Lipid and Blood Pressure Treatment Goals for Type 1 Diabetes

10-year incidence data from the Pittsburgh Epidemiology of Diabetes Complications Study

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OBJECTIVE — Subjects with type 1 diabetes are at high risk for many long-term complications, including early mortality and coronary artery disease (CAD). Few data are available on which to base goal levels for two major risk factors, namely blood pressure and lipid/lipoproteins. The objective of this study was to determine at which levels of LDL and HDL cholesterol, triglycerides, and blood pressure the relative risks of type 1 diabetic complications increase significantly.

RESEARCH DESIGN AND METHODS — Observational prospective study of 589 patients with childhood-onset type 1 diabetes (<17 years) aged ≥18 years at baseline; 10-year incidence of mortality, CAD, lower-extremity arterial disease, proliferative retinopathy, distal symmetric polyneuropathy, and overt nephropathy. Relative risks were determined using traditional groupings of blood pressure and lipid/lipoproteins, measured at baseline, using the lowest groupings (<100 mg/dl [2.6 mmol/l] LDL cholesterol, <45 mg/dl [1.1 mmol/l] HDL cholesterol, <100 mg/dl [1.1 mmol/l] triglycerides, <110 mmHg systolic blood pressure, and <80 mmHg diastolic blood pressure) as reference. Adjustments for age, sex, and glycemic control were examined.

RESULTS — Driven mainly by strong relationships (RR range 1.8–12.1) with mortality, CAD, and overt nephropathy, suggested goal levels are as follows: LDL cholesterol <100 mg/dl (2.6 mmol/l), HDL cholesterol >45 mg/dl (1.1 mmol/l), triglycerides <150 mg/dl (1.7 mmol/l), systolic blood pressure <120 mmHg, and diastolic blood pressure <80 mmHg. Age, sex, and glycemic control had little influence on these goals.

CONCLUSIONS — Although observational in nature, these data strongly support the case for vigorous control of lipid levels and blood pressure in patients with type 1 diabetes.

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Current lipid (1,2) and blood pressure (3) guidelines are somewhat "nondefinitive" in terms of recommendations for individuals with diabetes. There is, however, general agreement that people with diabetes form a uniquely high-risk group in terms of cardiovascular disease. Relative risks at all levels of blood pressure and cholesterol are increased more than twofold (4,5). This has led to recommendations (1,2) that diabetes could be treated as more than just another risk factor, such that individuals with diabetes should be treated more vigorously regarding cardiovascular risk factors, e.g., to the same levels as individuals with existing coronary artery disease (CAD) (6). This approach has received considerable support from the demonstration that risk of developing CAD is similar in individuals with diabetes but without CAD and in individuals with CAD but without diabetes (7). This approach is also supported by the results of the Hypertension Optimal Treatment (HOT) Study, which suggest that individuals with diabetes uniquely benefit from a diastolic blood pressure goal of 80 mmHg (8).

Guidelines for prevention of CAD in diabetes generally refer to type 2 diabetes and make little mention of, or specific recommendations for, type 1 diabetes. This largely reflects a relative lack of appropriate data (1). Because of the higher occurrence of other microvascular complications, setting goals is more complex in type 1 diabetes. This is particularly true because these complications may also relate to blood lipids and blood pressure. For example, renal disease (9–11) is predicted by blood lipids, and blood pressure predicts renal disease (12,13), neuropathy (14), and retinopathy (15,16). This is further complicated by a relationship between renal disease and CAD in type 1 diabetes (17,18). Finally, the relatively young age of type 1 diabetic patients and the influence of glycemic control on risk factors and complications add further dimensions to be considered.

