Rates of Progression in Diabetic Retinopathy During Different Time Periods

A systematic review and meta-analysis

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OBJECTIVE — This meta-analysis reviews rates of progression of diabetic retinopathy to proliferative diabetic retinopathy (PDR) and/or severe visual loss (SVL) and temporal trends.

RESEARCH DESIGN AND METHODS — This systematic literature review and meta-analysis of prospective studies assesses progression of retinopathy among diabetic patients without treatment for retinopathy at baseline. Studies published between 1975 to February 2008 were identified. Outcomes of interest were rates of progression to PDR and/or SVL. Pooled baseline characteristics and outcome measures were summarized using weighted averages of counts and means. Baseline characteristics and outcomes were compared between two periods: 1975–1985 and 1986–2008.

RESULTS — A total of 28 studies comprising 27,120 diabetic patients (mean age 49.8 years) were included. After 4 years, pooled incidence rates for PDR and SVL were 11.0 and 7.2%, respectively. Rates were lower among participants in 1986–2008 than in 1975–1985. After 10 years, similar patterns were observed. Participants in 1986–2008 studies had lower proportions of PDR and non-PDR at all time points than participants in 1975–1985 studies.

CONCLUSIONS — Since 1985, diabetic patients have lower rates of progression to PDR and SVL. These findings may reflect an increased awareness of retinopathy risk factors; earlier identification and initiation of care for patients with retinopathy; and improved medical management of glucose, blood pressure, and serum lipids. Differences in baseline characteristics, particularly in the prevalence and severity of retinopathy, could also have contributed to these temporal differences.

Diabetes Care 32:2307–2313, 2009

Diabetes affects more than 170 million individuals worldwide (1,2), and diabetic retinopathy is the most frequent cause of visual impairment among working-age individuals (3,4). In the last 3 decades, a relative decline in rates of diabetic retinopathy has been suggested by some studies, (5–8) possibly reflecting improved patient and physician awareness, screening, and prevention, as well as better management of diabetes (9). In 1985, the Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated the effectiveness of laser photocoagulation (10,11). Systemic control of both hyperglycemia and hypertension was shown to be important in the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) in the 1990s (12,13). Findings from these trials, other studies, and clinical practice guidelines may have led to increased public awareness to diabetes risk factors and a shorter time from onset to diagnosis, potentially altering the rates of diabetic retinopathy progression (9,14).

Understanding the natural history of diabetic retinopathy is also important for estimating sample size for testing new interventions in clinical trials. Already, inadequate sample size estimations may have resulted in underpowered trials (15). Traditionally, progression rates from the ETDRS and the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) were used for sample size calculations (16–22). However, these studies were conducted almost 30 years ago. Contemporary estimates for diabetic retinopathy progression are clearly needed, some of which may, in part, be provided by more recent studies, such as the Daily-Dose Consensus Interferon and Ribavirin: Efficacy of Combined Therapy (DIRECT) trial (23,24).

In this systematic review and meta-analysis, we summarized the best available evidence to provide contemporary data on the clinical course of diabetic retinopathy and to examine potential differences in rates of diabetic retinopathy progression over time.

RESEARCH DESIGN AND METHODS

— We conducted a systematic review and meta-analysis on the clinical course of diabetic retinopathy focusing primarily on two outcomes: *1*) progression to proliferative diabetic retinopathy (PDR) and *2*) progression to severe visual loss (SVL), defined as log–minimum angle of resolution (MAR) visual acuity (VA) <1.0 (defined as VA <5/200 in some studies [18]).

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Received 30 March 2009 and accepted 23 August 2009.
DOI: 10.2337/dc09-0615
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Search strategy to identify relevant studies

All studies published in English, French, German, Spanish, Italian, and Portuguese assessing the progression of diabetic retinopathy among patients with diabetes were included. Eligible studies included patients without and with diabetic retinopathy who had not received any specific ocular treatment for diabetic retinopathy (including photocoagulation, vitrectomy, and intravitreal injections). Among included studies were the control arms of clinical trials for treatment-naïve patients assessed for diabetic retinopathy progression. We allowed study samples with up to 15% of patients in control groups to receive laser or other diabetic retinopathy–specific treatment.

