Incidence of Proliferative Diabetic Retinopathy and Other Neovascular Sequelae at 5 Years Following Diagnosis of Type 2 Diabetes

William S. Gange,[1] Jennifer Lopez,[1] Benjamin Y. Xu,[1] Khristina Lung,[2] Seth A. Seabury,[1,2] and Brian C. Toy[1]

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

To determine the incidence and risk factors for developing proliferative diabetic retinopathy (PDR), tractional retinal detachment (TRD), and neovascular glaucoma (NVG) at 5 years after the initial diagnosis of type 2 diabetes.

RESEARCH DESIGN AND METHODS

Insured patients aged ≥18 years with newly diagnosed type 2 diabetes and 5 years of continuous enrollment were identified from a nationwide commercial claims database containing data from 2007 to 2015. The incidences of PDR, TRD, and NVG were computed at 5 years following the index diagnosis of type 2 diabetes. Associations between these outcomes and demographic, socioeconomic, and medical factors were tested with multivariable logistic regression.

RESULTS

At 5 years following the initial diagnosis of type 2 diabetes, 1.74% (1,249 of 71,817) of patients had developed PDR, 0.25% of patients had developed TRD, and 0.14% of patients had developed NVG. Insulin use (odds ratio [OR] 3.59, 95% CI 3.16–4.08), maximum HbA_{1c} >9% or >75 mmol/mol (OR 2.10, 95% CI 1.54–2.69), renal disease (OR 2.68, 95% CI 2.09–3.42), peripheral circulatory disorders (OR 1.88, 95% CI 1.25–2.83), neurological disease (OR 1.62, 95% CI 1.24–2.11), and older age (age 65–74 years) at diagnosis (OR 1.62, 95% CI 1.28–2.03) were identified as risk factors for development of PDR at 5 years. Young age (age 18–23 years) at diagnosis (OR 0.46, 95% CI 0.29–0.74), Medicare insurance (OR 0.60, 95% CI 0.70–0.76), morbid obesity (OR 0.72, 95% CI 0.59–0.87), and smoking (OR 0.84, 95% CI 0.70–1.00) were identified as protective factors.

CONCLUSIONS

A subset of patients with type 2 diabetes develop PDR and other neovascular sequelae within the first 5 years following the diagnosis with type 2 diabetes. These patients may benefit from increased efforts for screening and early intervention.

Diabetic eye disease is the leading cause of new blindness in those aged 20–64 years in the U.S. (1), with an estimated prevalence of vision-threatening retinopathy of

[1]Roski Eye Institute, Department of Ophthalmology, Keck School of Medicine, University of Southern California, Los Angeles, CA
[2]Keck-Shaeffer Initiative for Population Health Policy, Keck School of Medicine, University of Southern California, Los Angeles, CA

Corresponding author: Brian C. Toy, brian.toy@med.usc.edu

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4.4–8.2% among U.S. adults with diabetes (2,3). While numerous population-based studies have shown that the risk for diabetic retinopathy (DR) increases with duration of diabetes (4–8), proliferative DR (PDR) may still occur within the first 5 years after the diagnosis of type 2 diabetes (4–6,9). Therefore, for patients with type 2 diabetes, the American Academy of Ophthalmology recommends screening fundus examinations at diagnosis and at least yearly thereafter (10).

In 2018, there were ~34 million adults in the U.S. with diabetes, with an estimated 1.5 million people newly diagnosed with diabetes (1). Screening this growing population of patients with diabetes at guideline-recommended intervals presents a substantial public health challenge. While clinical trials have shown that up to 98% of blindness due to DR can be prevented with a combination of laser photocoagulation, intravitreal anti-vascular endothelial growth factor injections, and vitrectomy (11), if patients do not follow-up at recommended intervals, they are more likely to experience preventable vision loss or blindness (12). Given that just 30–40% of patients receive an eye examination in any of the first 5 years after the diagnosis with type 2 diabetes (13), and up to 37% of patients with type 2 diabetes have DR at diagnosis (9), a significant number of patients with newly diagnosed type 2 diabetes are at risk for preventable vision loss in the first 5 years after their initial diagnosis.

The incidence of PDR in the first 5 years after the de novo diagnosis of type 2 diabetes is not well known. Therefore, we performed a retrospective longitudinal cohort study using data from a large, nationwide commercial and Medicare Advantage claims database to determine the incidence of and risk factors for developing PDR within 5 years of a new diagnosis of type 2 diabetes in the U.S. Additionally, we report the cumulative incidence of tractional retinal detachment (TRD) and neovascular glaucoma (NVG), two vision-threatening sequelae of PDR often requiring urgent surgical intervention and their associated risk factors at 5 years following an index diagnosis of type 2 diabetes. To our knowledge, this is the first study to report the incidence and risk factors for TRD and NVG within 5 years of diagnosis of type 2 diabetes.