This report is designed to provide relevant epidemiologic data and at least partially fill the void noted by the American Diabetes Association (ADA), which stated, in reference to type 1 diabetes, that observational data on lipoproteins and coronary heart disease are relatively few (1). We have examined the predictive power of baseline lipid and blood pressure measures, using a range of "traditional" cutoff levels, in the 10-year follow-up data of the Pittsburgh Epidemiology of

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Abbreviations: ADA, American Diabetes Association; CAD, coronary artery disease; DCCT, Diabetes Control and Complications Trial; DSP, distal symmetric polyneuropathy; EDC, Pittsburgh Epidemiology of Diabetes Complications Study; LEAD, lower extremity arterial disease; ON, overt nephropathy; PR, proliferative retinopathy; RR, relative risk.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Diabetes Complications Study (EDC). The influences of age and glycemic control on the lipid and blood pressure predictions of macrovascular disease (coronary and lower-extremity arterial), microvascular disease (overt nephropathy, proliferative retinopathy, and distal symmetrical polyneuropathy), and total mortality are also considered.

RESEARCH DESIGN AND METHODS— The Pittsburgh Epidemiology of Diabetes Complications Study is a 10-year prospective study based on a well-defined cohort of adults with childhood-onset type 1 diabetes (<17 years). The study included a total of 658 eligible subjects (325 women and 333 men) diagnosed between 1 January 1950 and 30 May 1980 who were first seen at baseline (1986–1988). This report focuses on the 589 patients aged ≥18 years at baseline whose mean age at baseline was 28.7 years and in whom the duration of diabetes was 20.1 years. The patients were seen biennially thereafter. For this analysis, a prospective design was used in which baseline risk factors were compared with the incidence of complications during the following 10 years.

Before each cycle of examinations, information was collected from the participants of the study by questionnaire; questions concerned demographic characteristics, medical history, and health care behaviors as previously described (19,20). During each cycle, to document complications of diabetes, a trained internist recorded a standardized medical history and performed a clinical examination. CAD was defined as angina diagnosed by a clinic physician; myocardial infarction confirmed by Minnesota Q-wave electrocardiography (code 1.1 or 1.2) and/or validated hospital records; CAD death confirmed by death certificate; non–Q-wave ischemia confirmed by Minnesota codes 1.3, 4.1, 4.2, 5.1, 5.2, or 7.1; or coronary artery stenosis ≥50% confirmed by angiography. Lower-extremity arterial disease (LEAD) was defined as amputation for vascular cause, intermittent claudication (Rose questionnaire), or ankle brachial index <0.9.

A 12-lead electrocardiogram was obtained, along with blood pressures measured by a random-zero sphygmomanometer according to a standardized protocol (Hypertension Detection and Follow-Up) (21) after a 5-min rest period. Blood pressure levels were examined, using the mean of the second and third readings, in the following groups: systolic <110, 110–119, 120–129, ≥130 mmHg; diastolic <80, 80–84, 85–89, ≥90 mmHg. Patients taking medications to control blood pressure were placed in the highest categories.

Fasting blood samples were taken from each participant for the measurement of lipids, lipoproteins, and stable glycosylated hemoglobin (HbA_1). HDL cholesterol was determined by a heparin and manganese procedure, a modification (22) of the Lipid Research Clinics method (23). The concentration of HDL3 was measured after precipitation of HDL2 by dextran sulfate. Cholesterol was measured enzymatically (24), as were triglycerides (25). LDL cholesterol levels were calculated from measurements of the levels of total cholesterol, triglycerides, and HDL cholesterol (26). The lipids were examined in the following groups: HDL cholesterol <45, 45–54, ≥55 mg/dl (<1.1, 1.1–1.4, ≥1.4 mmol/l); LDL cholesterol <100, 100–129, 130–159, ≥160 mg/dl (<2.6, 2.6–3.3, 3.3–4.1, ≥4.1 mmol/l); triglycerides <100, 100–149, 150–199, ≥200 mg/dl (<1.1, 1.1–1.7, 1.7–2.2, ≥2.3 mmol/l). The few patients on lipid-lowering therapy ($n = 4$) were placed in the highest category for LDL cholesterol and triglycerides and the lowest category for HDL cholesterol.

