Diabetologia (2001) 44: 2203–2209

Diabetologia

Risk factors for progression to proliferative diabetic retinopathy in the EURODIAB Prospective Complications Study

M. Porta[1], A-K. Sjoelie[2], N. Chaturvedi[3], L. Stevens[4], R. Rottiers[5], M. Veglio[6], J. H. Fuller[4] and the EURODIAB Prospective Complications Study Group

[1] Diabetic Retinopathy Centre, Department of Internal Medicine, University of Turin, Turin, Italy
[2] Department of Ophthalmology, Odense University Hospital, Denmark
[3] Department of Epidemiology and Public Health, Imperial College of Medicine at St. Mary's, London, UK
[4] EURODIAB Department of Epidemiology and Public Health, University College London, UK
[5] Department of Endocrinology, University Hospital, Gent, Belgium
[6] Waldensian Hospital, Turin, Italy

Abstract

Aims/hypothesis. Proliferative diabetic retinopathy (PDR), a leading cause of blindness, cannot be totally prevented by optimizing metabolic and blood pressure control and responds to no specific treatment other than partially destructive retinal photocoagulation. Recognizing risk factors using large-scale epidemiological studies could help identify targets for treatment. The EURODIAB Prospective Complications Study (PCS) includes the largest cohort so far of patients with Type I (insulin-dependent) diabetes mellitus.
Methods. Baseline data were collected between 1989 and 1991 on 3250 patients who were recalled for follow-up. Physical examination, biochemical tests and assessment of complications were done on both occasions. In particular, 1249 patients had retinal photographs taken both basally and after an average of 7.3 years.
Results. Proliferative retinopathy had developed in 157 patients (cumulative incidence 17.3/1000 patient-years; 95 %-CI: 13.6–21.1). HbA_{1c} (standardized regression estimate – SRE = 3.03, CI 2.49–3.69), diabetes duration (1.71, 1.42–2.06), age at diagnosis < 12 (1.66, 1.11–2.50), diastolic blood pressure less than or equal to 83 (1.50, 1.03–2.20) and waist-to-hip ratio (1.50, 1.03–2.20) were all independent predictors for progression to PDR when entered simultaneously into a logistic regression model. Including retinopathy at baseline maintained the effects of metabolic control and pre-pubertal onset only. Including the albumin excretion rate maintained the effect of control but reduced SRE for pre-pubertal onset to 1.49 (0.94–2.33). There was no evidence for a threshold effect for HbA_{1c} concentrations at baseline and progression to proliferative retinopathy.
Conclusion/hypothesis. Metabolic control and duration of diabetes are strong indicators of progression to proliferative retinopathy. Onset of diabetes before puberty could be an additional independent risk factor. [Diabetologia (2001) 44: 2203–2209]

Keywords Diabetes, diabetic retinopathy, risk factors, glycaemic control, population studies, proliferative retinopathy, incidence, puberty, threshold effect.

Received: 17 May 2001 and in revised form: 16 August 2001

Corresponding author: M. Porta, Diabetic Retinopathy Centre, Department of Internal Medicine, University of Turin, Corso AM Dogliotti 14, 10126 Turin, Italy,
e-mail: massimo.porta@unito.it
Abbreviations: DCCT, Diabetes control and complications trial; DR, diabetic retinopathy; PCS, prospective complications study; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; WESDR, Wisconsin epidemiology study of diabetic retinopathy

Diabetic retinopathy (DR) remains a leading cause of loss of vision in Europe and North America [1–5] but the underlying pathogenesis is still not known, although a number of risk factors have been identified in the course of observation [6, 7] and intervention studies [8]. In addition, despite improvements in metabolic control, proliferative DR (PDR) continues to occur, making epidemiological approaches to the problem useful. The EURODIAB Prospective Complications Study (PCS) investigated the largest cohort of patients with Type I (insulin-dependent) diabetes mellitus so far and was specifically designed to collect

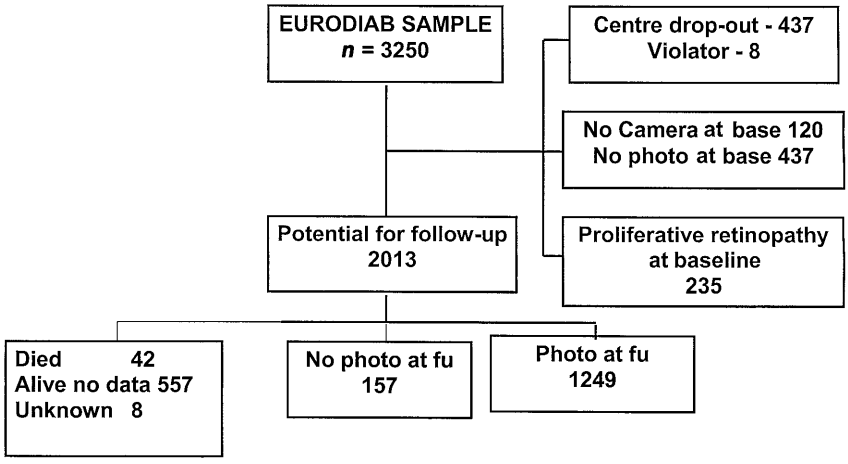

Fig. 1. Flow chart of sample used for analysis of progression to proliferative diabetic retinopathy in the EURODIAB PCS Study

data on potentially modifiable risk factors for retinopathy. This paper reports on the results of a 7.3 year follow-up of patients with Type I diabetes from different countries in Europe [7].

