05/08/2021

SUPPLEMENTARY MATERIAL

A Perspective

Understanding Metabolic Memory: The Prolonged Influence of Glycemia During the Diabetes Control and Complications Trial (DCCT) on Future Risks of Complications During the Study of the Epidemiology of Diabetes Interventions and Complications (EDIC) *

Lachin JM, The Biostatistics Center, George Washington University, Rockville, MD
Nathan DM, Massachusetts General Hospital, Harvard Medical School, Boston, MA
On behalf of the DCCT/EDIC Research Group*

* A complete list of the members of the DCCT/EDIC Research Group can be found in *N Engl J Med* 2017;376:1507–1516.

This Supplement includes a description of the statistical analyses used to generate Table 3 and presents additional Figures cited in the main text.

Statistical Analyses

Table 3 and the supplemental figures herein were based on EDIC data collected as of 9/13/2019, or up to 26 years of EDIC follow-up. In Table 3, for each outcome, the most recent prior publication among the references is cited. Each of those papers provides a detailed description of the statistical methods used to provide the results presented therein. The following is a summary.

Weibull regression models (1) for interval censored data were employed for analyses of 3+-step progression and proliferative diabetic retinopathy (PDR), whereas for other outcomes Cox Proportional Hazards models (1) were employed, to provide the results presented in Table 3. An overall model assessed the difference between groups in the risk of the outcome over the full EDIC 26 year period starting from the beginning of EDIC where day 0 is the date of the DCCT final closeout visit. A separate model only included events that occurred within the 10 years following EDIC day 0, i.e. through 3652.5 days (allowing for leap years), so all subjects event free as of 3653 days were administratively censored at that time. A third model only included subjects who were still at risk of an initial event as of 3653 days and counted events that occurred during the period from 3653 days to 9/13/2019.

Models for further 3+-step progression and onset of PDR were adjusted for primary vs. secondary cohort, baseline diabetes duration, DCCT closeout retinopathy status, and HbA1c at eligibility (2). The ocular surgery model was adjusted for baseline duration, baseline age, gender, HbA1c at eligibility, cohort, and baseline visual acuity (3). Models for persistent microalbuminuria and macroalbuminuria were adjusted for DCCT closeout albumin excretion rate (4). Models for any CVD and MACE were adjusted for baseline age, HbA1c at eligibility, baseline total cholesterol, and baseline smoking status. (5) All models were generated using SAS.

For Figure 3 (3+-step progression) in the main text, and Figure 3.A (proliferative diabetic retinopathy, PDR) in the supplementary material, the cumulative incidence functions were computed using the Turnbull estimates for interval censored data (6) with the "interval" package in R. Then a smooth estimate of the Turnbull step function is obtained using natural cubic splines with 4 degrees of freedom, and differentiating it yields the smooth hazards estimate. (7)
For figures 3B-F of the Supplementary material, Smoothed hazard plots were generated using Epanechnikov's kernel function which provided a smoothed Nelson-Aalen estimate of the underlying hazard function in SAS (1). Cumulative incidence plots were generated using the Kaplan-Meier method (1), starting with the date of the DCCT closeout visit as time zero in EDIC time with the "SURVMINER" package in R. Mediation of the treatment group effect was assessed by the change in the group effect after adjustment for a given time-dependent covariate.(8)

The analyses for any CVD and MACE employed the study day (since the day of randomization) at which either the event was observed for a patient, or if none, the study day at which the subject was right censored, i.e. the date at which the subject was last known to be event free. For other outcomes, the analysis employed the time from randomization to the visit at which the event was noted to have occurred, or the date of the event if available.

REFERENCES

1. Lachin JM. *Biostatistical Methods: The Assessment of Relative Risks*. 2nd ed. New York: Wiley, 2011.

2. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications Research Group (Writing Committee: Lachin JM, White N, Hainsworth D, Sun W, Cleary PA, Nathan DM). Effect of intensive diabetes therapy on the progression of diabetes retinopathy in patients with type 1 diabetes: 18 years of follow-up in the DCCT/EDIC. *Diabetes* 2015; 64: 631-642.

3. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications Research Group (Writing Committee: Aiello LP, Sun W, Das A, Gangaputra S, Kiss S, Klein R, Cleary PA, Lachin JM, Nathan DM). Intensive diabetes therapy and ocular surgery in type 1 diabetes. *New England Journal of Medicine.* 2015; 372:1722-33.

4. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications Research Group (Writing Committee: de Boer IH, Sun W, Gao X, Cleary PA, Lachin JM, Molitch M, Steffes MW, Zinman B). Effect of intensive diabetes treatment on albuminuria in type 1 diabetes: long-term follow-up of the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications study. *Lancet Diabetes Endocrinol* 2014; 2:793-800.

5. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications Research Group (Writing Committee: Gubitosi-Klug RA, Lachin JM, Backlund J-YC, Lorenzi GM, Brillon DJ, Orchard TJ). Intensive Diabetes Treatment and Cardiovascular Outcomes in Type 1 Diabetes: The DCCT/EDIC Study 30-Year Follow-up. *Diabetes Care.* 2016 May; 39(5): 686-693.

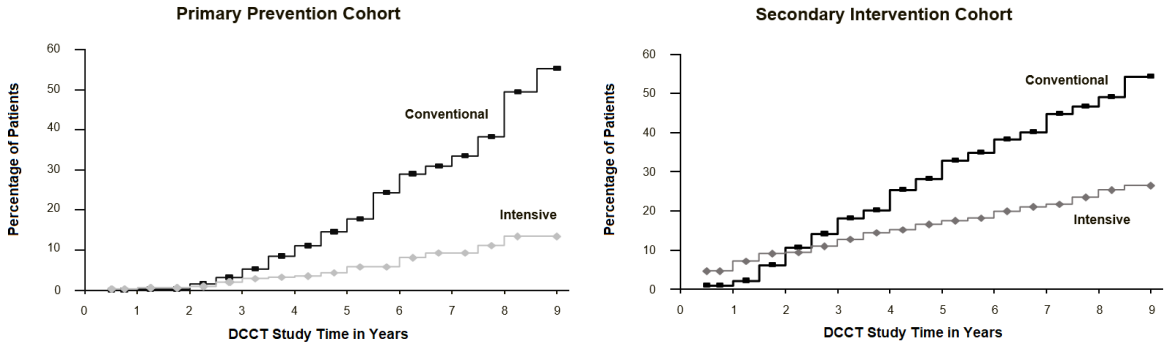
6. Turnbull BW. The empirical distribution function with arbitrarily censored and truncated data. *J R Stat Soc* [Ser B] 1976; 38:290–295

7. Hastie TJ. Generalized additive models. In *Statistical Models in S*. Chambers Hastie TJ, Eds. Pacific Grove, CA, Wadsworth & Brooks/Cole, 1992.

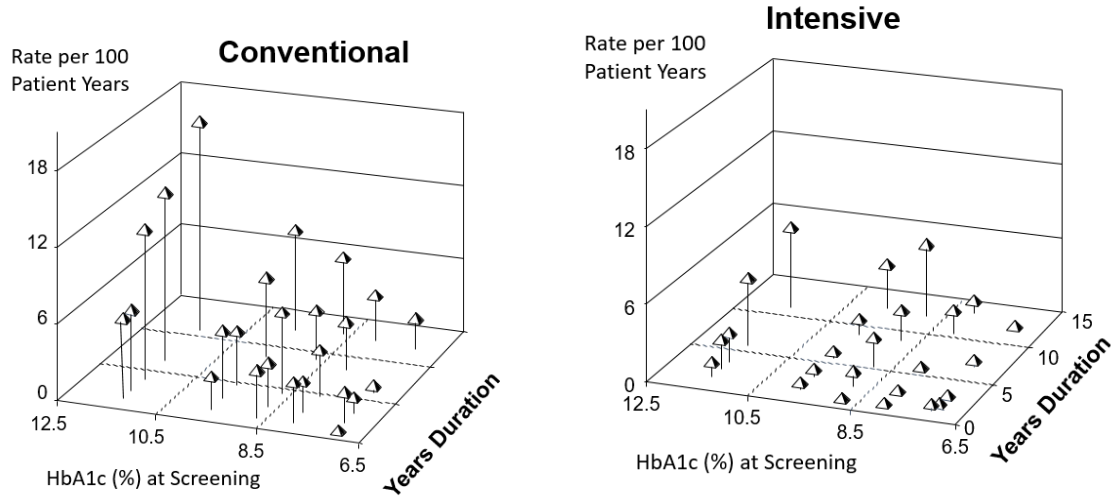
8. MacKinnon DP. *Introduction to Statistical Mediation Analysis*. New York, Erlbaum, 2008

SUPPLEMENTAL FIGURES

Supplementary Figure 1. Cumulative incidence of sustained progression of at least 3 steps on the final ETDRS scale of retinopathy severity within the DCCT intensive versus conventional treatment groups. A: Primary prevention cohort. B: Secondary intervention cohort. Adapted from (1) with permission from the *New England Journal of Medicine.* Risk reduction estimated from a Cox Proportional Hazards Model.

