Table 1 Appendix: Baseline characteristics of all DCCT/EDIC participants according to history of IHE over the course of DCCT/EDIC.

Factor of interest	No IHE	IHE	p-value
Number of subjects without/with IHE	1273	168	
Female Sex (%)	47.1	47.6	0.97
Age (years)	26.4 ± 7.1	29.9 ± 6.2	<0.0001
Body Mass Index (kg/m^2)	23 ± 3	24 ± 3	0.0014
LDL (mg/dl)	108 ± 28	121 ± 31	<0.0001
Triglycerides (mg/dl)	80 ± 47	88 ± 49	0.013
HDL (mg/dl)	51 ± 12	50 ± 12	0.16
Systolic Blood Pressure (mm Hg)	114 ± 12	117 ± 11	0.0019
Pulse (bpm)	76 ± 11	79 ± 11	0.0041
Smoking, n (%)	17.4	27.4	0.0024
Moderate/strenuous Exercise (%)	69.8	71.4	0.72
Positive Family history MI (%)	47.2	61.3	0.00080
Intensive Treatment (%)	49.8	45.8	0.38
HbA1c (%)	9.0 ± 1.6	9.3 ± 1.7	0.038
HbA1c (mmol/mol)	75 ± 17	78 ± 19	
Insulin dose (units/kg)	0.67 ± 0.25	0.68 ± 0.25	0.20
Past SH history (%)*	4.7	4.8	1
Surrogates of B-vascular damage severity			
Duration of diabetes (years)	5.5 ± 4.1	6.7 ± 4.4	0.00077
Median [IQR]	3.9 [2.2,8.7]	6.0 [2.4,11.0]	
DCCT-ETDRS	2.2 ± 1.6	2.9 ± 2.1	<0.0001
Median [IQR]	1[1,3]	2[1,4]	
GFR (ml/min/1.73 mm^2)	126 ± 14	124 ± 13	0.017
AER (mg/24h)	16 ± 19	18 ± 21	0.029
B-AER≥30mg/24h (%)	10.5	13.7	0.27
Neuropathy (Yes vs. No) (%)	8.4	20.2	<0.0001
Neuropathy and/or AER≥30mg/24h, n (%)	17.6	29.8	0.00024
DCSI	0.67 ± 0.73	0.96 ± 0.84	<0.0001
Median [IQR]	1.0 [0,1.0]	1.0 [0,1.25]	
CV-score (%)†	0.61 ± 0.40	0.93 ± 0.58	<0.0001
Median [IQR]	0.50 [0.34,0.77]	0.76 [0.50,1.27]	

Values presented as mean ± SD and prevalence (%), unless otherwise indicated. LDL-Low-Density Lipoprotein, TRG-Triglycerides, HDL-High-Density Lipoprotein, AER-Albumin Excretion Rate, GFR-Glomerular Filtration Rate. IQR-Interquartile Range. DCCT-ETDRS: steps on DCCT Early Treatment Diabetic Retinopathy Study severity scale [15,16]. Neuropathy: sensory peripheral and/or autonomic neuropathy. DCSI- Diabetes Complication Severity Index: at DCCT-baseline a measure related to severity of microvascular complications (retinopathy, nephropathy, and neuropathy). *SH during the year before baseline visit requiring IV glucose. †CV-score assessed by Swedish risk engine [23]; CVD history, a component of the Swedish risk model does not include CHF.

Appendix: Sensitivity analyses

Table 2 Appendix: Significance of interaction between SH and measures related to severity of microvascular complications at DCCT-baseline according to assumptions regarding origin of cardiovascular deaths.

Interaction between SH **and** baseline	All CV-deaths were of ischemic heart disease origin (main analysis)	None of the CV-deaths were of ischemic heart disease origin	CV-deaths for subjects with a coronary calcification score >0 Agatston units were of ischemic heart disease origin
	Number of subjects with events: 168 p-value	Number of subjects with events: 154 p-value	Number of subjects with events: 158 p-value
Diabetes Duration	<0.0001	<0.001	<0.001
DCCT-ETDRS	<0.01	<0.01	<0.01
DCSI	<0.001	<0.001	<0.001

For 14 subjects, death was the first IHD event. Models were adjusted for B-age, M-HbA1c, B-Family history of MI, M-LDL, C-Triglycerides (log-transformed), M-systolic blood pressure, C-Insulin dose, C-Insulin Regimen, Sex, any-stroke/CHF-history, and B-Neuropathy. If Cox regression hazard assumption was violated, interaction between time and covariate was included in model. DCSI model did not include B-Neuropathy as an adjustment factor (B-Neuropathy is counted for in DCSI). In models without the interaction, the association between SH and IHD was significant with p<0.05. DCCT-ETDRS: steps on DCCT Early Treatment Diabetic Retinopathy Study severity scale [15,16], DCSI- Diabetes Complication Severity Index. Information on coronary calcification score can be found [Cleary PA, Orchard TJ, Genuth S, et al., The effect of intensive glycemic treatment on coronary artery calcification in type 1 diabetic participants of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. *Diabetes*. 2006;55(12):3556-3565. DOI:10.2337/db06-0653].

