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# Variability in benefit from intensive insulin therapy on cardiovascular events in individuals with type 1 diabetes: A post hoc analysis of the DCCT/EDIC study

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## Abstract

**Aim:** To evaluate presence of treatment effect heterogeneity of intensive insulin therapy (INT) on occurrence of major adverse cardiovascular events (MACE) in individuals with type 1 diabetes.

**Methods:** In participants from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study, individual treatment effect of INT (≥3 daily insulin injections/insulin pump therapy) versus conventional therapy (once/twice daily insulin) on the risk of MACE was estimated using a penalized Cox regression model including treatment-by-covariate interaction terms.

**Results:** In 1441 participants, 120 first MACE events were observed and 1279 individuals (89%) were predicted to benefit from INT with regard to MACE risk reduction. The study population was divided into four groups based on predicted treatment effect: one group with no predicted benefit and three tertiles with predicted treatment benefit. The median absolute reduction in 30-year risk of MACE across groups of predicted treatment effect ranged from −0.2% (i.e. risk increase; interquartile range [IQR] −0.1% to −0.3%) in the group with no predicted benefit to 6.6% (i.e. risk reduction; IQR 3.8%–10.9%; number needed to treat 15) in the highest tertile of predicted benefit. The observed benefit of preventing microvascular complications was stable across all subgroups of predicted MACE benefit.

**Conclusions:** Although INT reduces the risk of MACE in the majority of individuals with type 1 diabetes, benefit varies substantially. These individual differences in the effect of INT underline the necessity for a better understanding of the individual response to intensive treatment.

KEYWORDS

cardiovascular diseases, insulin, randomized controlled trial, type 1 diabetes

## 1 | INTRODUCTION

Current guidelines with regard to insulin therapy in individuals with type 1 diabetes (T1D) are based on the results of the Diabetes Control and Complications Trial (DCCT).[1,2] This trial compared intensive insulin therapy (INT) (at least three daily insulin injections or insulin pump therapy) with conventional therapy (CONV; once or twice daily insulin) with regard to their effects on the development and progression of microvascular complications of T1D. INT resulted in an $HbA_{1c}$ level of ~53 mmol/mol (7%) after a mean follow-up of 6.5 years, compared to ~75 mmol/mol (9%) in the CONV group. In the INT arm, the risk of developing retinopathy, macroalbuminuria and neuropathy was reduced by 65%, 54% and 60%, respectively, compared with the CONV group.[3] The long-term follow-up study of DCCT, the Epidemiology of Diabetes Interventions and Complications (EDIC), showed that the differences in microvascular persisted over time.[4] In addition, there was a 32% relative reduction in risk of major adverse cardiovascular events (MACE) for individuals treated with INT versus (vs.) CONV over 30 years of follow-up (95% confidence interval [CI] −3% to 56%).[5]

It is, however, unclear which individuals benefit most from INT and which individuals experience no benefit in terms of vascular disease. Subgroup analyses are frequently used to assess such differences in treatment effect and have previously been performed for this trial.[6–8] However, there are important limitations to subgroup analyses, including lack of power in randomized controlled trials (RCTs) for detecting subgroup effects.[9] Also, subgroup analyses are based on single participant characteristics, whereas individual participants differ from another across many characteristics. An alternative approach is to develop a prediction model on the RCT data. The goal of this method is to provide individualized predictions of treatment effect while taking into account multiple prognostic factors,[9] thereby addressing some of the limitations of subgroup analyses. The aim of the current study is to explore the presence of heterogeneity of treatment effect of INT on the occurrence of MACE on the absolute scale in individuals with T1D. In addition, the aim is to identify participant characteristics associated with individual treatment effect from an intensive regimen and to evaluate the distribution of microvascular complications across groups of predicted treatment effect in terms of MACE risk reduction.