HbA_1 was originally measured in saline-incubated samples by microcolumn cation-exchange chromatography (Isolab, Akron, OH). On 26 October 1987, the method was changed to high-performance liquid chromatography (Diamat; Bio-Rad Laboratories, Hercules, CA). Readings with the two methods were shown to be almost identical ($r = 0.95$; Diamat HbA_1 = 0.18 + 1.00 Isolab HbA_1). The difference between the means of the two methods was 0.158% (normal range 4.9–7.3% HbA_1).

Nephropathy status was determined based on consistent results from at least two of three (24-h, overnight, random, or postclinic) timed urine albumin excretion rates. Urinary albumin was determined immunonephelometrically (27). Overt nephropathy (ON) was defined as an albumin excretion rate >200 μg/min or end-stage renal disease (renal dialysis or transplant). Proliferative retinopathy (PR) was determined by stereoscopic fundus photography and grades >60 on the modified Airlie House System or laser therapy for PR. Distal symmetric polyneuropathy (DSP) was based on a clinical neurological evaluation, performed by a trained internist, consistent with that used for the Diabetes Control and Complications Trial (DCCT) (28). A standard clinical history was recorded and included any concurrent disease processes that could cause neuropathy, exposure to known neurotoxins, and family history of neuromuscular disorders. Participants were questioned about sensory, motor, and autonomic symptoms. Positive responses were recorded: for example, numbness, dysesthesia and/or paresthesia, hypersensitivity to touch, and burning, aching, or stabbing pain in the hands and/or feet. A standard neurological examination included evaluation of reflex activity and sensation to light touch (cotton wool), pain (pinprick), vibration (tuning fork), and proprioception. Muscle weakness, coordination, and gait were also assessed. DSP was defined as the presence of two or more of the following: symptoms, sensory and/or motor signs, absent (or present only with reinforcement) tendon reflexes. From the 4-year follow-up examination (cycle 3) onward, DSP was confirmed using, in addition to the above, the presence of a vibratory threshold above the age-specific normal range using the Vibratron II tester (Physitemp Instruments, Clifton, NJ). The criteria for an abnormal vibratory threshold are >2.39, >2.56, and >2.89 vibration units for ages ≤35, 36–50, and >50 years, respectively (29). Vibratory sensory thresholds were measured on the plantar aspect of the great toe on the dominant side of the body and gave an assessment of large sensory nerve fibers. A forced-choice procedure for the determination of vibratory threshold was used. Precision (repeatability) data have been reported previously in detail (30). The coefficient of variation for the great toe was 8%.

Statistical analysis

Cox proportional hazards modeling was used to determine the relative hazard for each risk factor grouping; the lowest risk factor group was used as a reference. Adjustments for age and glycemic control were examined in separate models. To save space and confusion, confidence intervals around the relative risks have not been given, although significant *P* values

Table 1—*Distribution of lipids/lipoproteins and blood pressure: baseline EDC population aged 18+ years* (n = 589)

	Overall		Men		Women	
	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range
LDL cholesterol (mg/dl)	112.8	41.8	115.2	45.8	110.8	40.0
HDL cholesterol (mg/dl)	52.2	16.0	47.1	13.0	57.8	16.7
Triglycerides (mg/dl)	82.0	65.0	89.0	70.8	77.0	52.3
Systolic blood pressure (mmHg)	112.2	17.0	115.0	16.0	109.0	15.3
Diastolic blood pressure (mmHg)	72.0	14.0	77.0	14.0	69.5	11.0

($<$0.05) have been reported. Because age and duration are highly correlated (r = 0.84), adjustment for one effectively adjusts for the other. To save space, only age adjusted data are presented.

RESULTS — The study population for each analysis comprised all patients with the baseline measure of interest who did not have the specific complication of interest and for whom follow-up data were available. Therefore, the number of events/number of patients at risk was 67/589 for mortality, 105/540 for CAD, 92/542 for LEAD, 52/420 for ON, 120/351 for DSP, and 148/203 for PR. For reference purposes, the distribution of lipid fractions and blood pressures are listed in Table 1. The relative risks (RRs) associated with levels of each risk factor for the six complications studied compared with the lowest risk factor level for all subjects are shown in Table 2.