RESEARCH DESIGN AND METHODS

Data from Optum's deidentified Clinformatics Data Mart Database were reviewed. These deidentified data came from 47 million individuals privately insured through a single carrier at any point from 2007 to 2015. For each member, we had access to all medical and pharmacy claims that were filed with their health plan. In addition, demographic and socioeconomic data were provided. The University of Southern California Institutional Review Board determined that this study was exempt from Institutional Review Board review. This study complied with the Health Insurance Portability and Accountability Act and adhered to the tenets of the Declaration of Helsinki.

Selecting Patients

Individuals ≥18 years of age were determined to have a diagnosis of type 2 diabetes if they had any of the following: one inpatient claim with a diagnosis of type 2 diabetes, one prescription fill for diabetes medication (Supplementary Table 1) or two outpatient claims with a diagnosis of type 2 diabetes within 180 days. *International Classification of Diseases, Ninth Revision* (ICD-9) codes (ICD-9 codes 250.x0 or 250.x2) associated with these claims were used to identify patients with type 2 diabetes. Cases of concurrent pregnancy or gestational diabetes (ICD-9 codes 630–79, V22 or V23, V28.x, V61.6, V61.7, or 648.83), type 1 diabetes (250.x1 or 250.x3), or use of an insulin pump (V45.85, V53.91, V65.46, and 996.57) were excluded. To identify incident cases, individuals were required to have a 12-month window of continuous enrollment prior to the index type 2 diabetes diagnosis with no diabetes diagnosis or diabetes medication use. Additionally, patients were excluded if they had any diagnosis indicating the presence of diabetic eye disease prior to the index diagnosis of diabetes.

Two overlapping cohorts of patients were selected based on length of follow-up: a 2-year cohort, with 3 years of continuous enrollment (1 pre-, 2 post-diagnosis), and a 5-year cohort, with 6 years of continuous enrollment (1 pre-, 5 postdiagnosis). All included patients had continuous enrollment, and there was no movement into and out of the health insurance plan for any of these patients. For each patient, all inpatient, outpatient, and pharmacy claims in the year prior to index and for the 2- or 5-year period after the index diagnosis were tracked, depending on the cohort. The purpose of the 2-year cohort was to compare the incidence of outcomes over time and perform a sensitivity analysis to evaluate any potential risk factors for the rare diagnoses of TRD and NVG, which may not have been apparent in the 5-year regression.

Outcome Measures

The primary outcome measure was the incidence of PDR at 5 years. Secondary outcome measures included the incidence of TRD and NVG at 5 years. As a sensitivity analysis, the incidence for these outcomes was also computed at 2 years. Patients were identified as having PDR, TRD, or NVG based on the presence of ICD-9 or Current Procedural Terminology (CPT) codes as listed in Supplementary Table 2.

Statistical Analysis

Comparisons between the subset of patients who did and did not develop PDR within 5 years of their index type 2 diabetes diagnosis were performed by using descriptive analyses (χ^2 for categorical variables and *t* test for continuous variables). Multivariable logistic regression was used to test the association between the incidence of PDR, TRD, and NVG with the following factors: age at diagnosis, race/ethnicity, sex, education, income, Medicare insurance, medical comorbidities, insulin use, and maximum hemoglobin A_{1c} (max HbA_{1c}) in the 2- or 5-year period after diagnosis, depending on the cohort. Max HbA_{1c} values were binned into ordinal categories as follows: <6.5% (48 mmol/mol), 6.5% (48 mmol/mol) to 7.5% (58 mmol/mol), 7.5% (58 mmol/mol) to 9% (75 mmol/mol), and >9% (>75 mmol/mol). The single highest HbA_{1c} value in the period after the initial type 2 diabetes diagnosis was selected for each patient. All analyses were conducted on Unix workstations using SAS 9.4 (SAS Institute, Carey, NC) and Stata 16 (StataCorp College Station, TX) software. $P \leq$

0.05 was used to determine statistical significance.

