The Effect of Intensive Diabetes Treatment on Resting Heart Rate in Type 1 Diabetes

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study

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OBJECTIVE — Cardiovascular disease is a major cause of morbidity and mortality in individuals with type 1 diabetes. Resting heart rate (RHR) is a risk factor for cardiovascular disease in the general population, and case-control studies have reported a higher RHR in individuals with type 1 diabetes. In individuals with type 1 diabetes, there is a positive correlation between A1C and RHR; however, no prospective studies have examined whether a causal relationship exists between A1C and RHR. We hypothesized that intensive diabetes treatment aimed to achieve normal A1C levels has an effect on RHR in individuals with type 1 diabetes.

RESEARCH DESIGN AND METHODS — A total of 1,441 individuals with type 1 diabetes who participated in the Diabetes Control and Complications Trial (DCCT) had their RHR measured biennially by an electrocardiogram during the DCCT and annually for 10 years during the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study.

RESULTS — During the DCCT, intensive treatment was associated with lower mean RHR than conventional treatment, both in adolescents (69.0 vs. 72.0 bpm [95% CI 62.8–75.7 and 65.7–78.9, respectively], $P = 0.013$) and adults (66.8 vs. 68.2 [65.3–68.4 and 66.6–69.8, respectively], $P = 0.0014$). During follow-up in the EDIC, the difference in RHR between the treatment groups persisted for at least 10 years ($P < 0.0001$).

CONCLUSIONS — Compared with conventional therapy, intensive diabetes management is associated with lower RHR in type 1 diabetes. The lower RHR with intensive therapy may explain, in part, its effect in reducing cardiovascular disease, recently demonstrated in type 1 diabetes.

Diabetes Care 30:2107–2112, 2007

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Received for publication 11 August 2006 and accepted in revised form 23 April 2007.

Published ahead of print at http://care.diabetesjournals.org on 27 April 2007. DOI: 10.2337/dc06-1441.

Additional information for this article can be found in an online appendix at http://dx.doi.org/10.2337/dc06-1441.

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Abbreviations: DCCT, Diabetes Control and Complications Trial; ECG, electrocardiogram; EDIC, Epidemiology of Diabetes Interventions and Complications Study; RHR, resting heart rate; SBP: systolic blood pressure.

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

Cardiovascular disease is the major cause of mortality in individuals with diabetes (1,2) and consumes the majority of the health care expenditures attributable to diabetes in the U.S. (3). Resting heart rate (RHR) is a risk factor for cardiovascular disease and mortality in the general population (4–13). For example, after adjustment for other risk factors the odds ratio for all-cause mortality during 36 years of follow-up of individuals with hypertension in the Framingham Heart Study was 1.98 [95% CI 1.52–2.59] for men and 1.87 [1.37–2.56] for women for each heart rate increment of 40 bpm (8). Case-control studies have reported a higher RHR in individuals with type 1 diabetes compared with age-matched control subjects (14). In a study of 44 monozygotic twins discordant for type 1 diabetes (with a mean duration of type 1 diabetes of 14 years), RHR in the type 1 diabetic twin was, on average, 8 bpm higher than that in the nondiabetic co-twin ($P < 0.0005$) (15). Cross-sectional studies have reported an association between A1C and RHR in individuals with type 1 diabetes, with poor glycemic control being positively associated with RHR in a study of 148 children with type 1 diabetes (16). However, there was no association between change in A1C and change in RHR over a 1-year follow-up (16). These studies suggest that type 1 diabetes results in higher RHR. Further, the correlations observed with glycemia suggest that the level of metabolic control plays an important role in influencing RHR. However, there have been no prospective studies of intensive diabetes treatment (focused on improved glycemic control) on RHR in individuals with type 1 diabetes. We have examined whether intensive diabetes treatment with the aim of achieving glycemic levels as close to the nondiabetic range as possible affects RHR using data collected during the Diabetes Control and Complications Trial (DCCT) and its follow-up study, Epidemiology of Diabetes Interventions and Complications (EDIC). Specifically, we hypothesized that *1)* RHR at the DCCT baseline is associated with the duration of type 1 diabetes before

entry into the study and glycemic control, 2) there is an effect of intensive therapy, compared with conventional therapy, during DCCT on RHR, 3) any demonstrable effect of intensive therapy on RHR will be explained by differences in glycemic control between intensive and conventional therapy, and 4) any effect of intensive versus conventional therapy on RHR during the DCCT will continue during the EDIC follow-up, supporting the metabolic memory phenomenon that has been demonstrated for other complications.

