SUPPLEMENTARY DATA

The Risk of Severe Hypoglycemia in Type 1 Diabetes Over 30 years of Follow-up in the DCCT/EDIC Study

The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group*

Supplementary Table S1. Characteristics of subjects at DCCT closeout (1993) by treatment group

	DCCT Closeout	
	Conventional	**Intensive**
Number of subjects	708	699
Demographics		
Gender (% female)	46.3	49.2
Age (years)	33.1 ± 7.0	33.7 ± 7.0
Race (% Caucasian)	96.3	96.4
Overweight (%)		
Male (BMI >27.8)	19.6	29.8*
Female (BMI >27.3)	19.4	38.0†
Education (years)	14.9 ± 1.6	14.9 ± 1.6
Clinical history		
Duration (years)		
Primary cohort	8.5 ± 2.4	8.6 ± 2.3
Secondary cohort	15.5 ± 4.1	15.9 ± 4.0
HbA1c [% (mmol/mol)]	9.1 ± 1.5 (76.4 ± 16.9)	7.4 ± 1.1 (57.3 ± 12.0)†
Mean DCCT HbA1c [% (mmol/mol)]	9.1 ± 1.3 (75.9 ± 13.9)	7.2 ± 0.9 (55.6 ± 10.1)†
Insulin dose (U/kg/day)	0.66 ± 0.20	0.70 ± 0.25†
Regimen (%)		
CSII	1.6	41.0†
MDI	3.3	56.3
Standard	95.2	2.7
Systolic blood pressure (mmHg)	116.5 ± 11.9	116.6 ± 11.5
Diastolic blood pressure (mmHg)	74.3 ± 8.9	74.8 ± 8.7

Data are means ± SD, unless otherwise indicated.
CSII=Continuous subcutaneous insulin infusion; MDI=Multiple daily injections
*Difference between treatment groups is significant, P<0.01
†Difference between treatment groups is significant, P<0.001

SUPPLEMENTARY DATA

Supplementary Table S2A. Subgroup analyses for severe hypoglycemia in EDIC* by DCCT closeout characteristics

	Conventional (N=708)					Intensive (N=699)						
DCCT Closeout Characteristics	N	% with Event	# of Events	Mean Rate	Diff in Rate, P=	N	% with Event	# of Events	Mean Rate	Diff in Rate, P=	Rel. Risk 95% CI	Diff in RR, P=
Cohort												
Primary	341	50.4	658	37.8	0.6636	357	51.0	851	45.7	0.1008	1.2(0.9, 1.6)	0.3695
Secondary	367	48.8	672	35.5		342	51.5	632	35.7		1.0(0.8, 1.3)	
Gender												
Male	380	48.4	703	36.2	0.8837	355	49.3	729	39.5	0.6650	1.1(0.8, 1.5)	0.8285
Female	328	50.9	627	37.0		344	53.2	754	42.2		1.1(0.9, 1.5)	
Age												
Adolescent	98	57.1	244	47.6	0.0749	90	63.3	240	51.9	0.1190	1.1(0.7, 1.7)	0.8892
Adult	610	48.4	1086	34.8		609	49.4	1243	39.2		1.1(0.9, 1.4)	
Education (years)												
<12-16	361	51.2	687	37.4	0.7296	342	53.5	801	45.3	0.1757	1.2(0.9, 1.6)	0.4575
>=16	344	47.4	634	35.6		352	49.1	678	36.9		1.0(0.8, 1.4)	
Level of exercise												
Strenuous	49	53.1	136	55.1	0.1525	44	45.5	118	52.5	0.8312	1.0(0.4, 2.4)	0.4073
Hard	33	39.4	36	20.6		37	51.4	92	47.5		2.3(1.0, 5.4)	
Moderate	393	52.9	729	35.9		353	52.7	724	39.4		1.1(0.8, 1.4)	
Mild	228	44.3	423	36.6		259	50.2	545	40.6		1.1(0.8, 1.6)	
Body Mass Index (kg/m2)												
<25	376	51.3	763	39.7	0.2266	280	48.2	542	37.6	0.0497	0.9(0.7, 1.3)	0.1789
25-30	293	48.1	512	33.9		282	53.2	716	48.6		1.4(1.0, 2.0)	
>=30	39	43.6	55	27.0		137	53.3	225	31.4		1.2(0.7, 1.9)	