Table 3 Appendix: Hazard ratios for IHD events based on interaction between baseline DCSI and SH depending on whether DCSI score was based on single B-AER or B-AER and persistence.

Estimate for interaction of DCSI with SH with 95% CI	DCSI score based on B-AER ≥30mg/24h	DCSI score based on B-AER ≥30mg/24h at first two DCCT visits
p-value	2.21 [1.42-3.44].	2.09 [1.30-3.35]
Interpretation	<0.001 The hazard ratio for IHD based on SH increases 2.21-fold for each additional DCSI score	<0.01 The hazard ratio for IHD based on SH increases 2.09-fold for each additional DCSI score.

157 subjects with B-AER ≥30mg/24h at first visit, 68 subjects with B-AER ≥30mg/24h at first two DCCT visits. DCSI- baseline Diabetes Complication Severity Index.

Table 4 Appendix: Most important predictors for IHD including baseline retinopathy severity (DCCT-ETDRS) or baseline Diabetes Complication Severity Index (DCSI) as surrogate of microvascular damage severity for the subgroup of individuals with severe hypoglycemia during DCCT/EDIC follow-up.

Table 4a Appendix: Most important predictors for IHD including baseline retinopathy severity (DCCT-ETDRS) as surrogate of microvascular damage severity for the subgroup of individuals with severe hypoglycemia during DCCT/EDIC follow-up.

Predictor	HR	CI95%	z	p-value
M-Systolic Blood Pressure (mmHg)	1.05	1.03-1.08	4.67	<0.0001
B-Severity of Retinopathy	1.23	1.12-1.34	4.53	<0.0001
Stroke/CHF history (Yes vs. No)	4.99	1.78-13.95	3.06	<0.01
C-Insulin regimen (Standard vs. MDI/Pump)	2.28	1.32-3.93	2.95	<0.01
Sex (Female vs. Male)	1.73	1.17-2.55	2.77	<0.01
C-Triglycerides (log) (mg/dl)	1.64	1.13-2.38	2.60	<0.01
C-LDL (mg/dl)	1.01	1.00-1.01	2.27	<0.05
B-Neuropathy (Yes vs. No)	1.71	1.06-2.75	2.21	<0.05
M-Insulin dose (unit/kg/day)	3.28	1.10-9.76	2.14	<0.05
B-Age (years)	1.03	1.00-1.07	2.10	<0.05
B-Family history of MI (Yes vs. No)	1.51	1.02-2.23	2.04	<0.05

B- Baseline level, C-updated current level, M-updated mean level. DCCT-ETDRS: steps on DCCT Early Treatment Diabetic Retinopathy Study severity scale [15,16]. Stroke and congestive heart failure (CHF) events counted as any-stroke/CHF history if they occurred prior to an IHD event or censored date - Stroke/CHF history: 12 subjects with stroke/CHF history. Neuropathy includes sensory peripheral and/ or autonomic neuropathy. The z-value is a measure of the strength of association between covariate of interest and the outcome [9].

Table 4b Appendix: Most important predictors for IHD including baseline Diabetes Complication Severity Index (DCSI) as surrogate of microvascular damage severity for the subgroup of individuals with severe hypoglycemia during DCCT/EDIC follow-up

Predictor	HR	CI95%	z	p-value
M-Systolic Blood Pressure (mmHg)	1.06	1.03-1.08	4.67	<0.0001
B-DCSI	1.66	1.32-2.09	4.30	<0.0001
B-Age (years)	1.05	1.02-1.08	3.24	<0.01
Stroke/CHF History (Yes vs. No)	4.82	1.71-13.57	2.97	<0.01
C-Triglycerides (log) (mg/dl)	1.72	1.20-2.45	2.96	<0.01
C-Insulin regimen (Standard vs. MDI/Pump)	2.11	1.22-3.66	2.68	<0.01
Sex (Female vs. Male)	1.69	1.14-2.51	2.61	<0.01

C-Use of ACEI (Yes vs. No)	0.61	0.39-0.96	2.15	<0.05
B-Family history of MI (Yes vs. No)	1.53	1.04-2.72	2.14	<0.05
M-Insulin dose (unit/kg/day)	3.08	1.04-9.16	2.02	<0.05
C-Pulse (bpm)	1.02	1.00-1.04	1.98	<0.05

B-Baseline level, C-updated current level, M-updated mean level. Stroke and congestive heart failure (CHF) events counted as any-stroke/CHF history if they occurred prior to an IHD event or censored date -12 subjects with stroke/CHF history. The z-value is a measure of the strength of association between covariate of interest and the outcome [9]

Textbox-1 Appendix: Confounding positive/negative [1-14].

*U*nadjusted models should be interpreted cautiously due to possible confounding, sometimes referred as confounding bias. Confounding factors might distort an apparent association between the independent variable of interest and the outcome (dependent variable of interest).

*O*ne *technique* to reduce/eliminate confounding bias is using multivariable methods controlling (adjusting) for possible confounders. It allows assessment of the independent effect of each independent variable.