**Novelty statement**

**What is already known?**

- The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study demonstrated that intensive insulin therapy (INT) has beneficial effects on the risk of microvascular events and major adverse cardiovascular events (MACE) in individuals with type 1 diabetes, compared to conventional therapy

**What has this study found?**

- Although INT reduces the risk of MACE in the majority of individuals with type 1 diabetes, benefit varies substantially
- Higher age, smoking, higher $HbA_{1c}$, higher cholesterol levels, a worse kidney function, neuropathy and retinopathy were associated with the largest predicted benefit from intensive therapy

**What are the implications of the study?**

- Individual differences in the effect of INT underline the necessity for a better understanding of the individual response to intensive treatment

## 2 | METHODS

### 2.1 | Participants

Participants originated from the DCCT/EDIC study. The rationale and design of this RCT have been described elsewhere.[2,10] Briefly, DCCT (1983–1993) was conducted in 29 clinical centres in the USA and Canada and randomized 1441 persons with T1D, aged 13–39 years without a history of cardiovascular disease (CVD), to either INT or CONV in a 1:1 ratio. The INT group was treated with at least three insulin injections per day or insulin pump therapy. The CONV group used one or two insulin injections per day. The study consisted of two approximately equal-sized cohorts. The primary prevention cohort included persons with a diabetes duration of 1–5 years, albumin excretion rate (AER) of <40 mg/24 h and no retinopathy. The secondary intervention cohort included persons with a diabetes duration of 1–15 years, AER of ≤200 mg/24 h and mild to moderate non-proliferative diabetic retinopathy. The DCCT ended in 1993 after a mean follow-up of 6.5 years. All participants were then invited to participate in the ongoing EDIC follow-up study; 97% ($n = 1371$) of the surviving DCCT cohort was enrolled. From the start of EDIC, all persons were taught INT and referred to their usual health care team for routine care. The current study includes data from DCCT baseline through June 2017 (EDIC year 24). DCCT/EDIC was approved by the

institutional review boards of all participating centres and all participants provided informed consent.

## 2.2 | Data collection and outcome assessment during DCCT and EDIC

Smoking status and medication use were self reported. Blood pressure was measured twice at the right arm in a sitting position using a random-zero sphygmomanometer. $HbA_{1c}$ was measured by high performance liquid chromatography. AER was assessed using 4 h urine collections. Fasting lipids were measured centrally and LDL-cholesterol was calculated using the Friedewald formula.[2] Clinical neuropathy at baseline was defined as an abnormal neurologic examination that was consistent with the presence of peripheral sensorimotor neuropathy plus either abnormal nerve conduction in at least two peripheral nerves or unequivocally abnormal autonomic-nerve testing. Retinopathy at baseline was assessed using stereo fundus photography.[2] The primary outcome of interest of this post hoc analysis was the first occurrence of MACE, a composite outcome consisting of nonfatal myocardial infarction, nonfatal stroke and cardiovascular death. All cardiovascular events were adjudicated by a within-study Morbidity & Mortality Committee blinded to treatment assignment and glycaemic parameters.[11] The secondary outcomes of interest for this post hoc analysis included nephropathy and retinopathy. Nephropathy was defined by an AER ≥30 mg/24 h on two consecutive study visits and/or eGFR <60 mL/min/1.73 $m^2$ on two consecutive study visits and/or end-stage kidney disease. End-stage kidney disease includes kidney transplantation or dialysis. Retinopathy was defined by the presence of proliferative diabetic retinopathy and/or a history of panretinal scatter photocoagulation (laser) therapy, assessed using stereo fundus photography.

## 2.3 | Statistical analyses

Missing data on covariates were minimal (<1% per covariate) and were imputed by single imputation using bootstrapping and predictive mean matching. To model the effect of treatment, a Cox proportional hazards model for the prediction of MACE was developed in the DCCT study population. A 30-year risk horizon was chosen as the cardiovascular risk among this young population is relatively low on the short term. To minimize overfitting, predictors were prespecified based on occurrence in existing cardiovascular prediction models in T1D[12–15] and other studies on risk factors for CVD in T1D.[16–18] The following predictors were selected: age, sex, current smoking, systolic blood pressure (SBP, mm Hg), non-HDL-cholesterol (mmol/L), $HbA_{1c}$ (%), albuminuria (AER normal to mildly increased [0–30 mg/24 h] vs. moderately increased [30–300 mg/24 h]), clinical neuropathy and retinopathy (mild or moderate non-proliferative retinopathy vs. no retinopathy). All predictor values were determined at baseline. Interaction terms between all predictors and treatment were added to the model.[9] No selection based on statistical significance was applied in order to prevent overfitting. To limit the effect of outliers, continuous predictors were truncated at the 1st and 99th percentile. Quadratic and logarithmic associations between continuous predictors and the outcome were assessed by comparing model fit using Akaike's Information Criterion. The proportional hazards assumption was examined visually by plotting the Schoenfeld residuals. The final model coefficients were estimated using penalized estimation methods using an L2 quadratic (i.e. 'ridge') penalty to further prevent overfitting.[19] Model performance was assessed using a calibration plot of expected versus observed 30-year risks of the outcome and the C-statistic as a measure of discrimination. In addition, the performance for predicting treatment benefit was evaluated using the c-for-benefit. The c-for-benefit represents the probability that from two randomly chosen matched participant pairs with unequal observed treatment effect, the pair with greater observed treatment effect also has a larger predicted treatment effect.[20] A more detailed explanation of this metric is provided in Methods S1.