The patterns of risk and threshold levels associated with increased risk did not differ often by sex, although because of the smaller sample sizes, significance levels were generally smaller. The major differences for mortality were a stronger association in women with HDL cholesterol (e.g., 45–54 mg/dl [1.1–1.4 mmol/l], RR = 0.4 in women, $P < 0.05$, RR = 0.7 in men, NS) and triglycerides (e.g., 150–199 mg/dl [1.7–2.2 mmol/l], RR = 8.5 in women, $P < 0.001$, and RR = 2.4 in men, NS). Similarly, for CAD, HDL cholesterol was a stronger risk factor in women (45–54 mg/dl [1.1–1.4 mmol/l], RR = 0.2, $P < 0.001$) than in men (RR = 0.6, NS). For LEAD, little sex difference in RRs was seen, whereas for PR, little difference was seen, except for a remarkably high RR (9.1) in women with triglyceride levels of 150–199 mg/dl (1.7–2.2 mmol/l), $P < 0.001$, compared with an RR of 0.8 in men (NS). For DSP and HDL cholesterol, an interaction by sex was apparent; HDL cholesterol was positively related to DSP in men (e.g., 55 mg/dl [1.4 mmol/l], RR = 2.1, $P < 0.05$) and negatively in women (RR = 0.4, $P < 0.05$). LDL cholesterol was more strongly related to DSP in men, as was diastolic blood pressure (e.g., ≥90 mmHg, RR = 8.3, $P < 0.001$, in men vs. RR = 2.7 in women, NS). For ON, no major differences by sex were seen.

Adjustment for age (Fig. 1) had only a minimal effect, which was, as expected, a slight decrease in the magnitude of RR. For total mortality, all significant RRs remained, whereas for CAD, the only changes were for LDL cholesterol (100–129 and 130–159 mg/dl [2.6–3.3 and 3.3–4.1 mmol/l]; RRs reduced to 1.6 from 1.8 and 2.3, respectively). No differences in significance levels were seen for either LEAD or PR, whereas for DSP, the only loss of significance was for diastolic blood pressure 85–89 mmHg, with the RR decreasing from 2.0 ($P < 0.05$) to 1.8 (NS). RRs for ON were marginally strengthened by age adjustment. Figure 1*A* shows these age-adjusted RRs for the lipid/lipoproteins, and Fig. 1*B* shows the age-adjusted RRs for blood pressure.

Separate adjustment for HbA_1 also had only a minor effect, which was generally to increase the RRs. One major difference was for PR, wherein the RR for patients with increased LDL cholesterol was lost (e.g., LDL 130–159 mg/dl [3.3–4.1 mmol/l]), RR decreased from 2.0 ($P <$ 0.01) to 1.6 (NS). A similar effect was seen for DSP (RR for LDL cholesterol 130–159 mg/dl [3.3–4.1 mmol/l], reduced from 2.2, $P < 0.01$, to 1.9, $P < 0.05$).

Because of the increased risks seen in triglyceride concentrations across the two lowest groupings, further analyses were performed with groupings of patients

Table 2—*Relative risks by baseline lipid or blood pressure level: 10-year follow-up of the EDC cohort aged ≥18 years at baseline*