Materials and methods

We collected baseline data between 1989 and 1991 on 3250 patients with Type I diabetes. These were defined as patients diagnosed before 36 years of age and needing insulin therapy within a year of onset. The patients were recruited from 31 centres in 16 different countries and were between 15 and 60 years of age. Sampling was stratified according to age, sex and duration of disease, so that representation of the different subgroups would be similar. At the time of investigation, microvascular and macrovascular complications had been assessed, along with physical examination and biochemical variables, according to a standardized protocol [7].

The patients were recalled for follow-up assessment 6–8 years later. Data on mortality were also collected. Four centres declined to participate and, in those who continued the study, a number of patients either refused to be re-examined or could not be traced. For these patients, morbidity forms were completed from available hospital case notes or other sources of clinical data, detailing the presence or absence of severe complications at their most recent visit.

Of the original cohort of 3250 patients, 445 had either been recruited in centres that did not take part in the prospective study (437) or did not fulfil the inclusion criteria (8), 557 had no retinal photographs taken at baseline and 235 already had PDR to start with (Fig. 1). In total, 2013 patients were potentially available for prospective evaluation but 607 had either died or been lost to follow-up in participating centres, and only in 1249 was retinal photography done in the follow up study. The latter is the sample to which the analysis refers.

Physical examination, biochemical tests and assessment of complications were carried out with the same protocol and questionnaire used at baseline [7]. Local HbA_{1c} measurements for the previous 2 years (a maximum of eight) were recorded. Height, weight and waist-to-hip ratio were measured as well as resting blood pressure.

Retinal photographs were taken according to the EURODIAB protocol [9] which included $2 \cdot 45$–50° fields, macular-temporal and disc-nasal for each eye, and a test of visual acuity using Snellen or similar visual acuity charts. Slides were developed locally and graded by the Retinopathy Grading Centre, by graders who had no information about the patients, except their identity number. The same grading centre was used for both baseline and follow-up investigations.

Mild, moderate and severe non-proliferative retinopathy were defined as previously described [9]. Progression to proliferative diabetic retinopathy (PDR) was defined as appearance of new vessels or fibrous tissue or both on the optic disc or elsewhere and/or panretinal photocoagulation (PRP) done in the follow-up period, in patients who did not have PDR or PRP scars at baseline.

Baseline blood samples, from fasting patients where possible, had been sent to central laboratories for analysis. Measurements included total cholesterol, HDL cholesterol and triglyceride [10–12]. LDL cholesterol was calculated according to the Friedewald formula [13]. The reference range for the HbA_{1c} assay was 2.9–4.8 % [14]. Where possible, a sample was also assayed locally for HbA_{1c}. The fibrinogen and von Willebrand Factor (vWF) were measured according to standard methods [15]. The γ-glutamyltransferase concentrations were determined in plasma by a kinetic colorimetric method with L-gamma-3-carboxyl-4-nitranilide and glycylglycine as substrates (Roche Uni-Kit 2) using the Cobas-Bio centrifugal analyser. An aliquot of urine from one 24-h collection was sent to London for analysis of urinary albumin excretion [16].

The presence of cardiovascular disease at baseline was defined as a past history of a cardiovascular event, including myocardial infarction, angina, coronary artery bypass graft or stroke, or major Q waves on ECG (Minnesota codes 1.1 or 1.2) [17].

Statistical analysis. Linear regression was done by centre to compare the results of HbA_{1c} measured locally and centrally at the same time, both from the baseline. This provided a formula to convert locally measured HbA_{1c} to the centralized assay in each centre. An average of all local HbA_{1c} which had been measured for each individual, was calculated and converted to the central measure, as described above, in order to ensure that comparisons could be made of local measurements across centres. To allow comparisons with the DCCT, a formula was derived from a linear regression plot of measures of HbA_{1c} arrived at using the London laboratory against those ar-

Table 1. Comparison of baseline data for patients who did and did not attend a follow-up examination for retinal photographs (means or % ± SEM (25th and 75th percentiles for log-transformed data/ or where medians are presented))