RESEARCH DESIGN AND METHODS

— The inclusion and exclusion criteria for the DCCT and the treatment protocol have been described in detail (17). Briefly, 1,441 subjects with type 1 diabetes aged between 13 and 39 years were recruited into the DCCT between 1983 and 1989. The primary prevention cohort consisted of 726 subjects with no retinopathy, a urinary albumin excretion rate <40 mg/24 h and diabetes duration of 1–5 years. The secondary intervention cohort consisted of 715 subjects who had nonproliferative retinopathy, urinary albumin excretion rate ≤200 mg/24 h, and diabetes duration of 1–15 years. As part of the screening for the DCCT, individuals were excluded if they had hypertension (defined by systolic or diastolic blood pressure ≥140 or ≥90 mmHg, respectively), a history of symptomatic ischemic heart disease, or the presence of major electrocardiographic abnormalities suggestive of coronary heart disease, specifically myocardial infarction (17). Subjects in the primary prevention and secondary intervention cohorts were randomly assigned to either intensive or conventional treatment arms and assessed for complications at frequent follow-up visits. The intensive and conventional treatment groups maintained a separation of median A1C level of about 2 percentage points throughout the follow-up period (7.1 vs. 9.0%; $P < 0.001$). Baseline characteristics of participants have been provided elsewhere (41). The DCCT was terminated in 1993, after a mean duration of follow-up of 6.5 years, which was 1 year ahead of schedule, when the principal study questions concerning treatment effects had been answered. In 1994, 1,375 DCCT subjects (96% of the surviving cohort), 687 from the intensive arm and 688 from the conventional arm, agreed to participate in the EDIC follow-up study, which included annual examinations measuring diabetes complications (18). A1C was measured by high-performance liquid chromatography in a central laboratory at baseline and then quarterly during the DCCT and annually during the EDIC (19). For the analysis at the DCCT baseline and during DCCT treatment, individuals aged <18 years at the DCCT baseline ($n = 195$) (20) were analyzed separately from those aged ≥18 years because of a negative relationship between age and RHR during adolescence. All subjects were analyzed together during the EDIC, as all were aged >18 years at the start of the EDIC.

RHR

Twelve-lead resting electrocardiograms (ECGs) were obtained at the DCCT baseline, every 2 years (up to 8 years) during the DCCT, at closeout of the DCCT, and annually during the EDIC, according to the DCCT Manual of Operations (Chapter 18) (15). ECGs were obtained by a certified technician or research nurse at 29 clinics and read according to the revised Minnesota Code (21) (22) at the Central ECG Reading Unit (University of Minnesota, under the direction of Dr. Richard S. Crow). In brief, at least 1 full min of ECG tracing was obtained consisting of 5 s of each of the leads (I, II, III, aVR, aVL, aVF, and V1–V6).

An internal quality control surveillance program entailed the duplicate masked evaluation of 10% of ECGs and was used to estimate the reproducibility of the grading system. During the EDIC, 90% of ECGs scheduled were obtained, and 95% of those were coded as having no technical difficulties for Minnesota scoring. The coding procedure involved duplicate independent coding and tabulation with adjudication by the supervisor for codes on which there was disagreement. Four levels of quality control procedures were used: 1) training and repeat testing of coders; 2) daily intercoder independent comparisons; 3) internal recirculation of records; and 4) errors detected during serial comparison. RHR was obtained by measuring three complete R-R intervals from lead I to the nearest 0.5 mm and then converted to rate per minute (21). RHRs from ECGs with the specific Minnesota codes (atrial fibrillation [8-3-1], atrial flutter [8-3-2], supraventricular rhythm [8-4-1]; second degree atrioventricular block [6-2-1/2), ventricular rhythm [8-2-2], and electronic pacemaker [6-8]) were considered missing for the analysis.

Statistical analysis

General linear models were used for the analysis of the DCCT baseline for patients aged <18 years of age, whereas generalized estimating equations were applied for subjects aged ≥18 years because of the violation of normality of RHR. For the repeated measures of RHR during the DCCT and EDIC, analyses were performed using mixed linear models under the intent-to-treat assumption. All analyses used ln(RHR). The DCCT treatment analysis adjusted for the DCCT baseline RHR; the EDIC analysis adjusted for the DCCT closeout RHR as the EDIC baseline.

ln(RHR) was regressed against variables selected from the literature (23–26) measured at the DCCT baseline, including age, sex, duration of type 1 diabetes, eligibility A1C, clinic, smoking status, systolic blood pressure (SBP), triglycerides, HDL cholesterol, stimulated C-peptide, ethnicity (white or nonwhite), BMI, alcohol (yes/no), caffeine consumption, exercise, clinical neuropathy classification (27,28), R-R interval variation, Valsalva ratio (29), DCCT treatment group, and cohort. Medication use (ACE inhibitors, β-blockers, and calcium-channel antagonists) reported at each year during the EDIC were included in the EDIC analysis as a time-dependent covariates. Medication use was not reported during the DCCT.