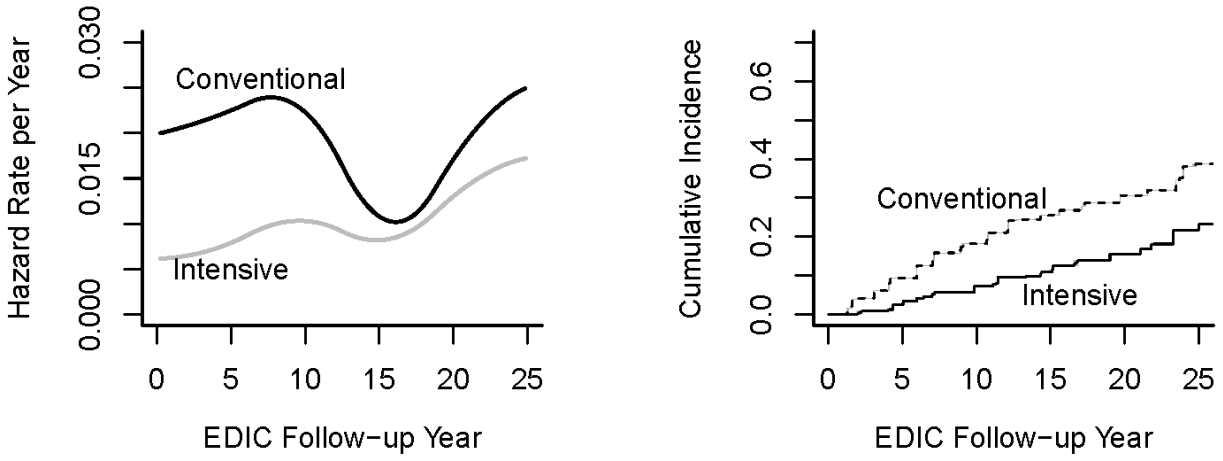


Supplementary Figure 2. The rate per 100 patient-years of sustained retinopathy progression within quintiles of the distribution of the HbA1c % at screening and within quintiles of the distribution of duration of diabetes (years). A: Conventional treatment group. B: Intensive treatment group. From (3), reprinted with permission of the American Diabetes Association. Copyright 1995. Additional analyses in (3) describe the association of these quantitative factors with the risks of progression.

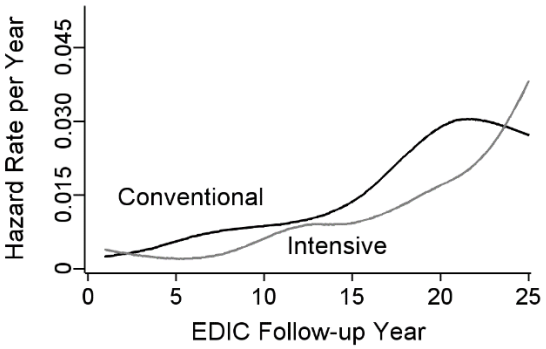


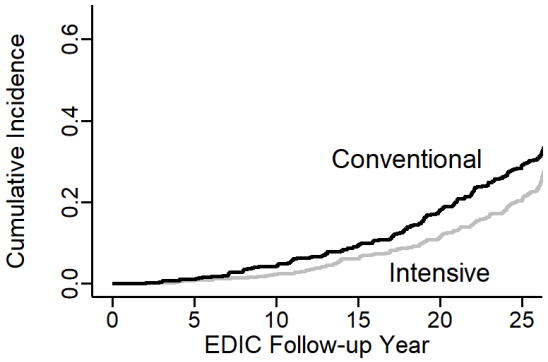
Supplementary Figure 3. For each outcome in Table 3 (except 3+ step retinopathy progression), the left figure presents the smoothed estimate of the day-to-day incidence (hazard) rate of the event within the former intensive versus conventional treatment groups over 26 years of EDIC follow-up that represents biological metabolic memory, and the right figure presents the cumulative incidence of progression epidemiological metabolic memory or the legacy effect.