Risk factor	Mortality	CAD	LEAD	Nephropathy	PR	DSP
LDL cholesterol (mg/dl)						
100–129	5.3*	1.8†	1.4	1.1	1.3	1.5
130–159 (ref >100)	5.6*	2.3*	2.5*	2.2†	2.0*	2.2*
≥160	12.1‡	3.0‡	2.5*	2.6†	1.9†	1.9†
Triglycerides (mg/dl)						
100–149	2.0	2.5†	1.2	1.8	1.0	1.5
150–199 (ref <100)	4.3‡	3.3*	1.2	3.2*	1.8	1.6
≥200	7.1‡	4.0‡	1.9	3.0*	1.6	1.5
HDL cholesterol (mg/dl)						
45–54	0.7	0.4‡	0.6	0.8	0.7	0.7
≥55 (ref <45)	0.5†	0.4‡	0.8	0.7	0.7	1.1
SBP (mmHg)						
110–119	2.1	1.8†	1.3	0.9	1.0	0.8
120–129 (ref <110)	3.0*	2.5*	1.7	1.4	1.6	0.9
≥130	7.2‡	5.6‡	4.0‡	2.3	2.7‡	4.0‡
DBP (mmHg)						
80–84	2.4*	1.4	1.9†	1.1	1.8†	0.8
85–89 (ref <80)	1.6	2.0	2.0†	2.5	2.4*	2.0†
≥90	4.0‡	4.2*	1.9	3.2	4.6‡	4.7*

*$P < 0.01$; †$P < 0.05$; ‡$P < 0.001$.