In the multivariate analyses, variables with $P < 0.05$ were considered significant and are mentioned in RESULTS; nonsignificant variables are not mentioned unless relevant. Interactions were not included in the models, except to determine whether treatment effects differed over time and to calculate the corresponding least-square means. The assumptions of normality and constant variance were not violated on the basis of the distribution of residuals and the residual versus predicted plot, respectively. To determine whether the treatment effect in the DCCT could be explained by differences in A1C, updated mean ln(A1C) was calculated during the DCCT and used as a time-dependent covariate. For the EDIC analysis, the mean DCCT ln(A1C) for all the visits during the DCCT was calculated for each individual, and the length of time in the DCCT was included. The differences in the sum of squares regression for treatment groups adjusted and unadjusted for mean ln(A1C) as described above were used to calculate the fraction of the treatment effect explained by A1C (30). Smok-

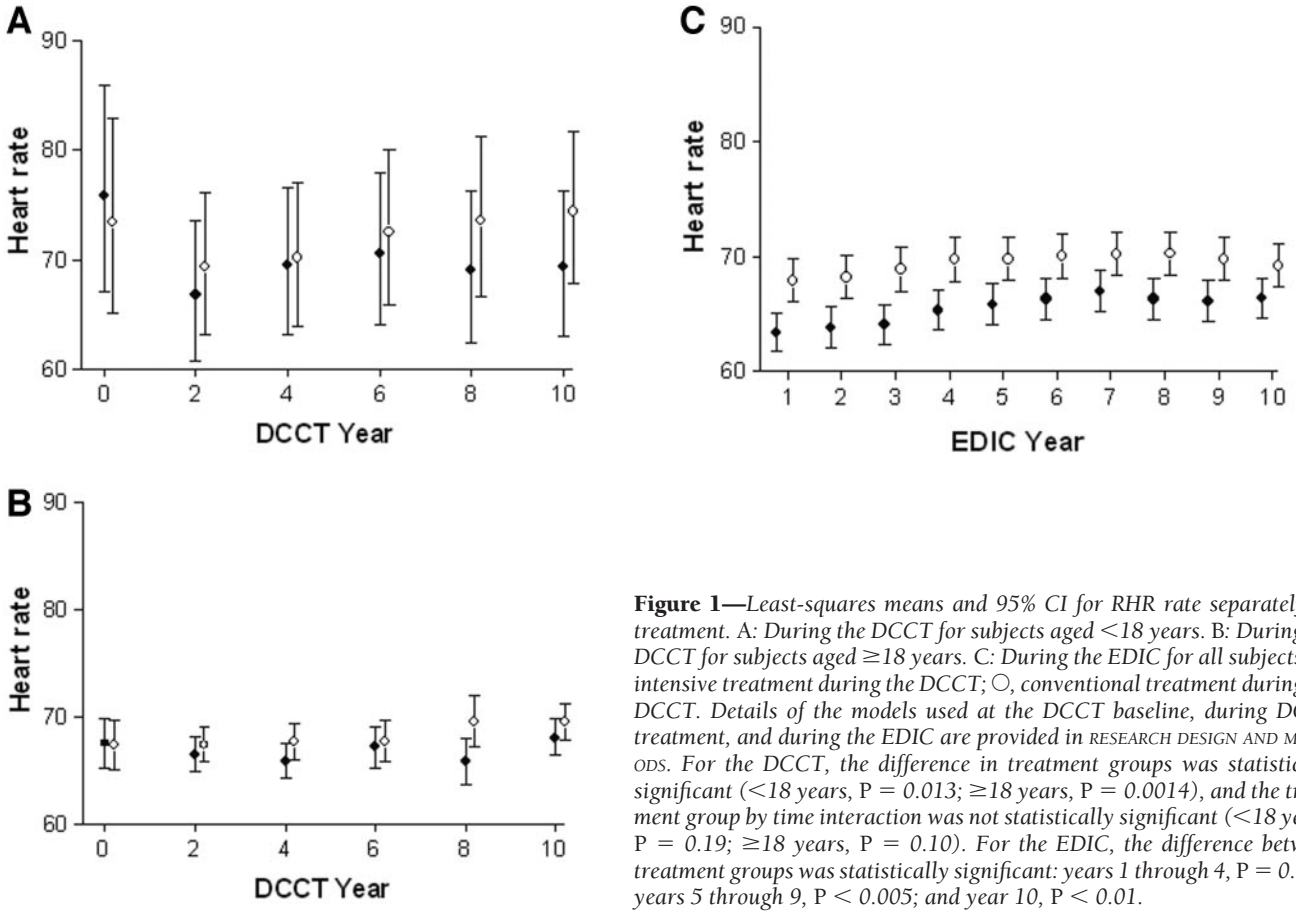

Figure 1—*Least-squares means and 95% CI for RHR rate separately by treatment.* A*: During the DCCT for subjects aged <18 years.* B*: During the DCCT for subjects aged ≥18 years.* C*: During the EDIC for all subjects.* ●*, intensive treatment during the DCCT;* ○*, conventional treatment during the DCCT. Details of the models used at the DCCT baseline, during DCCT treatment, and during the EDIC are provided in* RESEARCH DESIGN AND METHODS*. For the DCCT, the difference in treatment groups was statistically significant (<18 years,* P *= 0.013; ≥18 years,* P *= 0.0014), and the treatment group by time interaction was not statistically significant (<18 years,* P *= 0.19; ≥18 years,* P *= 0.10). For the EDIC, the difference between treatment groups was statistically significant: years 1 through 4,* P *= 0.001; years 5 through 9,* P *< 0.005; and year 10,* P *< 0.01.*

ing status and exercise status reported at each year during the DCCT and EDIC were added to the DCCT and EDIC analyses as time-dependent covariates, respectively, to determine whether the treatment effect could be explained by the addition of these variables. R-R variation at closeout of the DCCT was also added to the EDIC analysis, in addition to A1C, smoking status, and exercise status, to determine whether it provided any additional explanation of the treatment effect. The treatment effects explained by these additional variables in the DCCT and EDIC analyses were calculated similarly to those for A1C as mentioned above. The procedure of Holm (31) was used to correct for multiple comparisons. All statistical analyses were performed using SAS (version 8.2; SAS Institute, Cary, NC).