Risk factor	Retinal photograph at follow-up		
	No	Yes	*p* value
Number	764	1249	
Age (years)	32 ± 10	31 ± 9	0.5
Duration (years)	13 ± 9	13 ± 8	0.3
Central HbA_{1c} (%)	6.8 ± 1.9	6.5 ± 1.8	0.001
Systolic BP (mmHg)[a]	119 (108,127)	117 (109,130)	0.002
Diastolic BP (mmHg)[a]	74 (67,82)	74 (68,81)	1.0
AER (μg/min)[b]	13.7 (6.1,19.8)	3.5 (6.7,20.5)	0.8
Cholesterol (mmol/l)	5.3 ± 1.1	5.2 ± 1.1	0.005
Fasting triglyceride (mmol/l)[b]	0.99 (0.81,1.49)	0.90 (0.64,1.08)	0.0003
LDL cholesterol (mmol/l)	3.33 ± 0.99	3.24 ± 0.92	0.1
Fibrinogen (g/l)	3.13 ± 0.92	3.18 ± 0.89	0.4
Waist-to-hip ratio	0.85 ± 0.11	0.84 ± 0.10	0.3
Retinopathy at baseline (%)[c]	41 ± 1.8	39 ± 1.4	0.6
Age at diagnosis < 12 years (%)[c]	26 ± 1.6	24 ± 1.2	0.3

[a] Patients on treatment given the highest value of the distribution; medians are presented

[b] Log-transformation used

[c] ± standard error

rived at using the DCCT method. This was: DCCT HbA_{1c} = 1.0289 * London HbA_{1c} + 1.5263.

Baseline characteristics for incidence were calculated using multiple regression techniques for continuous variables, and simple proportions for categorical variables. In both cases, adjustment for potential confounders was made where appropriate. A breakpoint or threshold effect for the relation between HbA_{1c} and progression to PDR was tested by a two-phase segmented weighted regression analysis which fits two straight lines through a series of defined points [18]. These points were calculated by logistic regression adjusted for diabetes duration. This segmented regression was compared to the line of best fit, using weighted linear regression. Logistic regression was also used to test for a threshold effect [19].

Standardized regression effects for risk factors which were continuous variables were calculated by multiplying the beta estimate from logistic regression models by the standard deviation of that variable. In such a case, not all log transformed variables were converted back to anti-logarithms. This procedure allows the direct comparison of the degree of importance of each variable in accounting for the risk of progression to PDR. Multivariate models were restricted to those individuals who had complete data on all included risk factors, that is 1044 out of 1092 people who did not progress to PDR at follow-up, and 148 out of 157 of those who did.

All analyses were initially stratified by sex. Because there were no appreciable differences in risk of retinopathy or risk factor relationships, combined data only are presented here.

Results

The patients without follow-up photographs and altogether lost to follow-up had significantly higher HbA_{1c}, systolic blood pressure, total cholesterol and fasting triglyceride at baseline than the patients with follow-up pictures (Tab. 1).

The mean follow-up period was 7.3 years. During this time, 157 patients had developed PDR (cumulative incidence 17.3/1000 patient-years; 95%-CI 13.6 to 21.1). Distribution by sex was 82 out of 655 men (12.5%) and 75 out of 594 (12.6%) women who progressed to PDR. Incidence increased until 15 years of diabetes duration at baseline and plateaued thereafter.

For univariate analysis, factors measured at baseline and associated with progression to PDR (Table 2) included duration of diabetes, centrally measured HbA_{1c}, diastolic blood pressure, albumin excretion rate, total and LDL cholesterol, fasting triglyceride, all triglyceride (fasting and non-fasting) and waist-to-hip ratio. HbA_{1c} measured locally over the 2 years before follow-up examination was also associated with progression to PDR. There was no evidence of a significant breakpoint or threshold effect in the relation between HbA_{1c} measured at baseline and progression to PDR (Fig. 2).

Severity of DR at baseline was associated with progression, as 30 (4%) of those without DR developed PDR, compared to 61 (17%) of those with minimal DR, 40 (40%) of those with moderate DR and 26 (79%) of those with severe non-proliferative DR.

Onset of diabetes before puberty was also a risk factor for progression to PDR. Diabetes had been diagnosed before age 12 in 40% of the patients who progressed and 21% of those who did not.