A. Proliferative Diabetic Retinopathy

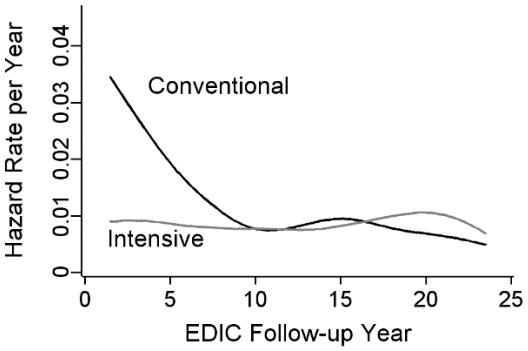


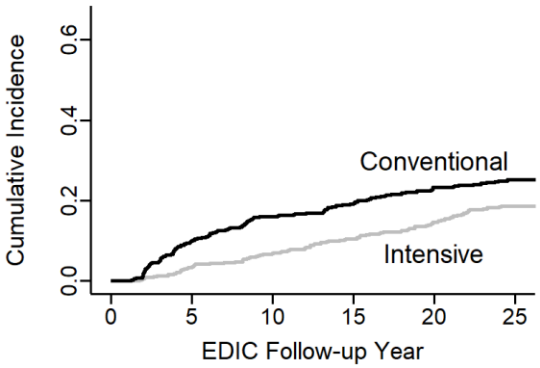
B. Ocular Surgery



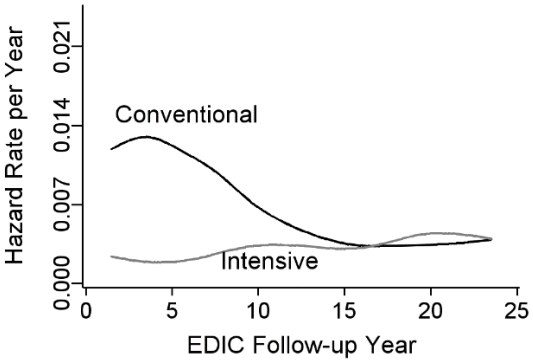


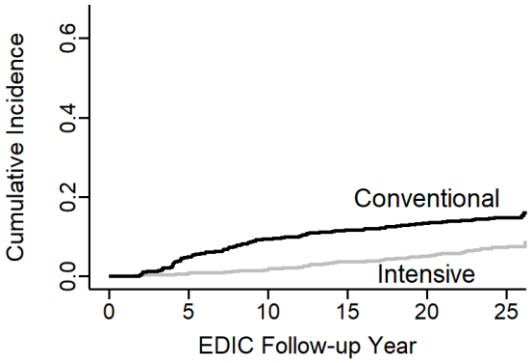
C. Microalbuminuria (≥30 mg/24 h)



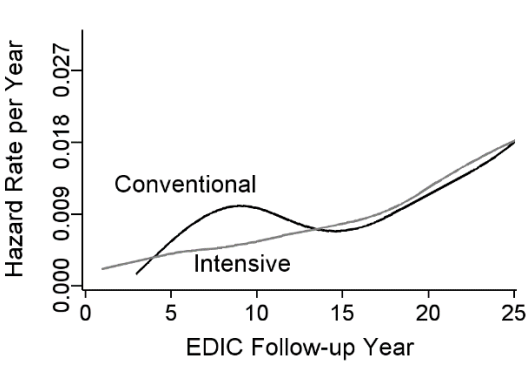


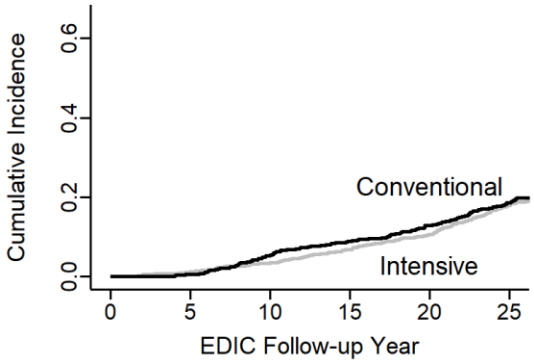
D. Macroalbuminuria (>300 mg/24 h)





E. Any Cardiovascular Disease





F. MACE (non-fatal myocardial infarction or stroke or CVD death)