Impact of HbA_{1c}, Followed From Onset of Type 1 Diabetes, on the Development of Severe Retinopathy and Nephropathy: The VISS Study (Vascular Diabetic Complications in Southeast Sweden)

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OBJECTIVE

HbA_{1c} is strongly related to the development of diabetes complications, but it is still controversial which HbA_{1c} level to strive for in the treatment of type 1 diabetes. The aim of the current study was to evaluate HbA_{1c}, followed from diagnosis, as a predictor of severe microvascular complications and to formulate HbA_{1c} target levels for treatment.

RESEARCH DESIGN AND METHODS

A longitudinal observation study followed an unselected population of 451 patients diagnosed with type 1 diabetes during 1983–1987 before the age of 35 years in a region of Southeast Sweden. Retinopathy was evaluated by fundus photography and nephropathy data collected from medical records. HbA_{1c} was measured starting from diagnosis and during the whole follow-up period of 20–24 years. Long-term weighted mean HbA_{1c} was then calculated. Complications were analyzed in relation to HbA_{1c} levels.

RESULTS

The incidence of proliferative retinopathy and persistent macroalbuminuria increased sharply and occurred earlier with increasing long-term mean HbA_{1c}. None of the 451 patients developed proliferative retinopathy or persistent macroalbuminuria below long-term weighted mean HbA_{1c} 7.6% (60 mmol/mol); 51% of the patients with long-term mean HbA_{1c} above 9.5% (80 mmol/mol) developed proliferative retinopathy and 23% persistent macroalbuminuria.

CONCLUSIONS

Long-term weighted mean HbA_{1c}, measured from diagnosis, is closely associated with the development of severe complications in type 1 diabetes. Keeping HbA_{1c} below 7.6% (60 mmol/mol) as a treatment target seems to prevent proliferative retinopathy and persistent macroalbuminuria for up to 20 years

PATHOPHYSIOLOGY/COMPLICATIONS

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Glycosylated hemoglobin (HbA_{1c}) was proposed as a long-term measure of average glycemia and introduced into clinical practice in the early 1980s (1). HbA_{1c} may reflect a pathogenic mechanism of glucose metabolism in diabetes complications, as it mirrors glycosylation of proteins (2). The Diabetes Control and Complications Trial (DCCT) and other interventional studies have convincingly demonstrated the importance of near-normal glycemic control, measured as HbA_{1c}, to prevent long-term microvascular complications in both type 1 and type 2 diabetes (3–6). The crucial role of good glycemic control is also shown in unselected population studies (7–9).

Since advanced diabetes complications, especially nephropathy, appear first after 15–20 years of diabetes duration (10,11), it has not until now been possible to study complications with a reliable measurement of glycemic control from diabetes onset. Besides glycemic control and diabetes duration, there is evidence that age at onset influences the development of microangiopathy (12). Children seem to be protected from severe microvascular complications before puberty, but the effect seems to disappear with time (13). A sufficiently long follow-up is therefore necessary to evaluate the importance of glycemic control, especially in childhood-onset diabetes.

There is still controversy as to how strict glycemic control should be to avoid severe complications (14,15). In clinical practice, it is of great importance to find the right balance between the risk for severe microvascular complications, potentially dangerous hypoglycemic events, and quality of life and to be able to recommend an optimal level of HbA_{1c} both in the short and long term. The aim with this study was to evaluate HbA_{1c}, followed from diagnosis, as a biomarker for risk of developing severe microvascular diabetes complications and to formulate HbA_{1c} target levels for treatment.

RESEARCH DESIGN AND METHODS

Patients

All 451 patients with type 1 diabetes diagnosed during 1983–1987 in Southeast Sweden were included. They had a clinical picture of type 1 diabetes before the age of 35 years and insulin treatment <6 months from diagnosis as described earlier (12). The patients received routine care. They were identified using local registers and validated with the help of the Swedish Childhood Diabetes Registry and the Diabetes Incidence Study in Sweden (DISS). Of the original cohort of 440 patients (12), 8 patients were shown to have type 2 diabetes and other types of diabetes, while 19 patients were added from Swedish Childhood Diabetes Registry; 58% were male and 42% female; 54% were diagnosed before the age of 15 years.

The 10-digit personal identity number, unique to Sweden, made it possible to track the patients. Data were retrospectively collected in the patients' records or by their physicians, using a questionnaire. Most of the patients were followed until 2005–2008. Mean (SD) duration at follow-up was 22.1 (2.0) years. For 17 patients, it was not possible to track data for the whole period of time; 11 patients were deceased, and 6 patients had moved abroad.