We searched MEDLINE, Current Contents, and the Cochrane Library for published studies from January 1975 through 20 February 2008. Search terms used included: "diabetes mellitus OR diabet* OR diabetes OR insulin* OR diabetic retinopathy" and "diabetic maculopathy OR macular edema, cystoid OR edema OR macul* OR exudate OR laser coagulation OR photocoagulat* OR vitrect* OR intravitr* OR triamcinolone." The use of medical subject headings (MeSH) terms and text words (or equivalent) in the appropriate syntax of each database were applied. We also reviewed PubMed for the 6 months prior to the search date (20 August 2007 through 20 February 2008) with no limits and Current Contents for the year prior to the search date (20 February 2007 through 20 February 2008). Additionally, manual reference checks were performed of bibliographies of articles and reviews published within the last 5 years (2004–2008).

Selection of studies

We selected prospective interventional or observational studies reporting the progression of diabetic retinopathy to PDR and/or progression to SVL at 4-, 5-, and 10-year time periods. Inclusion criteria (online-only appendix Table S1, available at http://care.diabetesjournals.org/cgi/content/full/dc09-0615/DC1) were patients not yet treated for diabetic retinopathy (i.e., treatment naïve) followed for at least 1 year, diabetic retinopathy assessed using retinal photography and/or fluorescein angiography, and categorized using the modified ETDRSDR severity grades: grade 1 (no diabetic retinopathy), grades 2 and 3 (nonproliferative diabetic retinopathy [NPDR]), and grade 4 (PDR).

In the initial screening, abstracts were reviewed by a single reviewer for obvious exclusion criteria. Full publications were retrieved for all citations accepted at the initial screening. The complete studies were then rescreened and reviewed by two investigators based on prospective protocol, with discrepancies resolved by consulting a third investigator. Studies were assigned a level of evidence using criteria from the Centre for Evidence-based Medicine in Oxford, U.K. (CEBM).

Data collection and definition

The study, patient, and treatment data were extracted. If necessary, contact and clarification was made with authors of accepted studies for specific data and analyses. VA assessments for baseline characteristics were reported as best-corrected distance VA. When reported, logMAR VA was preferentially extracted. Conversions between logMAR and Snellen values were performed using previously reported methods (The MNREAD Acuity Chart), with logMAR 0.0 corresponding to 20/20 Snellen and 1.0 corresponding to 20/200 Snellen. LogMAR values were then categorized into 0.0, >0.00–0.48, >0.48–1.0, and >1.0.

Data analysis

Outcome measures were estimated from the pooled data. Studies were stratified into two time periods (defined by start date of patient accrual)—1975–1985 and 1986–2008—with the 1985 cutoff selected to coincide with publication of ETDRS (19). Pooled baseline characteristics and outcome measures were summarized using weighted averages of counts, proportions, and means. Weighted average proportions were reported as percentages, whereas weighted means were reported with ranges. The number of patients enrolled was used to calculate study and patient demographics. For some studies, the number of eyes was used as the denomination; however, when only patient numbers were reported, it was assumed that only one eye per patient was studied. Meta-analyses were performed to pool within-study outcome measures. For efficacy outcomes of interest (PDR and SVL), meta-analyses for proportions with 95% CIs were performed across the studies using both fixed-effects (25,26) and restricted-maximum likelihood random-effects (27,28) models. Heterogeneity between studies was measured using the Cochran Q statistic for heterogeneity. For continuous outcomes, meta-analyses for means with 95% CIs were performed. To account for variations in baseline severity, analyses were stratified by baseline diabetic retinopathy status (no diabetic retinopathy and any diabetic retinopathy). Computations were performed using SPSS V14.0.

RESULTS

Study characteristics

Figure 1 shows the search yielded 3,130 abstracts screened for eligibility, of which 2,807 citations were rejected based on obvious exclusion criteria. Full articles of 323 citations were retrieved, and 76 met all eligibility criteria; 28 were primary studies, and 48 were related publications (same patient populations contributing additional data, e.g., outcome data at different time points).