Subsequently, the prediction model was used to estimate the 30-year risk of MACE for each participant as if the participant had been treated with INT and as if the participant had been treated with CONV. The absolute risk difference was defined as the 30-year risk of MACE with INT minus the 30-year risk of MACE with CONV. The study population was then divided into groups based on the predicted treatment effect (i.e. the absolute risk difference), as has been done before in methodologically comparable post hoc analyses of other trials.[21,22] To most effectively explore the subgroup with no predicted benefit from INT, the population was divided in 1 group with no predicted benefit (11% of the population) and those with predicted benefit were assigned to tertiles based on predicted benefit. Baseline characteristics were reported stratified by the four groups in order to identify participant characteristics associated with individual treatment effect. Baseline characteristics across the groups were compared using Kruskal–Wallis tests for continuous variables and chi-squared tests for categorical variables. The individual effect on a relative scale was evaluated by calculating the individualized hazard ratio (HR), which was calculated by first filling in the individual risk factors in the model with and without treatment status and then taking the difference of the linear predictor in these predictions. A more

detailed explanation is provided in Methods S2. Observed event rates of retinopathy and nephropathy were assessed across the same groups of predicted treatment effect with regard to risk reduction in MACE. To evaluate whether the findings would be similar for a larger combined end point, the analyses were replicated for any CVD (defined as nonfatal myocardial infarction or stroke, cardiovascular death, silent myocardial infarction, confirmed angina, revascularization or congestive heart failure). In addition, the analyses were repeated excluding individuals with missing data ($n = 5$). All analyses were performed with R statistical software (version 4.0.3; R foundation for Statistical Computing). All $p$-values were two-sided, with statistical significance set at 0.05, unless stated otherwise.

## 3 | RESULTS

### 3.1 | Baseline characteristics

The mean age was 27 ± 7 years and 53% of the participants were men. The median diabetes duration was 4 years (interquartile range [IQR] 2–9).

### 3.2 | Baseline risk of MACE and treatment effect of INT

During a median follow-up of 29.8 years (IQR 28.1–31.1), 120 participants experienced MACE. Incidence rates were lower in participants allocated to INT compared to participants allocated to CONV (2.7 vs. 3.3 per 1000 person-years). In Table S1, the subdistribution HRs for the predictor variables are shown. Predicted 30-year risk of MACE showed good agreement with observed 30-year risks. Assessment of discrimination provided a C-statistic of 0.730 (95% CI 0.685–0.775; Figure S1). The c-for-benefit was 0.609 (95% CI 0.544–0.675) (corresponding calibration plot shown in Figure S2). The median predicted 30-year risk of MACE under conventional treatment was 7.8% (range 1.2%–71.4%; Figure 1).

### 3.3 | Heterogeneity of treatment effects

The median estimated absolute risk difference in the 30-year risk of MACE when treated with INT was −0.9% (range −31.8% to +0.7%), i.e. 0.9% absolute 30-year risk reduction in comparison to CONV (Figure 1). The highest baseline risk was observed in individuals with the largest predicted treatment benefit (tertile 3; Figure 2). The median predicted individualized HR for treatment (i.e. the relative effect of INT vs. CONV) ranged from 1.04 (IQR 1.02–1.06) in participants with no predicted benefit to 0.55 (IQR 0.49–0.71) in tertile 3 of predicted benefit. The median absolute reductions in 30-year risk of MACE across groups of predicted treatment effect when treated with INT compared to CONV were 6.6% (IQR 3.8%; 10.9%; corresponding number needed to treat [NNT] 15), 1.2% (IQR 0.9%; 1.5%; NNT 89), 0.3% (IQR 0.2%; 0.5%; NNT 314) and −0.2% (i.e. risk increase; IQR −0.1%; −0.3%). Baseline characteristics stratified by the groups of predicted treatment effect are presented in Table 1. Participant characteristics associated with the largest treatment benefit on the absolute scale were, among others, a higher age, current smoking, higher $HbA_{1c}$, higher LDL-cholesterol, a worse kidney function and the presence of neuropathy and retinopathy. Repetition of the analyses in participants with no missing data ($n = 1336$) did not alter the results (Methods S3: Table SI and Figures SI–SIII).