The Research Ethics Committee of the Faculty of Health Sciences, Linköping University, approved the study.

Blood Pressure, Blood Lipids, and BMI

At the last follow-up date, data about blood pressure, blood lipids, height, and weight were collected from the patients' records as well as data about antihypertensive and lipid-lowering treatment.

For the whole population (data were stated as mean $\pm$ SD). BMI was 26.1 $\pm$ 4.3 kg/m^2, total cholesterol was 4.7 $\pm$ 1.0 mmol/L (181.5 $\pm$ 38.6 mg/dL), triglycerides were 1.2 $\pm$ 0.9 mmol/L (106.2 $\pm$ 79.6 mg/dL), systolic blood pressure was 124 $\pm$ 16 mmHg, and diastolic blood pressure was 74 $\pm$ 8 mmHg. BMI was significantly higher in patients with more advanced forms of retinopathy (moderate simplex and proliferative retinopathy), and triglycerides were significantly higher in patients with micro- and macroalbuminuria. Systolic blood pressure was significantly higher in patients with microalbuminuria and macroalbuminuria, and diastolic blood pressure was significantly higher in patients with microalbuminuria. The other associations were not statistically significant, but there was a trend to higher blood pressure and lipid values in patients with microvascular complications. Detailed data about BMI, lipids, and blood pressure are given in Supplementary Tables 1 and 2.

Of all patients, 27% had antihypertensive treatment at follow-up. Of these, 87% used an ACE inhibitor (67%) or angiotensin II receptor blockers (20%). Five percent had antihypertensive medication and previous microalbuminuria but were now normoalbuminuric. For 42%, the indication of antihypertensive treatment was hypertension with no signs of micro- or macroalbuminuria before onset of treatment. Seventy-two percent of the patients with antihypertensive treatment had no signs of proliferative retinopathy. In total, 14 and 23% had antihypertensive treatment without any signs of nephropathy or proliferative retinopathy, respectively. Lipid-lowering agents, in almost all cases, statins, were used in 28% of the patients.

HbA_{1c} Measurement

HbA_{1c} was measured regularly at the clinical visits, 2–4 times per year, and analyzed by local hospital laboratories. At the start of the study in January 1983, HbA_{1c} was analyzed by Isolab minicolumns (Fast Hb Test System, Isolab Inc., Akron, OH) at the four central laboratories. This was replaced during 1984–1987 by high-performance liquid chromatography methods measuring HbA_{1c} with high precision. The analyzing laboratories calculated intermethod calibrations and conversion factors when the methods were changed. From June 1994, hospital laboratories were participating in an interlaboratory quality program (Equalis, Uppsala, Sweden), where all laboratories analyzed two samples per month. In 1997, a nationwide standardization was introduced, and repeated comparisons were made with National Glycohemoglobin Standardization Program (NGSP) values, which showed the Swedish values to be 1.1% lower than NGSP values (16). The same was demonstrated in a study comparing HbA_{1c} measured in 1994 at the Linköping Hospital Laboratory with the DCCT laboratory (17). All values are converted by formulas to the new International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference values. The corresponding NGSP values are also stated, making it possible to compare the results with previous studies. The conversion formula is HbA_{1c} (NGSP) (%) = 0.0915 $\times$ HbA_{1c} (IFCC) (mmol/mol) + 2.153. The normal range is 27–42 mmol/mol (IFCC) corresponding to 4.6–6.0% (NGSP) (18). For many of the patients who moved, it has been possible to obtain their HbA_{1c}

values from their physicians, and conversions factors to the Equalis reference method was done by the local laboratory. However, 90% of the HbA_{1c} values come from laboratories in the catchment area. As a measure of long-term glycemic control, long-term mean HbA_{1c} was calculated and weighted for the time between the measurements ($wHbA_{1c}$) (19). All HbA_{1c} values, from diabetes diagnosis and until the year of laser therapy, onset of persistent macroalbuminuria, or last follow-up time were used for the calculations. For statistical analysis, $wHbA_{1c}$ was divided into five different classes. For some analyses, it was necessary to combine categories because of the absence of readings in the lowest categories.