RESULTS

A total of 277,401 (Supplementary Fig. 1) and 71,817 (Fig. 1) patients newly diagnosed with type 2 diabetes met all criteria and were included in the 2- and 5-year cohorts, respectively. At 5 years following the diagnosis of type 2 diabetes, 1,249 of 71,817 patients (1.74%) developed PDR (Supplementary Fig. 2). Patients who developed PDR within 5 years were older on average at diagnosis (61.6 ± 12.9 vs. 60.6 ± 13.9, $P < 0.001$) (Table 1) and more likely to be men (54.4% vs. 50.7%, $P = 0.008$). Patients developing PDR were more likely to be Hispanic (17.6% vs. 14.6%, $P = 0.003$), and less likely to be White (62.1% vs. 65.9%, $P = 0.005$). There were trends toward those with PDR having lower levels of education and income than those without PDR, but these differences were not statistically significant. Patients developing PDR were more likely to have other systemic complications of type 2 diabetes, including renal disease (6.7% vs. 1.6%, $P < 0.001$), neurological disease (5.6% vs. 1.9%, $P < 0.001$), and peripheral circulatory disorders (2.2% vs. 0.6%, $P < 0.001$). There were no differences in the rates of comorbid hypertension, dyslipidemia, or smoking between the two groups. Morbid obesity was less common among those developing PDR (9.9% vs. 12.8%, $P = 0.003$). Lastly, insulin use (40.2% vs. 13.4%, $P < 0.001$) was far more common, and max HbA_{1c} was higher (8.7% ± 2.4 [72 mmol/mol] vs. 7.6% ± 2.0 [60 mmol/mol], $P < 0.001$) among those developing PDR.

Multivariable logistic regression was used to identify independent factors for the development of PDR within 5 years (Table 2). The greatest independent risk factor for the development of PDR at 5 years was insulin use (odds ratio [OR] 3.59, 95% CI 3.16–4.08). Other significant risk factors included max HbA_{1c} >9% or >75 mmol/mol (OR 2.10, 95% CI 1.64–2.69), concomitant renal disease (OR 2.68, 95% CI 2.09–3.42), peripheral circulatory disorders (OR 1.88, 95% CI 1.25–2.83), and neurological disease (OR 1.62, 95% CI 1.24–2.11). Age at diagnosis was positively correlated with the risk of developing PDR, with risk peaking in the patients diagnosed between the ages of 65 and 74 (OR 1.62, 95% CI 1.28–2.03). Younger age (18–34 years) at diagnosis (OR 0.46, 95% CI 0.29–0.74), Medicare insurance (OR 0.60, 95% CI 0.70–0.76), morbid obesity (OR 0.72, 95% CI 0.59–0.87), and smoking (OR 0.84, 95% CI 0.70–1.00) were identified as independent negatively associated factors.

Other Neovascular Sequelae of Diabetic Eye Disease

In addition to reporting the incidence of PDR, we also studied other severe, vision-threatening neovascular sequelae of diabetic eye disease that often require urgent surgical intervention, including tractional retinal detachment (TRD) and neovascular glaucoma (NVG). Both were rare outcomes at 5 years, with just 183 patients (0.25%) developing TRD, and 102 patients (0.14%) developing NVG (Table 2). The two independent factors associated with the incidence of TRD at 5 years were insulin use (OR 3.57, 95% CI 2.57–4.96) and renal disease (OR 2.46, 95% CI 1.30–4.69). Max HbA_{1c} >9% or >75 mmol/mol (OR 2.12, 95% CI 1.35–3.33), concomitant peripheral circulatory disorders (OR 2.57, 95% CI 1.10–6.01), and Hispanic ethnicity (OR 1.76, 95% CI 1.35–2.29) were significant independent risk factors for the incidence of TRD at 2 years, but these were not statistically significant at 5 years.