Supplemental Tables S2 and S3 list study-level characteristics of the 28 included studies. Of these, 14 were conducted during 1975–1985 and the rest during 1985–2008. Among the accepted studies, different methods were used to ascertain and classify diabetic retinopathy, although many used the ETDRS severity scale (29–31). Definitions for vision loss also varied, with studies reporting VA change as VA ≥2 lines lost (or 10 ETDRS letters lost) or VA ≥3 lines lost (or 15 ETDRS letters lost and doubling of the visual angle).

Patient characteristics and reporting patterns

The 28 studies enrolled 27,120 diabetic patients assessed for diabetic retinopathy at the 4-, 5-, and 10-year time points. The mean patient age was 49 years, 46% were female, 48% had type 2 diabetes, and the mean diabetes duration was 11 years; 55% had no diabetic retinopathy at baseline, whereas 59% had baseline logMAR VA ≤0.0. Participants in 1986–2008 had similar sex distribution, age range, and diabetes duration as participants in 1975–1985; however, studies in the first time period enrolled more patients with type 1 diabetes (supplemental Table S4).

Progression to PDR and SVL

Nearly 60% of included studies reported progression to PDR, and 35% reported progression to SVL. In contrast, only 11% reported two-step and 4% three-step progression of diabetic reti-

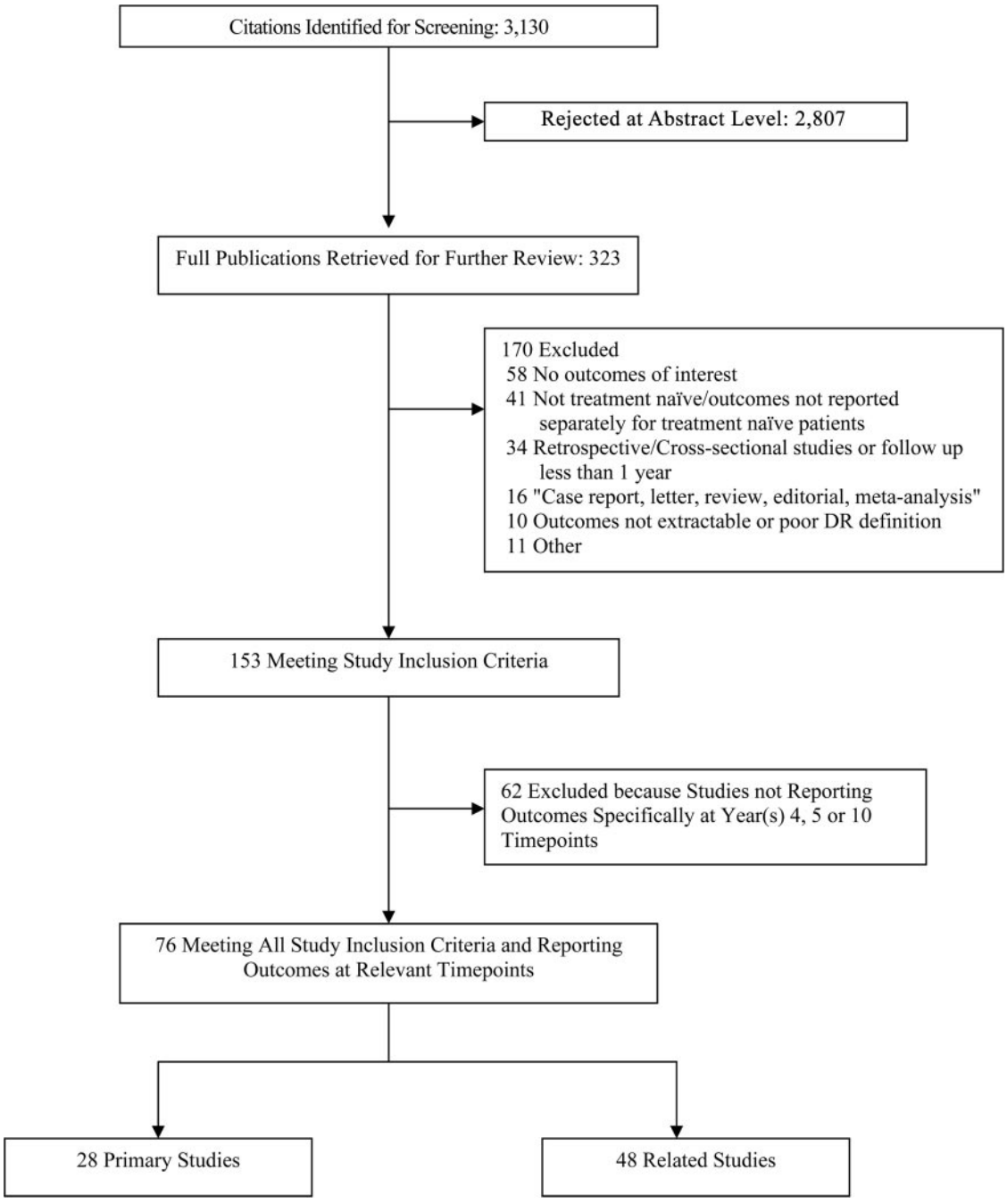

Figure 1—*Selection of studies for systematic review.*

nopathy, whereas the loss of two and three lines was reported in 16 and 9% of the included studies, respectively. Table 1 shows the incidence of each end point at the 4-, 5-, and 10-year time points, both overall and within each study period.

After 4 years, the pooled incidence of PDR and SVL was 11.0 and 7.2%, respectively. Table 2 shows the 4-, 5-, and 10-year incidence of PDR and SVL stratified for time period. For studies reporting outcomes after 4 years, 19.5% of patients in 1975–1985 developed PDR compared with only 2.6% in 1986–2008. For SVL, 9.7% of patients in 1975–1985 developed SVL compared with 3.2% in 1986–2008. Similar trends were seen for 5- and 10-year outcomes. For example, for studies reporting outcomes after 5 years, 18.0% of patients in 1975–1985 developed PDR versus 6.4% in 1986–2008; for SVL, corresponding rates were 13.7 versus 3.6%, respectively. Of studies reporting outcomes at 10 years, rates for PDR were 11.5% in 1975–1985 versus 6.6% in 1986–2008; for SVL, corresponding rates were 6.0 versus 2.6%, respectively.