T1D Duration (years)

<8	179	52.0	383	41.4	0.3906	172	50.0	382	42.9	0.7710	1.0(0.7, 1.6)	0.9120
8-16	367	46.9	625	33.3		336	52.1	672	38.6		1.2(0.9, 1.5)	
>16	162	53.1	322	38.8		191	50.8	429	42.9		1.1(0.8, 1.6)	

Mean DCCT HbA1c (%)

<7.032	32	56.3	64	38.7	0.2667	320	52.8	642	38.4	0.8185	1.0(0.5, 1.8)	0.5544
7.032-7.941	103	52.4	155	28.7		249	47.0	547	42.0		1.5(1.0, 2.2)	
7.941-9.161	248	52.4	437	34.0		103	55.3	245	46.1		1.4(0.9, 2.0)	
9.161+	325	45.8	674	40.9		27	55.6	49	38.7		0.9(0.5, 1.7)	

Insulin dose (U/kg)

<0.635	377	50.9	720	37.0	0.8588	318	50.6	747	45.2	0.1979	1.2(0.9, 1.6)	0.4160
>=0.635	331	48.0	610	36.1		381	51.7	736	37.2		1.0(0.8, 1.4)	

Prior hypoglycemia during DCCT (coma and/or seizure)

No	574	43.4	876	29.7	0.0000	432	39.6	505	22.4	0.0000	0.8(0.6, 1.0)	0.0928
Yes	134	76.1	454	66.6		267	70.0	978	70.8		1.1(0.8, 1.4)	

Cardiac Autonomic Neuropathy†

No	621	49.3	1182	36.9	0.9265	635	51.0	1340	40.6	0.7801	1.1(0.9, 1.4)	0.7930
Yes	78	51.3	138	36.0		52	55.8	116	43.7		1.2(0.6, 2.4)	

Rates defined as episodes per 100 patient-years of follow-up. Relative risk (INT vs. CONV) computed as ratio of event rates.

*Number of events in 3-month interval prior to annual visit. Exposure is 0.25 years per patient per visit.

†CAN defined as an R-R variation <15 or an R-R 15-20 in combination with a Valsalva Ratio ≤1.5 or a decrease >10 mm Hg in diastolic blood pressure.

SUPPLEMENTARY DATA

Supplementary Table S2B. Subgroup analyses for coma and/or seizure in EDIC* by DCCT closeout characteristics

DCCT Closeout Characteristics	Conventional (N=708)					Intensive (N=699)						
	N	% with Event	# of Events	Mean Rate	Diff in Rate, P=	N	% with Event	# of Events	Mean Rate	Diff in Rate, P=	Rel. Risk 95% CI	Diff in RR, P=
Cohort												
Primary	341	27.6	232	13.3	0.1982	357	30.0	274	14.7	0.2012	1.1(0.7, 1.6)	0.8753
Secondary	367	26.7	201	10.6		342	26.9	199	11.2		1.1(0.7, 1.5)	
Gender												
Male	380	25.5	220	11.3	0.5612	355	30.1	258	14.0	0.4772	1.2(0.8, 1.8)	0.3586
Female	328	29.0	213	12.6		344	26.7	215	12.0		1.0(0.7, 1.4)	
Age												
Adolescent	98	37.8	89	17.4	0.0331	90	28.9	75	16.2	0.3570	0.9(0.5, 1.7)	0.5661
Adult	610	25.4	344	11.0		609	28.4	398	12.6		1.1(0.8, 1.5)	
Education (years)												
<12-16	11	18.2	3	5.3	0.2366	11	27.3	12	23.9	0.2783	4.5(0.8,24.4)	0.1089
>=16	694	26.9	423	11.9		683	28.6	460	12.9		1.1(0.8, 1.4)	
Level of exercise												
Strenuous	49	32.7	44	17.8	0.4505	44	34.1	58	25.8	0.5103	1.4(0.4, 4.9)	0.8124
Hard	33	15.2	11	6.3		37	24.3	22	11.4		1.8(0.5, 6.5)	
Moderate	393	28.5	239	11.8		353	27.5	235	12.8		1.1(0.8, 1.6)	
Mild	228	24.6	134	11.6		259	29.3	156	11.6		1.0(0.7, 1.5)	
Body Mass Index (kg/m2)												
<25	376	31.1	270	14.1	0.0924	280	28.2	182	12.6	0.3877	0.9(0.6, 1.3)	0.1291
25-30	293	21.8	139	9.2		282	29.8	218	14.8		1.6(1.0, 2.6)	
>=30	39	28.2	24	11.8		137	26.3	73	10.2		0.9(0.4, 1.7)	