Because many of the above risk factors could be confounded by duration and HbA_{1c}, all other risk factors were adjusted for both. This attenuated or abolished many such associations with progression to PDR. The only factors which remained significantly associated with progression to PDR were: fasting triglyceride (0.99 vs 0.89 mmol/l, $p = 0.04$), waist-to-hip ratio (0.86 vs 0.84, $p = 0.04$) and albumin excretion rate [23 (95%-CI 19,28) vs 13 (12,13) μg/min, $p < 0.0001$]. Odds ratios adjusted for HbA_{1c} and duration of diabetes were significantly increased for val-

Table 2. Risk factors for incidence of proliferative retinopathy (means or % ± SEM (25th and 75 percentiles for log-transformed data/ or where medians are presented))

Risk factor	Progression to proliferative retinopathy		
	Yes	No	*p* value
Number	157	1092	
Age (years)	32 ± 0.8	31 ± 0.3	0.3
Duration (years)	17 ± 0.6	13 ± 0.2	0.0001
Central HbA_{1c} (%)	8.3 ± 0.2	6.3 ± 0.1	0.0001
Local HbA_{1c} (%)[a]	8.1 ± 0.1	6.4 ± 0.04	0.0001
Systolic BP (mmHg)[b]	119 (108,134)	117 (108,128)	0.1
Diastolic BP (mmHg)[b]	77 (70,88)	74 (67,83)	0.0008
AER (μg/min)[c]	29 (8,66)	12 (7,18)	0.0001
Cholesterol (mmol/l)	5.6 ± 0.10	5.1 ± 0.03	0.0001
Fasting triglyceride (mmol/l)[c]	1.11 (0.81,1.49)	0.88 (0.64,1.08)	0.0001
Triglyceride (mmol/l)[c]	1.15 (1.07,1.24)	0.92 (0.89,0.95)	0.0001
HDL cholesterol (mmol/l)	1.46 ± 0.04	1.51 ± 0.01	0.2
LDL cholesterol (mmol/l)	3.56 ± 0.10	3.20 ± 0.03	0.0003
Fibrinogen (g/l)	3.22 ± 0.10	3.17 ± 0.03	0.6
vWF (U/ml)[c]	1.15 (0.9,1.58)	1.10 (0.89,1.40)	0.4
γGT (U/l)[c]	11.8 (8.38,16.03)	10.5 (7.47,13.83)	0.06
Height (cm)	167 ± 0.8	170 ± 0.3	0.0004
Weight (kg)	66.0 ± 0.9	68.1 ± 0.4	0.03
Waist-to-hip ratio	0.86 ± 0.008	0.84 ± 0.003	0.007
BMI (kg/m^2)	23.5 ± 0.23	23.5 ± 0.09	0.8
Current smokers (%)	35 ± 4	30 ± 1	0.2
Inject insulin > × 2/day (%)	44 ± 4	51 ± 2	0.09
Insulin dose/weight (U/kg)[c]	0.68 (0.55,0.87)	0.64 (0.54,0.80)	0.1
Past history CVD (%)	6 (2,10)	7 (6,8)	0.6
Retinopathy at baseline (%)	81 (74.9,87.1)	33 (30.3,35.7)	0.001
Age at diagnosis < 12 years (%)	40 (32.4,47.6)	21 (18.8,23.2)	0.001

[a] Mean of previous two years worth of glycated haemoglobin, standardized to the central measurement

[b] Those on treatment given the highest value of the distribution; medians are presented

[c] Log-transformation was used

ues of diastolic blood pressure above 84 mmHg (OR = 2.2, 95%-CI 1.3–3.7, $p < 0.005$) and presence of retinopathy at baseline (OR = 10.1, 5.9–17.2, $p < 0.0001$) and decreased when patients were under 12 years of age at diagnosis (OR = 0.65, 0.44–0.98, $p < 0.04$).

HbA_{1c}, diabetes duration, an age of less than 12 years at diagnosis, diastolic blood pressure and a waist-to-hip ratio remained significant predictors for progression to PDR when entered simultaneously into a logistic regression model (Table 3). The strongest influence was from glycaemic control, with a standardized regression estimate of 3.03, followed by duration and onset before puberty. A second model which included the presence of retinopathy at baseline maintained the effects of metabolic control and onset before puberty only and abolished all the others. A third model, inclusive of AER, maintained a standardized regression estimate of 1.49 for onset of diabetes before puberty but this was no longer statistically significant. None of the other factors listed above, including locally measured HbA_{1c} had any additional impact.

Discussion

The results of the EURODIAB PCS indicate that, apart from previously known risk factors such as metabolic control, duration of diabetes and the presence and severity of retinopathy at baseline, onset of Type I diabetes before puberty could be an independent indicator of progression to PDR.