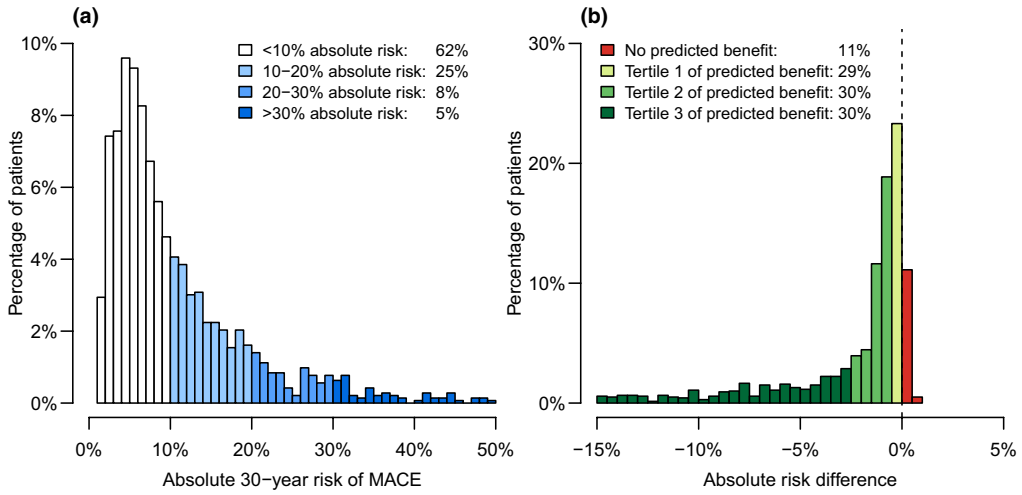


**FIGURE 1** (a) Distribution of the estimated absolute 30-year (untreated) risk of MACE. (b) Distribution of the absolute risk difference, defined as the 30-year risk of MACE with intensive insulin therapy minus the 30-year risk of MACE with conventional therapy.