SUPPLEMENTARY DATA

<table>
<tr><td colspan="12">T1D Duration (years)</td></tr>
<tr><td><8</td><td>179</td><td>27.4</td><td>119</td><td>12.9</td><td>0.5747</td><td>172</td><td>26.7</td><td>143</td><td>16.0</td><td>0.4369</td><td>1.2(0.7, 2.3) 0.8533</td></tr>
<tr><td>8-16</td><td>367</td><td>28.1</td><td>204</td><td>10.9</td><td></td><td>336</td><td>28.6</td><td>197</td><td>11.3</td><td></td><td>1.0(0.8, 1.4)</td></tr>
<tr><td>>16</td><td>162</td><td>24.7</td><td>110</td><td>13.3</td><td></td><td>191</td><td>29.8</td><td>133</td><td>13.3</td><td></td><td>1.0(0.6, 1.7)</td></tr>
<tr><td colspan="12"> </td></tr>
<tr><td colspan="12">Mean DCCT HbA1c (%)</td></tr>
<tr><td><7.032</td><td>32</td><td>28.1</td><td>25</td><td>15.1</td><td>0.2415</td><td>320</td><td>28.1</td><td>214</td><td>12.8</td><td>0.1956</td><td>0.8(0.4, 2.0) 0.1364</td></tr>
<tr><td>7.032-7.941</td><td>103</td><td>26.2</td><td>59</td><td>10.9</td><td></td><td>249</td><td>28.9</td><td>192</td><td>14.7</td><td></td><td>1.3(0.8, 2.4)</td></tr>
<tr><td>7.941-9.161</td><td>248</td><td>25.0</td><td>121</td><td>9.4</td><td></td><td>103</td><td>30.1</td><td>59</td><td>11.1</td><td></td><td>1.2(0.7, 1.9)</td></tr>
<tr><td>9.161+</td><td>325</td><td>28.9</td><td>228</td><td>13.8</td><td></td><td>27</td><td>22.2</td><td>8</td><td>6.3</td><td></td><td>0.5(0.2, 1.0)</td></tr>
<tr><td colspan="12"> </td></tr>
<tr><td colspan="12">Insulin dose (U/kg)</td></tr>
<tr><td><0.635</td><td>377</td><td>26.0</td><td>216</td><td>11.1</td><td>0.4121</td><td>318</td><td>29.2</td><td>239</td><td>14.4</td><td>0.3508</td><td>1.3(0.9, 2.0) 0.2143</td></tr>
<tr><td>>=0.635</td><td>331</td><td>28.4</td><td>217</td><td>12.8</td><td></td><td>381</td><td>27.8</td><td>234</td><td>11.8</td><td></td><td>0.9(0.6, 1.3)</td></tr>
<tr><td colspan="12"> </td></tr>
<tr><td colspan="12">Prior hypoglycemia during DCCT (coma and/or seizure)</td></tr>
<tr><td>No</td><td>574</td><td>22.1</td><td>275</td><td>9.3</td><td>0.0000</td><td>432</td><td>19.7</td><td>125</td><td>5.6</td><td>0.0000</td><td>0.6(0.4, 0.8) 0.0174</td></tr>
<tr><td>Yes</td><td>134</td><td>48.5</td><td>158</td><td>23.2</td><td></td><td>267</td><td>42.7</td><td>348</td><td>25.2</td><td></td><td>1.1(0.7, 1.6)</td></tr>
<tr><td colspan="12"> </td></tr>
<tr><td colspan="12">Cardiac Autonomic Neuropathy</td></tr>
<tr><td>No</td><td>621</td><td>27.1</td><td>376</td><td>11.7</td><td>0.6558</td><td>635</td><td>28.0</td><td>429</td><td>13.0</td><td>0.5842</td><td>1.1(0.8, 1.5) 0.4910</td></tr>
<tr><td>Yes</td><td>78</td><td>26.9</td><td>52</td><td>13.6</td><td></td><td>52</td><td>34.6</td><td>30</td><td>11.3</td><td></td><td>0.8(0.4, 1.8)</td></tr>
</table>