Table 3 shows that when stratified by baseline diabetic retinopathy status, for participants without diabetic retinopathy at baseline, PDR developed in 6.3% during 1975–1985 (two studies) compared with 2.6% during 1986–2008 (five studies); similarly, 2.0% developed SVL in 1975–1985 compared with none in 1986–2008. For participants with diabetic retinopathy at baseline, PDR developed in 39.7% of patients in 1975–1985,

Table 1—*Incidence rates of outcomes after 4, 5, and 10 years*

	4 years			5 years			10 years		
	κ	%	*n*	κ	%	*n*	κ	%	*n*
Incidence									
PDR	9	8.7	4,352	12	15.6	7,204	5	17.6	2,129
SVL	5	10.0	3,271	6	7.4	9,468	6	2.5	9,689
DME	5	24.0	2074	5	12.0	2,430	4	18.6	2,173
Photocoagulation	2	8.2	2,780	6	7.8	5,948	3	9.7	4,091
Retinopathy									
≥2-step progression	2	33.2	1,772	3	45.1	2,342	1	67.1	1,616
≥3-step progression	—	—	—	—	—	—	—	—	—
VA progression									
≥2 lines lost	1	2.8	174	3	18.1	623	—	—	—
≥3 lines lost	1	7.9	1,846	—	—	—	1	18.5	1,846

Data are κ (number of studies), percent (proportion of patients with event at each time point), or *n* (total number of patients at risk at each time point). Diabetic macular edema.

whereas no studies reported progression to PDR during 1986–2008; 17.5% progressed to SVL during 1975–1985 (two studies), whereas 5.4% progressed to SVL in 1986–2008 (one study).

CONCLUSIONS — This systematic review and meta-analysis provides estimates of the incidence of PDR and development of SVL in patients who were untreated for diabetic retinopathy at baseline. Our analyses show that the overall incidence of PDR and SVL observed in studies after 1985 (e.g., 2.6% for PDR and 3.2% for SVL at 4 years) were substantially lower than rates observed before 1985 (19.5% for PDR and 9.7% for SVL at 4 years). These findings support our a priori hypothesis that contemporary rates of progression to PDR and SVL are substantially lower and may reflect improvements in the overall care and management of diabetes and associated risk factors (e.g., hyperglycemia and hypertension) over time, together with earlier identification of type 2 diabetes.