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) followed 996 patients with young-onset diabetes for 14 years. Of these, 13% had PDR at baseline, and the rates of development over 4 [6], 10 [20] and 14 years [21] were consistent with the incidence rate observed in this paper. As with EURODIAB PCS, glycated haemoglobin, duration of diabetes, severity of retinopathy at baseline and diastolic blood pressure were among the strongest factors associated with progression to PDR and an association with hypertension was also observed. Similar indicators of risk for progression to PDR were reported in the Joslin Clinic series, in which 292 patients with Type I diabetes were followed up from diagnosis for up to 40 years and the incidence of new PDR was 3 for every 100 patient-years [22]. In the Diabetes Control and Complications Trial, which had a median observation time similar to ours, progression to PDR was 2.4 for every 100 patient-

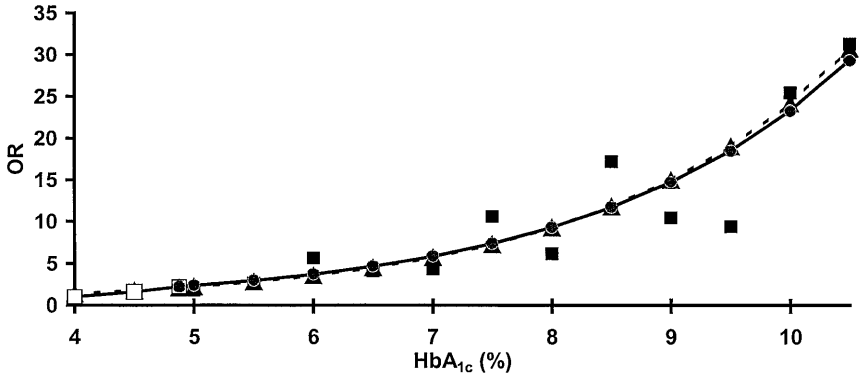

Fig. 2. Comparison of log-linear and breakpoint models for association between HbA_{1c} at baseline and progression to proliferative retinopathy, adjusted for diabetes duration; logistic (■); log-linear (▲); segment 1 (–□–); segment 2 (–●–)

years in the conventional treatment arm, reduced to 1.1 by intensive insulin treatment [8]. Unlike our series, however, these results refer to patients with minimal (< 5 microneurysms) DR at entry.

The standardized regression estimates carried out in this paper (Table 3) show that HbA_{1c} was the strongest predictor of progression to PDR. No evidence for a glycaemic threshold above which incidence of PDR escalated was observed (Fig. 2), in accordance with previous cohort studies [23–25] and the EURODIAB cross-sectional findings [7]. Increased AER was also independently associated with progression to PDR. Proteinuria was found to be associated with prevalence of PDR in cross-sectional studies [26] and with progression to PDR in longitudinal surveys [21, 27]. The observation that people with mild, moderate and severe non-proliferative lesions are more likely to develop PDR was also not surprising, as these patients have already gone through the initial stages of retinopathy, as reported previously [28,29].

Table 3. Standardized regression estimates for relation between key risk factors and progression to proliferative retinopathy

Risk factor	Standardized regression estimate (95%-CI)	*p*-value
Model 1		
Duration	1.71 (1.42,2.06)	0.0001
HbA_{1c}	3.03 (2.49,3.69)	0.0001
Waist-to-hip ratio	1.24 (1.04,1.47)	0.02
Diastolic BP > 83 mmHg	1.50 (1.03,2.20)	0.04
Age of diagnosis < 12 years	1.66 (1.11,2.50)	0.01
Model 2		
Duration	1.12 (0.89,1.42)	0.3
HbA_{1c}	3.24 (2.62,4.00)	0.0001
Waist-to-hip ratio	1.17 (0.96,1.42)	0.1
Diastolic BP > 83 mmHg	1.40 (0.93,2.08)	0.1
Age of diagnosis < 12 years	1.62 (1.06,2.48)	0.03
Baseline retinopathy	9.65 (5.64,16.51)	0.0001
Model 3		
Duration	1.08 (0.86,1.37)	0.5
HbA_{1c}	2.97 (2.40,3.68)	0.0001
Waist-to-hip ratio	1.14 (0.94,1.39)	0.2
Diastolic BP > 83 mmHg	1.17 (0.76,1.79)	0.5
Age of diagnosis < 12 years	1.49 (0.94,2.33)	0.08
Baseline retinopathy	8.84 (5.12,15.25)	0.0001
Albumin excretion rate	1.33 (1.12, 1.58)	0.001

Onset of diabetes in the pre-pubertal age, arbitrarily taken at 12 years of age, emerged as the second strongest predictor for progression to PDR, independent of diabetes duration (Table 3, Model 1), and remained a significant risk factor even after adjusting for retinopathy at baseline (Table 3, Model 2). This result was confirmed using a stratified approach by duration, and no significant interaction was found between age and duration on the association between pre-pubertal onset and risk of progression to PDR (data not shown). Only a further adjustment for albumin excretion rate attenuated the standardized regression estimates (Table 3, Model 3) for age at puberty from 1.62 to 1.49, still a clinically relevant effect, even though statistical significance was lost. However, even if one assumes that these two variables are not independent of each other, it would be more likely that age of onset influences albuminuria than vice versa.