Rates defined as episodes per 100 patient-years of follow-up. Relative risk (INT vs. CONV) computed as ratio of event rates.

*Number of events in 3-month interval prior to annual visit. Exposure is 0.25 years per patient per visit.

†CAN defined as an R-R variation <15 or an R-R 15-20 in combination with a Valsalva Ratio ≤1.5 or a decrease >10 mm Hg in diastolic blood pressure

Supplementary Table S3. Influence of HbA1c (time-dependent) on the risk of any severe hypoglycemia (first episode) in Poisson regression models

	Conventional		Intensive	
	β + SE	Relative Risk (95% CI)	β + SE	Relative Risk (95% CI)
DCCT: Current HbA1c (%), time-dependent, per 10% decrease	-4.47 ± 0.34	1.60 (1.49-1.72)	-2.30 ± 0.35	1.27 (1.19-1.37)
EDIC: Current HbA1c (%), time-dependent, per 10% decrease	-1.19 ± 0.34	1.13 (1.06-1.22)	-1.33 ± 0.35	1.15 (1.07-1.24)

Poisson models are unadjusted for other factors. The relative risk, presented per 10% decrease in HbA1c, is 0.9^{β}. Information about EDIC events was collected for the 3-month window prior to the annual visit. All models are significant at P<0.01.

Supplementary Table S4. Risk of any severe hypoglycemia (first episode) in EDIC jointly adjusting for DCCT closeout and time-dependent covariates

Severe	Conventional		Intensive	
	Relative Risk (95% CI)	p-value	Relative Risk (95% CI)	p-value
Male (y/n)	0.83 (0.67-1.04)	0.1123	0.78 (0.63-0.97)	0.0274
Adolescent (y/n)	1.30 (0.95-1.78)	0.1025	1.21 (0.89-1.65)	0.2316
Secondary cohort (y/n)	1.04 (0.76-1.43)	0.8049	1.03 (0.75-1.40)	0.8637
Duration of T1D (years)	0.99 (0.95-1.02)	0.3591	0.99 (0.96-1.02)	0.4024
Current regimen (CSII/Standard), time-dependent	0.60 (0.40-0.89)	0.0114	0.57 (0.33-1.00)	0.0506
Current regimen (CSII/MDI), time-dependent	0.63 (0.47-0.85)	0.0022	0.75 (0.59-0.96)	0.0236
Current insulin dose (U/kg), time-dependent	1.15 (0.72-1.83)	0.5666	1.19 (0.76-1.87)	0.4402
History of hypoglycemia (coma and/or seizure) during DCCT (y/n)	2.77 (2.17-3.55)	<0.0001	2.52 (2.03-3.14)	<0.0001
Current HbA1c (%), time-dependent, per 10% decrease	1.28 (1.23-1.33)	<0.0001	1.26 (1.22-1.31)	<0.0001