Retinopathy

Retinal screening using color fundus photography was planned every other year for each patient from the onset of diabetes or from 10 years of age. Three standard photographs were taken, after pupil dilation, of each eye: nasal to the optic nerve, the optic nerve and macula, and temporal to the macula. The prevalence of retinopathy was calculated by reevaluation of fundus photos taken between 2005 and 2008. If no photo was available during this period, the last photo, closest to these dates, was selected. The duration of diabetes at the date of photography was mean (SD) 20.8 (2.9) years. The date of the first laser treatment was collected from clinical records. Photographs or reliable data concerning previous laser therapy for proliferative retinopathy or maculopathy were available for 431 (96%) patients. Eleven patients had died, six patients had moved abroad, and three patients had not participated in screening. Two ophthalmologists (M.A. and M.D.) evaluated the photographs independently. The photographs were graded according to the Modified Airlie House protocol and grouped according to the worst eye into four classes: normal, slight simplex, moderate simplex, and proliferative retinopathy or maculopathy (or previous laser therapy) (20). If the grading was dissimilar, the ophthalmologists reevaluated the photos and then together decided the grading. The incidence of severe retinopathy, defined as the date of the first laser treatment for proliferative retinopathy or maculopathy, was also calculated.

Nephropathy

The patients were screened for proteinuria at their regular clinical visits, at least once every year. The urine sample was analyzed at the local hospital laboratory with quantitative immunoturbidometric methods, either as a timed overnight analysis or as a morning spot test.

Microalbuminuria was defined as an albumin excretion rate (AER) 20–200 μg/min or albumin/creatinine ratio of 3–30 mg/mmol. Macroalbuminuria was defined as an AER >200 μg/min or albumin/creatinine ratio >30 mg/mmol. For all patients with macroalbuminuria, the medical records were scrutinized to confirm that there was no other kidney disease explaining the condition. Data were available for 420 (93%) of the patients.

The prevalence of nephropathy was examined at the last follow-up and grouped as normoalbuminuria, microalbuminuria, or persistent macroalbuminuria. The 23 patients who were normoalbuminuric but treated with ACE inhibitors because of previous microalbuminuria were classified as microalbuminuria. In calculating the incidence of macroalbuminuria, the first year when macroalbuminuria became persistent was indicated as onset.

Statistical Analysis

Differences between groups were tested using *t* test or ANOVA with a post hoc Bonferroni test. Frequencies were compared using χ^2 tests. Life table analysis with Wilcoxon (Gehan) log-rank test was used for analysis of incidence of retinopathy and persistent macroalbuminuria.

The significance level was set as $P < 0.05$. SPSS version 21 was used for the analyses.

RESULTS

HbA_{1c}

In total, 24,640 HbA_{1c} values were collected, mean (SD) 54.9 (17.6) values per patient. For less than 6%, there was a gap of more than 2 years between measurements. Mean $wHbA_{1c}$ was 8.2% (95% CI 8.1–8.3%) (66 [65–67] mmol/mol) without sex difference. Distribution of $wHbA_{1c}$ is presented in Table 1. Only

Table 1—Prevalence of microvascular complications in different HbA_{1c} categories and long-term weighted mean HbA_{1c} in an unselected population of type 1 diabetes after 20–24 years of diabetes duration

	Prevalence in various HbA_{1c} categories NGSP values % (IFCC value mmol/mol)							Long-term weighted mean HbA_{1c}	
	≤6.7 (≤50)	6.8–7.6 (51–60)	7.7–8.6 (61–70)	8.6–9.5 (71–80)	>9.5 (>80)	All		NGSP value % mean (95% CI)	IFCC value mmol/mol mean (95% CI)
	n	*n*	*n*	*n*	*n*	*n*	%		
Retinopathy									
None	20	18	13	3	0	54	12.5	7.2 (6.9–7.4)	55 (52–58)
Mild simplex	16	56	46	23	4	145	33.6	7.8 (7.7–8.0)	62 (60–64)
Moderate simplex	1	39	69	46	19	174	40.4	8.4 (8.3–8.6)	68 (67–70)
Proliferative/laser therapy	0	1	14	19	24	58	13.5	9.4 (9.1–9.7)	79 (76–83)
All	37	114	142	91	47	431		8.2 (8.1–8.3)	66 (65–67)
Nephropathy									
Normoalbuminuria	30	102	119	64	25	340	81.0	8.0 (7.9–8.2)	64 (63–66)
Microalbuminuria	3	9	19	20	12	63	15.0	8.6 (8.3–8.9)	71 (68–74)
Macroalbuminuria	0	0	2	4	11	17*	4.0	10.1 (9.5–10.6)	86 (80–93)
All	33	111	140	88	48	420		8.2 (8.1–8.3)	66 (65–67)

$P < 0.001$ for HbA_{1c} and grade of retinopathy and nephropathy. Data were analyzed using one-way ANOVA and Bonferroni post hoc test. All differences significant in pairwise comparisons, apart from normoalbuminuria compared with microalbuminuria. *Three patients had end-stage renal disease: two patients kidney transplantation, one patient long-term dialysis.