*C*onfounding bias effect depends on the direction of the association between predictor of interest and outcome as well as on the direction of the association between confounder and both predictor of interest and outcome [2].

- *Confounding* is usually thought to be positive. The observed unadjusted association is biased away from the null hypothesis; in other words, the unadjusted association is overestimated.
- *Negative confounding* also exists, although less commonly. If negative confounding exists, the observed unadjusted association is biased toward the null hypothesis; the unadjusted association between the independent variable of interest and the outcome is underestimated.

*I*mportance to correct for such negative bias is exemplified in the following examples:

DCCT/EDIC study on CVD risk factors [8]: Current ACEI use was not a significant factor in univariate analyses for "any"-CVD (p>0.60) or MACE (p>0.80). However, in final models for both "any"-CVD and MACE, current ACEI use is listed as one of the most important risk factors (although protective) in CVD with p~0.03 and p~0.04, respectively. Current ACEI use became statistically significant after blood pressure was included in the model. In this DCCT/EDIC analysis, systolic blood pressure is a negative confounder [2]. By including

systolic blood pressure in the model, negative confounding bias due to systolic blood pressure was eliminated. Other examples can be found elsewhere [9-13].

In our current analysis, potential confounders were considered based on literature and clinical judgement [8,14-21]. Prior DCCT/EDIC studies indicate that lower HbA1c and younger age (entry into DCCT study as an adolescent) are significant predictors for SH [14,21]. Age and HbA1c were also found to be important CVD predictors [8].

In our analysis, we have the following scenario:

SH and IHD, as well as HbA1c and IHD, are positively correlated; with SH history and with increasing HbA1c, the risk for IHD increases. On the other hand, HbA1c is inversely (negatively) correlated with SH; the risk of SH increases with lower HbA1c. Similar correlations exist between age and IHD and age and SH. The IHD risk increases with older age. However, the SH risk increases with younger age.
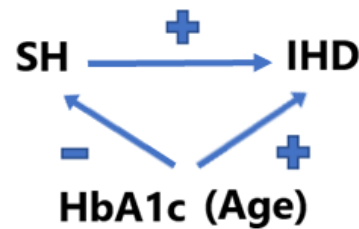
Accounting for the directions of associations between SH, HbA1c (Age), and IHD, we anticipated that both age and HbA1c are potential negative confounders of the association between SH and IHD [2]. Subsequently, the association between SH and IHD might be biased and underestimated if not controlled for these two potential confounders. In the current analysis, SH was a significant IHD predictor in basic model which adjusted for age and HbA1c. Significance remained in fully adjusted models; in addition to age and M-HbA1c, B-diabetes duration (or DCCT-ETDRS or DCSI), B-neuropathy (not included if DCSI was a factor in the model), M-SBP, any-stroke/CHF history, M-insulin dose, M-LDL, C-triglycerides, B-family history of MI, sex, and C-insulin regimen were included in the models. If any variable violated the Cox Hazard assumption, interactions of this variable with a function of time was included in the model.

References below provide substantial supportive literature to provide further justification of our statistical approach and the interpretation of our findings.

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Textbox-2 Appendix: Interactions [1-12].

- 1. The significance of the interaction term indicates that the effect of SH on the outcome IHD is conditional on the level of microvascular damage severity (moderator variable).

- 2. To reduce the chance of an artifact, interactions were probed using the computer method by Aiken [references 4,8 below]. The range of significance was found within the observable data range.

- 3. In the presence of a significant interaction, interpreting the effect of SH on IHD might be misleading or wrong.

  In the current analysis, basic and fully adjusted models showed a significant association between SH and IHD (main effect) in models without the interaction between SH and microvascular damage severity surrogates. Interpreting this main effect of SH leads to the conclusion that all participants with SH are at an increased risk for IHD. However, this is not true for each participant with a SH history during the combined DCCT/EDIC period. In fact, for the subgroup of patients with shorter diabetes duration (<5.7 years), retinopathy severity levels ≤2, or DCSI =0, SH was not an IHD risk factor. Moreover, for participants without any microvascular disease, the HR based on SH was less than 1 (probably due to a masking effect of HbA1c). In contrast, for participants with a diabetes ≥5.7 years, or participants with a retinopathy severity level >2, or subjects with a DCSI >0, SH was significantly associated with IHD.

- 4.Sub-analyses of stratified cohorts by diabetes duration <5.7/≥5.7 years, retinopathy severity levels <3/≥3, and DCSI 0/>0 supported point 3. In sub-analyses analyzing individuals with markers of microvascular damage severity in the lower range in contrast to the higher range, SH was not a significant IHD factor.

Important literature on interactions:

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Textbox-3 Appendix: CV-Score Information on CV-score as of 12/31/2013.

As of 12/31/2013, 1327 DCCT participants [9] were alive. CV-score at this follow-up end was calculated for ~93% of surviving participants who had a visit after 1/1/2012 (1232 subjects). Median CV-score was 4.2% [IQR: 2.8, 6.9%]. The Swedish risk score engine [23] was used to calculate this CV-score.