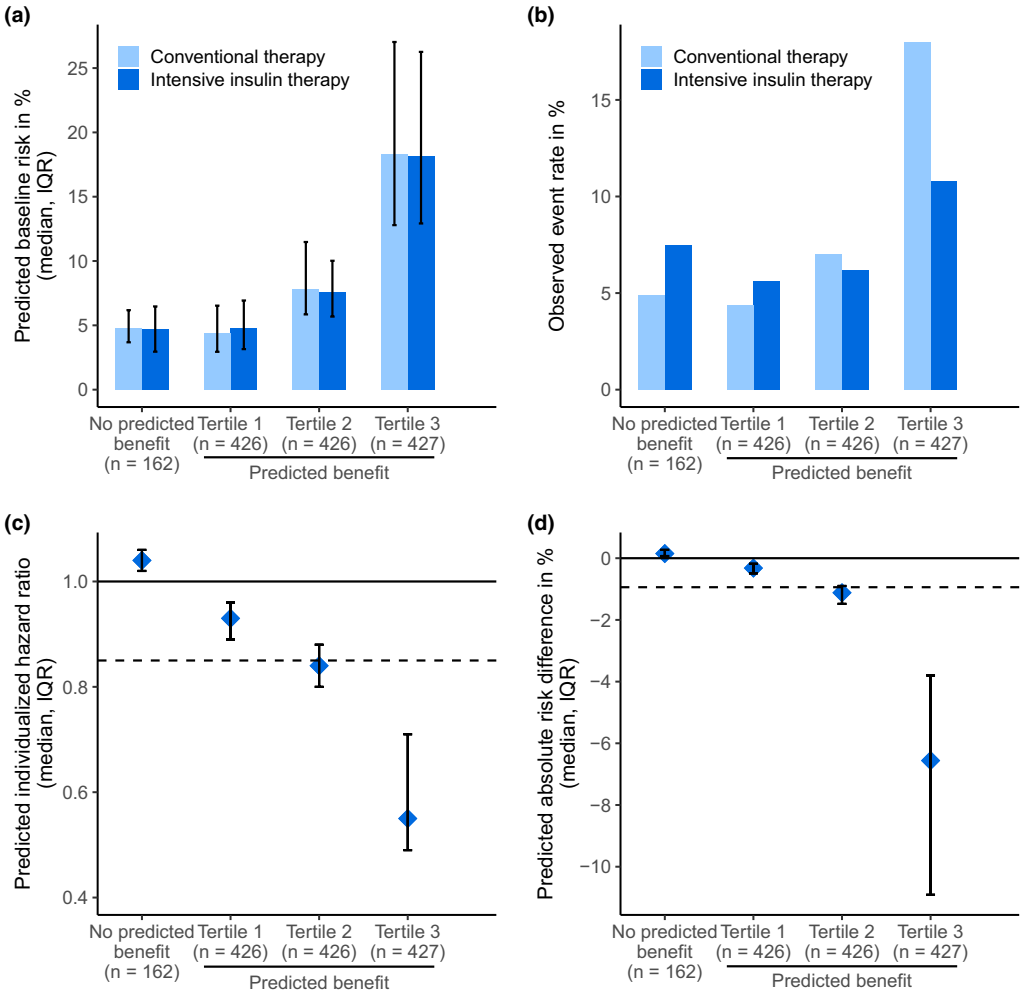


**FIGURE 2** Risk of MACE and treatment effect of intensive insulin therapy versus conventional therapy, stratified by groups of predicted treatment effect. (a) Predicted baseline 30-year risk of MACE (median, IQR). (b) Observed event rates of MACE. (c) Predicted individualized HR (median, IQR) of intensive insulin therapy versus conventional therapy. The dashed line indicates the overall median HR in the study population (HR 0.85 [IQR 0.73–0.94]). (d) Absolute difference in 30-year risk of MACE (median, IQR) when treated with intensive insulin therapy compared to conventional therapy. The dashed line indicates the overall absolute risk difference in the study population (−0.9%).

### 3.4 | Microvascular complications

During follow-up, 287 individuals developed nephropathy and 558 individuals developed retinopathy (Figure 3). Across the subgroups based on predicted benefit in terms of MACE risk reduction, event rates for both nephropathy and retinopathy were higher among individuals treated with CONV as compared to individuals treated with INT. Furthermore, event rates for both microvascular complications were comparable across the groups based on predicted treatment effect with regard to MACE risk reduction.

### 3.5 | Sensitivity analysis

During follow-up, 239 participants experienced any CVD. Incidence rates were 5.7 and 6.5 per 1000 person-years for participants treated with INT and with CONV, respectively. The baseline risk of any CVD was higher compared to MACE due to the higher incidence of any CVD. A similar pattern of heterogeneity was observed.

## 4 | DISCUSSION

This post hoc analysis of the DCCT/EDIC trial shows that there is heterogeneity of the effect of INT on the occurrence of MACE in individuals with T1D. Although INT is beneficial in terms of cardiovascular events in the majority of individuals with T1D, benefit varies substantially. Across the subgroups of predicted benefit in terms of MACE risk reduction, the observed benefit with regard to preventing microvascular outcomes seemed to be stable.