RESULTS — Average duration in the DCCT was 7.0 ± 2.0 (mean ± SD) years for subjects <18 years of age and 6.0 ± 1.6 years for those ≥18 years. DCCT baseline variables are provided in Table 1 of the online appendix (available at http://dx.doi.org/10.2337/dc06-1441) separately by age-group and assigned treatment. Significant differences between treatment groups were found in HDL cholesterol ($P = 0.0110$) for adolescents and in stimulated C-peptide ($P = 0.0299$) and SBP ($P = 0.0048$) for adults at the DCCT baseline. All of the other variables listed in Table 1 of the online appendix were similar among treatment groups. The number of subjects, RHR measures in each time period, and unadjusted RHR values by categorical covariates at the DCCT baseline, during the DCCT, and during the EDIC are provided in Table 2 of the online appendix, again with the values during the DCCT provided separately for subjects <18 and ≥18 years of age. The unadjusted RHR values by medication usage are provided in Table 3 of the online appendix. The unadjusted RHR values by time during the DCCT and EDIC are provided in Tables 4 and 5 of the online appendix, respectively. The least-square means for the treatment groups over time during the DCCT (provided separately for subjects <18 and ≥18 years of age) and during EDIC are presented in Fig. 1. There were a total of 18,960 RHR measures obtained throughout the study.

DCCT baseline analysis for subjects aged <18 years

General linear models were used for the analysis of the DCCT baseline for patients aged <18 years. *F* tests were used to determine statistical significance. At the DCCT baseline, RHR was significantly associated with exercise ($P = 0.027$). Univariate *t* tests were performed to determine which exercise levels differed from one another using a Holm adjustment; however, a significant difference could not be detected at the univariate level, which may be due to the small sample size. RHR was negatively associated with RR variation ($P = 0.0062$) and positively associated with SBP ($P = 0.0010$). Contrary to one of our hypotheses, there was no significant association between the DCCT baseline RHR and A1C ($P = 0.11$) or type 1 diabetes duration ($P = 0.59$). There was no significant difference in RHR by treatment group at the DCCT baseline ($P = 0.15$). The relatively small size of the <18-year-old cohort may have

limited our ability to establish a relationship with some of the variables examined.

DCCT baseline analysis for subjects aged ≥18 years

Generalized estimating equations were applied for subjects aged ≥18 years because of the violation of normality of RHR. Score χ^2 tests were used to determine statistical significance. At the DCCT baseline, RHR was significantly higher in women than in men ($P < 0.0001$), higher in smokers ($P = 0.0071$), lower in those who drank alcohol ($P = 0.040$), and lower in those who reported hard or strenuous exercise compared with moderate exercise (overall $\chi^2 = 12.94$, 3 d.f., $P = 0.0048$). RHR was positively associated with triglycerides ($P = 0.0004$), A1C ($P = 0.0019$), duration of type 1 diabetes ($P = 0.0007$), and SBP ($P = 0.0022$) and was negatively associated with R-R variation ($P < 0.0001$). Again, there was no significant difference between treatment groups ($P = 0.82$).