35% had wHbA$_{1c}$ lower than 7.1% (61 mmol/mol).

Retinopathy

The prevalence of different grades of retinopathy and relation to wHbA$_{1c}$ is shown in Table 1 and Figs. 1*A* and 2*A*. Only 12.5% of the patients had no signs of retinopathy, and 13.5% had laser-treated retinopathy. The indication for laser treatment was in all cases proliferative retinopathy, and all patients with proliferative retinopathy were laser treated. There were no cases of maculopathy. Almost all patients had developed some grade of retinopathy except for the group with HbA$_{1c}$ ≤6.7% (50 mmol/mol). In this group, half of the patients had no retinopathy, and none were laser treated.

As shown in Fig. 2*A* the prevalence of laser-treated retinopathy increases sharply with increasing HbA$_{1c}$ levels, and in the group with HbA$_{1c}$ >9.5% (80 mmol/mol), half of the patients were laser treated. In the HbA$_{1c}$ categories ≤7.6% (60 mmol/mol), only one patient had been laser treated after 15 years of diabetes duration and with wHbA$_{1c}$ 7.6% (60 mmol/mol) (Fig. 2*A*). The cumulative proportion of laser treatment was higher and occurred earlier with increasing HbA$_{1c}$ levels (Fig. 3*A*).