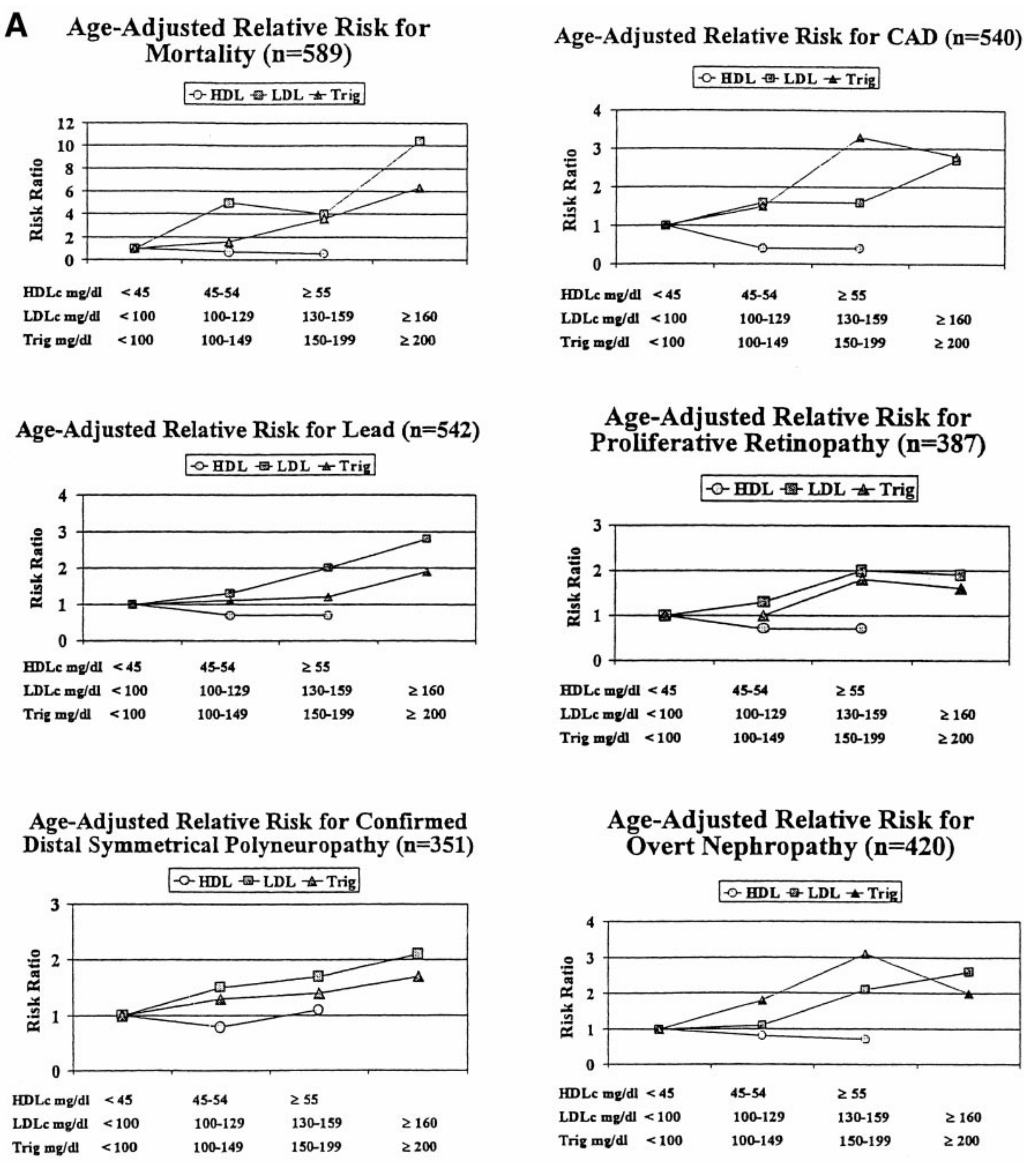

Figure 1—A: *Age-adjusted relative risks for lipid/lipoproteins versus complications in type 1 diabetes; EDC 10-year follow-up.* B: *Age-adjusted relative risks for blood pressure versus complications in type 1 diabetes; EDC 10-year follow-up.*

with triglyceride levels of 100–129 and 130–149 mg/dl (1.1–1.5 and 1.5–1.7 mmol/l), which revealed no difference in risk across these two categories, suggesting that 150 mg/dl (1.7 mmol/l) is the better cutoff level. Similar analyses were performed to examine HDL levels <45 mg/dl (1.1 mmol/l) (i.e., <35 and 35–44 mg/dl [<0.9 and 0.9–1.1 mmol/l]) with the same result, i.e., no lower discriminating threshold was apparent.

Finally, instead of age adjustment in the Cox model, analyses were repeated stratifying patients by age into two groups: 18–29 and ≥30 years of age (maximum n = 331 and 258, respectively). Few major differences were seen by age-group, with the "thresholds" reported above generally applying to both age-groups. However, one major difference was the effect of LDL cholesterol on mortality risk, with moderate RRs for patients aged 18–29 years (1.7–3.2) but extremely high RRs for patients aged ≥30 years (i.e., for LDL cholesterol 100–129, 130–159, ≥160 mg/dl [2.6–3.3, 3.3–4.1, ≥4.1 mmol/l], RR = 13.5, 10.4, and 27.4, respectively). For LEAD, the LDL cholesterol relationship was only seen in patients aged ≥30 years when the RR was significantly increased with or without HbA_1 adjustment, for the 130–159 and ≥160 mg/dl (3.3–4.1 and ≥4.1 mmol/l) group. The LDL cholesterol association was also weakened for DSP in the older age-group but remained significant in

