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 and 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.

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Rates of Progression in Diabetic Retinopathy During Different Time Periods

A systematic review and meta-analysis

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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 diabetes* OR diabetes retinopathy*” and “diabetic maculopathy OR macular edema, cystoid OR edema OR macul* OR exudate OR laser coagulation OR photocoagulat* OR vitrec* OR intravit* 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 ETDRS 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 re-screened 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, >0.0.0–0.48, >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-
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,
Rates of progression in diabetic retinopathy

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

| Incidence          | 4 years |           | 5 years |           | 10 years |
|--------------------|---------|-----------|---------|-----------|----------|
|                     | κ       | %         | n       | κ         | %        | n        |
| PDR                | 9       | 8.7       | 4,352   | 12        | 15.6     | 7,204    |
| SVL                | 5       | 10.0      | 3,271   | 6         | 7.4      | 9,468    |
| DME                | 5       | 24.0      | 2074    | 5         | 12.0     | 2,430    |
| Photocoagulation   | 2       | 8.2       | 2,780   | 6         | 7.8      | 5,948    |
| Retinopathy        |         |           |         |           |          |          |
| ≥2-step progression| 2       | 33.2      | 1,772   | 3         | 45.1     | 2,342    |
| ≥3-step progression| —       | —         | —       | —         | —        | —        |
| VA progression     |         |           |         |           |          |          |
| ≥2 lines lost      | 1       | 2.8       | 174     | 3         | 18.1     | 623      |
| ≥3 lines lost      | 1       | 7.9       | 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 latter 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       |
|-------------------------|----------------|----------------|
|                         | n/N Meta-analyzed (%) Mean (95% CI) | 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 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 3.6 (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  232/2,205 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-naive patients with diabetic retinopathy from larger population-based studies.

In conclusion, our systematic review and meta-analysis in treatment-naive 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 care.diabetesjournals.org
Rates of progression in diabetic retinopathy

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

|                        | 1975–1985 |                        | 1986–2008 |
|------------------------|-----------|------------------------|-----------|
|                        | \( \kappa \) | \( n/N \) | Meta-analyzed (\%) | Mean (95% CI) | \( \kappa \) | \( n/N \) | 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 | 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 | 261/1,138 | 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 (%) | | | | | | | |
| Systolic blood pressure (mmHg) | | | | | | | |
| Diastolic blood pressure (mmHg) | | | | | | | |
| Retinopathy level (%) | | | | | | | |
| No retinopathy | | | | | | | |
| NPDR | 2 | 164/285 | 57.5 | 1 | 54/160 | 34.0 |
| 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 \( \kappa \) (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).

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