**TABLE 1** Baseline characteristics stratified by groups of predicted treatment effect.

| | | Predicted benefit (increasing with tertiles) | | | |
|---|---|---|---|---|---|
| | **No predicted benefit ($n=162$)** | **Tertile 1 ($n=426$)** | **Tertile 2 ($n=426$)** | **Tertile 3 ($n=427$)** | ***p*-value** |
| Absolute difference in risk of MACE (range)[a] | 0% to +0.7% | 0% to −0.6% | −0.6% to −2.4% | −1.3% to −31.8% | |
| Allocated to intensive insulin treatment | 80 (49) | 198 (47) | 211 (50) | 222 (52) | 0.457 |
| Primary prevention cohort | 81 (50) | 240 (56) | 210 (49) | 195 (46) | 0.018 |
| Age (years) | 24 ± 6 | 23 ± 7 | 28 ± 7 | 31 ± 6 | <0.002[b] |
| Men | 162 (100) | 229 (54) | 162 (38) | 208 (49) | <0.002[b] |
| Duration of diabetes (years) | 4 (2–9) | 4 (2–8) | 4 (2–9) | 4 (2–9) | 0.131 |
| Current smoker | 0 (0) | 0 (0) | 3 (1) | 264 (62) | <0.002[b] |
| Medication use | | | | | |
| Insulin dose (units/kg/day) | 0.7 ± 0.3 | 0.7 ± 0.3 | 0.6 ± 0.2 | 0.6 ± 0.2 | <0.002[b] |
| Body mass index (kg/m$^2$) | 23.5 ± 2.7 | 23.1 ± 2.9 | 23.5 ± 2.9 | 23.5 ± 2.8 | 0.195 |
| Systolic blood pressure (mmHg) | 124 ± 9 | 114 ± 11 | 112 ± 11 | 113 ± 11.1 | <0.002[b] |
| Diastolic blood pressure (mmHg) | 77 ± 8 | 72 ± 8 | 72 ± 9 | 72 ± 9 | <0.002[b] |
| Laboratory values | | | | | |
| $HbA_{1c}$ (%) | 7.6 ± 0.7 | 8.4 ± 1.1 | 9.4 ± 1.5 | 9.9 ± 1.7 | <0.002[b] |
| $HbA_{1c}$ (mmol/mol) | 59 ± 8 | 69 ± 12 | 79 ± 17 | 85 ± 19 | <0.002[b] |
| LDL-cholesterol (mmol/L) | 2.5 ± 0.6 | 2.6 ± 0.7 | 3.0 ± 0.7 | 3.1 ± 0.8 | <0.002[b] |
| HDL-cholesterol (mmol/L) | 1.2 ± 0.3 | 1.3 ± 0.3 | 1.4 ± 0.3 | 1.3 ± 0.3 | <0.002[b] |
| Non-HDL-cholesterol (mmol/L) | 2.8 ± 0.7 | 3.0 ± 0.7 | 3.4 ± 0.8 | 3.5 ± 0.8 | <0.002[b] |
| Triglycerides (mmol/L) | 0.8 (0.6–0.9) | 0.7 (0.6–1.0) | 0.8 (0.6–1.1) | 0.9 (0.7–1.2) | <0.002[b] |
| eGFR (mL/min/1.73 m$^2$) | 128 ± 14 | 130 ± 15 | 125 ± 15 | 123 ± 12 | <0.002[b] |
| Albuminuria | | | | | 0.323 |
| AER 0–30 mg/24 h | 145 (90) | 388 (91) | 379 (89) | 372 (87) | N/A |
| AER 30–300 mg/24 h | 17 (11) | 38 (9) | 47 (11) | 55 (13) | N/A |
| Clinical neuropathy | 0 (0) | 5 (1) | 14 (3) | 73 (17) | <0.002[b] |
| Retinopathy | | | | | <0.002[b] |
| None | 81 (50) | 240 (56) | 210 (49) | 195 (46) | N/A |
| Microaneurysms only | 52 (32) | 128 (30) | 141 (33) | 128 (30) | N/A |
| Mild non-proliferative retinopathy | 18 (11) | 35 (8) | 46 (11) | 47 (11) | N/A |
| Moderate non-proliferative retinopathy | 11 (7) | 23 (5) | 29 (7) | 57 (13) | N/A |

*Note*: *p*-Values represent the probability of observing an association between the participant characteristics and the four groups of treatment effect. Data are presented as *n* (%), mean ± SD or median (IQR).

Abbreviations: AER, albumin excretion rate; eGFR, estimated glomerular filtration rate (estimated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula); $HbA_{1c}$, glycated haemoglobin; IQR, interquartile range; MACE, major adverse cardiovascular events; N/A, not applicable.

[a]Defined as the 30-year risk of MACE with intensive insulin therapy minus the 30-year risk of MACE with conventional therapy.

[b]Statistically significant at the Bonferroni-corrected α.

By demonstrating profound beneficial effects of INT on micro- and macrovascular outcomes, the DCCT/EDIC study has ensured that what was considered to be 'intensive therapy' in the study, is now considered to be standard of care for management of T1D.[1] Despite equivalent $HbA_{1c}$ levels in the two groups during EDIC ($HbA_{1c}$ ~64 mmol/mol [8%]), owing to the adoption of INT by the participants who were originally allocated to CONV as well as the return of all participants to their own health care providers, the benefits persisted beyond the end of DCCT.[23]

As demonstrated in this and other studies, there is a wide distribution in baseline risk of MACE among individuals

