.806–6.499
Insulin	11.139	7.585–16.359	3.625	1.843–7.129
Triglycerides (x 0.113 mmol/l)	0.991	0.984–0.999		
Hypertension	1.630	1.324–2.006	–	–
Previous CVD event	1.279	1.112–1.472	1.899	1.404–2.569
Albuminuria				
Normal albuminuria	1.0	–	1.0	–
Low albuminuria	1.095	0.930–1.289	1.681	1.135–2.487
Microalbuminuria	2.078	1.765–2.446	2.843	1.914–4.223
Macroalbuminuria	3.859	3.029–4.916	4.593	2.670–7.902
eGFR				
$\geq$90 ml/min/1.73 m^2	1.0	–	–	–
60–89 ml/min/1.73 m^2	1.091	0.921–1.278	–	–
30–59 ml/min/1.73 m^2	1.399	1.147–1.706	–	–
$<$30 ml/min/1.73 m^2	1.604	1.071–2.402	–	–

Variables excluded: triglycerides, HDL cholesterol, dyslipidemia. PDR = proliferative diabetic retinopathy; OR = odd ratio; CI = confidence interval; HbA_{1c} = hemoglobin A_{1c}; OHA = oral hypoglycemic agents; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate.

consistent with the observation that early-onset type 2 diabetes confers a high risk for premature DR, which is driven predominantly by hypertension and poor glycemic control [29]. Conversely, the inverse correlation of advanced DR with smoking is difficult to explain in the absence of data on the amount of smoking (number of cigarettes or smoking years). In fact, smoking was previously shown to be associated with DR in patients with type 1 diabetes, though the percentage of smokers among individuals with advanced DR was lower than in those with no or non-advanced DR [16]. However, in subjects with type 2 diabetes, either no effect or an inverse correlation of smoking with DR was reported [17,27,28]. In our study, the percentage of no smokers increased with increasing age and diabetes duration. This suggests that the inverse association of smoking with advanced DR might be driven by temporal trends in the smoking habits of the population, though regression analysis showed that the correlation of no smoking with advanced DR was independent of age and diabetes duration. The association of DR with CVD, albuminuria and, to a lesser extent, reduced eGFR confirms previous observations that DR is a risk factor for macro and microvascular complications of diabetes and also for mortality [30–32]. Finally, data from comparison of subjects with advanced and non-advanced DR suggest that a major determinant of progression toward advanced DR is severity of diabetes, as evidenced by the association with insulin treatment and prevalence of complications such as nephropathy.

Strengths of this study include the large size of the cohort, the completeness of data and the analysis of a contemporary dataset. Limitations include lack of data on visual acuity and particularly the use of funduscopy instead of the reference method for DR diagnosis, i.e. multifield stereoscopic retinal photography. However, fundus examination by an ophthalmologist is the most used method for DR screening and diagnosis in Italy, whereas fundus photography is rarely employed, due to the lack of trained and qualified personnel and abundance of ophthalmologists. Thus, prevalence rates derived from funduscopy data correspond to those observed under real-life conditions. On the other hand, the use of funduscopy instead of fundus photography did not allow centralized evaluation of DR and, hence, another potential limitation of the study was assessment by different ophthalmologists, though they were asked to fill in a standardized report format for classifying the RIACE participants. Thus, to account for the lower sensitivity of funduscopy and non-centralized fundus evaluation, we focused our analysis on advanced retinopathy, which is difficult to misclassify even with dilated funduscopy, also because of history of previous treatments. Possible selection bias which might have influenced prevalence rates cannot be excluded, since this survey involved only patients with type 2 diabetes visiting

hospital-based Diabetes Clinics. However, in Italy, about 80% of subjects with known diabetes are seen at these clinics at least once a year, thus the RIACE cohort might be considered as representative of the Italian population of subjects with type 2 diabetes. Finally, a limitation for the assessment of determinants of advanced DR is the cross-sectional design of the study.

In conclusion, data from this large cohort show an unexpected and alarming high prevalence of the advanced, sight-threatening lesions of that DR in contemporary subjects type 2 diabetes, especially in those with long disease duration. This suggests that the favorable effect of recent improvements in diabetes management on the prevalence of advanced DR has not emerged yet. Moreover, this study indicates that advanced DR correlates with indexes of glycemic exposure, hypertension, CVD events, albuminuria, and, inversely, with age at diabetes diagnosis and smoking.

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Meeting presentation

Data from the manuscript have been presented at the 72nd Annual Meeting of the American Diabetes Association, June 8–12, 2012, Philadelphia, PA.

Conflict of interest statement

None.

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