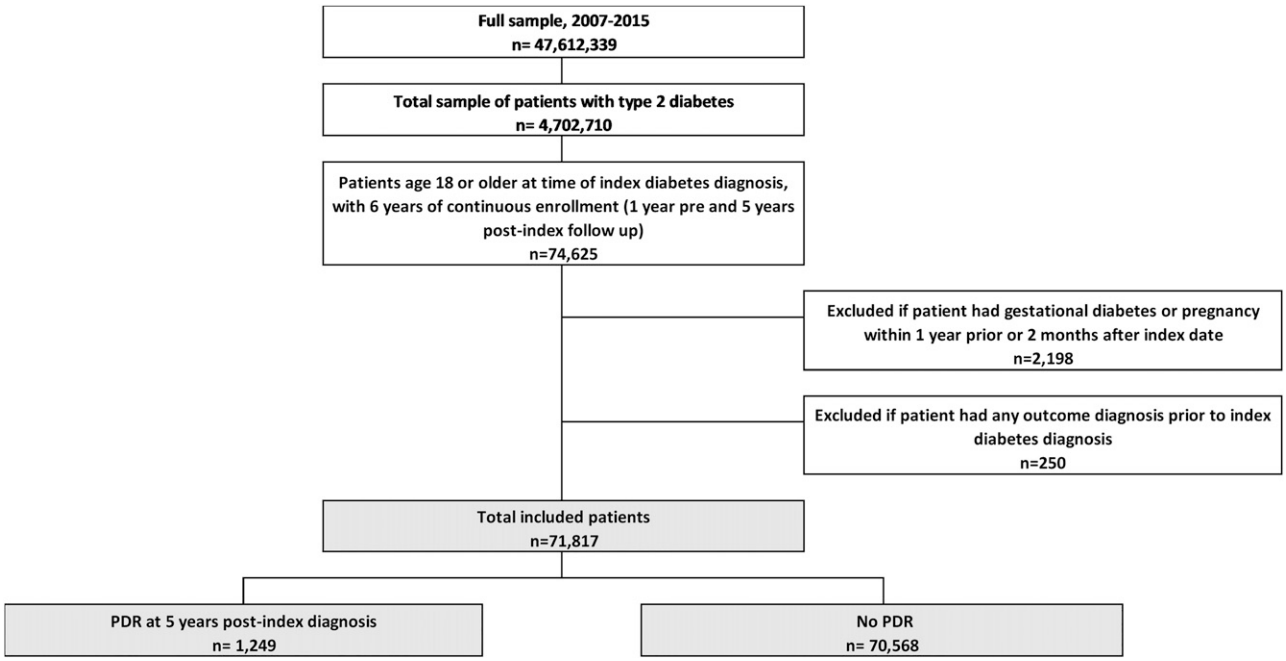

Figure 1—Five-year attrition diagram demonstrates how patients were included and excluded in the 5-year cohort. Patients were included if they had any of the following: one inpatient claim with a diagnosis of type 2 diabetes, one prescription fill for diabetes medication, or two outpatient claims with a diagnosis of type 2 diabetes within 180 days. Only patients with an index diagnosis prior to 1 October 2010 were included to allow for 5 years of follow-up.

Table 1—Descriptive statistics comparing patients with and without PDR at 5 years after the index type 2 diabetes diagnosis

Characteristics	PDR at 5 years	No PDR at 5 years	*P* value
Sample size, *n* (%)	1,249 (1.74)	70,568 (98.26)	
Age at diagnosis, mean (SD) years	61.6 (12.9)	60.6 (13.9)	**0.013**
Male, *n* (%)	680 (54.4)	35,757 (50.7)	**0.008**
Race/ethnicity, *n* (%)			
Non-Hispanic White	775 (62.1)	46,492 (65.9)	**0.005**
Black	176 (14.1)	8,909 (12.6)	0.12
Hispanic	220 (17.6)	10,287 (14.6)	**0.003**
Asian	38 (3.0)	2,610 (3.7)	0.22
Unknown	40 (3.2)	2,270 (3.2)	0.98
Education, *n* (%)			
High school diploma or less	451 (36.1)	23,773 (33.7)	0.07
Some college	657 (52.6)	38,274 (54.2)	0.25
4 year college degree or more	141 (11.3)	8,521 (12.1)	0.40
Income, *n* (%)			
<$40,000	335 (26.8)	17,819 (25.3)	0.21
$40,000–$49,000	96 (7.7)	5,969 (8.5)	0.33
$50,000–$99,000	419 (33.6)	22,439 (31.8)	0.19
$≥100,000	293 (23.5)	17,983 (25.5)	0.10
Unknown	106 (8.5)	6,358 (9.0)	0.52
Medicare, *n* (%)	522 (41.8)	29,413 (41.7)	0.94
Private insurance product, *n* (%)			
Exclusive provider organization	89 (7.1)	5,632 (8.0)	0.27
Health maintenance organization	498 (39.9)	24,463 (34.7)	**<0.001**
Indemnity	48 (3.8)	2,506 (3.6)	0.58
Other	148 (11.9)	9,147 (13.0)	0.25
Point of service	422 (33.8)	25,961 (36.8)	**0.029**
Preferred provider organization	44 (3.5)	2,859 (4.1)	0.35
Comorbidities, *n* (%)			
Hypertension	695 (55.6)	39,124 (55.5)	0.90
Dyslipidemia	312 (25.0)	18,078 (25.6)	0.61
DKA/HHS	15 (1.2)	275 (0.4)	**<0.001**
Renal disease	84 (6.7)	1,115 (1.6)	**<0.001**
Neurological disease	70 (5.6)	1,336 (1.9)	**<0.001**
Peripheral circulatory disorders	28 (2.2)	434 (0.6)	**<0.001**
Morbid obesity	124 (9.9)	9,005 (12.8)	**0.003**
Smoking	157 (12.6)	9,938 (14.1)	0.13
Other	63 (5.0)	939 (1.3)	**<0.001**
Insulin use, *n* (%)	502 (40.2)	9,445 (13.4)	**<0.001**
Max HbA_{1c}, mean % (SD), mmol/mol	8.7 (2.4), 72	7.6 (2.0), 60	**<0.001**

The bold *P* values indicate statistical significance ($P < 0.05$). DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state.