Analyses of RHR during the DCCT for subjects aged <18 years at baseline

Mixed linear models under the intent-to-treat assumption were used for RHR during the DCCT. During the DCCT, RHR was significantly higher in the group randomly assigned to conventional therapy than in the group assigned to intensive therapy ($P = 0.013$, least-squares mean 72.0 [95% CI 65.7–78.9] and 69.0 [62.8–75.7], respectively). RHR was also higher in women than in men ($P = 0.0004$) and increased over time ($P = 0.0001$). However, the difference between treatment groups did not change over time. The DCCT RHR was significantly positively associated with both the DCCT baseline RHR ($P < 0.0001$) and caffeine ($P = 0.028$) consumption. There was no significant association between RHR during the DCCT and baseline A1C ($P = 0.44$).

Analyses of RHR during the DCCT for subjects aged ≥18 years at baseline

As in the younger age-group, subjects randomly assigned to conventional therapy had higher RHR than those receiving intensive therapy ($P = 0.0014$, least-squares mean 68.2 [95%CI 66.6–69.8] and 66.8 [65.3–68.4], respectively). RHR increased over time during the DCCT ($P < 0.0001$). Women had higher RHR than men ($P < 0.0001$), as did those in the secondary cohort compared with those in the primary cohort ($P = 0.010$). The DCCT RHR was also positively associated with the following DCCT baseline variables: RHR ($P < 0.0001$), A1C ($P = 0.0001$), stimulated C-peptide ($P = 0.040$), and SBP ($P = 0.0008$).

In both age-groups, including the updated mean ln(A1C) during the DCCT in the model resulted in the treatment effect on RHR no longer being significant ($P = 0.61$ for the <18-year-old group vs. $P = 0.075$ for the ≥18-year-old group). This longitudinal measure of A1C explained 96% of the treatment effect on RHR in the <18-year-old group and 69% of the treatment effect in the ≥18-year-old group. When smoking status and exercise status were added to the model as time-dependent covariates, neither variable was found to be statistically significant for the <18-year-old group ($P = 0.38$ and $P = 0.11$), respectively. However, for the ≥18-year-old group, exercise status was statistically significant ($P = 0.002$), and the *P* value for the treatment effect increased to $P = 0.29$ compared with $P = 0.08$ when the longitudinal measure of A1C was included alone. Those who reported hard exercise had a statistically lower RHR than those who reported mild ($P = 0.001$) or moderate ($P = 0.002$) exercise. The longitudinal measure of A1C and exercise status together explained 90% of the treatment effect on RHR in the ≥18-year-old group.

Analysis of RHR during the EDIC

Both age-groups were analyzed together during follow-up in the EDIC because all were aged >18 years. ln(RHR) during the EDIC continued to be significantly higher in those who were randomly assigned to conventional treatment compared with the intensive treatment group in the DCCT ($P < 0.0001$, least-squares mean 68.0 [95%CI 66.5–69.6] and 66.6 [65.2–68.1], respectively). It also was higher in women than in men ($P = 0.024$) and in smokers ($P = 0.0051$). The EDIC RHR was positively associated with the DCCT closeout RHR ($P < 0.0001$) and with variables measured at the DCCT baseline, including triglycerides ($P = 0.050$), A1C ($P = 0.0001$), BMI ($P = 0.033$), and SBP ($P = 0.045$) and negatively with R-R variation ($P = 0.024$) and age ($P < 0.0001$). RHR differed over time during the EDIC ($P < 0.0001$); however, the former treatment effect did not change over time. Specifically, significant former DCCT treatment effects were observed throughout the EDIC: the difference in RHR between intensive and conventional treatment remained at years 1–4 ($P = 0.001$), at years 5–9 ($P < 0.005$), and at year 10 ($P < 0.01$). Of the 12,844 RHR measures during the EDIC, 2,336 (18%) were measured while an individual was taking an ACE inhibitor, 208 (2%) during β-blocker treatment, and 384 (3%) during treatment with a calcium-channel blocker. Of these medications, only β-blockers showed a significant association with RHR, with individuals having a lower RHR when they were being taken ($P < 0.0001$).