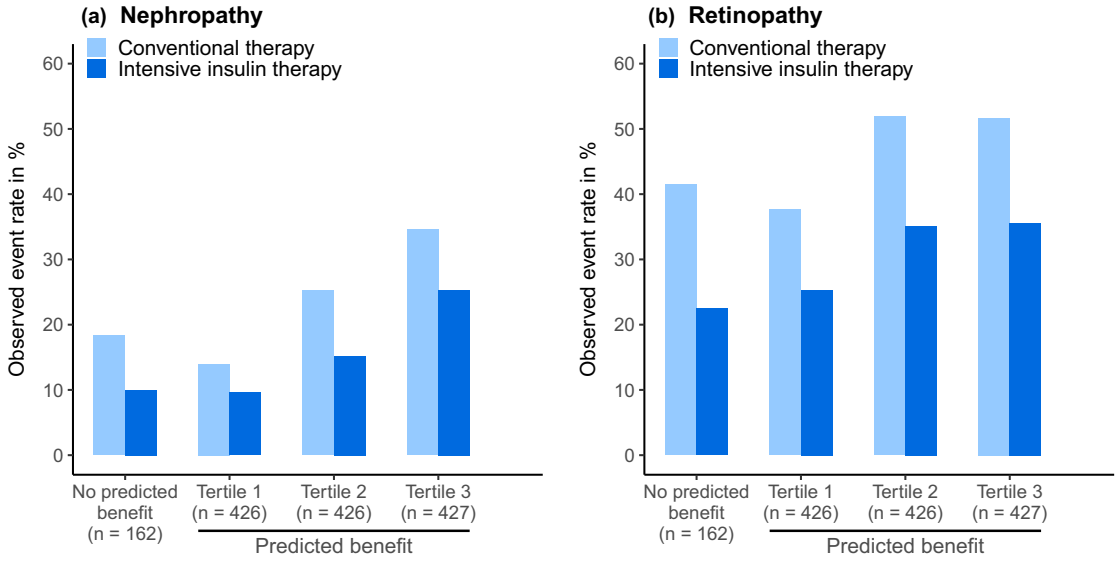


**FIGURE 3** Observed event rates of nephropathy and retinopathy across the groups of predicted treatment effect based on the absolute difference in risk of MACE. (a) Event rates of nephropathy in %. (b) Event rates of retinopathy in %.

with T1D.[18] With the variance in baseline risk, there is a natural variance in the absolute treatment effect as well. While previous DCCT/EDIC literature mainly elaborated on the effect of INT and the influence of cardiovascular risk factors on the risk of vascular disease or other diabetes-related complications for the whole study population[4–7,11,24–27] or using one-variable-at-a-time subgroup analyses,[6–8] the current study adds to this that the relative effect of an intensive regimen may differ across individuals with different characteristics. Besides the well-known cardiovascular risk factors used in the current prediction model, other factors such as the haptoglobin 2–2 genotype, which has been shown to increase the risk of a myocardial infarction in a subgroup of the DCCT/EDIC population, could also play a role.[28] The current study shows that the largest treatment benefit is predicted in participants with the highest baseline risk of MACE. The large expected benefit on the absolute and the relative scale can most likely be explained by the high mean $HbA_{1c}$ level. In this group, INT led to a reduction in mean $HbA_{1c}$ of 28 mmol/mol (from 85 mmol/mol [9.9%] to 57 mmol/mol [7.4%] at DCCT closeout), compared to an $HbA_{1c}$ reduction of only 2 mmol/mol (from 59 mmol/mol [7.6%] to 57 mmol/mol [7.4%]) in the group with no predicted benefit.

The treatment effect is thus mainly driven by the individuals with a high baseline risk of MACE, which might indicate that individuals with lower baseline risks of MACE may experience less benefit in terms of absolute risk reduction from intensive glucose control. It is important to realize that the small benefit in terms of MACE should be weighed against the large beneficial effects on the occurrence of microvascular complications. Across all groups based on predicted treatment effect in terms of MACE, event rates of nephropathy and retinopathy were higher among individuals treated with CONV compared to individuals treated with INT. The risk of clinical neuropathy was not assessed as data on this outcome was not available until EDIC year 24.