In terms of the principal risk factors for diabetic retinopathy, studies in the two time periods had relatively similar baseline duration of diabetes: 11.1 years for 1975–1985 versus 11.7 years for 1986–2008. However, in the later period, substantially greater proportion of participants had type 1 diabetes (71.1 versus 48.3%), which could partly explain lower rates of baseline NPDR and PDR. Studies of type 2 diabetic patients report only a nominal duration of diabetes because its onset is gradual. Thus, an earlier diagnosis of type 2 diabetes during 1986–2008 could partly explain lower baseline diabetic retinopathy during this period. Differences in baseline diabetic retinopathy severity between the two time periods (less severe after 1985) could also explain lower rates of progression to PDR and/or SVL after 1985.

Our review identified significant limitations in the literature. First, the observed differences in progression rates between the two periods were not independent of the distribution of the severity of diabetic retinopathy at baseline. Studies conducted earlier had larger proportions of more advanced diabetic retinopathy at baseline, and progression rates between the two time periods could not be formally compared without appropriate adjustments. However, there were insufficient studies to enable regression-based adjustments for baseline severity. Thus, we chose to stratify by baseline diabetic retinopathy severity, but even after stratification, the distribution of baseline diabetic retinopathy severity was not sufficiently balanced. Second, outcome reporting patterns varied. Baseline VA and progression of vision-loss measurements by the loss of two and three lines (or equivalent) or diabetic retinopathy progression by two- or three-step progression (or equivalent) were reported by only a few studies. The failure to report progression of visual loss limited the ability to explore the impact of diabetic retinopathy progression before the development of PDR or SVL. This may be important because current recommendations for diabetic retinopathy clinical trials emphasize the universal use of three-step progression of diabetic retinopathy as a disease progression marker at the 3-year time point (32). A third issue was the varying quality of diabetic retinopathy studies. We included only studies of treatment-naïve patients in which outcomes were reported separately by diabetic retinopathy severity at baseline and where diabetic retinopathy assessment involved retinal photography and/or fluorescein angiography. Although this improved comparability of studies, it limited the pool of data for analysis. Additionally, we included both interventional and prospective observational studies covering a wide range of study designs, sample sizes, treatment settings, and study inclusion criteria. Although these variations could be of concern, the broader inclusion reflected the diversity of diabetic retinopathy studies in the literature. Finally, there were insufficient data on ethnic composition or socioeconomic status to determine whether rates varied by these factors.

Because the availability of numerous treatment modalities would make a new prospective study of untreated patients impossible, our study provides the best available evidence from the literature, even with the limitation that exact underlying causes for the temporal differences cannot be fully explained. We identify several areas for future research. First, based on baseline diabetic retinopathy severity, researchers should consider contemporary rates of progression to PDR and/or SVL in estimating sample sizes for clinical trials. Second, future studies should report

Table 2—*Baseline distributions and 4-, 5-, and 10-year rates for PDF and SVL by time periods*