There were several independent risk factors for developing NVG at 5 years, including older age at diagnosis (55–64 years, OR 3.66, 95% CI 1.65–8.09; ≥75 years, OR 3.97, 95% CI 1.49–10.60), neurological disease (OR 2.90, 95% CI 1.40–5.98), and renal disease (OR 2.51, 95% CI 1.17–5.40). Additionally, insulin use (OR 2.30, 95% CI 1.45–3.67), Black race (OR 1.89, 95% CI 1.09–3.26), and Hispanic ethnicity (OR 1.85, 95% CI 1.11–3.10) were independent risk factors for the incidence of NVG at 5 years. Income >$100,000 was the lone protective factor (OR 0.44, 95% CI 0.20–0.97) for the development of NVG at 5 years. Max HbA_{1c} >9% or >75 mmol/mol (OR 3.21, 95% CI 1.51–6.84) was a significant risk factor at 2 years but was not statistically significant at 5 years (OR 1.99, 95% CI 0.85–4.66).

CONCLUSIONS

This study quantified the incidence of PDR, TRD, and NVG in the first 5 years after the diagnosis of type 2 diabetes in a large, nationwide sample. Additionally, it identified potential risk factors for the development of these severe manifestations of diabetic eye disease in the early period after the initial type 2 diabetes diagnosis. To our knowledge, this is the largest study to date tracking the development of PDR longitudinally from the initial diagnosis of type 2 diabetes, and it is the first study to determine the incidence and risk factors for the development of TRD and NVG within 5 years of the initial type 2 diabetes diagnosis.

Prior longitudinal, observational studies have been critical in developing our current understanding of the epidemiology of DR (Table 3). However, most of these studies were composed of racially homogenous patient populations (4–6, 14–17), with a relatively small number of patients newly diagnosed with diabetes

Table 2—Independent factors associated with the incidence of PDR, NVG, and TRD within the first 5 years after the index type 2 diabetes diagnosis

	PDR (*n* = 1,249 [1.74%])		TRD (*n* = 183 [0.25%])		NVG (*n* = 102 [0.14%])	
Characteristics	OR (95% CI)	*P* value†	OR (95% CI)	*P* value†	OR (95% CI)	*P* value†
Age at diagnosis (vs. 45–54), years						
18–34	0.46 (0.29–0.74)	0.001*				
55–64	1.25 (1.05–1.48)	0.012*			3.66 (1.65–8.09)	0.001*
65–74	1.62 (1.28–2.03)	<0.001*				
≥75	1.30 (1.00–1.68)	0.048*			3.97 (1.49–10.60)	0.006*
Race/ethnicity (vs. White)						
Black					1.89 (1.09–3.26)	0.023*
Hispanic					1.85 (1.11–3.10)	0.019*
Income >$100,000 (vs. $40,000–49,000)					0.44 (0.20–0.97)	0.041
Medicare	0.60 (0.70–0.76)	<0.001*				
Smoking	0.84 (0.70–1.00)	0.045*				
Renal disease	2.68 (2.09–3.42)	<0.001*	2.46 (1.30–4.69)	0.006*	2.51 (1.17–5.40)	0.018*
Neurological disease	1.62 (1.24–2.11)	<0.001*			2.90 (1.40–5.98)	0.004
Peripheral circulatory disorders	1.88 (1.25–2.83)	0.003*				
Morbid obesity	0.72 (0.59–0.87)	0.001*				
Insulin use	3.59 (3.16–4.08)	<0.001*	3.57 (2.57–4.96)	<0.001*	2.30 (1.45–3.67)	<0.001*
Max HbA_{1c} (vs. <6.5% or <48 mmol/mol)						
7.5% (58 mmol/mol)–9% (75 mmol/mol)	1.59 (1.22–2.08)	0.001*				
>9% (>75 mmol/mol)	2.10 (1.64–2.69)	<0.001*				

All variables were included in the regression analysis for each outcome, but only statistically significant results (i.e., independent factors) are displayed above for succinctness.†*P* values for all other covariates in the model, including sex, education level (4-year college vs. some college vs. high school or less), hypertension, dyslipidemia, and diabetic ketoacidosis/hyperosmolar hyperglycemic state were >0.05. *Also an independent factor at 2 years following diagnosis.