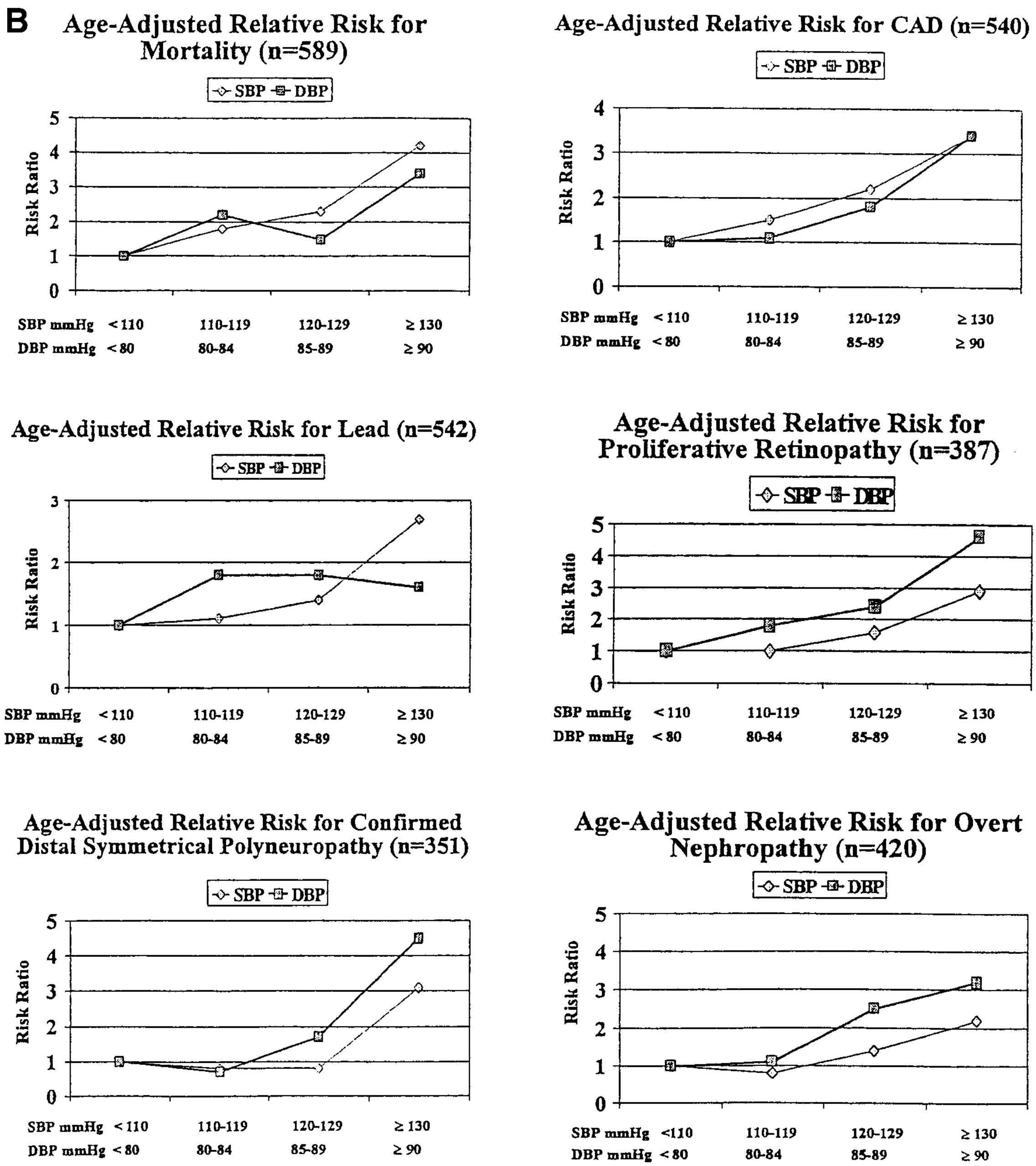

Figure 1. *Continued.*

those aged 18–29 years (e.g., LDL 130–159 mg/dl [3.3–4.1 mmol/l], RR = 2.8 [$P < 0.01$]) for patients aged 18–29 years and RR = 1.3 (NS) for those ≥30 years.

Based on these results, it is recommended that the treatment goals for type 1 diabetic patients should be LDL cholesterol <100 mg/dl (2.6 mmol/l), HDL cholesterol >45 mg/dl (1.1 mmol/l), triglycerides <150 mg/dl (1.7 mmol/l), systolic blood pressure <120 mmHg, and diastolic blood pressure <80 mmHg.

CONCLUSIONS — The above recommendations are based on the overall data presented for the six major complications, with a particular emphasis on total mortality and its two major contributors, CAD and ON. In terms of the lipid/lipoproteins, the goal LDL cholesterol level of 100 mg/dl (2.6 mmol/l) seems appropriate for mortality and CAD, although it could be argued that 130 mg/dl (3.3 mmol/l) would be more appropriate for the other complications. A higher goal for triglyceride concentration on the basis that 200 mg/dl (2.3 mmol/l) is the risk level for LEAD is outweighed by the predictive power of 150 mg/dl (1.7 mmol/l) for mortality, CAD, and ON. Therefore, these data strongly suggest that the triglyceride concentration should be lower than the inferred goal of 200 mg/dl (2.3 mmol/l) in the ADA and National Cholesterol Education Program guidelines (1,2) and provide considerable support for the LDL cholesterol goal of 100 mg/dl (2.6 mmol/l) advocated by the ADA for type 2 diabetes being extended to type 1 diabetes (6). It should be noted that all data in this report are "primary," i.e., based on incidence events in subjects free from the complication in question. We have insufficient follow-up time and sample size to assess goal levels for type 1 diabetic subjects with preexisting CAD, etc., and would therefore defer to the type 2 diabetes recommendations by default. With the exception of CAD, HDL cholesterol did not show strong and consistent associations. Because an HDL cholesterol level of 45–54 mg/dl (1.1–1.4 mmol/l) was equally as predictive as ≥55 mg/dl (≥1.4 mmol/l) for CAD, a goal of 45 mg/dl (1.1 mmol/l) is recommended.