In the WESDR, at 10-year follow-up [20], PDR was found less likely to have developed in patients who had been under 10 years of age at diagnosis, suggesting that pre-pubertal years might have a neutral effect on progression. Similar observations were reported by the Danish Study Group of Diabetes in Childhood [30]. Such a discrepancy could be due to the relative distribution of subjects, with short compared with long duration and early compared with later onset of diabetes in the WESDR and Danish studies, which recruited cohorts of consecutive patients. EURODIAB and its prospective arm, EURODIAB PCS, could be potentially better placed to check for the relative weight of age at onset as a risk factor, because patients had been stratified at baseline by age and duration. The presence of differences in risk factor concentrations at baseline between patients who were examined at follow-up and those who were not (Table 1) could raise the problem of

how representative of the initial cohort the sample described in this paper was. However, such differences should not affect the direction or strength of risk factor relations. For example, even if HbA_{1c} differed between patients who were and those who were not followed up, poor metabolic control probably does not increase the risk of developing PDR among progressors and reduce it among non-progressors.

Diastolic blood pressure and waist-to-hip ratio displayed weaker associations with progression to PDR, which disappeared after adjusting by severity of retinopathy at baseline (Table 3). Both variables are associated with the insulin-resistance syndrome, which in turn could be involved in the pathogenesis of the vascular complications of diabetes [31–33] and was separately reported to be associated with appearance of retinopathy in the EURODIAB PCS cohort [34]. However, the mechanisms leading to new vessel formation are likely to become self-supporting during the natural history of retinopathy and this might explain why at least some risk factors for non-proliferative lesions are not relevant to PDR.

Although metabolic control was the strongest modifiable risk factor for the deterioration of retinopathy, current approaches to intensive treatment are not likely, on their own, to completely abolish progression to PDR [8]. In particular, there appears to be no glycaemic threshold below which a patient can be sure to be protected from progression to PDR, indicating that other lines of intervention must be pursued. The observation that the risk of progression increases for values of diastolic blood pressure above 84 mmHg (Table 3), together with clinical trials showing the beneficial effect of aggressive antihypertensive treatment on retinopathy [35,36], further support adoption of the targets established by current WHO guidelines for the management of blood pressure in patients with diabetes as well [37]. The results of the EURODIAB PCS indicate that prevention of diabetes-related blindness depends on active control of blood glucose and blood pressure, coupled with regular screening for sight-threatening retinopathy [38], these remaining the best available options for intervention on modifiable risk factors.

Acknowledgements. This study was supported by grants from the Wellcome Trust and the European Community. We would like to thank all the investigators, and the patients, for their valuable participation in this study.

The EURODIAB Prospective Complications Study Group: *B. Karamanos, A. Kofinis, K. Petrou*, Hippokration Hospital, Athens, Greece; *R. Giorgino, F. Giorgino, G. Picca, A. Angarano, G. De Pergola*, Institute of Medical Clinics, Endocrinology and Metabolic Diseases, Bari University, Bari, Italy; *C. Ionescu-Tirgoviste, A. Coszma*, Clinic of Diabetes, Nutrition and Metabolic Diseases, Bucharest, Romania; *M. Songini*[*], A. Casu, M. Pedron, M. Fossarello[*], Department of Internal Medicine [*]San Michele Hospital, Cagliari, Italy; *J. B. Ferriss, G. Grealy, D. O' Keefe*, Cork Regional Hospital, Cork, Ireland; *M. Toeller, C. Arden*, Diabetes Research Institute, Heinrich-Heine University, Dusseldorf, Germany; *R. Rottiers, C. Tuyttens, H. Priem*, University Hospital of Gent, Belgium; *P. Ebeling,M. Kylliäinen, T. Kyostio-Renvall*, University Hospital of Helsinki, Finland; *B. Idzior-Walus, J. Sieradzki, K. Cyganek*, Department of Metabolic Diseases, Jagiellonian University, Krakow, Poland; *H. H.P.J. Lemkes*, University Hospital of Leiden, The Netherlands; *J. Nunes-Correa, M.C. Rogado, L. Gardete-Correia, M.C. Cardoso*, Portuguese Diabetic Association, Lisbon, Portugal; *G. Michel, R. Wirion, S. Cardillo*, Hospital Centre, Luxembourg; *G. Pozza, R. Mangili, V. Asnaghi*, San Raffaele Hospital, Milan, Italy; *E. Standl, B. Schaffler, H. Brand, A. Harms*, City Hospital Schwabing, Munich, Germany; *D. Ben Soussan, O. Verier-Mine, P. Fallas, M.C. Fallas*, Valenciennes Hospital Centre, France; *J. H. Fuller, J. Holloway, L. Asbury, D.J. Betteridge*, University College London; *G. Cathelineau, A. Bouallouche, B. Villatte Cathelineau*, Hospital Saint-Louis, Paris, France; *F. Santeusanio, G. Rosi, V. D'Alessandro, C. Cagini, P. Bottini*, Institute of Medical Pathology, Perugia, Italy; *R. Navalesi, G. Penno, S. Bandinelli, R. Miccoli*, Departments of Endocrinology and Metabolism, Pisa, Italy; *G. Ghirlanda, C. Saponara, P. Cotroneo, A. Manto, A. Minnella*, Universita Catholic University Sacro Cuore, Rome, Italy; *J. D. Ward, S. Tesfaye, S. Eaton, C. Mody*, Royal Hallamshire Hospital, Sheffield, UK; *M. Borra, P. Cavallo Perin, S. Giunti, G. Grassi, G.F. Pagano, M. Porta, R. Sivieri, F. Vitelli*, Department of Internal Medicine, University of Turin and ASO CTO/CRF/Maria Adelaide, Turin, Italy; *N. Papazoglou, G. Manes*, General Hospital of Thessaloniki, Greece; *M. Muggeo, M. Iagulli*, Chair of Metabolic Diseases, Verona, Italy; *K. Irsigler, H. Abrahamian*, Hospital Vienna Lainz, Austria; *S. Walford, E.V. Wardle, J. Sinclair, S. Hughes*, New Cross Hospital, Wolverhampton, UK; *G. Roglic, Z. Metelko, Z.R. Pepeonik*, Vuk Vrhovac Institute for Diabetes, Zagreb, Croatia.