Coma and/or seizure	Conventional		Intensive	
	Relative Risk (95% CI)	p-value	Relative Risk (95% CI)	p-value
Male (y/n)	0.75 (0.55-1.00)	0.0530	1.07 (0.80-1.42)	0.6731
Adolescent (y/n)	1.69 (1.15-2.48)	0.0078	0.85 (0.55-1.31)	0.4560
Secondary cohort (y/n)	1.21 (0.80-1.83)	0.3718	1.17 (0.78-1.75)	0.4554
Duration of T1D (years)	0.96 (0.92-1.00)	0.0587	0.98 (0.94-1.02)	0.4034
Current regimen (CSII/Standard), time-dependent	0.51 (0.29-0.88)	0.0154	0.43 (0.21-0.88)	0.0211
Current regimen (CSII/MDI), time-dependent	0.49 (0.33-0.73)	0.0004	0.69 (0.50-0.97)	0.0308
Current insulin dose (U/kg), time-dependent	1.18 (0.63-2.20)	0.6078	0.79 (0.43-1.42)	0.4236
History of hypoglycemia (coma and/or seizure) during DCCT (y/n)	2.86 (2.09-3.92)	<0.0001	2.74 (2.05-3.66)	<0.0001
Current HbA1c (%), time-dependent, per 10% decrease	1.37 (1.30-1.44)	<0.0001	1.20 (1.14-1.26)	0.0003

CSII=Continuous subcutaneous insulin infusion; MDI=Multiple daily injections

Time to first event using discrete time intervals during EDIC (regardless of prior DCCT hypoglycemia). Information about EDIC events was collected for the 3-month window prior to the annual visit. All covariates are fixed effects at DCCT closeout, except for the designated time-dependent covariates. The relative risk, presented per 10% decrease in HbA1c, is 0.9^{β}.

Supplementary Table S5. Risk of all severe hypoglycemia (all episodes) in EDIC jointly adjusting for DCCT closeout and time-dependent covariates

Severe	Conventional		Intensive	
	Relative Risk (95% CI)	p-value	Relative Risk (95% CI)	p-value
Male (y/n)	0.95 (0.73-1.24)	0.7262	0.87 (0.65-1.16)	0.3389
Adolescent (y/n)	1.47 (1.06-2.03)	0.0194	1.02 (0.72-1.43)	0.9237
Secondary cohort (y/n)	1.13 (0.82-1.56)	0.4721	1.55 (0.97-2.48)	0.0643
Duration of T1D (years)	0.98 (0.95-1.01)	0.1623	0.96 (0.91-1.01)	0.1000
Current regimen (CSII/Standard), time-dependent	0.55 (0.39-0.76)	0.0004	0.51 (0.33-0.78)	0.0018
Current regimen (CSII/MDI), time-dependent	0.62 (0.49-0.78)	<0.0001	0.64 (0.48-0.84)	0.0014
Current insulin dose (U/kg), time-dependent	1.00 (0.70-1.43)	0.9962	0.77 (0.50-1.17)	0.2131
History of hypoglycemia (coma and/or seizure) during DCCT (y/n)	2.15 (1.64-2.82)	<0.0001	3.18 (2.37-4.28)	<0.0001
Current HbA1c (%), time-dependent, per 10% decrease	1.28 (1.23-1.33)	<0.0001	1.31 (1.26-1.36)	<0.0001