The blood pressure recommendations pose an additional problem, in that these determinations were based on random zero readings, which are not generally used in clinical practice and tend to underrecord blood pressure (particularly systolic). For this reason, an argument could be made to increase the goal levels to 130/85 rather than the 120/80 advocated in Table 1. On the other hand, the predictive power of systolic blood pressure of 110 mmHg for CAD and diastolic blood pressure ≥80 mmHg for total mortality, LEAD, and PR justify our lower goal. The RR for diastolic blood pressure was also considerable (2–3), although it was not significant for ON, reflecting the relatively low number of events ($n = 52$).

The sex and age adjustments were generally minor and did not suggest a need for sex- or age-specific goals. Therefore, these goals would seem applicable to both men and women with type 1 diabetes aged 18–55 years. It should be noted that age and duration are highly correlated in this cohort ($r = 0.84$), and thus, controlling for age effectively controls for duration. Therefore, it follows that duration-specific or -adjusted target values are also not indicated. An additional question is whether these goals are appropriate for type 1 diabetic subjects aged <18 years. We have observed five incident CAD events (including one fatal) in subjects aged <18 years at baseline during the 10-year follow-up. Therefore, it would seem reasonable to extend these goals to younger subjects.

The issue of glycemic control is theoretically more complex, because one might argue that blood pressure and lipid goals should be set in the face of good glycemic control clearly indicated for all type 1 diabetic subjects (31). However, in practical terms, adjustment for HbA_1 had only a minor effect overall and marginally strengthened CAD associations. Although this latter observation might seem surprising, it is consistent with our repeated observations that glycemic control is not strongly associated with CAD in this cohort (18,32) and some (33) but not all (34) other type 1 diabetes cohorts. Prior glycemic control was also not associated with carotid intima-medial thickness in the major DCCT/EDC follow-up study (34). The interpretation of these data, including in this report the effect of controlling for glycemia, is clearly that blood pressure and lipid goals should be seen as separate issues (rather than being secondary to glycemia) and pursued just as vigorously in terms of mortality and CAD prevention. Furthermore, it is important to note that the absolute event rates for each complication are in the 2–5% rate per year, meeting the European and U.K. criteria of risk that justify pharmacologic intervention.

Clearly, the goals derived from these epidemiologic observations are only one of many factors to consider in developing management plans and thresholds for pharmacologic intervention. In particular, clinical trial evidence of benefit is desirable. Sadly, few such trials have been conducted in type 1 diabetes concerning lipids or blood pressure; however, those that have been conducted are generally positive though on a small scale (35,36). Given our current knowledge of the benefits of lowering lipid levels and blood pressure in type 2 diabetic and general populations, it seems unlikely that definitive trials will be conducted in type 1 diabetes. Although these goals are ambitious, given the efficacy of modern medications, particularly statins and angiotensin-converting enzyme inhibitors, we believe they are achievable for most patients. Finally, although these data demonstrate a strong relationship between blood pressure and lipids and the incidence of complications, they in no way diminish the need for optimal glycemic control for the prevention of type 1 diabetes microvascular complications, which has been well demonstrated both epidemiologically in this cohort (37) and interventionally in the DCCT trial (31).

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