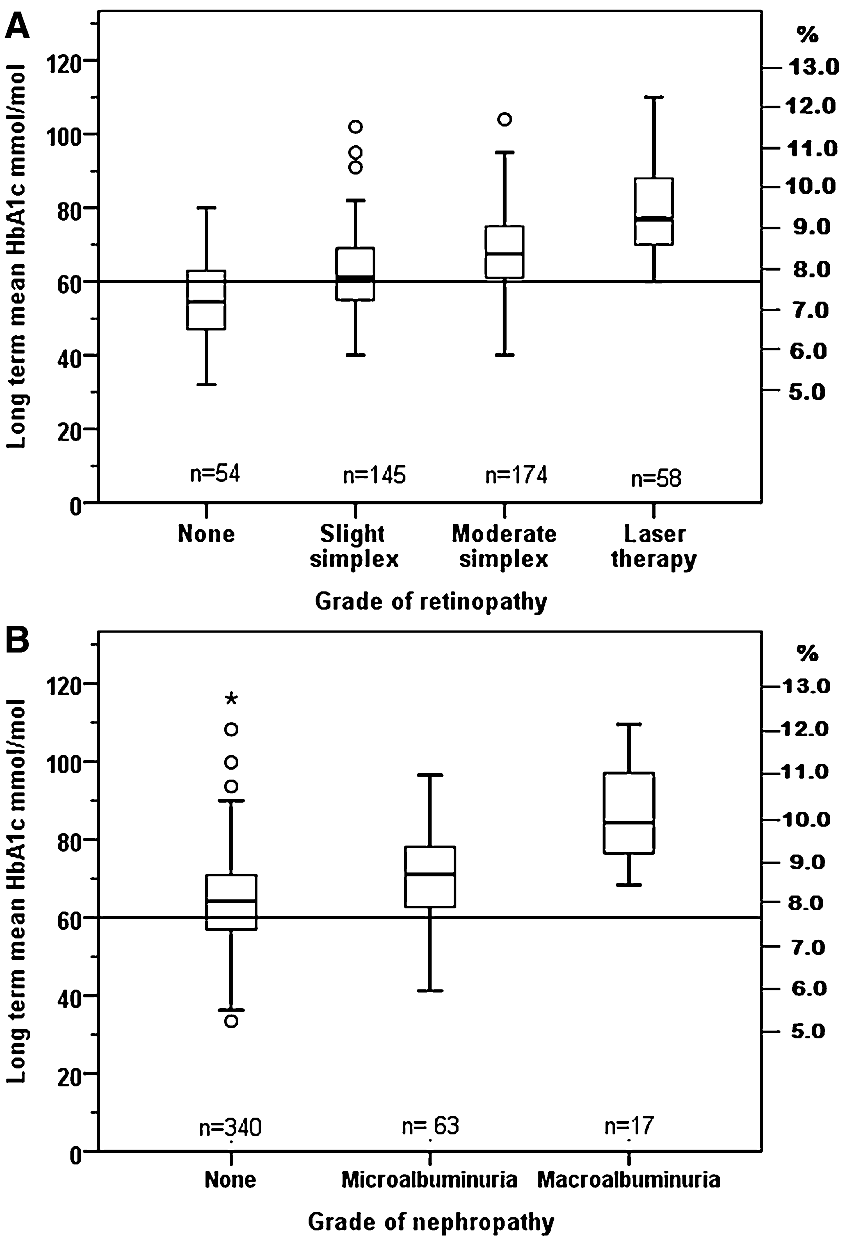

Figure 1—HbA$_{1c}$ range for patients with various grades of retinopathy (*A*) and nephropathy (*B*) in an unselected population of type 1 diabetes after 20–24 years of diabetes duration. Boundaries of box plots show quartiles, whiskers show nonoutlier range, unfilled circles show outliers, and asterisk shows extremes.

Nephropathy

As shown in Table 1 and Figs. 1*B* and 2*B*, of 420 patients evaluated for nephropathy, 63 (15%) had microalbuminuria according to our definition and 17 (4%) macroalbuminuria. While cases with microalbuminuria were found at all levels of wHbA$_{1c}$, macroalbuminuria was found only in the categories with HbA$_{1c}$ levels above 7.6% (60 mmol/mol) starting at a wHbA$_{1c}$ of 8.4% (68 mmol/mol). Of the 12 patients categorized as microalbuminuria in the groups with wHbA$_{1c}$ ≤7.6% (60 mmol/mol), 5 had reverted to normal and 5 had only marginally elevated AER after ACE-inhibitor therapy. There were highly significant differences in HbA$_{1c}$ levels between the various groups of albuminuria (Table 1 and Fig. 1*B*). The prevalence of macroalbuminuria increased sharply with higher HbA$_{1c}$ levels being 23% at HbA$_{1c}$ >9.5% (80 mmol/mol) (Fig. 2*B*). The cumulative proportion of persistent macroalbuminuria was increasing after ~15 years of diabetes duration (Fig. 3*B*). Two patients in HbA$_{1c}$ category 7.7–8.6% (61–70 mmol/mol) developed macroalbuminuria after 18 and 17 years of diabetes duration with wHbA$_{1c}$ 8.4% (68 mmol/mol) and 8.6% (70 mmol/mol), respectively. In contrast, one patient with wHbA$_{1c}$ 12.2% (110 mmol/mol) developed macroalbuminuria already after 9 years.

CONCLUSIONS

In this observational, population-based study, long-term wHbA$_{1c}$ was found to be a powerful biomarker for the development of laser-treated diabetic retinopathy and persistent macroalbuminuria in type 1 diabetes. No patient developed proliferative retinopathy or persistent macroalbuminuria below wHbA$_{1c}$ 7.6% (60 mmol/mol). The cumulative incidence of both complications increased steeply with increasing wHbA$_{1c}$ levels. Time to onset of complications was also influenced by HbA$_{1c}$ as in the primary prevention cohort of DCCT (5).

Even in very-well-controlled patients with wHbA$_{1c}$ ≤6.7% (50 mmol/mol), almost half of the patients had simplex retinopathy at follow-up. However, simplex retinopathy does not impair vision