When the mean value of all ln(A1C) levels in the DCCT was included in the mixed model, along with duration in the DCCT, the former DCCT treatment groups still had significantly different RHRs during the EDIC ($P = 0.0062$). In this model, 53% of the former DCCT treatment effect on RHR was explained by the mean DCCT ln(A1C). Further, after the addition of the DCCT closeout R-R variation and the time-dependent covariates for smoking status and exercise status to the prior model, 69% of the treatment effect was explained by the DCCT ln(A1C) ($P < 0.0001$), DCCT closeout R-R variation ($P = 0.0008$), smoking status ($P = 0.0007$), and exercise status ($P < 0.0001$). Those who reported mild exercise had a statistically higher RHR than those who reported moderate ($P = 0.0006$), hard ($P = 0.0035$), or strenuous ($P = 0.029$) exercise. RHR was also higher in smokers and negatively associated with the DCCT closeout R-R variation. Furthermore, the DCCT treatment group effect still remained significant ($P = 0.0228$).

CONCLUSIONS — The major results of this study support and extend the association of diabetes with faster RHR and of higher levels of glycemia with RHR previously demonstrated in cross-sectional studies. A significant treatment effect of intensive therapy on RHR occurred as early as 2 years after the initiation of the DCCT interventions (the earliest measure after randomization) in both age-groups and continued through closeout of the DCCT. A1C during the DCCT accounted for 96% of the treatment group effect in the <18-year-old age-group and 69% of the effect in those aged ≥18 years at baseline. When A1C levels were included in the analyses, the treatment effects in both age-groups were no longer significant. When the time-

dependent covariates for smoking status and exercise status were included in both models, exercise status was statistically significant ($P = 0.0021$) for the ≥18-year-old group only, in addition to A1C. A1C and exercise together explained 90% of the treatment group effect in those aged ≥18 years at baseline.

After closeout of the DCCT, the former intensive therapy was associated with significantly lower RHR up to EDIC year 10, consistent with long-term benefits of former intensive therapy, known as imprinting or metabolic memory (32,33). Although inclusion of the overall mean ln(A1C) during the DCCT accounted for 53% of the former treatment group differences during the EDIC, the treatment groups remained significantly different ($P = 0.0062$), implying that mechanisms other than those strongly correlated with mean A1C during the DCCT account for at least part of the imprinting phenomenon. Further, after the addition of the DCCT closeout R-R variation and the time-dependent covariates for smoking status and exercise status to the prior model, 69% of the treatment effect was explained by the DCCT ln(A1C) ($P < 0.0001$), DCCT closeout RR variation ($P = 0.0008$), smoking status ($P = 0.0007$), and exercise status ($P < 0.0001$), and the treatment effect continued to remain statistically significant ($P = 0.0228$). In individuals aged ≥18 years at the DCCT baseline, baseline RHR was positively associated with eligibility A1C, diabetes duration, and triglycerides and significantly different between sexes; however, these associations were not observed in individuals aged <18 years at the DCCT baseline. Other variables, such as exercise level, RR variation, and SBP were associated with RHR in both age-groups at baseline.

The mechanisms by which intensive diabetes therapy results in lower RHR compared with conventional therapy are not clear but include, at least in part, glycemic exposure or measures strongly correlated with it. It is possible that the higher RHR in individuals who received conventional treatment for type 1 diabetes is a reflex hemodynamic response to reduced stroke volume. This response could result from either diastolic dysfunction or a change in blood volume. However, no direct measures of diastolic function or blood volume have been made in this study. Previous analyses have shown that there was no significant effect of intensive treatment on diastolic blood pressure during the DCCT in either cohort. For SBP, individuals randomly assigned to intensive therapy had significantly higher blood pressure than conventionally treated individuals in the primary cohort ($P < 0.01$) but not in the secondary cohort ($P = 0.62$) (34). Alternatively, there may be direct mechanisms by which glycemic exposure results in the changes in RHR, such as the effects of intensive therapy on the autonomic nervous system demonstrated during the DCCT (29). However, when RR variation measured at closeout of the DCCT was included in the model for the analysis of RHR during the EDIC, the former treatment group effect remained significant, implying that there are other mechanisms apart from direct effects on the autonomic nervous system (as measured by R-R variation) that result in persistence of the treatment effect on RHR. Studies have reported positive associations between fasting insulin levels and RHR (35,36). Although insulin levels were not measured during the DCCT, insulin doses were significantly higher in the intensive than in the conventional treatment groups (37) and would be predicted to reduce the differences in RHR noted between the intensive and conventional treatment groups.