Coma and/or seizure	Conventional		Intensive	
	Relative Risk (95% CI)	p-value	Relative Risk (95% CI)	p-value
Male (y/n)	0.92 (0.66-1.27)	0.6106	1.02 (0.68-1.53)	0.9231
Adolescent (y/n)	1.67 (1.12-2.50)	0.0118	0.97 (0.57-1.63)	0.9046
Secondary cohort (y/n)	1.29 (0.85-1.94)	0.2308	1.75 (0.91-3.38)	0.0958
Duration of T1D (years)	0.98 (0.94-1.03)	0.4034	0.93 (0.86-1.00)	0.0664
Current regimen (CSII/Standard), time-dependent	0.63 (0.39-1.02)	0.0588	0.65 (0.30-1.41)	0.2760
Current regimen (CSII/MDI), time-dependent	0.61 (0.42-0.88)	0.0093	0.52 (0.36-0.74)	0.0003
Current insulin dose (U/kg), time-dependent	1.08 (0.63-1.85)	0.7872	0.60 (0.30-1.18)	0.1375
History of hypoglycemia (coma and/or seizure) during DCCT (y/n)	2.19 (1.61-2.99)	<0.0001	4.81 (3.34-6.93)	<0.0001
Current HbA1c (%), time-dependent, per 10% decrease	1.29 (1.23-1.35)	<0.0001	1.38 (1.29-1.47)	<0.0001

CSII=Continuous subcutaneous insulin infusion; MDI=Multiple daily injections

Time to any event using discrete time intervals during EDIC (regardless of prior DCCT hypoglycemia). Information about EDIC events was collected for the 3-month window prior to the annual visit. All covariates are fixed effects at DCCT closeout, except for the designated time-dependent covariates. The relative risk, presented per 10% decrease in HbA1c, is 0.9^{β}.

SUPPLEMENTARY DATA

Supplementary Table S6. Major accidents and role of hypoglycemia in DCCT and EDIC

	DCCT		EDIC	
	Conventional	**Intensive**	**Conventional**	**Intensive**
	Number of events (number related to hypoglycemia)			
Total accidents	24 (9)*	27 (13)†	72 (15)*	71 (15)†
Number of subjects	22	27	63	60
Women	10	7	24	27
Men	12	20	39	33
Accident Type				
Motor vehicle accidents: operator	13 (9)	15 (9)	28 (13)	26 (10)
Motor vehicle accidents: nonoperator	1 (0)	3 (0)	0 (0)	3 (1)
Bicycle accidents	2 (0)	1 (1)	1 (0)	4 (1)
Accidents involving power tools	3 (0)	0 (0)	0(0)	2 (1)
Sports-related accidents	---	---	6 (0)	7 (0)
Accidents involving horses	---	---	3 (0)	2 (0)
On-the job accidents	---	---	6 (0)	4 (0)
Falling accidents	---	---	11 (1)	10 (2)
Other accidents‡	5 (0)	8 (3)	17 (1)	13 (0)
Role of hypoglycemia				
No role	15	14	54	51
Possible cause	5	5	4	7
Probable cause	0	2	4	3
Principal cause	4	6	7	5

Major accidents including all events that resulted in hospitalization or death. During the DCCT, clinics obtained all relevant information on all adverse events including hospital records, police reports, etc.

Numbers in parentheses are events related to hypoglycemia (as possible, probable, or principal cause). Only non-fatal events are assigned a role of hypoglycemia in EDIC.

* Includes 1 accidental death during DCCT (MVA) and 2 during EDIC (MVA, CO poisoning).

† Includes 3 accidental deaths during DCCT (all MVA) and 5 during EDIC

SUPPLEMENTARY DATA

Supplementary Figure S1. Proportion of severe hypoglycemic events (left) or subset resulting in coma and/or seizure (right) during (A) DCCT and (B) EDIC. Black bars represent the intensive group. White bars represent the conventional group.