	1975–1985				1986–2008			
	κ	*n/N*	Meta-analyzed (%)	Mean (95%CI)	κ	*n/N*	Meta-analyzed (%)	Mean (95%CI)
Baseline distributions, 4 years								
GHb (%)	1	2,366		11.7 (10.2–13.2)	4	795		8.4 (7.3–9.5)
Systolic blood pressure (mmHg)	1	2,366		136.0 (114.4–157.6)	3	760		139.2 (127.4–151.1)
Diastolic blood pressure (mmHg)	1	2,366		79.0 (78.6–79.5)	2	600		78.8 (73.1–84.5)
Retinopathy level (%)								
No retinopathy	2	1,447/3,319	43.6		6	882/1,324	66.6	
NPDR	4	1,693/3,604	47.0		6	271/1,324	20.5	
PDR	4	460/3,604	12.8		6	42/1,324	3.2	
Presence of DME (%)	2	602/1953	30.8		3	78/775	10.1	
5-year incidence 4-year incidence								
PDR (%)	4	353/3,214		19.5 (2.4–36.6)*	5	26/1,138		2.6 (0.2–5.0)*
SVL (%)	3	320/2,967		9.7 (0.0–21.9)*	2	8/304		3.2 (0.0–9.2)*
Baseline distributions, 5 years								
GHb (%)	3	7,295		9.3 (7.8–10.7)	2	2,245		8.0 (7.9–8.1)
Systolic blood pressure (mmHg)	1	133		150.0 (146.9–153.1)	2	171		136.1 (121.2–151.0)
Diastolic blood pressure (mmHg)	1	133		93.0 (91.3–94.7)	2	171		81.1 (78.1–84.1)
Retinopathy level (%)								
No retinopathy	5	3,521/7,491	47.0		6	1,731/2,651		65.3
NPDR	6	3,387/7,702	44.0		6	762/2,651		28.7
PDR	6	787/7,702	10.2		6	138/2,651	5.2	
Presence of DME (%)	3	3,134/5,664	55.3		4	222/2,516	8.8	
5-year incidence								
PDR (%)	6	1,046/5,153		18.0 (3.5–32.5)*	6	78/2051		6.4 (0.4, 12.4)*
SVL (%)	4	689/7,595		13.7 (0.9–26.5)*	2	14/1,873		3.60 (0.0, 11.4)*
Baseline distributions, 10 years								
GHb (%)	4	9,777		9.3 (7.6–10.9)	3	796		8.2 (7.7–8.7)
Systolic blood pressure (mmHg)	5	9,910		139.0 (129.3–148.7)	2	684		138.3 (127.3–149.2)
Diastolic blood pressure (mmHg)	5	9,910		83.8 (78.6, 88.9)	2	684		81.5 (78.2, 84.8)]
Retinopathy level (%)								
No retinopathy	6	5,733/9,939	57.7		3	526/796	66.1	
NPDR	5	3,280/9,910	33.1		3	141/796	17.7	
PDR	4	732/5,981	12.2		2	0/408	0.0	
Presence of DME (%)	1	0/29	0.0		3	0/796	0.0	
10-year incidence								
PDR (%)	3	357/1,729		11.5 (0.0–25.7)*	2	17/400		6.6 (0.0, 18.3)*
SVL (%)	4	232/9,205		6.0 (0.9–11.1)*	2	11/484		2.6 (0.0–7.1)*

Data are κ (number of studies), *n* (total number of patients at risk at each time point), percent, or mean (95% CI). *Heterogeneity by Cochran Q: $P < 0.05$. DME, diabetic macular edema.

common nomenclature for diabetic retinopathy (i.e., ETDRS scales) and VA outcomes (e.g., logMAR VA categories or number of logMAR lines) so that progression rates can be estimated consistently. Third, there is a need for the publication of data on treatment-naïve patients with diabetic retinopathy from larger population-based studies.

In conclusion, our systematic review and meta-analysis in treatment-naïve patients with diabetes covering 1975–2008 show that contemporary rates of PDR and/or SVL are substantially lower than rates observed before 1985. Differences are explained, in part, by baseline differences in diabetic retinopathy severity, A1C, and possibly blood pressure levels. Limitations from the available literature data prevented in-depth exploration as to exact causes for these differences. Our analysis supports some studies that suggest changing patterns of care for diabetes, including earlier identification and initiation of care along with attention to appropriate management of diabetic

Table 3—*Baseline distributions and 4-year incidence of PDF and SVL by time periods and baseline retinopathy status*