No studies have addressed whether RHR is a risk factor for cardiovascular disease or mortality in individuals with type 1 diabetes although the effect in the general population is well established (see Introduction). Also, the clinical relevance of a 2–3 bpm difference in RHR is unknown. The results of the current study lead to a series of questions including whether RHR is associated with subclinical measures of cardiovascular disease (34,38). In the Pittsburgh Epidemiology of Diabetes Complications Study, RHR at baseline was significantly higher in those who developed overt nephropathy, compared with those who did not (82 ± 12 and 73 ± 10 [mean ± SD] bpm, respectively, $P = 0.002$) (39). Recent DCCT/EDIC results have shown that subjects who experienced more severe ("nonfatal myocardial infarction, stroke, or death from CVD") cardiovascular disease (CVD) outcomes ($n = 83$) had borderline higher RHR at the DCCT baseline than those without CVD ($n = 1,358$, 70 ± 12 vs. 68 ± 11 bpm; $P = 0.073$) (40). The cumulative difference in the covariate-adjusted heart beats between an individual randomly assigned to intensive versus conventional therapy with duration in the DCCT of 6 years and of 10 years in the EDIC results in 7.3 fewer months of heart beats for individuals aged ≥18 years and 7.6 for those aged <18 years.

In summary, the DCCT/EDIC study has shown that prior intensive treatment during the DCCT period, compared with conventional treatment, resulted in slightly, although significantly, decreased RHR for up to 10 years of follow-up after the randomized treatment difference in A1C had dissipated. This effect is largely explained by the difference in A1C that existed during the DCCT. Whether the lower RHR per se confers a benefit in terms of future CVD events or mortality remains to be seen, as follow-up of the cohort continues.

Acknowledgments— This work was supported by National Institute of Diabetes and Digestive and Kidney Diseases Contract N01-DK-6-2204. A.D.P. holds a Canada Research Chair in the Genetics of Complex Diseases.

References

1. Barrett-Connor E, Pyörälä K: Long-term complications: diabetes and coronary heart disease. In *The Epidemiology of Diabetes Mellitus: An International Perspective*. Ekoe JM, Zimmet P, Williams E, Eds. Chichester, U.K., Wiley, 2001. p. 301–318
2. Laing SP, Swerdlow AJ, Slater SD, Burden AC, Morris A, Waugh NR, Gatling W, Bingley PJ, Patterson CC: Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. *Diabetologia* 46: 760–765, 2003
3. Hogan P, Dall T, Nikolov P: Economic costs of diabetes in the US in 2002. *Diabetes Care* 26:917–932, 2003
4. Dyer AR, Persky V, Stamler J, Paul O, Shekelle RB, Berkson DM, Lepper M, Schoenberger JA, Lindberg HA: Heart rate as a prognostic factor for coronary heart disease and mortality: findings in three Chicago epidemiologic studies. *Am J Epidemiol* 112:736–749, 1980
5. Kannel WB, Kannel C, Paffenbarger RS Jr, Cupples LA: Heart rate and cardiovascular mortality: the Framingham Study. *Am Heart J* 113:1489–1494, 1987
6. Gillum RF: The epidemiology of resting heart rate in a national sample of men and women: associations with hypertension, coronary heart disease, blood pressure, and other cardiovascular risk factors. *Am Heart J* 116:163–174, 1988
7. Gillum RF, Makuc DM, Feldman JJ: Pulse rate, coronary heart disease, and death: the NHANES I Epidemiologic Follow-up Study. *Am Heart J* 121:172–177, 1991
8. Gillman MW, Kannel WB, Belanger A,