A. DCCT

B. EDIC*
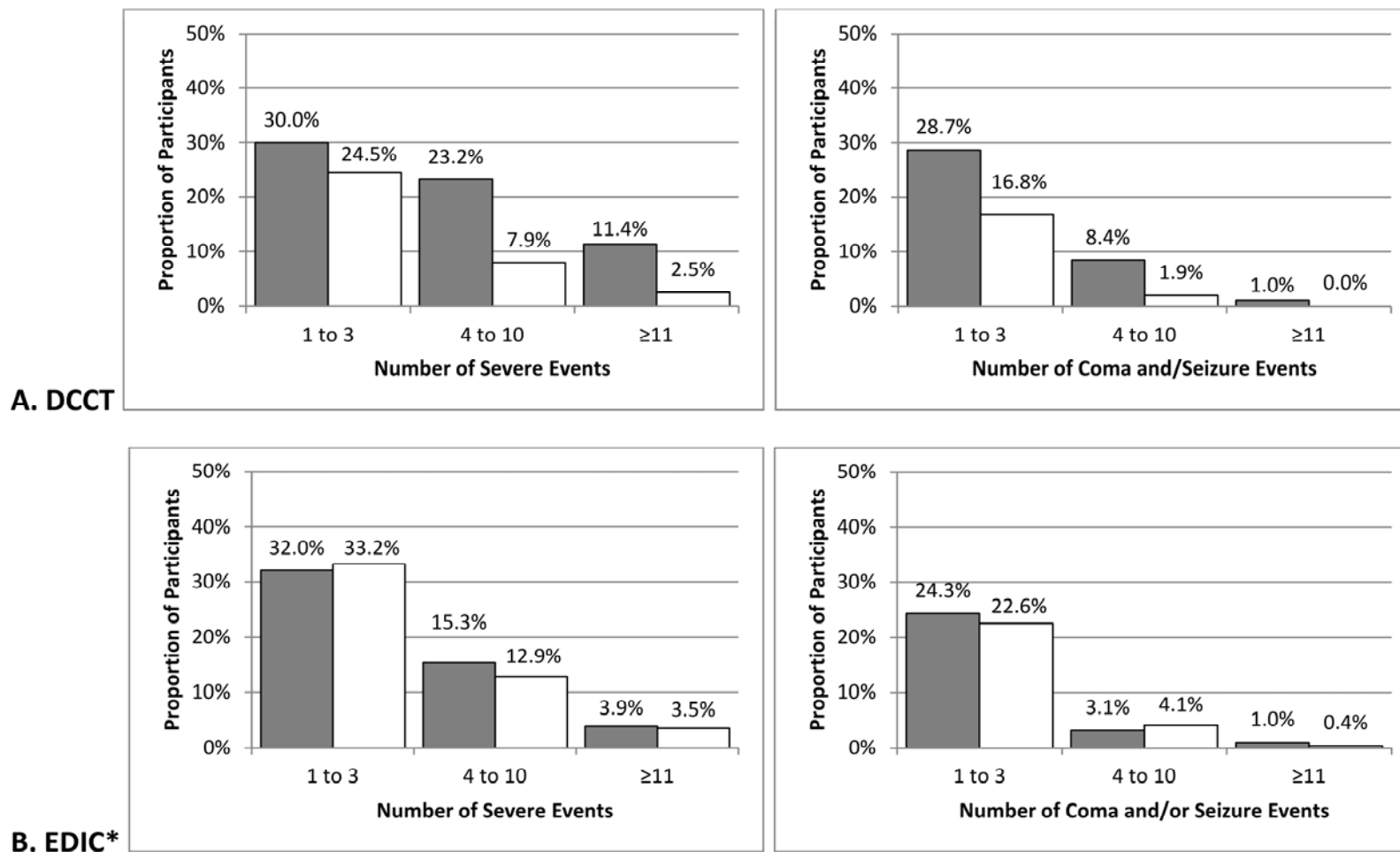
*Proportion of participants with an event in 3-month interval prior to annual visit

SUPPLEMENTARY DATA

Supplementary Figure S2. Cumulative percentage of subjects with (A) any severe hypoglycemia (first episode) and (B) resulting in coma and/or seizure, using discrete time intervals during EDIC (regardless of prior DCCT hypoglycemia). Numbers in parentheses represent subjects who are at risk of suffering a first episode. Information about EDIC events was collected for the 3-month interval prior to the annual visit. The EDIC period is based on N=699 subjects in the intensive group and N=708 subjects in the conventional group (N=34 subjects who were originally enrolled in the DCCT, did not have an EDIC visit).