(5,7,14–17). Additionally, most were insufficiently powered to report the 5-year cumulative incidence of PDR for patients with newly diagnosed type 2 diabetes, instead reporting the incidence of any DR, progression of DR, or rates not stratified by duration of diabetes (7,15–17). When the four studies presenting 5-year PDR incidence after the type 2 diabetes diagnosis were combined, <15 total patients developed PDR (5,6,18,19), making it difficult to extrapolate the incidence and risk factors for PDR development within 5 years of the type 2 diabetes diagnosis. Additionally, two of the four studies took place prior to 1995 (14,19), and one of the studies took place in India (6), further highlighting the need for relevant and current studies in the U.S.

The current study also highlighted racial health disparities in the incidence of PDR (Table 3) compared with prior studies, which were generally racially homogeneous. For the White population, the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) reported PDR incidence rates of 3% for those not using insulin and 4% for those using insulin at 4–8 years following diagnosis (19). Our study found lower rates of early PDR in White patients, with just 1.6% of patients developing PDR at 5 years. In Black patients, 1.9% developed PDR at 5 years in our study. For comparison, the Barbados Eye Study found 0 of 43 patients had developed PDR at 4 years after diagnosis (14). Hispanic patients had the highest incidence of PDR at 5 years in our study, at 2.1%. The Los Angeles Latino Eye Study (LALES) also found high rates at 2.8% (5). Lastly, we found the lowest 5-year incidence of PDR among ethnic groups in Asian patients, at 1.4%. This was similar to the findings by Raman et al. (6), who also reported low rates at 0.8% at 4–8 years following the type 2 diabetes diagnosis among patients in Chennai, India. Asians comprise a diverse ethnic group; therefore, further studies are warranted to investigate differences in development of DR among subsets of the Asian population.

As all patients in our study were continuously insured and thus had presumable access to health care, our results may help stratify patients in the U.S. for their risk of early development of PDR based on ethnicity, with Hispanic and Black patients having higher rates of early progression to PDR. In addition to type 2 diabetes being >60% more prevalent in the Black and Hispanic populations compared with the White population (20), Black and Hispanic patients have been shown to have higher HbA_{1c} levels, higher blood pressure, and higher LDL cholesterol compared with White patients (21). These disparities in cardiovascular factors associated with diabetes suggest better glycemic control and management of comorbidities is crucial for this population, and taken together with our finding of a higher incidence of PDR in the early period after diagnosis, suggest a need for earlier and more widespread screening for vision-threatening complications of pathologic neovascularization among Black and Hispanic patients (22). While high rates of type 2 diabetes among Hispanics may be partly due to genetic/epigenetic factors (23), many health care disparities, such as in access to care, contribute to higher rates of progression of diabetic eye

Table 3—Five-year cumulative incidence of PDR as reported in previous population-based studies and the current study

Study population and location	Dates of enrollment	Follow-up (years)*	Age range (years)	Total, *N*	Patients with new DM2 diagnosis, *n*	Cumulative incidence of PDR within 5 years, *n* (%)
White						
U.S. (present study)	2007–2010	5	≥18	47,267	47,267	775 (1.6)
Blue Mountains, Australia	1992–1994	5	≥49	139	Did not report	Did not stratify results by duration of DM2
Melbourne, Australia	1992–1994	5	≥40	121	42	Did not stratify results by duration of DM2
San Luis Valley, CO	1984–1988	4.8	20–74	72	Did not report	Did not stratify results by duration of DM2
Southern WI	1980–1982	4	≥30	485 Insulin users	96†	4%‡
				502 Noninsulin users	225†	3%‡
Black						
U.S. (present study)	2007–2010	5	≥18	9,085	9,085	176 (1.9)
Nakuru, Kenya	2007–2008	6	≥50	156	89	Did not stratify results by duration of DM2
Barbados	1988–1992	4	40–84	407	43	0 (0)
Hispanic						
U.S. (present study)	2007–2010	5	≥18	10,507	10,507	220 (2.1)
Los Angeles, CA	2000–2003	4	≥40	775	36	1 (2.8)
San Luis Valley, CO	1984–1988	4.8	20–74	172	Did not report	Did not stratify results by duration of DM2
Asian						
U.S (present study)	2007–2010	5	≥18	2,648	2,648	38 (1.4)
Shanghai, China	2007	5	20–90	322	6	Did not stratify results by duration of DM2
Chennai, India	2003–2006	4	≥40	958	244†	2 (0.8)§

DM2, type 2 diabetes. *Certain studies have longer follow-up, but for the purposes of identifying the 5-year incidence of PDR, the data interval closest to this time period was chosen. For studies with variable follow-up, the median follow-up is reported. †These patients had 0–4 years of DM2 at baseline, making average duration >5 years at follow-up. ‡Exact *n* not provided. §Data reported were severe non-PDR or PDR.

disease (24). Some studies suggest Hispanic and Black individuals are less likely to use eye care services (2,13). The findings in this study highlight the importance of improving access to care for these populations as well as improving health care literacy in order to emphasize the importance of routine diabetic eye examinations and glycemic control to prevent vision-threatening complications of diabetes.