D'Agostino RB: Influence of heart rate on mortality among persons with hypertension: the Framingham Study. *Am Heart J* 125:1148–1154. 1993
9. Shaper AG, Wannamethee G, Macfarlane PW, Walker M: Heart rate, ischaemic heart disease, and sudden cardiac death in middle-aged British men. *Br Heart J* 70: 49–55, 1993
10. Palatini P, Casiglia E, Julius S, Pessina AC: High heart rate: a risk factor for cardiovascular death in elderly men. *Arch Intern Med* 159:585–592, 1999
11. Greenland P, Daviglus ML, Dyer AR, Liu K, Huang CF, Goldberger JJ, Stamler J: Resting heart rate is a risk factor for cardiovascular and noncardiovascular mortality: the Chicago Heart Association Detection Project in Industry. *Am J Epidemiol* 149:853–862, 1999
12. Kristal-Boneh E, Silber H, Harari G, Froom P: The association of resting heart rate with cardiovascular, cancer and all-cause mortality: eight year follow-up of 3527 male Israeli employees (the CORDIS Study). *Eur Heart J* 21:116–124, 2000
13. Fujiura Y, Adachi H, Tsuruta M, Jacobs DR Jr, Hirai Y, Imaizumi T: Heart rate and mortality in a Japanese general population: an 18-year follow-up study. *J Clin Epidemiol* 54:495–500, 2001
14. Airaksinen KE: Electrocardiogram of young diabetic subjects. *Ann Clin Res* 17: 135–138, 1985
15. Lo SS, Sutton MS, Leslie RD: Information on type 1 diabetes mellitus and QT interval from identical twins. *Am J Cardiol* 72: 305–309, 1993
16. Torchinsky MY, Gomez R, Rao J, Vargas A, Mercante DE, Chalew SA: Poor glycemic control is associated with increased diastolic blood pressure and heart rate in children with type 1 diabetes. *J Diabetes Complications*, 2004. 18(4):220–3
17. The Diabetes Control and Complications Trial (DCCT): design and methodologic considerations for the feasibility phase: the DCCT Research Group. *Diabetes* 35: 530–545, 1986
18. Epidemiology of Diabetes Interventions and Complications (EDIC): design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. *Diabetes Care* 22:99–111, 1999
19. Steffes M, Cleary P, Goldstein D, Little R, Wiedmeyer HM, Rohlfing C, England J, Bucksa J, Nowicki M: Hemoglobin A1c measurements over nearly two decades: sustaining comparable values throughout the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications study. *Clin Chem* 51:753–758, 2005
20. White NH, Cleary PA, Dahms W, Goldstein D, Malone J, Tamborlane WV: Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after the conclusion of the Diabetes Control and Complications Trial (DCCT). *J Pediatr* 139:804–812, 2001
21. Prineas RJ, Crow RS, Blackburn H: *The Minnesota Code Manual of Electrocardiographic Findings: Standards and Procedures for Measurement and Classification*. Wright J, Ed. Littleton, MA: John Wright, 1982
22. Crow RS, Prineas RJ, Jacobs DR Jr, Blackburn H: A new epidemiologic classification system for interim myocardial infarction from serial electrocardiographic changes. *Am J Cardiol* 64:454–461, 1989
23. Wannamethee G, Shaper AG: The association between heart rate and blood pressure, blood lipids and other cardiovascular risk factors. *J Cardiovasc Risk* 1:223–230, 1994
24. Zhang J, Kesteloot H: Anthropometric, lifestyle and metabolic determinants of resting heart rate: a population study. *Eur Heart J* 20:103–110, 1999
25. Morcet JF, Safar M, Thomas F, Guize L, Benetos A: Associations between heart rate and other risk factors in a large French population. *J Hypertens* 17:1671–1676, 1999
26. Ferrieres J, Ruidavets JB: Association between resting heart rate and hypertension treatment in a general population. *Am J Hypertens* 12:628–631, 1999
27. The effect of intensive diabetes therapy on the development and progression of neuropathy: the Diabetes Control and Complications Trial Research Group. *Ann Intern Med* 122:561–568, 1995
28. Effect of intensive diabetes treatment on nerve conduction in the Diabetes Control and Complications Trial. *Ann Neurol* 38: 869–880, 1995
29. The effect of intensive diabetes therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT). *Diabetologia* 41:416–423, 1998
30. Neter J, Kutner M, Nachtsheim C, Wasserman W: Multiple regression II. In *Applied Linear Statistical Models.* Chicago, McGraw-Hill, 1996, p. 74–75, 91–92
31. Holm S: A simple sequentially rejective Bonferroni test procedure. *Scand J Stat* 6:65–70, 1979
32. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy: The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. *N Engl J Med* 342: 381–389, 2000
33. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group: Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA* 290:2159–2167, 2003
34. Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. *Am J Cardiol* 75:894–903, 1995
35. Gastaldelli A, Emdin M, Conforti F, Camastra S, Ferrannini E: Insulin prolongs the QTc interval in humans. *Am J Physiol* 279:R2022–R2025, 2000
36. Schroeder EB, Chambless LE, Liao D, Prineas RJ, Evans GW, Rosamond WD, Heiss G: Diabetes, glucose, insulin, and heart rate variability: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetes Care* 28:668–674, 2005
37. Implementation of treatment protocols in the Diabetes Control and Complications Trial. *Diabetes Care* 18:361–376, 1995
38. Nathan DM, Lachin J, Cleary P, Orchard T, Brillon DJ, Backlund JY, O'Leary DH, Genuth S: Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N Engl J Med* 348: 2294–2303, 2003
39. Yishak AA, Costacou T, Virella G, Zgibor J, Fried L, Walsh M, Evans RW, Lopes-Virella M, Kagan VE, Otvos J, Orchard TJ: Novel predictors of overt nephropathy in subjects with type 1 diabetes: a nested case control study from the Pittsburgh Epidemiology of Diabetes Complications cohort. *Nephrol Dial Transplant* 21:93–100, 2006
40. Nathan DM, Cleary PA, Backlund JYC, Genuth SM, Lachin JM, Orchard TJ, Raskin P, Zinman B: Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. *N Engl J Med* 353:2643–2653, 2005
41. The Diabetes Control and Complications Trial Group: 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, 1993