	1975–1985				1986–2008			
	κ	*n/N*	Meta-analyzed (%)	Mean (95%CI)	κ	*n/N*	Meta-analyzed (%)	Mean (95%CI)
Baseline distributions, no retinopathy at baseline								
GHb (%)	1	2,366		11.7 (10.2–13.2)	3	635		9.2 (8.3–10.1)
Systolic blood pressure (mmHg)	1	2,366		136.0 (114.4–157.6)	2	600		131.0 (113.4–148.7)
Diastolic blood pressure (mmHg)		2,366		79.0 (78.6–79.5)	2	600		78.8 (73.1–84.5)
Retinopathy level (%)								
No retinopathy	2	1,447/3,319	43.6		5	882/1,164	75.8	
NPDR	2	1,529/3,319	46.1		5	237/1,164	20.4	
PDR	2	339/3,319	10.2		5	33/1,164	2.8	
Presence of DME (%)	—	—		—	3	78/775	10.1	
4-year incidence								
PDR (%)	2	142/2,570		6.3 (1.6–10.9)	5	26/1,138		2.6 (0.2–5.0)
SVL (%)	1	41/1,823		2.0 (0.0–3.9)	1	0/174		0.0 (0.0–0.8)
Baseline distributions, any retinopathy at baseline								
GHb (%)	—	—		—	1	160		7.1 (6.8–7.5)
Systolic blood pressure (mmHg)	—	—		—	1	160		147.0 (144.2–149.8)
Diastolic blood pressure (mmHg)	—	—		—	—	—		—
Retinopathy level (%)								
No retinopathy	—	—		—	1	0/160	0.0	
NPDR	2	164/285	57.5		1	34/160	21.3	
PDR	2	121/285	42.5		1	9/160	5.6	
Presence of DME (%)	2	602/1953	30.8		—	—		—
4-year incidence								
PDR (%)	2	211/644		39.7 (21.2–58.3)	—	—		—
SVL (%)	2	279/1,144		17.5 (0.0–38.1)	1	8/130		5.4 (0.0–15.1)

Data are κ (number of studies), *n* (total number of patients at risk at each time point), percent, or mean (95% CI).

retinopathy, may have led to substantially lower rates of diabetic retinopathy progression and incident visual loss over time (33,34).

Acknowledgments— The research was supported by Pfizer. T.Y.W., R.K., M.L., H.F., and P.M. were paid consultants to Pfizer, and M.M., M.H.-M., and G.R. were employees of United BioSource Corporation (UBC) at the time the research was conducted and the article was developed. UBC is a consultancy whose activities on the project were funded by Pfizer. B.W. and A.P. are employees of Pfizer. T.Y.W. has been on advisory boards for Pfizer, Allergan, and Novartis and has received honoraria and travel and accommodation payments from them. He has also received research support from Pfizer. He has also been an investigator on clinical trials sponsored by them and has received payments to support the conduct of these trials. M.M. is employed by UBC. He has also not been an investigator on clinical trials sponsored by them and has not received payments to support the conduct of any trials. R.K. has been on advisory boards for AstraZeneca, Eli Lilly, Novartis, and Pfizer and has received honoraria and travel and accommodation payments from them. As of 1 January 2007, the employer of M.L., the Glostrup Hospital, but not M.L. receives funding from Eli Lilly, Novartis, Carl Zeiss Meditec, Alcon, and Pfizer for contractual projects by the Department of Ophthalmology involving the effort of M.L. Under Danish government policy, support for the costs of research, administered by the institution, does not constitute a conflict of interest. Before 1 January 2007, M.L. had personally administered contractual and financial relationships with the above-mentioned companies. H.F. currently serves on the Diabetic Retinopathy Clinical Research network Data and Safety Monitoring Committee (DSMC), Regeneron DSMC, and Optimedica advisory board and is a paid consultant to Pfizer, Alcon, Allergan, Ista, Eyetech, and Genentech. G.R. is employed by UBC. She has also not been an investigator on clinical trials sponsored by them and has not received payments to support the conduct of any trials. M.H.-M. is employed by UBC. She has also not been an investigator on clinical trials sponsored by them and has not received payments to support the conduct of any trials. B.W. is currently a paid employee of Pfizer. Prior to her employment at Pfizer, she had been a paid consultant and investigator on clinical trials for Allergan. A.P. is a paid employee of Pfizer. P.M. has been on advisory boards for Novartis, Pfizer, Allergan, and Solvay and has received honoraria and travel and accommodation payments from them. He has also been an investigator on clinical trials sponsored by these companies, as well as Eli Lilly, and has received payments to support the conduct of these trials. No other potential conflicts of interest relevant to this article were reported. The sponsor participated in the study design, data analysis and interpretation, and preparation and review of the manuscript.

T.Y.W. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Assistance with the literature screening, database development, data retrieval, analysis, and manuscript development was provided by A. Barsdorf, MA, of Pfizer and A. Rountree, BA, and S. Sharma, BA, of UBC and was funded by Pfizer.

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