Several previous studies using DCCT/EDIC data have shown that the presence and level of risk factors included in the model changed over time.[24–26] For example, $HbA_{1c}$ levels diverged during DCCT and converged during EDIC, LDL-cholesterol decreased with increasing availability of statins and SBP increased. It is possible to take change in risk factors into account by including time-varying covariates. This has been done in many previous studies using mean updated $HbA_{1c}$.[5,24,25,27] Although the treatment effect is mainly driven by this measure, the aim of the current study was to identify participant characteristics associated with the level of individual treatment effect from an intensive regimen that are available prior to starting therapy. In addition, the aim was to isolate the effect of INT versus CONV, which would otherwise partially be captured by changes in risk factor measurements during follow-up, thereby invalidating the study randomization. Hence, the prediction model in the current study was solely based on DCCT baseline variables. Since the model in this analysis performed well in terms of calibration, the effect of the risk factors appears to have remained stable over time. This is further supported by a recent study, where they found very little heterogeneity in HRs of well-known cardiovascular risk factors across time.[29] Another study showed that risk predictions were effectively equal when taking statin initiation during follow-up

into account (vs. ignoring it) and predictive performance was only minimally improved.[30]

A major strength of this study is the treatment effect modelling approach, capturing relative effect modification through inclusion of treatment-by-covariate interaction terms. This method overcomes the vulnerabilities of subgroup analyses. Subgroup analyses carry a high risk of chance findings, potentially resulting in the discovery of false subgroup effects and exaggerated effects.[9] Another strength is the use of RCT data. Because randomization remains the gold standard for the unbiased estimation of treatment effects, an RCT is the most desirable study design for the analysis of heterogeneity of treatment effect.[9] In addition, the percentage of missing data was very small, minimizing the risk of biased estimates. Lastly, the long follow-up duration allowed for a prediction horizon of 30 years, which is more informative than short-term estimations in this young population and which enabled us to demonstrate the long-term effects of INT versus CONV. Some limitations also need consideration. First, due to the small and relatively young study population, the number of events across the subgroups was small, limiting the statistical power. Second, no data regarding medication use other than insulin therapy was available at DCCT baseline, but the use of ACE-inhibitors was discouraged and statins were not in widespread use until the early 2000s.[25] Data on all-cause mortality were not available up to 2017, and therefore, the prediction model could not be adjusted for competing risks. This has possibly led to an overestimation of the absolute risk of MACE. However, the model still performed well, with good agreement between expected and observed risks. Third, this study started in 1983, with limited availability of insulins compared to the large range of insulin analogues now available. Most of the intensively treated individuals using multiple daily injections used NPH/lente insulins once or twice daily or ultralente insulins in combination with short-acting insulin before meals.[23] Fourth, as the prediction model was developed directly from the trial population and not externally validated, the model may suffer from overfitting. This is reflected in the relatively high c-for-benefit. A c-for-benefit above 0.6 is unusual, as it is difficult to predict treatment effect compared to predicting outcome risk.[20] However, in order to minimize overfitting, predictors were prespecified based on previous literature and the final model coefficients were estimated using penalized regression. Although several characteristics have been identified as being associated with treatment effect, it should be noted that this methodology is not suitable for inferring causal relationships between characteristics and treatment response, because many of these characteristics are interrelated. It can, however, be used to generate hypotheses about the possible mechanisms underlying heterogeneity of treatment effect found in the current study. It should also be kept in mind that differences in treatment effect of INT versus CONV would probably be smaller if the trial were conducted in the present time, due to improved recognition and treatment of cardiovascular risk factors nowadays. However, the intention of the model was to explore the presence of heterogeneity in this study population, not to develop a model for clinical practice.

In conclusion, this post hoc analysis of the DCCT/EDIC study demonstrates heterogeneity of the treatment effect of INT in individuals with T1D. Although INT is beneficial in terms of macrovascular events in the majority of individuals with T1D, benefit varies substantially. These individual differences in the effect of INT underline the necessity for a better understanding of the individual response to intensive treatment.

## AUTHOR CONTRIBUTIONS

Marga A. G. Helmink, Steven H. J. Hageman, Frank L. J. Visseren and Jan Westerink designed the study and analysed the data. Marga A. G. Helmink conducted the statistical analyses and drafted the manuscript. Steven H. J. Hageman, Frank L. J. Visseren, Wendela L. de Ranitz-Greven, Harold W. de Valk, Thomas T. van Sloten and Jan Westerink critically revised the manuscript for its intellectual content and gave final approval of the version to be published.

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For the current study, no funding was received.

## CONFLICT OF INTEREST STATEMENT

No conflicts of interest relevant to this article were reported.

## DATA AVAILABILITY STATEMENT

The datasets analysed in the current study are available in the NIDDK repository (https://repository.niddk.nih.gov/studies/edic/).

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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