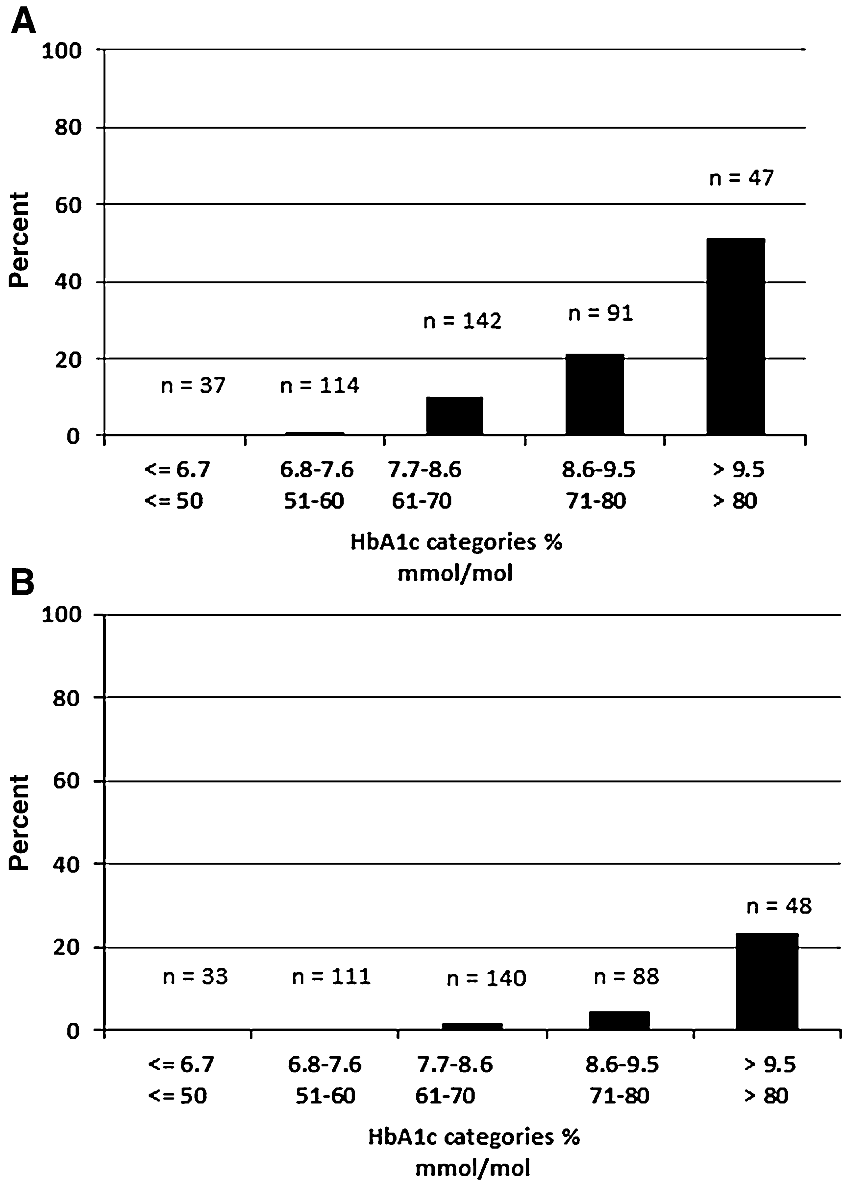

Figure 2—Prevalence of laser-treated proliferative retinopathy (*A*) and persistent macroalbuminuria (*B*) in an unselected population of type 1 diabetes after 20–24 years of diabetes duration for different categories of long-term weighted mean HbA_{1c}.

and is of no clinical importance, while proliferative retinopathy can cause blindness and should therefore be avoided. The same pattern applies to nephropathy, microalbuminuria being detected at all HbA_{1c} levels. Microalbuminuria, as with background retinopathy, gives no clinical symptoms, even if it may be a predictor of persistent macroalbuminuria. However, ~30–60% will revert to normal, especially after improved glycemic control (21,22). The few patients in our study with good glycemic control but with microalbuminuria had all reverted to normal after ACE-inhibitor therapy or had low-grade microalbuminuria.

The DCCT concluded that there was no glycemic threshold for long-term complications since the relative risk reduction for microalbuminuria and progression of retinopathy was the same down to normal values. However, the absolute risk was very low below HbA_{1c} 8.0% (64 mmol/mol) (23). Other authors have suggested a glycemic threshold of HbA_{1c} of ~8–9% (65–75 mmol/mol) (24–26). A distinction should, however, be made between mild and severe diabetes complications. In the Linköping complications study, the risk for laser-treated retinopathy and persistent macroalbuminuria was low below long-term mean HbA_{1c} 8.4% (68 mmol/mol) and 9.3% (78 mmol/mol) for laser-treated retinopathy and persistent macroalbuminuria, respectively. However, HbA_{1c} was not followed from diagnosis (9). In our present study, we found no cases of severe complications below HbA_{1c} 7.6% (60 mmol/mol). If the aim is to avoid all microvascular complications, there seems to be no threshold, since both microalbuminuria and simplex retinopathy occurred in patients with near-normal glycemic control. But if the aim is to prevent clinically significant complications, keeping HbA_{1c} below 7.6% (60 mmol/mol) as a treatment target seems to prevent proliferative retinopathy and persistent macroalbuminuria, at least for 20 years.