Aside from race/ethnicity, we found several independent risk factors for the development of PDR at 5 years, including insulin use (OR 3.59, 95% CI 3.16–4.08), max HbA_{1c} >9% or >75 mmol/mol (OR 2.10, 95% CI 1.64–2.69), older age at diagnosis (OR 1.62, 95% CI 1.28–2.03), comorbid renal disease (OR 2.68, 95% CI 2.09–3.42), peripheral circulatory disorders (OR 1.88, 95% CI 1.25–2.83), and neurological disease (OR 1.62, 95% CI 1.24–2.11). The presence of other microvascular comorbidities highlights two factors that may relate to more rapid development of PDR after the initial type 2 diabetes diagnosis: a delayed type 2 diabetes diagnosis and poor glycemic control. Unlike patients with type 1 diabetes, patients with type 2 diabetes often have asymptomatic hyperglycemia for years prior to diagnosis, leading to an average delay in diagnosis of 4–6 years following disease onset (25). With this knowledge, the risk factors identified in our study may represent those individuals not only with worse control of disease but who also had a longer duration of undiagnosed type 2 diabetes. This relationship between increasing patient age and potential longer duration of undiagnosed diabetes may represent a chronological or survival bias in our study. For example, patients diagnosed with diabetes at older ages may have had a longer duration of undiagnosed diabetes and may therefore be at a higher risk of complications such as PDR in the early period after diagnosis. Furthermore, while our sample did include a number of patients >65, we did not have data for patients who transitioned to Medicare not via Medicare Advantage. Thus, the older patients included in our sample may not be representative of all patients >65 years of age. Despite this, our results showing increased age is associated with higher rates of retinopathy are in line with prior landmark studies. The UK Prospective Diabetes Study (UKPDS) reported

the highest rates for progression of retinopathy in those diagnosed at age ≥58 (9), and Zhang et al. (2) found the highest prevalence of retinopathy in those >65 years.

Similar to retinopathy, renal disease, peripheral circulatory disorders, and neurological complications are signs of end-organ damage of diabetes. Patients with any of these risk factors early on in their disease course should be monitored closely for the impending development of PDR. For renal disease specifically, studies have found that microalbuminuria, one of the earliest signs of diabetic nephropathy, may be predictive of manifest DR (26). Furthermore, recent studies indicate that treating end-stage renal disease with initiating hemodialysis may also improve outcomes in DR (27).

Our study also noted multiple surprising factors that may be protective against the development of PDR, including younger age at diagnosis, Medicare insurance, morbid obesity, and smoking. The lower rates among patients in the 18–34 age-group suggests they were diagnosed closer to the onset of their type 2 diabetes, with less time to develop DR. Prior studies have found high rates of DR in patients diagnosed at younger ages (4), but this observation may be confounded by a longer duration of type 2 diabetes after the initial diagnosis. While the 18- to 34-year-old patients in our study had a fairly low risk for developing PDR during the early period after the initial type 2 diabetes diagnosis in our study, their lifetime risk of developing DR increases with type 2 diabetes disease duration. Patients with Medicare had lower rates of PDR in our study. Sloan et al. (28) also found an exceedingly low 6-year incidence of PDR (0.11–0.15%) among patients newly diagnosed with diabetes and Medicare insurance.

Morbid obesity was also protective in our study. Prior studies examining the association between PDR and obesity have demonstrated conflicting results, with some studies finding a protective effect (4,29–31), and others identifying obesity as a risk factor for DR (32,33). A recent meta-analysis found no association between BMI and DR (34). We chose to study morbid obesity rather than obesity, as prior studies have found greater sensitivity of ICD-9 coding for more advanced levels of obesity, because lower levels of obesity are often underreported (35). Lim et al. (31) attributed the protective effect of obesity to increased levels of C-reactive protein, which is proangiogenic and may improve retinal perfusion during preproliferative stages of DR. Unfortunately, our data set did not include metabolic markers other than HbA_{1c}.

Lastly, we found smoking to be slightly protective against the development of PDR. Early studies did not find a significant association between smoking and DR (36), although a recent meta-analysis suggested smoking was protective against PDR in patients with type 2 diabetes, postulating that lower systemic blood pressure in smokers may be responsible (37). While our study may support the conclusion of this recent meta-analysis, the association had only borderline significance (P = 0.045) despite our large sample size, suggesting any potential effect of smoking on development of PDR is likely small.