Steering Committee Members: *J. H. Fuller* (London), *B. Karamanos*, (Chairman) (Athens), *A-K. Sjolie* (Aarhus), *N. Chaturvedi* (London), *M. Toeller* (Dusseldorf), *G. Pozza* (Co-chairman) (Milan), *B. Ferriss* (Cork), *M. Porta* (Turin), *R. Rottiers* (Gent), *G. Michel* (Luxembourg). Co-ordinating Centre: *J. H. Fuller, N. Chaturvedi, J. Holloway, D. Webb, L. Asbury*, University College London. Central Laboratories: *G-C. Viberti, R. Swaminathan, P. Lumb, A. Collins, S. Sankaralingham*, Guy's and St Thomas Hospital, London, UK. Retinopathy Grading Centre: *S. Aldington, T. Mortemore, H. Lipinski*, Royal Postgraduate Medical School of Imperial College London, London, UK.

References

1. Dwyer MS, Melton LJ 3rd, Ballard DJ, Palumbo PJ, Trautman JC, Chu CP (1985) Incidence of diabetic retinopathy and blindness: A population-based study in Rochester, Minnesota. Diabetes Care 8: 316–322
2. Porta M, Tomalino MG, Santoro F et al. (1995) Diabetic retinopathy as a cause of blindness in the Province of Turin, North-West Italy, in 1967–1991. Diabet Med 12: 355–361
3. Trautner C, Haastert B, Giani G, Berger M (2001) Incidence of blindness in southern Germany between 1990 and 1998. Diabetologia 44: 147–150
4. Sjolie AK, Stephenson J, Aldington S et al. (1997) Retinopathy and vision loss in insulin-dependent diabetes in Europe. Ophthalmology 104: 252–260
5. Klein R, Klein BEK (1983) Vision disorders in diabetes. In: Hamman R, Harris MWH (eds) Diabetes in America, Bethesda, MO: US Health Service NIH Publications. No. 85–1468 National Institutes of Health, pp 1–36

6. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL (1984) The Wisconsin Epidemiologic Study of diabetic retinopathy II Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Arch Ophthalmol 102: 520–526
7. The EURODIAB IDDM Complications Study Group (1994) Microvascular and acute complications in insulin dependent diabetes mellitus: the EURODIAB IDDM Complications Study. Diabetologia 37: 278–285
8. The Diabetes Control and Complications Trial Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 329: 977–986
9. Aldington SJ, Kohner EM, Meuer S, Klein R, Sjolie A, The EURODIAB IDDM Complications Study Group (1995) Methodology for retinal photography and assessment of diabetic retinopathy: the EURODIAB IDDM Complications Study. Diabetologia 38: 437–444
10. Siedel J, Hagele EO, Ziegenhorn J, Wahlefeld AW (1983) Reagent for the enzymatic determination of serum total cholesterol with improved lipolytic efficiency. Clin Chem 29: 1075–1080
11. Bucolo G, David H (1973) Quantitative determination of serum triglycerides by the use of enzymes. Clin Chem 19: 476–482
12. Warnick GR, Albers JJ (1978) A comprehensive evaluation of the heparin-manganese precipitation procedure for estimating high density lipoprotein cholesterol. J Lipid Res 19: 65–76
13. Friedewald WT, Levy RI, Fredrickson DS (1972) Estimation of the concentration of low density lipoprotein in cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 18: 499–502
14. John GW, Gray MR, Bates DL, Beacham JL (1993) Enzyme immunoassay – a new technique for estimating HbA1 c. Clin Chem 39: 663–666
15. Ford I, Malik RA, Newrick PG, Preston FE, Ward JD, Greaves M (1992) Relationships between haemostatic factors and capillary morphology in human diabetic neuropathy. Thromb Haemost 68: 628–633
16. Kearney EM, Mount JN, Watts GF, Slavin BM, Kind PRN (1987) Simple immunoturbidometric method for determining urinary albumin at low concentrations using centrifugal analyser. J Clin Pathol 40: 465–468
17. Koivisto VA, Stevens LK, Mattock M et al. (1996) Cardiovascular Disease and Its Risk Factors in IDDM in Europe. Diabetes Care 19: 689–697
18. Jones RH, Molitoris BA (1984) A Statistical Method for Determining the Breakpoint of Two Lines. Anal Biochem 141: 287–290
19. Ulm K (1991) A Statistical Method for Assessing a Threshold in Epidemiological Studies. Stat Med 10: 341–349
20. Klein R, Klein BEK, Moss SE, Cruickshanks KJ (1994) The Wisconsin Epidemiologic Study of diabetic retinopathy. XIV. Ten-year incidence and progression of diabetic retinopathy. Arch Ophthalmol 112: 1217–1228
21. Klein R, Klein BEK, Moss SE, Cruickshanks KJ (1998) The Wisconsin Epidemiologic Study of diabetic retinopathy. XVII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. Ophthalmology 105: 1801–1815
22. Krolewski AS, Warram JH, Rand LI, Christlieb AR, Busick EJ, Kahn CR (1986) Risk of proliferative diabetic retinopathy in juvenile-onset type 1 diabetes: a 40-year follow-up study. Diabetes Care 9: 443–452
23. Anonymous (1996) The absence of a glycemic threshold for the development of long-term complications: the perspective of the Diabetes Control and Complications Trial. Diabetes 45: 1289–1298
24. Klein R, Klein BE, Moss SE, Cruickshanks KJ (1994) Relationship of hyperglycemia to the long-term incidence and progression of diabetic retinopathy. Arch Intern Med 154: 2169–2178
25. Danne T, Weber B, Hartmann R, Enders I, Burger W, Hovener G. (1994) Long-term glycemic control has a nonlinear association to the frequency of background retinopathy in adolescents with diabetes. Follow-up of the Berlin retinopathy study. Diabetes Care 17: 1390–1396
26. The association of microalbuminuria with diabetic retinopathy (1993) The Wisconsin Epidemiologic Study of Diabetic Retinopathy. Ophthalmology 100: 862–867
27. Kofoed-Enevoldsen A, Jensen T, Borch-Johnsen K, Deckert T (1987) Incidence of retinopathy in type I (insulin-dependent) diabetes:association with clinical nephropathy. J Diabetes Complications 1: 96–99
28. Early Treatment Diabetic Retinopathy Study Research Group (1991) Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS Report Number 12. Ophthalmology 98: 823–833
29. Klein R, Meuer SM, Moss SE, Klein BEK (1995) Retinal microaneurysm counts and 10-year progression of diabetic retinopathy. Arch Ophthalmol 113: 1386–1391
30. Olsen BS, Johannesen J, Sjølie AK et al. (1999) Metabolic control and prevalence of microvascular complications in young Danish patients with Type 1 diabetes mellitus. Diabet Med 16: 79–85
31. Stuhldreher WL, Becker DJ, Drash AL et al. (1994) The association of waist/hip ratio with diabetes complications in an adult IDDM population. J. Clin. Epidemiol 47: 447–456
32. Maneschi F, Mashiter K, Kohner EM (1983) Insulin resistance and insulin deficiency in diabetic retinopathy of non-insulin-dependent diabetes. Diabetes 32: 82–87
33. Yip J, Mattock MB, Morocutti A, Sethi M, Trevisan R, Viberti GC (1993) Insulin resistance in insulin-dependent diabetic patients with microalbuminuria. Lancet 342: 883–887
34. Chaturvedi N, Sjoelie AK, Porta M et al. (2001) Markers of insulin resistance are strong risk factors for the incidence of retinopathy in type 1 diabetes: findings from the EURODIAB PCS. Diabetes Care 24: 284–289
35. Chaturvedi N, Sjolie A, Stephenson JM et al. (1998) Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes. Lancet 351: 28–31
36. UK Prospective Diabetes Study Group (1998) Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 317: 703–713
37. 1999 World Health Organization-International Society of Hypertension (1999) Guidelines for the Management of Hypertension. Guidelines Subcommittee. J Hypertens 17: 151–183
38. Javitt JC, Aiello LP (1996) Cost-effectiveness of detecting and treating diabetic retinopathy. Ann Intern Med 124: 164–169