The strength of our study lies in the fact that we followed an unselected population, in routine care, with complete follow-up during a long period of time. This has been possible due to the unique personal identity number that everyone has in Sweden. To our knowledge, this is the first long-term follow-up of diabetes complications and HbA_{1c} measured from diabetes onset. The follow-up study after the DCCT, the Epidemiology of Diabetes Interventions and Complications (EDIC) study (27), could show a long-lasting effect of periods of good glycemic control on the incidence of retinopathy, often referred to as metabolic memory (28). The total glycemic exposure seems to be important for the development of microvascular complications, and Hirose et al. (29) recently demonstrated the importance of including HbA_{1c} values right from diabetes onset.

However, there are limitations in this type of long observational study in clinical settings. For a few patients, there were periods with longer intervals between measurements and hence with unknown glycemic control. The HbA_{1c} method changed during the follow-up period, but we were able to use conversion formulas to compensate for HbA_{1c} analysis using different methods. As described above, the methods were, even in the early stages, of high precision and standardized against a national standard and also compared with the NGSP values (16,17). This makes it possible to compare our results with the recommendation of HbA_{1c} targets after the DCCT study.

Since the follow-up period in this study was 20–24 years, the prognostic

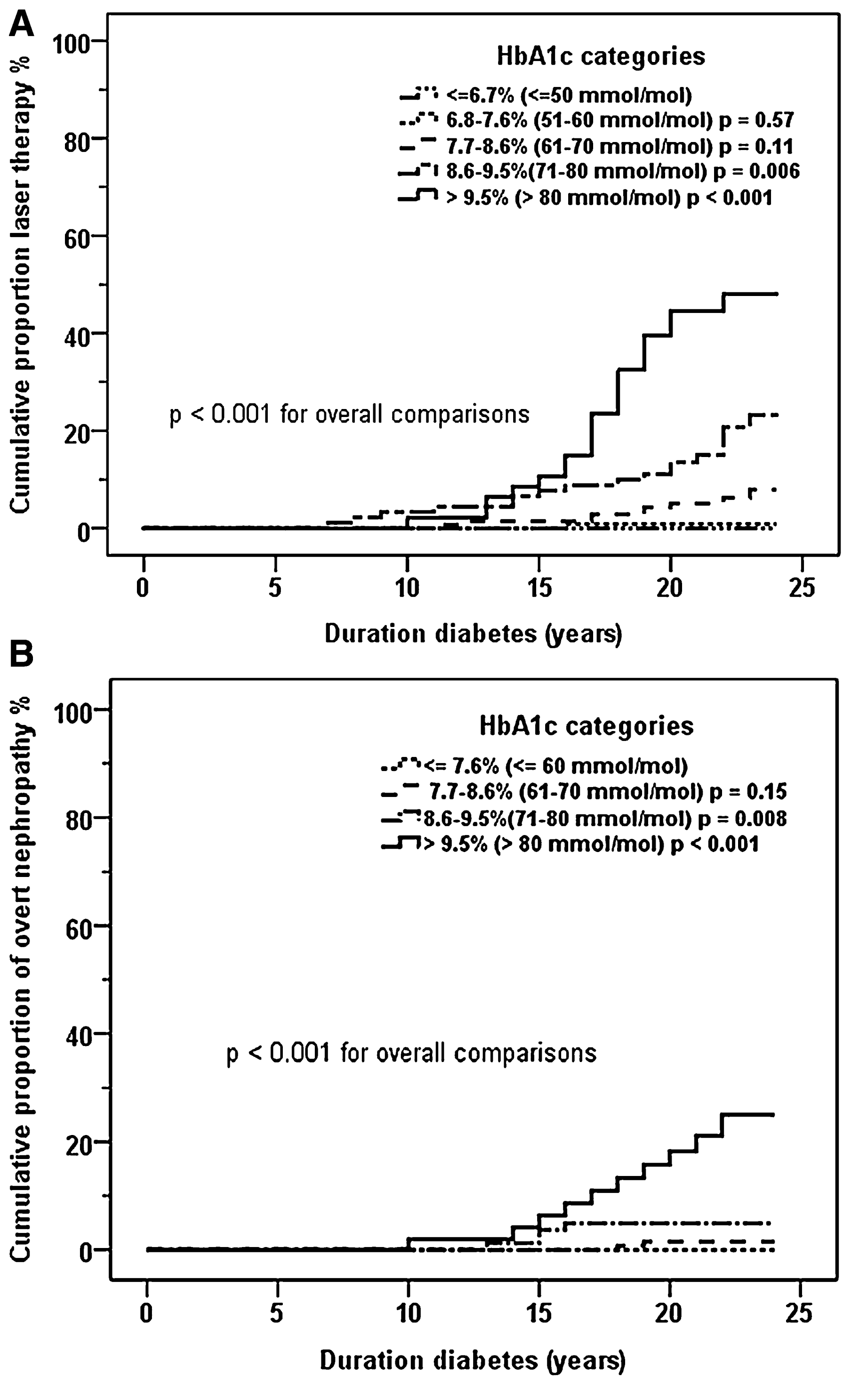

Figure 3—Cumulative proportion of laser-treated retinopathy (*A*) and persistent macroalbuminuria (*B*) in an unselected population of type 1 diabetes with different long-term weighted mean HbA$_{1c}$. *P* values for pairwise comparisons between the group with lowest HbA$_{1c}$ and all other groups indicated in the figure.

importance of our study for longer diabetes durations is limited. In previous studies, the incidence of overt nephropathy has been reported to level off after 25 years of diabetes duration (10,11). This is in contrast to severe retinopathy, where the prevalence is still steadily increasing at the higher HbA$_{1c}$ levels after 25 years of diabetes duration (10). It is therefore necessary to be cautious to extrapolate our results for longer diabetes duration than 20 years. It is also necessary to continue to perform very-long-term epidemiological studies.

It should be pointed out that other factors such as blood pressure, BMI, and lipids may influence the progression of diabetic microangiopathy. In our present study, we found an association between these risk factors and microvascular complications in cross-sectional analysis. Even if there is an association, it is impossible to know if it is a cause or a consequence of the complications. It is also possible that early antihypertensive treatment could alter the level of long-term HbA$_{1c}$, where severe diabetes complications occur, to a higher level. Quite a large proportion of the patients in our study had started antihypertensive treatment (mostly renin-angiotensin-aldosterone system inhibitors) without any signs of nephropathy (14%) or severe retinopathy (23%), and 28% used statins. Previous studies have shown that antihypertensive therapy can slow the progression of microalbuminuria to macroalbuminuria (30), but it is still unclear if early treatment can prevent the development of nephropathy and retinopathy, with conflicting results in different studies (31–33). The Renin Angiotensin System Study (RASS) suggested that the effect could also differ with the level of glycemic control (34). The use of lipid-lowering agents such as statins have also been found to alter the progression of both nephropathy and retinopathy. Even here the results from different studies so far are not conclusive (35,36). In our study, it is not possible to analyze further in order to see if these medications have influenced the impact of long-term mean HbA$_{1c}$ on the development of microvascular complications. Our results, however, must be viewed in the context of clinical guidelines for risk factor treatment.

Further analysis is also necessary to answer the question as to whether or not shorter periods of poor glycemic control are detrimental, especially during puberty. For all these reasons, it is necessary to be cautious when formulating distinct therapy goals.

Clinical Implications

The goal of treatment must be to prevent severe acute and chronic complications and to achieve as good a quality of life as possible. To reduce mortality, the most important factor is to avoid persistent macroalbuminuria, since the higher mortality in type 1 diabetes is mainly limited to patients with overt nephropathy (37–39). If the goal is to prevent persistent macroalbuminuria and proliferative retinopathy, wHbA$_{1c}$ below

~7.6% (60 mmol/mol) seems to be enough. This should be possible to achieve for most patients, even if it may be challenging in routine care. Mean HbA_{1c} in the intensive treatment group in the DCCT study was 7.2% (55 mmol/mol), but in the follow-up EDIC study, carried out over a 10-year period, HbA_{1c} rose to 8.0% (64 mmol/mol), which is in the same range as in our study.

In conclusion we found a strong association between $wHbA_{1c}$ and microvascular complications. Keeping the average HbA_{1c} below 7.6% (60 mmol/mol) seemed to be sufficient to prevent both persistent macroalbuminuria and severe retinopathy for at least up to 20 years and is a reasonable level to aim for in treatment of type 1 diabetes.

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Author Contributions. M.N. and H.J.A designed the study, did the literature research, made the statistical analysis, interpreted the data, and wrote the first draft of the article. M.A. and M.D. designed the study and evaluated the fundus photographs. M.F. made the statistical analysis and interpreted the data. J.L. designed the study, did the literature research, and interpreted the data. All authors reviewed and approved the final version of the report. M.N. is the guarantor of this work and, as such, 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.

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