In addition to reporting the incidence and risk factors for early development of PDR, our study was unique in reporting the incidence of NVG and TRD at 5 years following the diagnosis with type 2 diabetes. We found extremely low rates of these complications, with just 1 in 400 patients developing TRD and 1 in 700 patients developing NVG at 5 years. TRD and NVG are both end-stage manifestations of DR, which take many years of uncontrolled hyperglycemia to develop. Developing TRD and NVG so soon after the type 2 diabetes diagnosis likely reflects many prior years of undiagnosed type 2 diabetes. Similar to the risk factors for PDR, we found patients using insulin and those with renal disease were at higher risk for developing TRD and NVG. Additionally, there were socioeconomic factors that were associated with risk for NVG, including Black race (OR 1.89, 95% CI 1.09–3.26) and Hispanic ethnicity (OR 1.85, 95% CI 1.11–3.10). Lastly, patients making >$100,000 were less likely to develop NVG (OR 0.44, 95% CI 0.20–0.97). As a result, efforts should be made to increase screening efforts in Black and Hispanic patients as well as patients with lower levels of income. Ultimately, the small numbers of patients developing TRD and NVG at 5 years likely limited the ability to detect other associations.

Our study has several limitations. It was retrospective in nature; therefore, our study did not have predetermined intervals for eye examinations or standardized grading of fundus photos at screening examinations. Rather, our study relied on diagnoses submitted via medical claims data to measure our end points. While this method is highly cost-effective and allows for rapid study of much larger groups of patients than are feasible with prospective studies, the quality of the data are potentially lower than that for rigorously controlled, prospective studies. For example, other than identifying the presence of certain medical comorbidities (e.g., hypertension, dyslipidemia, renal disease) by codified diagnoses, we were unable to compare discrete clinical observations to assess the relationship between good or poor control of comorbidities (e.g., blood pressure, estimated glomerular filtration rate, microalbuminuria) and development of PDR, TRD, or NVG. While these represent limitations to claims-based types of studies as compared with studies with medical record review, a prior validation study found good concordance between the diagnosis of DR in clinic notes and those detected in a claims-based analysis as a proof of concept of this research strategy (38). Additionally, we aimed to include only patients with incident diabetes, using the method of Borkar et al. (39) to augment diagnosis ICD-9 codes with National Drug Code prescription codes in the identification and exclusion of patients with established type 2 diabetes. We believe that by applying these criteria in our study, we dramatically reduced the risk of misclassifying patients as newly diagnosed, but the risk is likely not entirely eliminated. For instance, one example of a false positive would be a patient with established type 2 diabetes who did not see a physician or fill any prescriptions for diabetes medication in the year prior to the index diagnosis. This may result in an increase in the observed incidence of PDR and other neovascular sequelae of diabetic eye disease in our study. On the other hand, another example of a false positive would be a patient who was prescribed metformin off-label for prediabetes. This may have decreased the observed incidence of PDR and other neovascular sequelae in our study.

Another limitation is that while all other variables were available for 90–100% of patients, HbA_{1c} laboratory values were only available for 48% of

patients at 5 years. This is due to the claims-based nature of our study. For this reason, we chose to use maximum HbA_{1c}, because monitoring for trends in HbA_{1c} was not feasible. Despite this limitation, this still left >34,000 patients with HbA_{1c} data at 5 years. Additionally, given our patients were not mandated to follow-up at strict intervals, we may have potentially missed patients with undiagnosed PDR. This likely led to an underestimation of the incidence of PDR at 5 years in our study.

In summary, just under 2% of patients with type 2 diabetes developed PDR within 5 years of the diagnosis. Numerous risk factors for early development of PDR were identified in this study, which may highlight groups of patients with longer duration of undiagnosed diabetes or worse control of diabetes following diagnosis. This study underscores the importance of adhering to guideline-recommended fundus screening at the time of diagnosis of type 2 diabetes and at least yearly thereafter, especially for patients with a history of insulin use, renal disease, max HbA_{1c} >9% (>75 mmol/mol), peripheral circulatory disorders, neurological disease, and older age at diagnosis. Additionally, the higher incidence of PDR at 5 years among Black and Hispanic patients may suggest a delay in the diagnosis of type 2 diabetes in these populations. Several strategies to improve adherence to screening at-risk populations have previously demonstrated success, including patient education programs (40), teleretinal screening programs (41), and provider financial incentives (42). Our data highlight a need to target these and other efforts toward specific subsets of the population with type 2 diabetes who are at risk for developing vision loss from PDR and its sequelae.

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